Amyloidosis and Fabry Disease

A Clinical Guide

Diane Ávila
Humberto Villacorta
Editors

Springer

Amyloidosis and Fabry Disease

Diane Xavier de Ávila • Humberto Villacorta Junior
Editors

Amyloidosis and Fabry Disease

A Clinical Guide

Springer

Editors
Diane Xavier de Ávila
Postgraduate Program in
Cardiovascular Science
Fluminense Federal University
Niteroi, Rio de Janeiro, Brazil

Humberto Villacorta Junior
Cardiology Division
Fluminense Federal University
Niterói, Rio de Janeiro, Brazil

Amyloidosis Center
Complexo Hospitalar de Niterói/DASA
Rio de Janeiro, Brazil

ISBN 978-3-031-17758-3 ISBN 978-3-031-17759-0 (eBook)
https://doi.org/10.1007/978-3-031-17759-0

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Cardiomyopathies are diseases that affect the cardiac muscle of many etiologies related to genetics or from acquired causes and that present a challenge in clinical practice—the frequent late diagnosis. The framework of precision medicine has been applied in cardiomyopathies and is changing the noninvasive diagnosis (biomarkers, advanced methods of cardiovascular imaging, and genetic tests) and the use of disease-modifying drugs. Therefore, early recognition has become possible, and the treatment in early stages has changed the morbimortality by reducing complications about the cardiovascular system and other organs. Basic research and clinical trials represent the basis of advances obtained in the last decade in cardiac disease in both amyloidosis and Fabry disease. The education of health professionals and researchers about these advances, in order to improve the quality of patient care, was the basis of the construction and legacy of this book.

The editors were trained and acted as researchers associated with the Cardiology Department and Postgraduate Degree in Cardiology Sciences at Universidade Federal Fluminense (UFF), a center dedicated to the study, teaching, and assistance of cardiomyopathies with 5 years of experience. Our founder, the Professor Emeritus Raul Carlos Pareto Júnior, investigated cardiomyopathies with emphasis on the search for the etiology to understand the pathophysiological findings and clinicals so that we could finally develop a personalized therapy strategy. In the 1980s, he came all this way studying alcoholic cardiomyopathy from electron microscopy/endomyocardial biopsy to the study of different phenotypes through the evaluation combining phonomecanocardiography and Doppler echocardiography.

I would like to thank the General Heart Diseases and Cardiomyopathies Service of the Instituto do Coração—InCor, where I had the opportunity to do my PhD with Professor Charles Mady and to know, in addition, to reinforce the importance of translational cardiology for better compression of cardiomyopathies, which has certainly contributed a lot with the development of graduate studies at the UFF.

In conclusion, this book was born due to a collaborative spirit from different leaders who study and act with their multidisciplinary teams, connecting patient needs to teaching and research, which represents a scientific reference not only for Brazilian cardiology but also for the entire American continent.

Evandro Tinoco Mesquita
Cardiology, Complexo Hospitalar de Niterói–DASA
Rio de Janeiro, Brazil
Cardiology Division, Federal Fluminense University
Niterói, Rio de Janeiro, Brazil
Interamerican Society of Cardiology (SIAC), Cuidad de México
Mexico PROCEPI, Niterói, RJ, Brazil
Cardiomyopathies Study Group DEIC/GEMIC
Rio de Janeiro, RJ, Brazil
Sixth ward Cardiology, Santa Casa de Misericórdia
Rio de Janeiro, RJ, Brazil
Cardiovascular Sciences, Federal Fluminense University
Niterói, RJ, Brazil

Acknowledgments

Humberto Villacorta Junior

Writing a book is not an easy task. In addition, it is not an immediate thing either, but rather the result of the learning you have had from your professional but also your personal life. Therefore, it is not the work of a single person but the result of many hands working together. In this way, I would like to thank those who have helped me along the way.

First and above all, I would like to thank God who gave me life and the gift that allowed me to be a doctor and a teacher. In times like this, being alive is also a gift. Thank God.

I would like to start with my thanks to Dr. Diane Ávila, who along with me is the Editor of this book. She was my student as a cardiology fellow, and after that, I became her advisor during her master's and PhD courses. She was the one who came up with this idea and convinced me to participate. Many thanks for moving me forward.

I am eternally grateful to Prof. Evandro Tinoco, who was my mentor in the field of heart failure and who gave me the opportunity to conduct research with cardiac biomarkers, especially natriuretic peptides. He is my eternal advisor. Thank you for the inspiration and the ideas for this book.

A very special thanks to the Heart Failure Department (DEIC) of the Brazilian Society of Cardiology. This group is outstanding and has been responsible for many achievements I have had in my professional life. It all started back in 2001, when the group organized the first National Heart Failure Meeting and wrote the first heart failure guidelines. I am proud to be a founding member.

My thanks to the group that studies rare diseases in Brazil and around the world. Many of them contributed as authors in this book. I am very grateful to everyone who agreed to write a chapter in this book.

And finally, my special thanks to my family. My mother, Jucelia Villacorta, my eternal teacher, thank you for your love. In memoriam, I would like to thank my father, Humberto Villacorta, from whom I had the honor to inherit the name and from whom I learned a lot. He was the one who taught me genetics and mathematics even before I learned it in the school. He would be proud of this achievement. I

would not have made this book without the support of my wife, Aline Villacorta. Thank you for everything and for the things we have accomplished together. In addition, all my love goes to my boys, Leonardo, Pedro, and Lucas. You are the best book I have ever written.

Diane Xavier de Ávila

First of all, I would like to thank God for this opportunity to be able to put together in this book so much special, useful, and productive information that will help so many professionals working with amyloidosis and Fabry disease. The life journey of such patients has made me think of what I could do in order to help them have the best life quality possible, and God has always given us strength to follow the right path doing that. The patients were my inspiration for the realization of this work.

In memoriam, I would also like to thank God for the opportunity to have been the granddaughter of Oswaldo Gomes Xavier Filho and Jair Carvalho Xavier. They had always taught me and given me all the necessary love and support to be a distinctly dedicated medical doctor, based on the beautiful example they always demonstrated to me. And all they did has become part of me. All this care and love they gave me will survive through my profession and my patients.

I would like to thank my father José and my mother Jarlene, my sisters Elaine and Aline, my brothers-in-law, nephews, and specially my husband Samuel and my daughter Alice for their love and for being so understanding in all moments. My godmother Giselle de Oliveira, thank you for the encouragement.

I would like to thank all *friends, all authors, and their families* that gave us the necessary support to do this work; we are really grateful for that; without them, this work would not have been possible.

I would like to express my gratitude for all the guidance in my master's and doctorate degree in heart failure by Humberto Villacorta at Fluminense Federal University in Brazil and, in addition, for accepting this partnership to carry out this work. Alex Santos, thank you for all encouragement in life and for improving my English. I would also like to thank all the professors on this journey, especially Professor Evandro Tinoco Mesquita, who is an important mentor to professionals and also a great stimulator of studies in Brazilian cardiology, thank you very much for everything. Cláudio Tinoco Mesquita, thank you for the partnership and stimulus to the study.

We are also very grateful to the publish and production team, Vanessa Shimabukuro—our first contact—Fabiola Josephine, and the other excellent professionals of Springer Nature that were attentive and patient with us.

Contents

Contributors

Adriana Aparecida Bau Faculdade de Ciências Médicas—Universidade Estadual de Campinas, São Paulo, Brazil

Adriana Bastos Carvalho Instituto de Biofísica Carlos Chagas Filho—UFRJ, Rio de Janeiro, RJ, Brazil

Adriana Pereira Glavam Instituto Nacional de Cardiologia, Rio de Janeiro, RJ, Brazil

Hospital Copa Star, Rio de Janeiro, RJ, Brazil

Clínica de Diagnóstico por Imagem CDPI/DASA, Rio de Janeiro, RJ, Brazil

Adriana Muralha Uveitis and Retina Unit, Department of Ophthalmology, Fluminense Federal University, Niterói, RJ, Brazil

Agueda Miranda Department of Gastroenterology and Hepatology, Federal University of the State of Rio de Janeiro—UNIRIO, Rio de Janeiro, RJ, Brazil

Alex dos Santos Félix Cardiovascular Imaging Department, Brazilian Society of Cardiology, Rio de Janeiro, RJ, Brazil

National Institute of Cardiology, Rio de Janeiro, RJ, Brazil

Cardiology—DASA, Rio de Janeiro, RJ, Brazil

Amanda Saavedra Department of Gastroenterology and Hepatology, Federal University of the State of Rio de Janeiro—UNIRIO, Rio de Janeiro, RJ, Brazil

Ana Flávia Malheiros Torbey Cardiology, Universidade Federal Fluminense, Niterói, RJ, Brazil

Ana Inês da Costa Bronchtein Clinical Arrhytmia, Rede D'or São Luiz, Rio de Janeiro, RJ, Brazil

Andréa Coy-Canguçu Faculdade de Medicina—Pontifícia Universidade Católica de Campinas, São Paulo, Brazil

Anelise Dias Uveitis & Retina Unit, Department of Ophthalmology, Fluminense Federal University, Niteroi, RJ, Brazil

Aristóteles Comte de Alencar Neto Cardiomyopathy Unit, Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil

Arsonval Lamounier Júnior Medicine School Universidade Vale do Rio Doce-UNIVALE, Governador Valadares, Brazil

Ashutosh Wechalekar National Amyloidosis Centre, University College London, London, UK

Aurea Lucia Alves de Azevedo Grippa de Souza Universidade Federal Fluminense, Niterói, RJ, Brazil

Bernardo Couto Neto Department of Orthopedics and Traumatology, Pedro Ernesto University Hospital, State University of Rio de Janeiro (UERJ), Rio de Janeiro, RJ, Brazil

Fluminense Federal University (UFF), Niterói, Brazil

Bruno Vaz Kerges Bueno Cardiomyopathy Unit, Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil

Caio Rebouças Fonseca Cafezeiro Cardiomyopathy Unit, Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil

Camila Nicolela Geraldo Martins Faculdade de Ciências Médicas—Universidade Estadual de Campinas, São Paulo, Brazil

Carolina Lavigne-Moreira Universidade de São Paulo—Ribeirão Preto—USPRP, Ribeirão Preto, Brazil

Caroline Bittar Braune Department of Neurology, Antônio Pedro University Hospital, Federal Fluminense University, Rio de Janeiro, RJ, Brazil

Hospital Universitário Gaffrée e Guinle—Universidade Federal do Estado do Rio de Janeiro (UNIRIO), Rio de Janeiro, RJ, Brazil

Cassiano Augusto Braga Silva Nephrology Service, Senhor do Bonfim Group, Feira de Santana, BA, Brazil

Charles Marques Lourenço Neurogenetics Unit—Inborn Errors of Metabolism Clinics, National Reference Center for Rare Diseases, Faculdade de Medicina de São José do Rio Preto (FAMERP), São Paulo, Brazil

Department of Specialized Education, Personalized Medicine Area, DLE/Grupo Pardini, Rio de Janeiro, RJ, Brazil

Cibele Franz Department of Gastroenterology and Hepatology, Federal University of the State of Rio de Janeiro—UNIRIO, Rio de Janeiro, RJ, Brazil

Claudio Tinoco Mesquita Nuclear Medicine and Molecular Imaging Department, Pró-Cardíaco Hospital, Rio de Janeiro, RJ, Brazil

Radiology Department, Federal Fluminense University, Niterói, RJ, Brazil

Cristiane de Carvalho Singulane Cardiomyopathy Unit, Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil

Department of Medicine, Division of Cardiovascular Medicine, University of Virginia, Charlottesville, VA, USA

Diane Xavier de Ávila Amyloidosis Center, Complexo Hospitalar de Niterói/DASA, Rio de Janeiro, Brazil

Cardiovascular Sciences Postgraduate Program, Fluminense Federal University, Niteroi, Niterói, RJ, Brazil

Cardiology, Conde Modesto Leal Municipal Hospital, Maricá, RJ, Brazil

Cardiology, Che Guevara Municipal Hospital, Maricá, RJ, Brazil

Edileide Barros Correa Dante Pazzanese, Institute of Cardiology, São Paulo, SP, Brazil

Eduarda Corrêa Maia Department of Medical School, Hospital Universitário Antônio Pedro, Niterói, Rio de Janeiro, Brazil

Elaine Xavier de Ávila Almeida Centro Geriátrico Nilton Macedo Moreira, Iguaba Grande, Brazil

Hospital Municipal Naelma Monteiro, Rio das Ostras, RJ, Brazil

Erivelton Alessandro do Nascimento Hospital Universitário Antônio Pedro—Universidade Federal Fluminense, Niterói, Brazil

Complexo Hospitalar de Niterói—CHN, Niterói, Brazil

Instituto Estadual de Cardiologia Aloysio de Castro—IECAC, Rio de Janeiro, Brazil

Centro Universitário de Volta Redonda—UniFOA, Volta Redonda, Brazil

Evandro Tinoco Mesquita Cardiology, Complexo Hospitalar de Niterói–DASA, Niterói, RJ, Brazil

Cardiology Division, Fluminense Federal University, Niterói, RJ, Brazil

Interamerican Society of Cardiology (SIAC), Cuidad de México, Mexico

PROCEPI, Niterói, RJ, Brazil

Cardiomyopathies Study Group DEIC/GEMIC, Rio de Janeiro, RJ, Brazil

Sixth Ward Cardiology, Santa Casa de Misericórdia, Rio de Janeiro, RJ, Brazil

Cardiovascular Sciences, Federal Fluminense University, Niterói, RJ, Brazil

Fabio Fernandes Cardiomyopathy Unit, Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil

Fabio Mastrocola Department of Cardiology, Federal University of Rio Grande do Norte, Natal, RN, Brazil

Fábio de Souza Hospital Universitário Gaffrée e Guinle—Universidade Federal do Estado do Rio de Janeiro (UNIRIO), Rio de Janeiro, RJ, Brazil

Fellype Carvalho Barreto Nephrology Service, Department of Internal Medicine, Federal University of Paraná, Curitiba, PR, Brazil

Filipe T. Gusman Department of Palliative Care, Hospital Pro Cardiaco, Rio de Janeiro, RJ, Brazil

Brazilian Academy of Palliative Care, Rio de Janeiro, Brazil

Frank Nunes Cesar Leite Hospital, Manhuaçu, MG, Brazil

Giovanna Provenzano Uveitis & Retina Unit, Department of Ophthalmology, Fluminense Federal University, Niterói, RJ, Brazil

Gustavo Horacio Cabrera Departamento de Ecocardiografia en Santa Maria de la Salud, Miembro del Intenational Board de enfermedad de Fabry, San Isidro, Argentina

Humberto Villacorta Junior Cardiology Division, Fluminense Federal University, Niterói, Rio de Janeiro, Brazil

Ibraim Masciarelli F. Pinto Cardiac Imaging, Instituto Dante Pazzanese de Cardiologia, São Paulo, SP, Brazil

Irene de Lourdes Noronha Division of Nephrology, University of São Paulo School of Medicine, São Paulo, Brazil

Ivana Burazor Institute for Cardiovascular Diseases 'Dedinje' Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Jacques Kaufman Department of Hematology, Hospital Universitário Antonio Pedro, Fluminense Federal University (HUAP/UFF), Rio de Janeiro, RJ, Brazil

DASA Group/Complexo Hospitalar de Niterói, Niterói, RJ, Brazil

Jade Cury-Martins Department of Dermatology, University of São Paulo, São Paulo, Brazil

Joelma Dominato Rocha Carvalho Cardiovascular Sciences Postgraduate Program, Fluminense Federal University, Niterói, RJ, Brazil

Jose Antonio Sanches Department of Dermatology, University of São Paulo, São Paulo, Brazil

Joseph Bruno Bidin Brooks Department of Function and Structure, Medical School, Universidade Metropolitana de Santos—UNIMES, São Paulo, Brazil

Juliana Grael Jorge Clinical Arrhytmia, Rede D'or São Luiz, Rio de Janeiro, RJ, Brazil

Jussara Bianchi Castelli Fleury Group, São Paulo, SP, Brazil

Heart Institute (InCor) of Hospital das Clínicas-FMUSP, São Paulo, SP, Brazil

Katia Luz Cardiologia, Complexo Hospitalar de Niterói, Niterói, RJ, Brazil

Kelma Macedo Pohlmann Simões Setor de Retina e Vítreo, Departamento de Oftalmologia, Universidade Federal do Estado do Rio de Janeiro (UNIRIO), Rio de Janeiro, Brazil

Leonardo Oliveira Mendonça Division of Clinical Immunology and Allergy, Hospital das Clínicas, Universidade de São Paulo, São Paulo, SP, Brazil

Department of Clinical Immunology and Allergy, Hospital 9 de Julho—Rede DASA, São Paulo, SP, Brazil

Center for Rare and Immunological Disorders, Hospital 9 de Julho—Rede DASA, São Paulo, SP, Brazil

Lidielle S. P. R. Pereira Hospital Pró-Cardíaco, Rio de Janeiro, Brazil

Liszt Palmeira de Oliveira Department of Orthopedics and Traumatology, Pedro Ernesto University Hospital, State University of Rio de Janeiro (UERJ), Rio de Janeiro, RJ, Brazil

Luciana Bastos Muniz Centro Municipal de Reabilitação Professora Dilma Coutinho da Silva, Saquarema, Brazil

Luis Gustavo Modelli de Andrade Departamento de Medicina Interna, Universidade Estadual Paulista, Botucatu, SP, Brazil

Luiz Fernando Onuchic Division of Nephrology, University of São Paulo School of Medicine, São Paulo, Brazil

Division of Molecular Medicine, University of São Paulo School of Medicine, São Paulo, Brazil

Marcelle Leitão Gomes Sá Pires Geriatrics Group—Clinic Care, Niterói, RJ, Brazil

Marcelo Dantas Tavares de Melo Department of Internal Medicine at the Federal University of Paraíba, João Pessoa, PB, Brazil

Clinical Medicine of State of Paraiba, João Pessoa, PB, Brazil

Cardiology at Federal University of Paraiba, João Pessoa, PB, Brazil

Marcelo Imbroinise Bittencourt UERJ, Rio de Janeiro, RJ, Brazil

Hospital Universitário Pedro Ernesto, Rio de Janeiro, RJ, Brazil

Geneone—DASA, Rio de Janeiro, RJ, Brazil

Marcia Maria Jardim Neurologia, Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil

Márcia Lyrio Department of Gastroenterology and Hepatology, Federal University of the State of Rio de Janeiro—UNIRIO, Rio de Janeiro, RJ, Brazil

Marcondes C. França Jr Department of Neurology, School of Medical Sciences—University of Campinas (UNICAMP), Campinas, SP, Brazil

Marcus Vinicius Simões Medical School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil

Maria Helena Vaisbich Pediatric Nephrology Unit, University of Sao Paulo, São Paulo, Brazil

Maria Luiza Benevides Department of Neurology, School of Medical Sciences—University of Campinas (UNICAMP), Campinas, SP, Brazil

Mário Martins dos Santos Motta Setor de Retina e Vítreo, Departamento de Oftalmologia, Universidade Federal do Estado do Rio de Janeiro (UNIRIO), Rio de Janeiro, Brazil

Marlene Antonia dos Reis Nephropathology Service, General Pathology, Federal University of Triângulo Mineiro, Uberaba, Brazil

Marly Uellendahl Escola Paulista de Medicina—Universidade Federal de São Paulo, São Paulo, SP, Brazil

DASA, São Paulo, SP, Brazil

Universidade de Pernambuco, Recife, Pernambuco, Brazil

Mayara Gabriele Toledo Department of Medical School, Hospital Universitário Antônio Pedro, Niterói, RJ, Brazil

Morie A. Gertz Division of Hematology, Roland Seidler Jr. Professor Department of Medicine, College of Medicine, Mayo Distinguished Clinician, Rochester, MN, USA

Murillo de Oliveira Antunes Clinical Research Center São Francisco, Hospital Universitário São Francisco, Universidade São Francisco, Bragança Paulista, SP, Brazil

Nágela Simão Vinhosa Nunes Hospital Universitário Antônio Pedro—Universidade Federal Fluminense, Niterói, Brazil

Complexo Hospitalar de Niterói—CHN, Niterói, Brazil

Nathalia Monerat Pinto Blazuti Barreto Department of Pesquisa Clínica, Hospital Pro Cardiaco, Rio de Janeiro, RJ, Brazil

Osvaldo J. M. Nascimento Department of Neurology, Fluminense Federal University, Niterói, RJ, Brazil

Otavio Rizzi Coelho-Filho Faculdade de Ciências Médicas—Universidade Estadual de Campinas, São Paulo, Brazil

Discipline of Cardiology, Department of Internal Medicine, Hospital das Clínicas, State University of Campinas, Cidade Universitária "Zeferino Vaz", Campinas, Brazil

Paulo Sgobbi Department of Neurology and Neurosurgery, Federal University of São Paulo, São Paulo, SP, Brazil

Pedro Tomaselli Universidade de São Paulo—Ribeirão Preto—USPRP, Ribeirão Preto, Brazil

Raquel Germer Toja Couto Antônio Pedro University Hospital of Universidade Federal Fluminense, Secretaria de Saúde do Distrito Federal, Niterói, RJ, Brazil

Raul N. G. Vianna Uveitis and Retina Unit, Department of Ophthalmology, Fluminense Federal University, Niterói, RJ, Brazil

Rejane Silva Rocha Instituto Oswaldo Cruz—FIOCRUZ, Rio de Janeiro, Brazil

Renata Adrielle Lima Vieira Departamento de Nutrição Clínica e Social, Universidade Federal de Ouro Preto, Ouro Preto, Brazil

Ricardo Vivacqua Cardoso Costa Hospital Procardiaco, Rio de Janeiro, Brazil

Roberta Pereira dos Santos Coelho Department of Pesquisa Clínica, Hospital Pro Cardiaco, Rio de Janeiro, RJ, Brazil

Roberta Shcolnik Szor Department of Hematology, DASA Group/Hospital 9 de Julho, São Paulo, SP, Brazil

Roberto J. P. Magalhães Department of Hematology, Hospital Universitário Antonio Pedro, Fluminense Federal University (HUAP/UFF), Rio de Janeiro, RJ, Brazil

DASA Group/Complexo Hospitalar de Niterói, Niterói, RJ, Brazil

Salvador Manoel Serra Instituto Estadual de Cardiologia Aloysio de Castro, Rio de Janeiro, Brazil

Samantha Vernaschi Kelmann Institution Children's Institute, University of São Paulo, São Paulo, SP, Brazil

Sandra Marques e Silva Cardiologia e Ecocardiografia, Hospital de Base do Distrito Federal (HBDF), Brasília, Distrito Federal, Brazil

Simone Cristina Soares Brandão Department of Medicine, Hospital das Clínicas, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil

Valdemir Melechco Carvalho Fleury Group, São Paulo, SP, Brazil

Valdênia P. de Souza Geriatrics Group—Clinic Care, Niterói, RJ, Brazil

Valkercyo Araújo Feitosa Division of Nephrology, University of São Paulo School of Medicine, São Paulo, Brazil

Viviane Tavares Carvalho Crelier Department of Neurology, Antônio Pedro University Hospital, Federal Fluminense University, Rio de Janeiro, RJ, Brazil

Wilson Marques Jr Universidade de São Paulo—Ribeirão Preto—USPRP, Ribeirão Preto, Brazil

Wolney de Andrade Martins Hospital Universitário Antônio Pedro—Universidade Federal Fluminense, Niterói, Brazil

Complexo Hospitalar de Niterói—CHN, Niterói, Brazil

Chapter 1
Introduction

Diane Xavier de Ávila and Humberto Villacorta Junior

As cardiologists, since the beginning of our training, we learned that most restrictive cardiomyopathies were rare and had a poor prognosis. Cardiac amyloidosis fits into this concept. In the past, we observed a few cases of amyloidosis. However, in the last decade, we have seen an increase in the number of cases, probably related to a higher awareness of the disease. Cardiac amyloidosis still has a poor prognosis. However, there is now an approved treatment for this condition, which contributes to increased survival. In addition, other specific treatments are being studied in ongoing clinical trials [1–12].

Fabry disease is another rare disease that is probably underdiagnosed. The disease usually manifests in childhood and adolescence, and the heart and kidneys may be affected in the course of the disease. When these organs are involved, the prognosis is poor, hence the importance of early diagnosis. Prior to 2001, there was no treatment for Fabry disease. However, as mentioned above about amyloidosis, specific treatment is now available [13, 14].

What do these diseases have in common? As said before, both are rare but probably underdiagnosed. Both are systemic diseases and may present to almost any specialty. Both may affect the kidney and the heart. From a cardiologic point of view, both may present with cardiac hypertrophy. Finally, both now have specific treatments, which, if used early, may contribute to better outcomes.

For the reasons mentioned above, we decided to put together an update on these two conditions in a medical book that has multispecialities with a multidisciplinary approach. The objective is to provide the clinician with practical information for the diagnosis, follow-up, and treatment of these diseases.

D. X. de Ávila (✉)
Amyloidosis Center, Complexo Hospitalar de Niterói/DASA, Rio de Janeiro, Brazil

H. V. Junior
Cardiology Division, Fluminense Federal University, Niterói, RJ, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_1

References

1. Maurer MS, Schwartz JH, Guandapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018;379:1007–16.
2. APOLLO-B: A study to evaluate patisiran in participants with transthyretin amyloidosis with cardiomyopathy (ATTR amyloidosis with cardiomyopathy). https://clinicaltrials.gov.br/ct2/show/NCT03997383.
3. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med. 2018;379(1):22–31. https://doi.org/10.1056/NEJMoa1716793.
4. Zhang X, Goel V, Attarwala H, et al. Patisiran pharmacokinetics, pharmacodynamics, and exposure-response analyses in the phase 3 APOLLO trial in patients with hereditary transthyretin-mediated (hATTR) amyloidosis. J Clin Pharmacol. 2020;60(1):37–49.
5. Titze-de-Almeida SS, Brandão PRP, Faber I, et al. Leading RNA interference therapeutics part 1: silencing hereditary transthyretin amyloidosis, with a focus on Patisiran. Mol Diagn Ther. 2020;24(1):49–59.
6. Adams D, Polydefkis M, Gonzales-Duarte A, et al. Long-term safety and efficacy of Patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study. Lancet Neurol. 2021;20(1):49–59.
7. Solomon SD, Adams D, Kristen A, Grogan M, et al. Effects of patisiran, an RNA interference therapeutic, on cardiac parameters in patients with hereditary transthyretin-mediated amyloidosis. Circulation. 2019;139(4):431–43.
8. Muchtar E, Dispenzieri A, Gertz MA, Kumar SK, Buadi FK, Leung N, et al. Treatment of AL amyloidosis: Mayo stratification of myeloma and risk-adapted therapy (mSMART) consensus statement 2020 update. Mayo Clin Proc. 2021;96(6):1546–77. https://doi.org/10.1016/j.mayocp.2021.03.012.
9. Sidiqi MH, Aljama MA, Buadi FK, Warsame RM, Lacy MQ, Dispenzieri A, et al. Stem cell transplantation for light chain amyloidosis: decreased early mortality over time. J Clin Oncol Off J Am Soc Clin Oncol. 2018;36(13):1323–9. https://doi.org/10.1200/JCO.2017.76.9554.
10. Sanchorawala V, Sun F, Quillen K, Sloan JM, Berk JL, Seldin DC. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem cell transplantation: 20-year experience. Blood. 2015;126(20):2345–7. https://doi.org/10.1182/blood-2015-08-662726.
11. Cibeira MT, Sanchorawala V, Seldin DC, Quillen K, Berk JL, Dember LM, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. Blood. 2011;118(16):4346–52. https://doi.org/10.1182/blood-2011-01-330738.
12. Palladini G, Kastritis E, Maurer MS, Zonder J, Minnema MC, Wechalekar AD, et al. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. Blood. 2020;136(1):71–80. https://doi.org/10.1182/blood.2019004460.
13. Banikazemi M, Bultas J, Waldek S, Wilcox WR, Whitley CB, McDonald M, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann Intern Med. 2007;146:77–86.
14. Muntze J, Gensler D, Maniuc O, Liu D, Cairns T, Oder D, et al. Oral chaperone therapy migalastat for treating Fabry disease: enzymatic response and serum biomarker changes after 1 year. Clin Pharmacol Ther. 2019;105:1224–33.

Part I
Amyloidosis

Chapter 2
Neurological Manifestations in ATTRv Amyloidosis

Osvaldo J. M. Nascimento, Wilson Marques Jr, Pedro Tomaselli, and Carolina Lavigne-Moreira

2.1 Introduction

Hereditary amyloidosis is an autosomal disease. The most common presentation is transthyretin amyloidosis (ATTRv), which results from a misfolding of a tetrameric protein called transthyretin (TTR). Particularly in elderly individuals, there is another type known as wild-type TTR (ATTRw), where the native TTR protein destabilizes and reaggregates, resulting in nonfamilial cases of TTR amyloidosis. In addition, other types of mutated proteins, such as gelsolin and α-chain, compose the hereditary amyloidosis group. A new nomenclature criterion was proposed in 2018 for these disorders because of TTR gene mutations: ATTRv (A for amyloidosis, TTR for transthyretin, and v for variant/mutant). The clinical presentation of ATTRv includes peripheral neuropathy (ATTRv-PN) and cardiomyopathy (ATTRv-CA), among other symptoms [1, 2]. ATTRv is a rare multisystem disease; peripheral neuropathy is the most frequent clinical manifestation and usually involves the autonomic compartment.

Over 140 mutations have been described in the TTR gene [3]. The mutated carrier protein has an unstable tetrameric structure, resulting in compromised transport of vitamin A and thyroxin. The unstable mutated TTR tetramers disaggregate into monomers that are transformed into amyloid fibrils. These fibrils are deposited in different tissues, mostly in the endoneurium of somatic and autonomic nerves, causing progressive functional and structural damage.

The most common ATTRv-PN clinical presentation is length-dependent sensorimotor neuropathy, commonly associated with mild or severe autonomic

O. J. M. Nascimento (✉)
Department of Neurology, Universidade Federal Fluminense—UFF, Rio de Janeiro, RJ, Brazil

W. Marques Jr · P. Tomaselli · C. Lavigne-Moreira
Universidade de São Paulo—Ribeirão Preto—USPRP, Ribeirão Preto, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_2

symptoms. The clinical course is progressive, with increased disability over time leading to death in approximately 10 years [4], mostly due to severe cardiac involvement. Delays in the diagnosis of this neuropathy are common, especially in nonendemic areas, where the recognition of the disease can occur 3–4 years after the beginning of the symptoms.

Alternative options for treatment are now available, with a possible reduction in multisystemic involvement, especially in neuropathy. In 1990, orthotopic liver transplantation (OLT) appeared to be the first efficacious alternative for treatment, although with a high rate of morbidity and mortality. Tafamidis was the first drug introduced for ATTRv-PN treatment, a TTR tetramer stabilizer, resulting in a reduction in disease progression. More recently, gene therapy was introduced, showing unequivocal efficacy.

The objective of this chapter is to broadly review the clinical aspects of ATTRv-PN.

2.2 Historical Notes

ATTRv-PN was first identified in a patient from a fishing village named Povoa do Varzim in Northern Portugal and was recently reported by the Portuguese neurologist Mario Corino da Costa Andrade in 1952. A short communication of the clinical characteristics of this new neuropathy was previously reported in 1951. During 1939 and the 40th decade, Andrade followed a 37-year-old woman (Fig. 2.1) with a clinical presentation of numbness associated with painful and tactile anesthesia mainly in the lower limbs, marked amyotrophy of the extremities, *steppage* gait, diarrhea, and weight loss. She also reported the same symptoms in other members

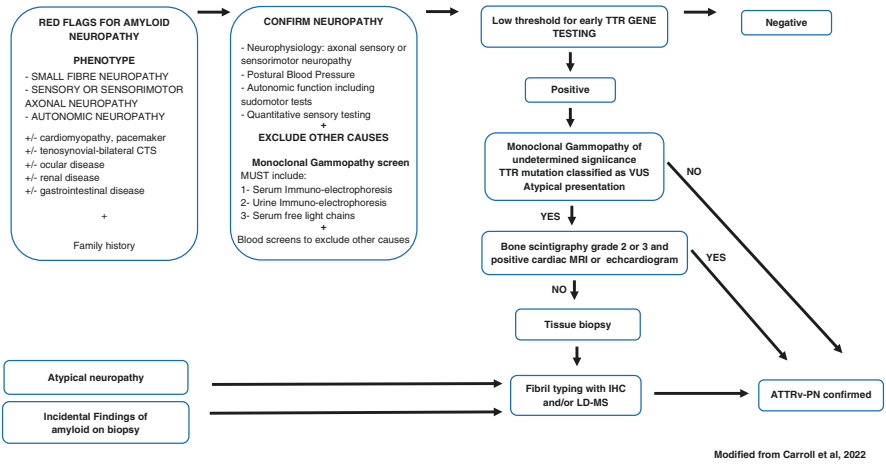


Fig. 2.1 Proprosed algorithm for diagnosis and follow-up of ATTRv-PN

of her family. Some of her neighbors presented similar clinical complaints. The disease was popularly called "*mal dos pezinhos*" (small feet disease).

After excluding other possible differential diagnoses, such as leprosy neuritis, syringomyelia, hypovitaminoses, unclassified gastrointestinal disorders, tabes dorsalis, and psychoneuroses, and other causes of sensorimotor and autonomic neuropathies, Dr. Corino de Andrade, who was 33 years of age, started a meticulous study of this new condition. In 1952, he published "A Peculiar Form of Peripheral Neuropathy", describing the clinical and histopathological findings of 74 cases. In this case series, an unknown amyloid deposit damaging mainly the sensory peripheral nerves with a strong familial characteristic called the attention for the necessity of genetic research for this condition. The disease was promptly named "Corino de Andrade's Disease". His constant interest in the knowledge of the disease's physiopathology resulted in the foundation, in 1975, of the Abel Salazar Biomedical Sciences Institute of Porto University and, subsequently, in 1989, the Paramyloidosis Study Center of Porto (PSCP). Neurologists and neuroscientists worldwide with a special interest in amyloid genesis and its consequences had this center as a reference, mainly in clinical and translational research of ATTRv. In 1978, Dr. Pedro Pinho Costa identified prealbumin (later named transthyretin) as the amyloid deposit precursor in different tissues and organs. In 1984, in PSCP, Dr. Maria João Saraiva identified a mutation in the TTR molecule: the substitution of methionine for valine at position 30 (Val30Met). Thus, the abnormal deposits of amyloid responsible for this devastating disease were clarified. Currently, the disease is identified all over the world, but appears endemic in some areas of Brazil, Japan, and Sweden. Brazil has the second highest incidence of ATTRv-PN, with a high concentration of cases in some areas in the north, northeast, and southeast of the country.

Antonio Rodrigues de Mello, in an article published in 1959, denominated the term "Familial Amyloidotic Polyneuropathy", accepted and referred to by Corino-Andrade e col., in 1969, after discussing the first and largest cohort genetic study of ATTRv-PN. In this study, Andrade et al. referred to the study of Juliao and Mignone entitled "Primary Amyloidosis with Meningoradiculoneuritic Involvement" in two Portuguese immigrants, one from Povoa do Varzim and the other from Coimbra; the second patient had a previous erroneous diagnosis of leprosy. The interest of Prof. Mello on ATTRv-PN at the Institute of Neurology of Brazil's University in Rio de Janeiro resulted in the development, in 1984, of the first referral center for ATTRv-PN, the Antonio Rodrigues de Mello's Paramyloidosis Center—CEPARM.

Historically, it has been considered that the TTR-Val30Met mutation appeared in the XV century around the Middle Age when naval navigation from Portugal to different ports was imperative, contributing to the dissemination of this gene mutation. In the last 38 years, after the first TTR mutation was revealed, almost a hundred and a half TTR mutations have been identified. During those years, as ATTRv is a multisystem disorder, a great number of health specialties (neurology, cardiology, gastroenterology, liver transplant surgery, nuclear medicine, neuroradiology, ophthalmology, nephrology, dermatology, orthopedics, psychology, physiotherapy, and others) were involved in the identification and treatment of the disease. In

addition to neurological compromise, the severity of cardiac involvement caught the attention of Corino de Andrade in a manuscript published in 1965.

In 1990, considering that most TTR is produced in the liver, OLT arose as a possible alternative treatment for ATTRv-PN, as performed by Holmgren et al. [5]. Since then, 2.294 OLTs were performed worldwide (results from the Familial World Transplant Registry, in 2019). The highest number of OLTs occurred in Portugal in 1025 patients, mostly in the cities of Lisbon and Porto.

Possible therapeutic processes in the production and stabilization of TTR molecules, avoiding the deposit of fragmented amyloid fibrils elsewhere in the body, target proteostasis (protein homeostasis), which includes the misfolding and aggregation of proteins. Dr. Jeffery W Kelly's group has studied such mechanisms since the 90s. This group developed the drug *Tafamidis*, which acts in the stabilization of the mutated TTR, therefore, preventing the formation of amyloid deposits in the tissues, with a consequent reduction in the progression of the disease. In 2006, Coelho et al. published the results of a multicenter randomized, double-blind controlled trial (eight sites in seven countries: Argentina, Brazil, France, Germany, Portugal, Spain, and Sweden) with Tafamidis 20 mg QD or placebo. This randomized controlled trial revealed as a secondary outcome a significant delay in polyneuropathy progression, with good tolerance in patients in the early stage of ATTRv-PN. In this study, 128 patients were randomized into two groups: an intervention group that received Tafamidis (n = 65) and a control group that received placebo (n = 63); from this group, 88 (69%) patients were waiting for an OLT. The authors observed a significant dropout rate in OLT in the group that received the intervention. This is dramatically being observed in recent years due to the new disease-modifying therapies for ATTRv. In November 2011, Tafamidis was approved as the first drug for ATTRv-PN.

In 2006, a new era urged therapeutic modalities for the treatment of ATTRv-PN: the intravenous injection of a gene silencing molecule of the faulty TTR, an interference RNA (RNAi), named patisiran. This mechanism was the result of studies performed by the groups of Dr. Craig Mello from the University of Massachusetts (U Mass) Medical School in Worcester and Dr. Andrew Fire from Stanford University in California, winners of the Medicine/Physiology 2006 Nobel Prize. Their first study, named "Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans", was published in February 1998 (Fire et al.) as a letter to Nature. A multicenter clinical trial named APOLLO was completed in 2017 [6] and demonstrated the efficacy and safety of patisiran in ATTRv-PN treatment.

From this moment, gene therapy became the spotlight. Inotersen, an antisense oligonucleotide (ASO), also appeared as a possible treatment; the drug interacts with RNA messengers and prevents abnormal TTR synthesis. Benson et al. [2] have already demonstrated the potential of this ASO in the treatment of transthyretin-associated polyneuropathy.

2.3 ATTRv-PN Genetic Aspects of Neural Damage

TTR protein is a stable homotramer molecule that is mainly present in the blood, functioning as a transporter to retinol binding protein and thyroxine (T4). It is a 55 kDa protein produced by the liver and the choroid plexus with a 48-h half-life in the human body. It is not naturally expressed in the peripheral nervous system of normal people. However, in patients with pathogenic variants, abnormal deposits of amyloid are found in the extracellular space of the peripheral nerve [7]. TTR plays an important role in motor and sensory nerve function; it enhances and accelerates peripheral nerve regeneration. TTR protein has neuritogenic activity mediated by the megalin receptor and an important role in retrograde axonal transport [8]. TTR knockout mice subjected to sciatic nerve injury present with a significant recovery delay and a decreased number of myelinated and unmyelinated axons on nerve pathology during the regeneration process [9]. To date, there is no homozygous individual with a loss-of-function variant in the TTR gene registered in the gnomAD database, suggesting that TTR is an essential protein-coding gene in humans.

Single nucleotide variations are the most common DNA abnormality found in affected patients. The clinical picture may vary across different patients. The main phenotype could be a pure neuropathy or a pure cardiac disease. However, some variants affect both the cardiac and peripheral nervous systems. These symptoms may be present in patients carrying different TTR variants, and the clinical phenotype of patients carrying the same variant may vary significantly, as it may be observed even within the same family [10]. This clinical variability may be partially explained by the high aforementioned genetic heterogeneity [11]. Some mutations are particularly associated with neuropathy, while others lead predominantly to cardiomyopathy, even though both clinical displays could be featured simultaneously to different extents. In the presence of a mutation, the homotramer structure becomes unstable and dissociates, and the variant monomers misfold, aggregate, and deposit in the extracellular space of several organs, mainly the peripheral nerves, cardiac system, kidney, and eyes [12, 13], leading to the multisystemic manifestations characteristic of this disease. In this sequence of events, dissociation into monomers is a key step in the aggregation of amyloid fibrils.

The pathophysiology of ATTRv seems to be complex. It is a gain-of-toxic-function disease. The direct effect of amyloid fibrils damages neighboring tissues, while nonfibrillar TTR (oligomeric TTR) induces neurodegeneration by toxicity. Microangiopathy seems to be important in the early phases, increasing the leakage of circulating TTR. Specifically, by addressing neuropathy, Schwann cells seem to be particularly affected, becoming atrophic and dysfunctional. Apparently, the mechanical effect seems to be more important in the early onset TTRv-PN Val30Met, while the direct toxic effect seems to be more important in the late-onset forms. At least partially, this is explained by the different constitutions of neurofilaments, which are thicker and longer in early onset patients [14].

2.4 Clinical Findings

ATTRv-PN may affect individuals over a wide age range (from the second to the ninth decade of life). Initial symptoms appear after a period of amyloid spread and deposits in tissues; the diagnosis is usually late, especially in nonendemic regions. Depending on ATTRv clinical presentation, patients can be divided into two groups: those with early onset (less than 50 years) or late onset (more than 50 years), with a prevalence of the second group in nonendemic countries. Most cases have no family background, with a Val30Met mutation.

2.4.1 Early Onset ATTRv

The usual clinical pattern of ATTRv-PN is length-dependent small-fiber polyneuropathy with thermalgesic sensory dissociation and autonomic dysfunction. At the beginning, pain and paresthesia in the distal legs are common complaints associated with progressive pinprick and thermal sensory loss, followed by light touch sensory loss. Hypo/arreflexia of ankle jerks is common. Autonomic symptoms, including diarrhea with or without alternate constipation, orthostatic hypotension, impotence, dry eyes, and mouth, are frequent at the beginning with consequent severe weight loss. In some cases, gastrointestinal symptoms may be present even before the onset of peripheral neuropathy, such as prolonged diarrhea, fecal incontinence, vomiting, and severe malnutrition. In others, autonomic manifestations may be the first symptoms of ATTRv-PN, such as the failure of sudomotor function. A bilateral carpal tunnel syndrome (CTS) can be observed at the beginning due to amyloid deposits in the wrist. Motor symptoms arise about 2 years after sensory/autonomic compromise, with an exception when the symptoms appear first in the hands, when the motor involvement can start in a period of 4–5 years. With the progression of the disease, gait disturbances become prominent with cachexia and limb ulceration, mainly in the feet. It is important to consider that the same genetic mutation may have different phenotypes, even within the same family. Death usually occurs approximately 10 years after the beginning of the disease [4].

ATTRv-FAP is a multisystemic condition, so despite the main symptoms being associated with peripheral neuropathy, health professionals should be alert to cardiac, ophthalmic, and renal manifestations. In addition, ATTRv-PN should be considered a multidisciplinary disease. Almost 50% of patients have cardiac subclinical involvement that, when clinically diagnosed, can represent heart failure in progression. Heart imaging and biomarkers during follow-up can help in a precocious and precise diagnosis. Cardiovascular compromise is seen in 38% of ATTRv-PN patients and is related to a strong risk for sudden death [4].

2.4.2 Late-Onset ATTRv

The late-onset phenotype includes severe sensory loss that involves small and large fibers, with a possible association with painful symptoms, early motor compromise, mild autonomic manifestations, and severe cardiac involvement. Family history may not be present. Late-onset cases are more frequent in nonendemic regions [3, 15–20]. Uncommon presentations, including ataxic neuropathy, motor predominant neuropathy, and upper-limb predominant multiple mononeuropathies, have also been reported [15].

2.4.3 Other Clinical Manifestations Associated with ATTRv

Several other neurological manifestations may be seen in ATTRv patients in addition to polyneuropathies [4]. Bilateral CTS is a frequent finding and may be the first manifestation of the disease. The clues to investigate ATTRv in patients with isolated bilateral CTS still need to be identified. The remaining neurological manifestations seem to be rare, although the longer survival time associated with the newly introduced treatments may change the usual natural history of the disease, as none of these treatments decrease the nonhepatic production of TTR. As an example, it seems that cognitive impairment is becoming more frequent, although no definite conclusion exists [21]. Meningeal infiltration may cause spinal stenosis or radiculopathies. Amyloid cerebral angiopathy may cause stroke and TIA-like episodes, hemorrhagic disease, and aura-like and epileptic seizures [4].

Cardiomyopathy is a clinical condition frequently observed in patients with early onset Val30Met. When ATTRv presents almost exclusively with a cardiac compromise, it is called ATTRv-CA [22, 23]. The ATTRv-CA phenotype includes atrioventricular and/or sinoatrial blocks, bundle branch, and thickness of ventricular walls, mainly of the interventricular septum [24]. A severe accumulation of amyloid in the heart progressively results in cardiac failure due to restrictive cardiomyopathy. Electrocardiograms can present alterations, such as disproportionately low QRS voltage and early conduction block [25]. Scintigraphy with pyrophosphate (PYP) and diphosphono-1,2-propanodicarboxylic acid (DPD) tracers is very helpful for the diagnosis of cardiomyopathy (ATTRv-CA) and for the diagnosis of polyneuropathy in the absence of a monoclonal gammopathy [26].

ATTRv-PN may also involve renal complications, usually subclinical in the first years, with proteinuria as the first laboratory finding. Cases with nephrotic or nephritic syndrome can progress to renal failure. This severe complication is seen in approximately one-third of Portuguese ATTRv-PN cases [27]. It is very important to follow up renal functioning of the kidney in ATTRv-PN patients.

Eye involvement is very common in the multisystemic pattern of ATTRv-PN; the clinical presentation is related to dry eyes, vitreous opacity, glaucoma, and amyloid angiopathy [28].

A myopathy with usually normal CK can rarely take place in the multisystem pattern of ATTRv. A classical myopathy pattern of symmetric weakness is referred. Mostly in the proximal lower limbs. Few patients can present distal and proximal weakness with sensory deficits from peripheral neuropathy and proximal weakness from myopathy, which mimics chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). [29, 30].

Central nervous system (CNS) symptoms can be commonly seen in the evolution of Val30Met ATTRv-PN due to the deposition of amyloid in the meningeal vessels of the brain and brainstem. Clinical symptoms include transient focal neurologic episodes (visual hallucinations, tingling, motor activity, hemiparesis aphasia, and visual loss), intracerebral hemorrhage, ischemic strokes, and cognitive deficits [31]. As these amyloid fibrils are formed mostly in the choroid plexus in the CNS, there is currently no available treatment with new disease-modifying therapies [32]. Oculoleptomeningeal amyloidosis (OLMA) is a rare condition characterized by early deposition of amyloid in cranial and spinal leptomeninges associated with ocular involvement. OLMA is a non-VAL30Met ATTRv with several different mutations, 14 at moment [32], including a Tyr69His ATTRv reported in Brazil [33].

2.5 ATTRv-PN Diagnosis

As a consequence of the variety in presentation, 32–74% of patients with ATTRv have received a misdiagnosis. The most common misdiagnosis is idiopathic axonal polyneuropathy, CIDP, lumbar stenosis, and, infrequently, motor neuron disease [34]. ATTRv should be suspected in patients with small fiber neuropathy and sensory or sensorimotor axonal neuropathy in the presence of red flags, such as (1) rapid progression; (2) family history of ATTRv; (3) bilateral CTS ; (4) autonomic involvement; (5) gastrointestinal symptoms; (6) unexplained weight loss; (7) cardiac disease (cardiac hypertrophy or arrhythmia); (8) kidney disease; and (9) ocular changes [35]. Noninvasive tests are available for the assessment of autonomic and somatic small fiber neuropathy, including quantitative sensory thresholds, sympathetic skin responses, electrochemical skin conductance, measurement of heart rate variability, and tilt tests [36]. Skin punch biopsy has become standardized and may be of utility in the early diagnosis of small fiber neuropathy, revealing reduced intraepidermal nerve fiber density and even amyloid deposits. It should be performed in cases, where the clinical presentation is not convincing [35].

Large fiber neuropathy is evaluated with nerve condition studies, and the classical finding is axonal sensory-motor polyneuropathy. However, patients with late-onset presentations, in particular, can have demyelinating neuropathy [36]. Electrophysiological red flags include prolonged distal motor latency of the median never, reduced sensory conduction velocity in the median and ulnar nerves, and motor axonal loss, most commonly in the median, ulnar, and tibial nerves. An ulnar never motor amplitude <5.4 mV and a sural nerve amplitude <3.95 mV were distinguishing characteristics of demyelinating ATTRv-PN [34].

As ATTRv is a systemic disease, a multidisciplinary approach should be performed in all patients. Screening for cardiac amyloidosis includes serum troponin and N-terminal-B-type natriuretic peptide (NT-proBNP), 12-lead electrocardiogram, Holter monitoring, echocardiography with global longitudinal strain, cardiac MRI, and nuclear scintigraphy using bone tracers, such as 99mTc-2,3-dicarboxypropane-1-1-diphosphonate (DPD) and 99MTc pyrophosphate (PYP) (A). Detection of DPD or PYP uptake with cardiac scintigraphy (grade 2 or 3), associated with typical abnormalities in echocardiography/cardiac MRI, in the absence of a monoclonal gamopathy, is sensitive in the diagnosis of TTR cardiac amyloidosis and can be used as a substitute for cardiac biopsy [37]. Renal involvement should be assessed by proteinuria and estimated glomerular filtration rate. Two other areas that should be monitored are the ophthalmologic involvement (keratoconjunctivitis sicca, secondary glaucoma, vitreous opacities, and pupilaries abnormalities) and the nutritional status [modified BMI: $kg/m^2 \times$ albumina(g/L)] [38, 39].

Across the last decade, ATTRv has been designed across its clinical spectrum, and new therapeutic strategies have been developed, making early diagnosis crucial to obtain a good prognosis. In this scenario, genetic testing gained even more importance, allowing prompt detection of specific amyloidogenic TTR mutations. A targeted approach to detect a specific mutation can be used for cases belonging to families with previous diagnosis. TTR gene sequencing, by the Sanger method, is required for index cases without family history, allowing detection of both predicted and unknown variants [35]. Sequence analysis of TTR identifies 99% of pathogenic variants found in exons 2–4 [37]. In a patient with a typical clinical picture, even from nonendemic regions and without a family history, the identification of a known pathogenic TTR gene mutation is diagnostic ATTRv [35].

Genetic testing should be offered to at-risk family members older than 18 years after careful genetic counseling. Prenatal gene testing can be performed in accordance with local ethical and political norms [34].

Biopsy has historically been required to confirm amyloid deposition. The most common tissue sites include the labial salivary gland, abdominal fat tissue, gastrointestinal tract, sural nerve, and other organs with evidence of involvement (e.g., heart, kidney). The patchy distribution of amyloid deposits limits its utility, as a negative result does not exclude the diagnosis of ATTRv. The sensitivity of a biopsy depends on the site of biopsy, age of the patient, pathogenic mutation, and skill of the pathologist. In some patients, multiple biopsy sites are needed to detect an amyloid deposit. Congo red-stained sections exhibit salmon-pink color under light microscopy and apple-green birefringence under polarized light. Immunohistochemistry with anti-TTR amyloids can identify TTR deposits, but does not differentiate between a variant and a wild-type transthyretin. Laser microdissection and mass spectrometry-based proteomic analysis can type the amyloid precursor protein, confirming ATTRv amyloidosis [37].

At this point, identification of amyloid deposits through tissue biopsy should be reserved to confirm ATTRv in atypical cases (mimicking CIDP, motor neuron disease) when a variant of unknown significance has been identified on gene

sequencing or when there is a comorbid condition that can cause a similar neuropathy (e.g., diabetes, alcoholism, and monoclonal gammopathy).

2.6 Neurophysiology (EMG) of ATTRV-PN

Through evaluations of sensory nerve action potentials (SNAP) and compound muscle action potentials (CMAP), nerve conduction studies (NCS) measure the function of the peripheral nerves. Speaking in a simplified way, SNAP and CMAP amplitude and area estimate the number of viable axons, while their conduction velocities reflect myelin anatomical and functional integrity. A huge limitation of the method is the lack of techniques to measure small fiber function in clinical laboratories. Instead, special techniques should be used [40]. Needle examination evaluates motor unit action potential number and integrity, allowing the detection of acute denervation and reinnervation [41].

EMG findings in ATTRv-pn are largely related to genotype, duration, and disease course. The most common form of ATTRv-pn (early onset TTRV30 M) is initially a small fiber neuropathy. Routine NCS is normal at this stage. Special techniques should be used for the early detection of nerve involvement. Sudoscan measures the electrochemical skin gradient and seems to be a promising technique [42]. Pain-related evoked potentials [43] have been evaluated as an alternative to laser-evoked action potentials and contact heat-evoked potentials, which are sophisticated techniques restricted to a few centers [40]. A sympathetic skin response is a widely available option, but its utility is questionable [40]. Autonomic evaluation may be a useful option, but the gold standard for small nerve fiber evaluation is skin biopsy [44].

As the disease progresses, larger sensory nerve fibers of the sural and fibular superficial nerves are compromised, and the respective SNAP amplitude progressively decreases, revealing distal axonal degeneration. Their conduction velocities are normal or mildly decreased. As the disease progressively worsens in a length-dependent pattern, there is successive compromising of SNAP of median and ulnar nerves, following involvement of the superficial radial and then the cutaneous lateral and medial nerves.

At some point of the disease, the motor nerve fibers also become involved, following the length-dependent pattern. Initially, the CMAP of the peroneal and posterior tibial nerves become involved. Later, the median and the ulnar potentials also progressively lose amplitudes. Similar to SNAP, conduction velocity is usually preserved or mildly affected, characterizing length-dependent axonal polyneuropathy. In this context, needle examination shows a progressive decrease in the number of motor units, whose morphology progressively becomes neurogenic, with increased amplitude and duration, reflecting the process of reinnervation. When reinnervation is unable to compensate for denervation, fibrillation potentials and positive waves appear, reflecting the presence of muscle fibers not linked to their nerve fibers.

In the late onset TTRV30Met and in most of the other variants, the disease is, since the beginning, an all-nerve fiber sensory and motor axonal length-dependent polyneuropathy.

Occasionally, patients with ATTRv may present a multifocal demyelinating pattern simulating CIDP. These patients are usually treated as having an inflammatory neuropathy, but the response to treatment is not satisfactory [45]. There is now the concept that all CIDP that do not improve to adequate immunosuppression should be tested for TTR amyloidosis.

Even rarer is the motor neuron-like presentation, whose needle examination simulates a motor neuron disease [34]. On the other hand, bilateral slowing at the CTS is frequently seen in these patients, sometimes as the first abnormality [34]. It is now also mandatory to test all patients with bilateral CTS and cardiac manifestations.

In conclusion, a proper EMG examination is a useful tool in the process of diagnosing, staging, and monitoring ATTRv-associated neuropathies.

References

1. Benson MD, Buxbaum JN, Eisemberg DS, Mrlini G et al. Amyloid nomenclature 2018: Recommendations by the International Society of Amyloidosis (ISA) nomenclature committee. Amyloid. https://doi.org/10.1080/13506129.2018.1549825.
2. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. New Engl J Med. 2018;379:22–31.
3. Pinto MV, Pinto LF, Dias M, et al. Late-onset hereditary ATTR V30 M amyloidosis with polyneuropathy: characterization of Brazilian subjects from the THAOS registry. J Neurol Sci. 2019;403:1–6.
4. Pinto MV, Barreira AA, Bulle AS, de Freitas MRG, et al. Brazilian consensus for diagnosis, management and treatment of transthyretin familial amyloid polyneuropathy. Arq Neuropsiquiatr. 2018;76(9):609–21.
5. Holmgren G, Steen L, Ekstedt J, Groth C-G. Biochemical effect of liver transplantation in two Swedish patients with familial amyloidotic polyneuropathy (FAP-met30). Clin Gen. 1991;40:242–6.
6. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2018;379:11–21.
7. Sousa MM, Cardoso I, Fernandes R, Guimarães A, Saraiva MJ. Deposition of transthyretin in early stages of familial amyloidotic polyneuropathy: evidence for toxicity of nonfibrillar aggregates. Am J Pathol. 2001;159:1993–2000.
8. Fleming CE, Mar FM, Franquinho F, Saraiva MJ, Sousa MM. Transthyretin internalization by sensory neurons is megalin mediated and necessary for its neuritogenic activity. J Neurosci. 2009;29:3220–32.
9. Fleming CE, Saraiva MJ, Sousa MM. Transthyretin enhances nerve regeneration. J Neurochem. 2007;103:831–9.
10. Ando Y, Ueda M. Diagnosis and therapeutic approaches to transthyretin amyloidosis. Curr Med Chem. 2012;19:2312–23.
11. Coelho T, Merlini G, Bulawa CE, Fleming JA, et al. Mechanism of action and clinical application of Tafamidis in hereditary transthyretin amyloidosis. Neurol Ther. 2016;5(1):1–25. https://doi.org/10.1007/s40120-016-0040-x.
12. Gertz MA, Mauermann ML, Grogan M, Coelho T. Advances in the treatment of hereditary transtyretin amyloidosis. Brain Behav. 2019:e01371.

13. Gertz MA, Scheinberg M, Waddington-Cruz M, Heitner SB, et al. Inotersen for the treatment of adults with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis. Exp Rev Clin Pharmacol. 2019;12(8):701–11.
14. Ticau S, Sridharan GV, Tsour S, et al. Neurofilament light chain as a biomarker of hereditary transthyretin-mediated amyloidosis. Neurology. 2021;96:e412–22.
15. Adams D, Lozeron P, Theaudin M, Mincheva Z, et al. Regional difference and similarity of familial amyloidosis with polyneuropathy in France. Amyloid. 2012;19(Suppl 1):61–4. https://doi.org/10.3109/13506129.2012.685665.
16. Misu K, Hattori N, Nagamatsu M, Ikeda S, et al. Late-onset familial amyloid polyneuropathy type I (transthyretin Met30-associated familial amyloid polyneuropathy) unrelated to endemic focus in Japan. Clinicopathol Genetic Features Brain. 1999;122(Pt 10):1951–62. https://doi.org/10.1093/brain/122.10.1951.
17. Conceição I, De Carvalho M. Clinical variability in type I familial amyloid polyneuropathy (Val30Met): comparison between late- and early-onset cases in Portugal. Muscle Nerve. 2007;35(1):116–8. https://doi.org/10.1002/mus.20644.
18. Ikeda S, Hanyu N, Hongo M, Yoshioka J, et al. Hereditary generalized amyloidosis with polyneuropathy. Clinicopathological study of 65 Japanese patients. Brain. 1987;110(Pt 2):315–37. https://doi.org/10.1093/brain/110.2.315.
19. Koike H, Tanaka F, Hashimoto R, Tomita M, Kawagashira Y, Iijima M, et al. Natural history of transthyretin Val30Met familial amyloid polyneuropathy: analysis of late-onset cases from nonendemic areas. J Neurol Neurosurg Psychiatry. 2012;83(2):152–8. https://doi.org/10.1136/jnnp-2011-301299.
20. Sekijima Y. Transthyretin (ATTR) amyloidosis: clinical spectrum, molecular pathogenesis and disease-modifying treatments. J Neurol Neurosurg Psychiatry. 2015;86(9):1036–43. https://doi.org/10.1136/jnnp-2014-308724.
21. Pinto MV, Milone M, Mauermann ML, et al. Transthyretin amyloidosis: putting myopathy on the map. Muscle Nerve. 2020;61(1):95–100.
22. Rapezzi C, Quarta CC, Riva L, Longhi S, Gallelli I, Lorenzini M, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. Nat Rev Cardiol. 2010;7(7):398–408. https://doi.org/10.1038/nrcardio.2010.67.
23. Yamamoto H, Yokochi T. Transthyretin cardiac amyloidosis: an update on diagnosis and treatment. ESC Heart Failure. 2019;6:1128–39. https://doi.org/10.1002/ehf2.12518.
24. Maurer MS, Hanna M, Grogan M, Dispenzieri A, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (transthyretin amyloid outcome survey). J Am Coll Cardiol. 2016;68(2):161–72. https://doi.org/10.1016/j.jacc.2016.03.596.
25. Garcia-Paiva P, Rapezzi C, Adler Y, Arad M, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC working group on myocardial and pericardial diseases. Eur Heart J. 2021;42(16):1554–68. https://doi.org/10.1093/eurheartj/ehab072.
26. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation. 2016;133(24):2404–12.
27. Lobato L, Rocha A. Transthyretin amyloidosis and the kidney. Clin J Am Soc Nephrol. 2012;7(8):1337–46. https://doi.org/10.2215/CJN.08720811.
28. Ando E, Ando Y, Okamura R, Uchino M, Ando M, Negi A. Ocular manifestations of familial amyloidotic polyneuropathy type I: long-term follow up. Br J Ophthalmol. 1997;81(4):295–8. https://doi.org/10.1136/bjo.81.4.295.
29. Pinto MV, Dyck PJB, Liewluck T. Neuromuscular amyloidosis: unmasking the master of disguise. Muscle Nerve. 2021;64(1):23–36.
30. Yamashita T, Ando Y, Katsuragi S, et al. Muscular amyloid angiopathy with amyloidogenic transthyretin Ser50Ile and Tyr114Cys. Muscle Nerve. 2005;31(1):41–5.
31. Maia LF, Magalhães R, Freitas J, Taipa R, et al. CNS involvement in V30 M transthyretin amyloidosis: clinical, neuropathological and biochemical findings. J Neurol Neurosurg Psychiatry. 2015;86(2):159–67. https://doi.org/10.1136/jnnp-2014-308107.

32. Sousa S, Coelho T, Taipa R. CNS involvement in hereditary transthyretin amyloidosis. Neurology. 2021;97(24):1111–9. https://doi.org/10.1212/WNL.0000000000012965.
33. Quintanilha GS, Cruz MW, Silva MTT, Chimelli L. Oculoleptomeningeal amyloidosis due to transthyretin p.Y89H (Y69H) variant. J Neuropathol Exp Neurol. 2020;79(10):1134–6.
34. Adams D, Koike H, Slama M, Coelho T. Hereditary transthyretin amyloidosis: a model of medical progress for a fatal disease. Nat Rev Neurol. 2019;15(7):387–404.
35. Alcantara M, Mezei MM, Baker SK, Breiner A, et al. Canadian guidelines for hereditary transthyretin amyloidosis polyneuropathy management. Can J Neurol Sci. 2022;49(1):7–18.
36. Tozza S, Severi D, Spina E, Iovino A, et al. The neuropathy in hereditary transthyretin amyloidosis: a narrative review. J Peripher Nerv Syst. 2021;26(2):155–9.
37. Carroll A, Dyck PJ, Carvalho M, Kennerson M, et al. Novel approaches to diagnosis and management of hereditary transthyretin amyloidosis. J Neurol Neurosurg Psychiatry. 2022;93:668–78.
38. Adams D, Cauquil C, Labeyrie C, Beaudonnet G, et al. TTR kinetic stabilizers and TTR gene silencing: a new era in therapy for familial amyloidotic polyneuropathies. Expert Opin Pharmacother. 2016;17(6):791–80. https://doi.org/10.1517/14656566.2016.1145664.
39. Adams D, Suhr OB, Hund E, Obici L, et al. European network for TTR-FAP (ATTReuNET). First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. Curr Pin Neurol. 2016;29(Suppl 1):S14–26.
40. Casanova-Molla J, Valls-Solé J. Electrodiagnosrtic testing of small fiber neuropathies: a review of existing guidelines. J Clin Neurophysiol. 2020;37:288–93.
41. Kimura J. Electrodiagnosis in diseases of nerve and muscle. 4th ed. Oxford: Oxford University Press; 2013.
42. Lefaucher J-P, Zouari HG, Gorram HG, Nordine T, Damy T, Planté-Bordeneuve V. The value of electrochemical measurement using Sudoscan in the assessment of patients with familial amyloid polyneuropathy. Clin Neurophysiol. 2018;129:1565–9.
43. Siedler G, Sommer C, Üçeyler N. Pain-related evoked potentials in patients with large, mixed, and small fiber neuropathy. Clin Neurophysiol. 2020;131:635–41.
44. Leonardi L, Adam C, Beaudonnet G, Beauvais D, Cauquil C, Not A, et al. Skin amyloid deposits and nerve fiber loss as markers of neuropathy onset and progression in hereditary transthyretin amyloidosis. Eur J Neurol. 2022;29(5):1477–87. https://doi.org/10.1111/ene.15268.
45. Gibani M, Hoare J, Carol J, Whelan CJ, Dungu JN, Gilbertson JA, Carolyn M, Gabriel CM. Hard to swallow: atypical transthyretin amyloid neuropathy mistaken for CIDP. Pract Neurol. 2014;14:354–6. https://doi.org/10.1136/practneurol-2014-000814.

Chapter 3
Neurological Manifestations in AL and Wild-Type ATTR Amyloidosis

Viviane Tavares Carvalho Crelier, Fábio de Souza, and Caroline Bittar Braune

3.1 Introduction

The pathophysiological mechanisms underlying all amyloid precursor proteins include misfolding from the native α helical configuration to the proteolysis-resistant β pleated sheet, with consequent tissue deposition. The extracellular deposition of amyloid occurs due to the inability to degrade these insoluble fibrils. Clinical manifestations depend on which organ this deposit occurs, which explains why the disease is so complex and overgrown with different manifestations [1].

Amyloidogenic disorders can be localized or systemic and hereditary or acquired. Regarding hereditary systemic forms that are transthyretin (TTR), the most common variant worldwide, apolipoprotein A1, gelsolin, lysozyme, fibrinogen, amyloid-β, and cystatin C. Concerning acquired systemic forms, special attention is given to primary systemic amyloid-immunoglobulin light chain (AL), serum amyloid A protein in secondary amyloidosis (AA), and β2-microglobulin (β2 M) in dialysis-associated amyloidosis [2]. In addition, wild-type TTR amyloidosis (ATTRwt) has been increasingly highlighted in neurological aspects [3]. This form will also be discussed throughout this chapter.

V. T. C. Crelier
Department of Neurology, Antônio Pedro University Hospital, Federal Fluminense University, Rio de Janeiro, RJ, Brazil

F. de Souza
Hospital Universitário Gaffrée e Guinle—Universidade Federal do Estado do Rio de Janeiro (UNIRIO), Rio de Janeiro, RJ, Brazil

C. Bittar Braune (✉)
Department of Neurology, Antônio Pedro University Hospital, Federal Fluminense University, Rio de Janeiro, RJ, Brazil

Hospital Universitário Gaffrée e Guinle—Universidade Federal do Estado do Rio de Janeiro (UNIRIO), Rio de Janeiro, RJ, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_3

Amyloid disorders preferentially affect nerve fibers of small diameter, that is, thinly myelinated Aδ fibers and unmyelinated C fibers that are responsible for sensory modalities of pain and temperature, and autonomic function. Accordingly, the classic neuropathy presentation is a diffuse, symmetrical, length-dependent small fiber neuropathy, involving in particular the unmyelinated C fibers of the autonomic nervous system [4].

3.2 AL Amyloidosis

Immunoglobulin light chain (AL) amyloidosis constitutes a disease in which the protein subunit is an immunoglobulin light chain fragment that is deposited in organs, leading to organ dysfunction [1]. It is an acquired disease, and a clonal population of bone-marrow plasma cells produces a monoclonal light chain of kappa or lambda type as either an intact molecule or a fragment. In AL amyloidosis, misfolded AL (predominantly lambda isotype) deposits can affect any tissue, except the central nervous system [5].

Regarding the pathophysiology, amyloid fibril deposition occurs in a patchy fashion and leads to direct blood vessel damage, mechanical compression, and potentially toxic effects. All these mechanisms contribute to tissue damage. The histologic findings on nerve biopsy include axonal degeneration in small myelinated and unmyelinated fibers with Wallerian degeneration. In addition, amyloid nodules can indent and compress myelinated fibers, so it is possible to visualize this process in the epineurium, perineurium, and endoneurium by light microscopy [2, 6].

This is the most common type of systemic amyloidosis that affects the neuromuscular system. The following frequencies of involvement are estimated: peripheral neuropathy in 15–35%, myopathy in 1.5%, heart in 75%, kidneys in 57%, and gastrointestinal tract in 17% of patients [5].

Although the classic presentation of length-dependent sensory predominant polyneuropathy with frequent autonomic involvement is the most common, it is important to remember the atypical presentations, principally because they often lead to delayed diagnosis. These presentations are predominantly upper limb neuropathy, pure small fiber neuropathy, and carpal tunnel syndrome (CTS) [2].

In clinical practice, faced with a patient with neuropathy, it is important to be aware of suspected amyloidosis, particularly those who have a compatible personal or family history associated with monoclonal protein or autonomic dysfunction.

Treatment needs to be individualized and will be discussed further in later chapters. However, it is interesting that patients who undergo autologous stem cell transplant (ASCT) may halt peripheral neuropathy progression, whereas conventional chemotherapy does not stabilize or improve the neuropathy. Novel agents for the treatment of AL amyloidosis have shown promising results, especially in patients ineligible for ASCT, such as daratumumab, bortezomib, and pomalidomide [5].

3.3 ATTRwt

TTR, a protein produced primarily by the liver either in its wild-type (wt) or variant forms, can cause amyloidosis. ATTRwt is classically known to be a disease that affects older people and is therefore also known as the "senile amyloidosis". This type of amyloidosis does not occur due to TTR gene mutation. The mechanism of amyloidogenesis in ATTRwt is still not fully elucidated, but it is postulated that aging may increase TTR instability [5].

ATTRwt was thought to be associated with a more uniform cardiac presentation. In this context, the classic presentation is hypertrophic heart failure with relatively preserved systolic function. Over time, and with better knowledge of the disease, it is relatively common to observe noncardiac involvement. Among the neurological manifestations, special attention is given to bilateral CTS, lumbar spinal stenosis, peripheral neuropathy, and, most recently, skeletal myopathy [7]. In this regard, in recent studies [8, 3], Russell et al. highlighted the neurological alterations of ATTRwt, and there are many prominent aspects. CTS is one of the most common extracardiac manifestations of ATTRwt [9]. Studies indicate that ATTR deposits can be identified years preceding the onset of cardiac amyloidosis [10, 11]. The prevalence of symptomatic CTS is thought to be higher in ATTRwt patients than in light chain (AL) amyloidosis patients. Russell and Nakagawa et al. reported that 68% of ATTRwt patients had symptomatic CTS [8, 9].

Considering the associated peripheral neuropathy, a case series of five ATTRwt patients with symptomatic polyneuropathy found that most had sensorimotor polyneuropathy, with a median PND score of 1 [3]. The retrospective cohort study by Russel et al. confirmed the high prevalence of CTS in this population (88%), with the majority consisting of symptomatic cases [9]. In addition, it also established a much higher frequency of other findings than previously recognized. Spinal stenosis was related in 37%, and approximately 50% of cases had polyneuropathy. This study also described the clinical and electrophysiologic features of ATTRwt neuropathy, which is still poorly described in the literature. Among the 21 patients with polyneuropathy, 9 were asymptomatic, 12 had sensory findings, and 9 had sensorimotor findings.

Yungher et al. described neuropathy findings as predominantly symmetric, with loss of vibration and temperature sensation in distal extremities, distal weakness, and absent or diminished ankle reflexes. Some patients presented with a radiculopathy pattern, and a minority of patients had neuropathic complaints [12].

The clinical aspects of polyneuropathy were analyzed by Russell et al. Most ATTRwt patients had pure sensory polyneuropathy, followed by sensorimotor polyneuropathy. The most common symptom in patients diagnosed with polyneuropathy was numbness, and the most common findings on physical examination were stocking/glove sensory loss and reduced or absent ankle reflexes [9].

Russell et al. suggested that peripheral neuropathy is more common than previously described among ATTRwt patients and that screening offered at the time of diagnosis results in important changes to patient management [9]. ATTRwt is

estimated to have a prevalence of 155–191 cases per million persons [1]. Therefore, ATTRwt-related polyneuropathy is probably still underestimated.

Electrophysiological studies performed by Yungher et al. in 12 ATTRwt patients evidenced sensorimotor neuropathy with axonal loss. No demyelinating findings were observed. The majority of patients ($n = 11$) also presented with median mononeuropathy at the wrists, as seen with CTS. Five patients (41.7%) had ulnar neuropathy. Half of the patients had electrophysiological evidence of lumbosacral radiculopathy [12].

Russel et al. also highlighted ulnar neuropathy as a potential neurological complication of ATTRwt, as it was present in 34% of patients. Many of them were asymptomatic, and the incidence in patients with ATTRwt was higher than expected in the general population of compatible age, suggesting that ATTRwt may be a risk factor for this condition [9].

TTRwt deposits have been found in the tendons, ligaments, and joints of elderly patients, but the clinical repercussions of this finding are still unclear [10]. Spinal stenosis is a degenerative condition that primarily affects people older than 60 years. ATTRwt in the ligamentum flavum has been reported in 33–45% of patients undergoing surgery that involves the excision of the ligamentum flavum. The prevalence of ATTRwt in the ligamentum flavum has been associated with increased age and increased thickness of this structure, suggesting a pathologic role in this process [10].

The association of CTS and spinal stenosis with ATTRwt is now better established. Although there are reports of polyneuropathy, as mentioned above, data are still incipient. Regarding the autonomic component, this is even less described. To contribute, in general, the research of dysautonomia requires more specific tests, and most of these methods to assess autonomic fibers are not easily available. In general, they are time-consuming and require highly specialized and expensive equipment, most only available in tertiary services and research centers [4].

To overcome these barriers, the Sudoscan® device allows rapid and objective evaluation of sweat gland innervation at the extremities. This tool acts by measuring electrochemical skin conductance (ESC) according to a chronoamperometric method [4]. Sixty-two patients with ATTRwt-cardiomyopathy (ATTRwt-CA) were compared with a control group of healthy elderly subjects by Kharoubi et al. Almost half of the patients with ATTRwt-CA (48.4%) presented autonomic neuropathy (AN). This confirms that the prevalence of distal neuropathy, specifically involving autonomic nerve fibers, is significantly increased in the context of ATTRwt-CA. Feet ESC reduction was associated with poor cardiac prognosis, highlighting the functional interest of this measure in daily practice [4].

The recent data suggest that routine neurologic evaluation may facilitate early detection and direct appropriate ATTRwt management. There is a higher prevalence of polyneuropathy and ulnar neuropathy than previously reported, along with an anticipated high prevalence of CTS and spinal stenosis [9].

In addition to the above findings, a pattern of myopathy is also seen in some patients. Hut et al. showed increased skeletal muscle uptake on bone scintigraphy in patients with ATTRwt cardiomyopathy [13, 14]. Most likely, due to the high

prevalence of ATTRwt, the frequency of ATTRwt myopathy could be underestimated [5, 14]. Muscle biopsy could be useful for patients with monoclonal gammopathy and cardiac uptake on bone scintigraphy. It is less invasive than cardiac biopsy when amyloid subtyping is necessary [5].

3.4 Conclusions

Neurological involvement, especially ATTRv neuropathy, has been known and studied for many years. It was reported by the Portuguese neurologist Mario Corino da Costa Andrade in 1952, and details of its presentation have been studied ever since. Whereas ATTRv polyneuropathy is better established, it is also imperative to know the neurological manifestations of AL and ATTRwt amyloidosis.

Screening for neurologic complications as part of the routine assessment for newly diagnosed ATTRwt patients should be considered. In addition, patients with polyneuropathy, bilateral CTS, lumbar spinal stenosis, and, most recently, skeletal myopathy should be evaluated for suspicion of ATTRwt.

Earlier diagnosis and consequently monitoring of these patients can change the long-term outcome, both in quality of life and mortality.

References

1. Gertz MA, Dispenzieri A. Systemic amyloidosis recognition, prognosis, and therapy: a systematic review. JAMA. 2020;324(1):79–89. https://doi.org/10.1001/jama.2020.5493.
2. Kaku M, Berk JL. Neuropathy associated with systemic amyloidosis. Semin Neurol. 2019;39(5):578–88. https://doi.org/10.1055/s-0039-1688994. Epub 2019 Oct 22.
3. Zivkovic S, Soman P, Lacomis D. Late-onset peripheral neuropathy in patients with wild type transthyretin amyloidosis (wtATTR). Amyloid. 2020;27(2):142–3. https://doi.org/10.1080/13506129.2019.1697224. Epub 2019 Nov 29.
4. Kharoubi M, Roche F, Bézard M, Hupin D, Silva S, Oghina S, Chalard C, Zaroui A, Galat A, Guendouz S, Canoui-Poitrine F, Hittinger L, Teiger E, Lefaucheur JP, Damy T. Prevalence and prognostic value of autonomic neuropathy assessed by Sudoscan® in transthyretin wild-type cardiac amyloidosis. ESC Heart Fail. 2021;8(2):1656–65. https://doi.org/10.1002/ehf2.13131. Epub 2020 Dec 22.
5. Pinto MV, Dyck PJB, Liewluck T. Neuromuscular amyloidosis: Unmasking the master of disguise. Muscle Nerve. 2021;64(1):23–36. https://doi.org/10.1002/mus.27150. Epub 2021 Jan 17.
6. Dyck PJ, Lambert EH. Dissociated sensation in amyloidosis. Compound action potential, quantitative histologic and teased-fiber, and electron microscopic studies of sural nerve biopsies. Arch Neurol. 1969;20(05):490–507.
7. Massie R. Peripheral neuropathy in wild-type amyloidosis: the more you look, the more you will find. Can J Neurol Sci. 2021;48(5):597–8. https://doi.org/10.1017/cjn.2021.1. Epub 2021 Jan 12.
8. Nakagawa M, Sekijima Y, Yazaki M, et al. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. Amyloid. 2016;23(1):58–63.

9. Russell A, Hahn C, Chhibber S, Korngut L, Fine NM. Utility of neuropathy screening for wild-type transthyretin amyloidosis patients. Can J Neurol Sci. 2021;48(5):607–15. https://doi.org/10.1017/cjn.2020.271. Epub 2020 Dec 21.
10. Godara A, Riesenburger RI, Zhang DX, Varga C, Fogaren T, Siddiqui NS, Yu A, Wang A, Mastroianni M, Dowd R, Nail TJ, McPhail ED, Kurtin PJ, Theis JD, Toskic D, Arkun K, Pilichowska M, Kryzanski J, Patel AR, Comenzo R. Association between spinal stenosis and wild-type ATTR amyloidosis. Amyloid. 2021;28(4):226–33. https://doi.org/10.1080/13506129.2021.1950681. Epub 2021 Jul 15.
11. Gioeva Z, Urban P, Meliss RR, Haag J, Axmann HD, Siebert F, Becker K, Radtke HG, Röcken C. ATTR amyloid in the carpal tunnel ligament is frequently of wildtype transthyretin origin. Amyloid. 2013;20(1):1–6. https://doi.org/10.3109/13506129.2012.750604. Epub 2012 Dec 17.
12. Wajnsztajn Yungher F, Kim A, Boehme A, Kleyman I, Weimer LH, Maurer MS, Brannagan TH 3rd. Peripheral neuropathy symptoms in wild type transthyretin amyloidosis. J Peripher Nerv Syst. 2020;25(3):265–72. https://doi.org/10.1111/jns.12403. Epub 2020 Jul 27.
13. Hutt DF, Quigley A-M, Page J, et al. Utility and limitations of 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in systemic amyloidosis. Eur Heart J Cardiovasc Imaging. 2014;15(11):1289–98.
14. Rapezzi C, Guidalotti P, Salvi F, Riva L, Perugini E. Usefulness of Tc-99 m-DPD scintigraphy in cardiac amyloidosis. J Am Coll Cardiol. 2008;51:1509–10.

Chapter 4
Amyloidosis and Dysautonomia

Ana Inês da Costa Bronchtein, Joelma Dominato Rocha Carvalho, and Juliana Grael Jorge

4.1 Introduction

4.1.1 The Autonomic Nervous System—Basic Physiology

The autonomic nervous system (ANS) is a complex neural organization involving the brain, spinal cord, and peripheral and somatic nervous systems. It is responsible for innervating every organ in our body and carrying out automatic and involuntary organic actions and reactions [1, 2]. One of its central functions is the regulation of homeostasis both during daily activity, physical activity, mental stress, and postural changes, controlled and integrated with the central nervous system (CNS) [3]. ANS is usually analyzed for its anatomical, neurochemical, and functional aspects. The basic organization involves two neuronal groups, arranged in series and connected by a chemical synapse. The second neuron is located in the autonomic ganglia, from which axon projection begins, which will innervate the target organs, called postganglionic neurons. The neurons that send axonal projections from the CNS to the ganglia, synapsing with the cell bodies present in these structures, are called preganglionic neurons [2]. Sympathetic preganglionic neurons are located in the thoracic and lumbar spinal cord segments; parasympathetic neurons are located in the brainstem and sacral spinal cord segment [1, 3]. The ANS is anatomically divided into three major arms: the enteric nervous system, the sympathetic system (cholinergic and noradrenergic arms), and the parasympathetic (cholinergic) system (Fig. 4.1). These systems allow rapid adjustments of blood pressure (BP), heart rate (HR),

A. I. da Costa Bronchtein (✉) · J. G. Jorge
Clinical Arrhytmia, Rede D'or São Luiz, Rio de Janeiro, RJ, Brazil

J. D. R. Carvalho
Universidade Federal Fluminense—Complexo Hospitalar de Niterói, Niterói, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_4

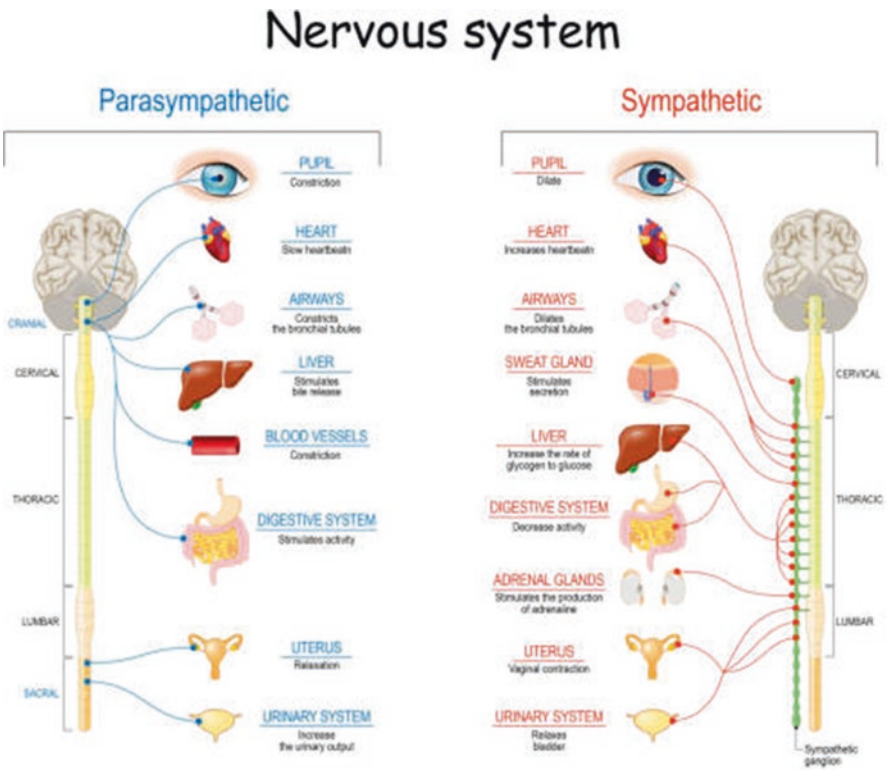


Fig. 4.1 Anatomical distribution of the autonomic nervous system

vascular reactivity, bowel, bladder, and sexual organ functions, pupils, sweating, and thermoregulation. In addition, the ANS is closely linked to many behaviors, emotions, and the immune system [3, 4].

Cardiovascular autonomic failures are primary or secondary disorders that are characterized by the disconnection of the interactive regulation of HR and BP between the CNS and the ANS, manifesting by baroreflex failure and causing failure in maintaining homeostasis [3]. This process may be paroxysmal or chronic, inducing alterations in both the sympathetic and parasympathetic systems and resulting in failure of action of one in response to the other (closed-loop system) [1].

The ANS cardiovascular arm constantly regulates HR and heart contractility, as well as arterial and venous vascular tone, aiming to maintain perfusion of oxygenated blood to the organs and ensure venous return. The cerebral circulation is protected by high-pressure baroreceptors that are reflexively mediated by sensors in the carotid sinus and aortic arch, promoting cerebral autoregulation [1, 3]. This system is called the baroreflex, and it is a key in the autonomic control of BP and HR and

has a strong predictive value in the clinical outcome of a number of cardiovascular conditions. BP is determined by HR, systolic volume, and peripheral vascular resistance, and its regulation is highly dependent on the sympathetic reflex, mediated by the baroreflex. The afferent activity triggered by high- and low-pressure baroreflex receptors determines the sympathetic action interfering with peripheral vascular resistance. These receptors, therefore, influence sympathetic flow through the afferent loop to the brain and through the efferent loop, increasing vascular tone through sympathetic stimulation. The result will be an increase in HR, vasoconstriction, venous return, and sodium and water retention by the kidneys [2] (Fig. 4.2).

Baroreflex sensitivity can be reduced by aging, hypertension, obesity, myocardial infarction, heart and kidney failure, and diseases, such as diabetes and amyloidosis. These conditions are associated with higher cardiac mortality and sudden death [1, 3, 5].

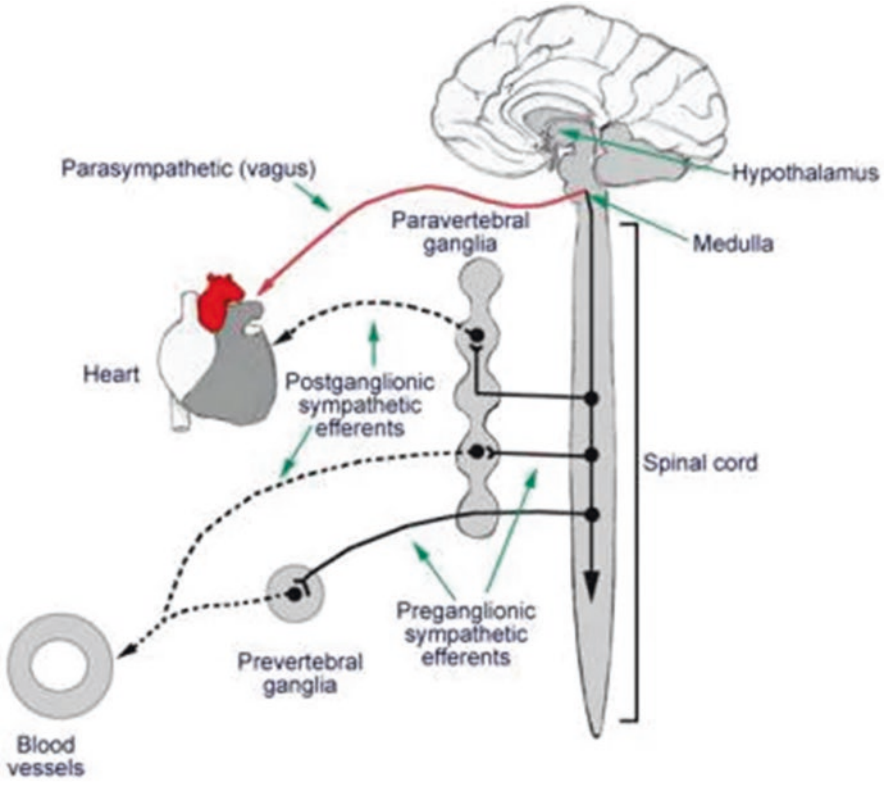


Fig. 4.2 Autonomic nervous system and interaction with the cardiovascular system

4.1.2 Autonomic Failure and Changes in Amyloidosis

Amyloidosis was first described in 1842 by Karl von Rokitansky (1804–1878) and named by Rudolph Virchow in 1853, with the first cases being secondary forms of amyloid disease associated with chronic infections, such as tuberculosis and osteomyelitis [6]. The first clinical description of peripheral nervous system involvement was by Königstein in 1925. Navasquez and Treble reported, in 1938, a case of polyneuropathy secondary to amyloidosis with associated autonomic changes. The diagnosis of the disease is often only made at autopsies, with postmortem studies showing that cardiac amyloidosis was present in 25% of people aged >85 years [3].

Cardiovascular dysautonomia encompasses other conditions, such as postural orthostatic tachycardia syndrome, inappropriate sinus tachycardia, classic or neurogenic orthostatic hypotension (nOH), chronic fatigue syndrome, carotid sinus hypersensitivity syndrome, and reflex syncope [1, 2]. The different types of cardiovascular dysautonomia may overlap and may also coexist with primary cardiac diseases such as nOH accompanying HF and ischemic disease, worsening the prognosis of the underlying diseases [1].

The term cardiovascular autonomic neuropathy (CAN) is the most commonly used to define dysautonomia with impaired cardiovascular sympathetic and/or parasympathetic ANS. CAN typically manifests with OH, reduced HR variability, sinus tachycardia at rest, and exercise intolerance [1]. It can be idiopathic, such as multisystem atrophy or pure autonomic failure, or secondary to systemic pathologies, such as diabetes mellitus, neurodegenerative diseases, Parkinson's disease, dementia syndromes, chronic renal failure, and amyloidosis. OH and nOH are the main manifestations of autonomic failure in amyloidosis [3].

It is essential to differentiate between nOH and non-nOH because of the worse prognosis of nOH, with higher all-cause morbidity and mortality. In nOH, the impaired vasoconstriction is due to permanent damage to sympathetic efferent activity. In nOH, it includes a variety of causes, such as the use of medications, antihypertensives, antidepressants, alpha-blocking agents, volume depletion , and chronic diseases leading to physical deconditioning [1, 3, 4].

4.2 Clinical Manifestations of Dysautonomia in Amyloidosis

Cardiac amyloidosis has a poor prognosis, usually worsened by the delay in diagnosis, since early stages of clinical presentation often go unnoticed or are underestimated in the clinical evaluation.

The presence of OH may be the initial sign of autonomic failure, and patients have significant baroreflex alterations, with inappropriate responses of increased HR to various stimuli due to sympathetic failure associated with parasympathetic failure [6]. The major challenge in these patients is to maintain blood flow above the level of the heart [3]. Failure in this compensation with consequent reduced venous

return to the heart produces inadequate cerebral perfusion, resulting in symptoms of syncope or presyncope [5].

Amyloid neuropathy may be complicated by autonomic dysfunction that manifests predominantly by the presence of amyloid substance in the autonomic nerves and ganglia, generating a chronic autonomic neuropathy. Amyloid neuropathy typical manifestations include sensory-motor neuropathy, autonomic dysfunction, cardiac, ocular and less common manifestations, such as renal involvement, and without treatment may lead to a progressive disabling neuropathy due to gastrointestinal (GI) dysautonomia [6]. Autonomic symptoms are key components of hereditary transthyretin (TTR) amyloidosis, contribute strongly to the burden of the disease, and usually occur early in the natural history of TTR amyloidosis. Similar to peripheral neuropathy, the progression of autonomic symptoms is unrelenting and closely related to the progression of somatic neuropathy. These symptoms can worsen non-neurological manifestations, such as dizziness, fatigue, and pain [7].

In a recent review [8], autonomic manifestations were present in 50–80% of the patients. The most common findings were OH, diarrhea, constipation, alternative diarrhea and constipation, erectile dysfunction, urinary incontinence, and xerostomia [9]. In addition, different autonomic manifestations may occur at different times. In studies involving patients with early onset disease, GI dysfunction and OH emerged in the early phase of the disease, whereas urinary manifestations appear halfway through the course of the disease. Heart rate variability (HRV) and OH are reliable markers of autonomic alterations and have been shown to be impaired very early in the disease, although it is difficult to estimate the exact timing of the onset of autonomic symptoms [10].

4.3 Diagnosis of Dysautonomia in Amyloidosis

Early diagnosis can bring important therapeutic and prognostic implications, as well as improvements in quality of life. Autonomic testing is imperative, as it enables diagnosis before disabling symptomatology [10].

The initial clinical assessment can be through questionnaires, such as the autonomic symptom profile [11], which contains 73 questions, and the Composite Autonomic Symptom Scale-31 [12], which uses the previous scale and quantifies the severity of the changes. More recently, a new Survey of Autonomic Symptoms Score [13] has been developed and validated, with a better sensitivity in detecting mild autonomic neuropathies, not requiring complementary methods, and might be a crucial clinical tool for the early detection of autonomic neuropathy (Table 4.1) [2]. Patients with questionnaire responses suggesting dysautonomia have a higher risk of nOH than the general population and should be routinely investigated.

Adapted of Rocha et al. [2]. The presence of three or more symptoms conferred 95% sensitivity and 65% specificity, while the presence of seven or more points determined 60% sensitivity and 90% specificity. Gastrointestinal symptoms were less correlated with other indices.

Table 4.1 Survey of autonomic symptoms—evaluate various organs and systems affected in dysautonomia

Symptom/health problem	Have you had any of the following health symptoms during the past 6 months? (1, yes; 2, no)	If you answered you have symptoms, how much would you say it bothers you? (1, not at all; 2, a little; 3, some; 4, moderate amount; 5, a lot)
1. Do you have lightheadedness?	1 or 2	1–5
2. Do you have a dry mouth or dry eyes?		
3. Are your feet pale or blue?		
4. Are your feet colder that the rest of your body?		
5. Is sweating in your feet decreased compared to the rest of your body?		
6. Is sweating in your feet decreased or absent (after exercise or during hot weather)?		
7. Is sweating in your hands in creased compared to the rest of your body?		
8. Do you have nausea, vomiting, or bloating after eating a small meal?		
9. Do you have persistent diarrhea (more than 3 loose bowl movements per day)?		
10. Do you have persistent constipation (less than 1 bowl movement every other day)?		
11. Do you have leaking of urine?		
12. Do you have difficulty obtaining an erection (men)?		

After identifying the patient at risk of OH, it is important to measure BP and HR in the supine position (after 15–20 min of lying down) and in the first and third minutes after standing up, which is considered the gold standard for diagnosing OH. These values should also be measured after 5 min of orthostasis.

OH may be subdivided into:

– Classic OH: sustained reduction of at least 20 mmHg of systolic BP (SBP) and/or 10 mmHg of diastolic BP (DBP) within 3 min in the standing position.
– Initial OH: fall in SBP >40 mmHg and/or at least 20 mmHg of DBP within 15 s of orthostasis, with a rapid and spontaneous return with a short period of hypotension (<40 s), may cause syncope.
– Late OH: beyond 3 min of active orthostasis. Slow, progressive drop in BP. The absence of bradycardia helps differentiate it from reflex syncope [2].

Many of these patients have supine hypertension (SBP ≥140 mmHg and/or DBP ≥90 mmHg). In this situation, OH should be considered if there is a decrease in SBP ≥30 mmHg and/or DBP ≥10 mmHg.

In OH patients, a compensatory HR elevation of at least 15 bpm is expected within 3 min in the standing position. If this does not occur, it suggests nOH (provided that there is no concomitant use of negative chronotropic drug or conduction system disease, or the patient has a pacemaker) [1].

It is important to review the patient's medication list to avoid effects on the baroreflex response, especially alpha- and beta-adrenergic blockers and centrally acting alpha-2 agonists.

Standard tests to assess autonomic function should be considered in patients with signs of autonomic dysfunction, such as a drop in BP in an orthostatic position, with chronotropic failure, or in the presence of autonomic symptoms, such as decreased sweating, constipation, neurogenic bladder, and/or erectile dysfunction [4].

Autonomic tests require continuous monitoring of BP and HR and can be obtained by digital plethysmography monitoring. The purpose of these tests is to assess the integrity of the sympathetic and parasympathetic nervous systems and correlate their alteration with the patient's symptoms. However, it is essential to emphasize that no single test can provide a global view of autonomic function; we will need to analyze the tests together according to the patient's clinical presentation [2].

4.3.1 Autonomic Assessment May Include the Following Methods

4.3.1.1 Tilt Table Test

The head up tilt test (HUTT) should be considered to confirm a diagnosis of reflex syncope in patients in whom this diagnosis was suspected but not confirmed by initial evaluation for the assessment of autonomic failure, especially for the reproduction of delayed OH (which could not be detected by active standing because of its delayed onset) [14].

The HUTT evaluates the orthostatic effects on BP and HR during a nonpotentiated phase and during the orthostatic and pharmacological stress that is usually performed with a vasodilator drug, such as nitroglycerin or isosorbide dinitrate. It consists of a table with a platform for foot support, safety belts, electrocardiographic monitoring of HR, and BP monitoring through beat-to-beat digital plethysmography. The patient initially remains lying down for 10–20 min (rest or passive phase), and then, the bed is tilted to 60 or 70 degrees. The tilting phase lasted from 20 to 45 min based on the protocol used.

Noninvasive and continuous monitoring systems of BP and ECG, associated with bioimpedance measurements, allow the evaluation of systolic volume, peripheral vascular resistance, and cardiac output, enabling the identification of the type of hemodynamic disorder presented. Thus, HUTT with hemodynamic parameters allows the identification of subclinical alterations in the integrity of the ANS, even without an evident pressure drop, which increases the sensitivity of the method [2].

Patients with dysautonomia and autonomic neuropathy related to amyloid disease may show patterns of classic OH with progressive and maintained hypotension during the tilt period, associated with depressed chronotropic response unresponsive to BP drop demonstrating a significant failure of the baroreflex response (Fig. 4.3).

4.3.1.2 24-h Ambulatory Blood Pressure Monitor

Daytime and nighttime autonomic balances affect not only HR but also BP. Typically, BP fluctuates, with higher levels during wakefulness and falling at night (nocturnal descent). The attenuated or reversed response demonstrates exacerbated sympathetic activity and may be present in patients with dysautonomia and has been associated with increased mortality.

More specifically, ABPM is useful in detecting nocturnal hypertension (predictor of cardiovascular events) and forms of early or postprandial OH, usually not discovered with the usual BP measurements. In addition, the presence of nocturnal hypertension may increase the risk of daytime hypotension [2].

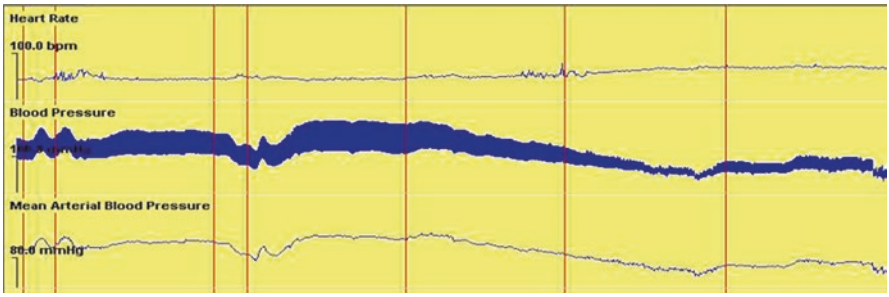


Fig. 4.3 Tilt table test showing classic nOH—progressive hypotension during orthostatic period and depressed chronotropic response after blood pressure drop

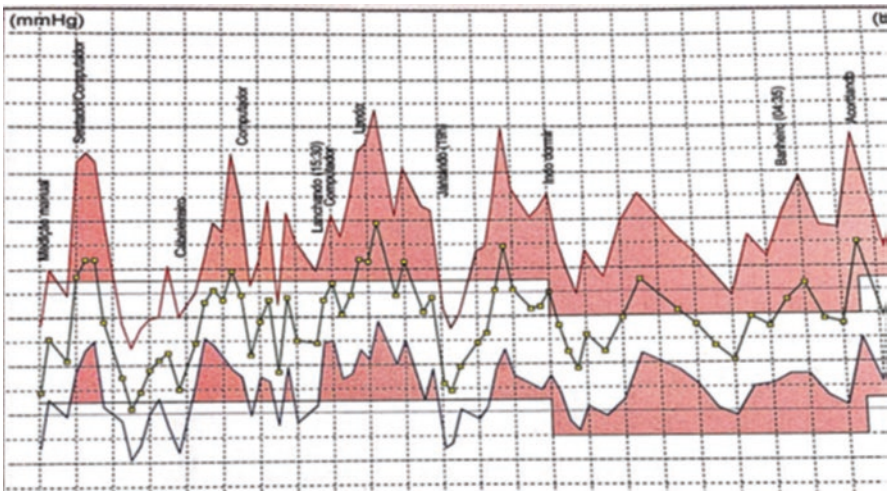


Fig. 4.4 Presence of supine hypertension during the night and orthostatic hypotension during the daytime

The presence of supine hypertension and a nondipper or negative dipper pattern on 24-h ABPM in patients with amyloidosis might be a sign of dysautonomia (Fig. 4.4).

4.3.1.3 Valsalva Maneuvere

The Valsalva maneuvere (VM) tests the integrity of both the cardiovagal parasympathetic response by analyzing HR and the sympathetic response by analyzing the behavior of BP [2]. The ratio is measured between the largest RR cycle in the relaxation phase divided by the largest RR cycle during the VM phase. It allows the evaluation of the parasympathetic and sympathetic systems when associated with continuous BP measurements.

There is strong evidence that the absence of a BP overshoot and an absence of an HR increase during the Valsalva is pathognomonic for neurogenic OH, occurring in primary and secondary autonomic failure, and the degree of hypotension and/or lack of compensation during forced expiration usually correlate with the degree of autonomic dysfunction [14].

Patients with nOH will not generate alpha-adrenergic sympathetic receptor-mediated vasoconstriction to compensate for hypotension during phase II of VM and will not be able to normalize venous return to produce the sudden BP elevation in phase IV (Fig. 4.5). When the afferent and efferent baroreflex vagal components are intact, HR increases while BP falls.

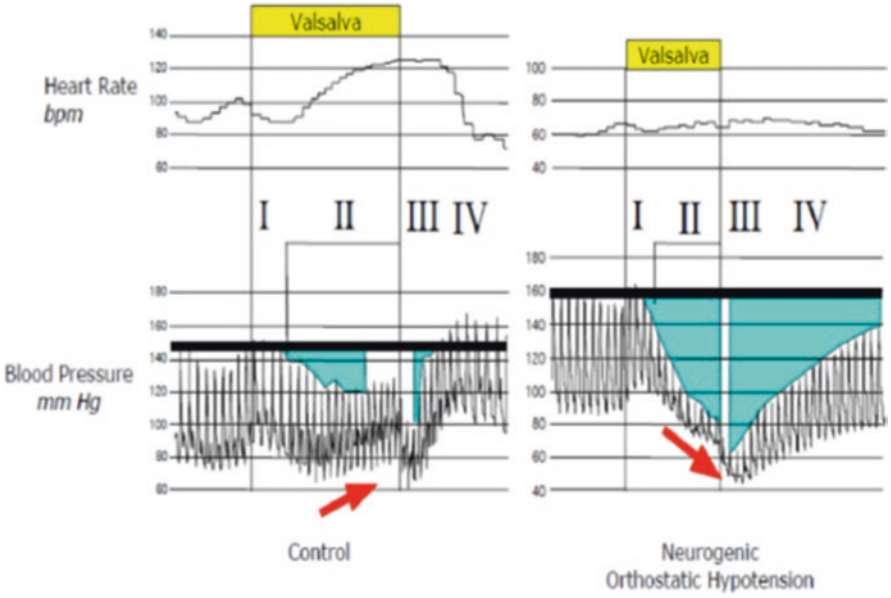


Fig. 4.5 Failure of hemodynamic sympathetic compensation with hypotension during phase II and lack of overshoot of phase IV. From Jain and Goldstein [15]

4.3.1.4 Isometric Exercise (Handgrip)

Faced with a pressure stimulus (handgrip), healthy subjects have an increase in BP and HR due to stimulation of sympathetic efferent pathways by activation of peripheral receptors. The maneuver is performed with a dynamometer or a partially inflated sphygmomanometer cuff, maintaining the pressure sustained for 3 min. In patients with efferent or central sympathetic lesions, these responses will be altered or absent.

4.3.1.5 Respiratory Maneuveres

Respiratory changes result in rapid responses in HR and usually reproduce cardiovagal activity. Physiologically, during deep inspiration, there will be a rise in HR and a fall in HR during expiration. This behavior is the basis of respiratory sinus arrhythmia. Hyperventilation will cause vagal withdrawal and HR increase, which may or may not be associated with a drop in BP. These responses might be reduced with aging. Usually, we calculate the average of the respiratory amplitudes in six cycles. The test evaluates the parasympathetic response to a respiratory stimulus [2].

Patients with dysautonomia related to amyloid disease may have reduced or absent HR oscillation during deep breathing. HR variation greater than 15 bpm is considered normal. Variations between 11 and 14 bpm were classified as borderline,

and those below 10 bpm were classified as pathological. The E:I ratio (maximum HR, measured in milliseconds, during expiration divided by the maximum HR during inspiration) in normal individuals should be greater than 1.2. These values should be adjusted according to age and sex.

4.3.1.6 Exercise Test

A significant drop in BP associated with a marked drop in systemic vascular resistance secondary to vasodilation in the skeletal muscles may occur during exercise in patients with autonomic failure. In physiological states, vasodilation is compensated by a cardiac output boost through increased sympathetic muscle traffic and sympathoadrenal activity. However, it does not occur in patients with autonomic failure, and BP usually falls during or immediately after the end of physical activity.

4.3.1.7 Carotid Sinus Compression

Carotid sinus compression should be performed in elderly individuals with syncope, presyncope, and/or a history of unexplained falls [2]. CSM should be performed with the patient in the supine and upright positions and with continuous beat-to-beat BP. A ventricular pause lasting >3 s and/or a fall in SBP >50 mmHg associated with symptoms of syncope or presyncope is known as carotid sinus syndrome, which is different from carotid sinus hypersensitivity present in 40% of the older population without any symptoms [14].

4.3.1.8 Heart Rate Variability/Spectral Analysis

HRV analysis is a noninvasive method to assess the autonomic influence on the heart. The 24 h Holter monitor allowed us to analyze cardiac cycles and HR variability.

Sympathetic and parasympathetic efferent reflexes acting on the sinus node produce constant modifications of the PP cycles in the electrocardiogram. The parasympathetic system (vagal) is the major system responsible for the variability of the normal PP cycles.

These cycle fluctuation evaluations will give us the indirect expression of the cardiac autonomic profile, and the greater the vagal action on the heart, the greater the fluctuations will be.

Low HRV indicates depression of vagal activity and/or exacerbation of sympathetic activity. Increased sympathetic activity displays an arrhythmogenic effect, while parasympathetic activity exerts a protective effect.

In healthy patients, increased RR variability represents a measure of autonomic integrity, while reduced HR variability is an early sign of autonomic imbalance [2].

HRV can be analyzed in the time domain or in the HR domain (spectral analysis).

Time Domain

The indices commonly used for HRV assessment in the time domain are:

- NN: average of normal sinus cycles evaluated, representing the average HR in the recording period (ms). To transform the cycle into HR, 60,000 is divided by the cycle average value, resulting in the average HR.
- SDNN: standard deviation of NN intervals measured during recording (ms). The SDNN is the "gold standard" for medical stratification of cardiac risk when recorded over a 24 h period. SDNN values predict both morbidity and mortality. Patients with SDNN values below 50 ms are classified as unhealthy (higher cardiovascular risk), 50–100 ms have compromised health, and above 100 ms are healthy.
- SDANN: standard deviation of the average NN intervals for each 5 min segment of a 24 h HRV recording. Increased risk cardiovascular risk if values <40 ms.
- pNN50: percentage of successive RR intervals that differ by more than 50 ms during recording. pNN50 is closely correlated with parasympathetic nervous system activity. Normal value 9 ± 7. Increased risk if <0.75.
- RMSSD: root mean square of successive RR interval differences (ms). The RMSSD is more influenced by the parasympathetic nervous system. Normal value 27 ± 12 ms. Increased risk if <15 ms.

The SDANN is the main index for post-MI risk stratification. RMSSD and pNN50 adequately define fluctuations in vagal activity.

Spectral Analysis

When the fluctuations of the electrocardiographic signal are periodically unfolded in their respective waves through the Fourier transform, we are facing frequency domain analysis or spectral analysis [2]. The analyzed curves will be distributed in different components, namely:

- Very low-frequency component: frequency responses between 0.001 and 0.04 Hz. This likely correlates with thermoregulation and renin-angiotensin mechanisms.
- Low-frequency (LF) component: encompassing the frequency responses between 0.05 and 0.15 Hz. Sympathetic activity is modulated by parasympathetic and vasoconstriction.
- High-frequency (HF) component: encompassing the responses between 0.15 and 0.40 Hz. Represents vagal modulation and sinus arrhythmymia.
- LH/HF ratio: vagal sympathetic balance.

Dysautonomic conditions promote alterations in the HF and LF components when faced with orthostatic stress. Spectral analysis is most sensitive in the early stages of CAN. The expected nocturnal increase in the high-frequency band of RR variability, which represents the vagal modulation of the heart, seems to be the

earliest abnormality detected. During the advanced stages of CAN, all components are eliminated.

4.3.1.9 Biochemical Tests

Epinephrine, norepinephrine, and dopamine are the most important plasma catecholamines in humans, reflecting sympathetic activity. Patients with autonomic failure, secondary to postganglionic neuron sympathetic dysfunction, may have reduced norepinephrine concentrations in the supine position.

On the other hand, individuals with autonomic failure from any cause often fail to raise their plasma norepinephrine levels when standing or being tilted in the HUTT.

In nOH, caused by various autonomic disorders, including CAN, the orthostatic increment of norepinephrine is attenuated (Fig. 4.6). Therefore, a plasma norepinephrine increment of less than 60% after 5 min of orthostasis supports the diagnosis of nOH.

4.3.1.10 Imaging Techniques Used to Assess Autonomic Innervation

Metaiodobenzylguanidine (123I-MIBG) single photon emission computed tomography (SPECT) and positron emission tomography (PET) have been used to assess ANS activity [4]. MIBG is an NE analog with a similar molecular structure. The role of 123I-MIBG has been well-studied in several clinical conditions, with prognostic value in heart failure, ischemic heart disease, ventricular arrhythmias, and cardiomyopathies.

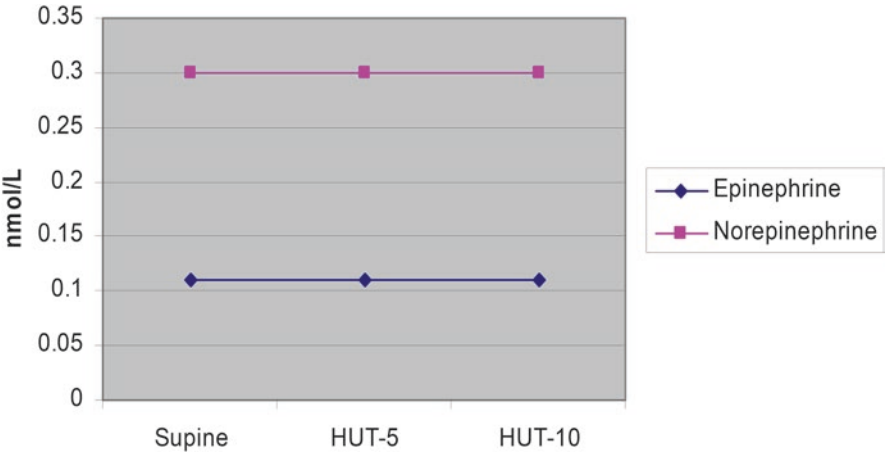


Fig. 4.6 Plasma levels of catecholamines showing absence of the orthostatic increment of norepinephrine and epinephrine during the head up tilt test

PET imaging offers several advantages over SPECT, including superior image resolution, allowing for a more specific regional analysis of cardiac neuron function [4]. PET examination facilitates the combined assessment of myocardial viability and perfusion together with innervation. It also offers the potential for imaging using autonomic receptors, as well as the global quantification of cardiac sympathetic and parasympathetic activity.

The most studied radiotracer for neuronal evaluation conducted with the PET technique in humans is carbon-11 (11C)-labeled meta-hydroxyephedrine (11C-HED), an analog to NE and 123I-MIBG, which is transported by the uptake-1 mechanism.

Other agents have been researched for their role in the direct visualization of adrenergic receptors. However, the main current limitations for assessing innervation by PET technology are the higher costs when compared to SPECT and shorter half-lives of radioisotopes. Consequently, very few centers perform cardiac sympathetic neuroimaging using PET scans.

4.4 Treatment

The standard treatment of cardiac amyloidosis involves the use of diuretics; however, diuretics must be prescribed with caution in patients who progress with associated nOH, and the hypovolemia induced by the action of the diuretic may be deleterious.

There is no available evidence in the setting of cardiac amyloidosis that demonstrates the benefits of drugs established for heart failure (HF) treatment, such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and angiotensin receptor–neprilysin inhibitors. Indeed, a retrospective study conducted on patients with ATTR showed decreased survival in this population [6]. These drugs have low tolerability, as their use might lead to hypotension and affect the autonomous nervous system.

Therefore, in the setting of cardiac amyloidosis, drugs established for HF treatment should be avoided whenever possible. In patients with HF with reduced ejection fraction, neurohumoral treatment can be considered if the abovementioned limitations are taken into account.

If HR control is necessary, amiodarone and beta-blockers should be preferred over digitalis derivatives and calcium channel blockers.

Dysautonomia treatment, particularly OH, should follow a progressive approach, including both nonpharmacological and drug treatment. The goal is to improve debilitating symptoms (particularly the risk of falls) and quality of life by increasing tolerance to longer periods of orthostasis and physical capacity.

Those involved in dysautonomic patient treatment should always be reminded that it is critical in clinical treatment to educate patients, family members, and

caregivers about the mechanisms involved in nOH genesis and daily activity situations that may favor a drop in BP. Examples include staying in high-temperature environments, hot baths, type and intensity of physical exertion, prolonged or rapidly reached orthostatic posture, ingestion of alcoholic beverages or large meals, particularly with carbohydrates, which may precipitate or worsen the symptoms [6].

Regardless of the etiology of dysautonomia, whenever possible, the interruption of use or the adjustment of the dosage of medications that potentiate OH should be considered. In cases with a definite indication, antihypertensives with a shorter half-life should be chosen, preferably with a single nighttime dosage. Drugs, such as nitrates and diuretics, which decrease preload, should be suspended or avoided. Other drugs that also worsen or contribute to OH are dopaminergic drugs, anticholinergics, tricyclic antidepressants, alpha-1-blockers, and other antihypertensives.

4.4.1 Pharmacological Interventions

- Review all pharmacological treatments, avoiding drugs that potentiate OH.
- Increase intravascular volume: fludrocortisone (0.1–0.3 mg/day—1× day)/eritropoetin (25–75 U/kg—3× week).
- Increased vascular resistance: Midodrine (2.5–10 mg, 3× day)/droxydopa (100–600 mg, 3× day)/atomoxetine (18–40 mg × day)/pyridostigmine (30–60 mg, 2–3× day)/pseudoephedrine (30 mg, 3× day)/ergotamine/caffeine (1 mg/100 mg/day).
- Octreotide (12.5–25 mcg, subcutaneous), 30 min to 1 h before a meal and acarbose 100 mg for postprandial OH.
- Combination therapy: fludrocortisone (0.1–0.3 mg/day, VO) and midodrine (2.5–10 mg, VO—3× day).

4.4.2 Physical Maneuveres

Patients with OH should be informed about simple physical maneuvers that can be used to raise BP during daily activities. Physical countermaneuvers include crossing legs, squatting, and tensing the muscles of the legs, arms, abdomen, buttocks, or the whole body. These maneuvers generate increases in cardiac preload and, consequently, in cardiac output, BP, and cerebral perfusion. The most basic maneuver is the activation of the calf muscle pump (“antigravitational” muscles). If the venous valves are competent, muscle activation increases cardiac venous and cardiac filling pressure. Small increases in BP can alter autoregulation and prevent presyncope and syncope.

4.4.3 Prevention and Treatment of Supine Hypertension

- Sleep with the head of the bed elevated (tilt head up training)
- Consume a carbohydrate-rich meal at bedtime
- Avoid drinking fluids before bedtime
- Avoid supine decubitus during the day

It is important to avoid the use of diuretics and long-acting antihypertensives, even if they control supine hypertension.

4.5 Conclusions

Dealing with cardiac amyloidosis with neuropathic involvement (CAN) and dysautonomia is a huge challenge, with many investigation steps. Physicians must be aware of all symptoms and presentations and the diversity of this complex condition. A detailed history and physical examination seeking supine hypertension and symptomatic OH are the primary steps to diagnosis. As a chronic condition, the patient should be seen frequently and continuously in the office and often needs a multidisciplinary approach to control symptoms.

References

1. Fedorowski A, Feigofsky S. Defining cardiac dysautonomia – different types, overlap syndromes; case-based presentations. J Atrial Fibrillation. 2020;13(1)
2. Rocha EA, Mehta N, Távora Z, et al. Dysautonomia: a forgotten condition—part 1. Arq Bras Cardiol. 2021;116(4):814–35.
3. Mathias CJ, Bannister R, Autonomic failure. A textbook of clinical disorders of the autonomic nervous system. 5th ed. Oxford; 2013.
4. Brito AX, Glavam A, Bronchtein AI, Rosado-de-Castro PH. Autonomic innervation evaluation in cardiac disease. Int J Cardiovasc Sci. 2021;34(6):702–13.
5. Bronchtein A, Souza OF. Sensibilidade barorreflexa. In Arritmias cardíacas-novas perspectivas diagnósticas RevinterVolume III Mathias C J and Bannister R. Autonomic failure A textbook of clinical disorders of the autonomic nervous system Fifth edition Oxford, 2013; 2007.
6. Bonderman D, Pölzl G, Ablasser K. Diagnosis and treatment of cardiac amyloidosis: an interdisciplinary consensus statement. Wien Klin Wochenschr. 2020;132:742–61.
7. Gonzalez-Duarte A. Autonomic involvement in hereditary transthyretin amyloidosis (hATTR amyloidosis). Clin Auton Res. 2018; https://doi.org/10.1007/s10286-018-0514-2.
8. Gonzalez-Duarte A. Characteristics and natural history of autonomic involvement in hereditary ATTR amyloidosis: a systematic review. Clin Auton Res. 2019; https://doi.org/10.1007/s10286-019-00630-y.
9. Gonzalez-Duarte A, Banuelos C, García K, et al. Autonomic description in patients with very early TTR amyloidosis. Neurology. 2018;381:114.
10. Kim DH, Zeldenrust SR, Low PA, et al. Quantitative sensation and autonomic test abnormalities in transthyretin amyloidosis polyneuropathy. Muscle Nerve. 2009;40(3):363–70.

11. Suarez GA, Opfer-Gehrking TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA. The autonomic symptom profile: a new instrument to assess autonomic symptoms. Neurology. 1999;52(3):523–8. https://doi.org/10.1212/wnl.52.3.523.
12. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a refined and abbreviated composite Autonomic symptom score. Mayo Clin Proc. 2012;87(12):1196–201. https://doi.org/10.1016/j.mayocp.2012.10.013.
13. Zilliox L, Peltier AC, Wren PA, Anderson A, Smith AG, Singleton JR, Feldman EL, Alexander NB, Russell JW. Assessing autonomic dysfunction in early diabetic neuropathy: the survey of autonomic symptoms. Neurology. 2011;76(12):1099–105. https://doi.org/10.1212/WNL.0b013e3182120147.
14. Brignole M, Moya A, Langen F, et al. ESC Guidelines for the diagnosis and management of syncope the task force for the diagnosis and management of syncope of the European Society of Cardiology. Eur Heart J. 2018;39:1883–948. ESC Guidelines. https://doi.org/10.1093/eurheartj/ehy0372018.
15. Jain S, Goldstein DS. Cardiovascular dysautonomia in Parkinson disease: from pathophysiology to pathogenesis. Neurobiol Dis. 2012;46(3):572–80. https://doi.org/10.1016/j.nbd.2011.10.025. Epub 2011 Nov 4.

Chapter 5
Cardiologic Manifestation in Amyloidosis

Aristóteles Comte de Alencar Neto, Caio Rebouças Fonseca Cafezeiro, Bruno Vaz Kerges Bueno, Cristiane de Carvalho Singulane, and Fabio Fernandes

5.1 Introduction

Cardiac amyloidosis (CA) is a relatively common cause of heart failure (HF) with preserved ejection fraction (HFpEF). Recently, emerging therapies have been shown to change the course of the disease and prolong survival. Therefore, it is crucial to know, understand, and recognize the clinical manifestations of the disease, its red flags, and the markers of cardiac involvement in amyloidosis [1–3].

There are 36 known amyloidogenic proteins, some of which are prone to developing CA. However, ATTR and AL amyloidosis are responsible for approximately 95% of all cases of CA. Therefore, this chapter will consider both types when discussing CA. While these two types of CA must be recognized as different entities with different clinical presentations, diagnostic pathways, and therapeutic options, they share some phenotypic similarities [2].

CA results from the progressive deposition of amyloid fibrils in the extracellular space, leading to a progressive increase in ventricular wall thickness and chamber stiffness. Amyloidosis involves several cardiac components, leading to both mechanical alterations, such as restrictive cardiomyopathy and aortic stenosis, as well as electrical alterations, such as cardiac conduction system disease and arrhythmias [1, 4, 5].

It is important to note that extracardiac changes, including bilateral carpal tunnel syndrome and spontaneous rupture of the biceps, may precede CA by a few years (Fig. 5.1). It is essential to recognize these findings as part of the constellation of clinical findings in a patient with CA [1, 4, 6].

A. C. de Alencar Neto · C. R. F. Cafezeiro · B. V. K. Bueno · C. de Carvalho Singulane
F. Fernandes (✉)
Cardiomyopathy Unit, Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, São Paulo, Brazil
e-mail: fabio.fernandes@incor.usp.br

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_5

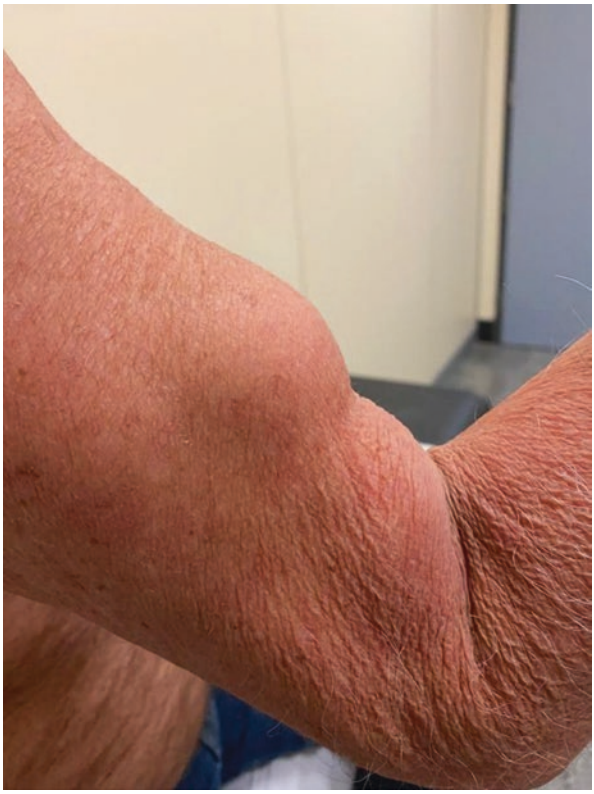


Fig. 5.1 Spontaneous biceps tendon rupture in a patient with ATTRW-CA. Authors' personal archive

5.2 Clinical Presentation

The natural history of CA includes progressive HF, complicated by arrhythmias and conduction system disease. Age, age of onset, phenotype, and clinical course vary with mutation type, fibril type (full length vs. fragments), and within families [2]. The most common clinical presentation of CA is HFpEF, although in late-stage cases, systolic dysfunction may occur. Dyspnea on exertion, which progresses relatively quickly, is the most common early manifestation. Due to the restrictive pattern of cardiomyopathy, right HF is also observed, resulting in lower extremity edema, jugular venous distention, hepatomegaly, and ascites (Figs. 5.2 and 5.3). In the face of advanced disease, signs and symptoms of low cardiac output are observed [1, 7].

On physical examination, jugular venous pressure frequently reveals an inspiratory rise (Kussmaul sign), which can also be present in patients with constrictive pericarditis. Unlike severe HF caused by most other etiologies, a third heart sound is uncommon in CA, as is a fourth heart sound. The Rivero-Carvallo maneuver is important to distinguish murmurs from right cameras, as valvular dysfunction due to amyloidosis is rarely severe, except for occasional tricuspid regurgitation.

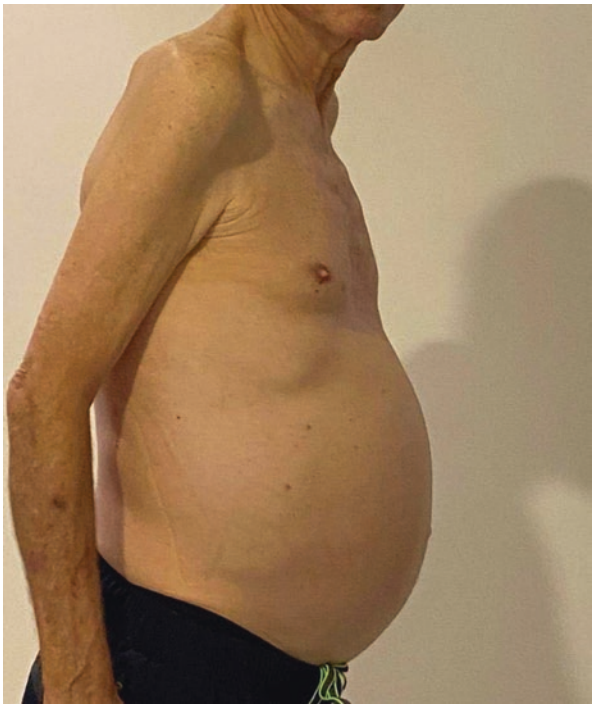


Fig. 5.2 Ascites in a patient with CA restrictive physiology. Authors' personal archive

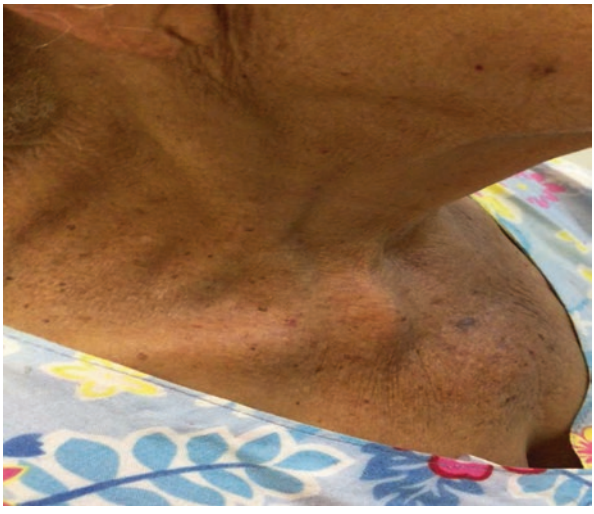


Fig. 5.3 Elevated jugular venous pressure in a patient with CA restrictive physiology. Authors' personal archive

Syncope or presyncope is frequently reported in CA due to orthostatic hypotension, dysautonomia, bradyarrhythmias, advanced atrioventricular blocks, and, less frequently, ventricular arrythmias. Recurrent syncope can be a diagnostic clue in CA, especially when there is no clear cause for the episodes [8]. Importantly,

patients with long-standing arterial hypertension are unable to tolerate their previous doses of antihypertensive medications. The need for a gradual drug reduction in these patients raises suspicion of CA (Table 5.1). In advanced disease, exertional syncope may occur, probably due to a low and fixed cardiac output. This is associated with a worse prognosis [7].

Sinus node dysfunction (SND) can manifest as sinus bradycardia, sinus pauses, or sinus arrest, presenting as dyspnea on exertion, asthenia, and syncope. Despite the high prevalence of conduction disease in CA and the predisposition for amyloid deposition in the atria, SND in CA appears to be less common. On the other hand, AV conduction disease is common in CA and is the main cause of indication for a cardiac pacemaker [9].

Amyloid fibrils are known to deposit in the left atrium, which may in part explain the intrinsic LA atriopathy. Abnormalities in left atrial size and function can also be explained by the decrease in LV compliance, leading to an increase in atrial pressure and restrictive cardiomyopathy patterns, creating an environment prone to the development of atrial arrhythmias.

Atrial fibrillation is the most common rhythm disturbance in CA, followed by premature atrial contractions and atrial tachycardia [10]. Palpitations can be the first manifestation and warrant further clinical investigation. Patients are at higher risk of thrombus formation, even in sinus rhythm; thus, early anticoagulation strategies aiming to reduce cardioembolic stroke, which is common in this population, are key. Importantly, concerns have been raised about the applicability of the CHADSVASC score in CA patients. Furthermore, such potential benefits of anticoagulation must be balanced against the potential risk of bleeding, which is also common in CA patients due to vascular fragility related to concomitant amyloid angiopathy [11].

Table 5.1 Cardiologic clues to amyloidosis

Cardiologic clues to amyloidosis
HFpEF, particularly in men >65 years of age
Intolerance to ACEi/ARB/ARNi and/or beta-blockers
Unexplained LV block with prior pacemaker implantation
Family history of cardiomyopathy
Infiltrative phenotype on echocardiogram (IVS ≥12 mm), biventricular hypertrophy, myocardial hyperefringence, valve thickening, thickening of the interatrial septum, biatrial enlargement
Concentric thickening of the LV walls with reduced or normal QRS amplitude in proportion to the increase in LV wall thickness
Low voltage complexes in ECG, pseudoinfarct pattern
Low flow/low gradient aortic stenosis in patients >60 years of age
Clinical presentation of late-onset hypertrophic cardiomyopathy in patients >60 years of age

Extracardiac symptoms provide important clinical clues in CA, as it is a heterogeneous disease that presents a different clinical spectrum depending on its subtype. In hereditary transthyretin (vATTR) amyloidosis, the Val142Ile variant causes cardiomyopathy in virtually all patients, with approximately 30% also experiencing both cardiac symptoms as well as mild peripheral neuropathy. Among those with the Val50Met variant, 43% have cardiomyopathy, and 95% have peripheral neuropathy [12].

Amyloid neuropathy is classically a symmetric, distal, ascending, and sensorimotor polyneuropathy. Neuropathy typically begins in the lower limbs, progresses to the upper limbs, and affects all functional classes of nerve fibers. The symptoms are characterized by numbness, paresthesia, and dysesthesia. There is a high incidence of carpal tunnel syndrome and autonomic neuropathy manifesting as orthostatic hypotension, hyperhidrosis, urinary incontinence, erectile dysfunction, alternating diarrhea and constipation, and orthostatic syncope [13].

Intestinal amyloidosis usually manifests as unexplained diarrhea, weight loss, malabsorption, or protein loss. Diarrhea is often prolonged and postprandial and may be accompanied by fecal incontinence or malnutrition. Amyloid deposition probably contributes to weight loss through increased metabolism due to increased inflammatory reactions and oxidative stress. Intestinal dysmotility manifests as constipation, abdominal pain, and progressive abdominal pain [14].

Hepatomegaly is a common exam finding and usually reflects hepatic congestion. An enlarged liver may also be due to direct amyloid infiltration in patients with AL amyloidosis. To differentiate the etiology of hepatomegaly, abdominal palpation including liver palpations is an important step. When hepatic infiltration occurs, the liver is hard, not pulsatile, massive, and irregular, which is quite distinct from the congested liver of HF [15].

AL amyloidosis patients, compared to ATTR patients with similar degrees of cardiac involvement, usually manifest more severe HF signs and symptoms. This presents a well-described paradox in that patients with ATTR are observed to have greater impairment in cardiac structure and function despite experiencing a more favorable prognosis compared to AL. One potential explanation is that direct light chain toxicity may accelerate cardiac disease progression in AL [7, 16]. Half of AL amyloidosis patients have renal involvement, 16% have liver disease, and 10% have neuropathy [17]. The signs in AL amyloidosis can be highly specific and include enlargement of the tongue and periorbital purpura. These do not occur in ATTR, but are only present in 15% of patients with AL and are not sensitive 19.

Nephrotic syndrome is a common manifestation of AL amyloidosis. Massive proteinuria with profound edema and hypoalbuminemia can occur with normal serum creatinine and blood–urea–nitrogen concentrations; however, evidence of mild renal dysfunction is frequently found [15].

References

1. Simões MV, Fernandes F, Marcondes-Braga FG, Scheinberg P, Correia EB, Rohde LEP, et al. Position statement on diagnosis and treatment of cardiac Amyloidosis—2021. Arq Bras Cardiol. 2021;117(3):561–98.
2. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 2019;73(22):2872–91.
3. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018;379(11):1007–16.
4. Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon B-G, Ikeda S-i, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8(1):1–18.
5. Tarasoutchi F, et al. Update of the Brazilian guidelines for valvular heart disease - 2020. Arq Bras Cardiol. 2020;115(4)
6. Mesquita ET, et al. Cardiac amyloidosis and its new clinical phenotype: heart failure with preserved ejection fraction. Arq Bras Cardiol. 2017;109(1)
7. Chamarthi B, et al. Features and prognosis of exertional syncope in light-chain associated AL cardiac amyloidosis. Am J Cardiol. 1997;80(9)
8. Marin-Acevedo JA, Sanchez-Alvarez C, Alsaad AA, Pagán RJ. Recurrent syncope, a clue in amyloid cardiomyopathy. Case Rep Med. 2018;2018
9. Donnellan E, et al. Prevalence, incidence, and impact on mortality of conduction system disease in transthyretin cardiac amyloidosis. Am J Cardiol. 2020:128.
10. Donnellan E, et al. Atrial fibrillation in transthyretin cardiac amyloidosis: predictors, prevalence, and efficacy of rhythm control strategies. JACC Clin Electrophysiol. 2020;6(9)
11. Nicol M, et al. Thromboembolism and bleeding in systemic amyloidosis: a review. ESC Heart Failure. 2022;9(1)
12. Connors LH, et al. Cardiac amyloidosis in African Americans: comparison of clinical and laboratory features of transthyretin V122I amyloidosis and immunoglobulin light chain amyloidosis. Am Heart J. 2009;158(4)
13. Suhr OB, et al. Myocardial hypertrophy and function are related to age at onset in familial amyloidotic polyneuropathy. Amyloid. 2006;13(3)
14. Dahiya DS, et al. Gastrointestinal amyloidosis: a focused review. World J Gastrointest Endosc. 2021;13(1)
15. Cuddy SAM, Falk RH. Amyloidosis as a systemic disease in context. Can J Cardiol. 2020;36(3)
16. Quarta CC, et al. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. Circulation. 2014;129(18)
17. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol. 1995;32(1)

Chapter 6
Syncope, Arrhythmia, and Cardiac Devices in Amyloidosis

Nágela Simão Vinhosa Nunes, Erivelton Alessandro do Nascimento, Katia Luz, and Wolney de Andrade Martins

6.1 Introduction

CA has been increasingly seen as a curable or halted disease due to the new therapeutic options that have emerged recently, which have changed the natural history of this catastrophic disease that englobes the heart. Current data demonstrate an incidence of CA of 18/100,000 people/year [1]. Advances in imaging methods have provided earlier noninvasive diagnosis, making the early initiation of treatment possible.

Traditionally, CA is a silent disease that progresses slowly as a consequence of amyloid fibril deposits that change the architecture of the heart, leading to diastolic impairment of the ventricles and atria followed by systolic function compromise and clinical signs of worsening HF and proper functioning of other organs related to the heart, such as the kidney and liver [2]. More than 30 types of amyloid proteins have been described, five of which can be deposited in cardiac tissue. They are (a)

N. Simão Vinhosa Nunes · W. de Andrade Martins
Hospital Universitário Antônio Pedro—Universidade Federal Fluminense, Niterói, Brazil

Complexo Hospitalar de Niterói—CHN, Niterói, Brazil
e-mail: nvinhosa@id.uff.br

E. A. do Nascimento (✉)
Hospital Universitário Antônio Pedro—Universidade Federal Fluminense, Niterói, Brazil

Complexo Hospitalar de Niterói—CHN, Niterói, Brazil

Instituto Estadual de Cardiologia Aloysio de Castro—IECAC, Rio de Janeiro, Brazil

Centro Universitário de Volta Redonda—UniFOA, Volta Redonda, Brazil
e-mail: erivelton_nascimento@id.uff.br

K. Luz
Complexo Hospitalar de Niterói—CHN, Niterói, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_6

immunoglobulin light chain proteins; (b) immunoglobulin heavy chain proteins; (c) transthyretin; (d) apolipoprotein 1, and (e) amyloid A [2]. Nonetheless, 95% of amyloid cardiac involvement is due to transthyretin (ATTR) in its hereditary (hATTR) or acquired form (wtATTR) and immunoglobulin light chain (AL) [3].

Heart failure with preserved ejection fraction (HFpEF) is the most frequent initial phenotype of CA, and whenever the diagnosis of HFpEF is made in the presence of red flags, CA should be considered [2, 4, 5]. They are as follows: presence of hypertrophy in echocardiogram without justifiable cause for that, electrocardiogram with low voltage QRS at frontal leads and absence of R growing at septal precordial leads (especially in the presence of hypertrophy), presence of peripheral sensitive and motor neuropathy, tunnel carpal syndrome, complaints related to lumbar spinal cord stenosis, tendinopathies leading to rupture and family history that englobe epidemiological and clinical findings compatible with the presence of a hereditary disease.

Syncope and arrythmias are common features in CA [6]. The kind of arrhythmia is influenced by the type of amyloid deposition, and the facilitating mechanism is multifactorial [7].

It is important to keep in mind that in transthyretin amyloidosis (ATTR), both the wild type (wtATTR) or hereditary one (hATTR), and in light chain amyloidosis (AL), syncope and rhythm disturbances may present as initial signs or symptoms and can also appear during the course of the disease. Therefore, these common features of this disease should be equally recognized as red flags, along with others, for the diagnosis of CA.

6.2 Syncope

6.2.1 Definition

Syncope is defined as transient loss of consciousness due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery. It is accompanied by loss of postural tone leading to falls and sometimes traumas, accompanied by amnesia about the event [8]. The symptoms immediately before syncope occurs are called prodromes and represent the beginning of the process of fainting when arterial pressure and consequently cerebral perfusion begin to drop. The duration of the prodrome is correlated with the nature of the event, as the shorter the prodrome is, the greater the chance of a sudden drop in arterial pressure, such as paroxysmal arrythmias, severe dysautonomia, abrupt loss of blood, traumatic cardiac tamponade, and massive pulmonary embolism.

6.2.2 Pathophysiology

The physiopathological mechanism of syncope is explained by global cerebral hypoperfusion, so for the occurrence of syncope, the arterial pressure should drop abruptly or progressively for some reason. There are three main

mechanisms that can result in syncope. They are (a) reflex, (b) orthostatic hypotension (OH), and (c) cardiac syncope. All these mechanisms are related to the impairment of two hemodynamic parameters: vascular peripheral resistance and/or cardiac output [9].

Reflex syncope, also known as vasovagal syncope, is the most common cause of syncope in all ages. The mechanism is related to vagal hyperstimulation leading to a sudden drop in heart rate and/or arterial pressure preceded by a trigger. The most common one is orthostatic stress, which evolves a lowering in venous return to the heart, which frequently occurs in hot places, when people persist a lot of time upstanding, that can be potentiated by hypovolemia or hypotensive drugs. In this specific situation, the lower blood volume that arrives in the heart provokes stimulation of mechanoreceptors of the ventricular wall through vigorous contraction of an "empty" heart that can trigger vagal response. There are other triggers, such as emotional (fear, pain, and phobia) and situational (micturition, gastrointestinal stimulation, such as swallow and defecation, cough, sneeze, after exertion, and less common ones, such as laughing and brass instrument playing). Prodromes are compatible with autonomic activation (pallor, sweating, and/or nausea), and this mechanism can also be present in patients affected by amyloidosis [8].

Syncope provoked by OH is common in Amyloidosis and seems to be multifactorial. The definition of OH is a drop of more than 20 mmHg in systolic arterial pressure (SAP) or more than 10 mmHg in diastolic arterial pressure (DAP) when patients adopt an orthostatic position compared with supine arterial pressure measures. When there is supine hypertension (>150/90 mmHg), the drop should be more than 30 mmHg in SAP and 15 mmHg in DAP. If the patient cannot adopt an orthostatic position, the diagnosis of OH is made if there is a drop of more than 15 mmHg in SAP or 7 mmHg in DAP in the sitting position [10].

Classically, OH can be caused by exacerbated venous pooling and can be provoked by prolonged bed rest and deconditioning, after exertion and carbohydrate-rich meals. Other important causes are polypharmacy, volume depletion, primary autonomic failure (that occurs in pure autonomic failure, multiple system atrophy, Parkinson's disease, and dementia with Lewy bodies) and secondary autonomic failure (resulting in diseases, such as diabetes, amyloidosis, spinal cord injuries, autoimmune autonomic neuropathy, paraneoplastic autonomic neuropathy, and kidney failure). The classical prodromes are dizziness, light-headedness, fatigue, weakness, visual and hearing disturbances, low back pain, neck and shoulder pain ("coat-hanger pain"), or precordial pain. According to the time of occurrence, HO is subdivided into a) initial OH, when it occurs within 15 s of orthostatism with a drop of 40 mmHg in SAP or 20 mmHg in DAP. It seems to be secondary to a transient mismatch between cardiac output and total peripheral resistance; b) classical OH, when it occurs between 15 s and 3 min of orthostatism due to impaired increase

in total peripheral resistance and HR in autonomic failure, resulting in pooling of blood, but can also be secondary to severe volume depletion; and c) delayed OH, when it occurs after 3 min of orthostatism, where the progressive fall in venous return and low cardiac output seems to be best explanation for it, and almost always it is caused by autonomic neuropathies, being classified as neurogenic OH (nOH) [9–12]. The changes in heart rate upon standing help to determine whether OH is neurogenic in origin. In patients with nOH, reduced sympathetic innervation causes the heart rate to increase much less than expected considering the magnitude of the BP decrease. Therefore, a blunted heart rate increase during hypotension suggests a neurogenic cause. A ratio between the increase in heart rate and fall in systolic BP upon standing or head-up tilt (ΔHR/ΔSBP ratio) <0.5 bpm/mmHg is higly suggestive of nOH. Conversely, a ΔHR/ΔSBP ratio ≥0.5 rule out a nonneurogenic cause [13]. Sometimes, it is necessary to perform a tilt table test to diagnose nOH, since the fall in blood pressure can occur several minutes after orthostatism, mainly in early disease. Other noninvasive autonomic tests, such as the heart rate variability, Valsalva test, respiratory test, and quotient 30:15 with orthostasis, may be equally useful in the evaluation of patients with dysautonomia [14].

Cardiac syncope encompasses all syncope events that can be caused by heart malfunctioning, either by pump deficit or by rhythm disorders resulting from conduction system disease or arrhythmogenic substrates present in heart muscle. Frequently, the prodromes are short or nonexistent and may be preceded by palpitations (when syncope is caused by tachyarrhythmias). Patients with cardiac syncope have been reported to have an increased risk for death from any cause, nonfatal myocardial infarction or death from coronary heart disease, and fatal or nonfatal stroke compared with controls. Several prognostic markers have been identified, and some risk calculators were developed to stratify this sudden death risk in patients with syncope, such as the OESIL Score, San Francisco Score, EGYS Score and Rose Score, among others [15–18].

The basic tools for thinking about cardiac syncope are based on two initial exams: electrocardiogram (ECG) and echocardiogram (ECHO). They are easy to perform in all medical centers and are essential in the stratification of sudden death risk in a patient with syncope. Therefore, the initial red flags for cardiac syncope are abnormal ECG and/or ECHO.

In amyloidosis, as in other scenarios, all these mechanisms are possible and not infrequently more than one of that contribute to the manifestation of syncope, but cardiac syncope should always be considered.

6.2.3 Syncope in Amyloidosis

CA initially presents as HFpEF with reduced left ventricular end diastolic volume and impaired diastolic functioning, resulting in diminished stroke volume and cardiac output. Dilatation of both atria develops as a consequence of raised left ventricular filling pressures due to interstitial amyloid deposition, which causes

restrictive cardiomyopathy. Because of this, arrythmias are common in CA, and the most common one is atrial fibrillation (AF), although complex ventricular arrhythmias are also seen. First degree, second degree, or advanced heart block has also been described, as well as sudden cardiac death. All these rhythm disturbances can cause syncope, as they can contribute to an additional decrease in cardiac output [2].

In AL, infiltration of cardiac structures, which is a consequence of plasma cell dyscrasia, can damage the tissues in two ways: first, AL deposits in the extracellular space of the myocardium and coronary blood vessels, which results in cardiomyocyte necrosis and interstitial fibrosis (as is the case in other varieties of amyloidosis). Second, it is thought that oxidative stress due to circulating light chain toxicity is directly myotoxic, which is unique to AL. In addition to diastolic dysfunction, AL can also manifest as a rhythm disturbance due to amyloid deposits in the conduction system [with sinoatrial fibrosis or atrioventricular (AV) fibrosis] [19].

ATTR is a condition in which transthyretin, a physiological protein primarily synthesized by the liver, misfolds into insoluble B-pleated sheets and deposits as amyloid in the extracellular space of the myocardium. Transthyretin (TTR) is always present in serum, and its physiological role is the transportation of retinol and thyroxine. The inherent propensity of TTR to fold and aggregate to form insoluble amyloid fibers can be increased by a single point mutation, as is the case in hereditary hATTR. The wtATTR is similar to hATTR, except that it is nonhereditary (sporadic) and the precursor protein is structurally normal TTR. It is known as "senile systemic amyloidosis" and almost exclusively affects men over the age of 60 years [20].

The hATTR's phenotype varies according to the causative genetic mutation. For example, those with the Val30Met transthyretin mutation commonly have conduction issues requiring pacemaker placement, while other variants, such as Val122Ile and Thr60Ala, commonly affect the cardiovascular system, but less frequently primarily affect the conduction system. Importantly, those with wtATTR are more likely to have rhythm disturbances (typically AF) than those with hATTR. A useful flag for suspecting ATTR is hypertension that resolves over time and an intolerance of angiotensin receptor blockers, angiotensin converting enzyme inhibitors or beta-blockers, which not infrequently leads to presyncope, syncope, and worsening fatigue on exertion [20–22].

The phenotype of hATTR tends to be either cardiac-predominant or neuropathy-predominant. This is determined by the site of an amino acid substitution on the TTR gene. The typical pattern of hATTR amyloid neuropathy is an ascending symmetrical length-dependent sensorimotor axonal polyneuropathy. Interestingly, those with the Val122Ile mutation have more severe neurological symptoms and walking disability than those with wtATTR. As in AL, hATTR is also associated with autonomic neuropathy, which primarily presents with gastrointestinal symptoms. Furthermore, carpal tunnel syndrome, tendon rupture, and lumbar spinal stenosis are all associated with hATTR and are red flags for the diagnosis. Occasionally, patients have ophthalmological involvement in the form of vitreous deposition. Unlike in AL amyloidosis, macroglossia does not commonly occur in hATTR, and renal involvement is less common. In wtATTR, the heart is usually the only

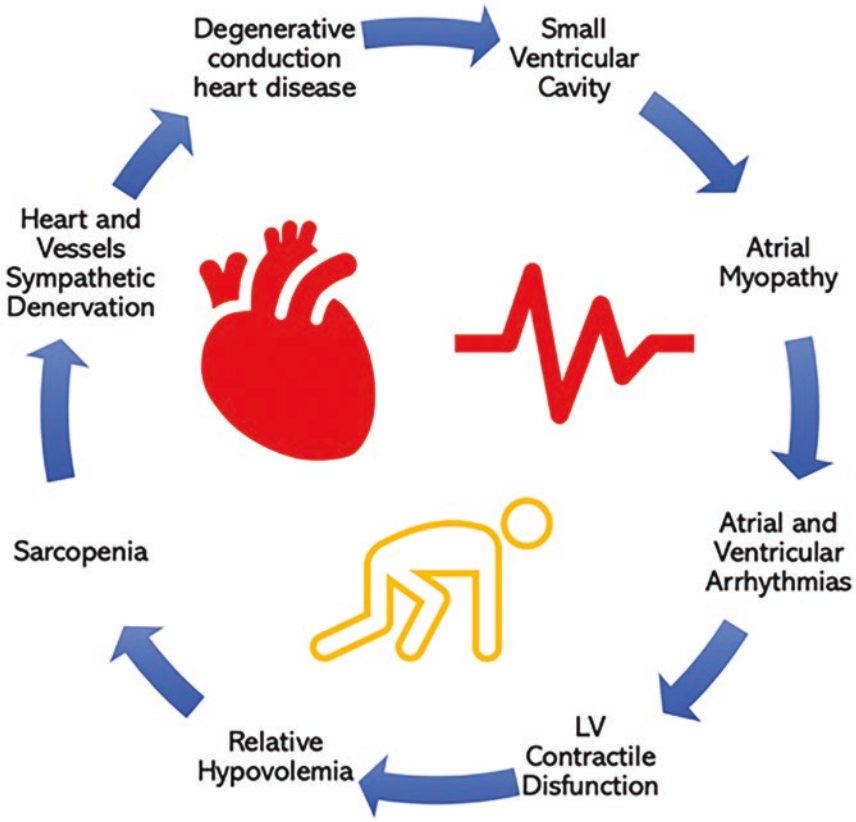


Fig. 6.1 The multifactorial cause of syncope in CA. *LV* left ventricle

clinically affected organ, but signs of HF may be preceded by lumbar spinal stenosis or bilateral carpal tunnel syndrome by 10–15 years [23].

Literature data show that syncope is an uncommon finding in ATTR (8%) and more frequent AL (20%) [24], and when it occurs during exertion, it represents the inability to increase cardiac output, which leads to high mortality. In addition, sensitivity to intravascular fluid depletion combined with autonomic neuropathy, depressed myocardial reserve, atrial dysfunction and rigidity, and the presence of arrhythmias contribute to the occurrence of syncope (Fig. 6.1). All these possibilities make syncope a multifactorial presentation in CA [25].

nOH (Fig. 6.2) is a prominent and disabling manifestation of autonomic dysfunction in patients with hTTR affecting an estimated 40–60% of patients and reducing their quality of life. As mentioned above, OH in patients with hTTR can be a consequence of HF due to amyloid cardiomyopathy or volume depletion due to diarrhea or drug effects, but when none of these circumstances are apparent, OH is usually neurogenic, i.e., caused by impaired norepinephrine release from

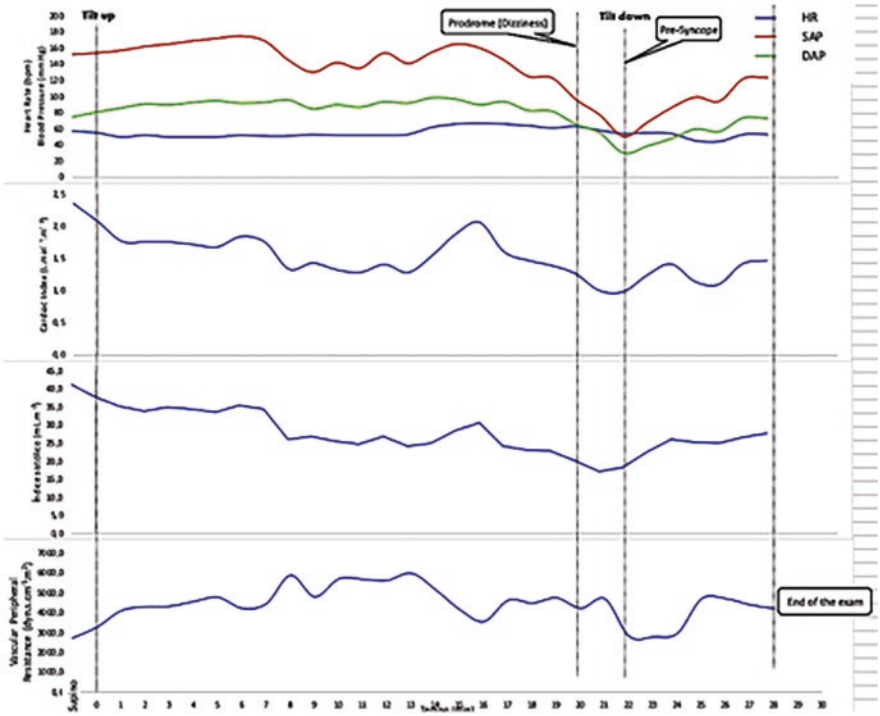


Fig. 6.2 Example of delayed orthostatic hypotension (nOH) in tilt-table-test. *HR* heart rate; *SAP* systolic arterial pressure; *DAP* diastolic arterial pressure. Authors' personal archive

sympathetic postganglionic neurons because of neuronal amyloid fibril deposition. It is frequent, early, and severe in patients with the early onset Val30Met mutation disease, but appears to be less severe in Val30Met cases with late-onset disease [26, 27]. OH is also prevalent and severe in patients with some non-Val30Met mutations. For instance, up to 100% of patients with the Ala97Ser mutation have OH, with 71% having frequent syncope, particularly in late stages of the disease. Conversely, OH appears to be infrequent in patients with TTR mutations with high prevalence in Scandinavian countries (e.g., Ala45Ser, Tyr69His, and Leu111Met) and in patients with the Val122Ile mutation, the most common TTR mutation in African Americans [28–30]. In a recent study involving >3000 subjects enrolled in the multinational, longitudinal, observational Transthyretin Amyloidosis Outcomes Survey, 58.7% had symptomatic OH. Moreover, the severity of the decrease in BP when standing appeared to worsen at annual follow-ups, reflecting the progressive nature of autonomic failure. More pronounced orthostatic BP reductions were associated with increasing age, worse polyneuropathy disability stage, and diarrhea.

Autopsy studies in patients with hTTR and severe OH showed amyloid-related degeneration of the peripheral autonomic nervous system, namely, anterior and posterior roots of the spinal cord, sympathetic ganglia, postganglionic sympathetic

nerves, and the vagus nerve. Neuronal density in the intermediolateral column of the spinal cord was reduced, and there was degeneration of sympathetic postganglionic cholinergic fibers. The plasma levels of norepinephrine, the main sympathetic neurotransmitter, are severely reduced and fail to increase when standing in patients with hTTR. Moreover, administration of norepinephrine elicits noteworthy increases in heart rate and blood pressure, indicating sympathetic denervation supersenstivity. The mechanisms of nOH in hTTR are similar to those of peripheral neurodegenerative synucleinopathies, i.e., Parkinson disease, dementia with Lewy bodies, and pure autonomic failure, in which dysfunction of the sympathetic nerves is mediated by accumulation of another misfolded protein, α-synuclein, highlighting the high affinity that both misfolded transthyretin and α-synuclein have for the autonomic nervous system. Furthermore, studies with 123I-metaiodobenzyiguanidine cardiac neuroimaging showed reduced cardiac sympathetic innervation, which can be present before any abnormal echocardiographic sign. Moreover, cardiac sympathetic denervation predicts worse prognosis [13].

6.2.4 Treatment

Treatment of syncope in CA, as in all other scenarios, involves, at first, the recognition of red flags of the disease, the diagnosis of certainly that the event was indeed syncope, the stratification of risk of death, ruling out rhythm disturbances and paying attention to the prescription so as not to add harm.

Drugs that reduce intravascular volume (diuretics), induce vasodilatation (sildenafil, nitrates) or block norepinephrine release/activity at the neurovascular junction (α-blockers, centrally acting α2-agonists, tricyclic antidepressants) worsen nOH and symptoms. Anemia can worsen nOH and should be investigated and treated. Correction of anemia with erythropoietin (25–50 units/kg, subcutaneous, three times a week) and iron supplements may be beneficial in patients with nOH, and it is crucial to make sure that there is no blood loss as a cause of hypovolemia [13]. Furthermore, anemia is a major high-risk feature in patients with syncope at initial evaluation in the emergency department when there is a suggestion of gastrointestinal bleeding [8].

Many drugs that are commonly prescribed to treat HF have been proven to be unhelpful in amyloidosis-induced HF. Angiotensin-converting-enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), and beta blockers all decrease mortality in most patients with HF; however, in patients with amyloidosis-induced HF, these drugs are detrimental. ACE inhibitors and ARBs promote hypotension due to autonomic dysfunction and can only be tolerated in low doses in patients with a predominant cardiac phenotype. Similarly, beta blockers have been shown to provoke bradyarrhythmias in these patients. Calcium channel blockers (CCBs) are ineffective due to strong binding of the drug to amyloid fibrils, leading to worsening HF, hypotension, and syncope. Strong binding to amyloid fibrils can also occur with the use of digoxin, leading to digitalis toxicity, which includes yellow-tinted vision, cholinergic agonism, and arrhythmias [2].

When OH is the cause of syncope, it is important that patients should be aware of the diuretic effects of alcohol and avoid sugary beverages (e.g., bottled juices and sodas) because of the hypotensive effects of high-glycemic index carbohydrates. Fluid intake should be 2–2.5 L/day. Patients should be encouraged to increase salt intake by adding 1–2 teaspoons of salt to a healthy diet. In patients with nOH, drinking 0.5 L of water produces a marked increase in BP, and this can be used as a rescue measure, since the pressor effect is quick (peaks in approximately 30 min), although short-lived [13]. Cardiomyopathy and HF are present in many patients, complicating the management of nOH, as treatment of HF typically involves reducing the cardiac preload with diuretics causing intravascular volume depletion, which worsens nOH. Similarly, diarrhea, a manifestation of gastrointestinal involvement in hTTR, causes volume depletion, which aggravates nOH. The challenge is to avoid both hypovolemia and hypervolemia in patients with mixed phenotypes of cardiomyopathy and neuropathy [11].

Daytime hypertensive episodes are of somewhat lesser importance, whereas sleep-time hypertension should be treated if BP is consistently higher than 160/90 mmHg in uncomplicated cases (i.e., symptomatic OH without concomitant target-organ damage) and preferably lower than 140/90 mmHg in patients with a history of cerebrocardiovascular disease, diabetes, or renal failure. A reverse dipping pattern in combination with OH is particularly detrimental and indicates a more than doubled risk of incident cardiovascular disease. Consequently, both the absolute reduction of nighttime BP and restoration of normal sleep-time dipping are crucial (preferentially with drugs of short action, such as losartan, captopril, and hydralazine) and can be easily monitored using repeated 24-h ambulatory BP monitoring and patient diaries [8]. However, in the most severe cases, discontinuation of antihypertensive treatment may be the only solution if the patient remains symptomatic despite treatment modification. Other educational methods are avoidance of immobilization, prolonged diurnal recumbence and physical deconditioning, gradual rising from supine and sitting positions, especially in the morning, after meals, and after urination/defecation, small and frequent meals, physical countermaneuvers (e.g., leg crossing, muscle tensing, and squatting) during standing and prodromal symptoms and head elevation 10°–30° during sleep [11].

Pharmacological treatment begins with drugs that avoid amyloid deposition acting as TTR stabilizers (diflunizal and tafamidis) and RNA interference agents (patisiran and inotersen) in ATTR (both hereditary and wild type) [31–33]. The AL type is preferentially treated with stem cell transplants, chemotherapy, and proteasome inhibitors. The goal of treatment for AL is to reduce the production of light chains, remove light chain amyloid deposits, and inhibit amyloid fibril formation. The current standard of care for AL patients is chemotherapy using cyclophosphamide, bortezomib, and dexamethasone (CyBorD). In a phase 3 ANDROMEDA study [34], daratumumab (DARA-SC), a drug used in the treatment of multiple myeloma, was studied in conjunction with CyBorD. This demonstrated robust hematologic and organ responses. In patients with cardiac involvement of amyloidosis, the median time to response was 114 days.

Even after nonpharmacologic methods have been properly implemented, many patients still require pharmacologic treatment to improve symptomatic nOH. Two

complementary strategies are commonly used: (1) expanding intravascular volume with fludrocortisone and (2) increasing peripheral vascular resistance with midodrine or droxidopa. Selection of one or the other or both depends on the specific features and needs of each patient as well as the degree of peripheral sympathetic denervation and degree of heart disease [13].

As in OH, treatment of reflex syncope evolves to avoid triggers, treat hypovolemia, stop polypharmacy, augment salt and water ingestion, and, sometimes, pharmacologic treatment with the same drugs mentioned above, i.e., midodrine and droxidopa (in the low blood pressure phenotype) if the nonpharmacological approach fails. Regarding the type of vagal response, if it has dominant cardioinhibition, cardiac pacing should be recommended predominantly in older patients, the specific population who is committed by CA. In the same group, if the prodomes are short or nonexistent, and the syncope causes remain unexplained, loop recorder implantation is recommended, as arrhythmias are the most likely occurrence [8].

Cardiac syncope in CA caused by rhythm disturbance will need a specific approach for each specific finding, as will be addressed next.

6.3 Arrhythmias

6.3.1 Pathophysiological Mechanisms of Cardiac Arrhythmias in CA

The mechanism involved in the genesis of cardiac arrhythmias in amyloidosis is not unique but multifactorial. The pathophysiology of CA with deposition of fibrillar proteins in the myocardial extracellular environment leads to increased filling pressures of cardiac cavities, which will culminate in electromechanical remodeling as a final pathway [7]. Amyloid deposits in the perivascular site, especially in the AL form, lead to microvascular dysfunction, and these inflammatory microregional changes can act as an arrhythmogenic substrate or even determine direct aggression with an increase in intracellular reactive oxygen species [35, 36]. The characteristic of infiltrative cardiomyopathy, associated with secondary inflammatory damage, or even the occupation of the extracellular space by polarized proteins, can directly damage the conduction system, leading to the emergence of conduction disorders, such as intraventricular conduction delay, AV node conduction disorders, or even sinus dysfunction [7].

6.3.2 Heart Conduction System Diseases

Cardiac involvement in amyloidosis can lead to conduction disturbances, with electrocardiographic manifestations (Fig. 6.3). These manifestations range from changes in QRS duration, intraventricular bundle branch blocks, fascicular blocks, or even

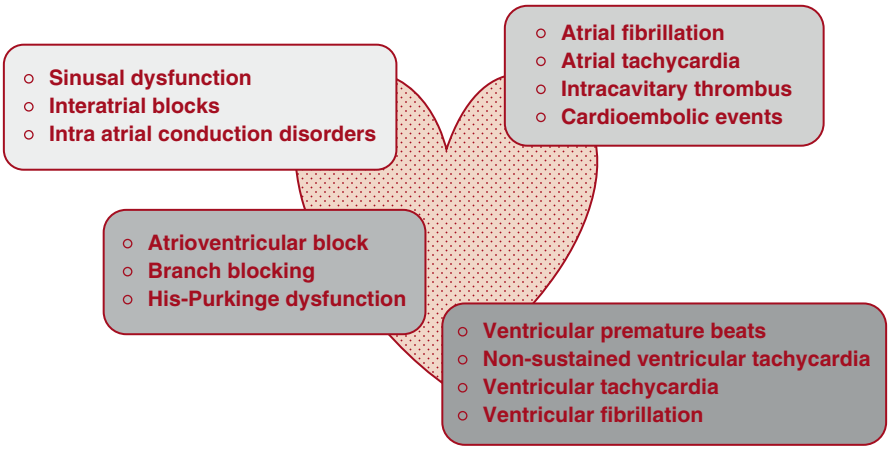


Fig. 6.3 Different disturbances of cardiac rhythm and conduction caused by amyloid deposits

AV blocks. At the atrial level, we can find sinus node dysfunction. However, the main form of conduction system involvement is His-Purkinje system dysfunction, manifested by the prolongation of the HV interval in the invasive electrophysiological study, an interval that extends from the beginning of the bundle of His potential to the beginning of intracavitary ventricular activation [37]. Spontaneous episodes of sinus dysfunction or even during an anesthetic act mediated by autonomic changes have been described [38]. These findings demonstrate the predilection for amyloid infiltration in the basal portion of the septum, leading to impairment of the His-Purkinje system [39].

The incidence of AV block is higher in the ATTR subtype, probably owing to the longer survival of these patients, which culminates in the progression of nodal dysfunction [7].

Small cohorts of patients with the AL type with advanced heart disease and routine looper recorder implantation showed that all deaths were preceded by bradycardia (mostly by total AV block) [6, 40].

Eoin et al. found a high prevalence of high-grade AV block requiring definitive pacemaker implantation in a cohort of 369 patients with ATTR. Approximately 9.5% had a diagnosis of ATTR at the time of definitive pacemaker indication, and at 28-month follow-up, 10% of patients with hATTR and 12% of patients with wtATTR had high-grade AV block with indication of pacemaker. The most evident conduction abnormalities on baseline ECG were increased QRS duration (present in 51% of wtATTR patients and 48% of hATTR patients), followed by first-degree AV block (present in 39% of wtATTR patients and 43% of patients with hATTR), but only increased QRS duration was associated with the development of subsequent high-grade AV block in this study [41].

Another remarkable finding in CA is the possibility of an HV interval prolongation with normal QRS duration (<120 ms) (Fig. 6.4), which is probably due to diffuse infiltration involving both left and right branches, leading to a balanced delay in intraventricular conduction, with a disproportionately narrow QRS [37].

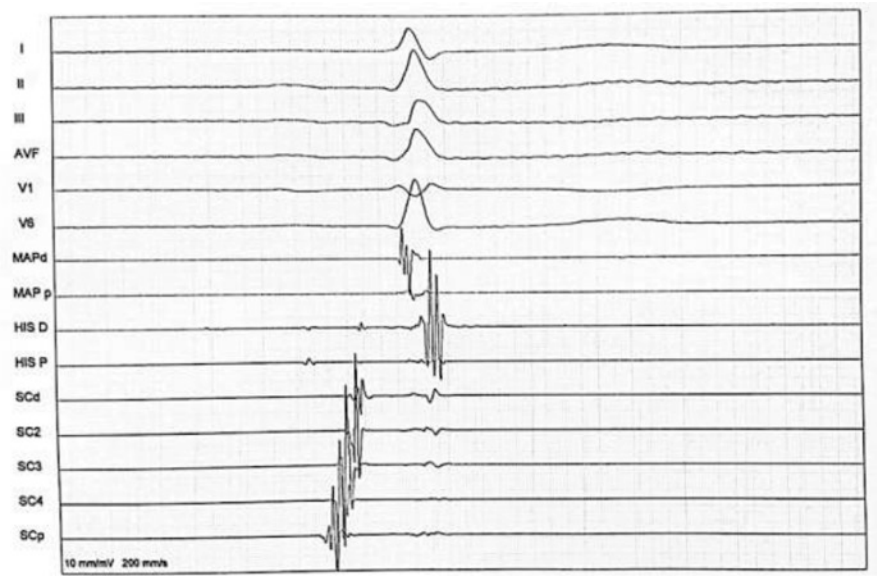


Fig. 6.4 His bundle potential during ablation procedure in patients with amyloidosis, normal QRS duration and His dysfunction - HV: 88 ms, AH: 83 ms. Authors' personal archive

6.3.3 Atrial Arrhytmias

The infiltrative deposit leading to restrictive cardiomyopathy also leads to increased intracavitary filling pressures and evolutionarily to the emergence of atrial and mechanical remodeling, both atrial and ventricular. In this context, the manifestation of atrial arrhythmias is not infrequent. AF represents the most frequent arrhythmia in CA [42].

Patients with the wtATTR form have a higher incidence of atrial arrhythmias, mainly atrial fibrillation, probably owing to the age at presentation, which already carries a higher incidence of AF [7]. Previous data show an incidence of approximately 62% AF in the ATTR form [43].

The emergence of both atrial tachycardia and AF leads to significant clinical intolerability, both due to the irregularity of the rhythm and the absence of effective atrial contractility, compromising ventricular filling. Patients with CA at the time of diagnosis usually present significant atrial remodeling, which, associated with the presence of AF, should be fully anticoagulated independent of the CHA2DS2-Vasc score. Despite the advances in radiofrequency ablation techniques, the rate of recurrence of AF after ablation is high, reaching 83%, while in patients with AF without CA, it reaches 23% [7].

Isolated atrial amyloidosis is frequently seen in elderly patients, and it is more prevalent in women and can be found in more than one-third of patients with persistent AF undergoing valve surgery, not being considered an atrial arrhythmia in the generalized form of CA [7].

Regarding the use of antiarrhythmic drugs, amiodarone represents a good option for rhythm control, and the use of beta-blockers, CCBs and digitalis should be done with caution, carefully evaluating the QT interval [7, 44].

6.3.4 *Ventricular Arrhythmias*

Advanced stages of heart failure are the main cause of death in patients with CA, and the emergence of ventricular arrhythmias is part of this scenario. AL has a higher incidence of ventricular arrhythmias than the ATTR type [7].

Electrophysiological data from patients with CA show an intraventricular conduction delay, a smaller and fractional epicardial potential, as well as a longer repolarization and more dispersed [45]. This favors the emergence of ventricular arrhythmias. Ventricular arrhythmias in CA are common. The presence of ventricular ectopic beats, nonsustained and sustained ventricular tachycardia, has been related to sudden cardiac death events [46]. A study that evaluated arrythmias with holter monitoring showed 72% of ventricular ectopic beats and 18% of nonsustained ventricular tachycardia in patients with AL-type amyloidosis [47]. Monomorphic ventricular tachycardia can be induced during an electrophysiological study or even documented in an implanted cardioverter–defibrillator, but it is infrequent in CA when compared with other cardiomyopathies [48].

In a previous study, Varr et al. (2014) suggested that the presence of nonsustained ventricular tachycardia in patients with CA should be considered a risk factor in decision making for cardioverter–defibrillator implantation [49].

Ventricular fibrillation can be caused by premature ventricular beats originating in the His-Purkinje system, especially in patients with ischemic cardiomyopathy; however, the cause of ventricular fibrillation in patients with CA is not well-understood [39].

6.3.5 *Sudden Cardiac Death and Cardioverter Defibrillator in CA*

Several studies have shown that half of patients with CA die suddenly; however, the implantation of a cardioverter defibrillator, both in primary and secondary prevention, is not a consensus [46]. The main factors that corroborate this scenario are the poor prognosis of these diseases, as they usually have low survival after diagnosis, and the need for high defibrillation thresholds in patients with CA. In addition, previously published data show that the main cause of sudden death in this population is related to electromechanical dissociation, culminating in pulseless electrical activity, and not due to malignant ventricular arrhythmias [50].

Implantation of a cardioverter defibrillator in CA is even more controversial, considering the stage of HF, as it is necessary 1-year survival to be eligible, and the presence of noncardiac factors that may influence short-term mortality.

Most studies evaluating cardioverter–defibrillator implantation have a small number of participants; in a series that evaluated 19 patients who had implanted an ICD, 11% received appropriate device therapy [51]. Another study found 28% of appropriate device therapy in 1 year [52].

6.3.6 Definitive Pacemaker in CA

Conduction disorders are markedly present in CA. Markedly, the infiltration of fibrillar proteins in the basal septal region influences the dysfunction of the His-Purkinje system, which may lead to the need for permanent pacemaker implantation.

Permanent pacemaker implantation is commonly required in patients with CA and severe conduction system disorders, especially in wtATTR patients [53].

Right ventricular (RV) cardiac pacing is a globally established technique capable of correcting bradyarrhythmia; however, RV pacing can lead to electrical dyssynchrony and, consequently, to mechanical dyssynchrony, with the possibility of worsening HF symptoms [54].

Regarding the best mode of cardiac pacing, the literature is still scarce about the indication of cardiac resynchronization therapy (CRT) preferential to single RV pacing in these patients, since the population of HF patients, where CRT is more effective, are those with left bundle branch block (LBBB) morphology, aiming to reduce symptoms and left ventricular size and increase left ventricular ejection fraction (LVEF). In contrast, patients with CA have a small LV cavity, ECG with various manifestations of non-LBBB conduction disturbances, and often develop AF, which makes these patients less eligible for CRT [6]. On the other hand, some case reports have demonstrated clinical and echocardiographic improvement in patients with advanced CA and HF. In a recent retrospective study with 78 patients with ATTR, CRT led to improvement in LVEF and functional class, reduction of mitral regurgitation, and stabilization of NT-ProBNP levels compared with those with exclusive RV pacing >40% [55]. Taking this into account, PM implantation in patients with ATTR can precipitate worsening of ventricular function with RV exclusive pacing >40%, since due to the high incidence of first-degree AV block and high-grade AV block in this population, it is not always possible to avoid a high percentage of RV pacing [41]. In addition, observational studies have shown that mechanical and electrical resynchronization seems to be more effective with His or left bundle branch stimulation (deep transseptal) [56], which may also be one of the options of choice soon. While randomized studies to answer these questions have not been published, the decision regarding the type of stimulation of patients with CA should be made after a multidisciplinary discussion, weighing the severity of symptoms and the risks combined with the expected benefit.

Thus, the type of ventricular stimulation should be discussed by a Heart Team, where His pacing in these patients can provide a more physiological stimulation [54, 57].

Application of multimodality imaging to identify areas of amyloid infiltration can optimize left ventricular pacing.

References

1. Gilstrap LG, Dominici F, Wang Y, El-Sady MS, Singh A, Di Carli MF, et al. Epidemiology of cardiac amyloidosis–associated heart failure hospitalizations among fee-for-service medicare beneficiaries in the United States. Circ Hear Fail. 2019;12(6):1–9.
2. Ash S, Shorer E, Ramgobin D, et al. Cardiac amyloidosis—a review of current literature for the practicing physician. Clin Cardiol. 2021;44(3):322.
3. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases Heart failure and cardiomyopathies. Eur Heart J. 2021;17:1554–68.
4. Mohammed SF, Mirzoyev A, Edwards WD, et al. Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. JACC Hear Fail. 2014;2(2):113–22.
5. van den Berg MP, Mulder BA, Klaassen SHC, et al. Heart failure with preserved ejection fraction, atrial fibrillation, and the role of senile amyloidosis. Eur Heart J. 2019;40:1287–93.
6. Cheung CC, Roston TM, Andrade JG, Bennett MT, Davis MK. Arrhythmias in cardiac amyloidosis: challenges in risk stratification and treatment. Can J Cardiol. 2020;36:416–23.
7. John R. Arrhythmias in cardiac amyloidosis. J Innov Card Rhythm Manag. 2018;9(3):3051–7.
8. Brignole M, Moya A, De Lange FJ, et al. 2018 ESC guidelines for the diagnosis and management of syncope. Eur Heart J. 2018;39(21):1883–948.
9. Society E, Eusem M, De LFJ, et al. 2018 ESC guidelines for the diagnosis and management of syncope. Rev Esp Cardiol (Engl Ed). 2018;71(10):837.
10. Brignole M, Moya A, De Lange FJ, et al. Practical instructions for the 2018 ESC guidelines for the diagnosis and management of syncope. Eur Heart J. 2018;39(21):e43–80.
11. Ricci F, De Caterina R, Fedorowski A. Orthostatic hypotension. J Am Coll Cardiol. 2015;66(7):848–60.
12. Ricci F, De Caterina R, Fedorowski A. Orthostatic hypotension: epidemiology, prognosis, and treatment. J Am Coll Cardiol. 2015;66(7):848–60.
13. Palma JA, Gonzalez-Duarte A, Kaufmann H. Orthostatic hypotension in hereditary transthyretin amyloidosis: epidemiology, diagnosis and management. Clin Auton Res. 2019;29(s1):33–44.
14. Rocha EA, Metha N, Távora-Mehta MZP, et al. Dysautonomia: a forgotten condition—part II. Soc Bras Cardiol. 2021;116(5):981–98.
15. Colivicchi F, Ammirati F, Melina D, Guido V, Imperoli G, Santini M. Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: the OESIL risk score. Eur Heart J. 2003;24(9):811–9.
16. Quinn J, McDermott D, Stiell I, Kohn M, Wells G. Prospective validation of the San Francisco syncope rule to predict patients with serious outcomes. Ann Emerg Med. 2006;47(5):448–54.
17. Del Rosso A, Ungar A, Maggi R, et al. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to a general hospital: the EGSYS score. Heart. 2008;94(12):1620–6.
18. Reed MJ, Newby DE, Coull AJ, Prescott RJ, Jacques KG, Gray AJ. The ROSE (risk stratification of syncope in the emergency department) study. J Am Coll Cardiol. 2010;55(8):713–21.
19. Grogan M, Dispenzieri A, Gertz MA. Light-chain cardiac amyloidosis: strategies to promote early diagnosis and cardiac response. Heart. 2017;103(14):1065–72.
20. Mankad AK, Shah KB. Transthyretin cardiac amyloidosis. US: Springer; 2017.

21. Castaño A, Drachman BM, Judge D, Maurer MS. Natural history and therapy of TTR-cardiac amyloidosis: emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs HHS public access. Heart Fail Rev. 2015;20(2):163–78.
22. Damy T, Costes B, Hagège AA, et al. Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. Eur Heart J. 2016;37(23):1826–34.
23. Nativi-nicolau J, Maurer MS. Amyloidosis cardiomyopathy: update in the diagnosis and treatment of the most common types. Curr Opin Cardiol. 2018;33(5):571–9.
24. Maurer MS, Hanna M, Grogan M, et al. Genotype and phenotype of transthyretin cardiac amyloidosis in the United States: the transthyretin amyloid outcome survey (THAOS). J Am Coll Cardiol. 2016;68(2):161–72.
25. Nunes NS, Paulo J, Carvalho M, et al. Syncope as a phenotypic expression of hereditary transthyretin amyloidosis Val142Ile (Val122Ile). Arq Bras Cardiol. 2020;114(4 suppl 1):1–3.
26. Vinicius Pinto M, Felipe Pinto L, Dias M, et al. Late-onset hereditary ATTR V30 M amyloidosis with polyneuropathy: characterization of Brazilian subjects from the THAOS registry. J Neurol Sci. 2019;403:1–6.
27. Gonzalez-Duarte A, Valdés-Ferrer SI, Cantú-Brito C. Characteristics and natural history of autonomic involvement in hereditary ATTR amyloidosis: a systematic review. Clin Auton Res. 2019;29(s1):1–9.
28. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. Genet Med. 2017;19(7):733–42.
29. Dungu JN, Papadopoulou SA, Wykes K, et al. Afro-Caribbean heart failure in the United Kingdom. Circ Hear Fail. 2016;9(9):1–10.
30. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 2019;73(22):2872–91.
31. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018;379(11):1007–16.
32. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2018;379(1):11–21.
33. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med. 2018;379(1):22–31.
34. Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. N Engl J Med. 2021;385(1):46–58.
35. Brenner DA, Jain M, Pimentel DR, et al. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. Circ Res. 2004;94(8):1008–10.
36. Dorbala S, Vangala D, Bruyere J, Quarta C, Kruger J, Padera R, et al. Coronary microvascular dysfunction is related to abnormalities in myocardial structure and function in cardiac amyloidosis. JACC Hear Fail. 2014;2(4):358–67.
37. Reisinger J, Dubrey SW, Lavalley M, Skinner MFR. Electrophysiologic abnormalities in AL (primary) amyloidosis with cardiac involvement. J Am Coll Cardiol. 1997;30(4):1046–51.
38. Chastan N, Baert-Desurmont S, Saugier-Veber P, Dérumeaux G, Cabot A, Frébourg T, et al. Cardiac conduction alterations in a French family with amyloidosis of the Finnish type with the p.Asp187Tyr mutation in the GSN gene. Muscle Nerve. 2006;33(1):113–9.
39. Ashraf I, Peck MM, Maram R, et al. Association of arrhythmias in cardiac amyloidosis and cardiac sarcoidosis. Cureus. 2020;12(8):1–10.
40. Sayed RH, Rogers D, Khan F, et al. A study of implanted cardiac rhythm recorders in advanced cardiac AL amyloidosis. Eur Heart J. 2015;36(18):1098–105.
41. Donnellan E, Wazni OM, Saliba WI, et al. Prevalence, incidence, and impact on mortality of conduction system disease in transthyretin cardiac amyloidosis. Am J Cardiol. 2020;128:140–6.
42. Isath A, Correa A, Siroky GP, Perimbeti S, Mohammed S, Chahal CAA, et al. Trends, burden, and impact of arrhythmia on cardiac amyloid patients: A 16-year nationwide study from 1999 to 2014. J Arrhythmia. 2020;36(4):727–34.

43. Hörnsten R, Pennlert J, Wiklund U, Lindqvist P, Jensen SM, Suhr OB. Heart complications in familial transthyretin amyloidosis: impact of age and gender. Amyloid. 2010;17(2):63–8.
44. Giancaterino S, Urey MA, Darden DHJ. Management of arrhythmias in cardiac amyloidosis. JACC Clin Electrophysiol. 2020;6(4):351–61.
45. Orini M, Graham AJ, Martinez-Naharro A, Andrews CM, De Marvao A, Statton B, et al. Noninvasive mapping of the electrophysiological substrate in cardiac amyloidosis and its relationship to structural abnormalities. J Am Heart Assoc. 2019;8(18):1–12.
46. Giancaterino S, Urey MA, Darden D, Hsu JC. Management of arrhythmias in cardiac amyloidosis. JACC Clin Electrophysiol. 2020;6(4):351–61.
47. Palladini G, Malamani G, Cò F, et al. Holter monitoring in AL amyloidosis: prognostic implications. Pacing Clin Electrophysiol. 2001;24(8 Pt 1):1228–33.
48. Barbhaiya CR, Kumar S, Baldinger SH, et al. Electrophysiologic assessment of conduction abnormalities and atrial arrhythmias associated with amyloid cardiomyopathy. Hear Rhythm. 2016;13(2):383–90.
49. Varr BC, Zarafshar S, Coakley T, et al. Implantable cardioverter-defibrillator placement in patients with cardiac amyloidosis. Heart Rhythm. 2014;11(1):158–62.
50. Falk RH, Rubinow ACA. Cardiac arrhythmias in systemic amyloidosis: correlation with echocardiographic abnormalities. J Am Coll Cardiol. 1984;3(1):107–13.
51. Kristen AV, Dengler TJ, Hegenbart U, et al. Prophylactic implantation of cardioverter-defibrillator in patients with severe cardiac amyloidosis and high risk for sudden cardiac death. Heart Rhythm. 2008;5(2):235–40.
52. Lin G, Dispenzieri A, Kyle R, Grogan M, Brady PA. Implantable cardioverter defibrillators in patients with cardiac amyloidosis. J Cardiovasc Electrophysiol. 2013;24(7):793–8.
53. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy. J Am Coll Cardiol. 2019;73(22):2872–91.
54. Zanon F, Ellenbogen KA, Dandamudi G, Sharma PS, Huang W, Lustgarten DL, et al. Permanent his-bundle pacing: a systematic literature review and meta-analysis. Europace. 2018;20(11):1819–26.
55. Donnellan E, Wazni OM, Saliba WI, et al. Cardiac devices in patients with transthyretin amyloidosis: impact on functional class, left ventricular function, mitral regurgitation, and mortality. J Cardiovasc Electrophysiol. 2019;30(11):2427–32.
56. Herweg B, Welter-Frost A, Vijayaraman P. The evolution of cardiac resynchronization therapy and an introduction to conduction system pacing: a conceptual review. EP Eur. 2021;23(4):496–510.
57. Fisher K, Lellouche N, Damy T, et al. Cardiovascular outcomes after cardiac ressynchronization in cardiac amyloidosis. ESC Heart Fail. 2022;9:740–50.

Chapter 7
Urological and Kidney Involvements in Amyloidosis

Valkercyo Araújo Feitosa, Luiz Fernando Onuchic, and Irene de Lourdes Noronha

7.1 Introduction

Amyloidosis is a disease caused by extracellular deposition of amyloid material, an insoluble fibrillary compound formed by misfolded proteins that acquire a self-aggregation capacity; ultimately, this process leads to tissue damage [1]. The diameter of these fibrils varies from 7 to 12 nm, and such structures have high affinity for the Congo red dye, displaying positive birefringence when viewed under polarized light [2].

The formation of amyloid fibrils involves a combination of factors, including sustained increase in protein concentration, a triggering factor for protein misfolding, such as a genetic variant, and/or proteolytic remodeling of a protein into an amyloidogenic fragment [3]. Notably, amyloid deposits are formed by the interaction of these fibrils with the amyloid P component, apolipoprotein E, and glycosaminoglycans, which are essential to assemble and maintain amyloid deposits in tissues. More than 30 amyloidogenic proteins have been identified in humans to date. Their corresponding clinical manifestations depend on the affected organ as well as on genetic and environmental factors. Approximately 12 of them can be deposited as amyloid in the kidney [3].

V. A. Feitosa (✉) · I. de L. Noronha
Division of Nephrology, University of São Paulo School of Medicine, São Paulo, Brazil
e-mail: irenenor@usp.br

L. F. Onuchic
Division of Nephrology, University of São Paulo School of Medicine, São Paulo, Brazil

Division of Molecular Medicine, University of São Paulo School of Medicine, São Paulo, Brazil
e-mail: lonuchic@usp.br

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_7

Kidney disease is a frequent manifestation of systemic amyloidosis and is often the major source of morbidity for individuals with these disorders. Without treatment, kidney disease usually progresses to end-stage renal disease (ESKD). Amyloidosis is responsible for ~1% of ESKD cases [4]. Urological dysfunction is often observed in familial amyloidotic polyneuropathy (FAP) in the early stage of the disease as a consequence of autonomic dysfunction. Primary localized amyloidosis of the genitourinary tract, in turn, is a rare entity characterized by limited deposition in renal pelvis, ureters, or bladder. Early therapeutic intervention in these patients is essential to avoid secondary injuries.

7.2 Renal Amyloidosis

Systemic amyloidosis is characterized by amyloid deposition in virtually any organ, while clinical manifestations are not specific to the amyloidosis subtypes. The organs/systems most often affected are the heart, kidneys, peripheral nerves, and gastrointestinal tract. The preferential involvement of a given organ, in turn, may suggest the pathogenic type of fibril. Of note, the kidney is the most frequently involved organ in AL, AA, ALECT2, AFib, and AApoA1 amyloidoses [5].

AL amyloidosis is the most common subtype of renal amyloidosis worldwide; however, epidemiological differences are observed among different countries. AL amyloidosis is more prevalent in developed countries, while AA amyloidosis prevails in developing countries due to the high prevalence of infectious diseases [6]. Along this line, a Mayo Clinic series comprising 474 patients with histologically proven renal amyloidosis revealed Ig-related amyloidosis in the vast majority of the cases (86%), followed by 7% of AA, 3% of ALECT2, and 1% of AFib [7]. Notably, however, AFib is the leading cause of hereditary renal amyloidosis in Europe and the United States [8, 9].

It is unclear what factors confer the propensity for amyloidogenic proteins to deposit in specific organs. Interestingly, mild differences in the amino acid sequence of such proteins can modify their tissue tropism [10]. Renal amyloidosis is associated with two main mechanisms of organ dysfunction: (a) as traditionally proposed, amyloid fibrils accumulate in the extracellular space, potentially causing physical disruption and malfunction of the surrounding tissue, and (b) direct cellular toxicity caused by amyloidogenic precursor proteins, folding intermediates, aggregates, or fibrils, a mechanism mediated through interaction with cell surface receptors or via entry into cells [10, 11]. Amyloid deposition begins in the mesangium, the main support for the glomerulus, and is accompanied by mesangial matrix destruction, which is replaced by fibrils. As more fibrils deposit, mesangial damage increases, apoptosis of mesangial cells progresses, and glomerular damage becomes cumulative [12].

Amyloidosis usually affects individuals from the fifth decade of life onward, with rare exceptions. Renal amyloidosis of any type is more common in male patients. Its most common clinical presentation is proteinuria, mainly composed of albumin, which can vary from a subnephrotic range to a massive (>20 g/day). Nephrotic syndrome is typical, while renal dysfunction may remain asymptomatic until it becomes significantly advanced. Isolated hematuria, on the other hand, is uncommon [10, 13, 14]. Hypoalbuminemia can be profound, and edema is often severe and refractory to diuretics. Hypotension is common, usually asymptomatic, and is characterized by postural hypotension that can be preceded by improvement of preexisting hypertension [10, 15].

AL amyloidosis is associated with the highest levels of proteinuria, lowest levels of serum albumin, and highest frequency of presentation with full nephrotic syndrome compared to other types of amyloidosis [16]. Treating edema is often challenging, particularly in AL amyloidosis, since the involvement of the heart, vessels, and autonomic nervous system leads to difficult-to-manage fluid retention and hypotension [10]. Unlike AL amyloidosis, which typically presents with nephrotic syndrome, several non-AL amyloidosis—including ALECT2, AApoAI and AApoAIV—may present with gradually worsening renal function not associated with significant proteinuria [16].

Renal impairment tends to progress less rapidly when tubulointerstitial rather than glomerular deposition predominates. Vascular involvement, in turn, may be accompanied by hypertension, an uncommon feature of amyloidosis [10]. Deposits confined to the tubulointerstitial or vascular compartments are observed in certain types of renal amyloidosis, leading to progressive renal dysfunction with mild or absent proteinuria. This clinical expression is observed in AApoAI, AApoAIV, and ALECT2 amyloidosis. Although rare, presentations of diabetes insipidus and Fanconi's syndrome have been described as a result of amyloid deposits in the collecting ducts and proximal convoluted tubules, respectively [14, 16, 17].

7.2.1 Types of Renal Amyloidosis

7.2.1.1 Immunoglobulin Amyloidosis

Immunoglobulin amyloidosis results from anomalous immunoglobulin fragments with amyloidogenic properties produced by monoclonal plasma cell disorders. Since the immunoglobulin structure comprises light chains and heavy chains, immunoglobulin-related amyloidosis is classified as light chain amyloidosis (AL), responsible for approximately 94% of the cases; heavy and light chain amyloidosis (AHL), including 5% of the patients; and heavy chain amyloidosis (AH), encompassing 1% of them [7, 18].

Misfolded immunoglobulins are generated by amyloidogenic clones, whereas the variable organ tropism can be determined by the light chain variable region gene and the family of the clone-associated gene in AL amyloidosis. The germline gene LV6–57 is common in AL amyloidosis and is associated with renal involvement [15].

According to different case series, AL clinically affects the kidneys in 50–80% of patients [10, 19]. Other studies report proteinuria in approximately 75% of AL cases, nephrotic syndrome in almost half of the cases and renal dysfunction in ~20% of them at diagnosis [19]. Hypertension is uncommon in AL amyloidosis; in fact, there is a tendency for hypotension and the development of symptomatic orthostatic hypotension. The diagnosis is often established based on a renal biopsy or following the development of proteinuria (>0.5 g/24 h) in a patient with a previous diagnosis of AL [15]. A study including more than 400 renal biopsies from patients with AL amyloidosis identified amyloid deposits in glomeruli (97%), vessels (56%), interstitium (58%), and tubular basement membrane (8%), findings that support proteinuria as an almost universal feature of this disease [7].

The investigation of AL requires the identification of monoclonal Ig: serum and urine protein electrophoresis, serum and urine protein immunofixation, and dosage of serum-free light chain (sFLC) are sensitive techniques to identify a monoclonal Ig component. The main route of clearance of the light chain is through the kidneys; therefore, as kidney function declines, an increase in the serum levels of both isotypes occurs. In parallel, the κ/λ serum ratio increases, since κ FLC serum concentration is more affected by renal function than λ FLC concentration. In this context, the κ/λ ratio shifts from 0.26–1.65 to 0.37–3.1 [14, 20].

7.2.1.2 Amyloid Protein A Amyloidosis

AA amyloidosis results from a persistently high production of serum amyloid A (SAA), an acute-phase reactant produced by hepatocytes in response to chronic inflammatory conditions. Such settings include chronic infections, such as tuberculosis, osteomyelitis, schistosomiasis, or bronchiectasis, and chronic inflammatory diseases, such as rheumatoid arthritis, Crohn's disease, or periodic febrile syndromes (e.g., familial Mediterranean fever, FFM) [21]. Idiopathic forms represent a significant and increasing proportion (~15%) of all diagnosed cases of AA amyloidosis.

The kidney is the main affected organ, leading more than 95% of patients to manifest proteinuria and approximately 75% of them to develop nephrotic syndrome [21]. Up to 10% of patients have reached ESKD at the time of diagnosis, while progressive renal dysfunction will occur if the underlying disease remains uncontrolled [21, 22]. Renal biopsy revealed moderate-to-severe glomerular involvement in all cases, most often including mesangial nodular amyloid deposits. Vascular involvement is seen in ~95% of biopsies, in addition to interstitial and tubular basement membrane involvement. Interstitial inflammation surrounding amyloid deposits is not uncommon and may be observed adjacent to vessels or tubules. Juxtaglomerular arterioles are frequently involved [16].

7.2.1.3 Leukocyte Chemotactic Factor 2 Amyloidosis

Amyloidosis caused by leukocyte chemotactic factor 2 (ALECT2) was recently described, representing the third cause of renal amyloidosis in the United States and accounting for approximately 2.5% of the cases of renal amyloidosis [23, 24]. It preferentially affects Hispanic, Egyptian, Indian, and Pakistani individuals and manifests as chronic renal dysfunction of no apparent etiology. Despite the ethnic preponderance, no pathogenic variants have been described to date. ALECT2 amyloidosis mainly affects the cortical interstitium, displaying a diffuse pattern and leading to interstitial inflammation, while medullary involvement is minimal or absent. This lesion is sometimes confused with interstitial fibrosis, suggesting that the disease is likely underdiagnosed. Glomerular involvement tends to be mild, so proteinuria is variable and rarely reaches nephrotic levels.

Hereditary Amyloidosis

Hereditary amyloidoses account for ~10% of systemic amyloidosis cases and result from variants in several genes, whose corresponding protein products assume amyloidogenic features [10, 25]. While AL is the most common subtype of amyloidosis, underdiagnosis of hereditary subtypes is frequent [26–28]. Among 350 cases with a preemptive diagnosis of AL amyloidosis evaluated in the United Kingdom, genetic and specific IHC analyses revealed that 34 (9.7%) had hereditary amyloidosis, and eight of whom (24%) had evidence of monoclonal gammopathy [26]. It is important to highlight that these diseases display autosomal dominant inheritance with variable penetrance, and their differential diagnosis should include hereditary amyloidosis even in the absence of a family history of amyloidosis [25].

7.2.1.4 Fibrinogen A-α Chain Amyloidosis

Fibrinogen α-chain amyloidosis is the most common hereditary renal amyloidosis in Europe and the United States. To date, 15 amyloidogenic *FGA* gene variants have been described. Among them, the most commonly reported is Glu545Val (E545 V) [29].

This disorder manifests after the third decade of life (mean age of 55 years) and presents with hypertension, proteinuria, and/or nephrotic syndrome with rapid progression to ESKD, which occurs approximately 5 years after the diagnosis. Despite its autosomal dominant inheritance, a family history of amyloidosis and/or CKD has been found in only 64% of cases [9]. Renal biopsy shows massive deposition of amyloid material in glomeruli, causing distortion and collapse of capillary loops. In contrast to this intense glomerular involvement, the interstitium and vessels display little or no amyloid deposition. The renal medulla is not affected. IF is negative for light chains, while IF or IHC analyses specific for fibrinogen can be used for diagnostic confirmation.

There is no specific treatment, and the Glu545Val variant is usually associated with late-onset disease, slow progression to ESKD, low penetrance, and a good outcome after kidney transplantation (KT). *FGA* frameshift variants, on the other hand, are associated with early onset disease, fast progression, and fast amyloid recurrence after KT [8–10, 30].

7.2.1.5 Transthyretin Amyloidosis

Two forms of transthyretin amyloidosis (ATTR) result from amyloidogenic transthyretin (TTR) proteins: (a) wild-type ATTR (ATTRwt) amyloidosis, formerly known as senile systemic amyloidosis, associated with aging and with a dominant cardiac phenotype, and (b) hereditary ATTR amyloidosis, also known as ATTRv, caused by mutations in the *TTR* gene. ATTRv is characterized by peripheral neuropathy and autonomic dysfunction and was previously called FAP. Although ATTRv is the most common form of hereditary amyloidosis, it usually does not involve the kidney.

Renal involvement in ATTRv is observed in only 15–20% of cases [31] and, based on IHC assessment, comprises less than 2% of the cases of renal amyloidosis [32]. Renal dysfunction or proteinuria does not seem to correlate with age, disease duration, or severity of neuropathic involvement. It must be noted that amyloid deposition has been described in glomeruli, vessels, and interstitium even in patients without evidence of renal involvement. Microalbuminuria represents the first stage of renal involvement. Up to half of the patients with microalbuminuria may progress to renal dysfunction within 2 years [33]. Among 403 patients with ATTR, up to one-third presented with proteinuria, and only 10% progressed to ESKD within 5–10 years of albuminuria onset [34].

7.2.1.6 Lysozyme Amyloidosis

Lysozyme amyloidosis is rare and usually presents with renal, hepatic, and/or intestinal involvement. Kidney involvement includes progressive renal dysfunction and nephrotic proteinuria [35]. Renal biopsy shows extensive amyloid deposition in the mesangium, capillary loops, and blood vessels. Medullary amyloid deposition can also be seen along the basement membrane of the collecting ducts and vasa recta. IHC can be used to confirm the diagnosis [16, 36]. Renal progression varies among patients. In a retrospective evaluation, the median time from discovery of renal dysfunction to ESKD was 11 years [37].

7.2.1.7 Apolipoprotein Amyloidosis

Mutated apolipoproteins AI, AII, CII and CIII, as well as wild-type apolipoprotein AIV, can serve as amyloidogenic precursors. AApoAI and AApoAIV amyloidoses manifest around the sixth decade of life with slow and progressive loss of renal

function, associated with mild or absent proteinuria [3, 10]. To date, pathogenic variants in the *APOA4* gene have not been detected. Renal biopsy shows marked amyloid deposition in the renal medulla along with tubulointerstitial nephritis, while glomeruli are spared [38].

In contrast, patients with ApoAII and ApoCII renal amyloidoses present with renal dysfunction and proteinuria, which may reach a nephrotic range [39, 40]. These amyloidoses can also affect the liver, skin, heart, and adrenals. Renal biopsy shows extensive deposition of amyloid material in the mesangium and capillary loops in AApoAII and predominantly glomerular involvement with mesangial expansion and asymmetrical nodules in AApoCII. The interstitium is typically spared, but larger vessels may be involved [41].

AApoCIII amyloidosis is a recently described form of renal amyloidosis [42]. Its manifestations include tubulointerstitial kidney disease, Sjögren's syndrome at the age of 20 years, and progressive renal insufficiency. Amyloid deposition was identified in the renal cortex, glomerul, with major mesangial distribution, peritubular basement membranes and interstitium. Deposition of amyloid fibrils affected mostly the vascular compartment wtih abundant amyloid deposits in the walls of arterioles leading to lumen obliteration [43].

7.2.1.8 Gelsolin Amyloidosis

The most common clinical signs of AGel (gelsolin amyloidosis), a rare type of amyloidosis, are progressive corneal lattice amyloidosis, cranial and peripheral neuropathy, and cutis laxa lesions, typically manifested in the fourth or fifth decades [44]. Proteinuria and renal failure are detected in 13% and 5% of patients, respectively [44]. Renal involvement is usually expressed as mild and intermittent proteinuria in heterozygotes for pathogenic *GSN* variants, while homozygous patients for such variants present proteinuria and may develop nephrotic syndrome as early as in the early twenties [45].

7.2.2 Histological Diagnosis in Renal Amyloidosis

The overall prevalence of renal amyloidosis in native kidney biopsies is 1.6% [32]. The finding of positive birefringence (green apple) in tissue samples stained with Congo red under polarized light is the gold standard for the diagnosis of amyloidosis; however, it is not specific for the subtype of amyloid regardless of the affected organ. Histological evaluation of the affected tissue is the most sensitive method for diagnosis.

Renal biopsy is often used for diagnosis and to identify amyloid precursors. Amyloid deposition occurs mainly in the glomeruli. It is characterized morphologically as an amorphous eosinophilic material in hematoxylin and eosin sections and is generically referred to as hyaline material. This deposit is mainly observed in

mesangium and capillary loops and takes on a salmon color when stained with Congo red.

There were no significant differences in the intensity of Congo red staining according to the type of amyloid [16]. While the nodular aspect can make a differential diagnosis of diabetic kidney disease and light chain deposition disease, the amyloid protein predominates in the affected tissues, with reduced collagen deposition in the extracellular matrix evinced by weak staining with periodic acid-Schiff [7, 46]. Tubulointerstitial deposits of amyloid, in contrast, produce tubular atrophy and interstitial fibrosis.

AFib, AApo AI/AII/AIV, and ALECT2 amyloidoses are associated with different distributions in the renal compartments compared with AL and AA. ALECT2 has a predominantly interstitial distribution and a variable degree of proteinuria [16]. This type of amyloidosis is likely underdiagnosed histologically unless Congo red stain is routinely performed on all native biopsies, which is not the current practice in most laboratories. AFib has a massive obliterative glomerular involvement that should strongly suggest the diagnosis [47]. AApo AI/AII/AIV also have a distinctive distribution: diffuse involvement of medullary interstitium (without involvement of cortical interstitium) with or without glomerular or vascular involvement [16]. Medullary-limited disease can elude pathologic diagnosis if the biopsy specimen consists only of the renal cortex [10]. The reasons for the heterogeneity of amyloid deposit distribution within the kidneys of different types of amyloidosis are not well-understood.

Under electron microscopy, the amyloid material appears as randomly deposited unbranched fibrils without specific orientation in the mesangium, vessels, and/or interstitium. The ultrastructural appearance of all types of amyloid is the same. The fibril size helps to differentiate between amyloidosis and other renal deposit diseases, such as fibrillar glomerulonephritis and immunotactoid glomerulonephritis. In these diseases, the fibrils present a diameter of 15–20 nm and 30–90 nm, respectively. Furthermore, the electronic micrographic appearance of amyloid fibrils is characteristic, enabling the establishment of the diagnosis even when Congo red staining is negative, which may occur in up to 5–13% of cases [10, 16, 46].

Many clinical implications depend on the type of amyloid detected. Therefore, once amyloidosis is diagnosed in a renal specimen, amyloid typing is imperative (Table 7.1). Commercially, immunofluorescence antibodies used in routine renal pathology practice are directed against epitopes on the constant domains of λ, κ, IgG (γ), IgM (μ), and IgA (α) and on fibrinogen. However, not all cases of AL amyloidosis can be detected with commercially available antibodies. This is because some of the amyloidogenic precursors are fragmented or misfolded, so they cannot be detected with the existing antibodies, as they lack the antigenic epitopes detected by these commercial antibodies [46, 48].

IHC can be used to aid in typing amyloid in renal AL and non-AL amyloidosis. The use of other antibodies against SAA, transthyretin, fibrinogen Aα-chain, lysozyme, apolipoprotein AI and LECT2 are also available by IHC, so they can be employed to confirm the diagnosis linked to the different subtypes of amyloid proteins. However, up to 20% of AA cases cannot be unequivocally diagnosed [16]. In

Table 7.1 Renal amyloidosis: pathology assessment and identification of amyloid precursors

Renal amyloidosis	Precursor protein	Pathology renal			LMD/MS	Genetic testing
		Light microscopy	IF	IHC		
AL/AH/AHL	Immunoglobulin light and/or heavy chain	Deposition in glomeruli, vessels and interstitium	Sensitivity 85% and specificity 92% for Ig	Available Definitive results are obtained in <60% of cases	Inconclusive cases	Not available
AA	Serum amyloid A	Glomeruli always affected. Vascular and interstitium involvement are commom	Negative	Available	Inconclusive cases	Not available
AFib	Fibrinogen A-chain	Massive glomerular deposition. Medulla and vessels not involved	Positive for fibrinogen	Available Not definitive in~10% [47]	Inconclusive cases	Available
ALECT2	Leukocyte chemotactic factor-2	Deposition in glomeruli, vessels and interstitium	Negative	Available High false-positive rate [49]	LMD/MS to avoid inaccurate diagnosis [49]	Not applicable
ATTR	Transthyretin	Deposition in glomeruli, vessels and interstitium	Negative	Available	Inconclusive cases	Available
ALys	Lysozyme	Deposition in glomeruli, vessels and interstitium	Negative	Available	Inconclusive cases	Available
AApoAI	Apolipoprotein AI	Deposition in inner medula. Interstitial nephritis	Negative	Available	Inconclusive cases	Available
AApoAII	Apolipoprotein AII	Deposition in glomeruli and vessels	Negative	Available	Inconclusive cases	Available
AApoAIV	Apolipoprotein AIV	Deposition restricted to renal medula. Cortex is spared	Negative	Available	Inconclusive cases	Not applicable
AApoCII	Apolipoprotein CII	Predominantly glomerular and medullary involvement. Minimal vessels/interstitial involvement	Negative	Not available	Inconclusive cases	Available
AApoCIII	Apolipoprotein CIII	Deposition in glomeruli, vessels and interstitium. Interstitial nephritis	Negative	Available	Inconclusive cases	Available
AGel	Gelsolin	Restricted to glomeruli, spares vessels and interstitium	Negative	Available	Inconclusive cases	Available

Abbreviations: *IF* Immunofluorescence (IgG, IgA, IgM, κ, λ and fibrinogen), *IHC* Immunohistochemistry, *LMD/MS* Laser microdissection/mass spectrometry, *Ig* Immunoglobulin

ALECT2, analysis by IHC can be diagnostic; nonetheless, this method may not be sufficient to make the diagnosis in cases with weakly positive staining [7, 49].

Laser microdissection/mass spectrometry (LMD/MS) is a relatively new technique used to diagnose and type amyloidosis. This methodology typically analyzes the protein profile of Congo red-positive areas dissected from a kidney biopsy. LMD is initially used to capture pure amyloid plaques (glomerulus, vessels, and/or interstitium) from routine formalin-fixed and paraffin-embedded tissues. The diagnosis and typing of amyloidosis by MS are based on finding the signature amyloid peptides, apolipoprotein E, and serum amyloid-P component [16]. This approach has been employed for diagnosis in cases initially classified as indeterminate.

A recent study compared the sensitivity and specificity of IF to LDM/MS in 170 cases of renal biopsies from patients with amyloidosis [50]. One hundred and four cases were identified as Ig amyloidosis, and 66 were identified as non-Ig amyloidosis. Compared to LDM/MS, the sensitivity and specificity of IF were 84.6% and 92.4%, respectively. IF failed to identify the amyloid protein in 12.3% of the cases with renal amyloidosis, revealing lower sensitivity and specificity than LMD/MS [50]. Although immunodetection methods can be helpful, LDM/MS is the technique of choice to confirm the diagnosis and accurately type amyloidosis [16]. However, currently, this method has limited availability and high cost and is most often reserved for negative IF/IHC or inconclusive cases. With the advent of LMD/MS for amyloid typing, the type of renal amyloidosis can be determined in >97% of cases [16].

7.2.3 Course and Prognosis of Renal Amyloidoses

Progressive deterioration in renal function is expected to occur in most forms of renal amyloidosis. Disease course and prognosis, however, vary according to the type of amyloid and treatment response [51]. Overall, renal deterioration tends to be faster in AL amyloidosis. Patients with renal amyloidosis who progress to ESKD can be treated with dialysis or kidney transplantation [51]. Selected individuals requiring dialysis due to AA or AL amyloidosis achieve comparable outcomes with renal transplantation to diabetic nephropathy [52]. However, amyloidosis is associated with poor patient survival, and an appreciable proportion of amyloid ESKD patients die of amyloidosis complications [51].

In AL amyloidosis, proteinuria >5 g/24 h and eGFR <50 mL/min at diagnosis have been associated with progression to dialysis in 60% and 85% of AL patients at 3 years, respectively [53–56]. Of note, renal failure limits therapeutic options. Whereas the hematologic response assessed by the rate of sFLC reduction is associated with overall and renal survival, progression to ESRD can occur despite patient survival. The renal response to therapy correlates with the hematological response. Therapy involves the administration of chemotherapy and/or autologous stem cell transplantation. Recently, the ANDROMEDA trial demonstrated that the addition of daratumumab to the regimen with bortezomib, cyclophosphamide, and

dexamethasone (CyBorD) was associated with higher frequencies of complete hematologic response and survival free from major organ deterioration or hematologic progression. At 6 months, renal responses were more frequently observed in the daratumumab group than in the control group (53.0% vs. 23.9%, respectively) [57].

In AA amyloidosis, renal dysfunction is an important predictor of patient outcome. Risk factors for ESKD include large amyloid deposition, longer duration of inflammatory disease, and elevated baseline serum creatinine at diagnosis. Adequate control of the underlying inflammatory disease has been shown to improve proteinuria and renal function [6, 13].

The short-term prognosis of ALECT2 amyloidosis is variable, with approximately one-third of patients developing ESKD 2 years after diagnosis [24]. A recent study reported a median estimated time from diagnosis to ESKD of 8.2 years [58].

In hereditary renal amyloidoses, renal transplantation seems to be a reasonable therapeutic option for patients who reach ESKD; however, the disease may recur [24]. Liver–KT may be a curative option in fibrinogen A-α and TTR amyloidosis; however, it is not appropriate for lysozyme or apoAI amyloidosis, since these precursor proteins are synthesized by the intestine and polymorphonuclear cells, respectively.

7.3 Urinary and Sexual Dysfunction in Hereditary TTR Amyloidosis

Overall, amyloidosis is a relatively rare cause of peripheral neuropathy, comprising only 3% of the cases detected by the Mayo Clinic peripheral nerve laboratory. However, hereditary amyloidosis derived from ATTRv is the most common amyloidosis associated with polyneuropathy worldwide. Therefore, urinary and sexual dysfunction secondary to neuropathy are not unusual.

The pathogenesis of lower urinary tract and sexual dysfunction in ATTR–FAP is complex and involves neurogenic, vasculogenic, and myogenic mechanisms. Mainly, the small fibers responsible for autonomic regulation and conduction of thermoalgic sensitivity are initially involved. Later, the disease affects motor fibers. The amyloid deposits in the endoneurium result in loss of sensory somatic long fibers and small myelinated Aδ fibers, both of which explain the findings of reduced bladder sensation. Sympathetic dysfunction explains decreased proximal urethra resistance. The effect of somatic innervation may be a key determinant of intrinsic sphincter deficiency [59].

Vesico-sphincter dysfunction in FAP occurs at an early stage of the disease, even in asymptomatic patients. The prevalence of lower urinary tract symptoms (LUTS) in ATTR-FAP patients is greater than 80%. In half of the patients, urinary symptoms appeared during the first 3 years of the disease [60]. LUTS is seen mostly in patients with early onset ATTR-FAP from endemic areas and is less prominent in late-onset sporadic cases from nonendemic areas [61].

The urinary symptoms follow a pattern, starting with difficulty in voiding (hesitancy and/or straining and/or intermittence) and stress incontinence, symptoms that become almost continuous as the disease progresses. Underactive bladder is suggestive of detrusor underactivity, a manifestation characterized by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation of filling, and a slow stream. Approximately 50% of patients have symptomatic or asymptomatic urinary infections in the course of disease, with a higher incidence in females [60]. High postvoid residuals also carry a risk of upper urinary tract damage. Similar to LUTS, sexual dysfunction may be an early occurrence in disease progression. The prevalence and severity of LUTS and sexual dysfunction, in fact, seem to strongly correlate with the overall autonomic dysfunction [59, 60].

Urinary tract abnormalities can be evaluated by ultrasound, especially in cases of chronic urinary retention. Urodynamic studies can be used for the diagnosis and follow-up of patients with neurogenic bladder. A multidisciplinary approach with a neurologist, nephrologist, and urologist is essential for adequate support. Recent pharmacological advances have expanded the approach to ATTR–FAP. Disease-modifying agents focusing on the amyloidogenic process have been identified, including the use of RNA-targeted therapies that interfere with hepatic TTR synthesis (e.g., patisiran) and TTR-stabilizing agents (e.g., tafamidis and diflunisal). These drugs prevent the release of amyloidogenic monomers. Tafamidis is approved for the treatment of stage 1 ATTR–FAP in Europe, Asia, and some countries in South America. Liver transplantation has been considered a therapeutic choice to cure ATTRv, particularly in early onset cases [61].

7.4 Localized Amyloidosis of the Genitourinary Tract

Localized amyloidosis accounts for 10–20% of cases of amyloidosis. It can be detected in many organs, including the skin, soft tissues, genitourinary system, respiratory system, and gastrointestinal tract [62]. Primary localized amyloidosis of the genitourinary tract is a rare entity characterized by small pseudotumors located in the renal pelvis, ureters, or bladder [63]. It more commonly affects the seminal vesicles, which represent the second most common urinary organ involved in amyloidosis (after the kidneys), and constitutes an incidental finding in prostatectomy specimens [63].

The main symptom is gross hematuria, isolated or associated with low back pain [63]. It is not uncommon for localized amyloidosis to present as a neoplastic process with a mass effect mimicking malignancy. Urologic investigations, such as pelvic ultrasonography, computed tomography, cystoscopy, and ureteroscopy, can be initially performed, and a high level of awareness of this entity is required by pathologists and clinicians for accurate diagnosis and patient management [62, 63]. The clinical and radiologic features mimic urinary tract cancer, and local treatment is indicated.

7.5 Conclusion

Amyloidosis is a multisystem disease that frequently affects the kidneys and manifests as nephrotic syndrome. Renal biopsy is often used for diagnosis and to identify amyloid precursors, providing a useful guide for the management and treatment of patients with this disease. Urinary dysfunction is highly prevalent in ATTR patients. Early diagnosis and multidisciplinary management are key to improving quality of life and preventing damage to the upper urinary tract. Localized amyloidosis of the genitourinary tract is a rare disorder, requiring prompt differential diagnosis with a neoplastic process.

References

1. Lachmann HJ, Hawkins PN. Systemic amyloidosis. Curr Opin Pharmacol. 2006;6(2):214–20. https://doi.org/10.1016/j.coph.2005.10.005.
2. Röcken C, Sletten K. Amyloid in surgical pathology. Virchows Arch. 2003;443(1):3–16. https://doi.org/10.1007/s00428-003-0834-y.
3. Picken MM. The pathology of amyloidosis in classification: a review. Acta Haematol. 2020:1–13. https://doi.org/10.1159/000506696.
4. Tang W, McDonald SP, Hawley CM, Badve SV, Boudville N, Brown FG, et al. End-stage renal failure due to amyloidosis: outcomes in 490 ANZDATA registry cases. Nephrol Dial Transplant. 2013;28(2):455–61. https://doi.org/10.1093/ndt/gfs492.
5. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet. 2016;387(10038):2641–54. https://doi.org/10.1016/S0140-6736(15)01274-X.
6. Hassen M, Bates W, Moosa MR. Pattern of renal amyloidosis in South Africa. BMC Nephrol. 2019;20(1):406. https://doi.org/10.1186/s12882-019-1601-x.
7. Said SM, Sethi S, Valeri AM, Leung N, Cornell LD, Fidler ME, et al. Renal amyloidosis: origin and clinicopathologic correlations of 474 recent cases. Clin J Am Soc Nephrol. 2013;8(9):1515–23. https://doi.org/10.2215/CJN.10491012.
8. Meyer L, Ulrich M, Ducloux D, Garrigue V, Vigneau C, Nochy D, et al. Organ transplantation in hereditary fibrinogen a α-chain amyloidosis: a case series of French patients. Am J Kidney Dis. 2020;76(3):384–91. https://doi.org/10.1053/j.ajkd.2020.02.445.
9. Stangou AJ, Banner NR, Hendry BM, Rela M, Portmann B, Wendon J, et al. Hereditary fibrinogen a alpha-chain amyloidosis: phenotypic characterization of a systemic disease and the role of liver transplantation. Blood. 2010;115(15):2998–3007. https://doi.org/10.1182/blood-2009-06-223792.
10. Dember LM. Amyloidosis-associated kidney disease. J Am Soc Nephrol. 2006;17(12):3458–71. https://doi.org/10.1681/ASN.2006050460.
11. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med. 2003;349(6):583–96. https://doi.org/10.1056/NEJMra023144.
12. Herrera GA, Teng J, Turbat-Herrera EA, Zeng C, Del Pozo-Yauner L. Understanding mesangial pathobiology in AL-amyloidosis and Monoclonal Ig light chain deposition disease. Kidney Int Rep. 2020;5(11):1870–93. https://doi.org/10.1016/j.ekir.2020.07.013.
13. Ozawa M, Komatsuda A, Ohtani H, Nara M, Sato R, Togashi M, et al. Long-term prognosis of AL and AA renal amyloidosis: a Japanese single-center experience. Clin Exp Nephrol. 2017;21(2):212–27. https://doi.org/10.1007/s10157-016-1271-y.

14. Yadav P, Leung N, Sanders PW, Cockwell P. The use of immunoglobulin light chain assays in the diagnosis of paraprotein-related kidney disease. Kidney Int. 2015;87(4):692–7. https://doi.org/10.1038/ki.2014.333.
15. Milani P, Merlini G, Palladini G. Light chain amyloidosis. Mediterr J Hematol Infect Dis. 2018;10(1):e2018022. https://doi.org/10.4084/MJHID.2018.022.
16. Sethi S, Theis JD. Pathology and diagnosis of renal non-AL amyloidosis. J Nephrol. 2018;31(3):343–50. https://doi.org/10.1007/s40620-017-0426-6.
17. Sethi S, Vrana JA, Theis JD, Leung N, Sethi A, Nasr SH, et al. Laser microdissection and mass spectrometry-based proteomics aids the diagnosis and typing of renal amyloidosis. Kidney Int. 2012;82(2):226–34. https://doi.org/10.1038/ki.2012.108.
18. Benson MD, Buxbaum JN, Eisenberg DS, Merlini G, Saraiva MJM, Sekijima Y, et al. Amyloid nomenclature 2020: update and recommendations by the International Society of Amyloidosis (ISA) nomenclature committee. Amyloid. 2020;27(4):217–22. https://doi.org/10.1080/13506129.2020.1835263.
19. Bergesio F, Ciciani AM, Manganaro M, Palladini G, Santostefano M, Brugnano R, et al. Renal involvement in systemic amyloidosis: an Italian collaborative study on survival and renal outcome. Nephrol Dial Transplant. 2008;23(3):941–51. https://doi.org/10.1093/ndt/gfm684.
20. Hogan JJ, Alexander MP, Leung N. Dysproteinemia and the kidney: Core curriculum 2019. Am J Kidney Dis. 2019;74(6):822–36. https://doi.org/10.1053/j.ajkd.2019.04.029.
21. Lachmann HJ, Goodman HJ, Gilbertson JA, Gallimore JR, Sabin CA, Gillmore JD, et al. Natural history and outcome in systemic AA amyloidosis. N Engl J Med. 2007;356(23):2361–71. https://doi.org/10.1056/NEJMoa070265.
22. Real de Asúa D, Costa R, Galván JM, Filigheddu MT, Trujillo D, Cadiñanos J. Systemic AA amyloidosis: epidemiology, diagnosis, and management. Clin Epidemiol. 2014;6:369–77. https://doi.org/10.2147/CLEP.S39981.
23. Benson MD, James S, Scott K, Liepnieks JJ, Kluve-Beckerman B. Leukocyte chemotactic factor 2: a novel renal amyloid protein. Kidney Int. 2008;74(2):218–22. https://doi.org/10.1038/ki.2008.152.
24. Said SM, Sethi S, Valeri AM, Chang A, Nast CC, Krahl L, et al. Characterization and outcomes of renal leukocyte chemotactic factor 2-associated amyloidosis. Kidney Int. 2014;86(2):370–7. https://doi.org/10.1038/ki.2013.558.
25. Rowczenio DM, Noor I, Gillmore JD, Lachmann HJ, Whelan C, Hawkins PN, et al. Online registry for mutations in hereditary amyloidosis including nomenclature recommendations. Hum Mutat. 2014;35(9):E2403–12. https://doi.org/10.1002/humu.22619.
26. Lachmann HJ, Booth DR, Booth SE, Bybee A, Gilbertson JA, Gillmore JD, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. N Engl J Med. 2002;346(23):1786–91. https://doi.org/10.1056/NEJMoa013354.
27. Murphy CL, Eulitz M, Hrncic R, Sletten K, Westermark P, Williams T, et al. Chemical typing of amyloid protein contained in formalin-fixed paraffin-embedded biopsy specimens. Am J Clin Pathol. 2001;116(1):135–42. https://doi.org/10.1309/TWBM-8L4E-VK22-FRH5.
28. Comenzo RL, Zhou P, Fleisher M, Clark B, Teruya-Feldstein J. Seeking confidence in the diagnosis of systemic AL (Ig light-chain) amyloidosis: patients can have both monoclonal gammopathies and hereditary amyloid proteins. Blood. 2006;107(9):3489–91. https://doi.org/10.1182/blood-2005-10-4148.
29. Chapman J, Dogan A. Fibrinogen alpha amyloidosis: insights from proteomics. Expert Rev Proteomics. 2019;16(9):783–93. https://doi.org/10.1080/14789450.2019.1659137.
30. Machado JR, Silva MV, Neves PD, Oliveira FA, Corrêa RR, Rodrigues WV, et al. Fibrinogen a alpha-chain amyloidosis: report of the first case in Latin America. Amyloid. 2013;20(1):52–5. https://doi.org/10.3109/13506129.2012.763029.
31. Hofer PA, Anderson R. Postmortem findings in primary familial amyloidosis with polyneuropathy. Acta Pathol Microbiol Scand A. 1975;83(3):309–22.

32. von Hutten H, Mihatsch M, Lobeck H, Rudolph B, Eriksson M, Röcken C. Prevalence and origin of amyloid in kidney biopsies. Am J Surg Pathol. 2009;33(8):1198–205. https://doi.org/10.1097/PAS.0b013e3181abdfa7.
33. Lobato L, Beirão I, Silva M, Bravo F, Silvestre F, Guimarães S, et al. Familial ATTR amyloidosis: microalbuminuria as a predictor of symptomatic disease and clinical nephropathy. Nephrol Dial Transplant. 2003;18(3):532–8. https://doi.org/10.1093/ndt/18.3.532.
34. Lobato L. Portuguese-type amyloidosis (transthyretin amyloidosis, ATTR V30M). J Nephrol. 2003;16(3):438–42.
35. Pepys MB, Hawkins PN, Booth DR, Vigushin DM, Tennent GA, Soutar AK, et al. Human lysozyme gene mutations cause hereditary systemic amyloidosis. Nature. 1993;362(6420):553–7. https://doi.org/10.1038/362553a0.
36. Granel B, Valleix S, Serratrice J, Chérin P, Texeira A, Disdier P, et al. Lysozyme amyloidosis: report of 4 cases and a review of the literature. Medicine (Baltimore). 2006;85(1):66–73. https://doi.org/10.1097/01.md.0000200467.51816.6d.
37. Sattianayagam PT, Gibbs SD, Rowczenio D, Pinney JH, Wechalekar AD, Gilbertson JA, et al. Hereditary lysozyme amyloidosis—phenotypic heterogeneity and the role of solid organ transplantation. J Intern Med 2012;272(1):36–44. https://doi.org/10.1111/j.1365-2796.2011.02470.x.
38. Persey MR, Booth DR, Booth SE, van Zyl-Smit R, Adams BK, Fattaar AB, et al. Hereditary nephropathic systemic amyloidosis caused by a novel variant apolipoprotein A-I. Kidney Int. 1998;53(2):276–81. https://doi.org/10.1046/j.1523-1755.1998.00770.x.
39. Yazaki M, Liepnieks JJ, Barats MS, Cohen AH, Benson MD. Hereditary systemic amyloidosis associated with a new apolipoprotein AII stop codon mutation Stop78Arg. Kidney Int. 2003;64(1):11–6. https://doi.org/10.1046/j.1523-1755.2003.00047.x.
40. Sethi S, Dasari S, Plaisier E, Ronco P, Nasr SH, Brocheriou I, et al. Apolipoprotein CII amyloidosis associated with p.Lys41Thr mutation. Kidney Int Rep. 2018;3(5):1193–201. https://doi.org/10.1016/j.ekir.2018.04.009.
41. Morizane R, Monkawa T, Konishi K, Hashiguchi A, Ueda M, Ando Y, et al. Renal amyloidosis caused by apolipoprotein A-II without a genetic mutation in the coding sequence. Clin Exp Nephrol. 2011;15(5):774–9. https://doi.org/10.1007/s10157-011-0483-4.
42. Valleix S, Verona G, Jourde-Chiche N, Nédelec B, Mangione PP, Bridoux F, et al. D25V apolipoprotein C-III variant causes dominant hereditary systemic amyloidosis and confers cardiovascular protective lipoprotein profile. Nat Commun. 2016;7:10,353. https://doi.org/10.1038/ncomms10353.
43. Gupta N, Kaur H, Wajid S. Renal amyloidosis: an update on diagnosis and pathogenesis. Protoplasma. 2020;257(5):1259–76. https://doi.org/10.1007/s00709-020-01513-0.
44. Schmidt EK, Mustonen T, Kiuru-Enari S, Kivelä TT, Atula S. Finnish gelsolin amyloidosis causes significant disease burden but does not affect survival: FIN-GAR phase II study. Orphanet J Rare Dis. 2020;15(1):19. https://doi.org/10.1186/s13023-020-1300-5.
45. Yamanaka S, Miyazaki Y, Kasai K, Ikeda S, Kiuru-Enari S, Hosoya T. Hereditary renal amyloidosis caused by a heterozygous G654A gelsolin mutation: a report of two cases. Clin Kidney J. 2013;6(2):189–93. https://doi.org/10.1093/ckj/sft007.
46. Novak L, Cook WJ, Herrera GA, Sanders PW. AL-amyloidosis is underdiagnosed in renal biopsies. Nephrol Dial Transplant. 2004;19(12):3050–3. https://doi.org/10.1093/ndt/gfh503.
47. Gillmore JD, Lachmann HJ, Rowczenio D, Gilbertson JA, Zeng CH, Liu ZH, et al. Diagnosis, pathogenesis, treatment, and prognosis of hereditary fibrinogen a alpha-chain amyloidosis. J Am Soc Nephrol. 2009;20(2):444–51. https://doi.org/10.1681/ASN.2008060614.
48. Herrera GA. Renal amyloidosis with emphasis on the diagnostic role of electron microscopy. Ultrastruct Pathol. 2020;44(4–6):325–41. https://doi.org/10.1080/01913123.2020.1844355.
49. Paueksakon P, Fogo AB, Sethi S. Leukocyte chemotactic factor 2 amyloidosis cannot be reliably diagnosed by immunohistochemical staining. Hum Pathol. 2014;45(7):1445–50. https://doi.org/10.1016/j.humpath.2014.02.020.

50. Gonzalez Suarez ML, Zhang P, Nasr SH, Sathick IJ, Kittanamongkolchai W, Kurtin PJ, et al. The sensitivity and specificity of the routine kidney biopsy immunofluorescence panel are inferior to diagnosing renal immunoglobulin-derived amyloidosis by mass spectrometry. Kidney Int. 2019;96(4):1005–9. https://doi.org/10.1016/j.kint.2019.05.027.
51. Gurung R, Li T. Renal amyloidosis: presentation, diagnosis, and management. Am J Med. 2022; https://doi.org/10.1016/j.amjmed.2022.01.003.
52. Law S, Cohen O, Lachmann HJ, Rezk T, Gilbertson JA, Rowczenio D, et al. Renal transplant outcomes in amyloidosis. Nephrol Dial Transplant. 2021;36(2):355–65. https://doi.org/10.1093/ndt/gfaa293.
53. Palladini G, Hegenbart U, Milani P, Kimmich C, Foli A, Ho AD, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood. 2014;124(15):2325–32. https://doi.org/10.1182/blood-2014-04-570010.
54. Charitaki E, Kastritis E, Petraki C, Liapis K, Adamidis K, Apostolou T, et al. Glomerular expression of matrix metalloproteinases in AL-amyloidosis and association with renal function at the time of kidney biopsy. Clin Nephrol. 2016;85(1):44–54. https://doi.org/10.5414/CN108670.
55. Drosou ME, Vaughan LE, Muchtar E, Buadi FK, Dingli D, Dispenzieri A, et al. Comparison of the current renal staging, progression and response criteria to predict renal survival in AL amyloidosis using a Mayo cohort. Am J Hematol. 2021;96(4):446–54. https://doi.org/10.1002/ajh.26092.
56. Kastritis E, Gavriatopoulou M, Roussou M, Migkou M, Fotiou D, Ziogas DC, et al. Renal outcomes in patients with AL amyloidosis: prognostic factors, renal response and the impact of therapy. Am J Hematol. 2017;92(7):632–9. https://doi.org/10.1002/ajh.24738.
57. Kastritis E, Palladini G, Minnema MC, Wechalekar AD, Jaccard A, Lee HC, et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. N Engl J Med. 2021;385(1):46–58. https://doi.org/10.1056/NEJMoa2028631.
58. Rezk T, Gilbertson JA, Rowczenio D, Bass P, Lachmann HJ, Wechalekar AD, et al. Diagnosis, pathogenesis and outcome in leucocyte chemotactic factor 2 (ALECT2) amyloidosis. Nephrol Dial Transplant. 2018;33(2):241–7. https://doi.org/10.1093/ndt/gfw375.
59. Bentellis I, Amarenco G, Gamé X, Jericevic D, El-Akri M, Voiry C, et al. Diagnosis and treatment of urinary and sexual dysfunction in hereditary TTR amyloidosis. Clin Auton Res. 2019;29(Suppl 1):65–74. https://doi.org/10.1007/s10286-019-00627-7.
60. Andrade MJ. Lower urinary tract dysfunction in familial amyloidotic polyneuropathy, Portuguese type. Neurourol Urodyn. 2009;28(1):26–32. https://doi.org/10.1002/nau.20600.
61. Adams D, Koike H, Slama M, Coelho T. Hereditary transthyretin amyloidosis: a model of medical progress for a fatal disease. Nat Rev Neurol. 2019;15(7):387–404. https://doi.org/10.1038/s41582-019-0210-4.
62. Al-Obaidy KI, Grignon DJ. Primary amyloidosis of the genitourinary tract. Arch Pathol Lab Med. 2021;145(6):699–703. https://doi.org/10.5858/arpa.2020-0102-RA.
63. Monge M, Chauveau D, Cordonnier C, Noël LH, Presne C, Makdassi R, et al. Localized amyloidosis of the genitourinary tract: report of 5 new cases and review of the literature. Medicine (Baltimore). 2011;90(3):212–22. https://doi.org/10.1097/MD.0b013e31821cbdab.

Chapter 8
Ophthalmological Manifestations in ATTRv Amyloidosis

Anelise Dias, Giovanna Provenzano, and Raul N. G. Vianna

Amyloidosis describes an assorted group of diseases. Each amyloid precursor protein is responsible for a specific disease entity. The most common types are primary, secondary, familial, and senile. Hereditary transthyretin (TTR) amyloidosis, traditionally known as familial amyloid polyneuropathy (FAP), is a progressive autosomal dominant neurodegenerative disease with variable expressivity [1]. In this disease, a normal soluble protein undergoes a mutation and forms deposits of insoluble fibrillar aggregates in extracellular tissue, causing obstruction, with local blood circulation failure and increased oxidative stress [2]. The TTR, which is synthesized by the liver, choroid plexus, and retinal pigment epithelium (RPE), is responsible for one of the most common forms of systemic and ocular amyloidosis [3].

The TTR amyloidosis associated with FAP (TTR–FAP) incidence shows considerable geographic differences, sometimes with pronounced regional groupings, as in northern Portugal, northwestern Ireland, and northern Sweden [4]. The disease is also frequently observed in the rest of Portugal and Sweden, Japan, Spain, Finland, France, and Brazil [5].

The most common mutation worldwide, especially in endemic regions, is Val30Met [6]. The onset of TTR–FAP varies from the second to the ninth decade of life, with a variable age of onset in different populations. The mutation prevalence in northern Sweden is 4%, with a penetrance of only 11% by 50 years of age [7], in Portugal (80% at 50 years) [8] and Brazil (83% at 63 years) [9].

A. Dias (✉) · G. Provenzano
Uveitis & Retina Unit, Department of Ophthalmology, Fluminense Federal University, Niteroi, Rio de Janeiro, Brazil

R. N. G. Vianna
Head Uveitis & Retina Unit, Department of Ophthalmology, Fluminense Federal University, Niteroi, Rio de Janeiro, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_8

The TTR–FAP is thought to affect men and women equally; however, women were significantly more likely to have eye involvement [10]. Another study shows that men get sick earlier than women, and the disease is more severe in maternal than in paternal inheritance [4].

Ocular involvement among TTR–FAP patients occurs in approximately 10% of patients, most often occurring later [11]. Some TTR variants are more correlated with ocular manifestations and are listed in Table 8.1. Despite being mostly a localized disorder, systemic associations may occur, being mandatory for a systemic evaluation [12–14]. Dammaco et al. analyzed ocular involvement in amyloidosis and described a localized ocular amyoloidois prevalence of 78.6%, followed by 16.2% for systemic amyloidosis. In addition, Demirci et al. described an association with systemic amyloidosis in 17% of the cases, while a localized conjunctival amyloidosis was seen in 83% of the patients. Furthermore, some authors described ocular involvement as the first manifestation of a systemic amyloidosis [14–16].

Intraocular synthesis of mutant TTR by RPE was shown to be mainly responsible for vitreous amyloid. Even after liver transplantation, patients continue to develop vitreous opacities and glaucoma [18]. There is evidence that after liver transplantation, eye disease may progress more quickly. In addition, patients may remain asymptomatic at disease onset. As a result, it is extremely important to carry out regular ophthalmological follow-ups, at least every 2 years, performing measurements of visual acuity, biomicroscopy with pupil examination, corneal confocal microscopy (CCM), anterior chamber and funduscopic examinations, tonometry, and visual field tests as needed [19, 20].

The TTR retinal deposits were found in the inner layers of the retina and not close to the RPE [21], as well as in the corneal endothelium, lens capsule, iris epithelium, ciliary pigment epithelium, vitreous body, conjunctiva, trabecular meshwork, lacrimal glands, and retinal nerve fibers [19]. As mutant TTR deposition can occur in different ocular tissues, the ophthalmologic manifestations are also varied, such as vitreous opacities, chronic open-angle glaucoma, abnormal conjunctival vessels, keratoconjunctivitis *sicca* and corneal neuropathy, accommodation defects, chorioretinal vascular changes, and pupillary abnormalities. Among the reviewed studies, the ocular involvement prevalence varied according to genetic composition, as well as the region of the population analyzed. Notably, Haraoka et al. described

Table 8.1 Some mutations were associated with ocular involvement according to www.amyloidosismutations.com [11, 17]

Ocular mutations			
Cys10Arg	Lys35Thr	Leu55Gln	Val71Ala
Ser23Asn	Ala36Pro	Leu55Arg	Gly83Arg
Val30Met	Trp41Leu	Leu55Pro	Ile84Asn
Val30Gly	Thr49Ala	Leu58Arg	Ile84Ser
Phe33Cys	Gly53Ala	Phe64Ser	Ala97Ser
Phe33Ile	Glu54Gly	Tyr69His	Tyr114Cys
Arg34Gly	Glu54Lys	Lys70Asn	Val122Ala

that the frequency of amyloid deposition was 85.7% in extraocular muscles and 100% in orbital adipose tissue. Moreover, according to Ando et al. and Mora-Horna et al., conjunctival alterations were the most common manifestation, while Banerjee et al. and Kang et al. pointed to the eyelids as the most frequent ocular site.

8.1 Retinal and Vitreous Alterations

Vitreous opacity is a common ocular manifestation in TTR–FAP (Fig. 8.1), which may be associated with systemic manifestations or even appear as the first symptom [22]. In this case, the ophthalmologist should refer these patients for a systemic workup.

Vitreous amyloidosis can be identified as bilateral sheet-like, cobweb-like, band-like, film-like, cotton-like, glass wool-like veils or string of pearl white opacities [23]. Vitreous amyloidosis is highly asymmetric, occurring in approximately 5.4–35% of cases [24]. In the vast majority of hereditary amyloidosis by TTR gene mutation cases, there are floaters associated with a progressive decrease in visual acuity, which can be severe, due to amyloid deposition in the vitreous [10]. However, we can find asymptomatic patients, who can be identified by indirect signs, such as glass wool appearance of vitreous, perivascular amyloid deposits in the retina and white opacities on the posterior lens capsule, called *pseudopodis lentis* [23].

The TTR have an affinity for basement membranes. As the vitreous matrix is composed predominantly of type 2 collagen, which is biochemically and structurally similar to the normal basement membrane collagen, TTR amyloid aggregates

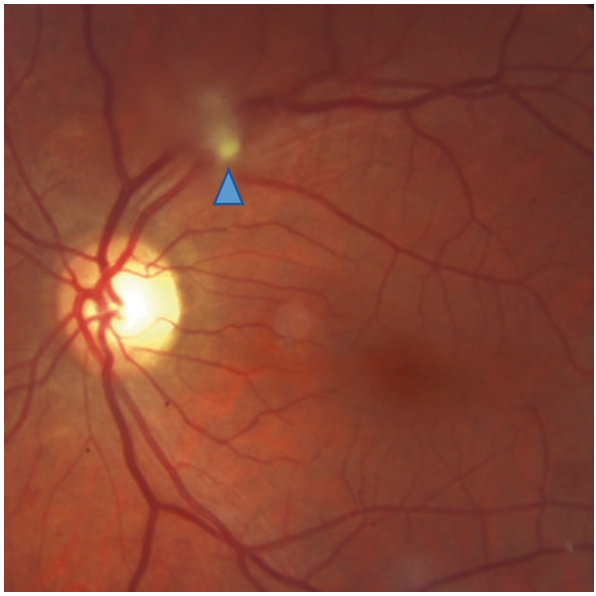


Fig. 8.1 Vitreous opacities in the eye of a patient with TTR-FAP. Observe the vitreous tuff (arrow) adjacent to the temporal branch of the retinal artery. (Courtesy of Anh-Danh Phan, MD)

form in the vitreous [25]. In some types of mutations, such as Arg34Gly, Glu54Lys, Thr49Ala, and Tyr114Cys, vitreous involvement is more prevalent, and onset occurs earlier [22].

Pars plana vitrectomy (PPV) is the only treatment available for vitreous amyloidosis to date to restore vision. This is a symptomatic treatment, as the continuous mutant TTR intraocular production by the RPE continues to occur; therefore, relapses can occur [26, 27]. The ideal to minimize chances of vitreous opacities recurrence is to perform an early and complete PPV. Early PPV performed before the appearance of pseudopodia lentis (points of adhesion of amyloid material in the posterior lens capsule) facilitates proper vitreous removal, decreasing intraoperative complications, for instance, early cataract development by touching the posterior capsule [26]. Extensive PPV with indentation-associated and retrolental vitrectomy is also important, as vitreous remnants may work as a support for amyloid material to redeposit into the vitreous cavity [26, 27]. During surgery, care must be taken to avoid retinal breaks, as there is strong vitreoretinal adhesion of these opacities to the perivascular regions, in the area behind the posterior lens capsule and along the vitreous base at the ora serrata [24].

Amyloid material can also deposit on the inner limiting membrane (ILM), which can cause recurrence of vitreous opacities, as well as wrinkling of the inner retinal surface. In this case, deposited amyloid material removal with ILM peeling should be performed [27].

8.2 Chronic Open-Angle Glaucoma

Among FAP complications, glaucoma is one of the most serious due to irreversible vision loss in these patients and occurs mainly in a late phase [28]. Glaucoma incidence differs in several studies, ranging from 5.4% [20] to 26% [29]. This difference in data occurs, because the glaucoma incidence varies according to the FAP genotype and the disease onset time [20, 23].

Pathophysiological mechanisms responsible for intraocular pressure (IOP) elevation include conjunctival and episcleral perivascular amyloid deposition, intratrabecular meshwork deposition, elevated episcleral venous pressure, and amyloid deposition on the pupillary border, which may precede glaucoma by months or years [23].

Erythropoietin (EPO) levels are elevated in the aqueous humor in glaucoma patients and are a protective factor for photoreceptors, RPE, and ganglion cells. However, this is not seen in patients with COAG and ATTRv amyloidosis, so more aggressive treatment is required in these cases to prevent rapid glaucoma progression [22].

Trabeculectomy with mitomycin C (antimetabolite) seems to be a promising treatment modality for glaucoma secondary to FAP in patients refractory to topical therapy, maintaining IOP equal to or less than 20 mmHg. Another possible treatment strategy is EPO, as it has been shown to have a protective effect on ganglion

cells, as mentioned previously [22]. Despite trabeculectomy being understood as the gold standard in glaucoma surgery, the use of drainage devices has increasingly assumed a primary role in the management of complicated glaucoma cases, with difficult IOP control [30].

8.3 Orbital and Adnexal Amyloidosis and Conjunctival Amyloidosis

Orbital and adnexal amyloidosis (OAA) and conjunctival amyloidosis are well-known but uncommon disorders predominantly seen in middle-aged patients with mostly no gender predilection, even though some studies have described a female preponderance [10, 14, 15].

Signs and symptoms of OAA are characterized by heterogeneous presentations with slow progression (mean duration of 2 years) and vague complaints [15]. The most common alterations are visible or palpable periocular mass or tissue infiltration and ptosis. Moreover, middle-aged patients with eye dryness, photophobia, periodical visual impairment, proptosis, acquired ptosis, acquired squint, recurrent conjunctival hemorrhage or "recurrent pterygium" should be investigated for ocular amyloidosis [10, 16].

Orbital amyloidosis is more commonly seen in primary amyloidosis and can be classified according to its orbital location. Extraorbital muscle and adnexal tissues usually present as bilateral infiltration with proptosis and ocular movement limitation. Other manifestations may be revealed according to the region of amyloid deposition. Importantly, middle-aged patients with progressive proptosis, acquired ptosis, accommodative paresis, muscular palsy and acquired adulthood squint should have ocular amyloidosis as a possible diagnosis [13, 15]. Eyelid infiltration may manifest as ptosis, eyelid thickening, echimosis, waxy eyelid papule with hemorrhagic appearance, and entropion. Unlike other periocular involvements, eyelid amyloidosis is more likely associated with secondary amyloidosis. Even though there is no consensus, some studies point out that periocular amyloidosis that spares the eyelid skin is probably localized [15].

Lacrimal gland involvement is a rare amyloid presentation, usually associated with eye dryness, slowly progressive swelling of the temporal upper eyelid, proptosis leading to lateral ptosis with an S-shaped deformity, and globe displacement with a superotemporal orbital mass. In extreme cases, keratoconjuntivitis *sicca* syndrome may be associated with the destruction of the lacrimal gland secondary to amyloid deposition [31]. Furthermore, the involvement of the lacrimal outflow system has also been described to be usually associated with epiphora and swelling overlying the region of amyloid deposition [32].

Conjunctival amyloidosis can occur anywhere in the conjunctiva with a slight predilection to the fornix and tarsal conjunctiva [33]. Symptoms may simulate conjunctival malignancies or inflammation, presenting as a conjunctival mass,

epiphora, blepharoptosis, or thickened palpebral conjunctiva [14]. In addition, abnormal conjunctival vessels characterized by segmental and fusiform dilation can be associated with recurrent subconjunctival hemorrhages [11]. The latter changes result from liver synthesis of TTR, and consequently, there is no progression after liver transplant [22]. The conjunctival lesions, sometimes misdiagnosed as recurrent pterygium, can be seen as a waxy confluent fusiform mass or polypoidal papules with a yellow or yellow–pink color associated with intrinsic vascularization [14]. Even though uncommon, chronic ocular inflammation, such as trachoma, rheumatoid arthritis, and recurrent bacterial conjunctivitis, may lead to secondary conjunctival amyloidosis [14].

Conjunctival amyloidosis and OAA have a clinical diagnosis confirmed with biopsy and histopathological analyses of the ocular lesion [10, 16]. However, because of their infrequency and heterogeneous presentations, these disorders are often overlooked and misdiagnosed. Even though rare, systemic associations have been described as mandatory for systemic screening to rule out other disorders, such as lymphoma, leukemia, metastatic carcinoma, sarcoidosis, and other granulomas [34]. Imaging examinations, such as magnetic resonance imaging and computed tomography, are helpful to localize and determine the extension of the affected orbital structures [15].

The standard treatment is debulking or complete excision of the lesion associated with cryotherapy, as well as the use of symptoms [14, 15]. The therapeutic management may depend on the extent of local involvement and systemic condition of the patient. The delay in recognizing such lesions may lead to a potentially complicated and extensive surgical procedure [14]. Once again, a systemic evaluation is mandatory for therapeutic optimization.

8.4 d. Keratoconjunctivitis Sicca and Neurotrophic Kerathopathy

Small fiber neuropathy is a main feature of TTR–FAP, with corneal involvement as an important characteristic. Observed as an isolated manifestation or associated with other ocular manifestations, the keratoconjunctivitis *sicca* is secondary to amyloid deposition in the corneal layers, causing the destruction of sensory innervation and progressively reducing corneal sensitivity [11, 22]. Amyloid lacrimal gland involvement and autonomic neuropathy may exacerbate the development of neurotrophic keratopathy, resulting in extreme outcomes, such as corneal ulcers and perforation. Characterized by substantial eye dryness and corneal hypoesthesia, some patients are asymptomatic, while others may experience excessive tearing, photophobia and foreign body sensation. Due to its vague symptoms, this disorder can be misdiagnosed. Other ocular locations may be concurrently involved, such as orbital and annexes amyloidosis, facilitating the clinical diagnosis [22]. In addition, Rousseau et al., using in vivo laser scanning CCM, observed corneal nerve damage

at a presymptomatic stage in patients with TTR–FAP and other small fiber neuropathies, which is a useful tool to diagnose and monitor the progression of such disorders [35].

Treatment for keratoconjunctivitis *sicca* mainly consists of preservative-free lubricating eye drops. Moreover, therapeutic contact lenses and topical antibiotics may be necessary. The main therapeutic goal is to relieve ocular discomfort and minimize corneal damage caused by corneal erosions. Penetrating keratoplasty may be an option for corneal haze secondary to amyloid deposition, even though new deposits will gradually accumulate in the graft [22, 35].

8.5 Pupillary and Lens Abnormalities

Pupillary indentations, secondary to intraocular production with deposition at the inner pupillary margin, are considered a pathognomonic alteration of ocular amyloidosis. Moreover, amyloid deposition at the iris sphincter muscle or ciliary ganglion may lead to anisocoria and pupillary light-near dissociation [11, 22].

Lens amyloid deposition can often occur asymmetrically in the posterior lens capsule, called *pseudopodis lentis*, and at the anterior lens capsule. The anterior deposit may lead to contrast sensitivity dysfunction, early cataract and loss of lens elasticity. Lens elasticity deficiency concurrent with characteristic autonomic neuropathy affecting ciliary muscle accommodation leads to early presbyopia [11, 22].

References

1. Tripathy K, Chawla R, Selvan H, Venkatesh P. Ocular manifestations of familial transthyretin amyloidosis. Am J Ophthalmol [Internet]. 2018;186:169–70. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002939417304804
2. Sekijima Y. Transthyretin (ATTR) amyloidosis: clinical spectrum, molecular pathogenesis and disease-modifying treatments. J Neurol Neurosurg Psychiatry [Internet]. 2015;86(9):1036–43. Available from: https://jnnp.bmj.com/lookup/doi/10.1136/jnnp-2014-308724
3. Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. Muscle Nerve [Internet]. 2007;36(4):411–23. Available from: https://onlinelibrary.wiley.com/doi/10.1002/mus.20821
4. Hund E, Singer R, Linke RP, Willig F, Grau A. Transthyretinassoziierte hereditäre Amyloidosen. Nervenarzt [Internet]. 2002;73(10):930–6. Available from: http://link.springer.com/10.1007/s00115-002-1345-9
5. Sousa A, Andersson R, Drugge U, Holmgren G, Sandgren O. Familial amyloidotic polyneuropathy in Sweden: geographical distribution, age of onset, and prevalence. Hum Hered [Internet]. 1993;43(5):288–94. Available from: https://www.karger.com/Article/FullText/154146
6. Schmidt H, Cruz MW, Botteman MF, Carter JA, Chopra A, Stewart M, et al. Global epidemiology of transthyretin hereditary amyloid polyneuropathy: a systematic review. Amyloid [Internet]. 2017;24(sup1):111–2. Available from: https://www.tandfonline.com/doi/full/10.1080/13506129.2017.1292903

7. Hellman U, Alarcon F, Lundgren H-E, Suhr OB, Bonaiti-PelliÉ C, Planté-Bordeneuve V. Heterogeneity of penetrance in familial amyloid polyneuropathy, ATTR Val30Met, in the Swedish population. Amyloid [Internet]. 2008;15(3):181–6. Available from: http://www.tandfonline.com/doi/full/10.1080/13506120802193720
8. Plante-Bordeneuve V. Genetic study of transthyretin amyloid neuropathies: carrier risks among French and Portuguese families. J Med Genet [Internet]. 2003;40(11):120e–120. Available from: https://jmg.bmj.com/lookup/doi/10.1136/jmg.40.11.e120
9. Saporta MAC, Zaros C, Cruz MW, André C, Misrahi M, Bonaïti-Pellié C, et al. Penetrance estimation of TTR familial amyloid polyneuropathy (type I) in Brazilian families. Eur J Neurol [Internet]. 2009;16(3):337–41. https://doi.org/10.1111/j.1468-1331.2008.02429.x.
10. Reynolds MM, Veverka KK, Gertz MA, Dispenzieri A, Zeldenrust SR, Leung N, et al. Ocular manifestations of familial transthyretin amyloidosis. Am J Ophthalmol [Internet]. 2017;183:156–62. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002939417303781
11. Minnella AM, Rissotto R, Antoniazzi E, Di Girolamo M, Luigetti M, Maceroni M, et al. Ocular involvement in hereditary amyloidosis. Genes (Basel) [Internet]. 2021;12(7):955. Available from: https://www.mdpi.com/2073-4425/12/7/955
12. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet [Internet]. 2016;387(10038):2641–54. Available from: https://linkinghub.elsevier.com/retrieve/pii/S014067361501274X
13. Al-Nuaimi D, Bhatt PR, Steeples L, Irion L, Bonshek R, Leatherbarrow B. Amyloidosis of the orbit and Adnexae. Orbit [Internet]. 2012;31(5):287–98. https://doi.org/10.3109/01676830.2012.707740.
14. Demirci H, Shields CL, Eagle RC, Shields JA. Conjunctival amyloidosis: report of six cases and review of the literature. Surv Ophthalmol [Internet]. 2006;51(4):419–33. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0039625706000804
15. Banerjee P, Alam M, Subramanian N, Kundu D, Koka K, Poonam N, et al. Orbital and adnexal amyloidosis: thirty years experience at a tertiary eye care center. Indian J Ophthalmol [Internet]. 2021;69(5):1161. Available from: https://journals.lww.com/ijo/Fulltext/2021/05000/Orbital_and_adnexal_amyloidosis__Thirty_years.30.aspx
16. Dammacco R, Merlini G, Lisch W, Kivelä TT, Giancipoli E, Vacca A, et al. Amyloidosis and ocular involvement: an overview. Semin Ophthalmol [Internet]. 2020;35(1):7–26. https://doi.org/10.1080/08820538.2019.1687738.
17. Rowczenio DM, Noor I, Gillmore JD, Lachmann HJ, Whelan C, Hawkins PN, et al. Online registry for mutations in hereditary amyloidosis including nomenclature recommendations. Hum Mutat [Internet]. 2014;35(9):E2403–12. https://doi.org/10.1002/humu.22619.
18. You J. Vitrectomy for vitreous amyloidosis. Int J Ophthalmol [Internet]. 2011;4(3):307–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22553668
19. Beirão JM, Malheiro J, Lemos C, Beirão I, Costa P, Torres P. Ophthalmological manifestations in hereditary transthyretin (ATTR V30M) carriers: a review of 513 cases. Amyloid [Internet]. 2015;22(2):117–22. https://doi.org/10.3109/13506129.2015.1015678.
20. Ando E, Ando Y, Okamura R, Uchino M, Ando M, Negi A. Ocular manifestations of familial amyloidotic polyneuropathy type I: long term follow up. Br J Ophthalmol [Internet]. 1997;81(4):295–8. https://doi.org/10.1136/bjo.81.4.295.
21. Haraoka K, Ando Y, Ando E, Sandgren O, Hirata A, Nakamura M, et al. Amyloid deposition in ocular tissues of patients with familial amyloidotic polyneuropathy (FAP). Amyloid [Internet]. 2002;9(3):183–9. https://doi.org/10.3109/13506120209114820.
22. Martins AC, Rosa AM, Costa E, Tavares C, Quadrado MJ, Murta JN. Ocular manifestations and therapeutic options in patients with familial amyloid polyneuropathy: a systematic review. Biomed Res Int [Internet]. 2015;2015:1–9. Available from: http://www.hindawi.com/journals/bmri/2015/282405/

23. Venkatesh P, Selvan H, Singh SB, Gupta D, Kashyap S, Temkar S, et al. Vitreous amyloidosis. Ophthalmology [Internet]. 2017;124(7):1014–22. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642016324769
24. Hashemian H, Jabbarvand M, Khodaparast M, Khalilipour E, Riazi H. Ocular Presentations of amyloidosis. In: Amyloidosis [Internet]. InTech; 2013. Available from: http://www.intechopen.com/books/amyloidosis/ocular-presentations-of-amyloidosis
25. Misumi Y, Ando Y, Ueda M, Obayashi K, Jono H, Su Y, et al. Chain reaction of amyloid fibril formation with induction of basement membrane in familial amyloidotic polyneuropathy. J Pathol [Internet]. 2009;219(4):481–90. https://doi.org/10.1002/path.2618.
26. Beirão NM, Matos E, Beirão I, Costa PP, Torres P. Recurrence of vitreous amyloidosis and need of surgical reintervention in Portuguese patients with familial amyloidosis ATTR V30M. Retina [Internet]. 31(7):1373–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21358362
27. Ferreira NN, Cunha Dias DA, Afonso Carvalho RP, Coelho PM, MT. Re-intervention in de novo vitreous opacities after pars plana vitrectomy in familial amyloidotic polyneuropathy TTR VAL30METPORTUGUESE patients. Retin Cases Brief Rep [Internet]. 2019;13(3):273–8. Available from: https://journals.lww.com/01271216-201901330-00020
28. Silva-Arajo AC, Tavares MA, Cotta JS, Castro-Correia JF. Aqueous outflow system in familial amyloidotic polyneuropathy, Portuguese type. Graefe's Arch Clin Exp Ophthalmol [Internet]. 1993;231(3):131–5. https://doi.org/10.1007/BF00920934.
29. Tsukahara S, Matsuo T. Secondary glaucoma accompanied with primary familial amyloidosis. Ophthalmologica [Internet]. 1977;175(5):250–62. Available from: https://www.karger.com/Article/FullText/308666
30. Kakihara S, Hirano T, Imai A, Miyahara T, Murata T. Baerveldt glaucoma drainage implant surgery for secondary glaucoma in patients with transthyretin-related familial amyloid polyneuropathy. Jpn J Ophthalmol [Internet]. 2020;64(5):533–8. https://doi.org/10.1007/s10384-020-00753-0.
31. Prabhakaran V, Babu K, Mahadevan A, Murthy S. Amyloidosis of lacrimal gland. Indian J Ophthalmol [Internet]. 2009;57(6):461. https://doi.org/10.4103/0301-4738.57160.
32. Kim J, Kim L, Kang SM. Primary systemic amyloidosis involving the lacrimal sac. Korean J Ophthalmol [Internet]. 2016;30(3):234. https://doi.org/10.3341/kjo.2016.30.3.234.
33. Mesa-Gutierrez J. Primary localized conjunctival amyloidosis: a case report with a ten-year follow-up period. Clin Ophthalmol [Internet]. 2008:685. Available from: http://www.dovepress.com/primary-localized-conjunctival-amyloidosis-a-case-report-with-a-ten-ye-peer-reviewed-article-OPTH
34. Shields JA, Shields CL. Conjunctival amyloidosis: Atlas of eyelid and conjunctival tumors. Lippincott Williams and Williams. Philadelphia: 1999, pp. 324–25.
35. Rousseau A, Cauquil C, Dupas B, Labbé A, Baudouin C, Barreau E, et al. Potential role of in vivo confocal microscopy for imaging corneal nerves in transthyretin familial amyloid polyneuropathy. JAMA Ophthalmol [Internet]. 2016;134(9):983. https://doi.org/10.1001/jamaophthalmol.2016.1889.

Chapter 9
Ophthalmological Manifestations in AL and Wild-Type ATTR Amyloidosis

Kelma Macedo Pohlmann Simões and Mário Martins dos Santos Motta

9.1 AL Amyloidosis

Immunoglobulin light chain (AL) amyloidosis is one of the most common types of systemic amyloidosis, with an incidence of 12 cases per million persons per year [1]. In AL amyloidosis, the insoluble protein subunit is an immunoglobulin light or heavy chain fragment that can deposit in any organ, with the exception of the central nervous system. AL amyloidosis occurs in patients with systemic disease, with multiple myeloma or as a localized amyloidosis [2]. Localized AL amyloidosis occurs because of the production of amyloidogenic light chains by clonal B cells in the affected tissue.

Ocular signs and symptoms usually appear after the clinical diagnosis of AL amyloidosis, but ocular manifestations can also be the initial feature. An ocular sign in AL amyloidosis that can be very specific is nontraumatic, bilateral periorbital purpura or ecchymosis, although it occurs in only 15% of cases [3]. In the most severe cases, it is recognized as "raccoon eyes", but it is considered a late sign of the disease [4].

Many other ocular sites can be involved in AL amyloidosis (systemic and localized forms), such as the eyelid, lymphatic gland, conjunctiva, ocular adnexa, orbit, extraocular muscles, and temporal artery [5, 6]. The symptoms will vary according to the site of amyloid deposition. Upper and lower eyelid swelling, tearing, foreign-body sensation, hyperemia of the bulbar conjunctiva, recurrent subconjunctival hemorrhages, unilateral salmon-like plaques in the tarsal, and/or bulbar conjunctiva can be present at the ocular surface [2]. Diplopia and ophthalmoplegia can be present in cases of extraocular muscle involvement, whereas ocular displacement and proptosis are present in cases of orbital mass involvement [2]. In cases of

K. M. P. Simões (✉) · M. M. dos Santos Motta
Setor de Retina e Vítreo, Departamento de Oftalmologia, Universidade Federal do Estado do Rio de Janeiro (UNIRIO), Rio de Janeiro, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_9

involvement of the temporal artery, jaw claudication, headache, decreased visual acuity, and diplopia are present and resemble giant cell arteritis, and a biopsy of the temporal artery with Congo red staining may be necessary to confirm the diagnosis of amyloidosis [7]. The trabecular meshwork can also be infiltrated with amyloid, resulting in glaucoma [8].

In cases of conjunctival mass, the diagnosis is established through biopsy followed by an immunohistochemical analysis. It is important to mention that excision should be followed by cryotherapy, but recurrences can occur if the lesion is not completely excised [9]. In cases of lachrymal gland involvement, ptosis and superior–temporal, nontender masses can be present, and the diagnosis can be confirmed with tissue biopsy [5]. The orbital mass can be biopsied, and if complete excision is not possible, adjuvant external beam radiotherapy reduces the risk of recurrence [10].

9.2 Wild-Type Amyloidosis

Wild-type amyloidosis, previously known as senile cardiac amyloidosis, has been described mainly in older adult males and is rapidly increasing in recognition [11]. With the aging of the worldwide population, wild-type amyloidosis will be the most common type of cardiac amyloidosis. To date, there are no specific signs of ocular involvement described in this type of amyloidosis, but it is very important to try to find clinical clues at the physical examination to help with the early diagnosis and management of this subtype of the disease.

References

1. Kyle RA, Larson DR, Kurtin PJ, Kumar S, Cerhan JR, Therneau TM, et al. Incidence of AL amyloidosis in Olmsted County, Minnesota, 1990 through 2015. Mayo Clin Proc. 2019;94(3):465–71.
2. Dammacco R, Merlini G, Lisch W, Kivelä TT, Giancipoli E, Vacca A, et al. Amyloidosis and ocular involvement: an overview. Semin Ophthalmol. 2020;35(1):7–26.
3. Merlini G, Dispenzieri A, Sanchorawala V, Schönland SO, Palladini G, Hawkins PN, et al. Systemic immunoglobulin light chain amyloidosis. Nat Rev Dis Primers. 2018;4(1):38.
4. Pereira VG, Jacinto M, Santos J, de Abreu TT. Periorbital purpura (raccoon's eyes). BMJ Case Rep. 2014;2014:bcr2013201407.
5. Leibovitch I, Selva D, Goldberg RA, Sullivan TJ, Saeed P, Davis G, et al. Periocular and orbital amyloidosis: clinical characteristics, management, and outcome. Ophthalmology. 2006;113(9):1657–64.
6. Blandford AD, Yordi S, Kapoor S, Yeaney G, Cotta CV, Valent J, et al. Ocular adnexal amyloidosis: a mass spectrometric analysis. Am J Ophthalmol. 2018;193:28–32.
7. Azarfar A, Sharma A, Parikh JG, Shaikh NM, King-Morris K. Ocular manifestation of giant cell arteritis vs AL-amyloidosis: similar presentations but different approaches. Mod Rheumatol Case Rep. 2021;5(1):117–22.

8. Reynolds MM, Veverka KK, Gertz MA, Dispenzieri A, Zeldenrust SR, Leung N, et al. Ocular manifestations of systemic amyloidosis. Retina. 2018;38(7):1371–6.
9. Prager AJ, Habib LA, Gambogi T, Busam KJ, Marr BP. Long-term follow-up of 4 patients with conjunctival amyloidosis. Ocul Oncol Pathol. 2018;4(5):313–7.
10. Khaira M, Mutamba A, Meligonis G, Rose GE, Plowman PN, O'Donnell H. The use of radiotherapy for the treatment of localized orbital amyloidosis. Orbit. 2008;27(6):432–7.
11. Rapezzi C, Lorenzini M, Longhi S, Milandri A, Gagliardi C, Bartolomei I, et al. Cardiac amyloidosis: the great pretender. Heart Fail Rev. 2015;20(2):117–24.

Chapter 10
Dermatological Manifestations

Jade Cury-Martins and Jose Antonio Sanches

10.1 Introduction

Cutaneous involvement by amyloidosis can occur as a skin-limited disorder, with no internal organ involvement or as a manifestation of systemic amyloidosis (SA) [1]. Of the many types of amyloid described, only some are associated with cutaneous manifestations (e.g., amyloid K, amyloid light chain, amyloid A, amyloid beta-2 microglobulin, and amyloid transthyretin) [2]. Table 10.1 shows the main subtypes of amyloidosis with cutaneous involvement and their associated subtypes of amyloid deposits.

Table 10.1 Main subtypes of amyloidosis with cutaneous involvement and associated subtypes of amyloid deposits

Type of amyloidosis	Type of amyloid deposit
Localized cutaneous amyloidosis (LCA)	
Pri mary LCA	
– Macular amyloidosis - Lichen amyloidosis (papular) - Nodular amyloidosis	Keratin derived (AK) Keratin derived (AK) Light immunoglobulin (AL)
Secondary LCA	Keratin derived (AK)—predominantly
Systemic amyloidosis with cutaneous involvement	
Immunoglobulin light chain amyloidosis	Light immunoglobulin (AL)
Secondary amyloidosis	Serum amyloid A (AA)
Dialysis-related amyloidosis	A beta-2 microglobulin
Heredofamilial amyloidosis	Transthyretin (ATTR)—most common

J. Cury-Martins (✉) · J. A. Sanches
Department of Dermatology, University of São Paulo, São Paulo, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_10

10.2 Localized Cutaneous Amyloidosis

10.2.1 Primary Localized Cutaneous Amyloidosis

In primary localized cutaneous amyloidosis (PLCA), amyloid deposits occur in previously normal skin, and there is no evidence of internal organ involvement. The main subtypes include macular, papular (lichen amyloidosis), and nodular amyloidosis [1–4].

– **Macular and lichen (papular) amyloidosis:** these are uncommon forms and can coexist on the same individual. They occur more often in Asian, South American, or Middle Eastern populations, arising in adulthood. It is usually sporadic, but might also be the manifestation of familial PLCA. Amyloid deposits are derived from keratin intermediate filament proteins, possibly related to degeneration of basal keratinocytes in the overlying epidermis, and therefore, some authors suggest the use of the term "keratinic" PLCA [1]. Chronic pruritus and rubbing/scratching might contribute to amyloid deposition.

10.2.1.1 Clinical Features

Macular amyloidosis is characterized by hyperpigmented thin plaques, with a typically reticulate or 'rippled' pattern and a gray-tan coloration (Fig. 10.1). Mild-to-moderate pruritus is usually present, but might be absent in a minority of cases. Lesions occur more often on the back (scapular region) and extensive surfaces of the extremities.

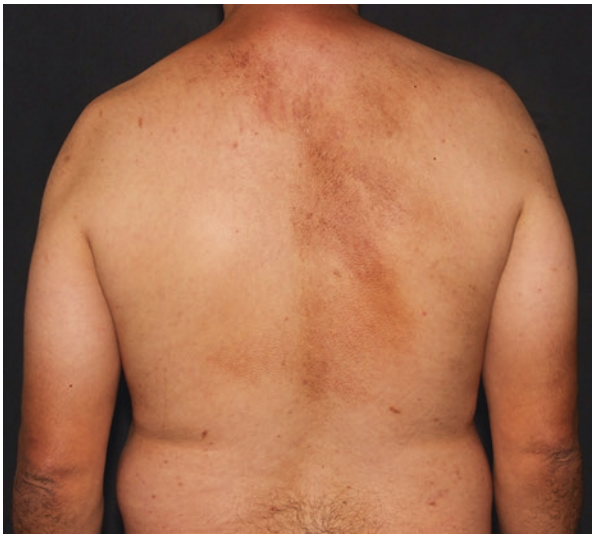


Fig. 10.1 Macular amyloidosis: hyperpigmented gray-tan plaques, with a 'rippled' pattern on the back. Courtesy from the Dermatology Department—University of São Paulo

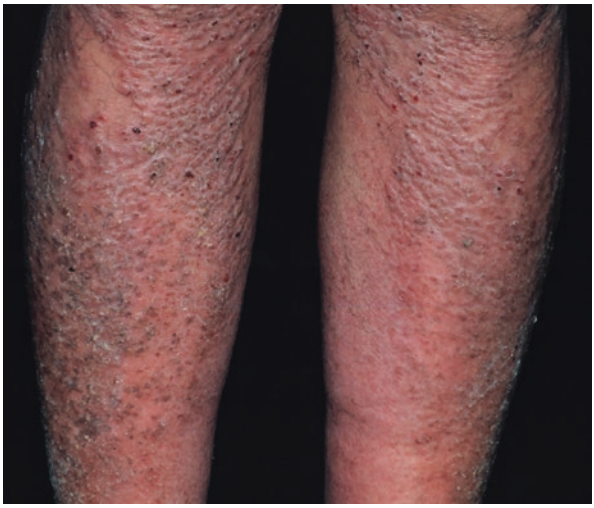


Fig. 10.2 Lichen amyloidosis: flesh-colored, scaly, hyperkeratotic, dome-shaped small papules coalescing into plaques on the shins. Courtesy from the Dermatology Department—University of São Paulo

Lichen amyloidosis manifests as pruritic, discrete, flesh-colored to hyperpigmented, scaly, hyperkeratotic, dome-shaped small papules (2–4 mm) that might coalesce into plaques with a rippled appearance (Fig. 10.2). Lesions occur more often on the shins, unilaterally, or progressing to symmetric bilateral involvement.

Some patients may have an overlap of both manifestations (macular and papular). Other common locations are the arms, back, calves, and dorsum of the feet. Unusual locations include the external auditory canal, upper lip, and nasolabial folds or the glans penis.

10.2.1.2 Histopathology

In both forms, small globules of pink material (amyloid) are present in the superficial dermis, most often in dermal papillae. Degeneration of basal keratinocytes with cytoplasmic vacuolization might be present, sometimes with intraepidermal cytoid bodies. Other findings include pigment incontinence, with admixed melanophages.

The amyloid deposit is more subtle in macular amyloidosis but more obvious in lichen amyloidosis. Lichen amyloidosis also demonstrates hyperkeratosis and epidermal acanthosis that may resemble lichen simplex chronicus.

Keratinocyte-derived amyloid stains with Congo red, crystal violet, and thioflavin T and is positive for cytokeratins, such as CK5, on immunohistochemistry.

10.2.1.3 Diagnosis

It is made based on the typical clinical aspects (type of lesion, location, and pruritus) added to the detection of amyloid deposits on histology after a punch biopsy.

10.2.1.4 Differential Diagnosis

For macular amyloidosis: notalgia paresthetica, confluent and reticulated papillomatosis, and tinea versicolor.

For lichen amyloidosis: lichen simplex chronicus, prurigo nodularis, hypertrophic lichen planus, and pretibial myxedema.

10.2.1.5 Treatment

Both forms are limited to the skin, with no potential for visceral involvement; therefore, the aims of treatment are to relieve symptoms and cosmetic appearance. There is a lack of high-quality trials, and available treatments are usually disappointing.

Topical corticosteroids are the most commonly used, such as cream, ointment, occlusive dressings, and intralesional injections. Other options include topical calcineurin inhibitors, phototherapy, emollients and keratolytic agents.

– **Nodular amyloidosis:** it is even more rare than macular and lichen amyloidosis, also occurring in adults with no gender predilection. Although it is caused by the deposition of light immunoglobulin chains (AL-type amyloid), it is considered a skin-limited disease with rare reports of associated hematologic dyscrasia [3, 4]. The immunoglobulin chains in this type of amyloidosis are usually secreted by a plasma cell-rich lymphoid infiltrate and are considered localized plasma cell dyscrasia.

10.2.1.6 Clinical Features

It usually manifests as asymptomatic, single or multiple waxy, yellow-to-brown nodules or plaques with a predilection for acral sites; the overlying epidermis might be normal or atrophic (Fig. 10.3).

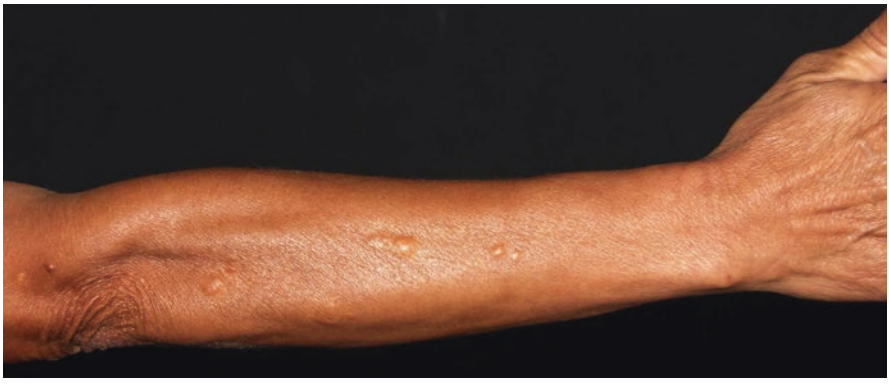


Fig. 10.3 Nodular amyloidosis: waxy yellow nodules on the forearms. Courtesy from the Dermatology Department—University of São Paulo

10.2.1.7 Histopathology

In nodular amyloidosis, diffuse amyloid deposits are found in the dermis, subcutis, and blood vessel walls, with a perivascular infiltrate of plasma cells. Immunohistochemistry for kappa and lambda light chain or in situ hybridization might demonstrate plasma cell clonality in some cases, with negative staining for cytokeratin.

10.2.1.8 Diagnosis

Based on clinical suspicion, diagnosis is confirmed by skin biopsy (punch or shave) showing amyloid deposits. Due to the rare but described risk of systemic disease, a review of symptoms and complementary exams to exclude systemic disease is suggested, with some authors recommending at least annual reevaluation of possible systemic involvement.

10.2.1.9 Differential Diagnosis

Cutaneous lymphomas, pseudolymphomas, leukemia cutis, and granulomatous nodules, such as sarcoidosis and granuloma annulare.

10.2.1.10 Treatment

Treatment is indicated for cosmetic reasons and usually includes physical removal or destruction of the nodules (surgical excision, dermabrasion, and electrodessication).

10.2.2 Secondary Localized Cutaneous Amyloidosis

It consists of the finding of small amounts of amyloid in nonhealthy/diseased skin. It might be found in cutaneous tumors (both benign and malignant, such as pilomatrixomas, basal cell carcinomas, and nevus), but it was also described in other cutaneous inflammatory diseases or after phototherapy (PUVA) treatments. In such cases, amyloid deposits usually originate from keratinocytes with positive immunostaining for cytokeratin [1].

10.2.3 Rare Variants of Primary Cutaneous Amyloidosis

Other very rare variants include poikiloderma-like cutaneous amyloidosis [5, 6] (in dermatology, poikilodermatous lesions are characterized by hypo-hyperpigmented macules, teleangiectasia, and atrophy) and amyloidosis cutis dyschromica, either sporadic or familial (characterized by asymptomatic, progressive, and diffuse hyper- and hypopigmentation) [7, 8].

10.3 Systemic Amyloidosis with Cutaneous Involvement

Skin involvement is present in 25–40% of cases of SA, mainly in immunoglobulin light chain (AL) amyloidosis but also in secondary systemic (AA) amyloidosis, dialysis-associated SA, and some forms of hereditary amyloidosis [3, 9–12].

10.3.1 Immunoglobulin Light Chain Amyloidosis (AL Amyloidosis)

Skin involvement is present in approximately 40% of patients and might provide an early clue to the existence of an underlying plasma-cell dyscrasia. In this group of patients, amyloid deposits consist of immunoglobulin light chain produced by plasma cells. Figures 10.4 and 10.5 illustrate some of the typical cutaneous findings of AL amyloidosis, as described below.

One of the most frequent sites of amyloid deposition is in the blood vessel wall of the dermis, resulting in wall fragility to minor traumas or even after an increase in hydrostatic pressure (Valsalva maneuver) and the development of purpuric lesions, petechiae, and ecchymoses, especially on areas of thin skin, such as the eyelids (Racoon eyes).

Other possible skin lesions are shiny or waxy, asymptomatic, dome-shaped papules that might appear translucent, resembling vesicles. These types of lesions are more frequent on the mucocutaneous junctions (such as the orbits, nares, lips, and genital) or flexural areas and are a result of amyloid deposition at the superficial dermis. Sometimes, lesions can form nodules or coalesce, forming plaques or larger tumefactions.

SA is the most common cause of macroglossia in adults and occurs in approximately 10% of patients. The tongue is usually diffusely enlarged and firm, with tooth indentations along the lateral borders.

Other less common skin findings include the following [11, 13]:

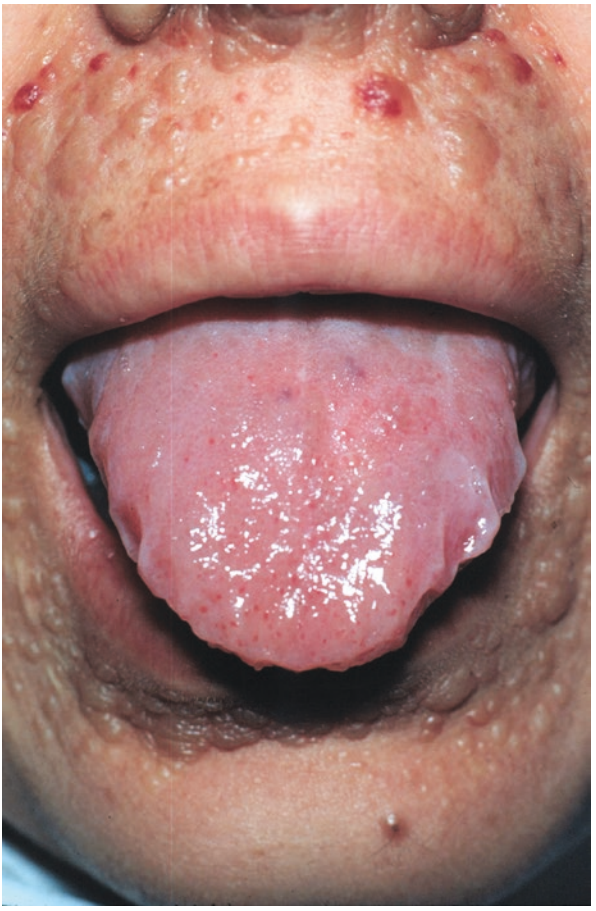


Fig. 10.4 Skin manifestations of systemic AL amyloidosis: shiny or waxy, dome-shaped papules, with a translucent appearance, some are purpuric due to blood vessel wall fragility; macroglossia with tooth indentations along the lateral borders. Courtesy from the Dermatology Department—University of São Paulo

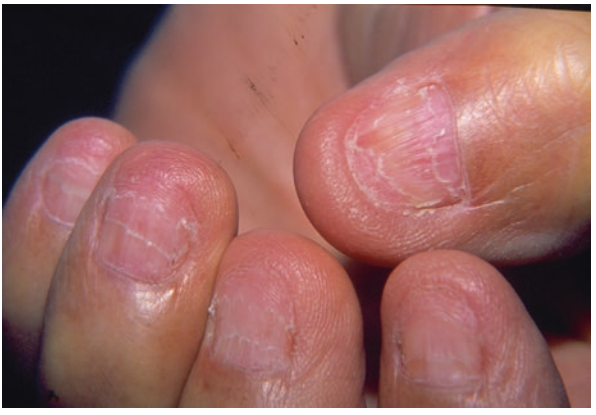


Fig. 10.5 Nail dystrophy associated with systemic AL amyloidosis. Courtesy from the Dermatology Department—University of São Paulo

- Milia on the hands.
- Bullous lesions might eventually occur on skin and mucous membranes as a result of cleavage within dermal amyloid deposits.
- Nail findings: brittleness, longitudinal ridging, crumbling, and nail dystrophy, usually due to amyloid infiltration of the nail matrix [11, 13].
- Scalp findings: diffuse nonscarring alopecia might be a sign of SA. It occurs due to the infiltration of hair follicles by amyloid protein or due to deposition in the perifollicular area causing vascular impairment, resulting in hair thinning.
- Scleroderma-like diffuse infiltration might rarely represent a manifestation of SA, with amyloid deposits found on skin biopsies of infiltrated skin [13, 14].
- Acquired cutis laxa: on this type of cutaneous manifestation, skin becomes loose, redundant and has a wrinkled appearance. Rarely, it can be associated with an SA, and in such cases, in addition to the fragmented elastic fibers on histology, amyloid deposits are found [15].

10.3.2 Secondary (AA) Amyloidosis

This group of SA occurs secondary to inflammatory and infectious conditions. Cutaneous involvement is rare, with reports of petechiae, purpura, and alopecia, but amyloid deposits may also be detected in clinically normal skin. Deposits are composed of serum amyloid A [16].

10.3.3 Dialysis-Related Amyloidosis (Beta-2 Microglobulin Amyloid)

Cutaneous involvement in this group of patients is also rare and is reported as hyperpigmentation, lichenoid eruptions, or nodules, with deposits of beta 2 microglobulin-derived amyloid, mainly in long-term hemodialysis patients [17].

10.3.4 Heredofamilial Amyloidosis

The most common hereditary variant of SA is hereditary transthyretin amyloidosis, which is related to the deposition of transthyretin amyloid. Cutaneous lesions may occur as ulcers, atrophic scars, and petechiae, with amyloid deposits in the vessels and in the sweat glands.

Other hereditary systemic amyloidoses, such as Muckle–Wells syndrome and familial Mediterranean fever, may develop other types of cutaneous manifestations not related to amyloid deposits, such as cold urticaria and Henoch–Schoenlein purpura, respectively [1].

References

1. Fernandez-Flores A. Cutaneous amyloidosis: a concept review. Am J Dermatopathol. 2012;34(1):1–14; quiz 5-7.
2. Molina-Ruiz AM, Cerroni L, Kutzner H, Requena L. Cutaneous deposits. Am J Dermatopathol. 2014;36(1):1–48.
3. Steciuk A, Dompmartin A, Troussard X, Verneuil L, Macro M, Comoz F, et al. Cutaneous amyloidosis and possible association with systemic amyloidosis. Int J Dermatol. 2002;41(3):127–32; discussion 33-4.
4. Kaltoft B, Schmidt G, Lauritzen AF, Gimsing P. Primary localised cutaneous amyloidosis—a systematic review. Dan Med J. 2013;60(11):A4727.
5. Heng JK, Ho SA, Tan KB. Poikiloderma-like cutaneous amyloidosis--a rare presentation of primary localized cutaneous amyloidosis. Dermatol Online J 2016;22(1).
6. Unni M, Ankad B, Naidu V, Sudakar RK. A familial poikiloderma-like cutaneous amyloidosis. Indian J Dermatol. 2014;59(6):633.
7. Qiao J, Fang H, Yao H. Amyloidosis cutis dyschromica. Orphanet J Rare Dis. 2012;7:95.
8. Kuseyri O, Haas D, Lang N, Schäkel K, Bettendorf M. Amyloidosis cutis Dyschromica, a rare cause of hyperpigmentation: a new case and literature review. Pediatrics. 2017;139(5)
9. Ferraresso MG, Bollea-Garlatti ML, Torre AC, Comparatore M, Nucifora E, Aguirre MA, et al. Systemic amyloidosis: the skin as a clue of an unexpected diagnosis. Int J Womens Dermatol. 2021;7:359–60.
10. Flores-Bozo LR, Echevarría-Keel J, Domínguez-Cherit J, Esquivel-Pedraza L, Méndez-Flores S. Mucocutaneous manifestations in systemic amyloidosis a retrospective analytical study in a tertiary care center. Int J Dermatol. 2019;58(9):1062–8.
11. Oberlin KE, Wei EX, Cho-Vega JH, Tosti A. Nail changes of systemic amyloidosis after bone-marrow transplantation in a patient with multiple myeloma. JAMA Dermatol. 2016;152(12):1395–6.
12. Kumar S, Sengupta RS, Kakkar N, Sharma A, Singh S, Varma S. Skin involvement in primary systemic amyloidosis. Mediterr J Hematol Infect Dis. 2013:e2013005, 5. p.
13. Drumm C, O'Reilly M, McCartney Y, O'Kane M. Myeloma-associated AL amyloidosis presenting with nail dystrophy and scleroderma-like skin changes. Clin Exp Dermatol. 2022;47(2):491–3.
14. Cho SB, Park JS, Kim HO, Chung KY. Scleroderma-like manifestation in a patient with primary systemic amyloidosis: response to high-dose intravenous immunoglobulin and plasma exchange. Yonsei Med J. 2006;47(5):737–40.
15. Vork DL, Shah KK, Youssef MJ, Wieland CN. Acral localized acquired cutis laxa as presenting sign of underlying systemic amyloidosis. J Cutan Pathol. 2020;47(11):1050–3.
16. Garo F, Chatelain J, Aglae C, Moranne O. Two cases of secondary AA amyloidosis involving the skin and chronic kidney infection with a nephrotic syndrome in a high-income country. BMJ Case Rep. 2021;14(6)
17. Shimizu S, Yasui C, Yasukawa K, Nakamura H, Shimizu H, Tsuchiya K. Subcutaneous nodules on the buttocks as a manifestation of dialysis-related amyloidosis: a clinicopathological entity? Br J Dermatol. 2003;149(2):400–4.

Chapter 11
Gastrointestinal Symptoms

Cibele Franz, Amanda Saavedra, Agueda Miranda, and Márcia Lyrio

11.1 Introduction

A varied range of gastrointestinal (GI) symptoms may appear in amyloidosis, and the clinical presentation and disease course are not predictable solely from genotype [1, 2]. Some mutations are associated with a mixed phenotype and, consequently, GI manifestations (Thr60Ala, Glu89Gln and Glu54Gln) [3–5]. This kind of symptom seems to depend on age (the phenotypic penetrance is age-dependent), environmental factors, the degree of amyloid fragmentation, and the location and extent of amyloid deposition with subsequent damage [6]. The pathogenesis is not fully understood, but it is generally suggested that GI symptoms arise due to motility disturbances of the GI tract caused by autonomic neuropathy [7] or to mucosal infiltration by fragments and/or intact serum amyloid protein [2, 5, 8].

GI manifestations in amyloidosis are more common in reactive amyloidosis, but may occur in primary amyloidosis (prevalence approximately 1%) [9, 10]. Primary amyloidosis usually presents with constipation and mechanical obstruction, while reactive amyloidosis presents with diarrhea (more common) and malabsorption, although this is not a rule [8, 9, 11]. Gastric and duodenal involvement can cause upper symptoms, including nausea, abdominal pain, and hematemesis, and small intestinal involvement can result in symptoms, such as diarrhea, steatorrhea, small intestinal bacterial overgrowth, GI bleeding, and obstruction. These kinds of GI disturbances present even before the onset of polyneuropathy in some cases [5, 6, 9, 12]. These symptoms vary in intensity and, depending on their severity, contribute to the worsening of the patient's nutritional status.

C. Franz (✉) · A. Saavedra · A. Miranda · M. Lyrio
Department of Gastroenterology and Hepatology, Federal University of the State of Rio de Janeiro—UNIRIO, Rio de Janeiro, RJ, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_11

The course of amyloidosis includes highly variable systemic clinical signs and symptoms. The disease could initiate with numerous nonspecific GI symptoms, and it increases the risk of misdiagnosis. In addition, GI manifestations may also mean worsening of disease progression. Radiologic and endoscopic findings of GI amyloidosis are nonspecific, and the diagnosis requires biopsy to identify amyloid infiltration and, sometimes, in addition to genetic tests.

Gastrointestinal tract sites involved in amyloidosis

Localization	Clinical Change	Symptoms	Most common in:
Oral cavity [13]	Macroglossia	None described	AL amyloidosis
Esophagus [14–16]	Mucosal infiltration Denervation of the esophagus—Achalasia Infiltration of the liver Infiltration in the vessels—ischemia	Heartburn to dysphagia Food impaction Esophageal varices (±hematemesis) Necrotizing esophagitis (±hematemesis)	AL amyloidosis Or AA amyloidosis
Stomach[a] [10, 12, 17–21]	Mucosal infiltration	Nausea, vomiting, abdominal pain Hematemesis Gastric outlet obstruction Gastroparesis Early satiety Unintentional weight loss	Primary amyloidosis AL amyloidosis and multiple myeloma Primary amyloidosis Secondary amyloidosis (sometimes in primary amyloidosis) ATTR amyloidosis ATTR amyloidosis
Small intestine	Direct amyloid infiltration of the small bowel mucosa or direct pressure damage to neural structures by amyloid deposits Amyloid deposition into the myenteric plexus and vascular supply Vascular infiltration Increased capillary permeability	Dismotility → bacterial overgrowth Malabsorption syndrome + dysautonomia (orthostatic hypotension). pseudo-obstruction Mucosal ischemia → hematochezia and malabsorption syndrome Protein-losing enteropathy	Primary amyloidosis or Secondary amyloidosis

Localization	Clinical Change	Symptoms	Most common in:
Colon [9, 24, 27, 28]	Mucosal and vascular infiltration Myenteric plexus can be replaced by other local enteric neurons Infiltration is within smooth muscle Mucosal infiltration	Diarrhea Constipation Bowel obstruction Hematochezia Perforations Pseudo-obstruction (self limited) Pseudo-obstruction (chronic course irreversible) Alternating diarrhea/ constipation	All of them AA amyloidosis AL amyloidosis ATTR amyloidosis
Liver [5, 15, 30–38]	Hepatic infiltration (sinusoidal) Amyloid protein in the liver parenchyma and arteriolar membranes	Hepatomegaly (painless) Cholestasis (elevated serum alkaline phosphatase levels) Jaundice (rare) Portal Hypertension → esophageal varices Liver spontaneous bleeding	AL amyloidosis or ATTR amyloidosis AA amyloidosis
Pancreas [12, 22, 24]	Amyloid deposition in the pancreas is rare Endocrine—the death of the islet cells from the accumulation and cytotoxic effects of human islet amyloid polypeptide. Exocrine—pancreatic infiltration, dysmotility and lack of proper absorption of bile acids	Pancreatic head mass Type 2 diabetes mellitus Steatorrhea Malabsorption syndrome	AL amyloidosis Local amyloidosis ATTR amyloidosis or AL amyloidosis
Retroperitoneal space [39]	Amyloid deposition in retroperitoneal space	Retroperitoneal mass	AL amyloidosis

[a]Gastric biopsies are essential for the diagnosis, since the endoscopic characteristics of lesions derived from amyloidosis are extremely similar to those of gastric primary malignant disease [20]

1. Oral cavity—Macroglossia is described as the most common condition attributed to amyloidosis due to infiltration of amyloid derivatives [13].
2. Esophagus—Symptoms range from heartburn to dysphagia and rarely hematemesis and food impaction secondary to achalasia (by denervation of the esophagus) [14]. In these cases, the cause for hematemesis seems to be esophageal variceal rupture (amyloid infiltration of the liver) or necrotizing esophagitis (amyloid deposition in the vessels resulting in ischemia) [15, 16].

3. Stomach—Nausea, vomiting, abdominal pain (mild to intense), hematemesis, or gastric outlet obstruction are present in primary amyloidosis [12]. Gastroparesis is frequent in secondary amyloidosis but can also be seen in other forms of amyloidosis [17, 18]. In approximately one-third of hereditary systemic amyloidosis patients, unintentional weight loss and early satiety are related [19]. Gastric biopsies are essential for diagnosis, since the endoscopic characteristics of lesions derived from amyloidosis are extremely similar to those of gastric primary malignant disease [20]. However, it appears to be difficult because of the infiltrative characteristic of the mucosa that amyloidosis has [10]. Gastric involvement should be considered in patients with multiple myeloma and obscure GI bleeding [21].
4. Small intestine—Symptoms come from direct amyloid infiltration of the small bowel mucosa or from direct pressure damage to neural structures by amyloid deposits [22].

   Digestion is affected by autonomic neuropathy of the enteric nervous system and myopathy secondary to smooth muscle amyloid infiltration. These factors have consequences on GI motility, reducing it. Therefore, bacterial overgrowth occurs as a result of dysmotility. Vascular infiltration, when present, triggers mucosal ischemia. All of these events contribute to the malabsorption syndrome [23]. The diagnosis should be made when intestinal malabsorption is accompanied by signs of dysautonomia (orthostatic hypotension). Amyloidosis may be responsible for pseudo-obstruction, including deposition into the myenteric plexus and vascular supply of the small intestine. These depositions seem to also be the cause of abdominal pain and intestinal bleeding [1, 25]. Protein-losing enteropathy is likely a result of increased capillary permeability with resultant loss of plasma proteins through the affected mucosa [22–26].
5. Colon—Patients may become symptomatic from motility disorders. The most common manifestations described are diarrhea, constipation, bowel obstruction, hematochezia, and perforations [9, 24, 27, 28]. Sometimes, in computed tomography (CT) scans, dilated bowel segments may be visualized. Similar to amyloidosis in the small intestine, pseudo-obstruction could also be seen in the large intestine. However, the clinical condition is different between AA amyloidosis and AL amyloidosis. Patients with pseudo-obstruction in AA amyloidosis typically have a clinical presentation that is self-limited (myenteric plexus can potentially be replaced by other local enteric neurons), as opposed to AL amyloidosis, which has a chronic irreversible course (the infiltration is within smooth muscle) [29]. Although papers about survival are rare, the prognosis of GI amyloidosis with colonic involvement (AL amyloidosis) was poorer than those without GI involvement [8]. In hereditary systemic amyloidosis, alternating diarrhea/constipation could occur in one-third of patients [19]. The increase in the number of organs and systems involved is associated with a worse prognosis.

6. Liver—Despite being the heart, kidney, and peripheral nerves most commonly affected by primary systemic amyloidosis, the liver is also a common site of amyloid deposition (70% of the patients had liver involvement) [30]. Deposition of amyloid in the liver rarely causes clinical manifestations, and it sometimes occurs with another cause involved [30, 31]. Hepatomegaly and elevated serum alkaline phosphatase levels are the most common specific clinical findings (81% and 86%, respectively) [32], with (rare) or without jaundice [33]. General symptoms associated with liver damage are involuntary weight loss and proteinuria [30]. Liver biopsy is a safe procedure, and some patients with the general symptoms cited before may benefit from it. Some studies have demonstrated that age, hepatic involvement, and heart involvement can significantly influence survival in these patients [30, 34]. In addition, portal hypertension (with or without ascites) and esophageal variceal bleeding could be found in AL-type amyloid. These complications are a consequence of deposits within the space of Disse leading to decreased sinusoidal space, which subsequently causes portal hypertension secondary [5, 15, 34]. The increase in resistance to blood flow in the liver generates symptoms similar to cirrhotic patients [35]. More massive infiltration results in an enlarged liver with rubber elastic consistency [36]. Splenomegaly can be associated with hepatomegaly in patients with amyloidosis in the majority of cases. In less than 30% of patients, infiltration by amyloid fibrils can result in hyposplenism, which is defined by the presence of Howell–Jolly bodies [37]. The capacity of the spleen to protect against encapsulated bacterial decay, therefore, requires increased monitoring in this patient population [5]. Liver spontaneous bleeding is attributed to secondary amyloidosis for deposition of amyloid protein in the liver parenchyma, and arteriolar membranes lead to a waxy liver texture with increased fragility; this pathological fragility makes the liver vasculature prone to hemorrhage and the liver parenchyma prone to spontaneous rupture [38].
7. Pancreas—Systemic amyloidosis can involve various organs; however, pancreatic involvement is rare. Amyloid deposition in the pancreas has been described in a limited number of case reports, and symptoms are derived from the exocrine or endocrine component [39]. Exocrine damage seems to contribute to weight loss and to worsening diarrhea. Type 2 diabetes mellitus could appear in secondary amyloidosis, and this is mainly in the setting of the death of islet cells from the accumulation and cytotoxic effects of human islet amyloid polypeptide [40]. This type of amyloid deposition is considered local amyloidosis and should not be mistaken for systemic disease. Moreover, a diagnosis of primary AL amyloidosis was reported using endoscopic ultrasound-guided fine-needle aspiration in a pancreatic head mass seen on abdominal CT [41]. Systemic AL amyloidosis can involve multiple visceral organs, including the mesentery and retroperitoneal space [39]. Pancreatic exocrine insufficiency should be excluded by normal blood amylase and lipase levels, normal fecal elastase levels and routine ultrasonography, and CT images of the pancreas [42].

11.2 Clinical Syndromes

1. **Systemic AL amyloidosis** is the most common type, associated with plasma cell dyscrasia, which produces immunoglobulin light chain that is amyloidogenic. The clinical manifestations of GI involvement are determined by the location and quantity of protein deposition [8]. The muscularis mucosae, submucosa, and muscularis propria are common, leading to polypoid protrusions and thickening of the ileocecal valve. Macroglossia occurs in 10–20% of patients with systemic AL amyloidosis [13]. In a cohort, the prevalence of symptomatic gastric involvement was only 1% among AL amyloidosis carriers [10]. Therefore, despite being rare, symptoms such as constipation, mechanical obstruction, or chronic intestinal pseudo-obstruction appear. Despite these changes, diarrhea can also arise in this subtype of amyloidosis [11].
2. **Systemic AA amyloidosis** is a disorder characterized by the extracellular tissue deposition of fibrils composed of fragments of and/or intact serum amyloid A (SAA) protein. Represent a potential complication of multiple chronic inflammatory conditions (rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, inflammatory bowel disease (IBD), psoriatic arthritis, familial periodic fever syndromes, chronic infections, and certain neoplasms). In general, in AA amyloidosis, the GI manifestations are derived from mucosal friability and erosions, resulting in diarrhea and malabsorption symptoms. When this friability is in the esophageal mucosa, there may even be necrotizing esophagitis [16].
3. **Hereditary systemic amyloidosis (ATTRv)** sets with symptoms derived from damage to the peripheral nervous system and/or cardiovascular system. Nevertheless, GI symptoms could appear before or be associated with the remaining manifestations [12]. Despite the fact that GI involvement is uncommon in other amyloidosis subtypes, it seems to be more frequent in ATTR patients. Wixner J et al. published recent data from a large international registry (1579 patients with hereditary transthyretin amyloidosis and 160 patients with wild-type transthyretin amyloidosis) and reported that 59% of all the patients had at least one GI symptom [unintentional weight loss (28.3%), early satiety (25%), and alternating diarrhea/constipation (22.9%)]. Constipation was often the first lower GI symptom reported, and fecal incontinence (5.6%) was rare. In addition, 69% of the Val30Met patients and 56% of the non-Val30Met patients reported GI symptoms after a median disease duration of 5 years [19]. On the other hand, in some specific variants with mainly cardiac manifestations (TTR L111 M and V122I mutations), the frequency of GI symptoms ranged from only 10–27%, and symptomatic gastroparesis seems to be more frequent [19]. Colonoscopy is essential for differentiating ATTR amyloidosis from colon cancer, CD, colonic obstruction, proctitis, and diverticulosis [1, 19].
4. **β2-Microglobulin** amyloidosis

Long-term dialysis for end-stage renal failure is the main factor in the development of β2-microglobulin amyloidosis. Whereas this protein is large and unable to cross the dialysis filter, levels of β2 M are elevated in patients on dialysis. This

disease uniquely occurs after long-term hemodialysis (over 14 years) [43]. GI manifestations are rare, but occult bleeding is the most common GI presentation when amyloidosis arises [44].

11.3 Special Situations

11.3.1 Inflammatory Bowel Disease and AA Amyloidosis

IBD is a chronic idiopathic inflammatory disorder affecting the GI tract [45]. Extraintestinal manifestations are common in patients with IBD and occur in 6–47% of patients with Crohn's disease (CD) or ulcerative colitis (UC) [46]. Renal and urinary involvement particularly occurs in 4–23% of patients with IBD. Among the renal complications of IBD, secondary amyloidosis (AA-type, AAA) is a rare but serious complication (nephritic proteinuria and uremia). A particular feature of renal AAA is maintenance of the regular size of the kidneys, together with the occurrence of hypotension instead of more common hypertension [47].

The literature is scarce about the prevalence of AAA in patients with IBD. Cuquerella et al., in a systematic review, estimated a frequency of 0.53% among cases of IBD (95% CI 0.32–0.75%) [48]. The prevalence of amyloidosis is higher in CD than in UC (1.05% vs. 0.08%). A clear predominance of men vs. women was consistently found among patients with IBD who developed amyloidosis (2:1). Usually, amyloidosis occurs in longstanding cases of IBD, and many years elapse between diagnosis and the presence of clinical amyloidosis. However, due to the diagnostic delay of intestinal disease, practically simultaneous diagnosis is not uncommon [48–50]. The analysis of the extension of IBD demonstrates that amyloidosis occurs frequently in the context of extensive bowel disease, mostly in cases of ileocolonic involvement (>50%) [48].

The gold standard for diagnosis is biopsies from the target organs (kidney, liver, and carpal tunnel), but endoscopic lesions suggesting amyloidosis may be observed in TGI. The positivity rates for amyloidosis histological deposits in TGI are as follows: duodenum 100%, stomach 83%, colon 67%, and rectum 67%. The duodenum also showed the highest amount of amyloid deposits [51].

The key treatment targets are to control the underlying IBD, to avoid the formation and tissue deposition of the SAA protein and to treat the affected organs by reducing the already established deposit. The best results have been reported with antitumor necrosis factor [TNF] drugs [52]. For many years, colchicine has been the only available drug to prevent amyloidosis. However, a reduction in amyloid deposition was not observed. Combining anti-TNF, immunosuppressants, and colchicine could improve prognosis. Measuring SAA seems helpful in monitoring amyloidosis progression, because C-reactive protein can be normal, even though amyloidosis does not respond to treatment [52, 53].

11.3.2 - Celiac Disease and Secondary Amyloidosis

The diagnosis of celiac disease is based on a combination of serology and small bowel biopsy. Clinical manifestations are derived from enteropathy caused by a gluten-mediated inflammatory response among genetically predisposed individuals. Serum anti-tissue transglutaminase antibody (anti-tTG) has high specificity for celiac disease (96–100%) [54]. There are some clinical reports about the correlation between celiac disease and amyloidosis [55–57]. Amyloid protein is a derivative of SAA protein, which is transcriptionally regulated by inflammatory cytokines. SAA protein levels have also been correlated with disease activity and progression. Patients with higher SAA levels have a higher burden of AA deposition, which is estimated by whole-body serum amyloid P component scintigraphy [31]. Considering that some patients with amyloidosis develop diarrhea, this fact should be investigated, since this symptom may be due not only to autonomic disorder but also to the emergence of a new entity, such as celiac disease. It has a specific treatment based on a gluten-free diet [54].

11.3.2.1 Diagnosis

The options from diagnosis include collection of material for histopathological analysis (gold standard) and/or positron emission tomography/CT using 18F-fluorodeoxyglucose (18F-FDG) and CT scan. The use of Congo red staining of the biopsy remains the most effective way to confirm this diagnosis, indicating the presence of amyloid in the affected organ or tissues. An abdominal fat pad aspirate, bone-marrow biopsy, and retal biopsy are the typical sites for biopsy (sensitivity 80–90%). If clinical suspicion remains high for amyloidosis despite a negative fat pad aspirate or bone-marrow biopsy, the affected organ should be biopsied [7, 8, 13, 58].

Cases of noninfectious chronic diarrhea that symptoms did not disappear with specific treatment of irritable bowel syndrome [associated with low fecal calprotectin (<71 μg) and negative anti-tTG] must be subjected to tests for amyloidosis (Congo Red; genetics; cardiology, and neurology). However, these tests should be performed early if polyneuropathy and/or cardiomyopathy present with GI manifestations. Colonoscopy is mandatory in cases with chronic constipation or chronic diarrhea [19].

11.3.2.2 Treatment

The treatment is based on decreasing the supply of precursor proteins for the synthesis of amyloid fibrils. Classification of severity as well as the staging of the patient in relation to the clinical condition are the best ways to choose the

medication. Low-risk patients (minimal organ involvement) are candidates for different doses and medications than moderate- or severe-risk patients. Regimens that were considered the standard of care for AL amyloidosis are based on the treatment of multiple myeloma. The management of AA amyloidosis is trying the underlying inflammatory disorder with a subsequent reduction in SAA protein production.

In general, GI symptoms respond during amyloidosis treatment. In AA amyloidosis patients with protein-losing enteropathy and refractory diarrhea, the resolution of the symptoms was achieved with steroids and octreotide [59]. Surgery is not recommended in bowel pseudo-obstruction, as it can cause further complications without any significant benefit [60]. In the rare cases of only localized GI amyloidosis without systemic involvement, observation without initiating treatment has been the preferred modality [61].

In ATTRv amyloidosis patients submitted to orthotopic liver transplantation, the stabilization of GI symptoms is generally observed [12, 19, 62]. Other treatments are TTR stabilizers (Tafamidis and Diflunisal—this last, off label) and suppression of gene expression in the liver by RNA interference (Patisiran) or oligonucleotide antisense (Inotersen). None of these studies specifically provided data on the treatment of GI symptoms [63]; however, the use of patisiran reduced autonomic dysfunction and stabilized nutritional status, suggesting an effect on GI autonomic function [64]. Symptoms such as early satiety, diarrhea, and constipation are treated with specific symptomatic medications.

Regardless of the amyloidosis treatment chosen, starting use in the early stages of the disease tends to dramatically reduce the development and chronicity of GI symptoms.

11.4 Summary

Amyloidosis is a rare disease with the potential to affect multiple organ systems, including the GI tract. In addition to being a rare disease, the diagnosis of amyloidosis is difficult due to the similarity of symptoms with other diseases. It is an important cause of unintentional weight loss. GI manifestations include dysmotility, malabsorption, diarrhea, bleeding, and rarely jaundice or portal hypertension. GI radiologic findings are typically nonspecific. The two pillars of treatment for amyloidosis consist of drugs to alleviate GI symptoms and drugs to reduce systemic disease progression. The patient's nutritional status should always be a concern throughout the follow-up.

References

1. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8:31.
2. Adams D, Suhr OB, Hund E, Obici L, Tournev I, Campistol JM, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. Curr Opin Neurol. 2016;26(Suppl 1):S14–26.
3. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol. 1995;32:45–59.
4. Gillmore JD, Lovat LB, Persey MR, Pepys MB, Hawkins PN. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. Lancet. 2001;358:24–9.
5. Syed U, Companioni RAC, Alkhawam H, Walfish A. Amyloidosis of the gastrointestinal tract and the liver: clinical context, diagnosis and management. Eur J Gastroenterol Hepatol. 2016;28:1109–21.
6. Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Manag Care. 2017;23:S107–12.
7. Ikeda S, Yanagisawa N, Hongo M, et al. Vagus nerve and celiac ganglionlesions in generalized amyloidosis. A correlative study of familial amyloid. J Neurol Sc. 1987;79:129–39.
8. Lim AY, Lee JH, Jung KS, Gwag HB, Kim DH, Kim SJ, Lee GY, Kim JS, Kim HJ, Lee SY, Lee JE, Jeon ES, Kim K. Clinical features and outcomes of systemic amyloidosis with gastrointestinal involvement: a single-center experience. Korean J Intern Med. 2015;30(4):496–505.
9. Wang C, Li Y, Jin Y, Zhou W, Zhu Y, Yao F, Qian J. Chronic diarrhea as the presenting feature of primary systemic AL amyloidosis: serendipity or delayed diagnosis? BMC Gastroenterol. 2013;13:1–5.
10. Menke DM, Kyle RA, Fleming CR, Wolfe JT 3rd, Kurtin PJ, Oldenburg WA. Symptomatic gastric amyloidosis in patients with primary systemic amyloidosis. Mayo Clin Proc. 1993;68:763–7.
11. Zhang J, Shao C, Zhu J, Tu C, Lv X. Abdominal distension and diarrhea as the main symptoms of primary amyloidosis: a case report and literature review. Exp Ther Med. 2016;11(5):1809–11.
12. Nakov R, Suhr OB, Ianiro G, Kupcinskas J, Segal JP, Dumitrascu DL, Heinrich H, Mikolasevic I, Stojkovic-Lalosevic M, Barbov I, Sarafov S, Tournev I, Nakov V, Wixner J. Recommendations for the diagnosis and management of transthyretin amyloidosis with gastrointestinal manifestations. Eur J Gastroenterol Hepatol. 2021;33(5):613–22.
13. Prokaeva T, Spencer B, Kaut M, Ozonoff A, Doros G, Connors LH, et al. Soft tissue, joint, and bone manifestations of AL amyloidosis: clinical presentation, molecular features, and survival. Arthritis Rheum. 2007;56:3858–68.
14. Bjerle P, Ek B, Linderholm H, Steen L. Oesophageal dysfunction in familial amyloidosis with polyneuropathy. Clin Physiol. 1993;13:57–69.
15. Damlaj M, Amre R, Wong P, How J. Hepatic ALECT-2 amyloidosis causing portal hypertension and recurrent variceal bleeding: a case report and review of the literature. Am J Clin Pathol. 2014;141(2):288–91.
16. Hasatani K, Shibata N, Naitou Y, Torii Y, Nishiyama S, Takahashi K, Fujinaga H, Hayashi Y, Aoyagi H, Tatsumi S, Ibe N, Urasaki K, Kaizaki Y. Case of acute necrotizing esophagitis associated with AA amyloidosis secondary to bronchiectasis. Nihon Shokakibyo Gakkai Zasshi. 2014;111:288–95.
17. Said SM, Grogg KL, Smyrk TC. Gastric amyloidosis: clinicopathological correlations in 79 cases from a single institution. Hum Pathol. 2015;46:491–8.
18. Suhr OB, Anan I, Ahlström KR, Rydh A. Gastric emptying before and after liver transplantation for familial amyloidotic polyneuropathy, Portuguese type (Val30Met). Amyloid. 2003;10:121–6.

19. Wixner J, Mundayat R, Karayal ON, Anan I, Karling P, Suhr OB, THAOS investigators. THAOS: gastrointestinal manifestations of transthyretin amyloidosis - common complications of a rare disease. Orphanet J Rare Dis. 2014;27(9):1–9.
20. Björnsson S, Jóhannsson JH, Sigurjónsson F. Localized primary amyloidosis of the stomach presenting with gastric hemorrhage. Acta Med Scand. 1987;221:115–9.
21. Gjeorgjievski M, Purohit T, Amin MB, Kurtin PJ, Cappell MS. Upper gastrointestinal bleeding from gastric amyloidosis in a patient with smoldering multiple myeloma. Case Rep Gastrointest Med. 2015;2015:1–6.
22. Ectors N, Geboes K, Kerremans R, Desmet V, Janssens J. Small bowel amyloidosis, pathology and diagnosis. Acta Gastroenterol Belg. 1992;55:228–38.
23. Lee JG, Wilson JA, Gottfried MR. Gastrointestinal manifestations of amyloidosis. South Med J. 1994;87:243–7.
24. Steen L, Ek B. Familial amyloidosis with polyneuropathy. A long-term follow-up of 21 patients with special reference to gastrointestinal symptoms. Acta Med Scand. 1983;214:387–97.
25. Ali MF, Patel A, Muller S, Friedel D. Rare presentation of primary (AL) amyloidosis as gastrointestinal hemorrhage without systemic involvement. World J Gastrointest Endosc. 2014;6:144–7.
26. Kawaguchi M, Koizumi F, Shimao M, Hirose S. Protein-losing enteropathy due to secondary amyloidosis of the gastrointestinal tract. Acta Pathol Jpn. 1993;43:333–9.
27. Kim SH, Kim JH, Gu MJ. Secondary intestinal amyloidosis presenting intractable hematochezia: a case report and literature review. Int J Clin Exp Pathol. 2014;7:1805–8.
28. Harada K, Ichikawa D, Konishi H, Komatsu S, Shiozaki A, Fujiwara H, et al. Perforation of the sigmoid colon and massive ischemia of the small intestine caused by amyloidosis associated with multiple myeloma: a case report. Int Surg. 2014;99:685–90.
29. Tada S, Iida M, Yao T, Kitamoto T, Yao T, Fujishima M. Intestinal pseudo-obstruction in patients with amyloidosis: clinicopathologic differences between chemical types of amyloid protein. Gut. 1993;34:1412–7.
30. Park MA, Mueller PS, Kyle RA, Larson DR, et al. Primary (AL) hepatic amyloidosis: clinical features and natural history in 98 patients. Medicine (Baltimore). 2003;82:291–8.
31. Lachmann HJ, Goodman HJB, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. N Engl J Med. 2007;356(23):2361–71.
32. Gertz MA, Kyle RA. Hepatic amyloidosis (primary [AL], immunoglobulin light chain): the natural history in 80 patients. Am J Med. 1988;85:73–80.
33. Levy M, Fryd CH, Eliakim M. Intrahepatic obstructive jaundice due to amyloidosis of the liver: a case report and review of the literature. Gastroenterology. 1971;61:234–8.
34. Huang X, Wang Q, Jiang S, Chen W, Zeng C, Liu Z. The clinical features and outcomes of systemic AL amyloidosis: a cohort of 231 Chinese patients. Clin Kidney J. 2015;8:120–6.
35. Bion E, Brenard R, Pariente EA, Lebrec D, Degott C, Maitre F, et al. Sinusoidal portal hypertension in hepatic amyloidosis. Gut. 1991;32:227–30.
36. Monzawa S, Tsukamoto T, Omata K, Hosoda K, Araki T, Sugimura K. A case with primary amyloidosis of the liver and spleen: radiologic findings. Eur J Radiol. 2002;41:237–41.
37. Browning MJ, Banks RA, Tribe CR, Hollingworth P, Kingswood C, et al. Ten years' experience of an amyloid clinic—a clinicopathological survey. Q J Med. 1985;54:213–27.
38. Lohana AK, Abid S, Sayani R, Tahir U, Shaikh PA. Hepatobiliary and pancreatic: bleeding in amyloid liver: a rare presentation of primary liver amyloidosis. J Gastrol Hepatol. 2019;1:1.
39. Ozdemir D, Dagdelen S, Erbas T. Endocrine involvement in systemic amyloidosis. Endocr Pract. 2010;16:1056–63.
40. Melato M, Antonutto G, Falconieri G. Amyloidosis and diabetes in humans. Pathol Res Pract. 1980;170(1–3):1–23.
41. Krishna SG, Bhutani MS, Mosher CH, Staerkel GA, Weston BR. A first report of endoscopic ultrasound for the diagnosis of pancreatic amyloid deposition in immunoglobulin light chain (AL) amyloidosis (primary amyloidosis). JOP. 2013;14:283–5.

42. Conceição IM, Miranda LC, Simões E, Gouveia RG, Evangelista TD, de Carvalho MA. Bone mineral density in familial amyloid polyneuropathy and in other neuromuscular disorders. Eur J Neurol. 2005;12:480–2.
43. Dulgheru EC, Balos LL, Baer AN. Gastrointestinal complications of β2-microglobulin amyloidosis: a case report and review of the literature. Arthritis Rheum. 2005;53:142–5.
44. Maher ER, Dutoit SH, Baillod RA, Sweny P, Moorhead JF. Gastrointestinal complications of dialysis related amyloidosis. BMJ. 1988;297:265–6.
45. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med. 2009;361:2066–78.
46. Danese S, Semeraro S, Papa A, et al. Extraintestinal manifestations in inflammatory bowel disease. World J Gastroenterol. 2005;14:227–36.
47. Pardi DS, Tremaine WJ, Sandborn WJ, et al. Renal and urologic complications of inflammatory bowel disease. Am J Gastroenterol. 1998;93:504–14.
48. Cuquerella JT, Bosca Watts MM, Ausejo RA. Amyloidosis in inflammatory bowel disease: a systematic review of epidemiology, clinical features and treatment. J Crohn's Colitis. 2016;1:1245–53.
49. Cohen H, Fishman AP. Regional enteritis and amyloidosis. Gastroenterology. 1949;12:502–208.
50. Zhong Q, Zhang A, Huang J, Yan W, Lin J, Huang Q, Huang X, Yu T, Zhu L, Xu C. Analysis and follow up of endoscopy results in 1099 patients with terminal ileum lesions. Can J Gastroenterol Hepatol. 2020:1–6.
51. Miyaoka M, Matsui T, Hisabe T, et al. Clinical and endoscopic features of amyloidosis secondary to CD: diagnostic value of duodenal observation and biopsy. Dig Endosc. 2011;23:157–65.
52. Said Y, Debbeche R, Hamzaoui L, et al. Infliximab for treatment of systemic amyloidosis associated with CD. J Crohns Colitis. 2011;5:171–2.
53. Cañas-Ventura A, Rodríguez E, Andreu M, Márquez L. Tocilizumab in amyloidosis-associated kidney disease secondary to inflammatory bowel diseases. Dig Dis Sci. 2013;58(9):2736–7.
54. European Society for the Study of Coeliac (ESsCD). European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterol J. 2019;7(5):583–613.
55. Kayhan B, Kuran OS, Turhan N, Akdoğan M, Sahin T. Is celiac sprue an etiology of amyloidosis? Turk J Gastroenterol. 2003;14(3):197–9.
56. Chhoda A, Jain D, Daga MK, Batra V. Celiac disease and secondary amyloidosis: a possible causal association? ACG Case Rep J. 2018;5:1–4.
57. Katsikas GA, Maragou M, Rontogianni D, Gouma P, Koutsouvelis I, Kappou-Rigatou I. Secondary cutaneous nodular AA amyloidosis in a patient with primary Sjögren syndrome and celiac disease. J Clin Rheumatol. 2008;14(1):27–9.
58. Fine NM, Arruda-Olson AM, Dispenzieri A, Zeldenrust SR, Gertz MA, Kyle RA, et al. Yield of noncardiac biopsy for the diagnosis of transthyretin cardiac amyloidosis. Am J Cardiol. 2014;113:1723–7.
59. Fushimi T, Takahashi Y, Kashima Y, Fukushima K, Ishii W, Kaneko K, et al. Severe protein losing enteropathy with intractable diarrhea due to systemic AA amyloidosis, successfully treated with corticosteroid and octreotide. Amyloid. 2005;12:48–53.
60. Liapis K, Michelis FV, Delimpasi S, Karmiris T. Intestinal pseudoobstruction associated with amyloidosis. Amyloid. 2011;18:76–8.
61. Petre S, Shah IA, Gilani N. Review article: gastrointestinal amyloidosis—clinical features, diagnosis and therapy. Aliment Pharmacol Ther. 2008;27:1006–16.
62. Suhr OB, Anan I, Ahlström KR, Rydh A. Gastric emptying before and. Gastric emptying before and after liver transplantation for familial amyloidotic polyneuropathy, Portuguese type (Val30Met). Amyloid. 2003;10:121–6.
63. Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Planté-Bordeneuve V, Lozeron P, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology. 2012;79:785–92.
64. Conceição I. Novel RNA-targeted therapies for hereditary ATTR amyloidosis and their impact on the autonomic nervous system. Review Clin Auton Res. 2019;29(Suppl 1):11–7.

Chapter 12
Hematological Associations in Amyloidosis

Jacques Kaufman, Roberto J. P. Magalhães, and Morie A. Gertz

12.1 Introduction

In systemic immunoglobulin light chain (AL) amyloidosis, a small B-cell clone, most commonly a plasma cell clone, produces monoclonal light chains that exert organ toxicity and deposit in tissue in the form of amyloid fibrils. Organ involvement determines the clinical manifestations, but symptoms are usually recognized late.

Discriminating patients with other forms of amyloidosis is difficult but necessary, and tissue typing with adequate technology available at referral centers is mandatory to confirm AL amyloidosis [1].

The clinical presentation of AL amyloidosis can vary widely and depends on the extent and number of organs affected. Initial symptoms at onset are often nonspecific (e.g., weight loss and fatigue). As the disease progresses, symptoms reflect the organs involved, most commonly the heart and the kidneys [2].

J. Kaufman · R. J. P. Magalhães
Department of Hematology, Hospital Universitário Antonio Pedro, Fluminense Federal University (HUAP/UFF), Rio de Janeiro, RJ, Brazil

DASA Group/Complexo Hospitalar de Niterói, Niterói, RJ, Brazil
e-mail: robmag@hucff.ufrj.br

M. A. Gertz (✉)
Division of Hematology, Roland Seidler Jr. Professor Department of Medicine, College of Medicine, Mayo Distinguished Clinician, Rochester, MN, USA
e-mail: gertm@mayo.edu

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_12

12.2 Epidemiology

The prevalence of the disease rises with increasing age. It doubles from age 35–54 compared to 65+ with reported mean age of 63, and 55% of patients are men [3]. There are two known risk factors for AL amyloidosis. The first is a pre-existing monoclonal gammopathy. Among patients with MGUS, the relative risk was 8.8 [4]. In one series of 1384 monoclonal gammopathy of undetermined significance (MGUS) patients followed for up to 50 years, 14 developed AL amyloidosis (1%). As many as 10–15% of patients with myeloma have overt, coexisting AL amyloidosis, and in another series, as many as 38% of myeloma patients were found to have covert coexisting AL amyloidosis [5]. Approximately 1% of 108 patients with pre-existing myeloma who are not diagnosed with AL amyloidosis simultaneously will go onto to develop AL amyloidosis [6]. The other identified risk factor is the existence of particular single nucleotide polymorphisms (SNPs). Associations were found in a genome-wide association study of 1229 AL amyloidosis patients. These data provide evidence for common genetic susceptibility to AL amyloidosis [7].

12.3 Incidence of AL Amyloidosis

The first study was carried out using the Olmsted County Project in Minnesota, USA, and reported an overall sex-adjusted and age-adjusted rate of 8.9 cases per million person-years between 1950 and 1989 and 10.5 cases of systemic AL amyloidosis per million person-years between 1970 and 1989 [8]. An update to this study that included patients from the same region between 1990 and 2015 demonstrated an incidence of 12 cases per million per year, which did not significantly differ from that reported in the earlier study [9].

12.4 Clinical Manifestations—Signs and Symptoms

Despite the etiological heterogeneity of systemic amyloidosis, the clinical manifestations of the different forms of amyloidosis largely overlap and depend upon the affected organ (Table 12.1). The signs and symptoms that should raise suspicion for the potential diagnosis of amyloidosis are usually nonspecific; therefore, establishing the diagnosis is difficult, and early diagnosis requires clinical suspicion [10]. For instance, recognition of the disease is delayed; in one report by Lousada et al., in 533 participants with AL amyloidosis, 37.1% of respondents, the diagnosis of amyloidosis was not established until 1 year after the onset of initial symptoms. Diagnosis was received after visits to 1, 2, 3, 4, or 5 physicians by 7.6%, 23.5%, 20.3%, 16.8%, and 31.8% of respondents, respectively. A correct diagnosis was most often made by hematologists/oncologists (34.1%) [11].

Table 12.1 Most common forms of systemic amyloidosis

Amyloid type	Precursor protein	Major organ involvement					
		Heart (bone tracer uptake)	Kidney	Liver	PNS	ANS	ST
AL amyloidosis(acquired)	Immunoglobulin light chain	+++ (usually absent, can be intense)	+++	++	+	+	++
ATTRv amyloidosis (hereditary)[a]	Mutated transthyretin	+++ (usually, intense can be absent in some variants)	−	−	+++	+++	−
ATTRwt amyloidosis(acquired)[a]	Wild-type transthyretin	+++ (usually, intense)	−	−	−	−	+
ApoAI amyloidosis(hereditary)	Mutated apolipoprotein AI	+ (present)	+	+++	−	−	−
AA amyloidosis (acquired)	Serum amyloid A protein	+	+++	+	−	+	−
ALECT(acquired)	Leucocyte chemotactic factor 2	−	+++	+	−	−	−

In AL amyloidosis, soft tissue involvement can manifest as macroglossia, shoulder pad sign, raccoon eyes, carpal tunnel syndrome, synovial enlargement, and firm, enlarged lymph nodes. In ATTRwt, carpal tunnel and lumbar stenosis are frequently reported. ANS, autonomic nervous system; PNS, peripheral neuropathic involvement; ST, soft tissue; ATTRv, transthyretin amyloidosis variants; AA, serum amyloid A; ApoAI, apolipoprotein AI; ALECT2, leukocyte chemotactic factor 2 amyloidosis

[a]Bone tracers validated for the detection of cardiac amyloidosis are ^{99m}Tc-diphosphonopropanodicarboxylic acid, ^{99m}Tc-pyrophosphate, and ^{99m}Tc-hydroxymethylene diphosphonate; +++, ≥50%; ++, 10%–30%; +, ≤10%; −, rare or not involved. Ref. [1]

Amyloidosis is particularly difficult to diagnose, because no single imaging, blood, or urine test is diagnostic for this disorder. The presenting symptoms often mimic those of more common disorders. The diagnosis of AL amyloidosis should be suspected in any patient with nondiabetic nephrotic syndrome, nonischemic cardiomyopathy with "hypertrophy" on echocardiography, or hepatomegaly [12].

In one study with 445 patients with light chain amyloidosis, only one-quarter of the patients had involvement of a single organ at presentation; the remaining patients had involvement of two organs (36%) or three or more organs (39%), and the organ affected establishes the prognosis.

Localized deposition of proteins that are normally deposited systemically can also occur, such as in localized AL amyloidosis, an intriguing condition characterized by localized growth of monoclonal plasma cells and the restriction of amyloid deposits to sites adjacent to the synthesis of the precursor [13].

The precise molecular mechanisms underlying amyloid organ targeting remain elusive. Several investigators have shown that certain structural features related to the light chain variable region gene and gene family confer a higher risk of involvement of specific organs, possibly through interactions with resident cells [15]. The

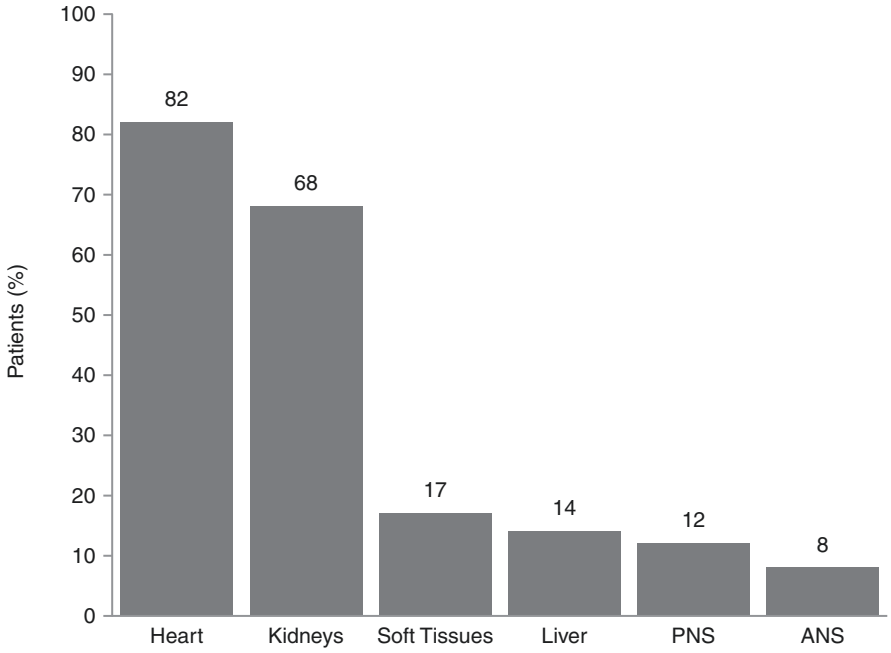


Fig. 12.1 Distribution of organ involvement in AL. Adapted from reference [15]

heart and the kidneys are the two most frequently affected organs in systemic AL amyloidosis, although all organs can be involved (Fig. 12.1).

Cardiac involvement is the critical determinant of survival of AL amyloidosis patients, and early diagnosis is correlated with better overall survival. Amyloid heart disease results in a restrictive cardiomyopathy that shares signs and symptoms with other etiologies of heart failure with preserved ejection fraction, such as fatigue, dyspnea, orthopnoea, paroxysmal nocturnal dyspnea, and peripheral edema. Dyspnea on exertion may be the most common early manifestation, since the atria are also abnormally stiff [16].

Electrocardiographic findings include low-voltage and pseudoinfarct patterns, which are present in approximately 45% of patients [17]. Normal voltage does not exclude the diagnosis, but the prevalence of low-voltage QRS complexes seems to be more common in AL amyloidosis than in ATTRm amyloidosis [18]. The echocardiogram typically shows concentric left ventricular thickening, often with right ventricular thickening. The left ventricular wall may be more echogenic due to extensive amyloid deposits, but the classical granular sparkling of the myocardium is not sensitive. The ejection fraction global longitudinal strain characteristically sparing the apex has the best accuracy in detecting cardiac amyloidosis [19]. AL cardiac amyloid patients had more frequent intracardiac thrombi than the other types detected by echocardiography in one series, even in sinus rhythm [20]. Cardiac magnetic resonance is particularly helpful when the echocardiogram is

inconclusive, but does not distinguish amyloid type. Nuclear scintigraphy imaging with ^{99m}Tc-pyrophosphate (PYP) and ^{99m}3,3diphosphono-1,2-propanodicarboxylic acid are useful for identifying ATTR amyloidosis, although, if a monoclonal protein is present, tissue confirmation of amyloid type is mandatory, because nuclear scintigraphy may be mildly positive in AL amyloidosis [21].

NT-proBNP and cardiac troponin are sensitive biomarkers not only for prognosis but also for early detection of cardiac amyloidosis. The NT-proBNP threshold is a matter of debate, since some patients had cardiac involvement detected by magnetic resonance imaging with no cardiac involvement by consensus criteria (NT-proBNP >332 pg/mL in the absence of renal impairment or atrial fibrillation or both) [22].

The kidneys are involved in 70% of patients with AL amyloidosis, often presenting as nonselective proteinuria or nephrotic syndrome. Patients with renal limited AL amyloidosis have lower involved serum FLC levels than patients with cardiac amyloidosis [23]. The median range of proteinuria was 5–6 g/24 h in a retrospective analysis of two cohorts of patients with renal involvement. Only 5% of patients were on dialysis at the time of diagnosis. Quantification of proteinuria is important to kidney involvement and, together with the estimated glomerular filtration ratio, discriminates patients with different probabilities of progression to renal failure [24]. The gold standard for proteinuria assessment is 24-h urine collection, and a movement toward replacing it with a spot urinary protein–creatinine ratio was unsuccessful, since there was a low correlation between the two modalities [25]. Enlarged kidneys are rarely seen in ultrasound or CT scans [10].

Peripheral neuropathy is not typically a prominent feature compared with signs of cardiac or renal dysfunction. It typically begins in the lower extremities as numbness paresthesia and dysesthesia, but if the disease progresses, patients may develop impaired vibration and proprioception sense, as large fibers become involved [26]. Electroneuromyography is often not helpful, as early neurologic involvement is small fiber neuropathy. Autonomic failure may be present and impact patient quality of life, since it can present as severe orthostatic hypotension, gastrointestinal motility abnormalities, such as gastroparesis or diarrhea, abnormal sweating, sexual (difficulty with erection and ejaculation) and genitourinary dysfunction (urinary frequency and urgency, incontinence, or increased residual urinary retention) [27].

Amyloid neuropathy can mimic chronic inflammatory demyelinating polyradiculoneuropathy, and the absence of improvement with immunomodulatory treatment and/or the presence of autonomic failure are characteristics that can favor amyloid etiology [28].

Carpal tunnel syndrome, which is often bilateral, can precede other signs and symptoms of AL amyloidosis [29]. The hand surgeon can contribute to earlier disease recognition by incorporating a tenosynovial or fascial biopsy into the perioperative period for carpal tunnel release. A proposed diagnostic algorithm is proposed [30]. (Fig. 12.2).

Some physical signs are not always present at diagnosis, but when they are seen, it should prompt the suspicion of the internist. As an example, in one study, the frequencies of those signs were described: macroglossia (14%); periorbital purpura (11%); submandibular swelling (15%); shoulder pad sign (4%); alopecia (5%);

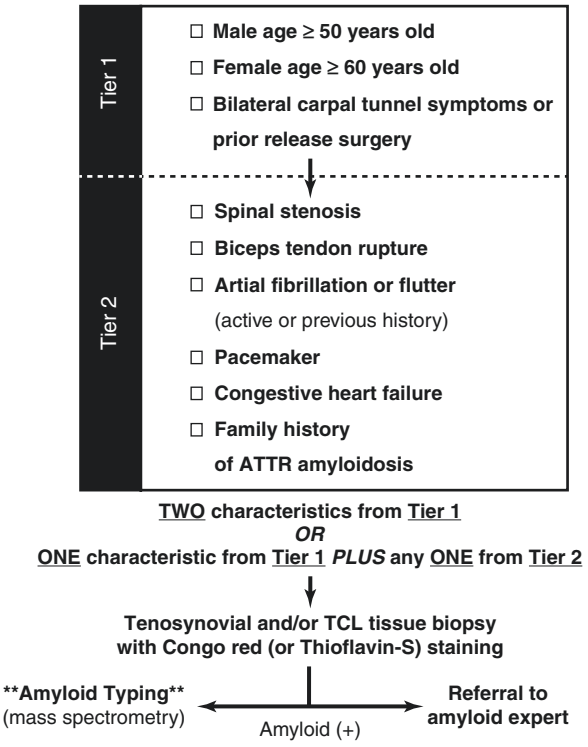


Fig. 12.2 Diagnostic algorithm proposed to patients presenting with bilateral carpal tunnel syndrome [30]

jugular vein distention (12%); and nail lesions (3%) [14]. Although not pathognomonic, if the diagnosis of amyloidosis is confirmed, macroglossia is only seen in AL amyloidosis [31]. (Fig. 12.3).

In a series of 816 patients with AL amyloidosis, 16% had hepatic involvement Hepatomegaly with no imaging abnormalities and an elevated alkaline phosphatase prompt suspicion of AL amyloidosis as the etiology of liver involvement. Predominant hepatic involvement is uncommon and is the most common clinical presentation of cholestasis associated with findings of sinusoidal portal hypertension that rapidly progress to terminal liver failure [32].

Bleeding diathesis is another manifestation of AL amyloidosis ranging from mild mucocutaneous bleeding, such as periorbital purpura, to a severe life-threatening disorder. Multiple mechanisms have been proposed to explain this, since vascular fragility to multiple clotting factor deficiencies. Factor X (FX) deficiency is the most widely recognized abnormality, and in a retrospective trial with 411 patients at Mayo Clinic, FX deficiency was found in 43% of patients. In the same trial, coagulation abnormalities were associated with advanced disease and inferior outcomes, highlighting the importance of screening at the diagnosis of AL amyloidosis [33].

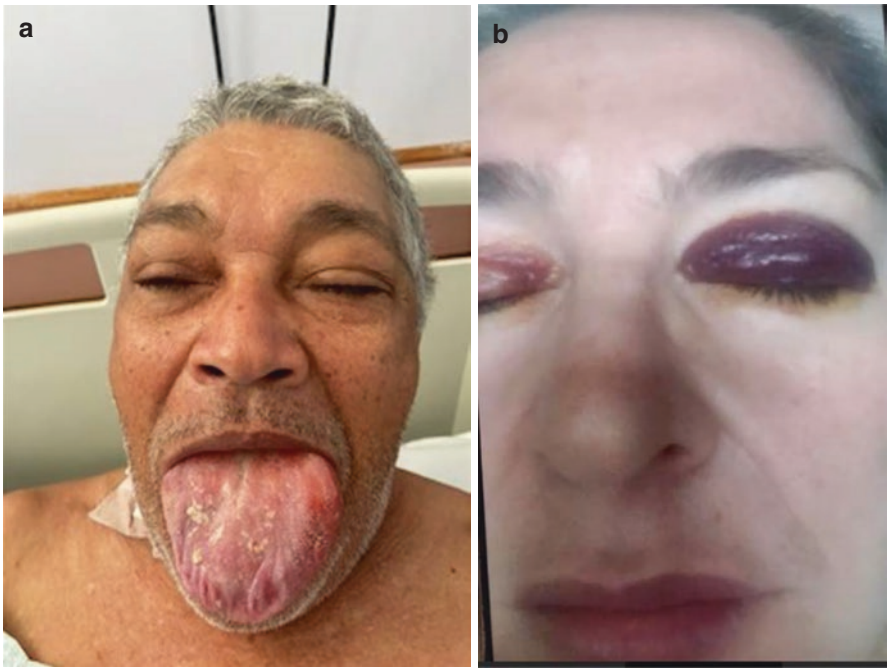


Fig. 12.3 (**a**) Macroglossia and (**b**) periorbital purpura in AL amyloidosis. Figures from the authors with consent of the patients

In addition, AL amyloidosis should be considered in patients with multiple myeloma (SMM) or MGUS with unusual features, such as weight loss, edema, and dyspnea in the absence of anemia [34]

12.5 Diagnosis

Monoclonal immunoglobulin can be detected in 99% of patients with AL amyloidosis using the combination of serum-free light chain (sFLC) analysis, serum protein electrophoresis, serum immunofixation electrophoresis (IFE) and urine IFE. The increase in sFLC can precede the development of AL amyloidosis for many years [35]. The high frequency of λ light chain proteinemia is a hallmark of AL amyloidosis [12].

Once a clinical suspicion of AL amyloidosis develops, tissue biopsy is required to confirm the diagnosis. Biopsy of the clinically involved organ is generally unnecessary. The combination of subcutaneous abdominal fat aspiration and bone-marrow biopsy yields 85% sensitivity [36]. Abdominal skin punch biopsy of the fat provides more material for analysis with a high sensitivity if the depth is >10 mm [37]. Minor salivary gland and labial salivary gland (LSG) biopsies are another alternative. LSG had 89% sensitivity in a small retrospective series [38].

The appropriate organ should only be biopsied if the suspicion is high because of the risk of postbiopsy hemorrhage, although in practice many patients underwent organ biopsy. It was more common with renal biopsies, which were performed in over half of patients with renal involvement [39].

12.6 MGUS and ATTR Amyloidosis

MGUS demonstrated an increasing prevalence with age, with some reports of 7.5% in patients above 85 years. Because of this, it is important to not rely solely on the finding of a monoclonal gammopathy to establish a diagnosis of AL amyloidosis in a patient with biopsy-proven amyloidosis. Studies have demonstrated the high prevalence of MGUS in patients with cardiac ATTRwt, with a prevalence in one series of 23%, higher than anticipated from epidemiological studies [40].

A rare but clinically important phenomenon is the occurrence of two different types of amyloidosis in individual patients. This is uncommon and was observed in <1% of the patients; however, the main coexistence was ATTR and AL amyloidosis [41].

References

1. Palladini G. Management of AL amyloidosis in 2020. ASH educational program.
2. Merlini G, Wechalekar AD, Palladini G. Systemic light chain amyloidosis: an update for treating physicians. Blood. 2013;121:5124–30.
3. Quock TP, Yan T, Chang E, Guthrie S, Broder MS. Epidemiology of AL amyloidosis: a real-world study using US claims data. Blood Adv. 2018;2:1046–53.
4. Kyle RA, et al. Long-term follow-up of monoclonal gammopathy of undetermined significance. N Engl J Med. 2018;378:241–9.
5. Desikan KR, et al. Incidence and impact of light chain associated (AL) amyloidosis on the prognosis of patients with multiple myeloma treated with autologous transplantation. Leukemia Lymphoma. 1997;27:315–9.
6. Madan S, et al. Clinical features and treatment response of light chain (AL) amyloidosis diagnosed in patients with previous diagnosis of multiple myeloma. Mayo Clin Proc. 2010;85:232–8.
7. da Silva Filho MI, et al. Genome-wide association study of immunoglobulin light 852 chain amyloidosis in three patient cohorts: comparison with myeloma. Leukemia. 2017;31(853):1735–42.
8. Kyle RA, et al. Incidence and natural history of primary systemic amyloidosis in 855 Olmsted County, Minnesota, 1950 through 1989. Blood. 1992;79:1817–22.
9. Kyle RA et al. Incidence of AL amyloidosis in Olmsted County, Minnesota, 1990 through 2015. Submitted (2018) (Kyle et al Accepted Mayo Clinic 128 Proc.)
10. Vaxman I, Gertz M. When to suspect a diagnosis of amyloidosis. Acta Hematol. 2020;143(4):304–11.
11. Lousada I, Comenzo RL, Landau H, Guthrie S, Merlini G. Light chain amyloidosis: patient experience survey from the Amyloidosis Research Consortium. Adv Ther. 2015;32(10):920–8.

12. Gertz MA. Immunoglobulin light chain amyloidosis: 2020 update on diagnosis, prognosis, and treatment. Am J Hematol. 2020;95(7):848–60.
13. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med. 2003;349:583–96.
14. Merlini G, Palladini G. Systemic amyloidoses: what an internist should know. Eur J Int Med. 2013;24:p729–39.
15. Merlini G, Dispenzieri A, Sanchorawala V, Schönland SO, Palladini G, Hawkins PN, Gertz MA. Systemic immunoglobulin light chain amyloidosis. Nat Rev Dis Primers. 2018;4(1):38.
16. Falk RH, Alexander KM, Liao R, Dorbala S. AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy. J Am Coll Cardiol. 2016;68(12):1323–41.
17. Murtagh B, Hammill SC, Gertz MA, Kyle RA, Tajik AJ, Grogan M. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. Am J Cardiol. 2005;95(4):535–7.
18. Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidoses: disease profiles and clinicalcourses of the 3 main types. Circulation. 2009;120:1203–12.
19. Pagourelias ED, Mirea O, Duchenne J, Van Cleemput J, Delforge M, Bogaert J, et al. Echo parameters for differential diagnosis in cardiac amyloidosis: a head-to-head comparison of deformation and non deformation parameters. Circ Cardiovasc Imaging. 2017;10(3):e005588.
20. Feng D, Syed IS, Martinez M, et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. Circulation. 2009;119:2490–7.
21. Grogan M, Dispenzieri A, Gertz MA. Light-chain cardiac amyloidosis: strategies to promote early diagnosis and cardiac response. Heart. 2017;103(14):1065–72.
22. Sharpley FA, Fontana M, Martinez-Naharro A, Manwani R, Mahmood S, Sachchithanantham S, Lachmann HJ, Gillmore JD, Whelan CJ, Hawkins PN. Cardiac biomarkers are prognostic in systemic light chain amyloidosis with no cardiac involvement by standard criteria. Haematologica. 2020;105:1405–13.
23. Sidana S, Tandon N, Gertz MA, et al. Clinical features, laboratory characteristics and outcomes of patients with renal versus cardiac light chain amyloidosis. Br J Hematol. 2019;185:701–7.
24. Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood. 2014;124:2325–32.
25. Mendelson L, Sanchorawala V, Connors L, Joshi T, Doros G, Pogrebinsky A, Havasi A. Correlation between 24-hour urine protein and random urine protein-creatinine ratio in amyloid light-chain. Amyloidosis Kidney Med. 2022;4(4):100427.
26. Namiranian D, Geisler S. Neuromuscular complications of systemic amyloidosis. Am J Med. 2022;135(Suppl 1):S13–9.
27. Wang AK, Fealey RD, Gehrking TL, Low PA. Patterns of neuropathy and autonomic failure in patients with amyloidosis. Mayo Clin Proc. 2008;83(11):1226–30.
28. Mathis S, et al. Amyloid neuropathy mimicking chronic inflammatory demyelinating polyneuropathy. Muscle Nerve. 2012;45(01):26–31.
29. Sperry BW, et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. JACC. 2018;72(17):2040–50.
30. Donnelly JP, et al. Carpal tunnel syndrome: a potential early, red-flag sign of amyloidosis. J Hand Surg Am. 2019;44(10):868–76.
31. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol. 2012;30(36):4541–9.
32. Varela M, et al. Hepatic failure due to primary AL amyloidosis. J Hepatol. 2003;39:290.
33. Abdallah N, Muchtar E, Dispenzieri A, Gonsalves W, Buadi F, Lacy MQ, Hayman SR, Kourelis T, Kapoor P, Go RS, Warsame R, Leung N, Rajkumar SV, Kyle RA, Pruthi RK, Gertz MA, Kumar SK. Coagulation abnormalities in light chain amyloidosis. Mayo Clin Proc. 2021;96(2):377–87. https://doi.org/10.1016/j.mayocp.2020.06.061.
34. Gertz MA, Dispenzieri A. Systemic amyloidosis recognition, prognosis, and therapy: a systematic review. JAMA. 2020;324(1):79–89. https://doi.org/10.1001/jama.2020.5493.

35. Weiss BM, et al. Increased serum free light chains precede the presentation of immunoglobulin light chain amyloidosis. J Clin Oncol. 2014;32(25):2699–704. https://doi.org/10.1200/JCO.2013.50.0892. Epub 2014 Jul 14.
36. Gertz MA, Lacy MQ, Dispenzieri A, Hayman SR, Kumar SK, Dingli D, Ansell SM, Gastineau DA, Inwards DJ, Johnston PB, Litzow MR, Micallef IN, Porrata LF, Leung N, Hogan WJ, Buadi FK. Autologous stem cell transplant for immunoglobulin light chain amyloidosis: a status report. Leuk Lymphoma. 2010;51(12):2181–7.
37. Bicong W, Pak DM, Smith KD, Shinohara MM. Utility of abdominal skin punch biopsy for detecting systemic amyloidosis. J Cutan Pathol. 2021;48(11):1342–6. https://doi.org/10.1111/cup.14070. Epub 2021 Jun 16
38. Suzuki T, Kusumoto S, Yamashita T, Masuda A, Kinoshita S, Yoshida T, Takami-Mori F, Takino H, Ito A, Ri M, Ishida T, Komatsu H, Ueda M, Ando Y, Inagaki H, Iida S. Labial salivary gland biopsy for diagnosing immunoglobulin light chain amyloidosis: a retrospective analysis. Ann Hematol. 2016;95(2):279–85. https://doi.org/10.1007/s00277-015-2549-y. Epub 2015 Nov 10
39. Muchtar E, Dispenzieri A, Lacy MQ, Buadi FK, Kapoor P, Hayman SR, Gonsalves W, Warsame R, Kourelis TV, Chakraborty R, Russell S, Lust JA, Lin Y, Go RS, Zeldenrust S, Rajkumar SV, Dingli D, Leung N, Kyle RA, Kumar SK, Gertz MA. Overuse of organ biopsies in immunoglobulin light chain amyloidosis (AL): the consequence of failure of early recognition. Ann Med. 2017;49(7):545–51.
40. Geller HI, Singh A, Mirto TM, Padera R, Mitchell R, Laubach JP, Falk RH. Prevalence of monoclonal gammopathy in wild-type transthyretin amyloidosis. Mayo Clin Proc. 2017;92(12):1800–5. https://doi.org/10.1016/j.mayocp.2017.09.016.
41. Hasib Sidiqi M, McPhail ED, Theis JD, Dasari S, Vrana JA, Drosou ME, Leung N, Suzanne Hayman S, Rajkumar V, Warsame R, Ansell SM, Gertz MA, Grogan M, Dispenzieri A. Two types of amyloidosis presenting in a single patient: a case series. Blood. Cancer J. 2019;9(3):30. https://doi.org/10.1038/s41408-019-0193-9.

Chapter 13
Orthopedic Care

Bernardo Couto Neto and Liszt Palmeira de Oliveira

13.1 Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) is the most common peripheral nerve compression syndrome and the most frequent neurologic disorder of the hand. It refers to compression of the median nerve at the wrist. It is the earliest and most common non-cardiac manifestation of systemic amyloidosis [1, 2]. The prevalence of CTS symptoms in patients with ATTR amyloidosis is as high as 68% [3, 4]. Onset of CTS symptoms typically precedes onset of cardiac symptoms and diagnosis in these patients by an average of 4–7 years [3–5].

Symptoms of CTS include paresthesia or numbness (or both) in the median nerve distribution (thumb, index finger, middle finger, and radial side of the ring finger). Nocturnal paresthesia in the radial three digits of the hand is nearly pathognomonic for CTS. Paresthesia also occurs, characteristically in "fixed wrist activities", such as reading a book, driving, or using a keyboard or mouse. With advanced nerve compression, weakness and atrophy of the abductor pollicis brevis and opponens pollicis may manifest. The surgical treatment (Fig. 13.1) consists of releasing the transverse carpal ligament. Immediately after release, the adjacent tenosynovium may be biopsied to establish the diagnosis of amyloidosis. Because CTS is the most prevalent upper extremity compressive neuropathy, an opportunity exists for early diagnosis and referral for initiation of treatment [6].

B. C. Neto (✉)
Department of Orthopedics and Traumatology, Pedro Ernesto University Hospital, State University of Rio de Janeiro (UERJ), Rio de Janeiro, RJ, Brazil

Fluminense Federal University (UFF), Niterói, Brazil
e-mail: bernardocouto@clinicadamao.com.br

L. P. de Oliveira
Department of Orthopedics and Traumatology, Pedro Ernesto University Hospital, State University of Rio de Janeiro (UERJ), Rio de Janeiro, RJ, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_13

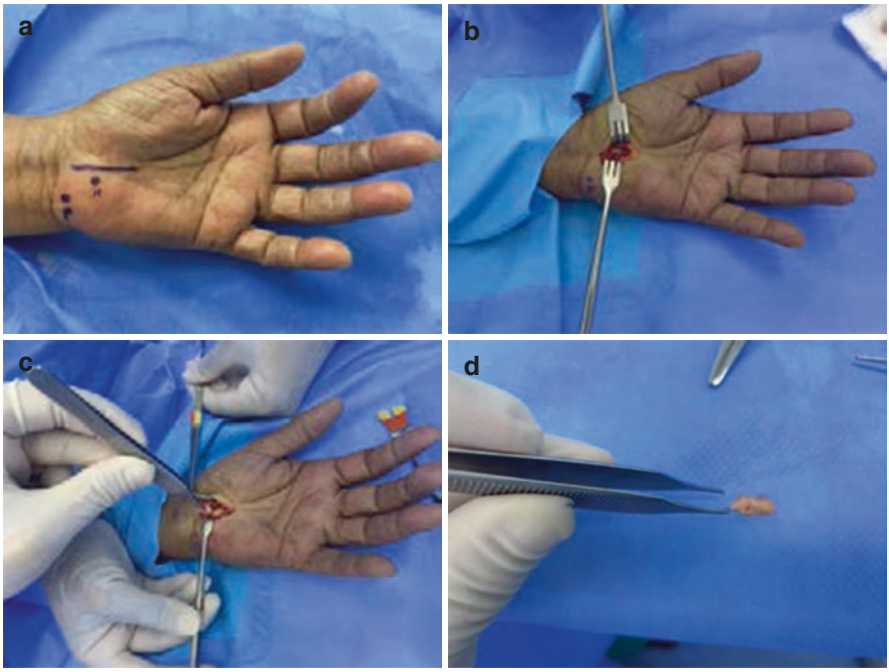


Fig. 13.1 (**a**) Reference points marking carpal tunnel surgical access. (**b**) Incision for carpal tunnel release. (**c**, **d**) Tenosynovectomy of flexor tendons inside the carpal tunnel and tenosynovium to be biopsied

13.1.1 Diagnosis

The hand surgeon can help with earlier disease identification by proceeding with a tenosynovial or transverse carpal ligament biopsy.

Sperry [7] (2018) proposed a diagnostic algorithm with two tiers:

- In *Tier 1*, the characteristics are as follows: male age ≥50 years, female age ≥60 years and bilateral carpal tunnel symptoms or prior release surgery.
- In *Tier 2*, the characteristics are spinal stenosis, biceps tendon rupture, atrial fibrillation or flutter (active or previous history), pacemaker, congestive heart failure, and family history of amyloidosis.

When two characteristics from Tier 1 or when one characteristic from Tier 1 plus one characteristic from Tier 2 are met, the biopsy is indicated.

It should be sent to pathology in standard formalin for Congo red staining, which allows identification of amyloid by its characteristic apple-green birefringence under polarized light microscopy, but does not provide any information on the amyloid type. Thioflavin staining for amyloid fibrils may also be used. If Congo Red or thioflavin staining is positive, then immunohistochemistry or mass spectrometry must be ordered to define the subtype [3].

If AL or ATTR amyloid is detected, patients should promptly be referred to a specialist with experience in managing amyloidosis. This approach is suggested for some studies in the literature [7–15].

Early diagnosis is important, because the therapies available for both AL and ATTR are most effective in earlier stages of the disease. The hand surgeon who makes the connection between CTS and amyloidosis creates an opportunity for early treatment and can positively impact a patient's life.

13.2 Tendinopathy

Tendinopathy is a term used to encompass painful conditions affecting the tendons of the wrist and hand and is perhaps the most common reason for a visit to a hand surgeon. Tendinopathy includes conditions such as tendon entrapment and stenosis (trigger finger, de Quervain disease), as well as inflammatory conditions (tenosynovitis). Tenosynovitis refers to inflammation of the synovial lining of a tendon sheath. Causes of inflammatory tenosynovitis are rheumatoid arthritis or other inflammatory arthropathies and deposition diseases, such as amyloidosis, crystalline tendinopathy (calcific tenosynovitis or gout) and septic tenosynovitis (bacterial, mycobacterial, and viral agents). Such proliferative tenosynovitis is relatively uncommon, is erosive, is not restricted to the retinacular thickenings of the tendon sheath, and may lead to tendon rupture [16]. A far more common condition than proliferative tenosynovitis is tendon entrapment caused by narrowing or stenosis of a tendon's sheath. There is a paucity of inflammatory tissue associated with tendon entrapment. All the conditions described here cause hand pain and disability.

13.2.1 Trigger Finger

This condition causes painful catching or popping of the involved flexor tendon as the patient flexes and extends the digit. The phenomenon of the trigger finger is due to mechanical impingement of the digital flexor tendons, as they pass through a narrowed retinacular pulley at the level of the metacarpal head [16]. Amyloid deposits have been identified in connective tissue beneath the synovial lining of the flexor tendon sheath in patients with idiopathic trigger finger [8]. In the general population, there seems to be a link between CTS and trigger finger, with concomitant occurrence in 16–61% of patients [17]. Most primary trigger digits in adults can be successfully treated nonsurgically with corticosteroid injection or splinting. Patients with trigger digits secondary to rheumatoid arthritis, other proliferative tenosynovitis or diabetes are counseled about the reduced success rate with this form of treatment and are not offered a second attempt at injection. Surgical treatment may be necessary in resistant trigger digits or chronic cases.

13.3 Distal Biceps Tendon Rupture

Geller et al. (2017) [18] revealed a high occurrence of distal biceps tendon rupture in patients diagnosed with ATTRwt cardiomyopathy. This condition occurs with an estimated incidence of 1.2 per 100,000 people per year. The mechanism of injury is typically a sudden load against a flexed biceps muscle. This injury is associated with sports, and the incidence is highest in men in the fourth decade of life. Spontaneous ruptures are lesions that occur with minimal or trivial trauma. A retrospective cross-sectional study compared the frequency of distal biceps tendon ruptures in patients with heart failure secondary to ATTRwt cardiomyopathy with that of patients with heart failure of other causes. In total, 111 patients were present, 108 of whom were men, with a mean age of 75 years studied. The incidence of distal biceps tendon rupture was 33.3% in patients with ATTRwt cardiomyopathy compared with 2.5% in patients with other causes of heart failure. In the ATTRwt group, distal biceps tendon rupture preceded the diagnosis of heart failure by 5 years.

In the geriatric age group, these ruptures are treated nonoperatively with rest and gentle range of motion. Four–six weeks after the injury, strengthening exercises are initiated. Potential underlying amyloidosis should be suspected in cases of spontaneous rupture of the distal biceps, especially in elderly patients.

13.4 Rotator Cuff Disease

Rotator cuff disease encompasses a broad spectrum of injury and pathology with an increasing incidence with age. Pain with overhead activity and loss of active range of motion of the shoulder are common symptoms. The glenohumeral joint is a common site of involvement of amyloidosis [19].

One-third to one-half of patients on long-term hemodialysis have pain and movement limitation of the shoulder. With the progression of amyloid infiltration of the rotator cuff tendons, minimally traumatic tendon rupture may occur. In advanced disease, anterior shoulder enlargement due to amyloid deposition in the periarticular connective tissue can be observed and is termed “the shoulder-pad sign.” Ultrasonography images of amyloidosis of the gleno-humeral joint show thickening of the rotator cuff tendon, thickening of the synovial sheath around the long head of the biceps tendon and thickening of the subdeltoid bursa. Thickening of the supraspinatus tendon greater than 7 mm is considered diagnostic for amyloidosis of the shoulder [20, 21]. On magnetic resonance imaging (MRI), early amyloidosis of the shoulder manifests with obliteration of the rotator interval and thickening of the

Fig. 13.2 Bilateral proximal biceps rupture in a patient diagnosed with ATTR

rotator cuff tendons. Massive rotator cuff tearing may be seen with advanced disease. In the elderly age group, spontaneous ruptures (Fig. 13.2) can be associated with amyloid infiltration of the proximal biceps tendon. An MRI-based classification system for amyloidosis of the shoulder, based on rotator cuff thickness and obliteration of the rotator interval findings, was proposed by Ando et al. [22]. However, the definitive diagnosis of amyloidosis is established histologically. Treatment options are dependent on the extent of disease and patient symptoms and may range from physical therapy to surgical repair using a variety of possible techniques.

13.5 Lumbar Spinal Stenosis

Lumbar spinal stenosis is a common source of back and leg pain. It can also cause neurogenic claudication and cauda equina syndrome. It refers to a narrowing in the vertebral area with compression of the neural elements in the neural foramen, lateral recess or central canal. It is a significant cause of disability in elderly individuals, and it is the most significant cause of spinal surgery in patients over 65 years of age [23]. Although a generalized understanding exists that amyloid can deposit in the ligamentum flavum, understanding is limited to a case series and sporadic case reports [24–26]. The utility of ligamentum flava biopsies for the early detection of amyloidosis has not been studied. Some authors have suggested biopsy or referral in the setting of abnormal nerve conduction studies or worsening symptoms despite surgical treatment [27]. These practices have not yet been proven beneficial.

Overview

Early diagnosis for both AL and ATTR amyloidosis is important, because the therapies available are most effective in earlier stages of the disease.

The presence of amyloid deposition can be detected at the time of common orthopedic surgeries, most commonly in older patients (≥70 years). Subtyping of the amyloid can enable diagnosis of light chain or TTR amyloidosis prior to cardiac manifestations. Biopsy at the time of routine orthopedic procedures should be considered for patients with suspected symptoms and signs of systemic amyloidosis [28]. Further prospective studies are needed to better determine when there may be clinical benefit of biopsy for amyloidosis. However, orthopedic surgeons are in a unique position to help their patients to recognize these symptoms and signs, perform biopsies when indicated, and refer to specialists when amyloid deposition is detected [6].

References

1. Kurer MHJ, Baillod RA, Madgwick JCA. Musculoskeletal manifestations of amyloidosis. A review of 83 patients on hemodialysis for at least 10 years. J Bone Joint Surg Br. 1991;73(2):271–6.
2. Sueyoshi T, Ueda M, Jono H, et al. Wild-type transthyretin-derived amyloidosis in various ligaments and tendons. Hum Pathol. 2011;42(9):1259–64.
3. Donnelly JP, Hanna M, Sperry BW, Seitz WH. Carpal tunnel syndrome: a potential early, red flag sign of amyloidosis. J Hand Surg Am. 2019;44(10):868–76.
4. Nakagawa M, Sekijima Y, Yazaki M, er al. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. Amyloid. 2016;23(1):58–63.
5. Papoutsidakis N, Miller EJ, Rodonski A, Jacoby D. Time course of common clinical manifestations in patients with transthyretin cardiac amyloidosis: delay from symptom onset to diagnosis. J Card Fail. 2018;24:131–3.
6. Zhang D, Makhni M, Kang J, Blazar P. Orthopedic manifestations of amyloidosis. J Am Acad Orthop Surg. 2021;29:e488–96.
7. Sperry BW, Reyes BA, Ikram A, et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. J Am Coll Cardiol. 2018;72:2040–50.
8. Cordiner-Lawrie S, Diaz J, Burge P, Athanasou NA. Localized amyloid deposition in trigger finger. J Hand Surg Br. 2001;26(4):380–3.
9. Kyle RA, Eilers SG, Linscheid RL, Gaffey TA. Amyloid localized to tenosynovium at carpal tunnel release. Natural history of 124 cases. Am J Clin Pathol. 1989;91(4):393–7.
10. Sekijima Y, Uchyama S, Tojo K, et al. High prevalence of wild-type transthyretin deposition in patients with idiopathic carpal tunnel syndrome: a common cause of carpal tunnel syndrome in elderly individuals. Hum Pathol. 2011;42(11):1785–91.
11. Stein K, Storkel S, Linke RP, Goebel HH. Chemical heterogeneity of amyloid in the carpal tunnel syndrome. Virchows Arch A Pathol Anat Histopathol. 1987;412(1):37–45.
12. Bastian FO. Amyloidosis and the carpal tunnel syndrome. Am J ClinPathol. 1974;61(5):711–7.
13. Neal NC, Mc Manners J, Stirling GA. Pathology of the flexor tendon sheath in the spontaneous carpal tunnel syndrome. J Hand Surg Br. 1987;12(2):229–32.
14. Nakamichi KI, Tachibana S. Amyloid deposition in the synovium and ligament in idiopathic carpal tunnel syndrome. Muscle Nerve. 1996;(10):1349–51.

15. Fernandez Fuertes J, Rodriguez Vicente O, Sanchez Herraez S, Ramos Pascua LR. Early diagnosis of systemic amyloidosis by means of a transverse carpal ligament biopsy carried out during carpal tunnel syndrome surgery. Med Clin (Barc). 2017;148(5):211–4.
16. Wolfe SW. Tendinopathy. In: Wolfe SW, Hotchkiss RN, Pederson WC, Kozin SH, Cohen MS, editors. Green's operative hand surgery. Philadelphia: Elsevier; 2017. p. 1904–25.
17. Gancarczyk SM, Strauch RJ. Carpal tunnel syndrome and trigger digit: common diagnoses that occur "hand in hand". J Hand Surg Am. 2013;38(8):1635–7.
18. Geller HI, Singh A, Alexander KM, et al. Association between ruptured distal biceps tendon and wild-type Transthyretin cardiac amyloidosis. JAMA. 2017;318(10):962–3.
19. Katz GA, Peter JB, Pearson CM, Adams WS. The shoulder-pad sign: a diagnostic freature of amyloid arthropathy. N Engl J Med. 1973;288:354–5.
20. Cardinal E, Buckwalter KA, Braunstein EM, Raymond-Tremblay D, Benson MD. Amyloidosis of the shoulder in patients on chronic hemodyalisis: sonographic findings. AJR Am J Roentgenol. 1996;166:153–6.
21. Sommer R, Valen GJ, Ori Y, et al. Sonographic features of dialysis-related amyloidosis of the shoulder. J Ultrassound Med. 2000;19:765–70.
22. Ando A, Hagiwara Y, Sekigurchi T, et al. Magnetic resonance imaging classification of hemodialysis-related amyloidosis of the shoulder: risk factors and arthroscopic treatment. Knee Surg Sports Traumatol Arthrosc. 2017;25:2217–24.
23. Kalichman L, Cole R, Kim DH, et al. Spinal stenosis prevalence and association with symptoms: the Framingham study. Spine J. 2009;9(7):545–50.
24. Down RS, Nail TJ, Arkun K, et al. Where neurosurgery meets heart failure: a case report of a patient with amyloid transthyretin wild type in the ligamentum flavum and cardiac tissue with bilateral carpal tunnel syndrome. World Neurosurg. 2019;131:104–7.
25. Westermark P, Westermark GT, Sush OB, Berg S. Transthyretin-derived amyloidosis: Most likely, a common cause of lumbar spinal stenosis. Ups J Med Sci. 2014;119:223–8.
26. Yanagisawa A, Ueda M, Sueyoshi T, et al. Amyloid deposits derived from transthyretin in the ligamentum flavum as related to lumbar spinal canal stenosis. Mod Pathol. 2015;28:201–7.
27. Adams D, Ando Y, Beirão JM, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. J Neurol (published online ahead of print January 6, 2020). https://doi.org/10.1007/s00415-019-09688-0
28. Wininger AE, Phelps BM, Le JT, et al. Musculoskeletal pathology as an early warning sign of systemic amyloidosis: a systematic review of amyloid deposition and orthopedic surgery. BMC Musculoskelet Disord. 2021;22(1):51.

Chapter 14
Serum Amyloid A Amyloidosis

Leonardo Oliveira Mendonça and Roberta Shcolnik Szor

14.1 Serum Amyloidosis (AA Amyloidosis): General Principles

Serum amyloid A (AA) amyloidosis results from the excessive production of serum amyloid A protein (SAA), an acute-phase protein produced by hepatocytes under inflammatory conditions. SAA acts in the immune regulation process as an opsonin for phagocytosis of bacteria and in the reverse transport of cholesterol in damaged tissues. Elevated levels of SAA occur in proinflammatory states under constant cytokine stimulation, such as tumor necrosis factor (TNF) and interleukins 1 and 6 (IL-1 and IL-6).

As occurs in other subtypes of amyloidosis, the aggregation of SAA and its deposition in tissues in the form of amyloid material lead to multisystem organ damage. The disease is marked by dysfunction of vital organs, with progressive and potentially fatal evolution. AA amyloidosis is, therefore, an acquired and systemic disorder, evolving in the course of other underlying chronic inflammatory conditions, such as infectious, autoimmune, autoinflammatory, and neoplastic diseases.

L. O. Mendonça (✉)
Division of Clinical Immunology and Allergy, Hospital das Clínicas, Universidade de São Paulo, São Paulo, SP, Brazil

Department of Clinical Immunology and Allergy, Hospital 9 de Julho—Rede DASA, São Paulo, SP, Brazil

Center for Rare and Immunological Disorders, Hospital 9 de Julho—Rede DASA, São Paulo, SP, Brazil
e-mail: lomendonca@h9j.com.br

R. S. Szor
Department of Hematology, Hospital 9 de Julho—Rede DASA, São Paulo, SP, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_14

It is slightly more predominant in men, with a median age at diagnosis of 50 years. In children, it is the most common subtype of systemic amyloidosis. The estimated incidence of AA amyloidosis is 1–2 cases per million person-years. In low-income and middle-income countries, chronic infections are the most frequent causes of AA amyloidosis. On the other hand, immune-mediated conditions, such as autoimmune and autoinflammatory diseases, play an important role in the development of AA amyloidosis in high-income countries. In recent decades, however, a reduction in the incidence of AA amyloid has been observed due to the better control of such underlying conditions. In the largest cohort on systemic amyloidosis to date, with approximately eleven thousand patients, the National Amyloidosis Centre of the United Kingdom reported an incidence of AA amyloidosis varying from 13% between 1987 and 2010 to 3% in the period from 2010 to 2019 [1, 2].

14.2 Clinical Presentation

According to the organs involved, a constellation of clinical manifestations may be observed in AA amyloidosis. Often, nonspecific signs and symptoms can be found and include fatigue, weight loss, and peripheral edema. Frequently, there is a delay in diagnosis due to late suspicion leading patients to undergo many exams and several specialist evaluations [3].

In AA amyloidosis, the main organ involved is the kidney, and in approximately 25% of the cases, the liver can also be affected. Less commonly involved organs are the heart, nervous system, spleen, gastrointestinal tract, and soft tissues (including lymph nodes). The main clinical manifestation is proteinuria, which is present in 95% of the cases and may reach the nephrotic range in 50% of patients. Renal dysfunction is not always associated, and approximately 10% of patients are already on renal replacement therapy at diagnosis. When hepatic involvement is present, hepatomegaly and high levels of canalicular injury serum markers are commonly observed. Imaging methods do not always show clear morphological changes in addition to an enlarged liver [3].

Once amyloidosis has been diagnosed, a multiorgan screening should be performed, including the kidney, liver, heart, somatic and autonomic peripheral nervous system, digestive tract, and soft tissues. In patients with advanced age, findings of very high levels of SAA, renal dysfunction, and involvement of the liver and heart are compatible with worse prognosis. Figure 14.1 summarizes the main clinical syndromes that should raise suspicion of systemic amyloidosis.

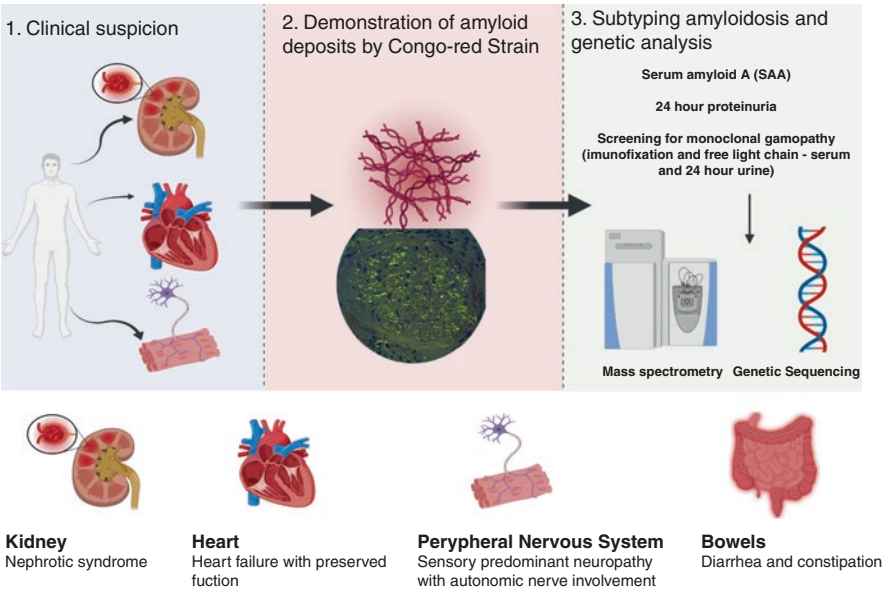


Fig. 14.1 Steps to be considered for the diagnosis of AA amyloidosis and main syndromic presentations by each organ involved. (1–3) Steps from clinical recognition, demonstration of the amyloid deposits in human tissue to the search for the underlying condition and subtyping amyloidosis. Organ figures indicate the main syndromic presentation. (*Figure was generated with Biorender and license was obtained*) (Abbreviations: *SAA* Serum amyloid A)

14.3 Diagnosis

Clinical suspicion is crucial in shortening the time to diagnosis, allowing early treatment, and preventing the progression of multiorgan dysfunctions. The final diagnosis of AA amyloidosis requires the presence of a clinical syndrome, followed by histological evidence of the amyloid deposit and, finally, the demonstration that SAA is the precursor protein.

The most reliable way of proving the amyloid deposit is by biopsying an involved organ. When performed in reference centers, kidney and liver biopsies are associated with a low rate of complications. However, these procedures are not risk-free. Thus, performing a fat pad aspirate or biopsy, a salivary gland, or a lip biopsy may help in the diagnostic process. In our experience of AA amyloidosis screening in patients at high risk of developing systemic amyloidosis, fat pad biopsies demonstrated 17% positivity. One may be aware that several factors may influence the

diagnostic yield with indirect biopsy sites. The proper sample collection, the quality of the Congo red dye, and the pathologist's expertise in analyzing the affected tissue are critical factors in the interpretation of the results. Thus, if an initial biopsy does not confirm the diagnosis of amyloidosis, and if the clinical suspicion remains, a biopsy of the affected organ, or another biopsy, must be considered.

Currently, the gold standard for precursor protein identification is mass spectrometry. However, the technique is not yet widely available due to its high complexity and cost. Other techniques to detect the precursor protein are based on immune-mediated methods, such as immunohistochemistry. Some complementary tests may indirectly help to define the amyloidosis subtype. Serum measurement of SAA should always be performed when AA amyloidosis is suspected, and screening for monoclonal gammopathy is important to rule out the light chain subtype. However, isolated finding of high levels of AA amyloid substance (SAA) does not confirm the diagnosis of SAA related amyloidosis [4].

Another point to be considered after the diagnosis of AA amyloidosis is made to understand the underlying condition of the diagnosis. In such a specific scenario, the genetic dissection of the inflammation unrevealed genes and disorders responsible for AA systemic amyloidosis. Therefore, it is mandatory to look after genes involved in the autoinflammatory and immune dysregulatory pathways. In this specific subgroup of disorders, nonsyndromic forms of recurrent fevers must be taken into account for differential diagnosis: (1) familial Mediterranean fever (FMF); (2) TNF receptor-associated periodic syndrome (TRAPS); and (3) hyper-IgD. FMF-affected individuals usually harbor pathogenic mutations in exon 10 of the MEFV gene in homozygous or compound heterozygous status, with the M694 V variant being a predictor of the development of AA amyloidosis. In TRAPS-affected patients harbor heterozygous pathogenic mutations in TNFRSF1A that are inherited in a autosomal dominant fashion, and no specific mutations are linked to the development of amyloidosis. Finally, individuals with hyper-IgD syndrome harbor pathogenic mutations in the MVK gene inherited in an autosomal recessive fashion, being the T237S associated with not severe phenotypes [5, 6].

14.4 Treatment

The treatment of AA amyloidosis aims to normalize the levels of SAA and prevent the formation of amyloid fibrils, thus stopping the progression of organic damage and ideally reversing the dysfunctions already installed. Therefore, treatment is directed to the underlying inflammatory condition. In chronic infections, antimicrobial treatment helps control inflammation. In rheumatological and autoinflammatory diseases, medications such as corticosteroids and immunosuppressive or immunobiological agents can be used (antagonists and monoclonal antibodies against TNF, IL-1, and IL-6). For FMF patients colchicine is effective in preventing both the disease attack and the development of AA amyloidosis. Blocking IL-1 using anakinra, canakinumab, or rilonacept can be effective in the reversion of AA

amyloidosis in hereditary autoinflammatory syndromes. In advanced cases of organic involvement, solid organ transplantation can be considered, such as kidney, liver, and heart transplantation. Supportive treatment is another essential measure for patient care in AA amyloidosis. It should be carried out with all the different specialists, according to the organs affected, and with the physician responsible for treating the underlying inflammatory disease [4, 5].

Although there are no defined response criteria in AA amyloidosis, response evaluation should assess both the underlying inflammatory condition and organ dysfunction. Serial measurements of SAA or other inflammatory markers, such as C-reactive protein or erythrocyte sedimentation rate, can be used. In addition, laboratory and imaging markers related to organ dysfunction should also be monitored, and their improvement and, ideally normalization denote the presence of an organic response [7].

References

1. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, Dispenzieri A, Katzmann JA, Melton LJ 3rd. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med. 2006;354(13):1362–9.
2. Ravichandran S, Lachmann HJ, Wechalekar AD. Epidemiological and survival trends in amyloidosis, 1987-2019. N Engl J Med. 2020;382(16):1567–8.
3. Brunger AF, Nienhuis HLA, Bijzet J, Hazenberg BPC. Causes of AA amyloidosis: a systematic review. Amyloid. 2020;27(1):1–12.
4. Blank N, Schönland SO. Autoinflammatorische syndrome und amyloid-A-Amyloidose [Autoinflammatory syndromes and AA amyloidosis]. Z Rheumatol. 2020;79(7):649–59. German.
5. Papa R, Lachmann HJ. Secondary, AA, amyloidosis. Rheum Dis Clin N Am. 2018;44(4):585–603.
6. Benson MD, Buxbaum JN, Eisenberg DS, et al. Amyloid nomenclature 2018: recommendations by the International Society of Amyloidosis (ISA) nomenclature committee. Amyloid. 2021;25:215–9.
7. Muchtar E, Dispenzieri A, Magen H, Grogan M, Mauermann M, McPhail ED, Kurtin PJ, Leung N, Buadi FK, Dingli D, Kumar SK, Gertz MA. Systemic amyloidosis from A (AA) to T (ATTR): a review. J Intern Med. 2021;289(3):268–92.

Chapter 15
Diagnostic Workflow of Cardiac Amyloidosis

Marcus Vinicius Simões and Edileide Barros Correa

15.1 Question 1: Is Cardiac Amyloidosis a Rare Disease?

Recent evidence has suggested that cardiac amyloidosis, particularly the ATTR form, is a more prevalent condition than previously estimated. Thanks to the advance of noninvasive diagnostic methods, mainly the use of scintigraphy with bone-avid tracers, the rate of ATTR diagnosis, mainly the ATTRwt form, is steadily growing [1]. ATTRwt has been reported in up to 13% of male elderly patients with HFpEF phenotype and left ventricular wall thickness >12 mm [2], and in up to 25% of hearts in autopsies of very elderly people [3]. A recent study reported a progressive increase in the prevalence of cardiac amyloidosis as the cause of heart failure with preserved ejection fraction in patients hospitalized with acute heart failure in the USA medical care system when comparing the data between 2000 and 2012, from 18 to 55.2/100,000 person-years [4].

It is also relevant to emphasize that AL amyloidosis was until recently the main cause of cardiac amyloidosis, albeit it is considered a rare disease with an estimated incidence of 6–10 cases/million person/year. This condition is associated with a poor prognosis, and an early diagnosis is critical for improving survival [5].

M. V. Simões (✉)
Medical School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil
e-mail: msimoes@fmrp.usp.br

E. B. Correa
Dante Pazzanese, Institute of Cardiology, São Paulo, SP, Brazil
e-mail: edileide.barros@dantepazzanese.org.br

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_15

15.2 Question 2: Can Amyloidosis Masquerade as Other Cardiac Diseases?

Cardiac amyloidosis may also mimic other heart diseases, such as hypertrophic cardiomyopathy, nonamyloid HFpEF, and low-flow/low-gradient aortic stenosis [6]. Cardiac amyloidosis may also present as atrioventricular block demanding pacemaker implantation or atrial arrhythmias without other apparent cause.

Thus, cardiac amyloidosis may be frequently underdiagnosed or receive a late diagnosis. More than 50% of ATTRv patients and 39% of ATTRwt patients have an incorrect initial diagnosis, with consequent inadequate treatment being prescribed for most of those patients. The delay in the correct diagnosis leads to worsening of structural cardiac changes and clinical deterioration, with consequent worse prognosis.

These factors indicate that a high suspicion of the disease is needed in different clinical scenarios to trigger a rational diagnostic workflow in a timely manner [7]. In the clinical scenario of amyloidosis, the principle that we cannot diagnose a disease in what we do not believe is used.

Figure 15.1 shows a proposal for the diagnostic workflow of cardiac amyloidosis based on the Position Statement for Diagnosis and Treatment of Cardiac Amyloidosis of the Brazilian Society of Cardiology.

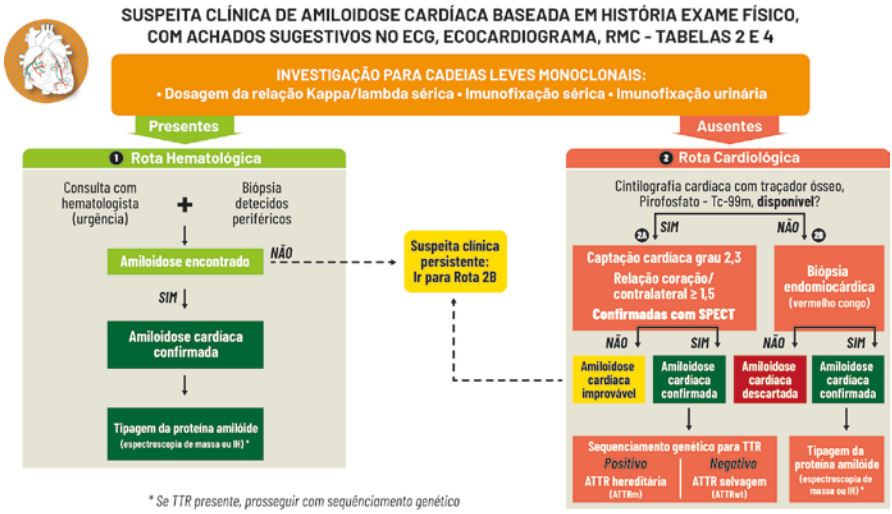


Fig. 15.1 Diagnosis work-up algorithm for cardiac amyloidosis, as proposed by the Brazilian Society of Cardiology

15.3 Question 3: What Are the Clinical Clues to Raise the Suspicion of Cardiac Amyloidosis?

The first and most fundamental step is ***setting the clinical suspicion***, which is based on suggestive findings derived from clinical history, physical examination, EKG, and echocardiogram. Fundamentally, cardiac amyloidosis should be suspected in elderly patients with heart failure and unexplained increased left ventricular wall thickness (interventricular septum ≥12 mm) presenting ≥1 red flag, and a list of more relevant red flags is depicted in Fig. 15.2.

The warning signs, or red flags, that may herald the presence of amyloidosis, are based on the multisystemic manifestations of amyloidosis that may involve, mainly: (1) nervous system, which may manifest as sensitive-motor polyneuropathy and/or autonomic dysfunction; (2) conjunctive tissue and skeleton, including carpal tunnel syndrome, spontaneous biceps tendon rupture, and stenosis of the vertebral channel; and (3) specific changes in cardiac imaging exams, such as the EKG showing decreased QRS voltage to LV mass ratio, echocardiogram depicting reduced longitudinal strain with apical sparing.

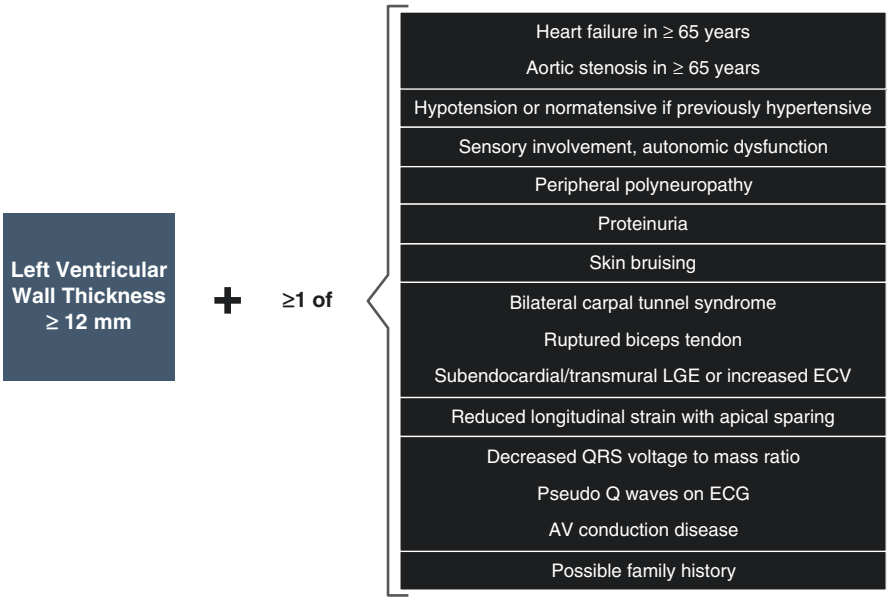


Fig. 15.2 Most important red flags to raise the suspicion of cardiac amyloidosis in patients with HFpEF exhibiting a potential phenotype of cardiac infiltration (interventricular septal thickness ≥12 mm). Adapted from ref. Garcia-Pavia et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2021; 21;42 (16):1554–1568

In patients with suspicion at the intermediate level, cardiac magnetic resonance imaging may importantly contribute to indicating the presence of amyloidosis. The findings of an increased T1-mapping signal, increased ECV and a suggestive diffuse subendocardial or myocardial transmural pattern of gadolinium late enhancement are highly indicative of cardiac amyloidosis.

15.4 Question 4: What Is the Next Step When Tests Are Suggestive of Cardiac Amyloidosis?

When the electrocardiogram and imaging tests are suggestive of cardiac amyloidosis, the next steps are toward confirming the diagnosis and identifying the type of precursor protein, noting that the diagnostic exams do not allow the differentiation between the types of amyloidosis.

We must initially and mainly rule out AL-CA, as this is considered a medical emergency, and the prognosis is better the faster the treatment is started. Thus, it is important to carry out immunofixation in blood and urine and the serum free light chain ratio, which detects an abnormal rate between kappa/lambda chains (>1.65 or <0.26).

Protein electrophoresis is not an adequate screening test, since this method may not detect the monoclonal component in blood and/or urine. Adding the serum free light chain ratio to immunofixation in blood and urine increases the detection sensitivity to >99% [8, 9].

Therefore, immunofixation in blood and urine associated with free light chain ratio analysis represents the best noninvasive method for detecting clonal light chains.

15.5 Question 5: When Laboratorial Tests Are Positive What Should Be Done?

It is important to note that despite having 99% sensitivity for identifying underlying substrate for AL-CA, an abnormal immunofixation and/or free light chain ratio is not specific for AL amyloidosis. Abnormal tests can occur in monoclonal gammopathy of uncertain significance and in renal failure. Up to 5% of the population >65 years of age has a monoclonal gammopathy of undetermined significance [10].

In addition, free light chains are filtered by the glomeruli, and renal dysfunction results in increased serum concentrations and an abnormal ratio between them, as it affects the excretion of free light chains differently. As a result, reference values with greater variation have been proposed in patients with renal failure [11].

Therefore, other conditions can lead to changes in the kappa/lambda ratio, which justifies the indication of performing a tissue biopsy to confirm the deposit with subsequent identification of the precursor protein as well as a referral to a hematologist. (Fig. 15.1).

15.6 Question 6: When and How Should Tissue Biopsy Be Undertaken?

The diagnostic accuracy of an extracardiac biopsy depends on the type of amyloidosis and on the examined tissue. In general, the yield of an extracardiac biopsy (abdominal fat pad, gingiva, skin, salivary gland, or gastrointestinal tract) is higher in AL-CA than in ATTRh, which is higher than ATTRwt. As light chain amyloidosis has multisystem involvement, i.e., affects numerous organs and tissues, an extracardiac biopsy, simple and safe, can be conclusive for the diagnosis and should be preferred initially. In AL-CA, the yield of a fat pad biopsy is >70% and is strongly associated with whole-body amyloid load. Congo red staining with birefringence under polarized light was used to determine the amyloid deposit. Therefore, in general, there is a higher chance of positive extracardiac biopsy results when the site is abdominal fat and the amyloidosis is AL, followed by ATTRv and ATTRwt [12–14].

In a series of 131 patients whose ATTR-CA diagnosis was confirmed by endomyocardial biopsy, abdominal fat biopsy was positive in 67% of ATTRh patients but only in 14% of ATTRwt patients [15].

However, in cases of localized amyloidosis, i.e., restricted to one organ or tissue, a subcutaneous fat tissue biopsy is seldom positive [16].

Therefore, although abdominal fat is the preferred initial site for extracardiac biopsies, a negative result should not exclude the diagnosis, and an endomyocardial biopsy should be performed if the suspicion is high, following route 2B (Fig. 15.1) [14].

In these cases, biopsy of the affected organ has 100% sensitivity and specificity. If the degree of suspicion of amyloidosis is low, a negative extracardiac biopsy may end the diagnostic outflow.

15.7 Question 7: What Is the Hematologist's Participation?

In light-chain amyloidoses, the hematologist has a central role both in terms of diagnosis and especially in treatment. In the diagnostic phase, bone marrow biopsy indicated for the identification of the underlying plasma cell disorder contributes to the diagnosis of AL amyloidosis by increasing the yield of fat aspiration or fat biopsy by approximately 89–90%. Therefore, only 11% of patients should require an endomyocardial biopsy when AL amyloidosis is suspected [17].

15.8 Question 8: After the Tissue Biopsy, Is the Diagnostic Work Done?

It should be pointed out that although Congo red staining can confirm amyloid infiltration in tissue, as typical apple-green birefringence using polarized light, it does not differentiate the type of amyloidosis. There is still this diagnostic stage left, the

identification of the type. Emphasizing the importance of this topic, one could be facing a patient with positive monoclonal light chain tests, a biopsy confirming amyloid deposits and not presenting light chain amyloidosis, but TTR amyloidosis with monoclonal gammopathy of uncertain significance, which can occur in 40% of cases [18].

In light of these aspects, since identifying the amyloid deposition type is fundamental for appropriate treatment, immunohistochemistry or, preferably, laser microdissection, and mass spectrometry of the amyloid biopsy material must be performed. Immunohistochemistry remains the most widely available method for identifying the deposition type. However, when amyloidosis is light chain, the results are not always conclusive; they may be positive for more than one type of antiserum, usually TTR and kappa or lambda light chain. This happens by the binding of the antibody with circulating proteins present in the pathological specimen. In a series, 8 of 15 patients with monoclonal gammopathy showed positive results in immunohistochemistry for TTR, and mass spectrometry demonstrated light chain amyloidosis in 5. Thus, mass spectrometry has become the new gold standard for identifying amyloid deposition type [7, 14, 19, 20].

Mass spectrometry involves laser microdissection and laser capture of amyloid. By mass spectrometry, one can separate atoms, isotopes, and fragments of molecules based on their mass. For negative monoclonal light chain results, i.e., when ATTR is more likely, although other rare forms of CA may also be diagnosed, the investigation should follow the cardiological route, taking two subroutes according to the availability of scintigraphy with bone markers. (Fig. 15.1).

15.9 Cardiological Route

When scintigraphy with bone tracers is available and monoclonal light chains are excluded, the diagnostic pathway should follow ***subroute 2A*** in the algorithm, which allows a noninvasive diagnosis route based on scintigraphy molecular images with bone avid tracers, without the need for endomyocardial biopsy (Fig. 15.1). In Brazil, the only available bone radiotracer is ^{99m}Tc-pyrophosphate. The images should include planar images of the anterior view of the chest, usually acquired 1 and/or 3 h after the radiotracer injection. Cardiac uptake grading 2 or 3 by the Perugini classification (equivalent to or greater than that of the costal archs) is considered positive for ATTR cardiac amyloidosis once light chains are excluded, since the uptake on the cardiac area is confirmed to be located in the myocardial walls of the left ventricle by the analysis of the SPECT images. In addition, a semiquantitative approach by calculation of the heart to contralateral regions of interest ratio (H/CL ratio) can also be used. In this approach, an H/CL uptake ratio $\geq$1.5 at 1 h or $\geq$1.3 at 3 h after tracer injection is considered positive for ATTR-CM (Fig. 15.3).

TTR gene sequencing should then be performed to determine whether the ATTR is hereditary or wild type. Differentiating between hereditary and wild-type ATTR has prognostic and therapeutic implications and is also important for family screening and genetic counseling.

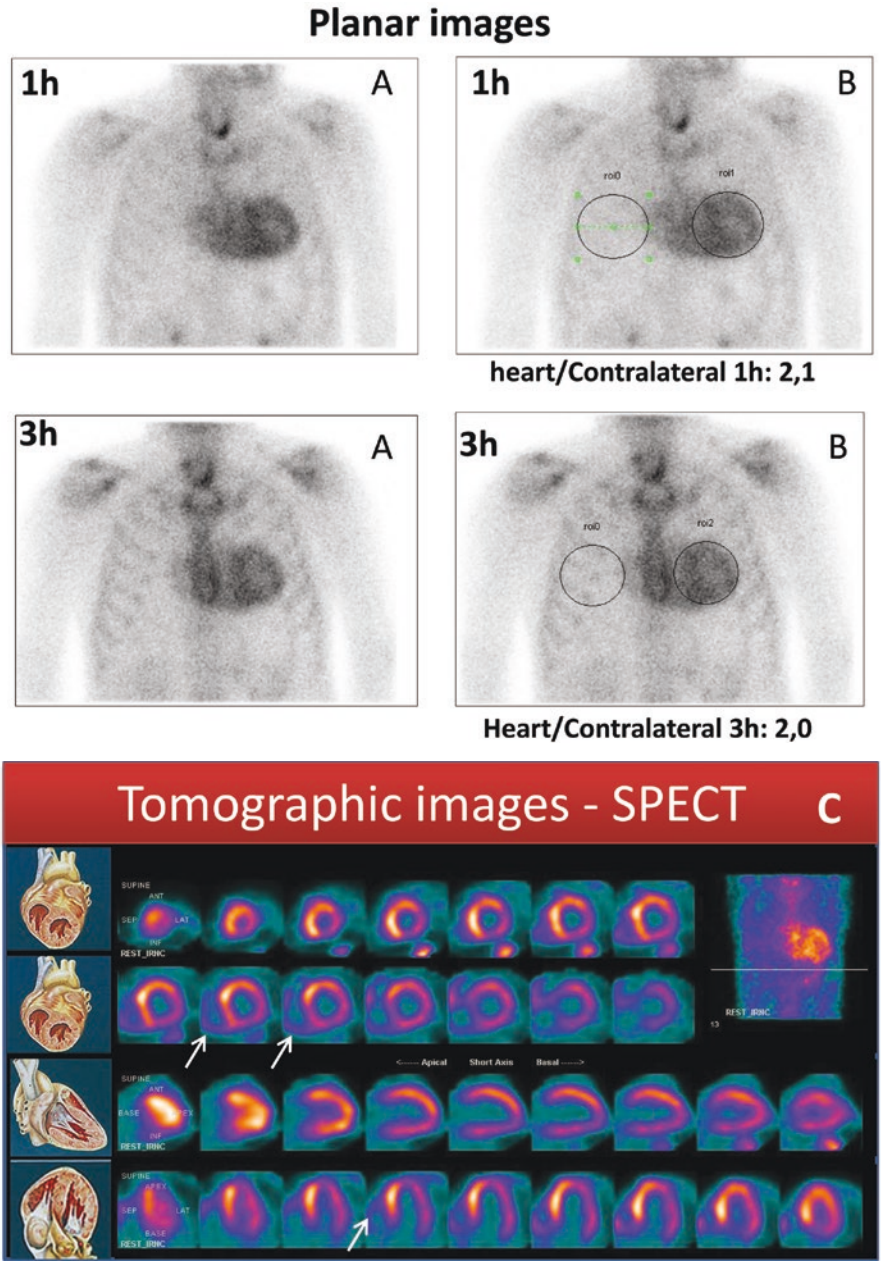


Fig. 15.3 Illustrative images of a patient with cardiac scintigraphy positive for ATTR-CM, with previous exclusion of immunoglobulin light chains. The planar images (left panel) show cardiac uptake superior to the rib uptake (Perugini grade 3) and a heart/contralateral ratio exceeding 1.5 at 1 h and 1.3 at 3 h after tracer injection. The SPECT images (right panel) show that cardiac uptake is located in the left and right ventricular walls (arrows), confirming the myocardial uptake of the bone seeking tracer ^{99m}Tc-pyrophosphate. Adapted from the ref. *Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis—2021. Simoes MV* et al. *Arq Bras Cardiol. 2021 Sep;117* (3)*:561–598*

When cardiac scintigraphy with bone tracers is negative and is associated with an absence of monoclonal light chains, CA is unlikely. However, when high clinical suspicion still persists, based mainly on the results of other imaging methods highly suggestive of amyloidosis, such as CMR, endomyocardial biopsy should be performed. Such cases could indicate ATTRv involving mutations with amyloid deposits that do not uptake bone tracers, such as early-onset V30 M and P64 L, in addition to other unusual types of amyloidosis.

When bone scintigraphy is unavailable, an invasive route with indication of endomyocardial biopsy is recommended to clarify the diagnosis ***(subroute 2B).***

References

1. Lane T, Fontana M, Martinez-Naharro A, Quarta CC, Whelan CJ, Petrie A, et al. Natural history, quality of life and outcome in cardiac transthyretin amyloidosis. Circulation. 2019;140(1):16–26.
2. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J. 2015;36:2585–94.
3. Tanskanen M, Peuralinna T, Polvikoski T, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. Ann Med. 2008;40:232–9.
4. Gilstrap LG, Dominici F, Wang Y, El-Sady MS, Singh A, Di Carli MF, et al. Epidemiology of cardiac amyloidosis-associated heart failure hospitalizations among fee-for-service Medicare beneficiaries in the United States. Circ Heart Fail. 2019;12(6):e005407.
5. Kyle RA, Linos A, Beard CM, Linke RP, Gertz MA, O'Fallon WM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. Blood. 1992;79(7):1817–22.
6. Rapezzi C, Lorenzini M, Longhi S, Milandri A, Gagliardi C, Bartolomei I, et al. Cardiac amyloidosis: the great pretender. Heart Fail Rev. 2015;20(2):117–24.
7. Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. Circulation. 2020;142(1):e7–e22.
8. Rajkumar SV. Multiple myeloma: 2011 update on diagnosis, riskstratification, and management. Am J Hematol. 2011;86(1):57–65.
9. Comenzo RL, Reece D, Palladini G, Seldin D, Sanchorawala V, Landau H, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia. 2012;26(11):2317–25.
10. Dispenzieri A, Katzmann JA, Kyle RA, Larson DR, Melton LJ, Colby CL, Therneau TM, Clark R, Kumar SK, Bradwell A, Fonseca R, Jelinek DF, Rajkumar SV. Prevalence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. Lancet. 2010;375:1721–8. https://doi.org/10.1016/S0140-6736(10)60482-5.
11. Hutchison CA, Harding S, Hewins P, Mead GP, Townsend J, Bradwell AR, Cockwell P. Quantitative assessment of serum and urinary polyclonal free light chains in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2008;3:1684–90. https://doi.org/10.2215/CJN.02290508.
12. Duston MA, Skinner M, Meenan RF, Cohen AS. Sensitivity, specificity, and predictive value of abdominal fat aspiration for the diagnosis of amyloidosis. Arthritis Rheum. 1989;32(1):82–5.

13. Van G II, Hazenberg BP, Bijzet J, van Rijswijk MH. Diagnostic accuracy of subcutaneous abdominal fat tissue aspiration for detecting systemic amyloidosis and its utility in clinical practice. Arthritis Rheum. 2006;54(6):2015–21.
14. Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. Circulation. 2017;135(14):1357–77.
15. Koike H, Katsuno M. Ultrastructure in transthyretin amyloidosis: from pathophysiology to therapeutic insights. Biomedicine. 2019;7(1):11.
16. Andrews TR, Colon-Otero G, Calamia KT, Menke DM, Boylan KB, Kyle RA. Utility of subcutaneous fat aspiration for diagnosing amyloidosis in patients with isolated peripheral neuropathy. Mayo Clin Proc. 2002;77(12):1287–90.
17. Muchtar E, Dispenzieri A, Lacy MQ, Buadi FK, Kapoor P, Hayman SR, Gonsalves W, Warsame R, Kourelis TV, Chakraborty R, Russell S, Lust JA, Lin Y, Go RS, Zeldenrust S, Rajkumar SV, Dingli D, Leung N, Kyle RA, Kumar SK, Gertz MA. Overuse of organ biopsies in immunoglobulin light chain amyloidosis (AL): the consequence of failure of early recognition. Ann Med. 2017;49(7):545–51.
18. Phull P, Sanchorawala V, Connors LH, Doros G, Ruberg FL, Berk JL, et al. Monoclonal gammopathy of undetermined significance in systemic transthyretin amyloidosis (ATTR). Amyloid. 2018;25(1):62–7.
19. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR 3rd, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009;114(24):4957–9.
20. Simões MV, et al. Position statement on diagnosis and treatment of cardiac amyloidosis—2021. Arq Bras Cardiol. 2021;117(3):561–98.

Chapter 16
The Echocardiogram in Amyloidosis

Marcelo Dantas Tavares de Melo and Alex dos Santos Félix

16.1 Introduction

Cardiac amyloidosis (CA) is a systemic disease caused by the extracellular deposition of insoluble amyloid fibrils in the heart [1]. Echocardiography is a key diagnostic method for the suspicion and diagnosis of amyloidosis and other cardiac infiltrative diseases. Most of the classic and more specific findings of the disease are not present until later stages of infiltrative burden [2], the reason why we must actively search for more sensitive echocardiographic markers that can detect it at an early stage and look for patterns that would indicate a higher probability of disease, allowing us to screen patients who would benefit from a more extensive investigation with other imaging modalities, such as cardiac MR and nuclear scintigraphy. The clinical outcome depends on the extent of tissue involvement and the type of deposited amyloid fibrils. CA should be suspected in cases of heart failure (HF) with preserved ejection fraction, unjustifiable left ventricular (LV) hypertrophy and systemic organ involvement, such as neuropathy, anemia, kidney dysfunction, bleeding and thrombosis, dysautonomia, and atrioventricular conduction

M. D. T. de Melo (✉)
Department of Internal Medicine at the Federal University of Paraíba, João Pessoa, PB, Brazil

Clinical Medicine of State of Paraiba, João Pessoa, PB, Brazil

Cardiology at Federal University of Paraiba, João Pessoa, PB, Brazil
e-mail: marcelot@alumni.usp.br

A. dos Santos Félix
Cardiovascular Imaging Department, Brazilian Society of Cardiology, Rio de Janeiro, RJ, Brazil

National Institute of Cardiology, Rio de Janeiro, RJ, Brazil

Cardiology—DASA, Rio de Janeiro, RJ, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_16

disturbances [3]. Predominant cardiac symptoms occur in only 20% of cases, and isolated cardiac involvement occurs in less than 5%, with the majority involving more than one organ [4].

Two main types of CA correspond to most cases: light chain (LC) and transthyretin (ATTR) CA. With the continuous development of effective pharmacological treatment options for this disease, it is also very important to have accurate quantitative parameters, which may have the capability to detect subtle changes that would help to monitor treatment response, determine prognosis, and help guide adjustments in therapy.

16.2 Light Chain Cardiac Amyloidosis

Amyloid fibrils in the CA are composed of monoclonal immunoglobulin LCs and are generally associated with cellular plasma disorders. It is a rare and rapidly progressive disease in which cardiac involvement is common and is a crucial factor in determining the clinical prognosis [5]. Mortality is high when cardiac involvement is present, and the prognosis is poor [6].

16.3 Transthyretin (ATTR) Cardiac Amyloidosis

In ATTR amyloidosis, the amyloid fibers come from the transthyretin protein produced in the liver. ATTR amyloidosis is more frequent from wild-type protein (ATTRwt) and less frequent from misfolding of variant TTR in patients with a mutation of the TTR gene (ATTRh) [7].

16.4 Echocardiography for the Diagnosis of Cardiac Amyloidosis

16.4.1 General Findings

The echocardiogram is the first-line cardiac imaging method for the diagnosis of CA. Particularly in the early stages, it lacks specificity to precisely distinguish amyloid from nonamyloid infiltrative or hypertrophic heart diseases [8]. The classical findings are biatrial enlargement, valvular and interatrial septal thickening, pleural and pericardial effusion, biventricular hypertrophy with a bright and sparkling appearance with preserved LV ejection fraction associated with diastolic

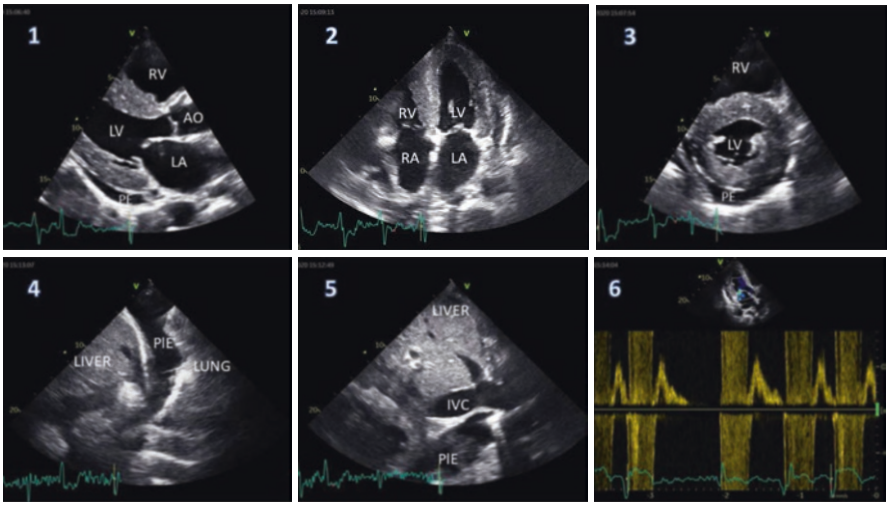


Fig. 16.1 1—Parasternal long axis showing valve thickening, pericardial effusion, left ventricular hypertrophy with a bright and sparkling appearance; 2—apical four-chamber presenting biatrial enlargement, right ventricular hypertrophy, interatrial septal thickening; 3—parasternal short axis with right ventricular enlargement, pericardial effusion and left ventricular hypertrophy; 4—lung ultrasound showing pleural effusion; 5—subcostal view with dilated inferior vena cava; 6—mitral flow disclosing irregular rhythm and mitral regurgitation. *AO* Aorta, *IVC* Inferior vena cava, *LA* Left atrium, *LV* Left ventricle, *PE* Pericardial effusion, *PlE* Pleural effusion, *RA* Right atrium, *RV* Right ventricle

dysfunction and restrictive pattern [9] (Fig. 16.1). However, most of these findings are usually found in an advanced stage of the disease and are also nonspecific to CA. The presence of a small A wave on mitral inflow Doppler, particularly in the absence of other features of restrictive LV filling, is a clue to identifying atrial dysfunction. Interestingly, left atrial thrombus is observed in up to 27% of patients, regardless of the presence of atrial fibrillation [10].

LC-CA is an urgent medical condition. The myocardial deposition is so rapid and consistent that we can see a monthly increase in myocardial thickness of 1.45–2.16 mm, as well as the development of HF and death within 6 months [11]. Deposition velocity is not the only cause of worse prognosis in LC type, and amyloid fiber exerts a direct toxic effect on tissues, especially in the heart. Based on that, it is possible to deduce that ATTR has higher LV hypertrophy than LC; pleural and pericardial effusion is more common in LC than ATTR; and asymmetric hypertrophy in ATTR, you can see some clues to help differentiate between LC and ATTR in Table 16.1. However, amyloidosis is always a daily challenge, starting in its diagnosis until its treatment, the reason why the use of multimodality imaging is strongly recommended.

Table 16.1 Findings in CA, most prevalent (or more intense) depending on the amyloid type. *ATTR* Transthyretin, *LC* light chain

Prevalent features	ATTR	LC
Ventricular hypertrophy	x	
Pericardium and pleural effusion		x
Pacemaker implantation	x	
Asymmetric left ventricular hypertrophy	x	
Reduced left ventricular ejection fraction		x
Advanced Diastolic dysfunction		x
Reduced left ventricular global longitudinal strain		x
		x
	x	
Atrial fibrilation		x
Intracardiac Thrombus		X

16.4.2 Role of Myocardial Deformation Analysis for the Diagnosis of Amyloidosis

Echocardiography is of paramount importance for the early diagnosis of amyloidosis, but many findings such as LV wall thickness ≥12 mm, valvular thickening, biatrial dilatation and diastolic dysfunction are not specific to this disease, especially when we consider that many of these patients have also coexistent pathologies, such as systemic hypertension and aortic stenosis, for example. For this matter, echocardiography, as any diagnostic method, has to be used in association with a comprehensive clinical evaluation, always balancing its findings to the estimated pretest probability of amyloidosis, which is elevated in the presence of any of the clinical, electrocardiographic and bio-humoral "red flags", with special attention to extracardiac signs, as ruptured biceps tendon, peripheral neuropathy, autonomic dysfunction, and carpal tunnel syndrome [12].

Myocardial deformation imaging analysis with two-dimensional strain (2DS), obtained from speckle-tracking echocardiography (STE), has become a valuable clinical tool for the study of a great array of cardiomyopathies and has been progressively incorporated into clinical practice because of its great feasibility, reproducibility, less angle dependency, and the ability to provide quantitative data that add incremental diagnostic capacity and relevant prognostic information. Despite some intervendor and intersoftware variability, successful efforts from the industry have achieved good results in reducing this problem, especially for global longitudinal strain (LS) [13, 14].

2DS can detect subclinical impairment of LV and right ventricular (RV) function in several cardiomyopathies and has been shown to be an early marker of myocardial dysfunction in hypertensive [15], hypertrophic [16, 17], ischemic [18], dilated idiopathic [19], arrhythmogenic [20], LV noncompaction [21], sarcoidosis [22], and

Chagas's disease [23, 24]. For infiltrative myocardial diseases, in particular, longitudinal deformation abnormalities are very prominent and proportional to the degree of myocardial infiltration, as we can see in Fabry's disease [25, 26], Friedreich ataxia [27], amyloidosis [2, 28], and other genetic infiltrative cardiomyopathies.

LS is consistently impaired in patients with CA and is directly correlated with grade of the amyloid burden on cardiac magnetic resonance (CMR) by late gadolinium enhancement and extracellular volume calculated from CMR-T1 weighted images [2, 29]. A regional pattern of relative preservation of longitudinal deformation in the apical segments has been described, delineating a basal-to-apical gradient, known as relative "apical sparing" (RELAPS) (Fig. 16.2). In the original work by Phelan et al., RELAPS was calculated using the equation: average apical LS/(average mid-walls LS + average basal-walls LS), and values >1.0 were described as sensitive and specific markers for the diagnosis of CA [29], with a sensitivity of 93% and specificity of 82% for the differentiation of CA from control patients with LV hypertrophy caused by aortic stenosis or hypertrophic cardiomyopathy (HCM) (AUC: 0.94). This regional pattern of LS is indistinctly seen in light-chain amyloidosis (AL), hereditary transthyretin (M-TTR), and wild-type transthyretin (WT-TTR) types of CA [28]. It is important to emphasize that the classic apical sparing pattern, although described as a hallmark of CA, may be absent, as exemplified in the study of Ternacle et al., where 52% of patients with CA diagnosis had a "nondiagnostic" RELAPS of <1.0 [28]. This may be explained in some cases by a low grade of amyloid burden, as we can see in the early stages of the disease. Other parameters based on LS have also been described as accurate in differentiating CA from other LV hypertrophic phenotypes, as demonstrated in the work by Liu et al., where the association of mitral E wave deceleration time <200 ms plus a value of regional LS septal apical/septal basal >2.1 (SAB) had a sensitivity of 88% and specificity of 100% to differentiate CA from controls, Fabry disease, Friedreich's ataxia,

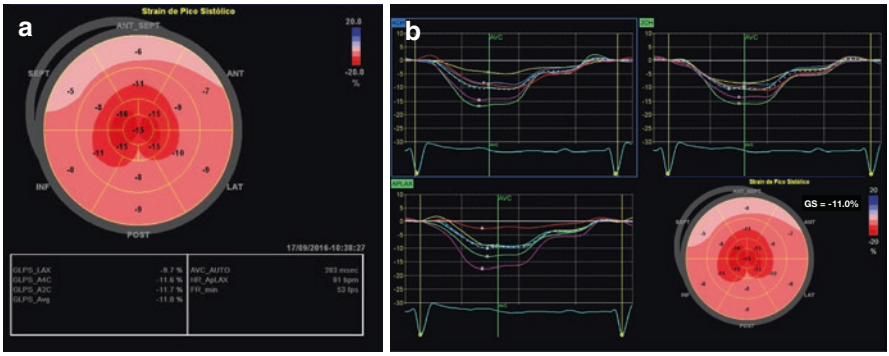


Fig. 16.2 AL Amyloidosis patient with markedly reduced bidimensional global longitudinal strain. In (**a**) the typical pattern on bulls-eye dysplay, with less reduced segmental strain on apical regions and more pronounced in basal and medial segments (relative apical sparing), resembling the so-called "cherry on top". In (**b**) strain curves per apical window and each segment are displayed, showing importantly reduced deformation in basal and medial segments

and arterial hypertension-related LV hypertrophy [30], and in the work of Pagourelias et al., where a ratio of LV ejection fraction (EF)/global LS >4.1 was the best parameter to differentiate CA from HCM, with superior performance than RELAPS or SAB, independent of CA type [31]. RV myocardial deformation is usually impaired in patients with CA [32] and may help to differentiate from other causes of hypertrophic phenotype (Fig. 16.3). A pattern of relative apical sparing was also described for the RV similar to what has been described in the LV in CA patients [33]. A study by Bellavia et al. showed that RV alterations may occur early in patients with AL CA, even in patients with normal LV thickness [34].

In CA, as seen in other infiltrative cardiomyopathies, there is also a significant compromise of other components of myocardial deformation, such as circumferential [35] and radial strain [36], twist and torsion (Fig. 16.4). In patients with systemic amyloidosis in the early stages of the disease, without any evidence of CA, twist and untwist can be enhanced [37], but deterioration of these parameters is progressive [38] and may lead in advanced cases to the rotation of LV base and apex in the same direction, creating a so-called rigid body rotation, losing the important contribution of torsional mechanics to cardiac performance.

LA strain is also severely impaired in CA patients as a result of both diastolic dysfunction and direct infiltration of the endocardial atrial wall (Fig. 16.5). In a recent study by Aimo et al. [39], only peak atrial LS (LA-PALS) displayed an independent association with the diagnosis of CA or ATTR-CA beyond standard echocardiographic variables and cardiac biomarkers. In the study of Harapoz et al. [40]

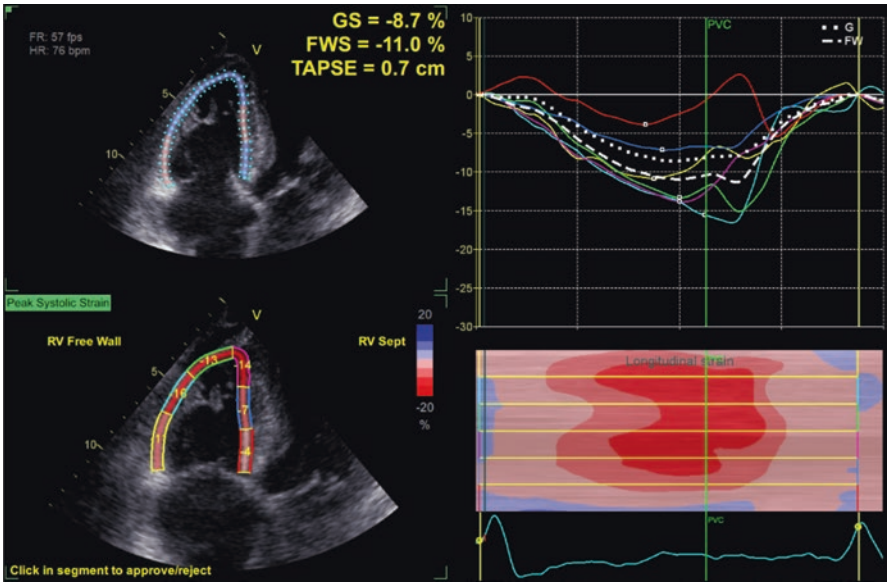


Fig. 16.3 ATTR-wt Amyloidosis patient, transthoracic echocardiogram from an apical right ventricular (RV) focused view. RV longitudinal strain markedly reduced due to infiltrative disease. Global RV longitudinal strain = −8.7%, RV free wall strain = −11.0%

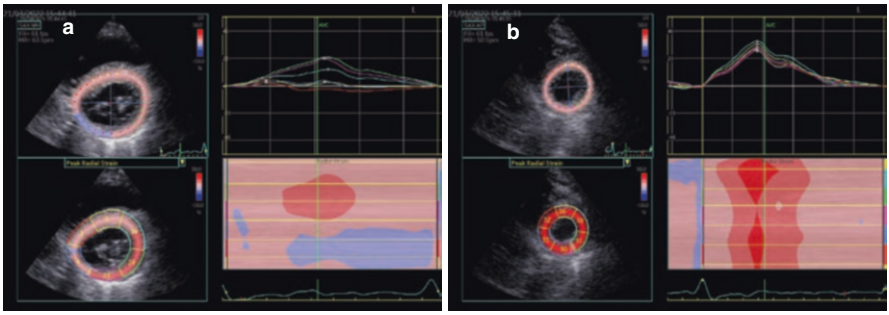


Fig. 16.4 ATTR-wt Amyloidosis patient with (**a**) markedly reduced basal (mitral valve level) radial strain and relatively preserved apical radial strain (**b**), showing that the relative apical sparing of deformation occurs not only with longitudinal deformation

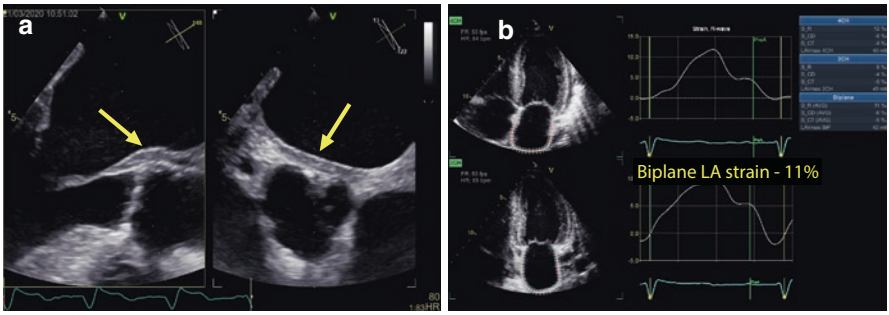


Fig. 16.5 ATTR-wt Amyloidosis patient. Transesophageal echocardiogram (**a**) showing infiltration of left atrial wall with amyloid (arrow). In (**b**) from a transthoracic echocardiogram (apical biplane—4 chamber and 2 chamber) we can see markedly reduced bidimensional longitudinal left atrium strain, resulting from diastolic dysfunction and contribution of atrial myopathy

with 40 patients with ATTR CA, an association between 99mTc-DPD-scintigraphy LA uptake and functional LA parameters was observed, of note LA emptying fraction ($r = -0.68$; $p < 0.001$) and LA reservoir strain (e) ($r = 0.70$; $p < 0.001$). LA minimal volumes (AUC = 0.83), LA maximal volumes (AUC = 0.84) and reservoir strain (AUC – 0.85) also demonstrated great accuracy in determining a subset of patients with atrial flutter and atrial fibrillation [40]. It has been recognized that advanced atrial infiltrative myopathy may cause severe dysfunction and loss of mechanical efficiency, leading to an "atrial electromechanical dissociation" (AEMD) [41]. In a large cohort of patients, Bandera et al. [42] showed AEMD (determined by STE analysis) in 22.1% of patients with sinus rhythm and was associated with a poorer prognosis. In a series of 156 patients with CA from the Mayo Clinic, intracardiac thrombi were detected by transesophageal echocardiography in 27% [10], and they can occur even in patients in sinus rhythm [43, 44] (Fig. 16.6).

3D strain may be useful to demonstrate alterations in all components of myocardial deformation in CA patients, with the advantage of using a single dataset for

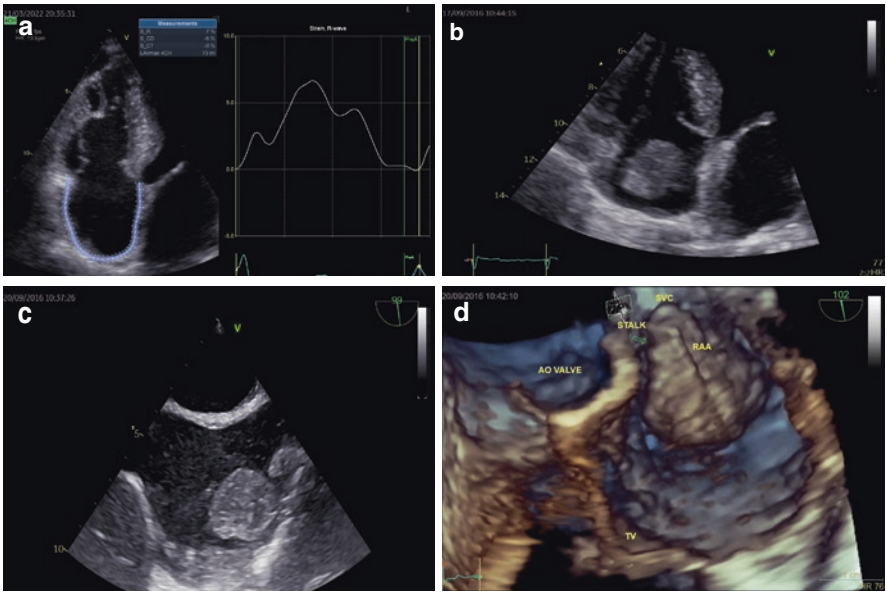


Fig. 16.6 AL cardiac amyloidosis patient in sinus rhythm. Transthoracic echocardiogram right atrial longitudinal strain (LS) analysis (**a**) showing reduced global LS (7%) because of markedly infiltration of right atrial wall with amyloid, leading to eletromechanical dissociation. In (**b**) from an apical RV focused view with zoom we can see a large thrombus inside the right atrium (RA). In (**c**) from a bicavam transesophageal view the large thrombus is attached to the right atrial (RA) appendage, seen with more details in (**d**) with three-dimensional rendered images. *TV* Tricuspid valve, *AO* Aortic, *SVC* Superior-Vena cava, *RA* right atrium

analysis, with simultaneous information from all the ventricular walls, useful for the evaluation of myocardial dissynchrony and avoiding some technical issues such as arrhythmias and out-of-plane motion. In the study of Vitarelli et al., peak basal LV rotation, RV basal LS and LV basal LS were able to discriminate patients with CA with great accuracy from other patients with LV hypertrophy and controls [45]. In a study by Baccouche et al. [46], using 3DE-derived LS, they demonstrated the same pattern of apical relative sparing, with a characteristic basoapical gradient (Fig. 16.7). Urbano-Moral et al. [32] found not only LV longitudinal and circumferential strain reduction in patients with CA (predominantly in basal segments) but also impairment of RV longitudinal strain and radial displacement (-9 ± 3 CA vs -17 ± 3 non CA; $P < 0.001$, and 2.7 ± 0.8 CA vs 3.8 ± 0.3 non CA; $P = 0.002$) by 3DE. Migrino et al. [47] evaluated intraventricular dyssynchrony by 3DE in AL amyloid patients with preserved EF and found that a 16-segment dyssynchrony index was significantly higher in amyloid patients than in the control group. From

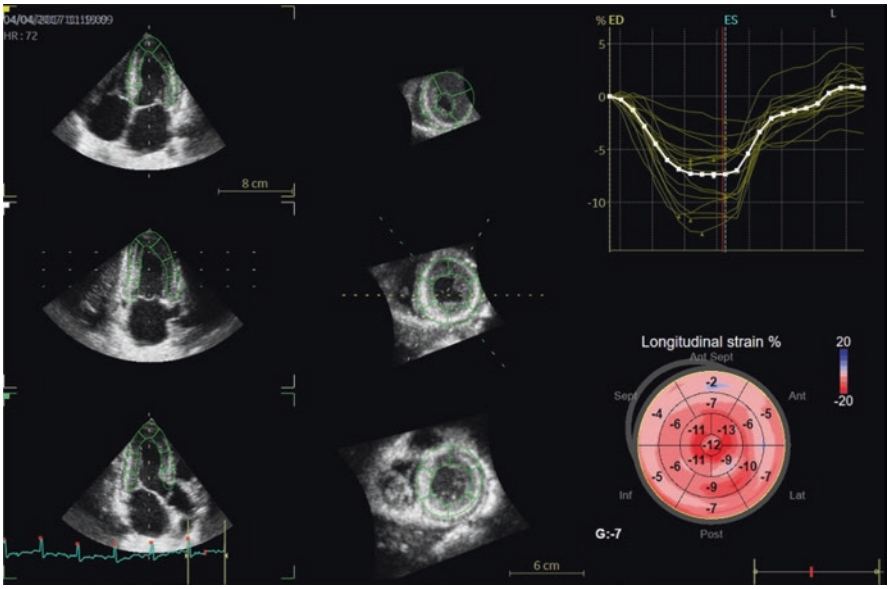


Fig. 16.7 ATTR cardiac amyloidosis. 3D Transthoracic echocardiogram longitudinal strain (LS) analysis. In the upper right corner we can see the strain curves for each segment. In the lower right corner a "bulls-eye" parametric representation of strain values, with the pattern of apical relative sparing, with characteristic basoapical gradient

the results of a subanalysis of the MAGYAR-Path study, it has been shown that patients with AL CA also had reduced right atrial global longitudinal (4.0 ± 5.2% vs. 8.2 ± 5.5%, $p = 0.02$) and area (7.8 ± 8.1% vs. 15.9 ± 10.3%, $p = 0.03$) strains [48].

Myocardial work (MW) is a new technique that evaluates myocardial energetics and mechanics, incorporating arterial blood pressure as an estimate of LV pressure (in cases where there are no obstructions to the LV outflow tract) and LS values for the construction of a "pressure × strain" loop, generated by specific software [49] (Fig. 16.7). In a study by Clemmensen et al. [50], patients with CA had a lower global LV myocardial work index (LVMWI) than the control group, with more pronounced alterations in the basal segments, and when submitted to stress echocardiogram (SE), an increase in LVMWI from rest to peak exercise was 1974 mmHg% (95% CI 1699–2250 mmHg%; $P < 0.0001$) in control subjects and only 496 mmHg% (95% CI 156–835 mm Hg%; $P < 0.01$) in patients with CA. A paper from Henein et al. [40] did not find significant differences in LVMI, global constructive work or wasted work between patients with CA and HF with septal hypertrophy and negative DPD scintigraphy (non-CA).

16.4.3 Role of 3D Echocardiography for Volumetric Analysis in Amyloidosis

3D echocardiography (3DE) has been demonstrated to be a valuable tool to accurately quantitate cardiac chamber volumes and function in normal patients and several cardiac diseases. In the study by Pradel et al. [3, 51], they showed 3D-derived LV EF to be more accurate than 2D EF in the differentiation of patients with AL CA according to Mayo Clinic (MC) staging groups. Patients in MC group II had a significantly lower global LS and radial strain obtained by 3DE than controls and MG group I patients. Left atrial (LA) volumes may also be a marker of more advanced disease in CA, and the study by Mohty et al. [3] showed that indexed LA volumes measured by 3DE are significantly higher in MCIII patients than in groups I and II, and there is also a clear deterioration in LA function, as shown by a reduced 3D-LA total emptying fraction (MCIII: 21 ± 13% vs. MCII: 31 ± 15% vs. MCI: 43 ± 7%, respectively, $p < 0.0001$) and worse 3D peak atrial LS (3D-PALS) (MCIII: 11 ± 9% vs. MCII: 18 ± 13% vs. MCIII: 20 ± 7%, respectively, $p = 0.007$).

16.4.4 Use of Contrast Echocardiography in Amyloidosis

Even in the absence of epicardial coronary disease, microvascular disease has been described in patients with CA [52]. There are only a few studies using contrast echocardiography (CE) in CA [53, 54]. Abdelmoneim et al. [54] reported the use of CE for myocardial perfusion in a patient with primary CA and normal coronary arteries, showing reduced coronary flow reserve during stress echocardiography with adenosine vasodilation. Contrast enhancement may also be used for endocardial border definition, with a more accurate estimation of LV volumes and EF.

16.4.5 Cardiac Elastography in Amyloidosis

Due to progressive infiltration, there is a progressive increase in myocardial stiffness and elevation of filling pressures. Intrinsic cardiac elastography (CE) has been described recently as a new tool that is able to noninvasively quantify myocardial elasticity [55]. It has been shown that patients with CA have markedly higher intrinsic velocity propagation of myocardial stretch (iVP) when compared to those with non-CA and normal subjects (3.2 ± 1.0 m/s, 1.8 ± 0.4 m/s, and 1.6 ± 0.2 m/s, respectively; $P < 0.0001$) and correlated with chamber stiffness.

16.5 Potential Role of Echocardiography in the Evaluation of Therapeutic Responsiveness

16.5.1 Conventional Parameters

The natural history of myocardial function in CA during its treatment is still a challenge. The standard parameters, such as LV wall thickness, cavity dimension, LV ejection fraction, or tissue Doppler, had low sensitivity and specificity to detect the progression of disease in untreated patients. Therefore, it is reasonable that these parameters are unsuitable for assessing therapeutic responsiveness. To date, we have few recommendations and more robust data on LC amyloidosis (Table 16.2) [56]. A publication by Tuzovic et al. showed a significant association between hematologic response to chemotherapy in AL CA patients and improvement of diastolic function parameters, such as E/e' ($r = -0.43$, $p = 0.01$) and LA stiffness ($r = -0.35$, $p = 0.05$) [57]. Despite the significant advances in the use of new disease-modifying drugs in ATTR, there are still no objective parameters to assess its therapeutic response in clinical practice, and there are also some important unanswered questions, such as which patients may have a better therapeutic response in the mid- and long-term. In the ATTR-ACT trial, ATTR patients with NYHA class 3, as a group, did not show a significant response to therapy with Tafamidis, considering all-cause mortality and the rate of cardiovascular-related hospitalizations, in the 30-month follow-up period [58]. Considering the high subjectivity of estimating functional class, some NYHA 3 patients may also benefit from treatment, and imaging parameters may serve as better and more robust prognosticators, predicting responsiveness to specific drugs and treatments. Identifying nonresponders among class two patients, for example, may also help to redirect to a different therapeutic approach, selection of a different drug class or even adjustment of doses.

Based on the available literature, it is common sense that ATTR patients must be treated as early as possible with disease-modifying drugs to achieve better clinical results. In patients with mutant forms of ATTR, it is very important to screen relatives for the presence of asymptomatic cardiac disease. Thinking about early

Table 16.2 Assessment of therapeutic response or disease progression during treatment of light chain cardiac amyloidosis

Therapeutic response
NT-proBNP reduction >30% and >300 ng/L in patients with baseline value greater than 650 ng/L Reduction of NYHA functional class greater than 2 classes with previous NYHA III or IV
Disease progression
NT-proBNP increase >30% or an increase of 300 ng/dL Troponin increase >33% Drop in left ventricular ejection fraction greater than 10%

therapeutic intervention in these patients could also pose the question of which parameter of improvement can be used in this scenario, considering that functional class (NYHA), hospitalizations and other usual clinical endpoints are only suitable for more advanced disease.

16.5.2 Advanced Techniques

Tridimensional echocardiography and STE are more accurate techniques, they may have a promising role in measuring treatment responsiveness in these patients in the near future. An interesting paper by Salinano et al., analyzing AL CA patients treated with high-dose melphalan or bortezomib, found no difference between the hematologic complete response (CR) group and the no CR group with respect to wall thickness, EF and diastolic function, with significant improvement in the CR group of LS and apical-to-basal strain ratio ($p < 0.05$) [59]. In the study of Giblin et al., retrospectively evaluating 45 ATTR-CM patients with a 1-year follow-up, values of LS and MW were compared between groups of treated and untreated patients with tafamidis [60]. They reported a greater deterioration of global LS ($p = 0.02$), myocardial work index and work efficiency ($p = 0.04$) in the group of untreated patients, with no differences in EF, circumferential and radial strain, twist or torsion.

16.6 Prognostic Value of Echocardiography in Amyloidosis

The main determinant in the prognosis of amyloidosis is the extent of cardiac involvement. The precise definition of cardiac involvement has evolved over the last three decades. Initially, cardiac involvement was defined by the presence of HF, pleural effusion, and cardiomegaly on chest radiography [61]. Later, imaging techniques such as echocardiography and cardiac MR proved to be more robust tools for the diagnosis and prognostic stratification of these patients. We currently use biomarkers such as BNP (or NT-proBNP) and troponin for prognostic classification models and staging of LC amyloidosis [62, 63]. Regardless of many publications showing the role of noninvasive methods in prognostication of CA, we do not have a consensus on which parameters we should use and their cutoff. Myocardial deformation parameters have become of great interest in this regard due to their quantitative analysis capability, high sensitivity and reproducibility. The study by Ternacle et al. [28], with 79 CA patients (wild-type ATTR, mutant ATTR-CM and AL-CM types) during a median follow-up of 11 months, found to be independent predictors of MACE: apical LS (cutoff: −14.5%), elevated NT-pro-BNP and NYHA class III or IV. Senapati et al., analyzing 97 patients with AL and ATTR CA, found that RELAPS was independently associated with the composite outcome of death or

heart transplantation at 5 years (HR 2.45; $p = 0.003$), remaining predictive of this primary outcome even on multivariable analysis ($p = 0.018$) [64]. A large study published by Buss et al., including 206 patients with AL CA, showed that Doppler-derived LS and 2D global LS were strongly associated with NT-proBNP levels and survival [65]. The best cutoff value of 2D global LS for distinguishing survivors from nonsurvivors in this population during a median follow-up of 1207 days was −11.78%, and in a multivariable echocardiographic Cox model, only diastolic function and 2D global LS remained independent predictors of survival. In a recent paper, Liu et al. enrolled 40 multiple myeloma patients with preserved EF before starting treatment with bortezomib, measuring global LS and MW parameters at baseline [66]. They found that global work efficiency (GWE) had a significant association with cardiac adverse events after 6 months of chemotherapy, AUC = 0.896 (95% CI: 0.758–0.970; $p < 0.05$). In a large study by Chacko et al., which studied 1240 patients with ATTR-CM from 2000 to 2019, with 766 wt-ATTR-CM and 474 m-ATTR-CM, stroke volume index, right atrial area index, global LS and E/e' were all independently associated with mortality ($p < 0.05$ for all) [67]. Severe aortic stenosis was also independently associated with prognosis, conferring a significantly short survival (median survival 22 vs. 53 months; $p = 0.001$). Koyama et al. found systolic basal septal strain (Doppler based) to be a significant predictor of clinical outcome in patients with CA, superior to other Doppler flow measurements and diastolic tissue velocities and strain rate indexes [68]. There was additive prognostic value even when HF was present. In a cohort of 5 years, including 249 patients with AL CA, male sex (HR: 2.2; $p = 0.005$), NT-proBNP (HR: 1.4; $p = 0.003$), troponin T levels (HR: 1.6; $p = 0.01$), pleural effusion (HR: 3.6; $p = 0.001$), E/A ratio (HR: 1.3; $p = 0.006$), RV systolic pressure (HR: 1.02; $p = 0.01$), and RV strain rate of the middle segment of the free wall (HR: 1.3; $p = 0.02$) were independent predictors of death [34]. RV LS has also been advocated as a prognostic factor in CA. In a study by Huntjens et al. studying 136 patients with CA, strain values from all chambers were significantly associated with survival in a median follow-up of 5 years. Peak longitudinal LA strain and RV free wall strain remained independently associated with survival in multivariable analysis [69]. Peak LA strain had the strongest association with survival ($p < 0.001$), and LA strain combined with global LV LS and RV free wall strain had the highest prognostic level ($p < 0.001$).

16.7 Conclusion

The echocardiogram is essential in CA to help in its diagnosis, therapeutic responses and prognostic stratification (Fig. 16.8). Two factors have recently contributed to the rise of interest in this singular cardiomyopathy: first, it has already received disease-modifying therapies, and second, there have been tremendous advances in cardiac imaging modalities, especially in echocardiography.

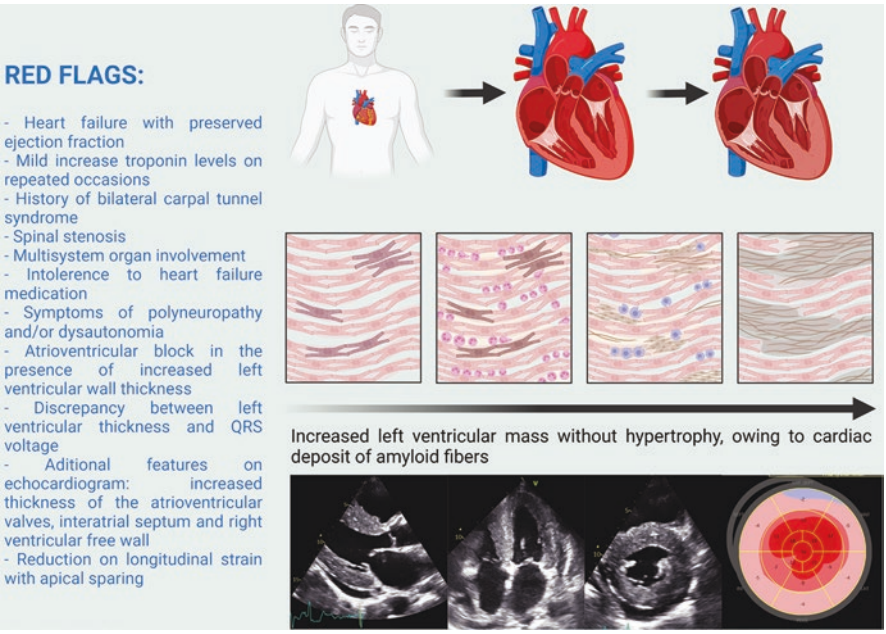


Fig. 16.8 The progression of cardiac amyloidosis pathophysiology and its main clinical red flags

References

1. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet. 2016;387(10038):2641–54.
2. Knight DS, Zumbo G, Barcella W, Steeden JA, Muthurangu V, Martinez-Naharro A, et al. Cardiac structural and functional consequences of amyloid deposition by cardiac magnetic resonance and echocardiography and their prognostic roles. JACC Cardiovasc Imaging. 2019;12(5):823–33.
3. Mohty D, Damy T, Cosnay P, Echahidi N, Casset-Senon D, Virot P, et al. Cardiac amyloidosis: updates in diagnosis and management. Arch Cardiovasc Dis. 2013;106(10):528–40.
4. Bodez D, Galat A, Guellich A, Deux J-F, Rosso J, le Bras F, et al. Les amyloses cardiaques : les reconnaître et les prendre en charge. Presse Med. 2016;45(10):845–55.
5. Zhang KW, Stockerl-Goldstein KE, Lenihan DJ. Emerging therapeutics for the treatment of light chain and transthyretin amyloidosis. JACC: basic to translational. Science. 2019;4(3):438–48.
6. Merlini G, Palladini G. Light chain amyloidosis: the heart of the problem. Hema. 2013;98(10):1492–5.
7. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy. J Am Coll Cardiol. 2019;73(22):2872–91.
8. Lee S-P, Park J-B, Kim H-K, Kim Y-J, Grogan M, Sohn D-W. Contemporary imaging diagnosis of cardiac amyloidosis. J Cardiovasc Imaging. 2019;27(1):1.
9. Dorbala S, Cuddy S, Falk RH. How to image cardiac amyloidosis. JACC Cardiovasc Imaging. 2020;13(6):1368–83.
10. Feng D, Syed IS, Martinez M, Oh JK, Jaffe AS, Grogan M, et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. Circulation. 2009;119(18):2490–7.

11. Gertz MA. Immunoglobulin light chain amyloidosis: 2018 update on diagnosis, prognosis, and treatment. Am J Hematol. 2018;93(9):1169–80.
12. Vergaro G, Aimo A, Barison A, Genovesi D, Buda G, Passino C, et al. Keys to early diagnosis of cardiac amyloidosis: red flags from clinical, laboratory and imaging findings. Eur J Prev Cardiol. 2020;27(17):1806–15.
13. Farsalinos KE, Daraban AM, Ünlü S, Thomas JD, Badano LP, Voigt J-U. Head-to-head comparison of global longitudinal strain measurements among nine different vendors. J Am Soc Echocardiogr. 2015;28(10):1171–1181.e2.
14. Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2018;19(6):591–600.
15. Soufi Taleb Bendiab N, Meziane-Tani A, Ouabdesselam S, Methia N, Latreche S, Henaoui L, et al. Factors associated with global longitudinal strain decline in hypertensive patients with normal left ventricular ejection fraction. Eur J Prev Cardiol. 2017;24(14):1463–72.
16. Yiu KH, Atsma DE, Delgado V, Ng ACT, Witkowski TG, Ewe SH, et al. Myocardial structural alteration and systolic dysfunction in preclinical hypertrophic cardiomyopathy mutation carriers. PLoS One. 2012;7(5):e36115.
17. De S, Borowski AG, Wang H, Nye L, Xin B, Thomas JD, et al. Subclinical echocardiographic abnormalities in phenotype-negative carriers of myosin-binding protein C3 gene mutation for hypertrophic cardiomyopathy. Am Heart J. 2011;162(2):262–267.e3.
18. Schroeder J, Hamada S, Gründlinger N, Rubeau T, Altiok E, Ulbrich K, et al. Myocardial deformation by strain echocardiography identifies patients with acute coronary syndrome and nondiagnostic ECG presenting in a chest pain unit: a prospective study of diagnostic accuracy. Clin Res Cardiol. 2016;105(3):248–56.
19. van der Bijl P, Bootsma M, Hiemstra YL, Ajmone Marsan N, Bax JJ, Delgado V. Left ventricular 2D speckle tracking echocardiography for detection of systolic dysfunction in genetic, dilated cardiomyopathies. Eur Heart J Cardiovasc Imaging. 2019;20(6):694–9.
20. Teske AJ, Cox MGPJ, te Riele ASJM, de Boeck BW, Doevendans PA, Hauer RNW, et al. Early detection of regional functional abnormalities in asymptomatic ARVD/C gene carriers. J Am Soc Echocardiogr. 2012;25(9):997–1006.
21. Bellavia D, Michelena HI, Martinez M, Pellikka PA, Bruce CJ, Connolly HM, et al. Speckle myocardial imaging modalities for early detection of myocardial impairment in isolated left ventricular noncompaction. Heart. 2010;96(6):440–7.
22. Schouver E-D, Moceri P, Doyen D, Tieulie N, Queyrel V, Baudouy D, et al. Early detection of cardiac involvement in sarcoidosis with 2-dimensional speckle-tracking echocardiography. Int J Cardiol. 2017;227:711–6.
23. Cianciulli TF, Albarracín GA, Napoli Llobera M, Prado NG, Saccheri MC, Hernández Vásquez YM, et al. Speckle tracking echocardiography in the indeterminate form of chagas disease. Echocardiography. 2021;38(1):39–46.
24. Romano MMD, Moreira HT, Marin-Neto JA, Baccelli PE, Alenezi F, Klem I, et al. Early impairment of myocardial deformation assessed by regional speckle-tracking echocardiography in the indeterminate form of chagas disease without fibrosis detected by cardiac magnetic resonance. PLoS Negl Trop Dis. 2020;14(11):e0008795.
25. Lu D-Y, Huang W-M, Wang W-T, Hung S-C, Sung S-H, Chen C-H, et al. Reduced global longitudinal strain as a marker for early detection of Fabry cardiomyopathy. Eur Heart J Cardiovasc Imaging. 2022;23(4):487–95.
26. Krämer J, Niemann M, Liu D, Hu K, Machann W, Beer M, et al. Two-dimensional speckle tracking as a noninvasive tool for identification of myocardial fibrosis in Fabry disease. Eur Heart J. 2013;34(21):1587–96.

27. Dedobbeleer C, Rai M, Donal E, Pandolfo M, Unger P. Normal left ventricular ejection fraction and mass but subclinical myocardial dysfunction in patients with Friedreich's ataxia. Eur Heart J Cardiovasc Imaging. 2012;13(4):346–52.
28. Ternacle J, Bodez D, Guellich A, Audureau E, Rappeneau S, Lim P, et al. Causes and consequences of longitudinal LV dysfunction assessed by 2D strain echocardiography in cardiac amyloidosis. JACC Cardiovasc Imaging. 2016;9(2):126–38.
29. Phelan D, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. Heart. 2012;98(19):1442–8.
30. Liu D, Hu K, Niemann M, Herrmann S, Cikes M, Störk S, et al. Effect of combined systolic and diastolic functional parameter assessment for differentiation of cardiac amyloidosis from other causes of concentric left ventricular hypertrophy. Circulation Cardiovasc Imaging. 2013;6(6):1066–72.
31. Pagourelias ED, Mirea O, Duchenne J, van Cleemput J, Delforge M, Bogaert J, et al. Echo parameters for differential diagnosis in cardiac amyloidosis. Circulation Cardiovasc Imaging. 2017;10(3)
32. Urbano-Moral JA, Gangadharamurthy D, Comenzo RL, Pandian NG, Patel AR. Three-dimensional speckle tracking echocardiography in light chain cardiac amyloidosis: examination of left and right ventricular myocardial mechanics parameters. Revista Española de Cardiología (English Edition). 2015;68(8):657–64.
33. Arvidsson S, Henein MY, Wikström G, Suhr OB, Lindqvist P. Right ventricular involvement in transthyretin amyloidosis. Amyloid. 2018;25(3):160–6.
34. Bellavia D, Pellikka PA, Dispenzieri A, Scott CG, Al-Zahrani GB, Grogan M, et al. Comparison of right ventricular longitudinal strain imaging, tricuspid annular plane systolic excursion, and cardiac biomarkers for early diagnosis of cardiac involvement and risk stratification in primary systematic (AL) amyloidosis: a 5-year cohort study. Eur Heart J Cardiovasc Imaging. 2012;13(8):680–9.
35. di Bella G, Minutoli F, Pingitore A, Zito C, Mazzeo A, Aquaro GD, et al. Endocardial and epicardial deformations in cardiac amyloidosis and hypertrophic cardiomyopathy. Circ J. 2011;75(5):1200–8.
36. Sun JP, Stewart WJ, Yang XS, Donnell RO, Leon AR, Felner JM, et al. Differentiation of hypertrophic cardiomyopathy and cardiac amyloidosis from other causes of Ventricular Wall thickening by two-dimensional strain imaging echocardiography. Am J Cardiol. 2009;103(3):411–5.
37. Cappelli F, Porciani MC, Bergesio F, Perfetto F, de Antoniis F, Cania A, et al. Characteristics of left ventricular rotational mechanics in patients with systemic amyloidosis, systemic hypertension and normal left ventricular mass. Clin Physiol Funct Imaging. 2011;31:159–65.
38. Porciani MC, Cappelli F, Perfetto F, Ciaccheri M, Castelli G, Ricceri I, et al. Rotational mechanics of the left ventricle in AL amyloidosis. Echocardiography. 2010;27(9):1061–8.
39. Aimo A, Fabiani I, Giannoni A, Mandoli GE, Pastore MC, Vergaro G, et al. Multichamber speckle tracking imaging and diagnostic value of left atrial strain in cardiac amyloidosis. Eur Heart J Cardiovasc Imaging. 2022; https://doi.org/10.1093/ehjci/jeac057.
40. Harapoz M, Evans S, Geenty P, Kwok F, Stewart G, Taylor MS, et al. Correlation of quantitative 99mTc DPD scintigraphy with echocardiographic alterations in left atrial parameters in transthyretin amyloidosis. Heart Lung Circ. 2022;31:804–14.
41. Santarone M, Corrado G, Tagliagambe LM, Manzillo GF, Tadeo G, Spata M, et al. Atrial thrombosis in cardiac amyloidosis: diagnostic contribution of transesophageal echocardiography. J Am Soc Echocardiogr. 1999;12(6):533–6.
42. Bandera F, Martone R, Chacko L, Ganesananthan S, Gilbertson JA, Ponticos M, et al. Clinical importance of left atrial infiltration in cardiac transthyretin amyloidosis. JACC Cardiovasc Imaging. 2022;15(1):17–29.
43. Daloia A, Vizzardi E, Chiari E, Faggiano P, Squeri A, Ugo F, et al. Cardiac arrest in a patient with a mobile right atrial thrombus in transit and amyloidosis. Eur J Echocardiogr. 2008;9:141–2.

44. Falk RH, Alexander KM, Liao R, Dorbala S. AL (light-chain) cardiac amyloidosis. J Am Coll Cardiol. 2016;68(12):1323–41.
45. Vitarelli A, Lai S, Petrucci MT, Gaudio C, Capotosto L, Mangieri E, et al. Biventricular assessment of light-chain amyloidosis using 3D speckle tracking echocardiography: differentiation from other forms of myocardial hypertrophy. Int J Cardiol. 2018;271:371–7.
46. Baccouche H, Maunz M, Beck T, Gaa E, Banzhaf M, Knayer U, et al. Differentiating cardiac amyloidosis and hypertrophic cardiomyopathy by use of three-dimensional speckle tracking echocardiography. Echocardiography. 2012;29(6):668–77.
47. Migrino RQ, Harmann L, Woods T, Bright M, Truran S, Hari P. Intraventricular dyssynchrony in light chain amyloidosis: a new mechanism of systolic dysfunction assessed by 3-dimensional echocardiography. Cardiovasc Ultrasound. 2008;6(1):40.
48. Nemes A, Földeák D, Domsik P, Kalapos A, Kormányos Á, Borbényi Z, et al. Right atrial deformation analysis in cardiac amyloidosis—results from the three-dimensional speckle-tracking echocardiographic MAGYAR-path study. Arq Bras Cardiol. 2018;111:384–91.
49. Russell K, Eriksen M, Aaberge L, Wilhelmsen N, Skulstad H, Remme EW, et al. A novel clinical method for quantification of regional left ventricular pressure–strain loop area: a noninvasive index of myocardial work. Eur Heart J. 2012;33(6):724–33.
50. Clemmensen TS, Eiskjær H, Mikkelsen F, Granstam S-O, Flachskampf FA, Sørensen J, et al. Left ventricular pressure-strain–derived myocardial work at rest and during exercise in patients with cardiac amyloidosis. J Am Soc Echocardiogr. 2020;33(5):573–82.
51. Pradel S, Magne J, Jaccard A, Fadel BM, Boulogne C, Salemi VMC, et al. Left ventricular assessment in patients with systemic light chain amyloidosis: a 3-dimensional speckle tracking transthoracic echocardiographic study. Int J Cardiovasc Imaging. 2019;35(5):845–54.
52. Modesto KM, Dispenzieri A, Gertz M, Cauduro SA, Khandheria BK, Seward JB, et al. Vascular abnormalities in primary amyloidosis. Eur Heart J. 2007;28(8):1019–24.
53. Nam MCY, Nel K, Senior R, Greaves K. Abnormal myocardial blood flow reserve observed in cardiac amyloidosis. J Cardiovasc Ultrasound. 2016;24(1):64.
54. Abdelmoneim SS, Bernier M, Bellavia D, Syed IS, Mankad SV, Chandrasekaran K, et al. Myocardial contrast echocardiography in biopsy-proven primary cardiac amyloidosis. Eur Heart J Cardiovasc Imaging. 2008;9(2):338–41.
55. Pislaru C, Pellikka PA, Pislaru SV. Wave propagation of myocardial stretch: correlation with myocardial stiffness. Basic Res Cardiol. 2014;109(6):438.
56. Comenzo RL, Reece D, Palladini G, Seldin D, Sanchorawala V, Landau H, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia. 2012;26(11):2317–25.
57. Tuzovic M, Kobayashi Y, Wheeler M, Barrett C, Liedtke M, Lafayette R, et al. Functional cardiac recovery and hematologic response to chemotherapy in patients with light-chain amyloidosis (from the Stanford University Amyloidosis Registry). Am J Cardiol. 2017;120(8):1381–6.
58. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018;379(11):1007–16.
59. Salinaro F, Meier-Ewert HK, Miller EJ, Pandey S, Sanchorawala V, Berk JL, et al. Longitudinal systolic strain, cardiac function improvement, and survival following treatment of light-chain (AL) cardiac amyloidosis. Eur Heart J Cardiovasc Imaging. 2017;18(9):1057–64.
60. Giblin GT, Cuddy SAM, González-López E, Sewell A, Murphy A, Dorbala S, et al. Effect of tafamidis on global longitudinal strain and myocardial work in transthyretin cardiac amyloidosis. Eur Heart J Cardiovasc Imaging. 2022;23:1029–39.
61. Desai HV, Aronow WS, Peterson SJ, Frishman WH. Cardiac amyloidosis. Cardiol Rev. 2010;18(1):1–11.
62. Dispenzieri A, Gertz MA, Kyle RA, Lacy MQ, Burritt MF, Therneau TM, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol. 2004;22(18):3751–7.

63. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol. 2012;30(9):989–95.
64. Senapati A, Sperry BW, Grodin JL, Kusunose K, Thavendiranathan P, Jaber W, et al. Prognostic implication of relative regional strain ratio in cardiac amyloidosis. Heart. 2016;102(10):748–54.
65. Buss SJ, Emami M, Mereles D, Korosoglou G, Kristen AV, Voss A, et al. Longitudinal left ventricular function for prediction of survival in systemic light-chain amyloidosis. J Am Coll Cardiol. 2012;60(12):1067–76.
66. Liu Z, Zhang L, Liu M, Wang F, Xiong Y, Tang Z, et al. Myocardial injury in multiple myeloma patients with preserved left ventricular ejection fraction: noninvasive left ventricular pressure-strain myocardial work. Front Cardiovasc Med. 2022;8:782580.
67. Chacko L, Martone R, Bandera F, Lane T, Martinez-Naharro A, Boldrini M, et al. Echocardiographic phenotype and prognosis in transthyretin cardiac amyloidosis. Eur Heart J. 2020;41(14):1439–47.
68. Koyama J, Falk RH. Prognostic significance of strain doppler imaging in light-chain amyloidosis. JACC Cardiovasc Imaging. 2010;3(4):333–42.
69. Huntjens PR, Zhang KW, Soyama Y, Karmpalioti M, Lenihan DJ, Gorcsan J. Prognostic utility of echocardiographic atrial and ventricular strain imaging in patients with cardiac amyloidosis. JACC Cardiovasc Imaging. 2021;14(8):1508–19.

Chapter 17
The Role of MRI in Amyloidosis

Ibraim Masciarelli F. Pinto and Marly Uellendhal

17.1 Introduction

Cardiac magnetic resonance (CMR) is a noninvasive imaging technique based upon the interaction of potent magnets with protons inside the nucleus of hydrogen atoms within the human body. It presents spatial resolution high enough to properly depict the different cardiac chambers and allows for proper definition of normal and abnormal cardiac anatomy, thus being useful in the evaluation of patients with different cardiac abnormalities [1, 2]. CMR also produces dynamic images with high contrast and spatial and temporal resolution to make this the gold-standard technique for the evaluation of systolic left and, particularly, right ventricular function, which makes CMR a very useful tool in the evaluation of patients with heart failure and suspected right or left ventricular dysfunction, providing useful diagnostic and prognostic information, as well as aiding in therapeutic decision making [3, 4]. In addition, CMR has a unique role in clinical practice, advancing data that can be effective in performing tissue characterization, which can be accomplished by two techniques. Delayed contrast enhancement (DE) has an established role in revealing areas that often present myocardial necrosis or fibrosis and is now a validated and key tool in the analysis of patients with different cardiac diseases [1, 3, 5]. More recently, the estimation of interstitial fibrosis and edema in earlier stages of myocardial disease,

I. M. F. Pinto (✉)
Cardiac Imaging, Instituto Dante Pazzanese de Cardiologia, São Paulo, SP, Brazil
e-mail: ibraim.pinto@grupofleury.com.br

M. Uellendhal
Escola paulista de Medicina -UNIFESP, São Paulo, SP, Brazil

DASA, São Paulo, SP, Brazil

Universidade de Pernambuco, Recife, Pernambuco, Brazil
e-mail: mauellendahl@gmail.com

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_17

which could be altered even in cases without DE, opened new perspectives for the use of CMR in patients with cardiomyopathies, making it even a choice to be considered to screen asymptomatic individuals at risk of developing myocardial disease, such as is the case of amyloidosis [1, 3, 5, 6].

Therefore, CMR characteristics make this imaging technique particularly useful in the investigation of the etiology of several myocardial diseases, including amyloidosis.

On one hand, CMR image quality heavily depends on cardiac rhythm and cooperation and could be harmed by long periods of scanning and in more advanced cases. DE and interstitial fibrosis detection are usually more robust and, thus, maintain the clinical relevance of CMR in such patients still very high, and it is possible to obtain relevant data on the etiology and prognosis of patients with myocardial disease [1, 3, 5, 6]. CMR still does not allow for the definitive confirmation of cardiac amyloidosis, but it provides data that might raise diagnostic suspicion and important prognostic data [1, 3, 5–8].

The aim of this chapter is to review how different data obtained by CMR may be helpful in the evaluation and study of cardiac amyloidosis and to underscore the clinical scenarios where using CMR could be particularly useful.

17.2 Evaluation of Cardiac Morphology

Cardiac amyloidosis implies changes in cardiac anatomy due to infiltration of abnormal proteins amid normal myocardial cells, which, in turn, takes on modifications in cardiac structure that may play a role in the diagnosis evaluation. There is usually atrial dilation, and the presence of atrial septum thickening (<4.0 mm) is highly associated with infiltrative processes [6, 9]. As the process progresses, there may be lentification of the blood flow and thrombi development, a phenomenon facilitated by the onset of arrhythmias, such as atrial fibrillation [6]. Most of these features may be assessed by other noninvasive techniques, but CMR presents good results and allows for flow quantification, especially after the introduction of 4D analysis, and grants superior anatomical evaluation [4, 6].

One of the anatomical hallmarks of cardiac amyloidosis is increased thickening (apparent hypertrophy) of the ventricular myocardium. Both ventricles may be involved, and the left ventricular walls may be thicker than what is observed in patients with high blood pressure and are commonly more marked in patients with

ATTR amyloidosis than in those with AL [6, 10]. CMR is attractive in this regard, because it grants detailed analysis of ventricular anatomy, particularly of the right ventricle, and may help to suspect infiltrative disease, particularly when there are coexisting conditions, such as aortic stenosis [4, 6, 11].

Pericardial effusion may also be present, and sometimes, it may represent a challenge to noninvasive imaging, such as Doppler-echocardiography, particularly in cases with poor acoustic windows, while CMR may easily evaluate the pericardium to detect and evaluate pericardial effusion [6, 10].

17.3 Ventricular Function Analysis

Precise evaluation of ventricular function is a key point in the diagnostic workflow of patients with cardiac amyloidosis, because it is an important prognostic determinant, as well as a relevant marker of patient response to therapy. CMR is considered the gold standard for the clinical evaluation of ventricular systolic function and may be very useful in this setting, particularly if Doppler-echocardiography is not unequivocal, if conflicting results are reported in consecutive echocardiographic evaluations, or if echocardiography results are inconsistent with the patient clinical presentation. CMR is more prone, although, to suffer interference from poor patient collaboration, severe cardiac arrhythmias and patient's inability to maintain apnea during the time required to generate images, and thus the method to evaluate ventricular function in clinical practice should be chosen after careful patient evaluation and discussing the case with the imaging team to avoid unnecessary costs and to optimize the diagnostic workflow [1, 7]. It is important to remember, although, that global systolic function could be preserved for long periods and evaluation of regional wall motion, especially if strain is available. This approach could be very useful in the early detection of patients with amyloidosis and should be used when screening family members of cases with confirmed cardiac amyloidosis, who might benefit from early diagnosis. At the same time, the contribution of CMR to the evaluation of diastolic function is somewhat limited, and the results may vary greatly from center to center depending on the available equipment and team expertise [6, 7, 10].

Figures 17.1 and 17.2 show examples of cardiac morphological changes in patients with cardiac amyloidosis that were revealed by CMR.

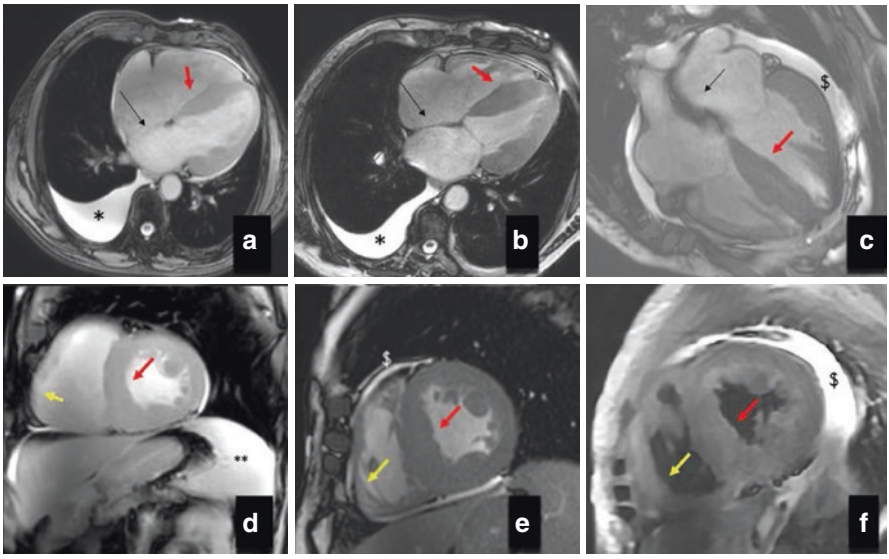


Fig. 17.1 Cardiac amyloidosis may present several morphologies, depending on the type, time of evolution, extension, ventricular overload and existent comorbities. There usually is atrial enlargement (**a**–**c**). Atrial septum may show normal thickness, or, more typically, may be mildly or more severely thickened (**a**–**c**, black arrows). It is also customary to observe enlargement of intraventricular septum (red arrows) in different degrees, just as it happens to the septal/left ventricle free wall ratio. Right ventricle, on the other hand, may show normal or enhanced thickness (normal—**d** yellow arrow, mild thickening—**e** yellow arrow, severe thickening—**f** yellow arrow). There often is pericardial effusion ($ at **c** and **f**). Pleural effusion (* at **a** and **b**) and ascites (** at **d**) may also be observed)

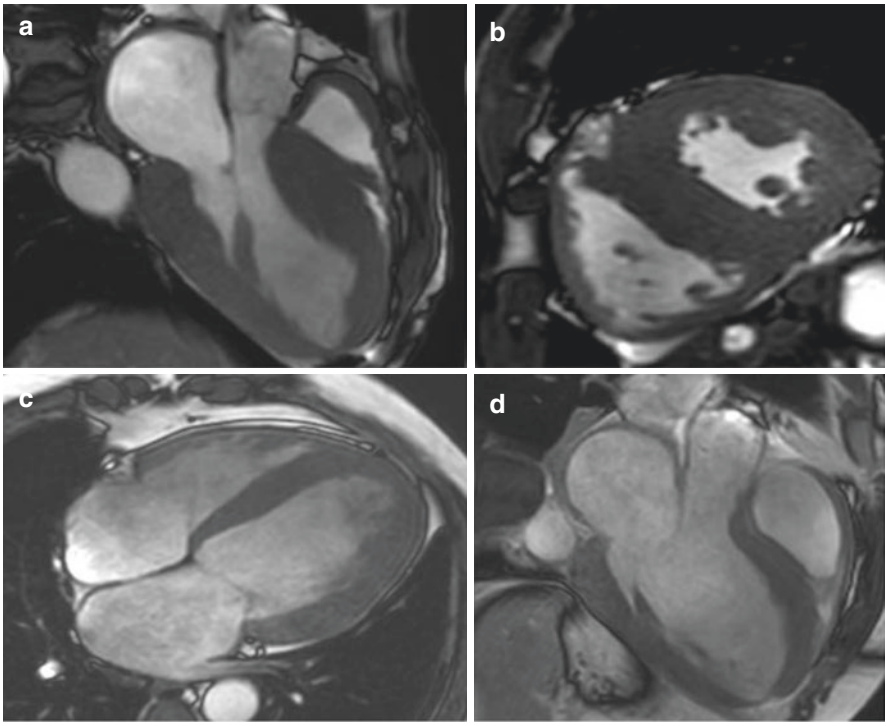


Fig. 17.2 Morphological and functional evaluation alone are not sufficient to grant the diagnosis of cardiac amyloidosis. (**a**, **b**) show the three chamber and short axis views that closely mimic hypertrophic cardiomyopathy, while patients in **c** and **d** were undergoing investigation for suspected dilated cardiomyopathy. Further investigation confirmed cardiac amyloidosis in both cases. This example highlights the fact that CMR investigation in patients with cardiomyopathy should be extensive and include myocardial characterization

17.4 Myocardial Characterization—Delayed Enhancement

Cardiac amyloidosis is characterized by the infiltration of abnormal protein within the myocardium that results in an enlarged interstitial compartment that can be identified by DE. This is a robust, reliable technique to identify areas of myocardial lesions and is one of the most important contributions of CMR in clinical practice. It is based on the dynamics of a liquid paramagnetic metal, gadolinium, which marks areas of necrosis following acute injury (e.g., ischemic or inflammatory) and chronic fibrosis and conditions that result in a large interstitial space. In the first condition, gadolinium may enter myocardial cells undergoing apoptosis due to the increased membrane cell permeability. In the latter, gadolinium diffuses from the blood vessels into the zones of fibrosis (with larger interstitial spaces and larger intercellular spaces). In both situations, regions containing the paramagnetic metal may be easily depicted by imaging sequences that nullify the normal myocardial signal, rendering it dark and causing injury zones to appear bright. This

phenomenon is called “delayed”, because it usually happens 7–15 min following gadolinium injection and was initially described to identify and quantify areas of myocardial infarction, but several papers have shown that it is also clinically relevant in nearly every type of heart disease [1, 10]. Experience has also demonstrated that gadolinium DE trends to present particular distribution patterns in different cardiomyopathies, including cardiac amyloidosis, and this is currently considered to be a relevant diagnostic criterion, particularly for morphological changes in this condition, which may be quite similar to other diseases that lead to ventricular overload and increased myocardial thickness. DE myocardial characterization may be a decisive finding in the diagnostic confirmation and may expedite the realization of further tests, such as genotyping, to assess amyloidosis subtype and thus proceed to proper management (Fig. 17.3) [2, 5, 10]. Typically, patients with cardiac amyloidosis present difficulty in programming the DE sequences because of the infiltrative, diffuse nature of the process that, many times, makes it very difficult to nullify the signal of the myocardium and to differentiate it from the areas containing the amyloid. For the same reason, the DE pattern may be different in particular cases of cardiac amyloidosis, and even though diffuse, subendocardial or transmural myocardial DE is more commonly related, the shape and location of the DE may vary among different patients. Sometimes it may be diffuse and mesocardial; other times, it is focal and endocardial or mesocardial or even diffuse and epicardial. The presenting pattern is also influenced by factors, such as the time of evolution of the

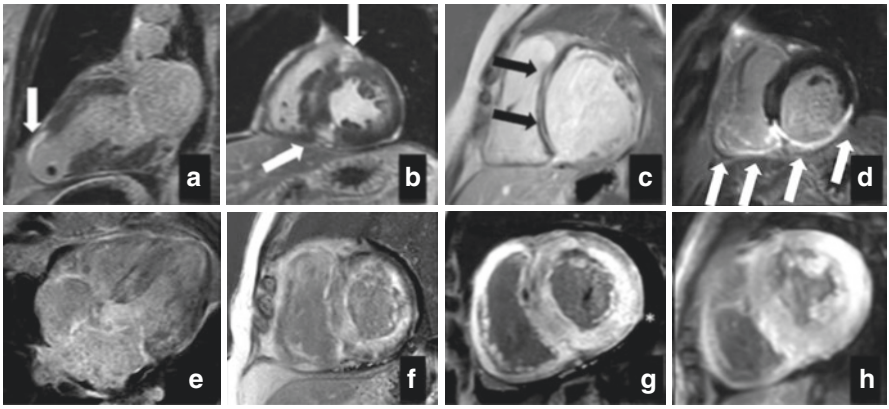


Fig. 17.3 DE patterns (arrow at Fig. 17.2**a**–**d**) are key information that may be obtained from CMR investigation of different cardiomyopathies and furnish prognostic data. Chagas disease shows apical DE, many times with intraventricular thrombi (2**a**). Patients with hypertrophic cardiomyopathy usually show mesocardial DE in the most thickened areas, especially the right/left ventricle junction points (2**b**). Dilated cardiomyopathy often shows thin, mesocardial DE more frequently at the septal wall (2**c**). CAD patients (2**d**) present the characteristic ischemic pattern (wave front progression/distribution in areas clearly associated with the coronary artery anatomy—inferior wall AMI in this case). More common patterns of cardiac amyloidosis, on the other hand, include subendocardial distribution (2**e** and 2**f**), but more advanced cases have extensive transmural DE (2**g** and 2**h**). Studies show that cases with large areas of transmural DE (2**h**) have a worse prognosis (3)

disease and the degree of established myocardial injury. Therefore, despite its great clinical contribution, DE should not be used as the only finding leading to the diagnosis of cardiac amyloidosis by CMR, but rather, it should be considered along with findings related to cardiac morphology and function, as discussed in the previous sections (Figs. 17.3 and 17.4). DE patterns, on the other hand, have limited utility in the differentiation of cardiac amyloidosis subtypes, despite the attempt by some groups to associate certain DE distribution characteristics with particular genetic mutations [2, 10].

Gadolinium can also be used to obtain prognostic information, and some authors have demonstrated that patients with large areas of DE are at higher risk of presenting adverse events. Fontana et al. evaluated 250 patients with cardiac amyloidosis and found that the quantified DE extension was an independent predictor of adverse events, even after several clinical and laboratory variables, including pro-BNP, ejection fraction, left and right ventricle indexed end systolic volumes, diastolic function and indexed ventricular mass, were included in the analysis. Findings such as this underscore the point that gadolinium DE is a fundamental step in the evaluation of patients with suspected confirmed cardiac amyloidosis, has an importance that cannot be overlooked and should be performed in all patients who do not present contraindications to the paramagnetic contrast media [5, 10].

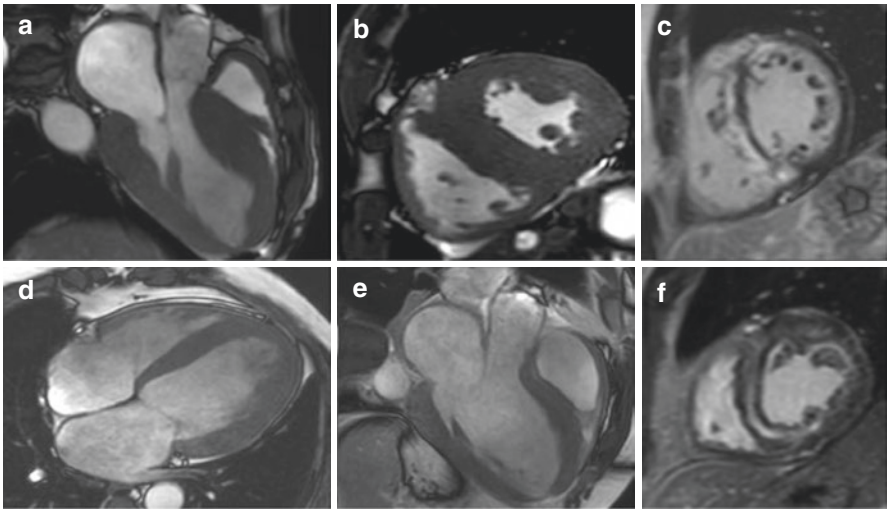


Fig. 17.4 Adding DE to CMR evaluation adds great diagnostic value in the assessment of patients with cardiomyopathies. This figure presents the DE findings of the same patients shown in Fig. 17.2 (**a**, **b**, **d**, and **e**). Diffuse subepicardial DE (**c**) and diffuse mesocardial DE (**f**) led to the suspicion that both patients presented cardiac amyloidosis as the cause of the morphological changes. Genetic tests confirmed the suspicion

17.5 Myocardial Characterization—T1 Mapping and Extracellular Volume

Although myocardial DE is a very useful technique that allows for obtaining diagnostic and prognostic data, a number of patients with advanced myocardial dysfunction do not show any degree of DE. This could happen for different reasons, including the fact that, at times, fibrosis develops in the myocardial interstitium and does not affect an area large enough to characterize DE by standard CMR imaging. More recently, an image sequence was developed that can determine changes in the myocardial magnetic relaxation time known as T1 that could be sensitive enough to reflect the presence of interstitial fibrosis, even in conditions that do not present DE. Such changes could indicate the presence of myocardial disease and have proven to be altered in many cardiomyopathies, including cardiac amyloidosis [6, 10, 12].

Native T1 is evaluated without the use of contrast media, and thus it is a very safe procedure that can be repeated and used to evaluate every subtype of patients, including those with renal failure undergoing dialysis. The major concern regarding T1 mapping is that reference values may vary from center to center, and every team involved in using CMR to evaluate cardiomyopathies should collect normal reference values and present the results compared to them [6, 10, 12].

The T1 mapping approach can be even more useful when paramagnetic contrast media can be used. If myocardial T1 is quantified before and after gadolinium injection, the contrast dynamic more accurately reflects the conditions of the interstitium and may be used to create an index of the extracellular volume (component of the intercellular space of the myocardium), which is typically increased in patients presenting infiltrative myocardial diseases, such as amyloidosis [6, 10, 12].

Pan et al. demonstrated that adding the extracellular volume to the CMR analysis of patients with suspected cardiac amyloidosis improved diagnostic accuracy when compared to the evaluation of DE alone (odds ratio 4.27; 95% CI 2.87–6.37 vs. odds ratio 2.60, 95% CI 1.90–3.56; $p = 0.03$). It should be noted, however, that in some cases, these new parameters were not sufficient to confirm the diagnosis and that patients who can receive contrast media should have DE sequences carefully performed and analyzed [12]. Figure 17.5 shows an example of T1 mapping and extracellular volume calculation in cardiac amyloidosis.

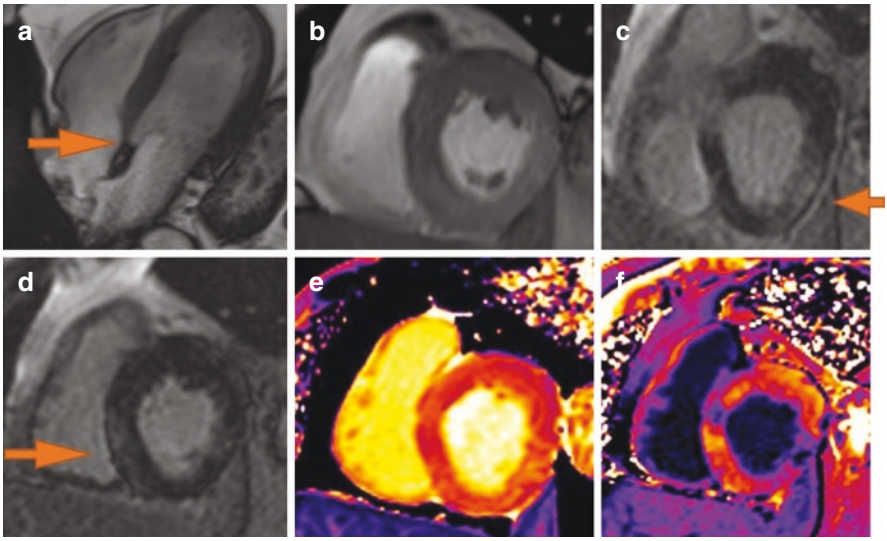


Fig. 17.5 Male, 74 years old, history of recent onset of intense fatigue. CMR showed localized thickening of the atrial septum with aneurysm of the fossa ovalis (**a**, arrow) and mild thickening (13 mm) of the left ventricle wall (**b**, arrow). DE was mild, located at the lateral wall (**c**, arrow) and at the interventricular septum (**d**, arrow). Increased native T1 (**e**) along with extracellular volume increase (5**f**, ECV = 0.41) led to the suspicion of cardiac amyloidosis, which was confirmed by genetic tests

17.6 Practical Contribution of CMR in Clinical Scenarios

17.6.1 Screening of Family Members of Patients with Cardiac Amyloidosis

As presented in this chapter, CMR may reveal morphological and functional changes related to the onset of cardiac amyloidosis, but these, as well as DE, may be present only later in the clinical course of the disease. T1 mapping techniques, on the other hand, are useful and present high negative predictive value. It has been reported that screening subjects with normal T1 values allows for ruling out cardiac amyloidosis. Conversely, changes and abnormalities in this test may prompt early diagnosis and lead to timely initiation of better therapeutic regimens [6, 10, 12].

17.6.2 Differential Diagnosis of Myocardial Hypertrophy

Different cardiac diseases may trigger myocardial hypertrophy, and this is a finding that may imply a challenging clinical situation. CMR plays a key role in such conditions, allowing for the identification of hypertrophy secondary to hypertension,

hypertrophic cardiomyopathy, Fabry disease, hypertrophy secondary to aortic stenosis and cardiac amyloidosis [1, 7, 8, 13]. To this end, it is fundamental that the imaging team perform a thorough scanning including the analysis of cardiac morphology and function, DE (typical findings according to the case etiology—Fig. 17.2), measuring native T1 and extracellular volume (both typically higher than reference values in cases of amyloidosis). Because of the quality of the results achieved, CMR is currently highly recommended in the evaluation of patients with thickened myocardium [1, 7, 8, 13].

17.6.3 Heart Failure with Preserved Ejection Fraction

Patients with cardiac amyloidosis may have preserved systolic function and ejection fraction while showing reduction in diastolic function, at times even in the absence of marked myocardial hypertrophy. Thorough CMR evaluation may play an important role in the analysis of such patients and raise the suspicion of cardiac amyloidosis as a cause of the reduction of diastolic function and allow for the correct diagnosis [1, 7].

17.6.4 Equivocal Results of Other Noninvasive Tests

One of the strengths of CMR is the low inter- and intraobserver variability in the evaluation of cardiac morphology and function, in addition to its unique capability of providing myocardial characterization. For such reasons, it should be the technique of choice whenever the need arises to eliminate uncertainties resulting from equivocal or conflicting results of other noninvasive techniques. CMR could, for example, confirm the precise myocardial thickness and provide detailed regional and global ventricular function analysis, along with tissue characterization. Such information may prove fundamental in confirming the diagnosis and identifying screened family members of patients with confirmed cardiac amyloidosis [7, 8, 14].

17.6.5 Elderly Patients with Aortic Stenosis

Cardiac amyloidosis and aortic stenosis are conditions that have a higher incidence in elderly patients and may coexist in up to 13.9–16% of the cases of aortic stenosis that are referred to undergo percutaneous treatment of the aortic valve [15]. For reasons exposed in the other clinical conditions, CMR could reveal the presence of cardiac amyloidosis differing DE patterns secondary to valvular disease or due to the presence of amyloidosis, and if DE is not present, T1 mapping techniques could

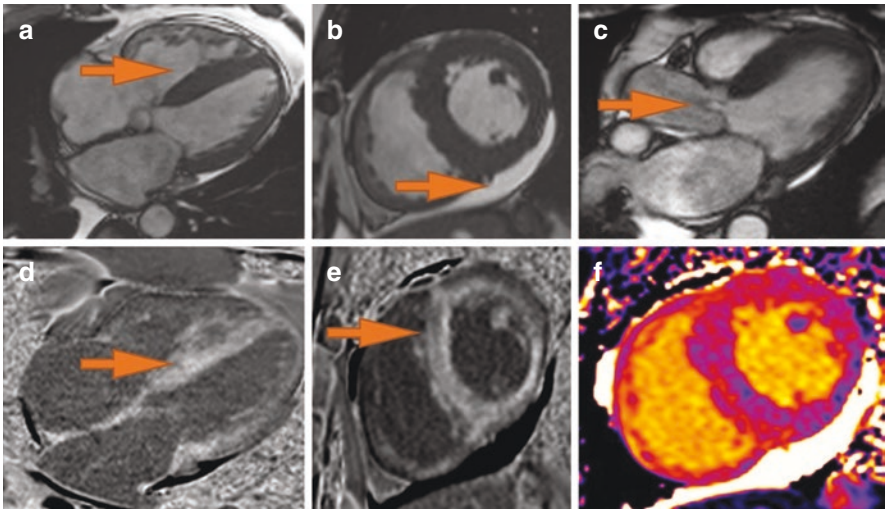


Fig. 17.6 Patient with severe aortic stenosis and marked left ventricular hypertrophy confirmed by CMR (14 mm—**a**, arrow), which also showed pericardial effusion (**b**, arrow) and a reduced area of aortic valve opening (**c**, arrow). DE was difficult to program (**d** and **e**), was diffuse and was more noticeable at the subendocardial and mesocardial walls (**d** and **e**, arrow). Native T1 was very high (**f**), as was extracellular volume (0.37). Genetic testing confirmed ATTR cardiac amyloidosis. The patient underwent successful TVR and specific treatment, presenting a great increase in quality of life at 3.4 years of follow-up

aid in the diagnostic evaluation. Typically, extracellular volume is significantly increased in patients with amyloidosis and may be very useful in this setting [11].

Figure 17.6 shows an example of a patient with coexistent aortic stenosis and cardiac amyloidosis.

17.6.6 Prognostic Evaluation and Treatment Monitoring

In addition to its diagnostic role, CMR may also be effective in adding prognostic information to patients with confirmed cardiac amyloidosis. Fontana et al. demonstrated that patients with large areas of DE and those with transmural DE patterns show a higher incidence of adverse events than those with subendocardial DE [5]. Native T1 and extracellular volume have the potential to furnish prognostic data, but there are still no consolidated data confirming this.

On the other hand, native T1 and extracellular volume estimates show great promise as tools to monitor patient responses to treatment and to guide management strategies. Should larger trials confirm these findings and CMR may have an ever more significant role in the follow up of patients with cardiac amyloidosis [6, 10, 12].

17.7 Conclusion

The low interobserver and intraobserver variability in CMR and its contribution to the evaluation of cardiac morphology and function makes it extremely useful in the analysis of patients with suspected or confirmed cardiac amyloidosis. It also produces images and data that reflect the presence and the degree of abnormal protein deposits in the myocardium even in early stages of the disease, using T1 mapping techniques, advancing diagnostic and prognostic information and being useful to monitor treatment response. These characteristics provide unique information and perspectives on the disease and may also help in the understanding of the process of cardiac injury, being a fundamental tool in both clinical management and research on this cardiomyopathy.

References

1. Sara L, Szarf G, Tachibana A, Shiozaki AA, Villa AV, de Oliveira AC, et al. II Guidelines on cardiovascular magnetic resonance and computed tomography of the Brazilian Society of Cardiology and the Brazilian College of Radiology. Arq Bras Cardiol. 2014;103(6 Suppl 3):1–86.
2. Zhao L, Tian Z, Fang Q. Diagnostic accuracy of cardiovascular magnetic resonance for patients with suspected cardiac amyloidosis: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2016;16:129.
3. Raman SV, Simonetti OP. The CMR examination in heart failure. Heart Fail Clin. 2009;5(3):283–300. v
4. Nguyen KL, Hu P, Finn JP. Cardiac magnetic resonance quantification of structure-function relationships in heart failure. Heart Fail Clin. 2021;17(1):9–24.
5. Fontana M, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banypersad SM, et al. Prognostic value of late gadolinium enhancement cardiovascular magnetic resonance in cardiac amyloidosis. Circulation. 2015;132(16):1570–9.
6. Baggiano A, Boldrini M, Martinez-Naharro A, Kotecha T, Petrie A, Rezk T, et al. Noncontrast magnetic resonance for the diagnosis of cardiac amyloidosis. JACC Cardiovasc Imaging. 2020;13(1 Pt 1):69–80.
7. Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. Circulation. 2020;142(1):e7–e22.
8. Wang TKM, Abou Hassan OK, Jaber W, Xu B. Multi-modality imaging of cardiac amyloidosis: contemporary update. World J Radiol. 2020;12(6):87–100.
9. Falk RH, Quarta CC, Dorbala S. How to image cardiac amyloidosis. Circ Cardiovasc Imaging. 2014;7(3):552–62.
10. Jurcut R, Onciul S, Adam R, Stan C, Coriu D, Rapezzi C, et al. Multimodality imaging in cardiac amyloidosis: a primer for cardiologists. Eur Heart J Cardiovasc Imaging. 2020;21(8):833–44.
11. Bohbot Y, Renard C, Manrique A, Levy F, Marechaux S, Gerber BL, et al. Usefulness of cardiac magnetic resonance imaging in aortic stenosis. Circ Cardiovasc Imaging. 2020;13(5):e010356.
12. Pan JA, Kerwin MJ, Salerno M. Native T1 mapping, extracellular volume mapping, and late gadolinium enhancement in cardiac amyloidosis: a meta-analysis. JACC Cardiovasc Imaging. 2020;13(6):1299–310.

13. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, et al. Magnetic resonance in transthyretin cardiac amyloidosis. J Am Coll Cardiol. 2017;70(4):466–77.
14. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail. 2019;12(9):e006075.
15. Castano A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J. 2017;38(38):2879–87.

Chapter 18
Proteomics by Mass Spectrometry in the Typing of Amyloidosis

Jussara Bianchi Castelli and Valdemir Melechco Carvalho

18.1 Introduction

The diagnosis of amyloidosis is established with the histological finding of tissue deposition of an anomalous Congo red positive protein, with yellow orange to apple green dichroic refraction under polarized light [1] (Fig. 18.1), still considered the gold standard [2]. After that, accurate typing of amyloidosis is indispensable to identify which of the currently 36 described proteins [3] is responsible for the formation of the amyloid deposit, although the three more common types are AL, ATTR, and AA [3, 4]. Thus, the underlying disease that produces such protein will be confirmed, and the appropriate treatment will be applied because the treatment approaches are quite different according to the type of amyloidosis. In other words, behind a similar physical, structural, optical appearance of the insoluble beta-sheet pleated arrangement of protein fibrils, responsible for the positivity to Congo red, there are proteins of different biochemical nature, secondary to different diseases. This causal disease is not always evident or its clinical manifestation overlaps with other clinical aspects, being necessary to do the reverse pathway, that is, to identify the protein composing the amyloid deposit to know which underlying disease is to be treated. In this context lies the importance of direct techniques for identifying the type of protein composing the amyloid through a direct analysis of the deposit in the tissue, such as proteomics by mass spectrometry. The latter has been considered

J. B. Castelli (✉)
Fleury Group, São Paulo, SP, Brazil

Heart Institute (InCor) of Hospital das Clínicas-FMUSP, São Paulo, SP, Brazil
e-mail: jussara.castelli@grupofleury.com.br

V. M. Carvalho
Fleury Group, São Paulo, SP, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_18

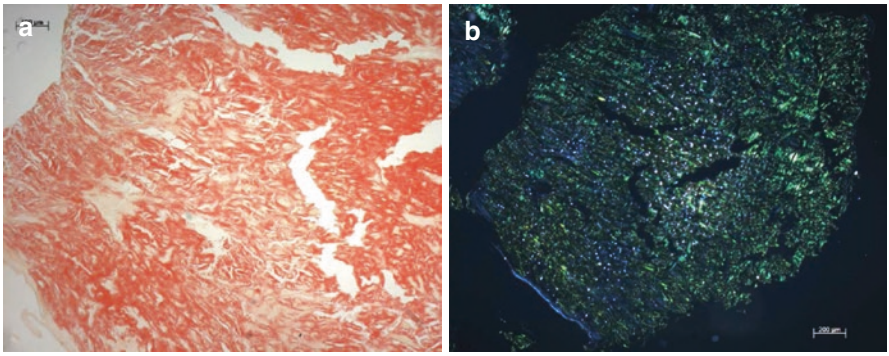


Fig. 18.1 The microphotograph shows a histological section of an endomyocardial biopsy stained with Congo red in (**a**) and the same material observed under polarized light (**b**). Note the apple-green or bottle-green refringence typical of the amyloid deposit. The mass spectrometry in this case resulted in ATTRv [Val122Ile]

currently the most specific and sensitive method for amyloid typing [4–6] for the identification of protein and demands the extraction of slight amyloid deposits, which demonstrates the power of this diagnostic resource, which will be the focus of this chapter.

18.2 What Is Proteomics

Protein identification is usually mediated by antibody detection, such as ELISA, Western blotting [7], immune-electron microscopy [immunogold] [2, 8] or immunofluorescence, and immunohistochemistry staining [7–9]. However, this approach is limited by antibody availability. Mass spectrometry (MS)-based assays have recently emerged as a powerful alternative able to directly identify proteins in tissues. Among the vast universe of MS-based assays, bottom-up proteomics is especially suitable for protein typing in tissues. This technique consists of digesting proteins excised from tissues into peptides by specific proteases and analyzing the digestion mixture by chromatography coupled to sequential, or tandem, mass spectrometry. This sophisticated technique, until recently restricted to research laboratories [7], has been gradually incorporated into clinical laboratories enabling amyloid fibril typing from fixed histological tissue sections [10] and rapidly became recognized as the new gold standard method for typing amyloidosis [8, 10].

The Genome Project gave birth to "The omics era" when fundamental interest switched from structural only biology to functional biology. Briefly speaking, that is when the branches of science known as "omics**" arise** with various disciplines ending in this suffix, such as genomics, transcriptomics, proteomics, and metabolomics. Proteomics is the study of the proteome, the set of all proteins expressed in a tissue, cell, or biological system at a given physiological moment.

The basic strategy of proteomics is a combination of an array of different techniques, including several approaches for sample preparation, protein or peptide separation, either by electrophoresis or chromatography, and analysis by diverse variants of MS. Finally, bioinformatics data processing, analysis, and interpretation are necessary to assess the results.

Unlike immunologically based techniques in which a single test will identify only a single amyloid fibril type, depending on the antibody being used, shotgun proteomics-based methods have the potential to unequivocally and efficiently identify all types of amyloid that may be present in a sample in a single assay [8].

The proteome profile found in amyloidosis is represented not only by the protein produced by the underlying disease or condition, but also by the so-called amyloid signature proteins. Signature proteins are integrated in all types of amyloidosis, and the most frequent are serum amyloid P component, apolipoprotein A-IV, and apolipoprotein E. Apolipoprotein A-I, heparan sulfate proteoglycan, vitronectin complement component C9, clusterin, fibulin-1, and three collagen proteins may also be detected [3, 4, 8, 11, 12]. Without the presence of these, we cannot recognize the proteome profile as amyloidosis.

The protein responsible for the amyloid deposit may also be inspected to detect anomalous peptide sequences and mirror the image of gene mutations. Protein genotyping is achievable by the analysis of the presence or absence of variant-specific peptides. The most common transthyretin variants, for example, can be identified by this strategy (as in the case of ATTRv with the Val122Ile mutation shown in Fig. 18.1), which was later confirmed by gene sequencing.

18.3 Technical Aspects of Proteomics by Mass Spectrometry—Specimen Preparation, Microdissection, Proteomic Analysis, and Results Interpretation

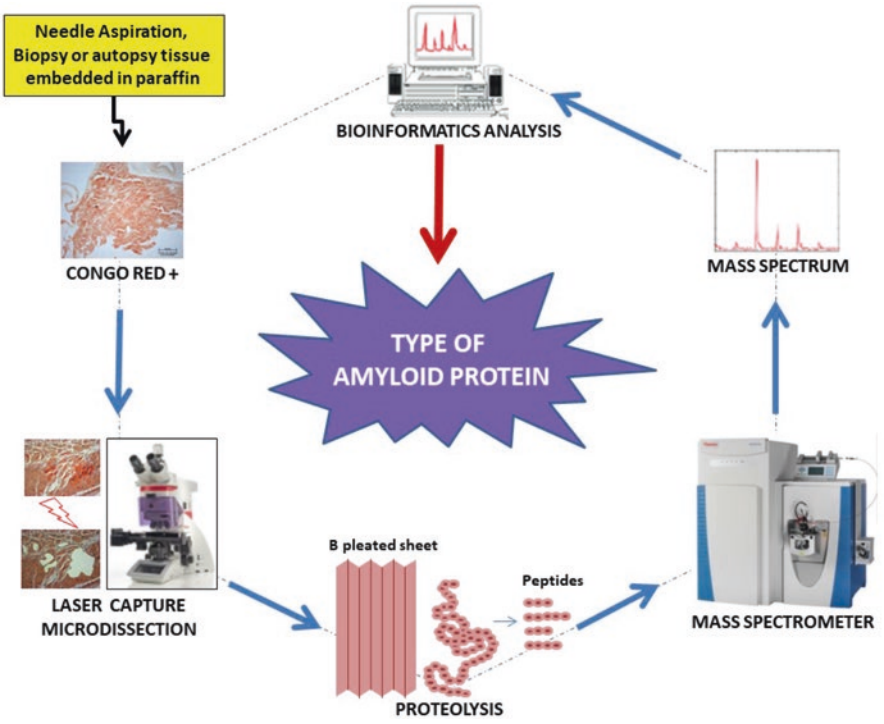
Conventional specimen preparation, e.g., formalin-fixed tissue from needle aspiration, biopsy or autopsy followed by standard tissue processing and paraffin embedding protocols, is compatible with proteomics-based amyloid typing protocols. Nevertheless, a few adjustments are necessary: conventional histological slides are prepared with an 8 μm paraffin tissue section stained by the Congo red histochemical technique to confirm the presence of amyloid deposits and recognize their distribution pattern and amount. If positive, new 8-μm paraffin tissue sections were made and placed on special histological slides suitable for laser cuts and stained with Congo red. Under laser microdissection microscopy, the positive tissue regions are dissected by laser capture microdissection (area approximately 1 mm^2) and processed by proteolysis and peptide extraction. Then, the peptide extracts obtained are analyzed by liquid chromatography coupled to high resolution tandem MS. The MS raw data files are queried using different proteomics processing software (e.g., MaxQuant and FragPipe). The results are assigned to peptide and protein

probability scores, which support protein identification. Flowchart 18.1 shows the steps of the MS proteomics exam.

The interpretation of the results is complex and based on a combination of parameters to generate a ranking of the most intense proteins, often reflected by quantifiers such as ion intensities and spectral counts. Figures 18.2 and 18.3 are examples of spreadsheets with the results for analysis.

There is no restriction on the type of tissue that can be tested for amyloid protein typing through MS proteomics, including bone and bone marrow samples that are also subjected to decalcification during tissue processing. Figure 18.4 show the most frequent types of tissues submitted to the MS, in addition to the adipose tissue shown hereafter in this chapter.

Usually, the same sample used to confirm the diagnosis of amyloidosis by Congo red staining can be used for MS since the provided paraffin block still contains enough sample without depletion due to previous cuts. In the case of abdominal fat, the volume of adipose tissue must be generous, approximately 2 × 2 × 2 cm (Fig. 18.5) since the amyloid deposit in this tissue is usually multifocal and represents interstitial deposits spread between adipocytes [the amyloid "rings" or stellate-like foci] (Fig. 18.6) rather than in solid masses of amyloid deposits.



Flowchart 18.1 This scheme explains the steps of mass spectrometric amyloid protein typing, from the entry of tissue embedded in paraffin to the identification of the protein

	A	B	C	D	E	F	G
1	Protein names	Number of pro	Intensity	Intensity Amiloide1	Intensity Amiloide2	Intensity Controle1	Intensity Controle2
2	Keratin, type II cytoskeletal 1	2	82.509.000.000	13.227.000.000	17.977.000.000	1.018.100.000	50.286.000.000
3	Myosin-7	13	79.353.000.000	34.945.000.000	35.629.000.000	1.111.000.000	7.668.300.000
4	Keratin, type I cytoskeletal 10	15	62.971.000.000	13.597.000.000	11.764.000.000	2.116.400.000	35.493.000.000
5	Actin, alpha cardiac muscle 1;Actin, aortic sr	3	59.351.000.000	22.182.000.000	29.328.000.000	1.506.000.000	6.334.700.000
6	Keratin, type II cytoskeletal 2 epidermal	1	55.174.000.000	9.352.600.000	9.624.700.000	671.580.000	35.525.000.000
7	Keratin, type I cytoskeletal 9	2	46.098.000.000	8.539.300.000	12.837.000.000	1.190.800.000	23.531.000.000
8		2	38.729.000.000	11.364.000.000	8.204.800.000	3.936.700.000	15.224.000.000
9	Ig lambda-2 chain C regions;Ig lambda-3 cha	5	18.211.000.000	6.703.500.000	10.746.000.000	123.880.000	637.990.000
10	Myosin light chain 3	2	17.043.000.000	8.171.000.000	6.709.000.000	309.150.000	1.854.100.000
11	Desmin	4	16.026.000.000	7.308.700.000	7.491.100.000	158.290.000	1.068.400.000
12	Serum albumin	2	14.833.000.000	4.709.900.000	7.229.900.000	260.140.000	2.633.400.000
13	Titin	1	12.722.000.000	5.436.200.000	6.844.700.000	23.862.000	416.990.000
14	Cytochrome b-c1 complex subunit 1, mitoch	2	1.249.100.000	576.770.000	479.420.000	0	192.900.000
15	Cysteine and glycine-rich protein 3	1	1.227.600.000	549.890.000	642.520.000	0	35.181.000
16	Apolipoprotein A-IV	2	1.213.100.000	584.890.000	586.020.000	0	42.143.000
17	LIM domain-binding protein 3	1	1.185.600.000	536.920.000	514.330.000	10.594.000	123.780.000
18	Myosin-1;Myosin-8	2	1.184.900.000	671.730.000	303.550.000	0	209.650.000
19	Peroxiredoxin-2	1	1.017.800.000	471.210.000	368.360.000	8.334.000	169.940.000
20	Sarcoplasmic/endoplasmic reticulum calciu	3	1.017.000.000	496.450.000	495.030.000	3.846.700	21.637.000
21	Vitronectin;Vitronectin V65 subunit;Vitrone	1	1.008.700.000	434.790.000	570.530.000	0	3.380.100
22	Pyruvate kinase PKM	2	962.820.000	410.020.000	528.520.000	0	24.284.000
23	Actin, cytoplasmic 2;Actin, cytoplasmic 2, N-	7	962.280.000	425.680.000	213.710.000	7.604.900	315.290.000
24	Histone H2B type 2-E;Histone H2B type 1-B;I	7	947.980.000	381.780.000	471.880.000	0	94.324.000
25	14-3-3 protein gamma;14-3-3 protein gamm	2	482.580.000	153.110.000	329.470.000	0	0
26	NADH-ubiquinone oxidoreductase 75 kDa su	1	481.700.000	202.700.000	189.860.000	2.834.300	86.303.000
27	Filaggrin-2	2	468.240.000	140.400.000	199.110.000	0	128.730.000
28	Clusterin;Clusterin beta chain;Clusterin alpl	1	460.640.000	208.100.000	243.930.000	0	8.609.600
29	Cytochrome c	2	458.300.000	218.750.000	188.140.000	0	51.416.000
30	Fibrinogen beta chain;Fibrinopeptide B;Fibr	2	457.900.000	32.625.000	54.250.000	43.808.000	327.210.000
31	Troponin C, slow skeletal and cardiac muscl	1	446.290.000	255.440.000	190.840.000	0	0
32	Voltage-dependent anion-selective channe	1	418.070.000	131.490.000	258.450.000	0	28.130.000
33	Apolipoprotein E	2	415.670.000	154.320.000	255.970.000	0	5.381.700

Fig. 18.2 The result of this case was lambda light chain amyloidosis [AL—lambda]. Note the presence of amyloid signature proteins

	A	B	C	D	E	F	G
1	Protein names	Number of proteins	Intensity	Intensity amiloide1	Intensity amiloide2	Intensity controle1	Intensity controle2
2	Keratin, type II cytoskeletal 1	1	58773000000	14402000000	4006900000	37824000000	2539900000
3		2	43842000000	10782000000	7732200000	19870000000	5458300000
4	Keratin, type I cytoskeletal 10	22	43344000000	13757000000	2543300000	25197000000	1846500000
5	Keratin, type I cytoskeletal 9	2	35660000000	9351900000	4265600000	20817000000	1225200000
6	Keratin, type II cytoskeletal 2 epidermal	4	28301000000	8567700000	1340000000	17193000000	1200000000
7	Transthyretin	1	17370000000	8396300000	8949900000	20992000	2948100
8	Myosin-7	7	15742000000	6400600000	2339100000	6641100000	361510000
9	Actin, alpha cardiac muscle 1;Actin, aortic smoot	3	14499000000	5484700000	2861600000	5593300000	559410000
10	Serum albumin	2	8727400000	5752500000	1105700000	1636300000	232840000
11	Keratin, type II cytoskeletal 5	2	5819600000	1114500000	96111000	4553000000	56019000
12	Keratin, type I cytoskeletal 14	8	5535000000	1138100000	74566000	4238700000	83586000
13	Myosin light chain 3	1	4760200000	1127100000	652460000	2785400000	195290000
14	Hornerin	2	4566400000	977230000	128130000	3440900000	20206000
15	Desmin	6	4565700000	2278700000	325680000	1817500000	143760000
16		1	4010100000	366240000	18098000	3620500000	5279500
17	Serum amyloid P-component;Serum amyloid P-c	1	3421400000	2733100000	633150000	55146000	0
18	Hemoglobin subunit beta;LVV-hemorphin-7;Spir	1	2500100000	1253600000	29279000	1183400000	33765000
19	Keratin, type I cytoskeletal 16	4	2409800000	289860000	0	2120000000	0
20		1	2106600000	801440000	0	1252500000	52634000
21	Apolipoprotein A-IV	2	1899300000	1865400000	26979000	6955100	0
22	Vitronectin;Vitronectin V65 subunit;Vitronectin	2	1819400000	1370000000	425990000	23440000	0
23	Complement factor H-related protein 1	1	1553800000	1175600000	378190000	0	0
24	Ig gamma-1 chain C region	1	1490100000	977780000	342560000	160070000	9730600
25	Myosin regulatory light chain 2, ventricular/card	2	1320500000	641120000	17626000	617760000	43997000
26	Titin	1	1223000000	457430000	70935000	687970000	6633500
27	Alpha-actinin-2	1	1173200000	382630000	36947000	737420000	16195000
28	Hemoglobin subunit alpha	2	1145600000	423860000	65719000	584780000	71196000
29	ATP synthase subunit beta, mitochondrial	1	1073700000	353110000	256220000	393400000	70967000
30	Neutrophil defensin 3;HP 3-56;Neutrophil defen	2	988180000	666830000	90271000	222760000	8314600
31	Filamin-C	3	974930000	278470000	61815000	624920000	9721000
32	Clusterin;Clusterin beta chain;Clusterin alpha ch	1	966670000	797500000	161490000	7681200	0
33	ATP synthase subunit alpha, mitochondrial	1	917670000	301350000	55113000	517490000	43716000

Fig. 18.3 The result of this case was transthyretin amyloidosis [ATTR]. As shown at the anterior, there are also amyloid signature proteins

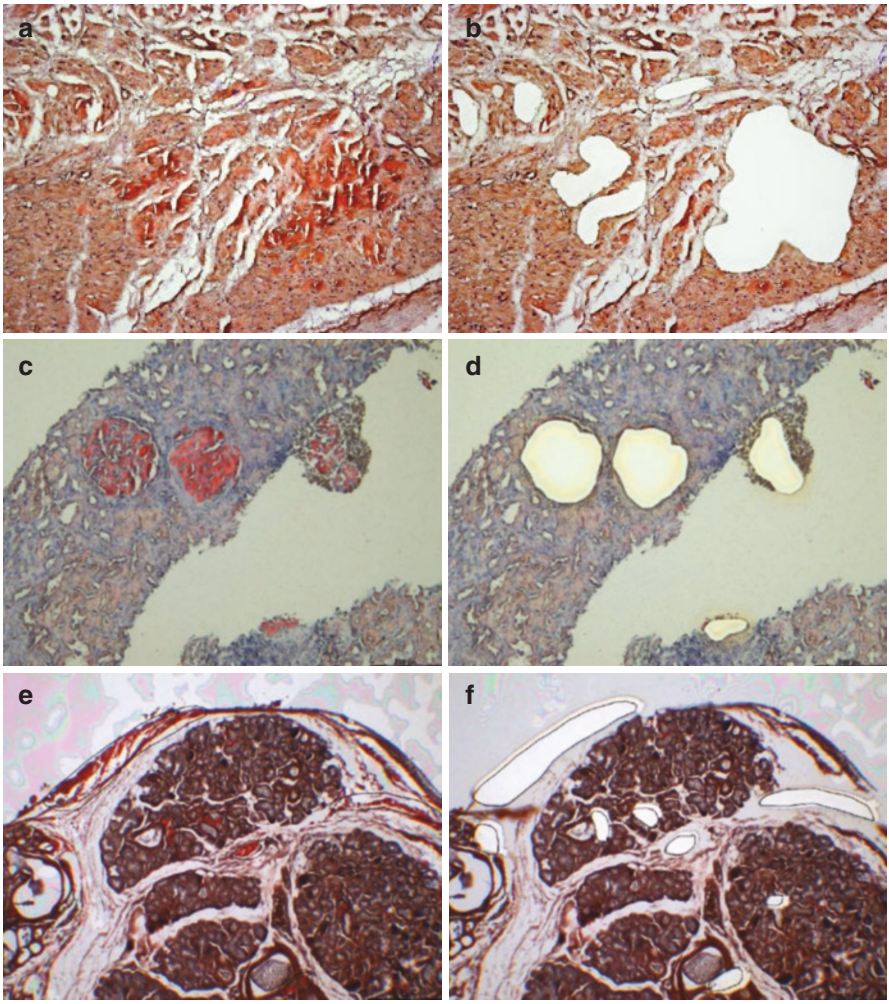


Fig. 18.4 Microphotographs of tissues cuts frequently used for amyloid protein typing, with the amyloid deposit stained by the technique of Congo red, before (left side) and after (right side) laser microdissection, in which we try to remove the deposit with the lower possible contamination of adjacent tissues (**a** and **b**, myocardium; **c** and **d**, kidney; **e** and **f**, salivary gland; **g** and **h**, bone marrow vesseld; **i** and **j**, sural nerve)

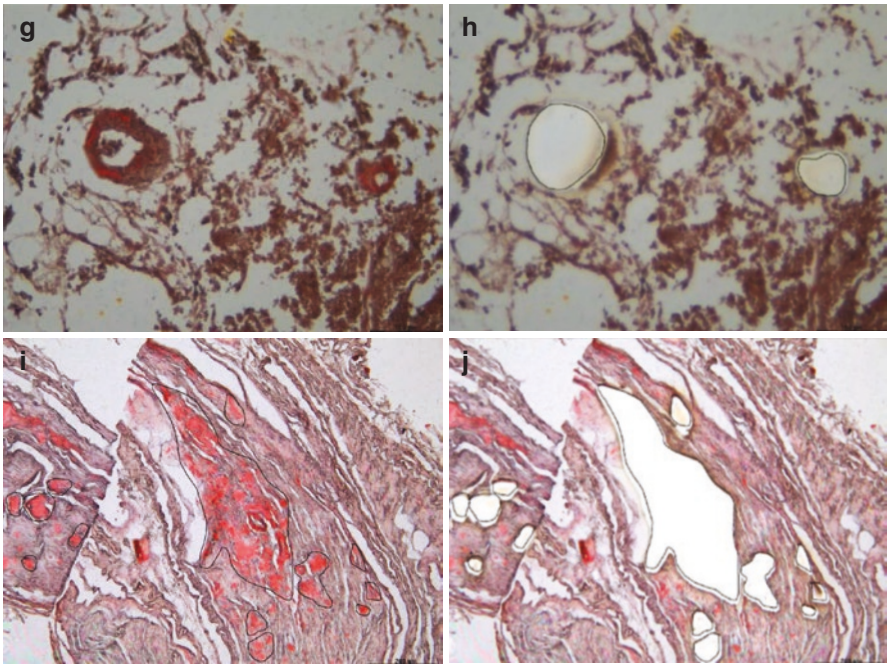


Fig. 18.4 (continued)

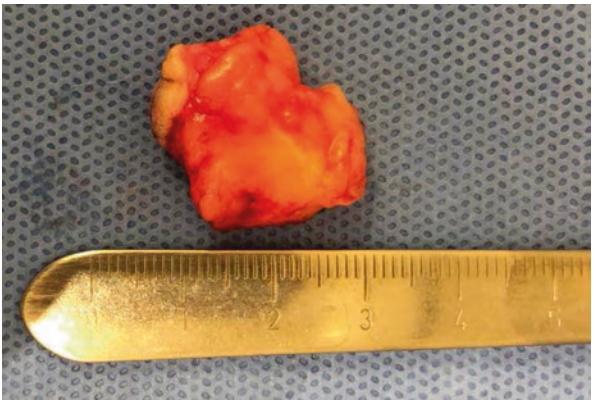


Fig. 18.5 This is an example of an abdominal fat biopsy with adequate sampling. Since the epidermis without dermatological alterations is not useful for the examination, it is possible to perform a biopsy through an incision and remove only the fat in an adequate volume

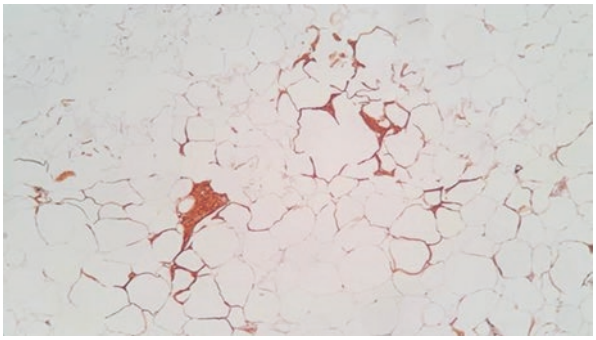


Fig. 18.6 The microphotograph shows adipose tissue with amyloid deposits marked by immunohistochemistry with an antibody to the lambda light chain. This case is an example of adipose tissue compromised by amyloid deposits in low quantity and multifocal distribution. Therefore, the volume of adipose tissue recommended in the text aims to gather sufficient material for analysis

References

1. Howie AJ. The nomenclature committee of the international society of amyloidosis: back toward "green birefringence". Amyloid. 2019;26(2):96.
2. Sipe JD, Benson MD, Buxbaum JN, Ikeda SI, Merlini G, Saraiva MJ, et al. Amyloid fibril proteins and amyloidosis: chemical identification and clinical classification International Society of Amyloidosis 2016 nomenclature guidelines. Amyloid. 2016;23(4):209–13.
3. Benson MD, Buxbaum JN, Eisenberg DS, Merlini G, Saraiva MJM, Sekijima Y, et al. Amyloid nomenclature 2020: update and recommendations by the International Society of Amyloidosis [ISA] nomenclature committee. Amyloid. 2020;27(4)
4. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR 3rd, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009;114(24)
5. Chapman J, Dogan A. Fibrinogen alpha amyloidosis: insights from proteomics. Expert Rev Proteomics. 2019;16(9)
6. Halloush RA, Lavrovskaya E, Mody DR, Lager D, Truong L. Diagnosis and typing of systemic amyloidosis: the role of abdominal fat pad fine needle aspiration biopsy. Cytojournal. 2010;6:24.
7. Anderson NL, Matheson AD, Steiner S. Proteomics: applications in basic and applied biology. Curr Opin Biotechnol. 2000;11(4)
8. Dasari S, Theis JD, Vrana JA, Rech KL, Dao LN, Howard MT, et al. Amyloid typing by mass spectrometry in clinical practice: a comprehensive review of 16,175 samples. Mayo Clin Proc. 2020;95(9)
9. Kebbel A, Rocken C. Immunohistochemical classification of amyloid in surgical pathology revisited. Am J Surg Pathol. 2006;30(6):673–83.
10. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet. 2016;387(10038):2641–54.
11. Winter M, Tholey A, Krüger S, Schmidt H, Röcken C. MALDI-mass spectrometry imaging identifies vitronectin as a common constituent of amyloid deposits. J Histochem Cytochem. 2015;63(10)
12. Palstrøm NB, Rojek AM, Møller HEH, Hansen CT, Matthiesen R, Rasmussen LM, et al. Classification of amyloidosis by model-assisted mass spectrometry-based proteomics. Int J Mol Sci. 2021;23(1)

Chapter 19
The Role of Nuclear Medicine in the Diagnosis of Amyloidosis

Claudio Tinoco Mesquita, Simone Cristina Soares Brandão, and Adriana Pereira Glavam

19.1 Introduction

Amyloidosis is a systemic infiltrative disease and when cardiac involvement is present, the prognosis is always poorer. Cardiac Amyloidosis (CA) is characterized by the extracellular deposition of misfolded proteins which aggregate as amyloid fibrils. The most predominant types of CA are amyloid immunoglobulin light chain (AL) and amyloid transthyretin (ATTR). The latter is further subtyped into hereditary (ATTRv), which results from protein mutations, and wild type, in the past known as senile type (ATTRw) [1].

The diagnosis of CA remains challenging. Endomyocardial biopsy is still considered the gold standard for diagnosing CA. Nevertheless, significant improvements in noninvasive imaging methods have led to fewer cases where biopsies are required [2–6]. In this scenario, nuclear medicine has achieved a central role. Currently, myocardial scintigraphy with bone-seeking tracers is the only noninvasive method

C. T. Mesquita
Nuclear Medicine and Molecular Imaging Department, Pró-Cardíaco Hospital, Rio de Janeiro, RJ, Brazil

Radiology Department, Federal Fluminense University, Rio de Janeiro, Brazil
e-mail: claudiotinocomesquita@id.uff.br

S. C. S. Brandão (✉)
Department of Medicine, Hospital das Clínicas, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil
e-mail: simone.brandao@ufpe.br

A. P. Glavam
Instituto Nacional de Cardiologia, Rio de Janeiro, RJ, Brazil

Hospital Copa Star, Rio de Janeiro, RJ, Brazil

Clínica de Diagnóstico por Imagem CDPI/DASA, Rio de Janeiro, RJ, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_19

capable of differentiating ATTR CA from AL CA which represents a paradigm shift in diagnosis. It is important to highlight that although scintigraphy has become a cornerstone of ATTR CA diagnosis, it must be evaluated in concomitance to monoclonal gammopathies test results [7]. Positron emission tomography associated with computed tomography (PET/CT) has also emerged as a potential noninvasive method to assess amyloid burden and response to treatment [8].

In this chapter, the authors propose a review of the current role of nuclear medicine in the diagnosis and prognosis of ATTR CA alongside a discussion about future directions in this promising field.

19.2 Imaging Targets in Cardiac Amyloidosis

Amyloid deposits in the myocardium interstice are the imaging direct targets to diagnose, prognose, and type CA. It consists of insoluble b-pleated sheets of fibrils formed from misfolded precursor proteins, as well as non-fibrillar components of serum amyloid P (SAP), glycosaminoglycans, and calcium [4–9].

Nuclear medicine methods act on a molecular level and can directly (PET/CT) or indirectly (scintigraphy and PET/CT) identify amyloid deposits, even before structural and functional changes can be observed on echocardiography or Cardiac Magnetic Resonance (CMR). Early diagnosis impacts prognosis and nuclear medicine can be a game-changer in this context [4–9].

Comprehending the pathophysiology encompassing CA is essential to explaining imaging findings. Extracellular amyloid infiltration leads to remodeling of the extracellular matrix and expansion of extracellular volume, rarefaction of capillary density, edema, and changes in cardiomyocyte volume leading to thickening and stiffness of ventricular walls. In the process of time, high ventricular filling pressure causes ventricular dysfunction. Atrial wall infiltration may be present as well and induces functional and electrical changes [10].

Typically, echocardiography and CMR can detect CA in the late stages of the disease. Indirect targets for imaging findings are interstitial expansion (increased ventricular and atrial wall thickness, late gadolinium enhancement, and abnormal gadolinium kinetic), inflammation, and edema (increased T2 signal on CMR). However, CMR can also direct imaging of amyloid fibrils using T1 maps. Moreover, nuclear technics can image indirect targets as increased tissue calcium (scintigraphy with bone-seeking tracers and 18F sodium fluoride PET) as well as the amyloid fibrils themselves. Amyloid-binding PET tracers, such as C-11-PIB, F-18-florbetapir, and F-18-florbetaben, are structurally like thioflavin-T and are supposed to bind to the b-pleated sheet structure of the amyloid fibril [4, 9, 10].

19.3 Cardiac SPECT in the Diagnosis of Amyloidosis

The potential use of ^{99m}Tc-labeled bone-seeking tracers to diagnose CA has been investigated for many years. Initial studies revealed high-diagnostic accuracy for

CA. Even so, other authors described different results and the interest in this field of work had diminished [11, 12]. Just recently, Perugini et al. demonstrated greater binding avidity of 3.3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) to ATTR rather than AL which has renewed expectations regarding the noninvasive diagnosis of ATTR CA [13].

Lately, ^{99m}Tc-labeled myocardial bone-avid radiotracer has emerged as an essential tool for the diagnosis of ATTR CA. Technetium-99m pyrophosphate (^{99m}Tc-PYP), ^{99m}Tc-DPD, and hydroxymethylene diphosphonate (^{99m}Tc-HMPD) have all shown high accuracy for imaging cardiac TTR amyloid [7].

The precise molecular mechanism behind differential uptake in ATTR and AL CA is not well known, but has been postulated that it might be related to a higher calcium content, i.e., microcalcifications in TTR amyloid fibrils. The phosphate domains in those tracers are supposed to bind to calcium in transthyretin fibrils [14–16]. It is important to point out that in the past years those tracers were primarily used to detect myocardial necrosis. Animal models experiments have revealed binding sites to bone-avid radiotracers such as microcalcifications, calcium deposits, and intracellular calcium PYP. Amyloid fibrils are mainly formed by the precursor protein, heparan sulfate proteoglycan, and a calcium-dependent P-component that holds fibrils together. Pepys et al. [14] suggest that the P-component could bind to amyloid fibrils via a calcium-mediated mechanism elucidating the process underlying bone-seeking tracers uptake in CA as well. Afterward, Stats et al. [16] showed microcalcifications in endomyocardial biopsies samples. ATTR fibrils usually have a higher concentration of microcalcifications than AL, even so, in a few cases of AL CA the amount of microcalcifications is comparable. This finding suggests a pathophysiological basis to explain why patients with AL CA may have positive scans and reassure the importance of always excluding plasma cell gammopathies.

^{99m}Tc-PYP is the only agent approved by the Food and Drug Administration (FDA) to be used in ATTR CA diagnosis in the USA and is the most used in Brazil as well. ^{9m}Tc-DPD and ^{99m}Tc-HMPD are currently the most used in Europe and other countries. On this basis, studies comparing the accuracy of those agents are scant in literature, but it seems they perform equally on ATTR CA diagnosis. As well, grading systems and imaging protocols may differ in different countries [17, 18]. Of note, ^{99m}Tc methylene diphosphonate (^{99m}Tc-MDP) is currently used for bone scintigraphy, but not recommended for ATTR CA diagnosis because of its low sensitivity [13].

19.4 Imaging Protocols

Nowadays, ^{99m}Tc-PYP and ^{99m}Tc-DPD are the most widely used radiotracers for the diagnosis and prognosis of ATTR CA. Still, data about technical aspects regarding how to image and interpret scans are not consistent in the published literature and consequently not in clinical practice as well. Lately, Practice Points and Consensus have been published in order to guide good practice [18–21].

19.5 ^{99m}Tc-DPD Imaging Protocol and Interpretation

The only formal contraindication to the test is pregnancy, which is very unlikely in daily practice since amyloidosis is a disease of older patients and no specific test preparation is required. These recommendations apply to all three radiotracers (^{99m}Tc-PYP, ^{99m}Tc-DPD, and ^{99m}Tc-HMPD).

An activity dose of 10–20 mCi (370–740 MBq) of ^{99m}Tc-DPD is administered intravenously. After 2 or 3 h of injection, a whole-body scan in the anterior and posterior views and chest anterior and lateral views are acquired followed by chest/cardiac single photon emission computed tomography (SPECT) imaging. Whenever possible, a hybrid acquisition using SPECT/CT is advisable.

A visual or semiquantitative analysis can be done at 3 h of planar imaging. Radiotracer uptake into the bones (rib) is compared to heart uptake and scored as previously described by Perugini et al. [13]: grade 0 (no heart uptake and normal rib uptake), grade 1 (heart uptake is mild and less than rib uptake), grade 2 (heart uptake is moderate and equal to rib uptake), and grade 3 (heart uptake is high and greater than rib uptake with mild or absent rib uptake). Heart uptake must be confirmed in SPECT or SPECT/CT images. Scans showing visual scores of greater than or equal to 2, i.e., 2 or 3 on SPECT images, are classified as positive and suggestive of ATTR CA. The final diagnosis encompasses the exclusion of monoclonal gammopathy.

As the visual analysis is hugely dependent on observer proficiency, it performed poorly when estimating the degree of amyloid burden [22]. In order to increase the diagnostic accuracy of the test, Rapezzi et al. [23] described a quantitative analysis that is performed by calculating the ratio between radiotracer uptake in the heart and radiotracer uptake in the body: heart/whole-body ratio (H/WB). This method has the advantage of quantitation of radiotracer retention, but requires a long time, since a late whole-body imaging must be performed, and its value is not well-established with SPECT. Interestingly, different from ^{99m}Tc-PYP scintigraphy, ^{99m}Tc-DPD might have a role in detecting extracardiac AL when no heart uptake is revealed [24].

19.6 ^{99m}Tc-PYP Imaging Protocol and Interpretation

^{99m}Tc-PYP has been used for different purposes in clinical practice: bone scintigraphy, blood pool imaging for gastrointestinal bleeding, and radionuclide ventriculography, and in the past for identification of myocardial infarction.

An activity dose of 10–20 mCi (370–740 MBq) of ^{99m}Tc-PYP is administered intravenously. After 2–3 h of injection, anterior and lateral chest planar imaging are acquired, followed by a Cardiac SPECT imaging. Whenever possible, a hybrid acquisition using SPECT/CT is advisable.

A visual or semiquantitative analysis can be obtained using planar imaging. Radiotracer uptake into the bones (rib) is compared to heart uptake and rated as previously described by Perugini et al.: grade 0 (no heart uptake and normal rib

uptake), grade 1 (heart uptake less than rib uptake), grade 2 (heart uptake equal to rib uptake), and grade 3 (greater than rib uptake with mild/absent rib uptake). Heart uptake must be confirmed in SPECT or SPECT/CT images. Scans showing visual scores of greater than or equal to 2, i.e., 2 or 3 on planar and SPECT images, are classified as positive and suggestive of ATTR CA, in case of excluding monoclonal gammopathy.

^{99m}Tc-PYP also allows quantitative analysis. Bokhari et al. [25] defined a simpler technique based on drawing a circular region of interest (ROI) over the heart on the anterior chest planar imaging and mirroring this ROI over the contralateral chest to adjust for background and ribs. Heart -to-contralateral lung uptake ratio (H/CL) is calculated as a ratio-of-heart ROI mean counts to contralateral chest ROI mean counts. H/CL >1.5 at 1 h-imaging and H/CL >1.3 at 3-h imaging is highly accurate to diagnose ATTR CA. Hence, some caution is needed when drawing the ROI, such as size adjustment to maximize coverage of the heart without including adjacent lung and avoiding sternal, ribs, and right ventricle areas in order to obtain reliable ratios. Even so, H/CL may be falsely low or high in situations like prior myocardial infarction and pleural effusion.

Some technical and pathophysiological considerations regarding bone-seeking scintigraphy must be highlighted.

Planar imaging alone is limited in spatial resolution when compared to SPECT or SPECT/CT: myocardial uptake cannot be differentiated from blood pool uptake, overlying rib uptake may add counts to the region of the heart, and attenuation correction is not feasible. SPECT overcomes these limitations and should always be performed [26]. Indeed, Régis et al. [27] showed that visual analysis on SPECT imaging has led to less scans interpreted as equivocal when compared to quantitative analysis (H/CL).

Hutt et al. [28] have demonstrated that myocardial and bone uptake over time is distinct. As the peak of myocardial counts on planar images occurs after 1 of injection of ^{99m}Tc-DPD followed by a progressive decline over time, bone counts increase gradually and peak after 2–3 h. Therefore, 1-hour imaging is more sensitive, and 3-h imaging is more specific for ATTR CA diagnosis. Similar kinetics is observed with the other radiotracers. It is important to highlight that a 1-h imaging protocol is equivalent to 3-h protocol since SPECT/CT images are incorporated which impacts positively on patient comfort and laboratory outthought [29, 30].

19.7 Critical Points Concerning ^{99m}Technetium-Labeled Cardiac Scintigraphy for Suspected Amyloidosis

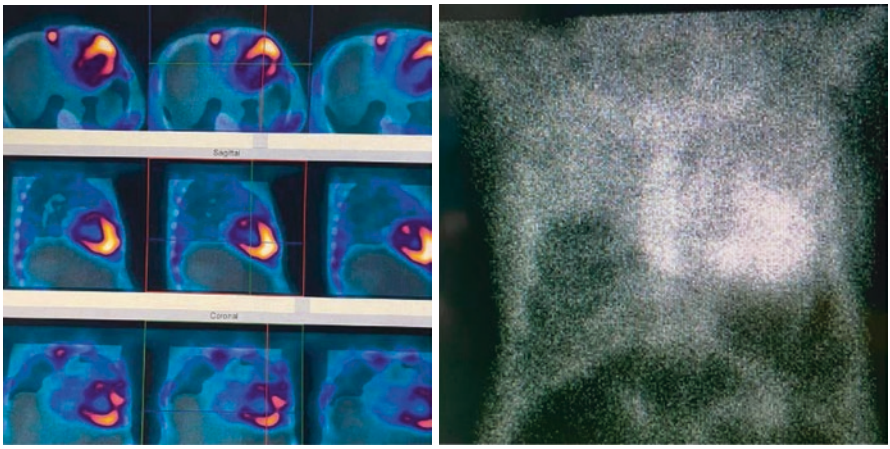
The initial description of a semiquantitative visual assessment of planar images based on comparing uptake between the bone (rib) and myocardium was proposed by Perugini et al. [13]. The results showed that a grade 2 or 3 was 100% sensitive at detecting ATTR cardiac amyloidosis and 100% specificity at differentiating ATTR

from AL or unaffected controls. The utility of such a method to distinguish AL and ATTR is crucial in the workup of amyloidosis patients [31], but some critical aspects need to be highlighted to avoid mistakes:

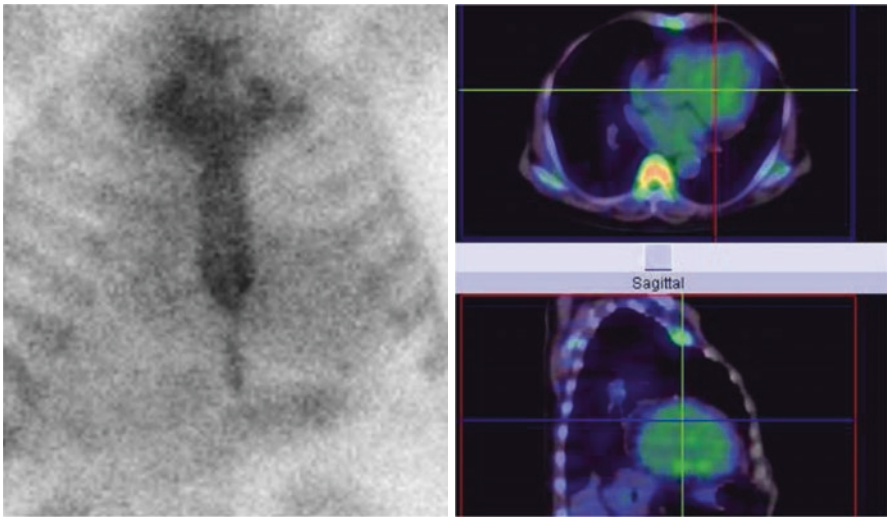
1. Cardiac uptake with bone tracers is not specific for ATTR-CA. In a large cohort of patients with AL CA, 99mTc-DPD scintigraphy showed cardiac uptake in 40%, including grade 2–3 in 10% of all patients (25% of those with cardiac 99mTc-DPD uptake) [32].
2. The reason for cardiac DPD/PYP/HMDP preferentially in ATTR-CA is not determined. Despite some suggestions relating cardiac microcalcifications as a possible explanation [16], this does not explain why 18F-NaF PET have a relatively low sensitivity with high specificity [33]. 18F-NaF PET/MRI may have a better diagnostic performance when semiquantification is used [34].
3. To avoid falsely classifying patients with AL-CA as ATTR-CA, it is always required evaluation for AL amyloidosis by serum FLCs, serum, and urine immunofixation in all patients undergoing 99mTc-PYP/DPD/HMDP scans for cardiac amyloidosis [18]. Incorrect diagnosis leads to inappropriate therapy and worse patient outcomes. The imaging physician must clearly communicate the need to correlate imaging and laboratory findings to achieve correct diagnosis.
4. A negative scan does not exclude ATTR-CA. False negative is early disease with mild infiltration. Also important is that certain specific genetic variants such as Phe64Leu and Val30Met are not positive in bone tracer scans [35, 36]. Even patients with severe myocardial infiltration may demonstrate a false negative Tc-PYP scans as recently showed by Emory University group in patients with Val122Ile ATTR-CA [36]. This emphasizes the need for genetic testing and endomyocardial biopsy when there are inconsistent results in the clinical and laboratory evaluation.
5. Planar imaging and H/CL ratio alone are insufficient for diagnosis of ATTR cardiac amyloidosis. SPECT imaging is necessary to demonstrate myocardial uptake of 99mTc-PYP/DPD/HMDP [18]. False positive results are commonly derived from blood pool uptake. Recently, expert consensus recommendations for multimodality imaging in cardiac amyloidosis were revised and the recommended time between injection of 99mTc-PYP and scan 2- or 3-h imaging with 1-h imaging being optional.
6. Another important revision is that SPECT imaging is required in all studies (irrespective of time between injection and scan) to directly visualize tracer uptake in the myocardium [18, 37].
7. Recent data now suggest that the use of cadmium zinc telluride (CZT) SPECT for 99mTc-PYP/DPD/HMDP imaging is an alternative for planar imaging. New studies are needed to establish if better quantification can be achieved with CZT SPECT [37, 38].
8. New methods to improve the amyloid burden quantification in the myocardial are crucially needed. Since the introduction of approved therapies for transthyretin cardiac amyloidosis, there is a need to evaluate the direct effect of these agents in stopping or reversing the amyloid deposition. 99mTc-pyrophosphate

cardiac imaging using a CZT SPECT/CT scanner generated indexes such as SUVmax and SUVmean, which can provide absolute quantitation of 99mTc-pyrophosphate uptake [39].

Illustrative Cases



Case 1: Male patient with 74 years presenting with severe right heart failure demonstrating moderate ascites without portal hypertension. Transthoracic echocardiogram showed significant left ventricular hypertrophy (15 mm) and preserved ejection fraction. 99mTc-pyrophosphate planar imaging (right) demonstrated cardiac uptake higher than observed in ribs (Periguni score 3+). SPECT demonstrating diffuse uptake in myocardium. This case is a true positive of cardiac amyloidosis. After the adequate exclusion of monoclonal gammopathy, a diagnosis of ATTR-cardiac amyloidosis can be correctly made.



Case 2: Female patient with 52 years presenting with dyspnea and fatigue. Transthoracic echocardiogram showed borderline left ventricular hypertrophy (12 mm) and preserved ejection fraction. 99mTc-pyrophosphate planar imaging (left) demonstrated cardiac uptake like the observed in ribs (Periguni score 2+). SPECT demonstrating blood pool uptake and no accumulation in the myocardium. This case is a false positive for cardiac amyloidosis.

19.8 False-Positive and False-Negative Scenarios in Bone-Seeking Scintigraphy [2–4, 31]

As mentioned before, bone-seeking scintigraphy is a highly accurate method to diagnose ATTR CA. However, some peculiar scenarios should always be considered.

Listed below are the major causes of false-positive and false-negative results observed on bone-seeking cardiac scintigraphy.

Possible False-Positives of Scintigraphy for Detecting ATTR CA:

1. AL CA is the most common and important cause of misdiagnosis. Most clinicians are not familiar with the fact that nearly 20% of scans can be positive in patients with AL CA or the screening to rule out is not or incompletely performed.
2. Blood pool uptake in planar images. Despite being not recommended, some labs still use solely planar images to diagnose CA and a blood pool can be interpreted as a positive scan. Cardiac uptake on planar images must always be confirmed in SPECT or SPECT/CT images.
3. Rib fractures, valvular, and annular calcifications. In this case, these structures may overlay the heart, thereby affecting H/CL results. Currently, H/CL alone is not recommended to diagnose CA.
4. Myocardial infarction (acute or subacute). Focal uptake can be present, and scintigraphy should not be used to diagnose CA in this early phase (<4 months).
5. Hydroxychloroquine cardiotoxicity requires histological confirmation.
6. Rare forms of CA like hereditary apolipoprotein A1.

Possible False Negatives of Scintigraphy for Detecting ATTR CA:

1. Early-stage disease. The myocardial infiltration can be minimal and not detectable.
2. Some pathogenic TTR mutations. Phe64Leu, Val30Met, Se77Tyr, Glu61Ala. Echocardiogram or CMR may show typical findings, but scintigraphy is negative. Endomyocardial biopsy, genetic testing, and sometimes PET/CT scans can be helpful.
3. Myocardial infarction (chronic phase). Amyloid deposition and thus radiotracer uptake will be present only in viable tissue. In the context of an extensive cardiac scar, the degree of radiotracer uptake on planar imaging may be mild. However, this can be reconciled using SPECT imaging.
4. Delayed or premature acquisition protocol. Labs should always perform scans according to guidelines.

19.9 Role of Cardiac SPECT in the Context of Multimodality Imaging for Cardiac Amyloidosis Diagnosis

Currently, the most applied noninvasive methods to diagnostic and prognostic purposes in CA are echocardiography, CMR, and scintigraphy with bone-seeking tracers [1, 9, 10, 18].

Echocardiography is the first-line method used to assess CA because it is widely available and of low cost. Typical echocardiographic findings in CA include biventricular wall thickening, increased ventricular mass, normal to small ventricular size, bi-atrial enlargement, diastolic biventricular dysfunction, and preserved ejection fraction (EF). In CA, left ventricular (LV) EF (LVEF) is preserved until late to end-stage disease, but longitudinal LV contraction is impaired early in the disease [40]. A regional pattern of strain with severe impairment at the mid and basal segments and relative apical sparing of longitudinal strain is sensitive (93%) and specific (82%) to differentiate CA from other causes of LV hypertrophy [41] and abnormal global longitudinal strain is an independent predictor of poor survival in both forms of CA [40, 42, 43]. Right ventricular (RV) involvement is most commonly observed in ATTR CA [9]. Unexplained RV thickening and impaired longitudinal strain can be a red flag for initial disease and worse prognosis [44, 45]. RV dilatation in end-stage disease also portends a worse prognosis [46].

CMR provides better spatial resolution than echocardiography, allowing improved morphological and functional analysis. Besides, it is exceptional in tissue characterization. Subendocardial or transmural late gadolinium enhancement (LGE) is the most typical pattern [47, 48]. Sensitivity and specificity are 86% and 92%, respectively [49]. LGE is highly prevalent (100% RV and 96% LV) and more extensive in ATTR, but does not distinguish between CA forms. Nonetheless, it is a strong predictor of mortality in both forms of CA [50]. A limitation of LGE is that it is not simply quantifiable, which makes it inaccurate for tracking changes over time and monitoring treatment. The newer quantitative technique of T1 mapping can overcome this limitation and potentially detect amyloid infiltration earlier in the disease process than LGE and follow changes over time as well monitoring treatment response [50–53].

The only imaging modality that can accurately diagnose ATTR CA without the need for invasive endomyocardial biopsy is nuclear scintigraphy using bone-seeking radiotracers [7, 17].

Perugini et al. [13] have first described that ^{99m}Tc-DPD scintigraphy is well accurate for diagnosis and differentiates ATTR from AL in patients with documented CA (LV thickness >12 mm identified in echocardiography). The presently known as Perugini visual score was used to identify patients with ATTR CA. Some years later, Hutt et al. [54] confirmed Perugini's findings and also demonstrated that stratification by Perugini grade of positivity had no prognostic value. Later on, other authors have confirmed scintigraphy as an accurate diagnostic method even when other types of bone-seeking tracers were used [25, 55].

Rapezzi et al. [23] validated ^{99m}Tc-DPD scintigraphy as an early diagnostic method, even before the appearance of echocardiography abnormalities and established ^{99}Tc-DPD myocardial uptake (H/WB) as a prognostic determinant of cardiac outcomes either alone or in combination with LV wall thickness.

In a multicentric study, Castano et al. [56] pointed out that semiquantitative data obtained from ^{99m}Tc-PYP scintigraphy were associated with worse survival and consequently poor prognosis among patients with ATTR CA; and, that the test could be reproducibly performed at multiple sites with high accuracy. Sperry et al. [57] showed a pattern similar to apical sparing in scintigraphy too and also associated with prognosis. Furthermore, absolute quantification using SPECT/CT might be valuable for improving the diagnosis and prognosis of ATTR CA [58].

Quite a few studies have confirmed scintigraphy as an excellent method for early diagnosis [23, 59]. However, the scintigraphy role in following up is still uncertain [60]. In this context, data from CMR studies are very promising [61].

Gillmore et al. [7] have revolutionized clinical practice by proposing that ATTR CA could be noninvasively diagnosed using bone-seeking scintigraphy. In this multicenter study involving 1217 patients with suspected CA, any myocardial radiotracer uptake (grade 1, 2 or 3) was >99% sensitive and 86% specific for detecting ATTR CA, with false-positive cases being attributed to AL CA. Indeed, 30% of patients with CA AL may have positive scans. Grades 2 or 3 of myocardial radiotracer uptake and the absence of monoclonal gammopathies in serum or urine had a specificity and positive predictive value of 100% to detect ATTR CA. Of note, these results were obtained in a population of patients with a high pretest probability of CA: symptoms of heart failure and echocardiogram or CMR consistent with CA. More studies are needed to confirm if these findings can be used in the general population without all these characteristics of this population.

19.10 Myocardial Innervation Evaluation in CA

Cardiac dysautonomia is common in both types of CA (ATTR and AL types) [62]. This is due to amyloid infiltration into the myocardial and conduction tissue, resulting in conduction and rhythm disorders. Amyloid deposits impair the function of sympathetic nerve endings. Disturbance of myocardial sympathetic innervations may play an important role in the remodeling process. Imaging of myocardial innervation in patients with amyloidosis has been mainly focused on visualizing the effects of amyloidosis on the sympathetic nerve system [62, 63].

Conventional nuclear imaging by means of 123-Iodine-metaiodobenzylguanidine (^{123}I-mIBG) is the most widely used modality for this indication [62]. It is a chemical modified analogue of norepinephrine that can detect myocardial innervation changes [64]. ^{123}I-mIBG cardiac scintigraphy is well-established in patients with heart failure [65] and plays an important role in evaluation of sympathetic innervation in CA [18, 62].

^{123}I-mIBG is stored in vesicles in the sympathetic nerve terminals and is not catabolized like norepinephrine [64]. Cardiac ^{123}I-mIBG uptake can be evaluated using both planar and tomographic imaging, thereby providing insight into global and regional sympathetic innervation. Standardly assessed imaging parameters are the heart-to-mediastinum ratio (HMR) and washout rate (WR), usually derived from planar images. Decreased HMR 3–4 h after ^{123}I-mIBG injection (late HMR) and increased WR indicate cardiac sympathetic denervation and are associated with poor prognosis [62, 64]. SPECT provides additional information and has advantages for evaluating abnormalities in regional distribution in the myocardium [65]. ^{123}I-mIBG is mainly useful in patients with ATTRv CA and ATTRw CA, not in AA and AL amyloidosis [62]. The potential role of PET for cardiac sympathetic innervation in amyloidosis has not yet been identified [62, 66].

In a review paper that included 16 studies on this subject [62], the results were summarized and divided into three main topics: the imaging of cardiac innervation itself, the implications of this imaging method, and the relation with other nuclear medicine imaging techniques in CA. In relation to the imaging of cardiac innervation, ATTRv type amyloidosis patients are studied most extensively, showing the most pronounced reduced late HMR. Also, AL type amyloidosis patients tend to have decreased late HMR compared to healthy control subjects; however, to a lesser extent compared to both ATTRv CA and ATTRw CA type patients [62, 67–69]. In a study with 61 CA patients (39 AL, 11 AA, 11 ATTR), late ^{123}I-mIBG HMR was lower and WR was higher in patients with echocardiographic signs of amyloidosis. In ATTR CA patients without echocardiographic signs of amyloidosis, HMR was lower than in patients with the other CA types (2.0 ± 0.59 vs. 2.9 ± 0.50, $p = 0.007$). Then, ^{123}I-mIBG scintigraphy could detect cardiac denervation in ATTR CA patients before signs of amyloidosis are evident on echocardiography [69]. However, due to the large overlap of late HMR ranges in ATTR and AL type amyloidosis patients, ^{123}I-mIBG scintigraphy is not capable of discriminating between these amyloidosis subtypes [69].

Mean late HMR differs substantially between the different publications [62]. This variability is mainly due to non-homogeneity in^{123}I-mIBG imaging acquisition. HMR varies between different gamma camera systems (venders), but more importantly between the application of low energy and medium energy collimators [62, 64]. Generally, HMR is higher on images acquired with medium energy collimators compared to images acquired with low energy collimator [70]. Based on these differences in HMR, cutoff values for the different collimators are proposed, as well as conversion algorithms. Additional SPECT scanning may be of value in the evaluation of regional cardiac sympathetic innervation abnormalities. Most patients (both AL and ATTR type amyloidosis) with low HMR show reduced tracer accumulation in the infero-postero-lateral segments [69]. Unfortunately, this may not be considered as a characteristic finding in amyloidosis patients, since a defect in ^{123}I-mIBG accumulation in the inferior myocardial wall is also reported in healthy control subjects [71]. This is considered because of physiological ^{123}I-mIBG accumulation in the liver overprotecting the infero-posterior myocardial wall [18, 62, 64, 71].

Concerning the clinical implications of this imaging technique, in patients with heart failure, the ADMIRE-HF demonstrated that reduced late HMR is associated with an increased risk of developing ventricular arrhythmia and is associated with poor survival [72]. In fact, reduced late HMR is a stronger prognostic factor than LVEF for developing severe adverse cardiac events in patients with ischemic heart disease [65]. In amyloidosis patients with impaired cardiac sympathetic innervation, decreased survival rates are also established [73]. Late HMR was identified as an independent prognostic factor for 5-year all-cause mortality, with a 42% mortality rate for those patients with late HMR <1.60, compared to only 7% in patients with late HMR ≥1.60 (hazard ratio 7.2, $P < 0.001$) [73].

In the AL type population, very little is known about the consequences of reduced late HMR. Follow-up of the available studies in this population is too limited to identify arrhythmogenic consequences of impaired cardiac sympathetic innervation [62, 69]. Data on the contribution of reduced late HMR to cardiovascular outcome measurements in patients with ATTR CA amyloidosis seem to be incomplete. Moreover, the actual incidence of ventricular arrhythmia, sudden cardiac death, or appropriate implantable cardioverter-defibrillator (ICD) shocks in amyloidosis patients with impaired cardiac sympathetic innervation is not fully elucidated. Therefore, the question whether amyloidosis patients will benefit from prophylactic ICD remains unanswered [62].

In comparison to other nuclear medicine imaging techniques, cardiac ^{123}I-mIBG scintigraphy cannot discriminate between ATTR CA and AL CA as bone tracer scintigraphy does. Moreover, since both ATTRw and ATTRv patients show decreased late HMR, this exam alone could not differentiate between autonomic neuropathy and cardiomyopathy. Bone tracer accumulation predominantly occurs in ATTRw CA patients, probably as a result of the underlying cardiomyopathy. On the contrary, patients with ATTRv type amyloidosis without cardiomyopathy tend to show no myocardial bone tracer accumulation and normal biomarkers (N-terminus pro-brain natriuretic peptide, and troponin-T) [62]. Within these patients, late HMR is generally lower in the subgroup of patients with other symptoms of polyneuropathy [74]. Future studies should focus on the possible additive value of bone scintigraphy in relation to ^{123}I-mIBG scintigraphy in getting a better understanding of the complementary contribution of neuropathy and cardiomyopathy to each other in ATTR type amyloidosis patients [62].

19.11 Diagnostic Algorithms of Cardiac Amyloidosis

Guidelines and consensus support a non-biopsy diagnosis of ATTR CA using ^{99m}Tc-PYP/DPD/HMDP scintigraphy. Gillmore et al. [7] showed that scintigraphy is highly sensitive, but not so specific for ATTR CA diagnosis and most false-positive scans were attributed to AL CA. Ruling out monoclonal gammopathies is essential. There is no consensus if laboratory tests to exclude AL should be done before or after scintigraphy is performed. It is important to point out that up to 40% of patients

with ATTR CA can have a monoclonal gammopathy of unknown significance (MGUS) and an endomyocardial biopsy is necessary to confirm ATTR CA [75]. After ATTR CA is confirmed, TTR gene sequencing and genetic counseling for relatives are advised.

Some diagnostic algorithms of CA have been proposed [3, 6, 18]. Indeed, they are quite similar. The most important difference is regarding when tests to exclude gammopathies should be done, i.e., before scintigraphy or after.

19.12 Quantitative Studies to Assess Disease Activity and Response to Therapy

^{99m}Tc-labeled bone-seeking tracers cardiac scintigraphy to diagnose and prognosis ATTR CA is not an absolute quantitative method since visual and semiquantitative analysis compare cardiac radiotracer uptake to other tissues.

Perugini et al. [13] demonstrated that visual analyses accurately discriminate patients with ATTR CA from those with AL CA and controls. However, the Perugini score was not a predictor of prognosis [54]. Of note, ATTR is a systemic disease and abnormal protein deposits can be present in extracardiac sites. The main criterion used to differentiate grade 2 from grade 3 of the Perugini score is the reduction in bone uptake. So, in some cases, grade 3 might be related to extracardiac uptake rather than true greater cardiac uptake. This hypothesis might explain why the visual score has not been proven to be useful in risk stratification [58].

In order to improve the measurement of cardiac uptake of ^{99m}Tc-labeled bone-seeking tracers, semiquantitative ratios, namely, H/CL and H/WB, have been proposed. Yet, this technique still relies on extracardiac sites as comparators. Castano et al. [56] described that H/CL has prognostic significance, but the cutoff value for diagnosis and worse prognosis is narrow. Also, the role of H/WB is still uncertain [76]. Accordingly, semiquantitative assessment did improve diagnosis but not prognosis.

As postulated, the exact mechanism behind bone-seeking tracer uptake in ATTR CA is not recognized, but it's reasonable to assume that a greater cardiac amyloid deposition may be associated with more scan uptake and consequently worse prognosis and that changes in amyloid burden could be assessed by changes in radiotracer uptake. Planar imaging carries important limitations and SPECT is strongly recommended to improve the diagnostic performance of scintigraphy. Recently, a lot of effort has been made to develop SPECT-based quantitative techniques to evaluate burden amyloid as well as response to novel therapies [58].

At the present time, absolute quantitation of myocardial uptake can be assessed by SPECT. Quantitative SPECT images can be reconstructed using proper commercially available software, CT-based attenuation correction, scatter correction, and iterative reconstruction technique. Comparable with PET, the images represent parametric maps of radiopharmaceutical distribution with units of kBq/mL

standardized to the time of injection and can be corrected for injected dose and volume of distribution to give standard uptake value (SUV). Cardiac metabolic activity (CMA) and cardiac metabolic volume (CMV) also can be used to assess amyloid burden [50].

Ramsay et al. [77] demonstrated that quantitative HDP SPECT/CT can discriminate between individuals with cardiac ATTR from the population without this disease (p = 0,002). The SUV maximum (SUVmax) was sufficiently similar between individuals without cardiac ATTR that a 99% reference interval for HDP uptake could be calculated, providing an upper limit cut point of SUVmax 1.2. Individuals with cardiac ATTR had SUVmax well above. Still, its role in disease management warrants further assessment.

In a single-center, retrospective analysis of ^{99m}Tc-DPD scans, Scully et al. [78] showed that SPECT/CT quantification is possible and outperforms planar quantification techniques. Moreover, SUV retention index differentiates Perugini grade 2 or 3 and may be an important tool to monitor response to therapy.

Miller et al. [79] assessed the diagnostic accuracy and clinical significance of ^{99m}Tc-PYP quantitation. Radiotracer activity in the myocardium was calculated using cardiac pyrophosphate activity (CPA) and volume of involvement (VOI) activity. CPA had the highest diagnostic accuracy (AUC 0.996, 95% CI 0.987–1.00) and was significantly higher compared to the Perugini score (AUC 0.952, P = 0.016). Quantitative assessment of myocardial radiotracer activity with CPA or VOI has high diagnostic accuracy for ATTR-CM. Both measures are potential noninvasive markers to follow the progression of disease or response to therapy.

Dorbala et al. [39] were pioneers in demonstrating that absolute quantification is possible to be done using ^{99m}Tc-PYP-Cadmium-Zinc-Telluride-Based SPECT/CT.

19.13 Myocardial Blood Flow Evaluation in CA

Coronary microvascular dysfunction (CMD) can result from structural and functional abnormalities at the intramural and small coronary vessel level affecting coronary blood flow autoregulation and consequently leading to impaired coronary flow reserve (CFR) [80]. Endothelial and CMD often coexist with epicardial coronary artery disease (CAD), but are also commonly seen in patients with various forms of heart disease, including CA [18, 80–82].

Interstitial and perivascular amyloid deposits may compress coronary microvessels, thereby increasing coronary microvascular resistance. Increased LV mass may reduce capillary density and decrease diastolic perfusion from high LV filling pressures. Autonomic dysfunction may also result in vasomotor dysfunction [80]. Angina without epicardial CAD has been well-described in patients with amyloidosis [83]. Myocardial perfusion abnormalities can be detected in patients with AL and ATTR CA and may precede the clinical diagnosis of CA [83].

Dorbala et al. [81] studied 31 patients, including 21 with definite CA without epicardial CAD and 10 patients with hypertensive left ventricular hypertrophy (LVH). All of them underwent rest and vasodilator stress N-13 ammonia PET and 2D echocardiography. Global LV myocardial blood flow (MBF) was quantified at rest and during peak hyperaemia, and CFR was computed (peak stress MBF / rest MBF) adjusting for rest rate pressure product. Compared to the LVH group, the amyloid group showed lower rest MBF (0.59 ± 0.15 vs. 0.88 ± 0.23 mL/g/min, $P = 0.004$), stress MBF (0.85 ± 0.29 vs. 1.85 ± 0.45 vs. mL/min/g, $P < 0.0001$), CFR (1.19 ± 0.38 vs. 2.23 ± 0.88, $P < 0.0001$), and higher minimal coronary vascular resistance (111 ± 40 vs. 70 ± 19 mm Hg/mL/g/min, $P = 0.004$). Additionally, more than 95% of all amyloid subjects presented significantly reduced peak stress MBF (<1.3 mL/g/min). In multivariable linear regression analyses, a diagnosis of amyloidosis and increased LV mass and age were the only independent predictors of impaired coronary vasodilator function. Absolute MBF and CFR were substantially reduced in patients with CA, despite absence of epicardial CAD [81].

CMD from amyloid deposits may potentially explain a greater vulnerability of these individuals to ischemia and subclinical impairment of LV systolic function [80]. Myocardial ischemia from CMD may predispose some of these patients to sudden cardiac death. More studies are required to understand whether CMD improves after successful anti-amyloid therapy.

19.14 PET Tracers for Amyloid Detection and to Evaluate Disease Progression

PET is another nuclear technique that can be used to evaluate CA. Literature data about the role of this technique to assess CA are scant when compared to scintigraphy with bone-seeking tracers, but still very promising. PET imaging offers the advantage of higher spatial resolution and allows absolute quantification of amyloid burden and, therefore, changes after treatment. Two classes of PET radiotracers may be used: 18F Sodium Fluoride (^{18}F-NaF) and amyloid-binding radioactive tracers [9, 17].

19.14.1 ^{18}F-Sodium Fluoride

^{18}F-Sodium Fluoride (^{18}F-NaF) was used in the past for prostate cancer screening and has been studied more recently in CAD as a novel method to predict cardiac events. Like bone-seeking tracers used in scintigraphy,^{18}F-NaF also binds to microcalcifications, so it is reasonable to assume that it could be used to detect CA and differentiate ATTR from AL CA. Also, Castano et al. [60] demonstrated that

bone-seeking tracer scintigraphy is not currently useful to monitor response to treatment and ^{18}F-NaF could be useful in this scenario.

Morgenstern et al. [84] showed that ^{18}F-NaF is an effective PET radiotracer to image ATTR CA. Qualitative and quantitative analysis demonstrated higher uptake in ATTR CA when compared to AL CA patients and controls.

Martineau et al. [85] examined the sensitivity of ^{18}F-NaF PET to detect ATTR CA. Although the degree of myocardial uptake was significantly greater in ATTR patients compared to AL and control subjects, it was low and inferior to the blood pool leading to a modest sensitivity when qualitative and quantitative methods were used, 57% and 75% respectively. These findings were quite different from those obtained with scintigraphy [7]. Zhang et al. [86] were pioneers in comparing the sensitivity of ^{18}F-NaF PET in detecting CA to that of ^{99m}Tc-PYP. Both qualitative and quantitative analyses showed that PET sensitivity was significantly inferior to that of ^{99m}Tc-PYP. So, currently, data do not support the use of ^{18}F-NaF PET to diagnose ATTR CA.

19.14.2 Amyloid PET Tracers

Amyloid-binding radioactive tracers were originally developed to image brain beta-amyloid deposits in patients with Alzheimer's disease, but recently, some studies have demonstrated its capacity to bind to cardiac amyloid deposits and opened a new field of investigation. These tracers are structurally like thioflavin-T and bind to the beta-pleated motif of amyloid fibril irrespective of the precursor amyloid protein [9] ^{11}C-Pittsburgh Compound-B (^{11}C-PIB) and ^{18}F-labelled agents such as ^{18}F-florbetapir and ^{18}F-florbetaben have been successfully used to assess Alzheimer's disease and more recently as a new technique to diagnose CA [87].

Antoni et al. [88] demonstrated that ^{11}C-PiB can accurately differentiate controls from patients with confirmed CA. However, it was not capable of differentiating ATTR from AL CA. Later on, Rosengren et al. [89] showed that ^{11}C-PiB could also accurately distinguish AL from ATTR CA patients since quantitative methods have shown that radiotracer uptake was significantly higher in AL CA. However, the need for an onsite cyclotron for production, due to its short half-life, limits its availability and clinical use.

^{18}F-labeled amyloid imaging tracers have a longer half-life, thus, allowing their use in laboratories without a cyclotron. Initial studies using ^{18}F-Florbetapir [90, 91] have demonstrated a significant radiotracer uptake in patients with CA and no uptake in controls. Although uptake was higher in AL than in ATTR CA, it was not sufficient to discriminate AL from ATTR CA. Studies using ^{18}F-Florbetaben have demonstrated similar findings [92]. More recently, Genovesi et al. [93] demonstrated in a prospective study that ^{18}F-Florbetaben uptake over time was significantly higher in patients with AL CA than in ATTR CA allowing type differentiation.

Importantly, only amyloid-binding PET tracers can adequately image AL CA and identify systemic amyloid deposits.

Regarding the response to therapy, initial data are promising, but more studies are needed to warrant its clinical use [9].

In conclusion, further large multicenter studies would be necessary to substantiate the diagnostic accuracy of PET for the detection of CA [94].

19.15 Future Perspectives

Certainly, we have learned much about CA over the past few years. Great achievements in multimodality imaging methods have led to the noninvasive diagnosis of ATTR CA in a substantial number of patients. Meanwhile, improvements in clinical treatment, with novel drugs, brought the opportunity for better outcomes. Even so, some uncertain issues demand further investigation.

Bone-seeking tracers scintigraphy has proved to be highly accurate in the diagnosis of ATTR CA, but these data were obtained from a population with a high likelihood of disease. May we extrapolate to a less selected one? Is the method accurate for screening in patients with aortic stenosis or bilateral carpal tunnel syndrome, currently known as red flags of disease? Its utility remains unproven and ongoing studies will provide insight into this matter. In this respect, the implementation of appropriate screening programs for ATTR CA is also mandatory to increase awareness of the disease.

A better understanding of amyloidogenesis pathophysiology and differences between the phosphate-derived radiotracers with respect to diagnosis, subtyping, and prognostication of ATTR is crucial. Also, technical refinements on scan acquisition and standardization of radioisotope dose, incubation time, and analytic ROI methods are needed.

SPECT and PET/CT are promising tools for quantification and assessment of response to therapy, but more robust data are needed to define their accuracy and additive value to the care of patients with cardiac amyloidosis.

Clinical Case

A 70-year-old-male with a history of hypertension, diabetes, and dyslipidemia presented with progressive exertional dyspnea that had persisted for the previous month. Bilateral Carpal Tunnel Syndrome Operation in 2013. Patient was admitted to the cardiac care unit for acute heart failure (HF) in the New York Heart Association (NYHA) class IV. Transthoracic echocardiogram revealed bi-atrial enlargement. Normal ventricle size. Severe concentric left ventricular hypertrophy (19 mm), preserved overall systolic biventricular function (Fig. 19.1). Impaired relaxation and elevated filling pressures with restrictive mitral inflow pattern were consistent with diastolic dysfunction grade III. Mild mitral and tricuspid regurgitation were also

noticed. A pattern of apical sparing on the longitudinal strain was observed too (Fig. 19.2). A Cardiac MRI was pursued and depicted heterogeneous subendocardium late gadolinium enhancement encompassing atrium, interatrial septum, interventricular septum, and right and left ventricles consistent with infiltrative disease (Figs.19.3 and 19.4). Cardiac amyloidosis was suspected and 99mTc-PYP scintigraphy was performed. Planar images showed abnormally increased radiotracer activity in the heart (Perugini grade 3) with a calculated heart-to-contralateral ratio (H/CL) of 1.7. (Fig. 19.5) SPECT/CT images confirmed uptake throughout the myocardium and right ventricle (Figs. 19.6 and 19.7). Gamophathies were excluded. Genetic testing showed the mutation Val142Ile confirming ATTR CA.

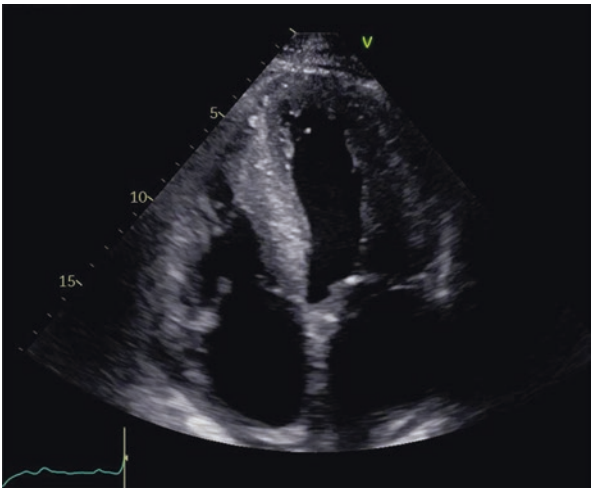


Fig. 19.1 Echocardiogram 4-chamber view (Author's personal archive)

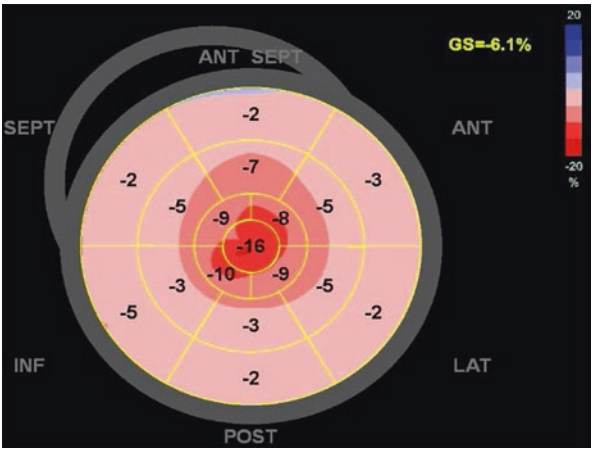


Fig. 19.2 Bull's eye strain showing preservation of apical deformity. (Author's personal archive)

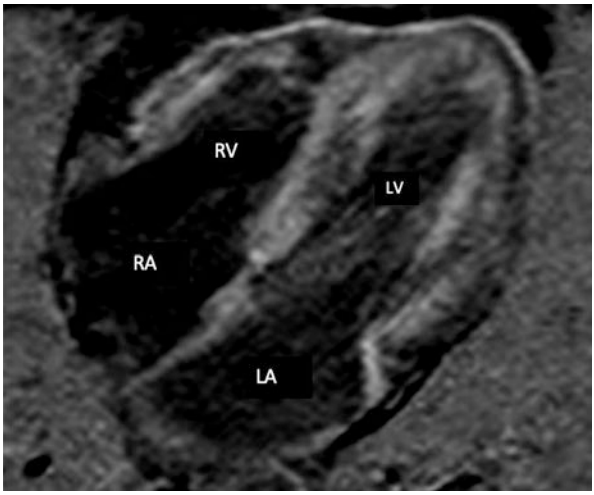


Fig. 19.3 Diffuse subendocardial LGE in 4-chamber CMR (Author's personal archive)

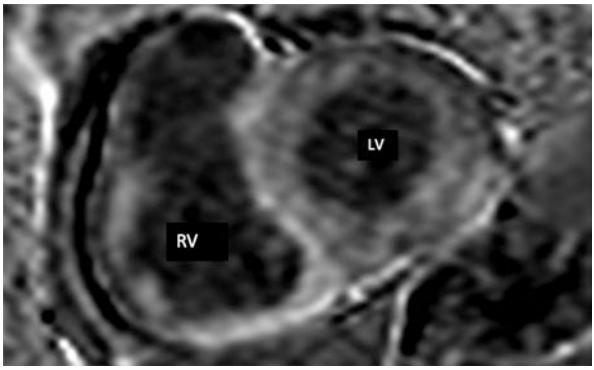


Fig. 19.4 Diffuse subendocardial LGE in short axis CMR (Author's personal archive)

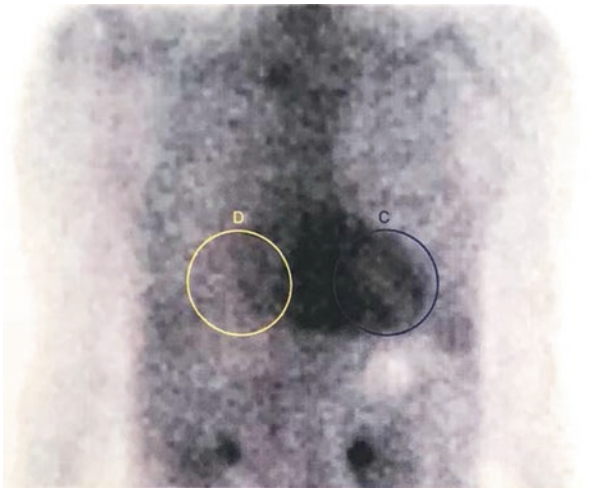


Fig. 19.5 99m-Tc-PYP anterior planar Image showing cardiac uptake greater than ribs (Perugini grade 3) and H/CL = 1.7 (Author's personal archive)

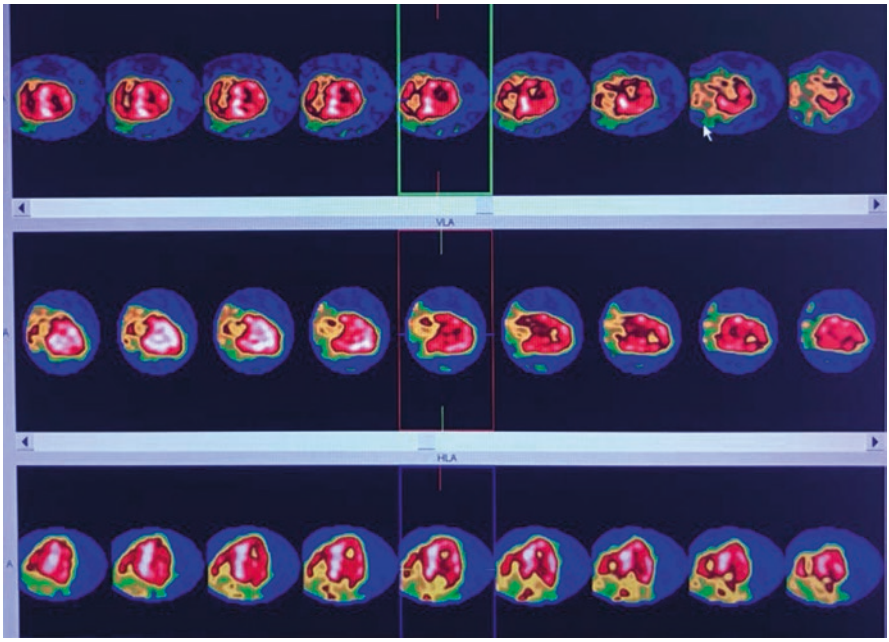


Fig. 19.6 SPECT imaging showing diffuse uptake throughout the myocardium and right ventricle (Author's personal archive)

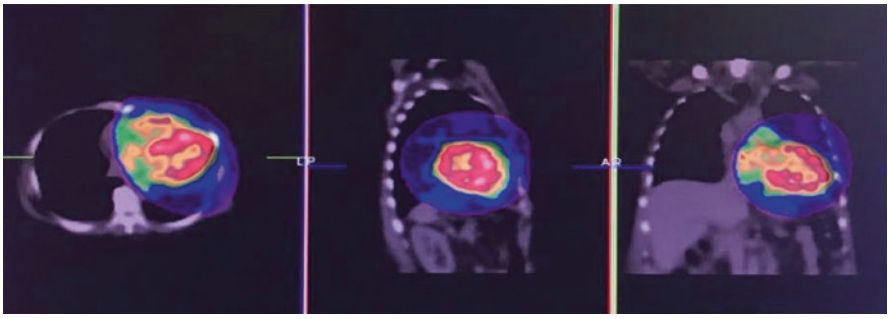


Fig. 19.7 Fused SPECT/CT imaging (Author's personal archive)

References

1. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 2019;73(22):2872–91.
2. Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. Circulation. 2020:1–16.

3. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on myocardial and pericardial diseases. Eur J Heart Fail. 2021;23(4):512–26.
4. Jurcuţ R, Onciul S, Adam R, Stan C, Coriu D, Rapezzi C, et al. Multimodality imaging in cardiac amyloidosis: a primer for cardiologists. Eur Heart J Cardiovasc Imaging. 2020;21(8):833–44.
5. Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. JACC Hear Fail. 2019;7(8):709–16.
6. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Hear Fail. 2019;12(9):1–11.
7. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation. 2016;133(24):2404–12.
8. Li W, Uppal D, Wang YC, Xu X, Kokkinidis DG, Travin MI, et al. Nuclear imaging for the diagnosis of cardiac amyloidosis in 2021. Diagnostics. 2021;11(6):1–13.
9. Dorbala S, Cuddy S, Falk RH. How to image cardiac amyloidosis: a practical approach. JACC Cardiovasc Imaging. 2020;13(6):1368–83.
10. Fontana M, Ćorović A, Scully P, Moon JC. Myocardial amyloidosis: the exemplar interstitial disease. JACC Cardiovasc Imaging. 2019;12(11P2):2345–56.
11. Wizenberg TA, Muz J, Sohn YH, Samlowski W, Weissler AM. Value of positive myocardial technetium-99m-pyrophosphate scintigraphy in the noninvasive diagnosis of cardiac amyloidosis. Am Heart J. 1982;103(4):468–73. https://doi.org/10.1016/0002-8703(82)90331-3.
12. Gertz MA, Brown ML, Hauser MF, Kyle RA. Utility of technetium Tc 99m pyrophosphate bone scanning in cardiac amyloidosis. Arch Intern Med. 1987;147(6):1039–44.
13. Perugini E, Guidalotti PL, Salvi F, Cooke RMT, Pettinato C, Riva L, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. J Am Coll Cardiol [Internet]. 2005;46(6):1076–84. https://doi.org/10.1016/j.jacc.2005.05.073.
14. Pepys MB, Dyck RF, de Beer FC, Skinner M, Cohen a S. Binding of serum amyloid P-component (SAP) by amyloid fibrils. Clin Exp Immunol [Internet]. 1979;38(2):284–93. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1537850&tool=pmcentrez&rendertype=abstract%5Cn, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1537850/?tool=pubmed
15. Suhr OB, Lundgren E, Westermark P. One mutation, two distinct disease variants: unravelling the impact of transthyretin amyloid fibril composition. J Intern Med. 2017;281(4):337–47.
16. Stats MA, Stone JR. Varying levels of small microcalcifications and macrophages in ATTR and AL cardiac amyloidosis: implications for utilizing nuclear medicine studies to subtype amyloidosis. Cardiovasc Pathol [Internet]. 2016;25(5):413–7. https://doi.org/10.1016/j.carpath.2016.07.001.
17. Singh V, Falk R, Di Carli MF, Kijewski M, Rapezzi C, Dorbala S. State-of-the-art radionuclide imaging in cardiac transthyretin amyloidosis. J Nucl Cardiol [Internet]. 2019;26(1):158–73. https://doi.org/10.1007/s12350-018-01552-4.
18. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 1 of 2—evidence base and standardized methods of imaging. J Nucl Cardiol [Internet]. 2019;26(6):2065–123. https://doi.org/10.1007/s12350-019-01760-6.
19. Sharmila D, Sabahat B, Glaudemans AWJM, Edward M, Renee B-P, et al. ASNC and EANM cardiac amyloidosis practice points (HMDP) imaging for transthyretin cardiac amyloidosis. Am Soc Nucl Cardiol; 2019
20. Imaging P, Amyloidosis C. ASNC cardiac amyloidosis practice points (www.asnc.org).
21. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, et al. Addendum to ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 1 of 2-evidence base and standardized

methods of imaging. J Nucl Cardiol [Internet]. 2021;28(4):1769–74. https://doi.org/10.1007/s12350-020-02455-z.
22. Caobelli F, Braun M, Haaf P, Wild D, Zellweger MJ. Quantitative 99mTc-DPD SPECT/CT in patients with suspected ATTR cardiac amyloidosis: feasibility and correlation with visual scores. J Nucl Cardiol [Internet]. 2019; https://doi.org/10.1007/s12350-019-01893-8.
23. Rapezzi C, Quarta CC, Guidalotti PL, Pettinato C, Fanti S, Leone O, et al. Role of 99mTc-DPD scintigraphy in diagnosis and prognosis of hereditary transthyretin-related cardiac amyloidosis. JACC Cardiovasc Imaging [Internet]. 2011;4(6):659–70. https://doi.org/10.1016/j.jcmg.2011.03.016.
24. Sachchithanantham S, Hutt DF, Quigley AM, Hawkins P, Wechalekar AD. Role of 99mTc-DPD scintigraphy in imaging extra-cardiac light chain (AL) amyloidosis. Br J Haematol. 2018;183(3):506–9.
25. Bokhari S, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. 99mTc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging. 2013;6(2):195–201.
26. Asif T, Gomez J, Singh V, Doukky R, Nedeltcheva A, Malhotra S. Comparison of planar with tomographic pyrophosphate scintigraphy for transthyretin cardiac amyloidosis: perils and pitfalls. J Nucl Cardiol [Internet]. 2021;28(1):104–11. https://doi.org/10.1007/s12350-020-02328-5.
27. Régis C, Harel F, Martineau P, Grégoire J, Abikhzer G, Juneau D, et al. Tc-99m-pyrophosphate scintigraphy for the diagnosis of ATTR cardiac amyloidosis: comparison of quantitative and semi-quantitative approaches. J Nucl Cardiol. 2020;27(5):1808–15.
28. Hutt DF, Quigley AM, Page J, Hall ML, Burniston M, Gopaul D, et al. Utility and limitations of 3,3-diphosphono-1, 2-propanodicarboxylic acid scintigraphy in systemic amyloidosis. Eur Heart J Cardiovasc Imaging. 2014;15(11):1289–98.
29. Sperry BW, Burgett E, Bybee KA, McGhie AI, O'Keefe JH, Saeed IM, et al. Technetium pyrophosphate nuclear scintigraphy for cardiac amyloidosis: Imaging at 1 vs 3 hours and planar vs SPECT/CT. J Nucl Cardiol [Internet]. 2020; https://doi.org/10.1007/s12350-020-02139-8.
30. Masri A, Bukhari S, Ahmad S, Nieves R, Eisele YS, Follansbee W, et al. Efficient 1-hour Technetium-99 m pyrophosphate Imaging protocol for the diagnosis of transthyretin cardiac amyloidosis. Circ Cardiovasc Imaging. 2020;(February):1–9.
31. Hanna M, Ruberg FL, Maurer MS, Dispenzieri A, Dorbala S, Falk RH, et al. Cardiac scintigraphy with technetium-99m-labeled bone-seeking tracers for suspected amyloidosis: JACC review topic of the week. J Am Coll Cardiol. 2020;75(22):2851–62.
32. Quarta CC, Zheng J, Hutt D, Grigore SF, Manwani R, Sachchithanantham S, et al. 99mTc-DPD scintigraphy in immunoglobulin light chain (AL) cardiac amyloidosis. Eur Heart J Cardiovasc Imaging. 2021;22(11):1304–11.
33. Kim SH, Kim YS, Kim SJ. Diagnostic performance of PET for detection of cardiac amyloidosis: a systematic review and meta-analysis. J Cardiol [Internet]. 2020;76(6):618–25. https://doi.org/10.1016/j.jjcc.2020.07.003.
34. Abulizi M, Sifaoui I, Wuliya-Gariepy M, Kharoubi M, Israël JM, Emsen B, et al. 18F-sodium fluoride PET/MRI myocardial imaging in patients with suspected cardiac amyloidosis. J Nucl Cardiol. 2019;
35. Pilebro B, Suhr OB, Näslund U, Westermark P, Lindqvist P, Sundström T. 99mTc-DPD uptake reflects amyloid fibril composition in hereditary transthyretin amyloidosis. Ups J Med Sci. 2016;121(1):17–24.
36. Yadalam A, Ceballos A, Bigham T, Rim A, Yalamanchili S, Brown MT, et al. False negative cardiac scintigraphy in patients with Val122Ile transthyretin cardiac amyloidosis. J Am Coll Cardiol [Internet]. 2022;79(9):427. https://doi.org/10.1016/S0735-1097(22)01418-8.
37. Tshori S, Livschitz S, Volodarsky I, Fabrikant J, George J. Evaluation of ATTR-cardiac amyloidosis employing Tc-99m pyrophosphate scintigraphy using planar, SPECT and gated SPECT imaging on dedicated cardiac CZT camera. Eur Heart J. 2020;41(Supplement_2):2020.

38. Sikanderkhel S, Liu Y-H, Liu C, Miller E. Suv quantification of 99Mtc-Pyp Imaging in Ttr-cardiac amyloidosis using a Czt camera: a new tool in the armamentarium. J Am Coll Cardiol [Internet]. 2018;71(11):A1689. https://doi.org/10.1016/S0735-1097(18)32230-7.
39. Dorbala S, Park MA, Cuddy S, Singh V, Sullivan K, Kim S, et al. Absolute quantitation of cardiac 99mTc-pyrophosphate using cadmium-zinc-telluride-based SPECT/CT. J Nucl Med. 2021;62(5):716–22.
40. Quarta CC, Solomon SD, Uraizee I, Kruger J, Longhi S, Ferlito M, et al. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. Circulation. 2014;129(18):1840–9.
41. Phelan D, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. Heart. 2012;98(19):1442–8.
42. Koyama J, Falk RH. Prognostic significance of strain doppler imaging in light-chain amyloidosis. JACC Cardiovasc Imaging [Internet]. 2010;3(4):333–42. https://doi.org/10.1016/j.jcmg.2009.11.013.
43. Senapati A, Sperry BW, Grodin JL, Kusunose K, Thavendiranathan P, Jaber W, et al. Prognostic implication of relative regional strain ratio in cardiac amyloidosis. Heart. 2016;102(10):748–54.
44. Bellavia D, Pellikka PA, Dispenzieri A, Scott CG, Al-Zahrani GB, Grogan M, et al. Comparison of right ventricular longitudinal strain imaging, tricuspid annular plane systolic excursion, and cardiac biomarkers for early diagnosis of cardiac involvement and risk stratification in primary systematic (AL) amyloidosis: a 5-year cohort stud. Eur Heart J Cardiovasc Imaging. 2012;13(8):680–9.
45. Cappelli F, Porciani MC, Bergesio F, Perlini S, Attanà P, Pignone AM, et al. Right ventricular function in AL amyloidosis: characteristics and prognostic implication. Eur Heart J Cardiovasc Imaging. 2012;13(5):416–22.
46. Patel AR, Dubrey SW, Mendes LA, Skinner M, Cupples A, Falk RH, et al. Right ventricular dilation in primary amyloidosis: an independent predictor of survival. Am J Cardiol. 1997;80(4):486–92.
47. Syed IS, Glockner JF, Feng DL, Araoz PA, Martinez MW, Edwards WD, et al. Role of cardiac magnetic resonance Imaging in the detection of cardiac amyloidosis. JACC Cardiovasc Imaging [Internet]. 2010;3(2):155–64. https://doi.org/10.1016/j.jcmg.2009.09.023.
48. Fontana M, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banypersad SM, et al. Prognostic value of late gadolinium enhancement cardiovascular magnetic resonance in cardiac amyloidosis. Circulation. 2015;132(16):1570–9.
49. Zhao L, Tian Z, Fang Q. Diagnostic accuracy of cardiovascular magnetic resonance for patients with suspected cardiac amyloidosis: a systematic review and meta-analysis. BMC Cardiovasc Disord [Internet]. 2016;16(1):1–10. https://doi.org/10.1186/s12872-016-0311-6.
50. Fontana M, Banypersad SM, Treibel TA, Maestrini V, Sado DM, White SK, et al. Native T1 mapping in transthyretin amyloidosis. JACC Cardiovasc Imaging. 2014;7(2):157–65.
51. Banypersad SM, Sado DM, Flett AS, Gibbs SDJ, Pinney JH, Maestrini V, et al. Quantification of myocardial extracellular volume fraction in systemic AL amyloidosis: an equilibrium contrast cardiovascular magnetic resonance study. Circ Cardiovasc Imaging. 2013;6(1):34–9.
52. Mongeon FP, Jerosch-Herold M, Coelho-Filho OR, Blankstein R, Falk RH, Kwong RY. Quantification of extracellular matrix expansion by CMR in infiltrative heart disease. JACC Cardiovasc Imaging [Internet]. 2012;5(9):897–907. https://doi.org/10.1016/j.jcmg.2012.04.006.
53. Fontana M, Banypersad SM, Treibel TA, Maestrini V, Sado D, White SK, et al. AL and ATTR cardiac amyloid are different: native T1 mapping and ECV detect different biology. J Cardiovasc Magn Reson. 2014;16(S1):1–2.
54. Hutt DF, Fontana M, Burniston M, Quigley AM, Petrie A, Ross JC, et al. Prognostic utility of the Perugini grading of 99m Tc-DPD scintigraphy in transthyretin (ATTR) amyloidosis and its relationship with skeletal muscle and soft tissue amyloid. Eur Heart J Cardiovasc Imaging. 2017;18(12):1344–50.

55. Yamamoto Y, Onoguchi M, Haramoto M, Kodani N, Komatsu A, Kitagaki H, et al. Novel method for quantitative evaluation of cardiac amyloidosis using 201TlCl and 99mTc-PYP SPECT. Ann Nucl Med. 2012;26(8):634–43.
56. Castano A, Haq M, Narotsky DL, Goldsmith J, Weinberg RL, Morgenstern R, et al. Multicenter study of planar technetium 99m pyrophosphate cardiac Imaging: predicting survival for patients with ATTR cardiac amyloidosis. JAMA Cardiol. 2016;1(8):880–9.
57. Sperry BW, Vranian MN, Tower-Rader A, Hachamovitch R, Hanna M, Brunken R, et al. Regional variation in technetium pyrophosphate uptake in transthyretin cardiac amyloidosis and impact on mortality. JACC Cardiovasc Imaging. 2018;11(2):234–42.
58. Ramsay SC, Cuscaden C. The current status of quantitative SPECT/CT in the assessment of transthyretin cardiac amyloidosis. J Nucl Cardiol [Internet]. 2019; https://doi.org/10.1007/s12350-019-01935-1.
59. Minutoli F, Di Bella G, Mazzeo A, Laudicella R, Gentile L, Russo M, et al. Serial scanning with 99mTc-3, 3-diphosphono-1, 2-propanodicarboxylic acid (99mTc-DPD) for early detection of cardiac amyloid deposition and prediction of clinical worsening in subjects carrying a transthyretin gene mutation. J Nucl Cardiol [Internet]. 2019; https://doi.org/10.1007/s12350-019-01950-2.
60. Castaño A, DeLuca A, Weinberg R, Pozniakoff T, Blaner WS, Pirmohamed A, et al. Serial scanning with technetium pyrophosphate (99mTc-PYP) in advanced ATTR cardiac amyloidosis. J Nucl Cardiol. 2016;23(6):1355–63.
61. Martinez-Naharro A, Abdel-Gadir A, Treibel TA, Zumbo G, Knight DS, Rosmini S, et al. CMR-verified regression of cardiac AL amyloid after chemotherapy. JACC Cardiovasc Imaging [Internet]. 2018;11(1):152–4. https://doi.org/10.1016/j.jcmg.2017.02.012.
62. Slart RHJA, Glaudemans AWJM, Hazenberg BPC, Noordzij W. Imaging cardiac innervation in amyloidosis. J Nucl Cardiol. 2019;26(1):174–87.
63. Jonker DL, Hazenberg BPC, Nienhuis HLA, Slart RHJA, Glaudemans AWJM, Noordzij W. Imaging cardiac innervation in hereditary transthyretin (ATTRm) amyloidosis: a marker for neuropathy or cardiomyopathy in case of heart failure? J Nucl Cardiol [Internet]. 2018; https://doi.org/10.1007/s12350-018-01477-y.
64. Flotats A, Carrió I, Agostini D, Le Guludec D, Marcassa C, Schaffers M, et al. Proposal for standardization of 123I-metaiodobenzylguanidine (MIBG) cardiac sympathetic imaging by the EANM cardiovascular committee and the European Council of Nuclear Cardiology. Eur J Nucl Med Mol Imaging. 2010;37(9):1802–12.
65. Pontico M, Brunotti G, Conte M, Corica F, Cosma L, De Angelis C, et al. The prognostic value of 123I-mIBG SPECT cardiac imaging in heart failure patients: a systematic review. J Nucl Cardiol [Internet]. 2021; https://doi.org/10.1007/s12350-020-02501-w.
66. Wan N, Travin MI. Cardiac Imaging with 123I-meta-iodobenzylguanidine and Analogous PET tracers: current status and future perspectives. Semin Nucl Med [Internet]. 2020;50(4):331–48. https://doi.org/10.1053/j.semnuclmed.2020.03.001.
67. Hongo M, Urushibata K, Kai R, Takahashi W, Koizumi T, Uchikawa S, et al. Iodine-123 metaiodobenzylguanidine scintigraphic analysis of myocardial sympathetic innervation in patients with AL (primary) amyloidosis. Am Heart J. 2002;144(1):122–9.
68. Lekakis J, Dimopoulos MA, Prassopoulos V, Mavrikakis M, Gerali S, Sifakis N, et al. Myocardial adrenergic denervation in patients with primary (AL) amyloidosis. Amyloid. 2003;10(2):117–20.
69. Noordzij W, Glaudemans AWJM, Van Rheenen RWJ, Hazenberg BPC, Tio RA, Dierckx RAJO, et al. 123I-labelled metaiodobenzylguanidine for the evaluation of cardiac sympathetic denervation in early stage amyloidosis. Eur J Nucl Med Mol Imaging. 2012;39(10):1609–17.
70. Nakajima K, Matsumoto N, Kasai T, Matsuo S, Kiso K, Okuda K. Normal values and standardization of parameters in nuclear cardiology: Japanese society of nuclear medicine working group database. Ann Nucl Med. 2016;30(3):188–99.

71. Gill JS, Hunter GJ, Gane G, Camm AJ. Heterogeneity of the human myocardial sympathetic innervation: in vivo demonstration by iodine 123-labeled meta-iodobenzylguanidine scintigraphy. Am Heart J. 1993;126(2):390–8.
72. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial Iodine-123 meta-Iodobenzylguanidine Imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView myocardial Imaging for risk evaluation in heart failure) study. J Am Coll Cardiol [Internet]. 2010;55(20):2212–21. https://doi.org/10.1016/j.jacc.2010.01.014.
73. Coutinho MCA, Cortez-Dias N, Cantinho G, Conceição I, Oliveira A, Bordalo E, Sá A, et al. Reduced myocardial 123-iodine metaiodobenzylguanidine uptake: a prognostic marker in familial amyloid polyneuropathy. Circ Cardiovasc Imaging. 2013;6(5):627–36.
74. Coutinho CA, Conceição I, Almeida A, Cantinho G, Sargento L, Vagueiro MC. Early detection of sympathetic myocardial denervation in patients with familial amyloid polyneuropathy type I. Rev Port Cardiol [Internet]. 2004;23(2):201–11. http://europepmc.org/abstract/MED/15116456
75. Phull P, Sanchorawala V, Connors LH, Doros G, Ruberg FL, Berk JL, et al. Monoclonal gammopathy of undetermined significance in systemic transthyretin amyloidosis (ATTR). Amyloid [Internet]. 2018;25(1):62–7. https://doi.org/10.1080/13506129.2018.1436048.
76. Gallini C, Tutino F, Martone R, Ciaccio A, Costanzo EN, Taborchi G, et al. Semi-quantitative indices of cardiac uptake in patients with suspected cardiac amyloidosis undergoing 99mTc-HMDP scintigraphy. J Nucl Cardiol [Internet]. 2021;28(1):90–9. https://doi.org/10.1007/s12350-019-01643-w.
77. Ramsay SC, Lindsay K, Fong W, Patford S, Younger J, Atherton J. Tc-HDP quantitative SPECT/CT in transthyretin cardiac amyloid and the development of a reference interval for myocardial uptake in the non-affected population. Eur J Hybrid Imaging. 2018;2(1):1–13.
78. Scully PR, Morris E, Patel KP, Treibel TA, Burniston M, Klotz E, et al. DPD quantification in cardiac amyloidosis: a novel Imaging biomarker. JACC Cardiovasc Imaging. 2020;13(6):1353–63.
79. Miller RJH, Cadet S, Mah D, Pournazari P, Chan D, Fine NM, et al. Diagnostic and prognostic value of technetium-99m pyrophosphate uptake quantitation for transthyretin cardiac amyloidosis. J Nucl Cardiol [Internet]. 2021;28(5):1835–45. https://doi.org/10.1007/s12350-021-02563-4.
80. Bravo PE, Di Carli MF, Dorbala S. Role of PET to evaluate coronary microvascular dysfunction in non-ischemic cardiomyopathies. Heart Fail Rev. 2017;22(4):455–64.
81. Dorbala S, Vangala D, Bruyere J, Quarta C, Kruger J, Padera R, et al. Coronary microvascular dysfunction is related to abnormalities in myocardial structure and function in cardiac amyloidosis. JACC Hear Fail. 2014;2(4):358–67.
82. Migrino RQ, Truran S, Gutterman DD, Franco DA, Bright M, Schlundt B, et al. Human microvascular dysfunction and apoptotic injury induced by AL amyloidosis light chain proteins. Am J Physiol Heart Circ Physiol. 2011;301(6):2305–12.
83. Al Suwaidi J, Velianou JL, Gertz MA, Cannon RO, Higano ST, Holmes DR, et al. Systemic amyloidosis presenting with angina pectoris. Ann Intern Med. 1999;131(11):838–41.
84. Morgenstern R, Yeh R, Castano A, Maurer MS, Bokhari S. 18Fluorine sodium fluoride positron emission tomography, a potential biomarker of transthyretin cardiac amyloidosis. J Nucl Cardiol. 2018;25(5):1559–67.
85. Martineau P, Finnerty V, Giraldeau G, Authier S, Harel F, Pelletier-Galarneau M. Examining the sensitivity of 18F-NaF PET for the imaging of cardiac amyloidosis. J Nucl Cardiol. 2021;28:209–18.
86. Zhang LX, Martineau P, Finnerty V, Giraldeau G, Parent MC, Harel F, et al. Comparison of 18F-sodium fluoride positron emission tomography imaging and 99mTc-pyrophosphate in cardiac amyloidosis. J Nucl Cardiol. 2022;29:1132–40.

87. Kim YJ, Ha S, Kim Y, il. Cardiac amyloidosis imaging with amyloid positron emission tomography: a systematic review and meta-analysis. J Nucl Cardiol [Internet]. 2020;27(1):123–32. https://doi.org/10.1007/s12350-018-1365-x.
88. Antoni G, Lubberink M, Estrada S, Axelsson J, Carlson K, Lindsjö L, et al. In vivo visualization of amyloid deposits in the heart with 11C-PIB and PET. J Nucl Med. 2013;54(2):213–20.
89. Rosengren S, Skibsted Clemmensen T, Tolbod L, Granstam SO, Eiskjær H, Wikström G, et al. Diagnostic accuracy of [11C]PIB positron emission tomography for detection of cardiac amyloidosis. JACC Cardiovasc Imaging. 2020;13(6):1337–47.
90. Dorbala S, Vangala D, Semer J, Strader C, Bruyere JR, Di Carli MF, et al. Imaging cardiac amyloidosis: a pilot study using 18F-florbetapir positron emission tomography. Eur J Nucl Med Mol Imaging. 2014;41(9):1652–62.
91. Osborne DR, Acuff SN, Stuckey A, Wall JS. A routine PET/CT protocol with streamlined calculations for assessing cardiac amyloidosis using 18F-florbetapir. Front Cardiovasc Med. 2015;2(May):1–9.
92. Law WP, Wang WYS, Moore PT, Mollee PN, Ng ACT. Cardiac amyloid imaging with 18F-Florbetaben PET: a pilot study. J Nucl Med. 2016;57(11):1733–9.
93. Genovesi D, Vergaro G, Giorgetti A, Marzullo P, Scipioni M, Santarelli MF, et al. [18F]-Florbetaben PET/CT for differential diagnosis among cardiac immunoglobulin light chain, transthyretin amyloidosis, and mimicking conditions. JACC Cardiovasc Imaging. 2021;14(1):246–55.
94. Kircher M, Ihne S, Brumberg J, Morbach C, Knop S, Kortüm KM, et al. Detection of cardiac amyloidosis with 18F-Florbetaben-PET/CT in comparison to echocardiography, cardiac MRI and DPD-scintigraphy. Eur J Nucl Med Mol Imaging. 2019;46(7):1407–16.

Chapter 20
Genetics and Epigenetics of Transthyretin Amyloidosis

Marcelo Imbroinise Bittencourt and Adriana Bastos Carvalho

20.1 Genetics

20.1.1 TTR Structure and Function

Transthyretin, encoded by the TTR gene, is one of the major amyloidogenic proteins in systemic amyloidosis. It is mainly synthesized by the liver but also by the choroid plexus in the brain, pancreatic islets, and retinal epithelial cells. The presence of genetic variants in TTR causes hereditary (or familial) amyloidosis, which is the most common autosomal-dominant form of the disease [1–3].

The protein was originally discovered in the cerebrospinal fluid (CSF) in 1942 and subsequently found in plasma samples. Its function is related to the transport of thyroxine (T4) and retinol binding protein (RBP), which, in turn, is a carrier for retinol. The name transthyretin is derived from the molecules that it *trans*ports: *thy*roxine and *retin*ol (through RBP) [1].

TTR is in the long arm of chromosome 18 and has a length of 7 kb and four exons. Exon 1 codes for a signaling peptide of 20 amino acids, which is removed before extracellular secretion, and the first three residues of the mature protein. Exon 2 codes for amino acid residues 4–47, exon 3 codes for residues 48–92, and exon 4 codes for residues 93–127. Hence, TTR is composed of a total of 147 amino

M. I. Bittencourt (✉)
UERJ, Rio de Janeiro, RJ, Brazil

HUPE/UERJ, Rio de Janeiro, RJ, Brazil

Geneone—DASA, Rio de Janeiro, RJ, Brazil
e-mail: mib@cardiol.br

A. B. Carvalho
Instituto de Biofísica Carlos Chagas Filho—UFRJ, Rio de Janeiro, RJ, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_20

acids, but only 127 are present in the mature protein [4]. Each exon encodes one of four monomers that circulate as a homotetramer with a central channel. Each monomer consists of eight β-strands that form two β-sheets. TTR dimers are formed via hydrogen bonds between two monomers, while tetramers are formed by hydrophobic dimer-dimer interactions. Each homotetramer has two binding sites for thyroxine and four binding sites for RBP; however, due to negative cooperativity, TTR only binds one thyroxine and two RBP molecules. In addition, TTR only binds RBP if it is bound to retinol [1, 2].

Several mouse models have been generated to demonstrate the role of TTR in amyloidosis in vivo. The first model, published in 1991, introduced the human Val30Met mutation in mice and showed amyloid deposition at 24 months of age [5]. Interestingly, further studies showed that human TTR reaches the adult level in the serum of these mice at one month of age, although amyloid deposition only started at nice months of age [6]. This underscores the importance of aging and environmental factors to the development of the phenotype (see Epigenetics).

20.1.2 Clinical and Populational Features of Amyloidosis

Transthyretin amyloidosis (ATTR) is a disease caused by fibrils derived from transthyretin that deposit in tissues and organs such as the heart and nerves. Because it has been part of the rare disease scenario for a long time, it was always difficult to make the diagnosis [7]. However, with advances in the methods of cardiac imaging and the wider use of genetic tests, this reality has changed in recent years [8, 9]. Patients are being identified in early stages of the disease, especially those with ATTR, which, together with the AL form, are responsible for most cases of amyloid cardiomyopathy. ATTR can be subclassified into wild-type ATTR when TTR gene sequencing is normal or hereditary ATTR when such sequencing reveals a disease-causing genetic variant. The clinical manifestations that may occur in ATTR are peripheral small fiber neuropathy, autonomic neuropathy, cardiomyopathy, or a mixed phenotype. This variable expressivity is related to the type of variant, geographic distribution, and age of onset.

20.1.3 Epidemiology and types of variants

There are approximately 140 genetic variants in the TTR gene, mostly in exons 2 and 3 [4]. Knowledge of disease-causing genetic variants in ATTR is important because we are often able to correlate specific genotypes with clinical presentations, age of onset, organs involved, and prognosis. Some known ATTR genotypes with their respective characteristics are detailed in Table 20.1 [8].

Some variants are endemic in certain places. The Val122Ile (Val142Ile) variant is the most common in the US, with a known prevalence in Afro Americans [10]. It is

Table 20.1 Genetic variants determining hereditary ATTR (adapted from Ref. [8])

	Val122Ile	Thr60Ala	Val30Met	Ile68Leu	Leu111Met
Prevalence	3–4% Afro-american	1% Irish	Worldwide mutation	Unknown	Unknown
Age of onset (Years)	>65	>60	30–40 in endemic áreas, 50–60 in nonendemic areas	>60	>30
Male: Female	3:1	Unknown	2:1	Male predominance	Unknown
Ethnicity	African/ Afrocaribbean	Caucasian	N/A	Caucasian	Danish
Geographic distribution	USA, Caribbean, Africa	USA, Ireland, Germany, England	Sweden, France, Portugal, Japan	Italy	Denmark
Cardiac phenotype	Always present	42%	Late onset cases	Present	Always present
Extracardiac manifestations	Peripheral neuropathy (10%) and carpal tunnel syndrome	Peripheral neuropathy	Peripheral and autonomic neuropathy	Carpal tunnel syndrome	Carpal tunnel syndrome

a common cause of heart failure in this population, especially among the elderly [11, 12]. Another very frequent variant is Thr60Ala, present in 20% of patients in the THAOS registry [13]. Similar to the Val122Ile variant, it also has late penetrance and predominates in men. However, the clinical phenotype is mixed, associating cardiomyopathy and autonomic neuropathy [14]. The Val30Met (Val50Met) variant, on the other hand, is associated with Portuguese ancestry and is the one most found worldwide. When it manifests early symptoms, it is primarily a neurological disease, with virtually no restrictive cardiomyopathy [8, 15]. In the late onset type, cardiac involvement is very common [16]. Both the Val122Ile (or Val142Ile) and Val30Met (Val50Met) variants are present in the Brazilian population [17].

20.1.4 Inheritance and Penetrance Patterns

Hereditary ATTR is an autosomal-dominant disease; therefore, it is common to find patients carrying the genotype in all generations of a family [8]. However, it has quite variable penetrance in the different variants. A curious case is the variant Val30Met (Val50Met), which starts early and has high penetrance in endemic areas (Portugal and Japan), while in nonendemic areas (Sweden), it starts later and has low penetrance. Other studies show that the Val122Ile variant has low and age-related penetrance (approximately 60 years old) [18, 19]. Therefore, we always perform genetic testing when ATTR is diagnosed (see item iii), regardless of family history.

20.1.5 Family screening

Family screening is the main indication for genetic testing in patients with ATTR. In the most diverse approaches already published, genetic evaluation is consensually indicated for all to differentiate wild-type ATTR from hereditary ATTR (Fig. 20.1). It is important to emphasize that both forms differ in terms of prognosis, possibility of cardiac involvement, and need for family counseling [17]. The entire TTR gene must be sequenced, not just the most frequent variants. When identifying a pathogenic or probably pathogenic variant, we must search for it in relatives following the genetic cascade.

After identifying asymptomatic carriers of the disease-causing variant, the question that arises is: What is the time to start monitoring, since it is a disease that starts late? Recent publications have been seeking strategies for this issue, as we can see in Fig. 20.2 [8]

It is currently recommended to start monitoring asymptomatic carriers 10 years before the presumptive age of disease onset [8, 20]. It is essential to identify the beginning of the disease because of the opportunity to start specific treatment. Drugs with the property of stabilizing or even silencing the production of the TTR protein have changed the natural history of the disease when started early. We emphasize the need for pre- and postgenetic testing counseling in these patients to clarify the advantages, disadvantages, and challenges of the exam, especially to minimize the psychological impacts on the patient and family that may come with the result. Multidisciplinary approaches involving cardiologists, geneticists, and psychologists can contribute to this goal.

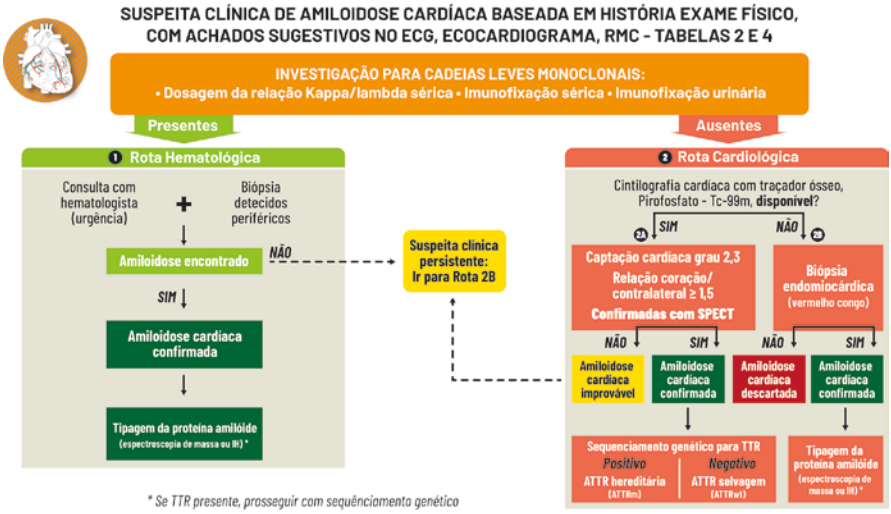


Fig. 20.1 Approach to the patient with clinical suspicion of cardiac amyloidosis [4]

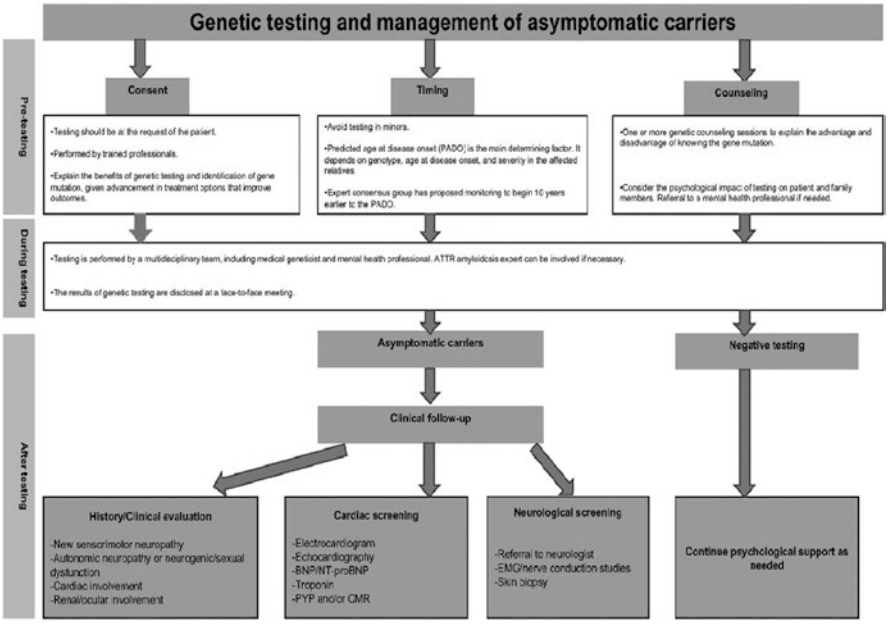


Fig. 20.2 Approach to the asymptomatic carrier [8]

20.1.6 Clinical Applicability of Genetic Testing

Genetic evaluation is fundamental in identifying the genotypes that will determine the different clinical phenotypes and prognosis. In addition, it provides the opportunity to follow individuals in a preclinical situation. In these cases, clinical evaluation is recommended, looking for signs and symptoms of cardiac, neurological, and dysautonomia involvement [21]. In a study published by Damy T et al., using the combination of genetic testing with NT-PROBNP, it was possible to diagnose familial amyloidotic polyneuropathy as well as to identify with great precision the moment when carriers of the familial mutation (half of them Val50Met) began to develop cardiomyopathy [22]. Other tests that are used in this monitoring of disease onset are troponin dosage, electrocardiogram, echocardiogram, pyrophosphate scintigraphy, and cardiac magnetic resonance.

20.2 Epigenetics

Although all cells in the human body possess near-identical DNA sequences, specialized tissues are differentiated in their function by gene expression profiles. This is largely controlled by epigenetics, which refers to the study of modifications in

DNA, such as methylation and histone modifications [23, 24]. Methylation consists in the addition of methyl groups to nucleotides that lead to modifications of DNA structure and repression of gene transcription by reducing availability to the transcriptional machinery. Histone modifications, such as acetylation, methylation, phosphorylation, and ubiquitination, also play an important role in epigenetics through the control of chromatin structure [23, 24]. Depending on the type of modification, gene transcription may be activated or repressed.

Epigenetics is also one of the mechanisms responsible for incomplete penetrance and variable expressivity in patients harboring the same pathogenic variants. In a study of epigenomic profiles of African Americans with Val122Ile variant, researchers found that heart disease was associated with differentially methylated sites in genes involved in transport and clearance of amyloid deposits and cardiac fibrosis [25]. Epigenetics might also help to explain why the symptoms of amyloidosis caused by this variant are presented with a later onset (after age 60-70). The concept of "epigenetic clocks" demonstrates the mechanistic role played by epigenetics in aging: the measurement of specific methylation sites can predict chronological age in several species, including humans [26]. Therefore, such age-related modifications might regulate the expression of genes that are important for the development of the phenotype.

References

1. Ueda M. Transthyretin: Its function and amyloid formation. Neurochem Int. 2022;155:105313.
2. Liz MA, Coelho T, Bellotti V, Fernandez-Arias MI, Mallaina P, Obici L. A narrative review of the role of transthyretin in health and disease. Neurol Ther. 2020;9(2):395–402.
3. Gopal DM, Ruberg FL, Siddiqi OK. Impact of genetic testing in transthyretin (ATTR) cardiac amyloidosis. Curr Heart Fail Rep. 2019 Oct;16(5):180–8.
4. Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy [Internet]. Muscle Nerve. 2007;36:411–23. https://doi.org/10.1002/mus.20821.
5. Yi S, Takahashi K, Naito M, Tashiro F, Wakasugi S, Maeda S, et al. Systemic amyloidosis in transgenic mice carrying the human mutant transthyretin (Met30) gene. Pathologic similarity to human familial amyloidotic polyneuropathy, type I. Am J Pathol. 1991 Feb;138(2):403–12.
6. Takaoka Y, Tashiro F, Yi S, Maeda S, Shimada K, Takahashi K, et al. Comparison of amyloid deposition in two lines of transgenic mouse that model familial amyloidotic polyneuropathy, type I. Transgenic Res. 1997;6:261–9. https://doi.org/10.1023/a:1018454527309.
7. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail. 2019 Sep;12(9):e006075.
8. Alreshq R, Ruberg FL. Clinical approach to genetic testing in amyloid cardiomyopathy: from mechanism to effective therapies [Internet]. Curr Opin Cardiol. 2021;36:309–17. https://doi.org/10.1097/hco.0000000000000841.
9. Martinez-Naharro A, John Baksi A, Hawkins PN, Fontana M. Diagnostic imaging of cardiac amyloidosis [Internet]. Nat Rev Cardiol. 2020;17:413–26. https://doi.org/10.1038/s41569-020-0334-7.
10. Jacobson DR, Pastore RD, Yaghoubian R, Kane I, Gallo G, Buck FS, et al. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans [Internet]. New Engl J Med. 1997;336:466–73. https://doi.org/10.1056/nejm199702133360703.

11. Buxbaum J, Alexander A, Koziol J, Tagoe C, Fox E, Kitzman D. Significance of the amyloidogenic transthyretin Val 122 Ile allele in African Americans in the Arteriosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) Studies [Internet]. Am Heart J. 2010;159:864–70. https://doi.org/10.1016/j.ahj.2010.02.006.
12. Damrauer SM, Chaudhary K, Cho JH, Liang LW, Argulian E, Chan L, et al. Association of the V122I hereditary transthyretin amyloidosis genetic variant with heart failure among individuals of African or Hispanic/Latino ancestry. JAMA. 2019;322(22):2191–202.
13. Maurer MS, Hanna M, Grogan M, Dispenzieri A, Witteles R, Drachman B, et al. Genotype and phenotype of transthyretin cardiac amyloidosis [Internet]. J Am Coll Cardiol. 2016;68:161–72. https://doi.org/10.1016/j.jacc.2016.03.596.
14. Sattianayagam PT, Hahn AF, Whelan CJ, Gibbs SDJ, Pinney JH, Stangou AJ, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant [Internet]. Eur Heart J. 2012;33:1120–7. https://doi.org/10.1093/eurheartj/ehr383.
15. Rapezzi C, Quarta CC, Riva L, Longhi S, Gallelli I, Lorenzini M, et al. Transthyretin-related amyloidoses and the heart: a clinical overview [Internet]. Nat Rev Cardiol. 2010;7:398–408. https://doi.org/10.1038/nrcardio.2010.67.
16. Suhr OB, Lindqvist P, Olofsson B-O, Waldenström A, Backman C. Myocardial hypertrophy and function are related to age at onset in familial amyloidotic polyneuropathy [Internet]. Amyloid. 2006;13:154–9. https://doi.org/10.1080/13506120600876849.
17. Simões Mv Correia Eb Fernandes. Amiloidose Cardíaca. In: Albuqueque JAF, editor. Insuficiência cardíaca DEIC-SBC. Manole; 2021.
18. Yamashita T, Asl KH, Yazaki M, Benson MD. A prospective evaluation of the transthyretin Ile122 allele frequency in an African-American population [Internet]. Amyloid. 2005;12:127–30. https://doi.org/10.1080/13506120500107162.
19. Quarta CC, Cristina Quarta C, Buxbaum JN, Shah AM, Falk RH, Claggett B, et al. The amyloidogenic V122I transthyretin variant in elderly black Americans [Internet]. N Engl J Med. 2015;372:21–9. https://doi.org/10.1056/nejmoa1404852.
20. Conceição I, Damy T, Romero M, Galán L, Attarian S, Luigetti M, et al. Early diagnosis of ATTR amyloidosis through targeted follow-up of identified carriers of TTR gene mutations. Amyloid. 2019;26(1):3–9.
21. Dyck PJB, González-Duarte A, Obici L, Polydefkis M, Wiesman JF, Antonino I, et al. Development of measures of polyneuropathy impairment in hATTR amyloidosis: From NIS to mNIS 7 [Internet]. J Neurol Sci. 2019;405:116,424. https://doi.org/10.1016/j.jns.2019.116424.
22. Damy T, Deux J-F, Moutereau S, Guendouz S, Mohty D, Rappeneau S, et al. Role of natriuretic peptide to predict cardiac abnormalities in patients with hereditary transthyretin amyloidosis. Amyloid. 2013;20(4):212–20.
23. Berdasco M, Esteller M. Clinical epigenetics: seizing opportunities for translation. Nat Rev Genet. 2019;20(2):109–27.
24. Alaskhar Alhamwe B, Khalaila R, Wolf J, von Bülow V, Harb H, Alhamdan F, et al. Histone modifications and their role in epigenetics of atopy and allergic diseases. Allergy Asthma Clin Immunol. 2018;14:39.
25. Pathak GA, Wendt FR, De Lillo A, Nunez YZ, Goswami A, De Angelis F, et al. Epigenomic profiles of African American *Transthyretin* Val122Ile carriers reveals putatively dysregulated amyloid mechanisms [Internet]. https://doi.org/10.1101/2020.04.15.20066621.
26. Unnikrishnan A, Freeman WM, Jackson J, Wren JD, Porter H, Richardson A. The role of DNA methylation in epigenetics of aging [Internet]. Pharmacol Ther. 2019;195:172–85. https://doi.org/10.1016/j.pharmthera.2018.11.001.

Chapter 21
Cardiopulmonary Exercise Testing and Cardiac Rehabilitation in Amyloidosis

Ricardo Vivacqua Cardoso Costa, Salvador Manoel Serra, and Ivana Burazor

21.1 Cardiopulmonary Exercise Testing

Through direct measurements of respiratory gases, cardiopulmonary exercise testing (CPET) allows a physiological assessment of the functional condition and multifactorial analysis of metabolic, ventilatory, and hemodynamic variables.

It can provide critical prognostic parameters, especially in patients with heart failure [1]. Heart failure (HF) is a prevalent disease with reduced survival and is one of the leading causes of hospitalization and death in several countries, including Brazil [2]. Patients with HF exhibit a worse prognosis than the general population. However, there seems to be no difference in overall mortality regarding the HF subtypes when stratified by preserved, intermediate, or reduced ejection fraction [3].

The CPET makes it possible to obtain variables of important prognostic accuracy that define conduct, such as the selection of candidates for heart transplantation, left ventricular assist devices, and cardiac rehabilitation programming. It is essential to know which parameters can best stratify the higher risk of mortality [4]. It is a procedure that allows the objective and quantitative assessment of functional capacity by measuring the volume of oxygen consumption at peak effort ($V'O_2$ peak), which, when lower than 14 mL kg^{-1} min^{-1}, expresses greater severity; the relationship between ventilation and production of carbon dioxide volume ($VE/V'CO_2$) and obtaining the slope by linear regression of the $VE/V'CO_2$ ratio, greater than 34, is

R. V. C. Costa (✉)
Hospital Procardiaco, Rio de Janeiro, Brazil

S. M. Serra
Instituto Estadual de Cardiologia Aloysio de Castro, Rio de Janeiro, Brazil

I. Burazor
Institute for Cardiovascular Diseases 'Dedinje', University of Belgrade, Faculty of Medicine, Belgrade, Serbia

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_21

also of expressive importance in the prognostic assessment of patients with chronic heart failure [5].

Other variables are also used to assess a worse prognosis. Oxygen pulse ($V'O_2$/heart rate), related to systolic volume, lower than 12 mL kg^{-1} min^{-1}/bpm indicates left ventricular dysfunction [6]. Oxygen kinetics (or T 1/2) is the time in seconds after maximal effort in which peak $V'O_2$ is reduced by 50% when above 120s. It indicates the risk of mortality and central cardiovascular dysfunction [4]. OUES (oxygen uptake efficiency slope) slope of oxygen consumption efficiency ($V'O_2$) concerns the logarithm of ventilation base 10 [7]. Circulatory power consists of the product of peak $V'O_2$ by systolic blood pressure. Values below 2389 mL/mmHg, without beta-blockers, and below 1530 mL/mmHg, with the use of beta-blockers, characterize patients with an unfavorable prognosis [8]; $V'O_2$ at the anaerobic threshold, when lower than 11 mL kg^{-1} min^{-1}, is considered more severe and has a worse prognosis [9].

Studies consider the $VE/V'CO_2$ slope a guiding parameter in the therapy and prognosis of patients with CHF [10] and the ventilatory and functional classification [11]. Other authors highlight the ventilatory efficiency ($VE/V'CO_2$ slope) at the submaximal effort and the circulatory power at the maximum effort as predictors for heart transplantation, artificial ventricle implantation, or death [9].

Research on cardiorespiratory functional assessment in patients with amyloidosis highlights peak $V'O_2$ [12] and ventilatory efficiency [13] as prognostic inference parameters for survival or death in these patients.

Study on CPET in amyloidosis [14] came up with the following results of prognostic value, rehospitalization or death: peak $V'O_2$ less than or equal to 13.0 mL kg^{-1} min^{-1}, circulatory power equal to and less than 1730 mmHg/min/mL/min, slope $VE/V'CO_2$ greater than 37. Additionally, NTproBNP was greater than or equal to 1800 ng/L. Patients with cardiac amyloidosis AL (immunoglobin light chain) and TTR (transsterritin) were selected.

No significant differences in the prognosis for mortality or hospital admission were observed between the two types of cardiac amyloidosis. They consider that amyloidosis can affect other organs, such as the liver, kidneys, and peripheral innervation, leading to important physical deconditioning.

It has been shown that cardiovascular rehabilitation improves the functional condition, mainly due to the beneficial effects in improving peripheral oxidative function [15].

The authors conclude that the CPET performed in patients with amyloidosis can provide determinants of exercise intolerance with relevant prognostic information. In addition, peak $V'O_2$ and circulatory power were also considered independent predictors of death or hospitalization in patients with AL and TTR cardiac amyloidosis [14].

21.2 Cardiac Rehabilitation

It is universally recognized and scientifically based that, except under conditions that contraindicate it, staying physically active and adopting proper lifestyle habits prevent and treat heart disease.

Rehabilitation programs for patients with heart disease are currently indicated for reducing cardiovascular and global morbidity and mortality, reducing the hospitalization rate, and improving patients' functional condition and quality of life, justifying their emphatic recommendation by medical societies worldwide (Fig. 21.1) [16–22]. However, similar to the beginnings of the treatment of heart diseases, whose emphasis was exclusively on drug and/or surgical treatment, programs and guidelines for rehabilitation applied to patients with amyloidosis are still very limited.

Although it is an uncommon disease, the recent attention directed to it has increased its diagnosis, with an appreciation of the need for its precocity. This attitude avoids greater severity and mortality, expressing the potential value of expanding the spectrum of treatment, including specific rehabilitation programmes, in a patient with amyloidosis.

Depending on the modality, patients with amyloidosis may have localized involvement, with amyloid protein deposits in specific parts of the body not reaching the body as a whole. However, there is often involvement of the heart, eyes, kidneys, central and peripheral nervous system, and liver. In addition, nonspecific clinical manifestations are frequently observed and include fatigue, weight loss, peripheral edema, and orthostatic hypotension, increasing the risk of falls and worsening the patients' condition [23, 24].

Cardiac amyloidosis is a disease that tends to worsen, usually progressing to heart failure due to ventricular wall thickening and restrictive heart disease with progressive stiffening and resistance to ventricular filling. The atria can also be affected, more commonly in elderly individuals, and obstructions in the coronary arteries and their severe consequences can occur [25].

The evolutionary process involving multiple organs requires a broad understanding of the patients' rehabilitation process. In this sense, it is crucial to emphasize lifestyle changes within individual limitations to those with stable amyloidosis.

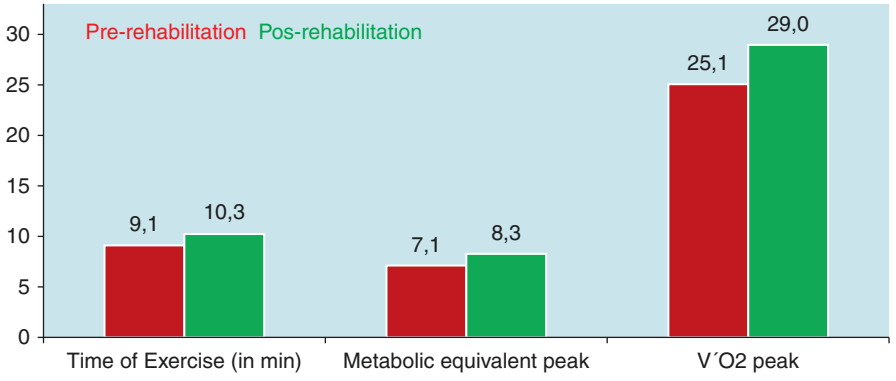


Fig. 21.1 The effect of a cardiac rehabilitation program, with 50 sessions of supervised physical exercise in an in-hospital environment, showed a significant increase of 17% in the patients' average maximal aerobic condition, resulting in a reduction in mortality of approximately 13%

21.3 Healthy Lifestyle

Rehabilitation programs must involve several behaviors that allow for better quality and a potential perspective of a longer life span. They're part:

1. Encouraging the proper use of prescribed medication.
2. Permanent cessation of smoking.
3. Stress management and adequate sleep hours.
4. Adherence to healthy eating.
5. Regular practice of physical activity.

To universally achieve all these rehabilitation goals for patients who may have a broad functional impairment, doctors from other specialties should participate in rehabilitation. Other professionals, such as psychologists, nutritionists, physical educators, and physiotherapists, can also participate.

21.4 Physical Activity

Patients with amyloidosis often have involvement of organs other than the heart. Therefore, it is evident that there is the need to identify conditions that may eventually limit or contraindicate the practice of regular physical exercise. If there are no more significant restrictions, the individualized prescription of activities may be similar to that usually directed to patients with heart failure and/or coronary artery disease [26].

Rehabilitation programs usually include exercise modalities with aerobic components when patients walk and/or cycle. After the essential assessment of the patient's clinical condition, the six-minute walk test, the performance of an exercise stress test or cardiopulmonary exercise test (CPET) allows the assessment of limiting symptoms or not, possible motor difficulties, changes in blood pressure or in the electrocardiogram—either the presence of myocardial ischemia or arrhythmogenic potential—and the patient's tolerance and functional limitation to exercise. Such an evaluation will make it possible to contraindicate or indicate these exercises and identify the intensity to be prescribed during the sessions.

In the absence of limitations identified in the exercise test, the exercise intensity may be based on the heart rate (HR), ranging from 60% to 80% of the difference between the maximum HR reached in the test and the HR before starting the exam, and add this result with the same pretest HR, with a variation of 5 beats more or less [26]. With CPET, the training HR should be the one just below the anaerobic threshold, increasing progressively until the HR is below the respiratory compensation point, also with a variation of 5 beats and depending on the patient's functional evolution and the absence of symptoms or other changes [27].

The subjective feeling of tiredness, assessed using the Borg scale, should also be used, starting with intensity from grades 2 to 3 to, if possible, grades 5 to 7 on the scale from 0 to 10.

Not exclusively, but of even greater importance in patients with amyloidosis, a condition that may have additional limitations with involvement of multiple organs, exercises should be preceded by a warm-up period and followed by a progressive reduction in intensity.

Muscle strength exercises should also be applied and involve most muscle groups, with 8 to 15 repetitions at an intensity of 30–40% of one repetition maximum. With the adaptation and increase in strength, the tendency is to progressively increase the intensity of the percentage of a maximum repetition, not exceeding 70%, and, concomitantly, to decrease the number of repetitions [27]. Similar values of the subjective feeling of tiredness on the Borg scale should also be used for muscle strengthening exercises.

Balance, motor coordination, flexibility, stretching exercises, and respiratory muscle strengthening exercises should be included in physical exercise sessions, particularly in elderly patients, who benefit even more from them, as well as patients with heart failure and pulmonary functional impairment [27]. It is important to note that amyloidosis more frequently affects individuals in a higher age group.

Thus, in recent years, there has been a need to update the core components of cardiac rehabilitation intervention in traditional and new qualifying diagnoses for referral. It was recommended that all patients should be enrolled in an exercise-based cardiac rehabilitation programme with multiple facets. Inpatient rehabilitation should begin as soon as possible after hospital admission, while structured outpatient cardiac rehabilitation is crucial for the development of a lifelong approach. The new proposed model, home-based individual cardiac rehabilitation (alone or in combination with center-based cardiac rehabilitation), is also feasible using technology-based telemedicine programmes, in combination with home visits and telephone support when appropriate [28]. Further research and registries are required to investigate the impact of those programmes on amyloidosis patients.

21.5 Conclusion

The diversity of presentations of amyloidosis requires individual aspects of initial assessment and constant proximity and monitoring of patients during activities. However, the expansion of the rehabilitation experience, still very restricted in this condition, may promote the adoption of procedures with potential benefits to patients affected by amyloidosis. Furthermore, the improvement in physical fitness, the increase in oxygen consumption at peak exercise, and favorable effects on other vital variables, conditions usually promoted by cardiac rehabilitation, can potentially promote an improvement in the quality and, possibly, in the life expectancy of the patients.

References

1. Guazzi M, Bandera F, Ozemek C, Systrom D, Arena R. Cardiopulmonary exercise testing: what is its value? J Am Coll Cardiol. 2017;70(13):1618–36.
2. Diretrizes Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436–539.
3. Delepaul B, Robin G, Delmas C, Moine T, Blanc A, Fournier P, et al. Who are patients classified within the new terminology of heart failure from the 2nd ESC guidelines? ESC Heart Fail. 2017;4(2):99–104.
4. Ávila DX, Vivacqua RC, Serra S, Montera MW, Tinoco E, Siciliano A. The unssurpassed value of cardiopulmonary exercise testing in assessing the prognosis of heart failure. ESC Congress. 2020:554702.
5. Robbins M, Francis G, Pashkow FJ, Snader CE, Hoercher K, Young JB, Lauer MS. Ventilatory and heart rate responses to exercise: better predictors of heart failure mortality than peak oxygen consumption. Circulation. 1999;100(24):2411–7.
6. Oliveira RB, Myers J, Araujo CGS, Abella J, Mandic S, Froelicher V. Maximal exercise oxygen pulse as a predictor of mortality among male veterans referred for exercise testing. Eur J Cardiovasc Prev Rehabil. 2009;16:358–64.
7. Hollemberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. J Am Coll Cardiol. 2000;36:194–201.
8. Cohen-Solal A, Tabet JY, Logeart D, Bourgain P, Tokmakova M, Dahan M. A noninvasibiliy determined surrogate of cardiac power ("circulatory power") at peak exercise is a powerful prognostic factor in chronic heart failure. Eur Heart J. 2002;23:814.
9. Lala A, Shah KB, Lanfear E, Thibodeau JT, Palardy M, et al. Predictive value of cardiopulmonary exercise testing parameters in ambulatory advanced heart failure. J Am Coll Cardiol HF. 2021;9:226–36. https://doi.org/10.1016/j.chf.2020.11.008.
10. Agostini P, Sciomer S, Palermo P, et al. Minute ventilation/carbon dioxide production in chronic heart failure. Eur Respir Rev. 2021;30:200141. https://doi.org/10.1183/16000617.0141-2020.
11. Guazzi M, Borlaung B, Metra M, Losito M, Bandera F. et al. Revisiting and implementing the Weber and ventilatory functional classifications in heart failure by cardiopulmonary imaging phenotyping, J Am Heart Assoc. 10:e018822. https://doi.org/10.1161/JAHA.120.018822.
12. Hein S, Aus Dem Siepen F, Bauer R, Katus HA, Kristen AV. Peak V'O_2 is an independent predictor of survival in patients with cardiac amyloidosis. Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis. 2018;25(3):167–73.
13. Yunis A, Doros G, Luptak I, Connoros LH, Sam F. Use of ventilatory efficiency slope as marker for increased mortality in wild-type transthyretin cardiac amyloidosis. Am J Cardiol. 2019;124(1):122–30.
14. Nicol M, Deney A, Vergaro G, Emdin M, Carecci A, et al. Prognostic value of cardiopulmonary exercise testing in cardiac amyloidosis. Eur J Heart Fail. https://doi.org/10.1002/ejhf.2016.
15. Vivacqua CR, Nóbrega ACL, Serra SM, et al. Influence of skeletal muscle mass on ventilatory and hemodynamic variables during exercise in patients with chronic heart failure. Arq Bras Cadiol. 2003;81(6):576–80.
16. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. J Am Coll Cardiol. 2016;67(1):1–12.
17. Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, et al. Exercise based rehabilitation for heart failure. Cochrane Database Syst Rev. 2014;(4):CD003331.
18. Muela HCS, Bassan R, Serra SM. Avaliação dos benefícios funcionais de um programa de reabilitação cardíaca. Rev Bras Cardiol. 2011;24(4):241–50.
19. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint Task Force of

the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315–81.
20. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128(8):873–934.
21. Task Force M, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949–3003.
22. Herdy AH, Lopez-Jimenez F, Terzic CP, Milani M, Stein R, Carvalho T, et al. Consenso Sul-Americano de Prevenção e Reabilitação Cardiovascular. Arq Bras Cardiol. 2014;103(2 Suppl 1):1–31.
23. Simões MV, Fernandes F, Marcondes-Brazão F, et al. Posicionamento sobre diagnóstico e tratamento da amiloidose cardíaca – 2021. Arq Bras Cardiol. 2021;117(3):561–98.
24. Redder E, Compston A, Efebera A. Rehabilitation of the amyloidosis patient. JNCCN. 2020;18(3):5.
25. Júnior ESP, Silva MVS, Cerqueira PA. Amiloidose cardíaca: etiologia, aspectos clínicos, diagnóstico e tratamento. RevSaúde.com. 2019;15(3):1596–9.
26. Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate: a longitudinal study. Ann Med Exp Biol Fenn. 1957;35(3):307–15.
27. Bassan F, Serra S. Manual da síndrome coronariana crônica. Sociedade de Cardiologia do Estado do Rio de Janeiro. 2021;5:56–72.
28. Ambrosetti M, Abreu A, Corrà U, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology Eur J Prev Cardiol. https://doi.org/10.1177/2047487320913379.

Chapter 22
Treatment of Transthyretin Amyloidosis

Fabio Mastrocola, Frank Nunes, and Paulo Sgobbi

22.1 Introduction

Historically, transthyretin-related amyloidosis (ATTR) is considered a rare, progressive, and fatal disease. Although there are reports in the medical literature of cases with a clinical picture compatible with amyloidosis since the seventeenth century, the first probable case of primary amyloidosis was described by Samuel Wilks in 1856 [1, 2]. A series published in 1952 by Corino Andrade of 74 patients from multiple families who had peripheral sensorimotor neuropathy and amyloid deposits on nerve biopsy drew attention to an inherited form of amyloidosis [3].

In recent years, there have been major advances in diagnostic methods and therapeutic options for ATTR. Evidence that ATTR can be confirmed by noninvasive diagnostic methods in several situations allows for an easier, more accessible, and earlier diagnosis. The consequence is the possibility of diagnosis in early stages of the disease, where the load of amyloid deposits in tissues is not yet so advanced. As will be seen in this chapter, initiation of treatment earlier in the course of the disease translates into greater therapeutic efficacy and better prognosis.

In the field of treatment, in recent years, there has been unprecedented progress with the discovery of specific therapeutic agents that act at different points in the amyloidogenic cascade. Newly approved drugs and potential therapies currently

F. Mastrocola (✉)
Department of Cardiology, Federal University of Rio Grande do Norte, Natal, RN, Brazil

F. Nunes
Cesar Leite Hospital, Manhuaçu, MG, Brazil

P. Sgobbi
Department of Neurology and Neurosurgery, Federal University of São Paulo, São Paulo, SP, Brazil
e-mail: sgobbi@unifesp.br, paulo.sgobbi@unifesp.br

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_22

under investigation combined with new diagnostic resources bring hope that the dismal course of amyloidosis natural history can finally be changed.

22.2 Pathophysiology

Proteins generally need a specific three-dimensional conformation to be soluble and function properly. In some situations, soluble proteins can form insoluble aggregates. This modification can occur in functional situations such as the formation of actin filaments, but also in pathological situations such as the formation of amyloid fibrils [4].

Amyloid formation begins when a protein loses or fails to acquire its physiological folding. This misfolded protein aggregates with other proteins or similar peptides forming oligomers that circulate in the blood and are deposited as highly organized, insoluble, degradation-resistant proteinaceous fibrils in the interstitial (extracellular) space of target organs. To date, more than 30 proteins have been described with the potential for misfolding and subsequent fibril formation causing amyloidosis, including transthyretin.

Transthyretin (TTR) is a protein produced predominantly in the liver and to a small extent in the choroid plexus and retinal pigment epithelium. Its main function is to transport retinol (vitamin A) and, to a lesser extent, thyroxine (T4) in the bloodstream. It is a tetramer formed by four subunits of identical monomers arranged as 2 dimers with weak linkages. In both hereditary amyloidosis (ATTRv) and wild-type amyloidosis (ATTRwt), the tetramer presents kinetic instability and dissociates to form dimers and monomers that undergo a process of misfolding and reorganization as amyloid aggregates called amyloid fibrils. Fibrils can deposit and accumulate in the interstitial space of various organs and systems, especially in the nervous system and the heart, leading to changes in the function and structure of affected organs [5].

As in other neurodegenerative diseases, the deposition of transthyretin-derived amyloid protein occurs before the onset of symptoms and promotes tissue damage through physical compression of cells, obstruction of capillaries, cellular toxicity, and disturbances of the blood-neural barrier that allow the entry of anomalous circulating TTR protein into the endoneural space. The presence of mutant TTR protein leads to the production of inflammatory cytokines and activates apoptosis pathways of endothelial cells, leading to microangiopathy in a similar way to what occurs in more common neuropathic diseases such as diabetic neuropathy [1, 6, 7].

After dysfunction of the blood-neural barrier, destruction of Schwann cells ensues in small diameter nerve fibers (nonmyelinated Schwann cells); accordingly, cells located adjacent to the deposit of amyloid fibrils become distorted and atrophic, suggesting direct damage by invasion of amyloid fibrils. Blood-neural barrier dysfunction and loss of Schwann cells activate degenerative processes in nerve fibers, such as increased oxidative stress and release of inflammatory cytokines that perpetuate the mechanism of blood-neural barrier dysfunction with microischemia and increased capillary permeability, apoptosis of Schwann cells of larger nerve fibers, and axonal loss after destruction of Schwann cells [1, 6, 7].

Cardiac involvement is triggered by multifactorial mechanisms. In addition to the extracellular deposition of amyloid fibrils, other factors may contribute to myocardial damage in ATTR: inflammation caused by proteotoxicity of amyloid fibrils or prefibrils, reactive oxygen species generated by oxidative stress, apoptosis, and autophagy. The consequence of this complex pathological mechanism is the loss of normal tissue architecture, functional alterations, progressive thickening and rigidity of the biventricular wall in the absence of compensatory ventricular dilatation, and biatrial, interatrial, and interventricular septum infiltration. From early diastolic dysfunction, the disease progresses to restrictive cardiomyopathy with conduction system involvement, arrhythmias, and severe systolic dysfunction in later stages [5, 6].

22.3 Treatment of Heart Failure in ATTR

The great advance in the specific treatment of amyloidosis in the last decade is the result of the development of new drugs that have had recent positive results in randomized controlled trials, and there is an expectation of new therapeutic options awaiting the results of ongoing studies.

However, few studies in the literature have specifically analyzed drug therapies for heart failure (HF) in the context of TTR amyloidotic cardiomyopathy (ATTR-CM). There are peculiarities in the pathophysiology of ATTR-CM, such as its restrictive nature with a relatively small ventricular cavity with a low and fixed stroke volume that requires a higher heart rate to maintain cardiac output. With scarce data on the specific treatment of HF in ATTR-CM, there are literature consensus and reviews with expert opinions that currently guide clinical practice. In the era of personalized medicine, there is an urgent need for studies that shed light on the treatment of HF in these individuals [7].

22.3.1 Diuretics

In ATTR-CM, given its restrictive pathophysiology, small increases in end-diastolic volume can cause a rapid increase in intracardiac pressure with consequent systemic and pulmonary congestion. In this sense, diuretics represent the first-choice treatment for ATTR heart failure. Large doses may be necessary, with the loop diuretic being the first choice and often used in combination with a potassium-sparing diuretic. Due to the frequent edema of intestinal loops, bumetanide and torsemide are preferable to furosemide because of their better bioavailability.

Careful titration is necessary to avoid excessive diuresis leading to a significant reduction in preload and consequent renal function deterioration. Similarly, patients who present with dysautonomia and orthostatic hypotension may experience symptomatic worsening with overly aggressive diuresis [8, 9]. In selected cases, especially in patients with advanced functional class, there is evidence that the management of hypervolemia with regular visits to an outpatient clinic for venous

diuretic therapy contributes to reducing the number of visits to the emergency department and the proportion of hospitalization days [10].

22.3.2 Digoxin

An in vitro study from the 1980s is the scientific basis for relating an avidity of the drug to extracellular amyloid fibrils, which theoretically could increase the concentration of digoxin in the body and the risk of digitalis intoxication. The study analyzed the binding of digoxin with isolated amyloid fibrils of light chain (AL) and AA (serum amyloid A). ATTR amyloid fibrils have not been studied [11].

A recent retrospective cohort study with a small sample of patients analyzed the use of digoxin in patients with ATTR-CM, mainly for heart rate control in atrial fibrillation and showed that the vast majority (88%) had no side effects related to the use of digoxin, especially when administered at a low dose (0.125 mg/day). Regular measurement of serum digoxin levels is recommended [12].

22.3.3 Levosimendan

Prognostic benefits of inotropics in these patients is uncertain, but studies with levosimendan have shown positive effects on systemic and pulmonary hemodynamics on the relief of symptoms of heart failure with reduced ejection fraction [13].

22.3.4 Sodium Glucose Cotransporter 2 (SGLT2i) Inhibitors

Despite recent and robust studies on the efficacy of SGLT2i in patients with heart failure with preserved ejection fraction (HFpEF) and especially heart failure with reduced ejection fraction (HFrEF), there is a lack of data in the literature evaluating its tolerability and efficacy in ATTR-CM carriers. In a recent cohort study of 15 diabetic patients with ATTR-CM who used SGLT2i, the main evidence of the study was good tolerability. Data on functional class improvement are conflicting, but the small sample size precludes a definitive conclusion [14].

22.3.5 Calcium Antagonists

Nondihydropyridine calcium antagonists should be avoided in patients with ATTR-CM because of their important negative inotropic, chronotropic, and dromotropic effects. As with digoxin, an experimental study from the 1980s also demonstrated the binding avidity of nifedipine by amyloid fibrils [15].

22.3.6 Angiotensin-Converting Enzyme (ACEi) Inhibitors and Angiotensin II Receptor Blockers (ARB)

Despite the demonstrated benefit of ACEi and ARB in reducing mortality and improving functional class in patients with HFrEF, data are scarce to assess the benefits of these drug classes in ATTR-CM. Both classes promote neurohormonal blockade with consequent reduction of systemic vascular resistance (SVR). With its peculiar pathophysiology, the drop in SVR in ATTR-CM can cause a significant drop in mean arterial pressure, as the heart may not be able to compensate for it with an increase in cardiac output due to its fixed systolic volume. In addition, some patients with ATTR dysautonomia, especially in the hereditary type, have orthostatic hypotension that can be aggravated by the use of ACEi or ARB [9].

Due to this theoretical unfavorable hemodynamic profile of these classes in patients with ATTR-CM, their indication should be judicious for the treatment of hypertension or HF, and limited literature data from cohort studies have not shown a benefit in improving survival with the use of these drugs [16].

22.3.7 Beta Blockers

Similar to ACEi and ARB, the literature consensus based on expert opinions is against the routine use of beta-blockers based on individual experience and theoretical pathophysiological assumptions. Patients with ATTR-CM are very dependent on heart rate to maintain cardiac output, as they have a small ventricular cavity and fixed systolic volume due to their restrictive physiology. Furthermore, the prevalence of conduction disorders is high in this population. The use of beta-blockers in ATTR-CM can mitigate this compensatory increase in heart rate and cause reduced cardiac output, fatigue, worsening of conduction disturbance, and syncope.

Antagonistic results have been found in recent cohort studies that evaluated the use of beta-blockers. In a recent publication, 309 patients with ATTR-CM were followed at a referral service, Columbia University Irving Medical Center, NY. Discontinuation of beta-blocker use, particularly in patients with advanced disease, was associated with a reduction in mortality. The authors correlate the better prognosis of withdrawal with the dependence of the higher heart rate on the maintenance of cardiac output [16]. Paradoxically, the observational, multicenter, prospective AMI-GAL study followed 128 patients with ATTR-CM for a mean time of 520 days and showed that beta-blocker use was correlated with lower all-cause mortality. The main indication for the use of the drug was heart rate control in patients with atrial fibrillation and flutter. The overall prevalence of beta-blocker

withdrawal due to side effects was 25%. Some of the hypothetical reasons raised by the authors for the favorable clinical outcome with the use of the drug for patients who tolerated the use of beta-blockers are longer ventricular filling time in patients with atrial tachyarrhythmias, improvement in ventricular dynamics in patients with dynamic outflow tract obstruction of the left ventricle (LV) in patients with asymmetric ventricular hypertrophy, antiischemic and antioxidant properties of the class, and pharmacodynamic benefits similar to patients with HFrEF of other etiologies [17].

However, the results of these cohort studies are only hypothesis generators. The heterogeneity of baseline characteristics of the drug group and the placebo group, the small sample size, nonrandomization, selection, and information collection biases may have influenced the results. Until more concrete data from randomized controlled studies are obtained, it is reasonable to maintain beta-blockers rather than a systematic suspension, especially if the indication is for situations such as the presence of flutter or atrial fibrillation and anti-ischemic therapy (Table 22.1).

Table 22.1 Heart failure therapies in ATTR-CM

Therapies for heart failure in ATTR-CM	
Loop diuretics	**Recomended.** Prefer bumetanide and Torsemide. Furosemide accetable Avoid underfilling Consider association of thiazide diuretic if needed
Beta-blockers	Avoid Cautious use in arrhythmias
ACE inhibitor/ARB	Should be avoided, especially in autonomic disfunction (ATTRv) Very cautious use in HFrEF without hypotension
Sacubitril-valsartana	Avoid May exacerbate hypotension
Mineralocorticoid receptor antagonist	Consider in conjunction with loop diuretics if adequate blood pressure and renal function
Digoxin	Use cautiously in tachycardia setting (AF/flutter)

Summary of the main points of the treatment of HF in ATTR-CM
• Diuretics are the class of choice in the initial approach, as they promote symptom relief by reducing systemic and pulmonary congestion triggered by the restrictive pathophysiology caused by amyloid infiltration
• Loop diuretic is the first choice. Combination with a potassium-sparing diuretic is often necessary with close monitoring of renal function and potassium
• Due to the scarcity of concrete evidence to date on the reduction of mortality with the use of ACEI/ARB in patients with cardiac amyloidosis, its use should be routinely avoided. Consider use with caution in patients with reduced EF without dysautonomia/orthostatic hypotension
• Nondihydropyridine calcium antagonists should be avoided. Digoxin should also be avoided but can be used with caution especially in cases of ATTR-CM with atrial fibrillation for heart rate control. Further studies are needed to assess the efficacy and safety of these classes in patients with ATTR-CM
• The use of beta-blockers may interfere with the compensatory elevation of heart rate imposed by the restrictive pathophysiology of ATTR-CM and worsen cardiac output. Special care should also be taken with its use in patients with amyloidosis and conduction disorders. However, they may be useful in clinical stabilization in selected cases of patients with atrial flutter/fibrillation or as anti-ischemic therapy
• Regardless of the CHA_2DS_2-VASc score, in the presence of atrial fibrillation, patients with ATTR-CM should receive oral anticoagulation with DOACs or warfarin (for more information, refer to Chap. 5—Syncope, Arrhythmias and Cardiac Devices)

22.4 Symptomatic Treatment of Dysautonomic Manifestations

Symptomatic treatment is essential for improving the quality of life of patients with ATTR, especially the hereditary type, and should always involve nonpharmacological measures and drug treatment. Symptomatic treatment is complex and challenging, especially for autonomic dysfunctions, given that an autonomic manifestation can lead to the worsening of another symptom of the disease (for example, diarrhea can worsen orthostatic hypotension) or the treatment adopted for a symptom can lead to deterioration of another manifestation of the disease (volume expansion measures for the treatment of orthostatic hypotension can worsen heart failure, medications for neurogenic bladder management can lead to worsening of hypotension) [18].

22.4.1 Erectile Dysfunction

Erectile dysfunction is an early autonomic manifestation in male patients with ATTRv that usually leads to a great impact on quality of life by interfering with the sense of well-being, causing great social stigma and psychological impacts, generating physical discomfort and deterioration of social relationships [18, 19].

Nonpharmacological measures for the treatment of sexual dysfunction involve the use of penile prostheses and vacuum constriction devices that can be difficult for the patient to accept [18, 19].

Phosphodiesterase type 5 inhibitors (PDE5i) are the most commonly used pharmacological intervention for the treatment of sexual dysfunction. PDE5i can be used orally (e.g., sildenafil) or through intracavernous or intraurethral applications (e.g., alprostadil) that improve the erection process, although they often cause orthostatic hypotension. Before initiating pharmacological treatment with the use of phosphodiesterase type 5 inhibitors, patients should undergo a cardiological evaluation to search for orthostatic hypotension and should be recommended to avoid the orthostatic position for a few hours after the use of the medication [18, 19].

22.4.2 Urinary Dysfunction

Urinary dysfunction in ATTRv patients is classically called neurogenic lower urinary tract dysfunction (NLUTD). The main symptoms of NLUTD are (a) related to voiding (e.g., hesitancy, straining, or intermittent urinary stream); (b) overactive bladder defined as a complex of symptoms resulting from overactivity of the detrusor musculature, classically reported as an increased duration of urinary time with or without the sensation of incomplete bladder emptying usually accompanied by hesitation with weak urinary stream and reduced sensation of bladder filling; and (c) urinary incontinence [18, 19].

Lower urinary tract dysfunction in ATTR patients can lead to important clinical complications such as recurrent urinary tract infections and upper urinary tract changes such as hydronephrosis [18, 19].

Nonpharmacological interventions for the treatment of urinary dysfunction involve behavioral measures such as decreasing fluid intake at night, avoiding performing the Valsalva maneuver, physical therapy for pelvic floor rehabilitation, scheduled urination at regular intervals, and intermittent bladder catheterization procedures. Intermittent bladder catheterization is recommended for symptomatic patients with a postvoid residual volume of 100 mL or for any patient with a postvoid residual volume between 300 and 400 mL [18, 19].

For the treatment of stress urinary incontinence, the first nonpharmacological measure to be adopted is physical therapy for pelvic floor rehabilitation for patients with preserved voluntary contraction of the pelvic muscles, and in cases of failure of conservative measures, surgical interventions with agents of volume, slings, periurethral balloons, and artificial devices to control the urinary sphincter may be indicated [18, 19].

Pharmacological measures for the treatment of urinary dysfunction have as main objectives the improvement of urinary incontinence, improvement of bladder compliance, relief of nocturia, and prevention of recurrent urinary tract infections. Duloxetine, a serotonin-noradrenaline reuptake inhibitor, is the only pharmacological treatment that has shown efficacy in a randomized, placebo-controlled clinical trial for the treatment of stress urinary incontinence in male and female patients and should be the drug of choice for ATTRv patients complaining of urinary incontinence. Desmopressin, a synthetic analog of vasopressin with antidiuretic action, is

the drug of choice for the treatment of patients complaining of nocturia and evidence of nighttime polyuria (indicated by the ratio of nocturnal urine volume/24-h urine volume greater than 20% in young patients and greater than 33% in elderly patients) [18, 19].

Antimuscarinic agents or blockers of type a1 adrenergic receptors are the first line of treatment for altered bladder compliance, and in cases of therapeutic failure, intravesical injection of botulinum toxin may be an alternative measure [18, 19].

22.4.3 Gastrointestinal Dysfunction

Autonomic dysfunctions related to the gastrointestinal tract have the greatest impact on the quality of life of ATTRv patients, are usually difficult to control, and have a direct and indirect impact on other clinical manifestations and patient survival [18, 20].

The most important nonpharmacological measure for weight loss consists of regular nutritional monitoring with a specialized professional to adjust the quality and quantity of the diet, as well as to guide the use of nutritional supplements. The most commonly used drug to control body weight is cholestyramine, which is associated with parenteral diet and vitamin supplementation [18, 20]. Guidances on meal frequency and fractionation are important nonpharmacological measures for patients with symptoms of gastroparesis, and in cases of therapeutic failure, dopamine receptor antagonists and motilin receptor agonists are the most commonly used drugs [18, 20].

Diarrhea control should initially be attempted with the pharmacological use of loperamide at a dose of 2–16 mg/day or octreotide 100 mg/day, and in refractory cases, stoma surgery can be performed. The treatment of constipation involves changing the diet with a greater intake of foods rich in fiber and the use of laxative drugs such as antibiotics, polyethylene glycol (PEG), and sodium picosulfate [18, 20].

22.4.4 Orthostatic Hypotension

The treatment of orthostatic hypotension can be performed with nonpharmacological interventions aimed at increasing the patient's blood volume, such as increasing fluid intake and a diet without sodium restriction, with the use of compression stockings of the lower limbs to facilitate venous return, lower limb elevation when in the supine position, guidance on changing the position, and avoiding situations that cause dehydration [18, 21].

Pharmacological treatment of orthostatic hypotension can be performed with the use of midodrine at a dose of 2.5–40 mg/day, fludrocortisone 0.05–0.2 mg/day, or droxidopa at a dose of 300–1800 mg/day [18, 21].

22.5 Specific Treatment of ATTR

The liver is responsible for the production of more than 90% of circulating TTR, and because of this, liver transplantation is an effective way to reduce the progression of the disease and improve the survival of patients who have the hereditary type. In patients with ATTR with advanced cardiac involvement, combined heart and liver transplantation or isolated heart transplantation may be indicated. However, the benefits of transplantation are counterbalanced by the high perioperative morbidity and mortality and the chronic adverse effects of immunosuppression.

Recent data show a significant improvement in short- and long-term survival after heart transplantation in the last two decades, with a similar success rate for heart transplantation indicated for amyloidosis when compared to heart transplantation for other indications [22]. In a 20-year retrospective analysis of the Familial Polyneuropathy World Transplant Registry, the largest multicenter database of liver transplantation in patients with familial amyloid polyneuropathy (FAP), the median 20-year survival of the 1940 transplant patients was 55.3%. In multivariate analysis, independent predictors of survival were early disease onset (<50 years of age), Val30Met mutation (p. Val50Met) versus non-Val30Met, short disease duration, and high body mass index [23].

In some patients undergoing liver transplantation, despite elimination of the source producing mutant TTR proteins, progression of amyloid fibril deposits in the heart or other organs may occur. The seeding hypothesis based on the experimental work by Saelices et al. may explain this phenomenon. According to this, the transplanted liver will secrete wild-type TTR that will replace the circulating mutant TTR. Residual niches of amyloid deposits in other organs, including the myocardium, will favor the conversion of wild-type TTR produced by the new liver into amyloid fibrils, perpetuating the disease. Postmortem analysis studies of patients with liver transplantation for FAP support this theory [24–26]. Another cohort study identified a late age of disease onset (>50 years of age) in patients carrying the Val30Met mutation (p. Val50Met) as a risk predictor for increased interventricular septum thickness with the development of cardiomyopathy after liver transplantation [27]. More data on the role of specific drug treatment for ATTR post-transplantation are expected in the coming years.

For many years, liver transplantation or combined liver and heart transplantation was the only specific treatment for ATTR. The limitations of the strict selection criteria and the scarcity of organ donors made this therapeutic option inaccessible to most patients with ATTR.

In November 2011, the European Medicines Agency (EMA) approved the use of tafamidis for the treatment of amyloid polyneuropathy, and since then, a new era of therapeutic options for amyloid neuropathy and heart disease has begun. Therapies that have already been proven effective or are currently being explored in clinical trials act at different points in the amyloidogenic cascade from synthesis to degradation/resorption of tissue amyloid infiltrates (Fig. 22.1). They can be divided into:

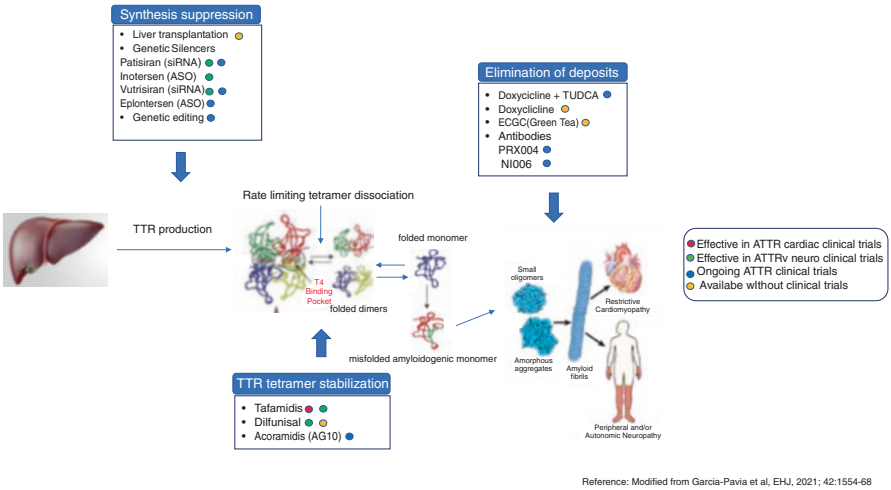


Fig. 22.1 Therapies for TTR amyloidosis act at different points in the amyloidogenic cascade. Reference: Modified from Garcia-Pavia et al., EHJ, 2021; 42:1554–68

1. Therapies that suppress the precursor either through gene expression silencing techniques through RNA interference and antisense oligonucleotides or through gene editing therapy through the CRISPR–Cas9 system (clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease).
2. Stabilization of the protein precursor to maintain its normal conformational structure.
3. Degradation/reabsorption of amyloid fibrils.

22.6 Antisense Oligonucleotide

Antisense oligonucleotides (ASOs) are small-sized, single-stranded synthetic nucleic acid molecules formed on average by 8–20 nitrogenous bases that are capable of altering the intermediary metabolism of RNA molecules (transcription, translation, or degradation) and consequently the synthesis of proteins related to the target RNA molecule [28].

Oligonucleotides exert their control over protein synthesis through three modes: (1) degradation of mRNA molecules with a sequence complementary to that of the oligonucleotide using the endonuclear system of the RNase H enzyme; (2) blockade of mRNA translation by ribosomes; and (3) modulation of the splicing of pre-mRNA molecules [28].

22.6.1 Inotersen

Inotersen is a second-generation antisense oligonucleotide of the 2′-MOE type that has a sequence of nitrogenous bases complementary to the 3′-UTR of the mRNA encoding the human TTR protein; inotersen hybridization with mRNA molecules encoding human TTR protein forms a complex of an RNA double helix that is destroyed by the enzymatic activity of RNase H1 (Fig. 22.2), preventing the production of mutant and wild-type TTR protein and consequently the formation of amyloid fibrils [28].

The safety and efficacy of inotersen was evaluated in a 15-month, double-blind, randomized, placebo-controlled phase 3 (NEURO-TTR) study in patients with hereditary transthyretin-related amyloidosis with polyneuropathy (ATTRv-PN) in stage 1 (patients able to walk without assistance) and stage 2 (patients able to walk with assistance) [28, 29].

Patients were randomized in a 2:1 ratio to receive weekly subcutaneous injections of 300 mg inotersen or placebo. The primary endpoints of the study were to assess change in the Modified Neuropathy Impairment Score + 7 (mNIS + 7) scale with high scores indicating greater impairment of neurological function and changes in the patient-reported Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) with high scores indicating a worse quality of life and any decrease in the scales indicating a clinical improvement [28, 29].

A total of 172 patients were recruited, with 112 patients in the group assigned to receive inotersen and 60 patients in the placebo group, with participants having the following characteristics: mean age 59 years, 69% male, 67% were in stage 1 disease, and 63% had cardiomyopathy [28, 29]. Of the total randomized patients, 139 participants (81%) completed the study, with 25 patients discontinuing in the inotersen group and 8 patients in the placebo group, with adverse events being the major cause of discontinuation among patients receiving inotersen (16 patients, 14%). After 15 months of study, the two primary endpoints reached statistically significant differences between the inotersen and placebo groups [28, 29].

On average, patients who received inotersen had a 5.8 point gain (95% CI, 1.6–10) on the mNIS + 7 scale from baseline versus a 25.5 point increment (95% CI, 20.2–30.8) in the group that received placebo. Regarding quality of life assessed by the Norfolk QOL-DN questionnaire, patients treated with Inotersen had a mean gain of 1 point (95% CI, −3.2–5.2) versus a mean increase of 12.7 points (95% CI, 7.4–17.9) in the participants of the placebo group [28, 29]. Final analysis showed that 36% of patients in the inotersen group showed no worsening of their neurological functions (no increase in score from baseline) as assessed by the mNIS + 7 scale, and 50% of patients treated with inotersen showed an improvement in quality of life in the Norfolk-QOL-DN questionnaire score [28, 29].

Regarding the safety profile, there were 5 deaths during the clinical study, all in the inotersen group; four of the five deaths were related to the evolution of the disease, and 1 patient had a fatal intracranial hemorrhage in association with a significant decrease in the number of platelets (<10,000 per mm^3), a hematological

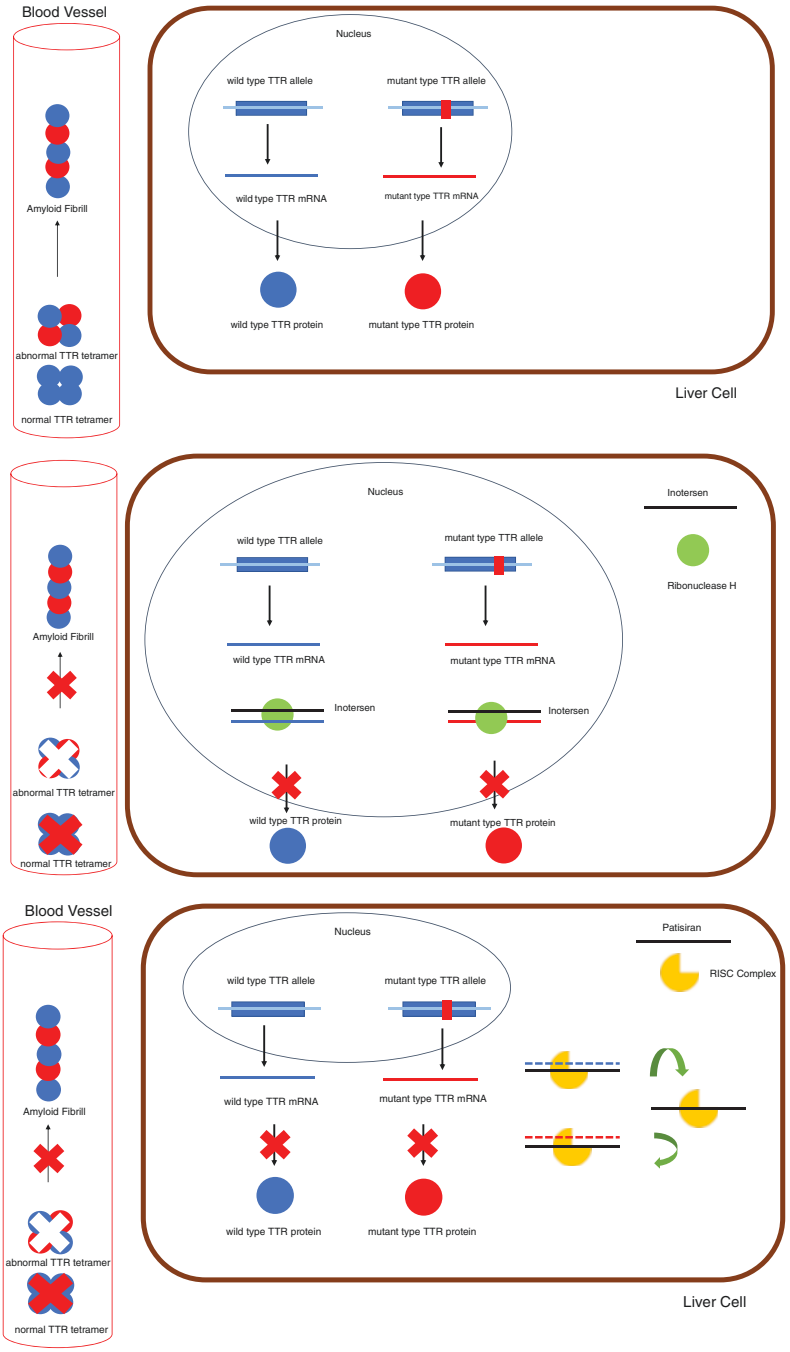


Fig. 22.2 Action mechanisms of the silencers of TTR production

complication related to the use of inotersen [29]. Glomerulonephritis occurred in 3 patients (3%) treated with inotersen.

Regarding safety data, thrombocytopenia with platelet counts below 140,000 per mm^3 was more common in patients treated with Inotersen (60 of 112, 54%) than in the placebo group (8 patients out of 60, 13%). Thrombocytopenia with a platelet count of less than 25,000 per mm^3 occurred in 3 patients (3%) only in the inotersen group [29].

In both the whole study population and in the subgroup with cardiac disease, no differences in global longitudinal strain or other echocardiographic variables (wall thickness, LV mass, LV ejection fraction, and lateral E/e′) were observed between the inotersen and placebo groups at the 15-month follow-up [29].

The NEURO-TTR study concluded that the use of inotersen is related to an improvement in quality of life and in the neurological course of the disease in ATTRv patients and that important adverse events such as thrombocytopenia and glomerulonephritis are treatment-related and need attention and special follow-up [29].

In a recent publication of safety and efficacy data from patients with ATTRv treated with inotersen after a 2-year period of the open-label extension phase of the NEURO-TTR study, patients initially treated with inotersen maintained their use of the drug and had a 70–80% reduction in plasma levels of TTR protein, and patients who received placebo in the NEURO-TTR had the same reduction in plasma levels of TTR; the reduction observed in both groups was maintained after 104 weeks of evaluation compared to baseline of the study. Regarding the primary endpoint of change in mNIS + 7 scale score, patients who were treated with inotersen in the NEURO-TTR study had lower mNIS + 7 than patients in the placebo group at the beginning of the extension phase, indicating better neurological function in patients who were treated early, and this difference is maintained after 104 weeks [30].

The conclusion of the extension phase study was that treatment with inotersen slows disease progression and reduces deterioration in quality of life in ATTRv patients and that early treatment with inotersen resulted in greater long-term disease stabilization than late onset and that monitoring measures of renal function and platelet count are necessary and effective, with no new adverse events observed [30].

How to use inotersen in clinical practice
Tegsedi® (Inotersen) 284 mg/1.5 mL
Indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis
Dose: 284 mg subcutaneous (SC) once a week
No dose adjustment is required for patients with mild or moderate renal or hepatic impairment
Should not be used during pregnancy
A concern is that glomerulonephritis and thrombocytopenia have occurred in patients treated with inotersen
Contraindications:
• Platelet count < 100 × 109/L prior to treatment
• Urine protein to creatinine ratio (UPCR) ≥ 113 mg/mmol (1 g/g) prior to treatment

How to use inotersen in clinical practice
• Estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73 m^2
• Severe hepatic impairment
UPCR and eGFR should be monitored every 3 months or more frequently, as clinically indicated
Platelet count should be monitored every 2 weeks during treatment
Oral supplementation of approximately 3000 IU vitamin A per day

22.6.2 Eplontersen

Eplotersen is an oligonucleotide of similar design and with an identical sequence to inotersen conjugated to a triantennary GalNAc (GalNAc3) moiety. This moiety acts as a ligand for productive receptor-mediated uptake by the high-capacity asialoglycoprotein receptors (ASGR) expressed by hepatocytes. After cell internalization, the GalNAc3 moiety is metabolized to release 'free ASO' inside hepatocytes for binding to the target mRNA. In an in vitro study, in HepatoPac cell culture, eplontersen exhibited dose-dependent reductions in wild-type TTR mRNA expression, but was approximately 50 times more potent than inotersen when compared at the same concentration.

Eplontersen administered by subcutaneous injection once every 4 weeks is being tested in phase 3 studies in stage 1 or 2 patients with hereditary ATTR-PN (NCT05071300) in the NEURO-TTRansform study, completion date through June 2024 [31, 32] and in transthyretin-mediated amyloid cardiomyopathy (hereditary and wild type) in the CARDIO-TTRansform trial (NCT04136171).

Ionis Pharmaceuticals announced in June 2022 the results from a 35-week interim analysis of the phase 3 NEURO-TTRansform study. Eplontersen demonstrated a statistically significant change from baseline in the co-primary endpoints of percent change in serum TTR concentration and modified Neuropathy Impairment Score + 7 versus historical placebo arm from NEURO-TTR (inotersen). Eplontersen also met its secondary endpoints, showing significant improvement in patient-reported quality of life (Norfolk-QoL-DN). In the study, eplontersen demonstrated a favorable safety and tolerability with no specific concerns. The final primary endpoint analysis will be completed at week 66 and all patients will be followed until week 85 when they will have the option to transition into the open label extension study.

22.7 Interference RNA (siRNA)

Interfering RNAs (siRNAs) are double-stranded RNA molecules that do not encode proteins, but are able to induce the silencing of specific genes by targeting molecules of mRNA for degradation, thus controlling the process of protein synthesis and gene expression [33, 34] (Fig. 22.2).

22.7.1 Patisiran

Patisiran is a siRNA encapsulated by a lipid nanoparticle. It binds to the 3′-UTR portion of the mutated and normal TTR protein-producing messenger RNA. The lipid nanoparticle ensures great affinity and penetrance in the liver tissue through uptake by the apolipoprotein E receptor, mediated by low-density lipoprotein receptors present on the surface of hepatocytes. Following nanoparticle internalization and release into the cytoplasm, the siRNA molecule is recognized by a protein complex that attaches its guide strand, while the passenger strand is degraded. This process gives rise to a RISC complex (RNA-induced silencing complex) containing the argonaut protein (AGO), which will cleave complimentary TTR protein-producing mRNA, ultimately interrupting the production of wild and mutated TTR protein [33–35].

The safety and efficacy of patisiran was evaluated in a phase 3, multicenter, double-blind, randomized, placebo-controlled study called APOLLO, which lasted 18 months in patients with ATTRv-PN [36, 37].

Patients were randomized in a 2:1 ratio to receive patisiran at a dose of 0.3 mg/kg of body weight or placebo intravenously every 3 weeks, and randomization was performed taking into account the NIS scale score (5 to 49 versus 50 to 130), age of early disease onset (<50 years of age) in the presence of Val30Met (p. Val50Met) variant versus the other pathogenic variants, and according to previous use of a transthyretin stabilizer [36, 37].

The primary objective of the study was to assess the change from baseline to 18 months in the mNIS + 7 scale score. The secondary objectives of the study were (1) assessment of quality of life using the Norfolk-QOL-DN questionnaire; (2) muscle strength using the NIS-W scale; (3) functional disability assessed by the R-ODS (Rasch-built Overall Disability Scale); (4) gait speed assessed by the 10-m walk test; (5) nutritional status through modified body mass index (mBMI); and (6) autonomic function using the COMPASS-31 scale (Composite Autonomic Symptom Score 31) [36, 37].

A total of 225 patients were randomized, with 148 patients assigned to treatment with patisiran and 77 patients in the placebo group. In the group of patients treated with patisiran, there was a rapid and sustained reduction in serum TTR protein levels over the period of 18 months with an average reduction of 81% compared to the placebo group and with no differences regarding patient age, sex, or genotype [36, 37].

Regarding the primary endpoint, changes from baseline in the mNIS + 7 scale were significantly smaller in patients treated with patisiran than in patients treated with placebo, indicating an improvement over polyneuropathy. The mean score on the mNIS + 7 scale at baseline was 80.9 in the patisiran group and 74.6 in the placebo group, and after 18 months, the mean change in the mNIS + 7 scale from baseline was −6.0 for patients treated with patisiran versus 28.0 points for patients receiving placebo, with a mean difference between groups of −34.0 points (95% CI, −39.9 to −28.1; $p < 0.001$) being statistically significant; the effects of patisiran on

the mNIS+7 scale could be observed as early as after 9 months of treatment. After 18 months, 56% of patients receiving patisiran showed a decrease in score on the mNIS + 7 scale, indicating an improvement in polyneuropathy compared to only 4% of patients receiving placebo [36, 37].

Regarding secondary outcomes, the change in Norfolk-QOL-DN questionnaire score from baseline was smaller in patisiran-treated patients than in the placebo group, indicative of a better quality of life in patisiran-treated patients.

Statistically significant differences between the groups were observed for all other secondary outcomes evaluated favoring the group treated with patisiran, including in relation to the autonomic function assessed by the COMPASS 31 scale [36, 37].

Regarding the safety profile, adverse events leading to discontinuation of the study regimen were more frequent in the placebo group, present in 14% of patients versus 5% in the patisiran-treated group [36, 37]. There were 7 (5%) deaths in the group of patients treated with patisiran and 6 (8%) deaths in the placebo group, with none of the deaths related to the drug or study procedures, but due to complications expected in ATTRv patients [36, 37]. Common adverse events that occurred more frequently in the patisiran-treated group than in the placebo group were peripheral edema (30% versus 22%) and infusion-related reactions (19% versus 9%), with infusion-related infusions being mild or moderate [36, 37]. No clinically relevant laboratory changes in platelet counts or markers of renal and liver function were observed during the study [36, 37].

A recent publication with long-term safety and efficacy data with 12-month outcomes of ATTRv-PN patients treated with patisiran with data from 211 patients, of which 25 patients are part of the extension phase of the phase 2 study, 137 patients derived from the patisiran group, and 49 patients from the placebo group in the APOLLO Study showed the long-term benefit and acceptable safety profile of the drug [38]. Patients derived from the phase 2 study extension and patients in the patisiran group in the APOLLO study continued to show improvement in neurological function (verified as a decrease in the mNIS + 7 scale score) after 12 months, as did patients derived from the placebo in the APOLLO study [38].

Regarding the quality of life measured by the Norfolk-QOL-DN questionnaire, patients from the placebo group in the APOLLO study after 12 months experienced an improvement in quality of life with a reduction in the Norfolk-QOL-DN score, but did not reach the quality of life that they had at the beginning of APOLLO, and patients treated with patisiran from the beginning continued to show improvement in quality of life with reduced scores on the Norfolk-QOL-DN questionnaire [38].

All other secondary endpoints observed in the APOLLO study continued to improve in patients derived from the open-label phase of the phase 2 study and in patients treated initially with patisiran in the APOLLO study, and patients who initially received placebo and then received patisiran also experienced an improvement in secondary outcomes in relation to the values presented at the end of APOLLO [38].

Regarding the safety profile, common adverse events defined as those occurring in $\geq$10% of patients were diarrhea, peripheral edema, and infusion-related reactions [38].

The conclusion drawn from this open-label extension study is that treatment with patisiran maintains its clinical efficacy in improving neuropathy, increasing quality of life, and improving other important long-term ATTRv-related outcomes and that even patients treated late with patisiran may present improvement in neuropathy, quality of life, and other compromised functions with an acceptable safety profile without any new adverse events and without the need for laboratory monitoring of renal and hepatic function as well as platelet count [38].

The benefit of patisiran in ATTR-CM was evaluated in an exploratory analysis in a prespecified subpopulation of patients from the APOLLO study with evidence of cardiac amyloid involvement ($n = 126$; 56% of total population). Patisiran decreased the mean left ventricular wall thickness and NT-proBNP and improved global longitudinal strain compared with placebo at month 18. In a post hoc analysis, patisiran treatment reduced combined all-cause hospitalization and mortality compared with placebo at month 18. The results of this subgroup analysis suggest that patisiran may halt or reverse the progression of the cardiac manifestations of ATTRv amyloidosis [39].

After these promising results from APOLLO, an ongoing trial, APOLLO-B (NCT03997383), is evaluating change from baseline at month 12 in the 6-Minute Walk Test (6-MWT) comparing patisiran and placebo. The secondary endpoints are composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF Visits, change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) Score and composite endpoint of all-cause mortality, frequency of CV Events (CV Hospitalizations and urgent HF Visits), and change from baseline in 6-MWT [40].

In August 2022, Alnylam-pharmaceuticals reported positive results from APPOLO-B phase 3 study of patisiran in patients with ATTR amyloidosis with cardiomyopathy. Patisiran met the primary endpoint with statistically improvement in 6-minute walk test compared to placebo at 12 months; also met the first secondary endpoint with statistically significant improvement in quality of life ((KCCQ-OS). Patisiran demonstrated safety and good tolerability profile.

How to use patisiran in clinical practice
ONPATTRO® (patisiran)—2 mg/mL (10 mg/5 mL)
Indicated for the treatment of hereditary transthyretin-mediated amyloidosis in adult (>18 years) patients with stage 1 or stage 2 polyneuropathy (European Medicines Agency and Brazil) or for any stage of polyneuropathy (FDA, Canada and Japan)
Dose: 0.3 mg/kg (maximum 30 mg) IV once every 3 weeks
No dose adjustment is necessary in patients with mild or moderate renal impairment (eGFR≥30/min/1.73 m^2). Onpattro has not been studied in patients with severe renal impairment, end-stage renal disease, or with moderate or severe hepatic impairment
Do not use during pregnancy
Vitamin A supplementation at approximately 2500 IU vitamin A per day is advised
Should be administered by a healthcare professional.

How to use patisiran in clinical practice
Patients should receive premedication prior to administration to reduce the risk of infusion-related reactions (IRR). Each of the following medicinal products should be given on the day of infusion at least 60 min prior to the start of infusion:
• Intravenous corticosteroid (dexamethasone 10 mg, or equivalent)
• Oral paracetamol (500 mg)
• Intravenous H1 blocker (diphenhydramine 50 mg, or equivalent)
• Intravenous H2 blocker (ranitidine 50 mg, or equivalent)

22.7.2 Revusiran

ENDEAVOUR was a phase II trial designed to evaluate the effect of revusiran, an investigational siRNA directed against hepatic TTR mRNA, on the 6-min walk test distance and on serum TTR in patients with ATTRv-CM. The study was prematurely discontinued after 6.71 months due to an observed mortality imbalance between treatment arms (12.9% patients on revusiran and 3.0% on placebo). Most deaths in both treatment arms were due to heart failure (HF) [41].

22.7.3 Vutrisiran

Vutrisiran is a new RNAi agent administered subcutaneously and conjugated to trivalent GalNAc with a 3-month interval of administration. The efficacy and safety of vutrisiran are currently being investigated in two randomized phase 3 trials.

In the HELIOS-A, a phase 3, open label study, patients with ATTRv polyneuropathy were randomized (3:1) to receive 25 mg SC vutrisiran once every 3 months or 0.3 mg/kg IV patisiran every 3 weeks. The primary endpoint is change from baseline in the Modified Neurologic Impairment Score + 7 (mNIS + 7) at month 9 compared to an external control, the APOLLO placebo group ($n = 77$). HELIOS-A enrolled 164 patients (vutrisiran, $n = 122$; patisiran, $n = 42$) [42]. Vutrisiran treatment significantly improved mNIS + 7 vs external placebo (change from baseline: $-2.2 \pm 1.4 \times 14.8 \pm 2.0$), 50.4% of patients in the vutrisiran group showed improvement in mNIS + 7 vs 18% in the placebo group; also resulted in statistically improvement in quality of life (Norfolk QOL-DN), gait speed (10-m walk test), nutritional status (mBMI), and disability (R-ODS) at 9 months. Vutrisiran achieved rapid, sustained reduction in serum TTR levels, similar to patisiran. Vutrisiran met all secondary endpoints measured at 18 months, including statistically significant improvements in neuropathy impairment, quality of life (QoL), gait speed, nutritional status, and overall disability, relative to placebo and noninferiority of serum TTR reduction relative to the patisiran arm. Vutrisiran treatment resulted in mNIS + 7 improvement relative to baseline at 18 months in 48.3% of patients, compared with 3.9% of patients who received placebo.

Vutrisiran demonstrates encouraging safety and tolerability profiles. There were three study discontinuations (2.5%) due to adverse events in the vutrisiran arm by month 18, one due to a nonfatal event of heart failure and two due to deaths, neither of which was considered related to the study.

In HELIOS-A, patients treated with vutrisiran also showed improvement in exploratory cardiac endpoints, including NT-proBNP and echocardiographic parameters relative to placebo, as well as technetium uptake, relative to baseline, in a planned cohort of patients, suggesting the potential for reducing amyloid burden in the heart.

HELIOS-B (NCT04153149) will evaluate the efficacy and safety of vutrisiran 25 mg administered subcutaneously once every 3 months compared to placebo in patients with ATTR amyloidosis with cardiomyopathy [43]. The primary composite endpoint will be cause mortality and cardiovascular (CV) recurrent events (CV hospitalizations and urgent heart failure visits at 30 months).

Silencers highlights
1. More than 90% of transthyretin is produced in the liver and new drugs that lead to a suppression of hepatic synthesis of the protein in both the mutant and wild-type form have shown efficacy in reducing the progression of stage 1 and 2 polyneuropathy in ATTRv, with the publication of 2 pivotal trials in 2018, the NEURO-TTR and APOLLO
2. There are 2 main classes that lead to the degradation of the mRNA responsible to produce transthyretin, significantly reducing the amount of circulating transthyretin
• Inotersen is an antisense oligonucleotide (ASO) applied subcutaneously once a week. It was evaluated in the NEURO-TTR study and reduces deterioration in quality of life and slows progression of neurological disease, but with important treatment-related adverse effects such as thrombocytopenia and glomerulonephritis that deserve special monitoring
• Patsiran is an interfering RNA (siRNA) given at a dose of 0.3 mg/kg IV every 3 weeks. It was evaluated in the APOLLO study and showed improvement in polyneuropathy and quality of life. Adverse reactions that were more frequent compared to placebo were infusion-related reactions (IRR). There is a need to use premedication before the infusion
In Helios A trial, vutrisiran demonstrated halting or reversal of polyneuropathy, with improvements in neuropathy impairment and QoL relative to baseline, with good safety profile. Vutrisiran is currently under review by multiple regulatory authorities around the world. The U.S. Food and Drug Administration (FDA) approved AMVUTTRA™ (vutrisiran) in 14th of June 2022, an RNAi therapeutic for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults based on this trial
Eplontersen is being tested in phase 3 studies in stage 1 or 2 patients with hereditary ATTR-PN, completion date through June 2024
• Analysis of the subgroup of patients with cardiomyopathy from the APOLLO study suggests that patisiran may halt or reverse the progression of the cardiac manifestations of ATTRv
Three ongoing, randomized, double-blind, multicenter, placebo-controlled trials are evaluating the efficacy and safety of genetic silencers in patients with Transthyretin Amyloidosis cardiomyopathy, either hereditary or wild-type ATTR
1. APOLLO B-Patisiran 0.3 Mg/Kg IV 3/3w, Estimated Completion Date June 2025. 340 participants. Primary outcomes measures: change from baseline to month 12 in 6-Minute Walk Test (6-MWT). Patisiran met the primary endpoint with improvement in 6-MWT compared to placebo at 12 months. Also met the first secondary endpoint with statistically significant improvement in quality of life ((KCCQ-OS)

Silencers highlights
2. HELIOS B-Vutrisiran 25 Mg SQ 3/3 M, Estimated Completion Date June 2025. The new siRNA that has the advantage of being applied subcutaneously every 3 months. 655 participants. Primary measures: all-cause mortality and recurrent CV events (CV outcomes hospitalizations and urgent HF visits) in 30 months
3. CARDIO-TTRansform- eplontersen, a new ASO, sc 4/4w, estimated completion date June 2024. 750 participants. Primary measures: composite outcome of cardiovascular (CV) mortality and recurrent CV clinical outcomes at Week 120

22.8 Transthyretin Stabilizers

Transthyretin is a tetrameric protein composed of 4 identical monomers. In the 1990s, Kelly et al. demonstrated that the dissociation of tetramers into monomers was quickly followed by incorrect folding of monomers and the formation of fibrillar aggregates, which is a crucial and limiting step in the amyloidogenic process [44, 45]. The identification of mutations in the TTR gene that would favor a greater dissociation of transthyretin and lead to amyloidosis and, conversely, the discovery of the benign variant Thr119Met (p. Thr139Met), which conferred greater stability to the tetramer by creating hydrogen bonds between the serine residues, preventing its dissociation even in the presence of known amyloidogenic variants such as Val30Met (p. Val50Met) and leading to milder or asymptomatic conditions [46, 47], made it possible to identify an important mechanism for the discovery and/or development of new drugs, which would in the future revolutionize the treatment of transthyretin-associated amyloidosis, with the emergence of tafamidis, the first transthyretin-stabilizing drug approved for clinical use in Europe in 2011 for familial amyloidotic polyneuropathy.

22.8.1 Tafamidis

Tafamidis is a selective stabilizer of TTR, which binds with negative cooperativity to the two binding sites of thyroxine in its native tetrameric form, preventing its dissociation into monomers, which is the rate-limiting step in the amyloidogenic process. It similarly stabilizes both the mutant transthyretin tetramer, including the most common forms Val30Met (p. Val50Met) and Val122Ile (p. Val142Ile), and the wild type [48, 49].

It was approved by the European Medicines Agency (EMA) in November 2011 based on the results of the Pivotal (Fx-005) [50], a multicenter, randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of tafamidis meglumine 20 mg orally once daily in 128 patients with stage I amyloidotic polyneuropathy associated with transthyretin (TTR) with Val30Met (p. Val50Met) mutation during 18 months of follow-up. The coprimary outcomes were the Lower Limb

Neuropathic Impairment Score (NIS-LL), the Norfolk-Diabetic Neuropathy Quality of Life scale, and the Total Quality of Life (TQOL) score. Despite not reaching statistical significance in the coprimary outcomes in the analysis by intention to treat, possibly due to a greater than expected number of patients who underwent liver transplantation (they were considered nonresponders), in the per-protocol and secondary outcome analysis, there was benefit in the use of tafamidis, as shown by the proportion of patients without neurological progression defined by the NIS-LL of 60.0% for the intervention group and 38.1% for the placebo ($p = 0.041$) and less reduction in quality of life (TQOL). The drug was well tolerated, with no significant increase in adverse events compared to placebo. Unblinded (open label) extension studies, ranging in duration from 30 months to 8.5 years, demonstrated a sustained effect in reducing the progression of polyneuropathy and good tolerance to tafamidis and suggested an increase in survival [51–53]. Data from the Transthyretin Amyloidosis Outcomes Survey (THAOS), initiated in 2007, the largest ongoing observational study of both hereditary (ATTRv) and wild-type (ATTRwt) patients at multiple centers around the world, corroborated the safety and efficacy of tafamidis in slowing the progression of polyneuropathy [54, 55].

The FDA considered the data insufficient, not approving the use of tafamidis in the United States in 2012. It is currently approved in more than 40 countries for the treatment of early-stage familial amyloidotic polyneuropathy [51].

A Portuguese study carried out in the postmarketing period, basically composed of patients with polyneuropathy and Val30Met (p. Val50Met) mutation, showed that the response is variable, with 34% of patients presenting a complete response (responders) and stopping the progression of the disease, 36% presenting a partial response, with stabilization in some components of the disease but not others, and 30% presenting nonresponders, in which the disease continues its progression despite treatment [56]. Factors associated with better response were early-stage disease, female sex, and high serum native TTR value at the beginning of treatment. Therefore, it is of great importance to assess the response to treatment early and consider other therapies if the response is not satisfactory. Partial responders or nonresponders could show better results with the 80 mg dose; however, this dose has not been tested in polyneuropathy trials.

In 2018, an important trial was published, the ATTR-ACT (The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial), showing that tafamidis was superior to placebo in the treatment of amyloidotic cardiomyopathy (ATTR-CM) associated with transthyretin. It was a randomized, multicenter, double-blind study with 441 patients, 76% wild type and 24% hereditary, with a mean age of approximately 75 years, with almost 90% men, NYHA I to III, who were divided into 3 groups, in a 2:1:2 ratio, for tafamidis meglumine 80 mg, 20 mg or placebo for 30 months. There was a reduction in the primary end point all-cause mortality of 30% (hazard ratio 0.7 and $p < 0.001$), with 78 deaths/264 in the tafamidis group (29.5%) vs 76/177 in the placebo group (42.9%), with an NNT of 7, followed, in a hierarchical manner, by a 32% reduction in the second primary outcome of hospitalizations for cardiovascular causes. In addition, there was a reduction in secondary outcomes, with less decline in the 6-Minute walk test and quality of life score as measured by

the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) [57]. The survival benefit was identified from 18 months after the start of treatment, while the reduction in the decline in functional capacity occurred from the sixth month and the reduction of biomarkers (NT-proBNP) after 9 months. There were a greater number of hospitalizations for cardiovascular causes in NYHA III patients who used tafamidis, probably due to increased survival in those with more advanced disease. It should be noted that both the 20 and 80 mg doses reduced total mortality and hospitalizations for cardiovascular causes, but with greater stabilization of transthyretin, evidenced by the higher serum TTR value and more pronounced reduction in NT-proBNP at 30 months in the 80 mg group. However, the study was not designed for comparison between doses but between the tafamidis (20 mg + 80 mg) × placebo group.

Upon completing the 30-month follow-up proposed in the original study, patients could be included in the ATTR-ACT and long-term extension study (LTE), which would assess the long-term results, for 60 months, of using tafamidis. In this study, participants in the intervention group continued the same doses, whereas those who received placebo were randomized again in a 2:1 ratio for the 80 mg or 20 mg dose, stratified by the type of TTR (ATTRwt and ATTRv). As of July 2018, the LTE protocol promoted the switch, in all patients, to tafamidis in the free acid form of 61 mg in a single tablet, which is equivalent to tafamidis meglumine 80 mg (4 cps of 20 mg). The average total time from tafamidis use to replacement was 39 months.

In the analysis of the ATTR-ACT (30 months) and the extension study (LTE) with a mean follow-up of 51 months, a relative reduction in total mortality of 30% was observed with the 80 mg dose compared to the 20 mg dose ($p = 0.0374$), with evidence of even greater benefit (43% reduction) after adjusting for covariates such as age and NT-proBNP, as the subgroup that received the 80 mg dose was older (76 × 73.5 years, $p = 0.04$) and had more advanced disease [58].

Tafamidis was also relatively well-tolerated at long-term follow-up, with no significant difference in adverse effects between doses, with a similar discontinuation rate (17.6% at the 80 mg dose and 20% at the 20 mg dose) [56]. Diarrhea was slightly more common with the 80 mg dose (8%) versus the 20 mg dose (2.3%), but less common than placebo (10.2%) at 30 months [57].

A recent publication comparing only the group that received 80 mg in the ATTR-ACT + LTE trial versus the placebo group, which was later randomized in the extension study (LTE) to doses of 20 or 80 mg, with a total of 58 months of follow-up, showed a reduction in total mortality of 41% (hazard ratio 0.59 with $p < 0.001$), with benefit independent of functional class and type of amyloidosis (TTRv or TTRWt). Even patients randomized late to tafamidis (after 30 months), with more advanced disease, would still show benefit in reducing outcomes compared to the expected mortality curve for the placebo group. The predicted survival curve estimate for 5 years of follow-up indicates that 53.2% of those randomized to treatment with tafamidis will be alive, with better outcomes in the wild type and in NYHA I or II at the beginning of the study, emphasizing the need for early diagnosis and rapid initiation of treatment [59].

Use of tafamidis in clinical practice
Presentation
• Vyndaqel® (tafamidis meglumine) 20 mg, cp. Packs with 30 and 120 cps
• Vindamax® (tafamidis free acid) 61 mg, cp (equivalent to 80 mg of tafamidis meglumine)
This formulation was approved by the FDA in 2019, by the EMA in 2020 and is not yet available in Brazil
• Dose for neurological impairment: 20 mg tafamidis meglumine orally once daily for stage I hereditary polyneuropathy (EMA approved indication)
• Dose for cardiological or mixed involvement: 80 mg of tafamidis meglumine (4 cps 1x daily) or Vyndamax 61 mg, 1cp, orally, 1× daily for patients with NYHA I to III cardiomyopathy, both in the wild form (ATTRwt) and in the hereditary (ATTRv)
Usage guidelines:
• Swallow the tablet whole, without chewing, with or without food
• We suggest using the tablet at night, due to the lower perception of possible side effects such as abdominal discomfort
• No dose adjustment is necessary for patients with renal impairment as tafamidis is metabolized by glucuronidation. However, safety data in patients with advanced kidney disease are scarce (patients with eGFR < 25 mL/min/1.73 m^2 were excluded from the ATTR-ACT trial). No adjustment required for patients with mild or moderate hepatic impairment
• Use on people over 18 years old. Safety not established for use in pregnant or lactating women
A major limitation for use in clinical practice is the high cost, with an estimated cost in the United States of more than 200 thousand dollars/year in the treatment of cardiomyopathy, requiring a 90% reduction in its price to be considered cost-effective [60]

Does tafamidis interfere with thyroid function?
Although tafamidis binds to the 2 thyroxine binding sites, transthyretin is responsible for the transport of a small portion of thyroxine (T4), only 5–15%, with the rest being transported by thyroxine-binding globulin and to a lesser extent by albumin. Therefore, the drug does not significantly interfere with the transport of thyroid hormones [61]

22.8.2 Other Transthyretin Stabilizers

After the discovery of the mechanism responsible for the formation of fibrillar aggregates resulting from the dissociation of transthyretin, two classes of drugs, which bind to thyroxine binding sites, emerged as promising in the stabilization of the tetramer and with the potential to delay/prevent the amyloidogenic process. Tafamidis is derived from benzoxazole acid and a second group that belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDS), such as diflunisal [62] and mefenamic acid [63, 64]. However, a concern with the chronic use of drugs in this class, as they inhibit the cyclooxygenase enzyme, would be the potential for adverse effects on renal, gastrointestinal, and cardiotoxicity functions.

22.8.3 Diflunisal

A low-cost, generic drug of the NSAID class has been shown to stabilize transthyretin in vitro [64, 65]; reduced the progression of polyneuropathy in a randomized, double-blind, placebo-controlled study with 130 patients (64 in the diflunisal group and 66 in the placebo) with familial amyloidotic polyneuropathy (FAP-ATTR), 54.6% with the Val30Met (p. Val50Met) mutation, receiving diflunisal 250 mg orally twice a day for 2 years. The primary outcome was the Neuropathy Impairment Score Plus 7 Nerve Tests (NIS + 7), which ranges from 0 (no neurological impairment) to 270 and combines clinical neurological assessment and tests of nerve conduction. There was a significant reduction in the elevation in NIS + 7 (intention to treat analysis) in the group that used diflunisal, as it increased by 25 points in the placebo group and 8.7 in the intervention group ($p < 0.001$), showing a reduction in the progression of polyneuropathy. The secondary quality of life outcome assessed by the 36-item Short-Form Health Survey (SF-36) questionnaire also showed better results in the intervention group, with a gain in quality of life compared to placebo. At 2 years of treatment, 29.7% of the diflunisal group had stable neurological involvement (increase < 2 points on NIS + 7), compared to only 9.4% in the placebo group ($p = 0.007$). There was a considerable rate of treatment discontinuation before completing the 2 years of the study, with 40 in the placebo group and 27 in the intervention group, the main reason being the referral for liver transplantation due to disease progression. Drug discontinuation due to adverse effects occurred in 4 patients in the diflunisal group and 2 in the placebo group, with good drug tolerance over the 2 years of the study. There were 13 deaths (9 in the placebo group and 4 in the intervention group) [66].

Regarding transthyretin-related amyloid cardiomyopathy (ATTR-CM), a study has shown that diflunisal is safe in selected patients with ATTR-CM [67], stabilizes parameters related to ventricular function [68], provides stability, increases TTR serum levels, with a reduction in cardiac biomarkers and a smaller decrease in ejection fraction [69], and has a mortality reduction similar to that of tafamidis in a retrospective, nonrandomized, single-center cohort of 120 patients (13 used diflunisal and 16 used tafamidis) [70].

A systematic review and meta-analysis published in 2021 evaluated six studies published from 2012 to 2020, with the most consistent data on the use of diflunisal in ATTR-CM, with approximately 400 patients, mean age of participants from 68.5 years, 84.8% men, NYHA I to III (only 2 studies described the functional class), with patients presenting both wild-type (ATTRwt) and hereditary (ATTRv) cardiomyopathy. Four of these studies were nonrandomized and single-arm, and the other 2 were retrospective and nonrandomized, comparing the use of diflunisal versus no treatment. The studies showed that diflunisal was safe and well-tolerated in patients with cardiomyopathy and had a low rate of discontinuation due to significant adverse effects, the main side effects being gastrointestinal and transient worsening of renal function (infrequent in the first year of use). The 2 studies comparing diflunisal versus no treatment showed an increase in serum TTR, indicating greater

stabilization of transthyretin, improvement in indexed left atrial volume, troponin I, and global longitudinal strain, as well as reduced mortality and need for heart transplantation [71].

A retrospective cohort study from the Boston University Center for Amyloidosis was recently published, with 104 patients in the wild-type (ATTRwt-CM), 97% male, mean age 75.8 years, NYHA I to III, with eGFR > 45 ml/min/1.73 m^2, with 35 patients who used diflunisal (34%). The treatment group was younger (73.8 × 76.8 years), with lower BNP and better kidney function than the untreated group. In the 3.4-year follow-up, 52 deaths occurred, 4 in those who used diflunisal (11.4%) and 48 in those who did not use it (69.6%). After adjusting for age, BNP, troponin, glomerular filtration rate, intraventricular septum thickness, and ejection fraction, there was an 82% reduction in mortality (HR 0.18, 95% CI 0.06–0.51, $p = 0.0006$), without significant changes in BNP, troponin, intraventricular septal thickness, and ejection fraction, demonstrating stability in echocardiographic and biomarker parameters in patients who received diflunisal. Fourteen patients discontinued treatment (57% due to worsening renal function), but only 3 discontinued treatment in the first year (9%) [72].

Despite the marked reduction in mortality, even after adjustments for confounding variables, this is a retrospective study, with possible biases, especially selection, being another hypothesis generator that should be corroborated in randomized, double-blind studies of adequate quality.

The great advantage of diflunisal would be its cost (estimated at 500 dollars a year), which is much lower than that of tafamidis.

Use of diflunisal in clinical practice
• Diflunisal 250 mg or 500 mg, cp
• 1 tablet of 250 mg twice daily or half of 500 mg twice daily (presentation available in the United States) orally, swallow whole tablet without chewing, administer with meals or milk to decrease gastrointestinal side effects
• It showed a reduction in the progression of polyneuropathy in a randomized study, even so its use is still considered off-label, as this recommendation is not included in the drug leaflet
• Off-label use for cardiomyopathy (ATTR-CM), evidence of reduced outcomes based on retrospective studies
• Much lower cost than tafamidis, as it is a generic drug
• Do not start if eGFR < 45 ml/min/1.73 m^2, use of high doses of diuretics, or decompensated HF
• After onset repeat renal function in 2 weeks. Main side effects are gastrointestinal and worsening of kidney function

22.8.4 Acoramidis (AG10)

A transthyretin stabilizer that was developed to mimic the mechanism that occurs in the presence of the benign variant Thr119Met, which has been shown to prevent or reduce tetramer dissociation. The phase III, ATTRibute-CM, multicenter,

double-blind study included 632 participants with ATTR-CM, both wild-type and hereditary, NYHA I to III who were randomized 2:1 to acoramidis 800 mg twice daily × placebo. The study was designed in two parts: part A, the primary outcome of which is the change from baseline in the 6-Minute walk test (6MWD) at 12 months; and part B, which will assess mortality for all causes and hospitalizations from cardiovascular causes at 30 months and in a hierarchical manner [73]. The company Bridge Pharma released the preliminary results of part A, which did not reach statistical significance in the primary outcome related to 6MWD, with a reduction of 9 m in the acoramidis group × 7 m in the placebo group. Improvement in quality of life was observed by KCCQ-OS, a lower increase in NT-proBNP and an increase in serum TTR. The drug was well tolerated. What caught our attention in the study was that the decline in functional capacity (6MWD) in the placebo group was much smaller than expected, which was a fall >40 m considering the untreated (placebo) arms of other studies, such as ATTR-ACT. The independent data monitoring committee recommended the continuation of the study, and the steering committee cochairs and Bridge Pharma believe that the drug still has the potential to show benefit at 30 months (part B).

22.8.5 Tolcapone (Tasmar®)

A drug approved by either the FDA or EMA for the treatment of Parkinson's disease was shown to effectively stabilize transthyretin, both TTRwt and TTRv (Val122Ile), by binding to thyroxine binding sites. It showed stabilization of transthyretin in phase 2 studies [74]. Phase III studies are still needed, showing a reduction in clinical outcomes. Due to its lower cost and good tolerance, it may be a good option in the future.

Main points of stabilizers
• The limiting step of the amyloidogenic process is the dissociation of the tetramer from transthyretin
• Transthyretin-stabilizing drugs prevent or delay this process
• The drug with the best evidence in reducing clinical outcomes is tafamidis
• Tafamidis reduced the progression of polyneuropathy and improved the quality of life in patients with neurological involvement by stage I ATTRv, at a dose of 20 mg once daily
• Tafamidis at doses of 20 and 80 mg, reduced all-cause mortality, hospitalizations for cardiovascular causes, had less loss of functional capacity assessed by the 6-min walk test and better quality of life compared to placebo, according to study data ATTR-ACT, over 30 months of follow-up
• Tafamidis was well-tolerated at both 20 and 80 mg doses
• The 80 mg dose led to greater stabilization of TTR and greater fall in NT-proBNP at 30 months. It should be noted that the study was not designed to compare the efficacy between doses
• In the extension study (LTE), the 80 mg dose promoted a 30% relative reduction in mortality compared to the 20 mg dose

Main points of stabilizers
• The recommended dose for the treatment of ATTR-CM both ATTRwt and ATTRv is 61 mg Tafamidis free acid (Vindamax®) or 80 mg tafamidis meglumine (Vyndaqel®), 4 tablets of 20 mg once daily
• The major limitation for the use of tafamidis is the high cost, which is not considered cost-effective
• Diflunisal has been shown to reduce polyneuropathy progression and improve quality of life in patients with polyneuropathy (ATTRv) in a randomized trial
• Showed a reduction in mortality, biomarkers, and echocardiographic parameters in retrospective studies on ATTR-CM in both ATTRwt and ATTRv
• Its use is still considered off-label and requires good quality randomized studies to assess its efficacy in amyloidotic cardiomyopathy
• It has the advantage of being much cheaper and becomes an option in places where tafamidis and silencers (patisiran, inotersen) are not available for financial reasons
• The primary concern is worsening glomerular filtration rate with chronic use and gastrointestinal effects. Do not use if eGFR < 45 ml/min/1.73 m^2
• Acoramidis (AG10) did not reach the primary endpoint in part A of the ATTRibute-CM study. However, the study will continue to assess mortality at 30 months (part B)
• Approved Parkinson's drug Tolcapone has been shown to satisfactorily stabilize TTR in phase II studies. Phase III studies are still needed

22.9 Amyloid Fibril Disruption Therapy

22.9.1 Doxycycline and Tauroursodeoxycholic Acid (TUDCA) or Ursodeoxycolic Acid (UDCA)

Most drugs for the treatment of transthyretin-related amyloidosis act by preventing or reducing the formation and deposition of amyloid fibrils, but with no effect on fibrils already deposited in organs and tissues.

Doxycycline is an antibiotic of the tetracycline group, which has been shown to remove TTR amyloid deposits in preclinical studies, reducing the extracellular matrix remodeling proteins that accompany fibrillar deposition but not of nonfibrillar TTR deposition. On the other hand, tauroursodeoxycholic acid (TUDCA), a biliary acid, was shown to be effective at lowering deposited nonfibrillar TTR, as well as the levels of markers associated with prefibrillar TTR. The combination of the two drugs showed a synergistic effect on the degradation of amyloid deposits [75].

A phase II clinical, single arm study, with a small number of patients, with oral administration of doxycycline 100 mg 2× daily + TUDCA 250 mg 3× daily for 12 months, suggested that the association could stabilize the neurological and cardiac involvement of ATTR with a reasonable tolerability profile [76]. Another study, also without a control group (observational cohort study), with a greater number of participants, 53 patients with amyloid cardiomyopathy (ATTR-CM), mean age of 71 years, 89% wild type and 87% men, used the combination of doxycycline and ursodiol (ursodeoxycholic acid) with a median follow-up of

22 months, with 11% not tolerating the therapy due to gastrointestinal or dermatological side effects. Regarding clinical outcomes, there was no worsening of functional class (NYHA), cardiac biomarkers, or echocardiographic parameters, with 38% showing improvement in global longitudinal strain (−12 to −17; $p < 0.01$), particularly in younger patients with less advanced disease [77]. The results of this study showed that drug administration was well-tolerated in approximately 90% of cases and was associated with clinical and markers of disease progression stabilization.

A randomized, open-label phase III study (NCT01171859) with more than 100 patients with ATTR cardiomyopathy (ATTRv or ATTRwt) is evaluating doxycycline 100 mg twice daily + TUDCA 250 mg thrice daily orally versus conventional treatment, and its primary endpoint is to compare survival at 18 months [78]. The results from phase III studies are expected, as the major advantage of this association would be its low cost, unlike other disease-modifying therapies with much higher cost.

22.9.2 Green Tea Extracts (EGCG)

Epigallocatechin-3-gallate (EGCG), the most abundant catechin (polyphenol) in green tea (GT), is a natural compound with very low toxicity that inhibits fibril formation from several amyloidogenic proteins in vitro, including TTR [79], and converts existing fibrils into nonfibril conformers [80].

EGCG binds at the surface of the protein in a region involving amino acid residues at the interface of both dimers, promoting tetramer conformational stabilization [81]. EGCG acts not only as an inhibitor of TTR amyloid formation, but also as a disruptor of amyloid fibrils [82, 83].

A series of 19 patients with ATTR cardiomyopathy (both hereditary and wild type) evaluated by standard blood tests, echocardiography, and cardiac MRI before and after consumption of GT and/or green tea extracts (GTE) for 12 months showed no increase in left ventricular (LV) wall thickness or LV myocardial mass observed by echocardiography. In the subgroup of patients evaluated by cardiac MRI ($n = 9$), a mean decrease in LV myocardial mass (−12.5%) was detected in all patients. Total cholesterol and LDL cholesterol decreased significantly during the observational period. No serious adverse effects were reported by any of the participants [84]. This observational report suggests an inhibitory effect of GT and/or GTE on the progression of cardiac amyloidosis. Another cohort of 25 patients with ATTRwt-CM who underwent clinical examination, echocardiography, cardiac magnetic resonance imaging ($n = 14$), and laboratory testing before and after daily consumption of GTE capsules containing 600 mg epigallocatechin-3-gallate for at least 12 months showed a significant decrease in left ventricular (LV) myocardial mass by 6% by cMRI and total cholesterol by 8.4%. LV ejection fraction by cMRI and LV wall thickness by echocardiography remained unchanged. This study supports LV mass stabilization in patients with ATTRwt-CM with good tolerability.

Good quality randomized trials are needed to establish the real benefit of ECGC in the treatment of ATTR. However, due to its low cost and good tolerability, it becomes an off-label option, especially in places without access to therapies with the best level of evidence.

Highlights
Doxycycline disrupts amyloid fibrils in vitro and in animal models synergistically with tauroursodeoxycholic acid (TUDCA)
Phase I and II studies show ATTR neuropathy and cardiomyopathy stabilization, with acceptable tolerability. Phase III study in ATTR cardiomyopathy, not yet published, may provide further evidence on the efficacy and safety of this low-cost combination
The recommended dose is Doxycycline 100 mg 1 cp 2× day and TUDCA 250 mg 3× a day
Do not take the drug before bedtime, avoid use in patients with a history of esophagitis and use sunscreens due to the increased risk of photosensitivity skin lesions
Do not use in pregnant or breastfeeding women
EGCG a natural compound, present in green tea, with very low toxicity acts as inhibitor of TTR amyloid formation and as disruptor of amyloid fibrils
Preclinical and small, single arm, nonrandomized, phase I and II studies suggest an inhibitory effect on the progression of cardiac amyloidosis with good tolerability
The recommended dose is ECCG 600 mg 1 cp a day
Doxy/TUDCA and/or ECGC are off-label options to be considered when other therapies with better evidence as tafamidis or TTR silencers are inaccessible

After discussing the main treatments of ATTR amyloidosis, a flow chart to guide treatment is shown below (Fig. 22.3).

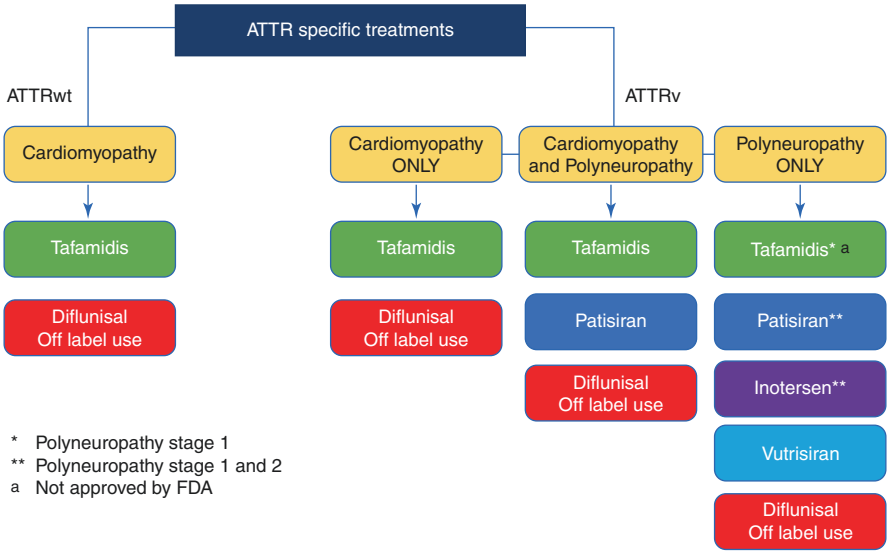


Fig. 22.3 Specific treatments for transthyretin amyloidosis. Reference: Modified from Garcia-Pavia et al., EHJ, 2021; 42:1554–68

22.10 Emerging Therapies

22.10.1 Gene Editing Therapy

In 2020, the Nobel Prize in Chemistry was awarded to researchers Emmanuelle Charpentier and Jennifer Doudna for the discovery of the most widely used gene editing method today, the Clustered Regularly Interspaced Short Palindromic Repeats and associated Cas9 endonuclease system (CRISPR/Cas9). ATTR amyloidosis is an ideal model for the application of this technique in vivo, being a monogenic disease in which almost all TTR production occurs in the liver.

NTLA-2001 is a therapy based on this technique administered intravenously in a single dose that consists of two active components: the Cas9 protein that recognizes a specific sequence in TTR and promotes double-strand cleavage and an RNA guide that directs the Cas9 protein for this specific sequence in the TTR gene. Endogenous DNA repair mechanisms link the ends of the cut, introducing insertions or deletions of bases generating missense or nonsense mutations that will decrease the amount of full-length mRNA levels and, consequently, of the target protein (knockout mutation). NTLA-2001 uses a lipid nanoparticle to load these molecules and guide them to the hepatocyte, where uptake occurs via LDL receptors [7, 85, 86].

In an ongoing phase 1 clinical study that evaluated safety and pharmacodynamic effects in six patients with ATTRv and polyneuropathy (three receiving a dose of 0.1 mg/kg and three receiving a dose of 0.3 mg/kg), the mean reduction in serum TTR up to 28 days from baseline was 52% in the lowest dose group and 87% in the highest dose group. No serious adverse events were observed. The study is still ongoing to assess the durability of efficacy and safety of the treatment, and these initial results should be carefully evaluated due to the small sample size and the very short follow-up [86].

22.10.2 Immunotherapeutic Agents

One of the promising lines of research is the extraction of amyloid deposits in tissues through monoclonal antibodies. NI006 is a monoclonal antibody that targets misfolded and aggregated forms of both ATTRwt and ATTRv. A phase 1, randomized, placebo-controlled, double-blind trial in subjects with amyloid transthyretin cardiomyopathy (ATTR-CM) is currently enrolling (NCT04360434). PRX-004 is a monoclonal antibody that binds to misfolded amyloid TTR, but not to native circulating TTR, thus clearing amyloid deposits in the myocardium, as investigated in a phase 1 study (NCT03336580).

Serum amyloid P component (SAP) is a nonfibrillar plasma glycoprotein formed in the liver that binds to all types of amyloid fibrils. Experimental and phase 1 studies with monoclonal antibodies directed to SAP resulted in a complement-dependent phagocytic clearance of amyloid deposits in tissues [87]. However, a recent phase 2

study failed to show an improvement in cardiac burden after treatment with an anti-SAP antibody with an early termination of the study [88].

22.11 Treatment Response and Disease Progression Markers

With the advent of specific treatments for amyloidosis, determining the response to treatment is an important measure to guide clinical management. There is still no consensus on the best way to monitor this response, but clinical/functional, laboratory, and imaging parameters have been used separately and mainly together to determine the effectiveness of treatment with regression or stabilization and, in other cases, progression of the disease.

22.11.1 Treatment Response Markers

Stabilizers such as tafamidis, diflunisal, and acoramidis act by reducing the rate of degradation of TTR molecules in the process of forming amyloid fibrils by maintaining their three-dimensional conformation. By stabilizing the tetramer preventing its dissociation and unfolding, stabilizers can increase the serum level of TTR in patients whose levels would be reduced by the pathophysiological mechanism of the disease, theoretically being a surrogate of treatment efficacy. Corroborating this hypothesis, cohort studies with small samples demonstrate an increase in the serum level of TTR with the use of stabilizers when compared before and after treatment [89, 90]. To date, serum TTR measurement is not part of clinical practice in the follow-up of patients with ATTR. Its serum level varies according to age, sex, and ethnicity. It is an acute-phase negative protein whose levels may be reduced in inflammatory states such as infections or in a deficient nutritional state. Conversely, its serum levels decrease when the patient receives treatment with silencers that are potent inhibitors of its hepatic synthesis.

There are several advantages of measuring biomarkers in ATTR, being useful in population screening for early disease detection, risk stratification, disease progression, and response to treatment. Several randomized clinical studies that investigated the efficacy of new drugs in the specific treatment of amyloidosis followed the variation in the concentration of biomarkers at baseline and at follow-up, mainly natriuretic peptides such as NT-proBNP and, more rarely, troponins. In the ATTR-ACT study, at the 30-month follow-up, there was an increase in NT-proBNP concentration but a smaller increase in the tafamidis group when compared to the control group [57]. In the APOLLO study, at the 18-month follow-up, there was a reduction in NT-proBNP concentration from baseline in the patisiran group, which did not occur in the placebo group (55% reduction in concentration at 18 months compared to placebo) [36].

The effect of patisiran on cardiac amyloid burden measured by extracellular volume (ECV) mapping on cardiac magnetic resonance imaging was evaluated in a small prospective study with 16 patients with hereditary ATTR with a 12-month follow-up. The variation in ECV was compared to a historical control group of 16 patients with similar baseline characteristics who did not receive specific treatment. In the patisiran group, a reduction in ECV was observed in 38%, an increase in 19% and there was no change in 44%. In the control group, there was no change in 44% of patients, while 56% had an increase in ECV [91]. In another cohort study, the effect of tafamidis treatment on the ECV of patients with wild-type ATTR-CM was analyzed in three groups: tafamidis 61 mg (mean follow-up 9 months), historical group tafamidis 20 mg (mean follow-up 11 months), and historical group patients without specific treatment (mean follow-up 12 months). The study showed a stabilization of ECV in both tafamidis groups, while there was a marked expansion of ECV in the historical group without specific treatment. The difference in ECV of the 61 mg tafamidis group was statistically significant compared to the no specific treatment group [92]. Both studies should be considered hypothesis generators that need confirmation in larger studies and with adequate methodology.

Neurofilament light chain (NfL) may serve as a biomarker of active nerve damage and polyneuropathy due to TTR amyloid deposition, making it useful as a potential biomarker of disease progression and treatment response in ATTRv polyneuropathy [93]. This marker is not yet available in clinical practice.

Main points of treatment response markers (Cardiomyopathy)
The optimal method of monitoring response to amyloid treatment is currently poorly understood
Multiple markers may be used including clinical parameters, biomarkers, and cardiac imaging
NT-proBNP and troponin are important prognostic markers and should be performed routinely
Serial Tc-PyP/DPD is not appropriate for monitoring response to therapy [94]
Novel PET tracers like 11c-Pittsburgh B and 18F-Florbetapir are under investigation
TTR measurement is not part of clinical practice until the moment
ECV is markedly elevated in ATTR-CM and correlates with histologic amyloid burden [95]. ECV by CMR is highly reproducible and is a promising method for monitoring response to treatment

22.11.2 Disease Progression Markers

In the absence of a consensus, in 2021, an international group of experts developed recommendations for the monitoring of patients with ATTR-CM [96]. In this document, 11 parameters were selected from three different types of domains: (1) domain of clinical and functional outcomes; (2) domain of biomarkers and laboratory markers; and (3) domain of imaging and electrocardiographic parameters (Table 22.2). For the authors, the minimum criterion to confirm the progression of the disease would be the advancement of at least one of the parameters in each of the three domains (Tables 22.3 and 22.4).

Table 22.2 Domains and parameters for determining cardiac amyloidosis progression

Parameter and domain	Clinical features	Threshold indicating disease progression	Recommended reassessment frequency
Clinical and functional			
Medical and clinical history	Hospitalization for cardiovascular causes	Worsening indicated by any hospitalization related to decompensated HF within 6 months	6 months
NYHA class	NYHA class change	Increase of a measured class during a 30-day stability period	6 months
QoL: EQ-5D tool and KCCQ		A 5-point decrease in the KCCQ represents deterioration (a 10-point decrease represents moderate deterioration); 10% decline in EQ-5D score represents deterioration	6–12 months
Functional capacity	6MWT	Reduction of 30–40 m every 6 months (in the absence of an obvious noncardiovascular cause)	6 months
Biomarkers and laboratory markers			
NT-proBNP		30% increase with 300 pg/ml cutoff. To be measured over a 30-day period of stability and at the same atrial rhythm	6 months
Troponin (ultrasensitive)		30% increase	6 months
Clinical staging system		Progress in NAC staging score	6 months
Imaging and electrocardiographic parameters			
Echocardiography	LV measures wall thickness/mass	≥2 mm increase in LV wall thickness	6–12 months
	Measurements of systolic function	≥5% decrease in LV ejection fraction; ≥5 ml decrease in stroke volume; ≥1% increase LV global longitudinal strain	12 months
	Worsening of diastolic function	Stepwise increase in diastolic functioning grade; consistent with deterioration in diastolic function	12 months
ECG/Holter ECG	New onset of arrhythmic/ conduction disturbances	New-onset bundle branch block New-onset AV block (of any degree) Sinus pauses, sinus node dysfunction, AF with a very slow ventricular response without pharmacologic treatment (<50 bpm)	6 months

HF heart failure, *NYHA* New York Heart Association, *QoL* quality of life, *EQ-5D* EuroQol five dimensions, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *6MWT* 6-min walk test, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *NAC* UK National Amyloidosis Centre, *LV* left ventricular, *ECG* electrocardiogram, *AV* atrioventricular, *AF* atrial fibrillation. Adapted from Eur J Heart Fail. 2021 Jun;23(6):895–905

Table 22.3 Clinical and treatment assessment directed for hereditary TTR amyloidosis. In the wild type, cardiac involvement is predominant and may be associated with bilateral carpal tunnel syndrome, lumbar spinal stenosis or other neurological impairment, but usually without significant dysautonomic manifestations [96, 97]

Domain	Function or Clinical Manifestation	Assessment	Frequency
Neuropathy	Pain / Sensosry Loss	Neurological Examination Nerve Conduction Study VAS	6-12 months
	Motor	Neurological Examination PND score 10MWT Time Up and Go Test NIS	6-12 months
Dysautonomia	Gastrointestinal	Clinical Interview mBMI COMPASS-31	6-12 months
	Cardiovascular	Clinical Interview HRV Test MIBG Cardiac Scintigraphy Supine and Orthostatic BP	6-12 months
	Sexual	Clinical Interview COMPASS-31	12 months
	Urinary Tract	Clinical Interview COMPASS-31 Urodynamic Assessment	6-12 months
	Sudomotor	Sudoscan®	12 months
Cardiac	Arrhythmia	Clinical Interview ECG 24-hour Holter ECG	6-12 months
	Heart Failure	Clinical Interview NYHA Class 6MWT NT-proBNP Troponin Echocardiogram Cardiac MRI DPD/PYP Scintigraphy*	6-12 months
Ocular	Vision	Clinical Interview Ophthalmologic Examination Tonometry Slit Lamp Examination	12 months
Renal	Renal Function	Clinical Interview eGFR Urine Proteinuria	12 months
Quality of Life	Physical Health Mental Health Disability	Norfolk-QoI-DN SF-36 KCCQ R-ODS	6-12 months

10MWT **10-meter walk test,** *6MWT* **6-min walking test,** *BP* **Blood Pressure,** *COMPASS-31* **CompositeAutonomicSymptomScore-31,***DPD* **^{99m}Tc-diphosphono-1,2-propanodicarboxylicacid,** *ECG* **electrocardiogram,** *eGFR* **estimated glomerular filtration rate,** *HRV test* **Heart rate variability test,** *KCCQ* **Kansas City Cardiac Questionnaire,** *mBMI* **modified body mass index,** *MIBG* **metaiodobenzylguanidine,** *MRI* **Magnetic Resonance Image,** *NIS* **Neurological Impairment Score,** *Norfolk-Qol-DN* **Norfolk Quality of Life-Diabetic Neuropathy,** *NYHA* **New York Heart Association,** *PND* **Polyneuropathy Disability,** *PYP* **^{99m}Tc-pyrophosphate,** *R-ODS* **Rasch-built Overall Disability Scale,** *SF-36* **36-item Short Form Health Survey,** *VAS* **Visual Analog Scale**

[a]Consider DPD/PYP scintigraphy only for diagnosis of cardiomyopathy. Should not be used to monitor response to treatment

Table 22.4 Adapted from Conceição et al. 2019. Amyloid 2019 [97]

Criterias for recognition of disease progression (ATTRv)
General Domain Appearance of new manifestations such as erectile dysfunction, urinary incontinence or postural hypotension Worsening of modified BMI in at least 20%
Neurological domain Increase of more than 10 points in NIS scale Decrease of more than 50% in the amplitude of potentials in at least two distinct nerves
Cardiac domain* Refer to table 2
Oftalmological Domain Increase in intraocular pressure > 20 ou 5 mmHg Appearance of vitreous, corneal or crystalline deposits
Renal Domain Decrease of glomerular filtration rate >50% Appearance of proteinuria at nephrotic levels

As evidenced throughout the chapter, transthyretin amyloidosis is a multisystemic disease, especially in hereditary types, and requires multidisciplinary team follow-up, with nonpharmacological measures such as cardiac and neurological rehabilitation and symptomatic and specific treatment for the disease, providing improvement in morbidity and mortality. Reducing drug prices or developing less expensive agents is extremely important for ATTR-specific treatments to become widely available.

Despite major advances in the diagnosis and treatment of transthyretin amyloidosis, there are still many questions that need to be answered in the coming years, especially with good quality randomized trials.

Open questions in transthyretin amyloidosis treatment
• Definition and measurement of disease progression
• Definition of early responders/nonresponders to specific therapies
• Comparison between disease-modifying drugs in ATTR
• Criteria for switching from one drug to another
• Role of combined therapy
• Early initiation of therapy
– ATTRv mutation carriers without phenotype
– ATTR cardiac amyloidosis without heart failure
• Efficacy of heart failure drugs in ATTR-CM

Adapted from Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, 2021, EJHF

References

1. Kyle RA. Historical review. Amyloidosis: a convoluted study. Brit J Hematol. 2001;114:529–38.
2. Wilks S. Cases of lardaceous disease and some allied affections, with remarks. Guys Hosp Rep. 1856;2:103–32.
3. Andrade C. A peculiar form of peripheral neuropathy. Familiar atypical, generalized amyloidosis with special involvement of the peripheral nerves. Brain. 1952;75:408–27.
4. Morgan GJ. Transient disorder along pathways to amyloid. Biophys Chem. 2022;281:106711. https://doi.org/10.1016/j.bpc.2021.106711. Epub 2021 Oct 30. PMID: 34839162
5. Griffin JM, Rosenblum H, Maurer M. Pathophysiology and therapeutic approaches to cardiac amyloidosis. Circ Res. 2021;128:1554–75.
6. Nativi-Nicolau JN, Karam C, Khella S, Maurer MS. Screening for ATTR amyloidosis in the clinic: overlapping disorders, misdiagnosis, and multiorgan awareness. Heart Fail Rev. 2021; https://doi.org/10.1007/s10741-021-10080-2. Epub ahead of print
7. Griffin JM, Rosenthal JL, Grodin JL, Maurer MS, Grogan M, Cheng RK. ATTR amyloidosis: current and emerging management strategies. JACC CardioOncol. 2021;3(4):488–505.
8. Adam RD, Coriu D, Jercan A, Bădeliţă S, Popescu BA, Damy T, Jurcuţ R. Progress and challenges in the treatment of cardiac amyloidosis: a review of the literature. ESC Heart Fail. 2021;8(4):2380–96.
9. Kim MM, Kolseth CM, Carlson D, Masri A. Clinical management of amyloid cardiomyopathy. Heart Fail Rev. 2021; https://doi.org/10.1007/s10741-021-10159-w.
10. Vaishnav J, Hubbard A, Chasler JE, Lepley D, Cuomo K, Riley S, Menzel K, Fajardo J, Sharma K, Judge DP, Russell SD, Gilotra NA. Management of heart failure in cardiac amyloidosis using an ambulatory diuresis clinic. Am Heart J. 2021;233:122–31.
11. Rubinow A, Skinner M, Cohen AS. Digoxin sensitivity in amyloid cardiomyopathy. Circulation. 1981;63(6):1285–8.
12. Donnelly JP, Sperry BW, Gabrovsek A, Ikram A, Tang WHW, Estep J, Hanna M. Digoxin use in cardiac amyloidosis. Am J Cardiol. 2020;133:134–8.
13. Aimo A, Rapezzi C, Arzilli C, Vergaro G, Emdin M. Safety and efficacy of levosimendan in patients with cardiac amyloidosis. Eur J Intern Med. 2020;80:114–6.
14. Zampieri M, Argirò A, Allinovi M, Perfetto F, Cappelli F. SGLT2i in patients with transthyretin cardiac amyloidosis, a well-tolerated option for heart failure treatment? Results from a small, real-world, patients series. Intern Emerg Med. 2022; https://doi.org/10.1007/s11739-022-02944-8. Epub ahead of print
15. Gertz MA, Skinner M, Connors LH, Falk RH, Cohen AS, Kyle RA. Selective binding of nifedipine to amyloid fibrils. Am J Cardiol. 1985;55(13 Pt 1):1646.
16. Cheng RK, et al. Lack of association between Neurohormonal blockade and survival in transthyretin cardiac amyloidosis. J Am Heart Assoc. 2021;10(24):e022859. https://doi.org/10.1161/JAHA.121.022859. Epub 2021 Nov 3
17. Barge-Caballero G, Barge-Caballero E, López-Pérez M, Bilbao-Quesada R, González-Babarro E, Gómez-Otero I, López-López A, Gutiérrez-Feijoo M, Varela-Román A, González-Juanatey C, Díaz-Castro Ó, Crespo-Leiro MG. Beta-blocker exposure and survival in patients with transthyretin amyloid cardiomyopathy. Mayo Clin Proc. 2022;97(2):261–73.
18. Gendre T, Planté-Bordeneuve V. Strategies to improve the quality of life in patients with hereditary transthyretin amyloidosis (hATTR) and autonomic neuropathy. Clin Auton Res. 2019;29(Suppl 1):25–31.
19. Bentellis I, Amarenco G, Gamé X, et al. Diagnosis and treatment of urinary and sexual dysfunction in hereditary TTR amyloidosis. Clin Auton Res. 2019;29(Suppl 1):65–74.
20. Obici L, Suhr OB. Diagnosis and treatment of gastrointestinal dysfunction in hereditary TTR amyloidosis. Clin Auton Res. 2019;29(Suppl 1):55–63.
21. Palma JA, Gonzalez-Duarte A, Kaufmann H. Orthostatic hypotension in hereditary transthyretin amyloidosis: epidemiology, diagnosis and management. Clin Auton Res. 2019;29(Suppl 1):33–44.

22. Barrett CD, Alexander KM, Zhao H, Haddad F, Cheng P, Liao R, Wheeler MT, Liedtke M, Schrier S, Arai S, Weisshaar D, Witteles RM. Outcomes in patients with cardiac amyloidosis undergoing heart transplantation. JACC Heart Fail. 2020;8(6):461–8.
23. Ericzon B-G, Wilczek HE, Larsson M, Wijayatunga P, Stangou A, Pena JR, Furtado E, Barroso E, Daniel J, Samuel D, Adam R, Karam V, Poterucha J, Lewis D, Ferraz-Neto B-H, Cruz MW, Munar-Ques M, Fabregat J, Ikeda S-I, Ando Y, Heaton N, Otto G, Suhr O. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? Transplantation. 2015;99(9):1847–54.
24. Saelices L, Chung K, Lee JH, Cohn W, Whitelegge JP, Benson MD, Eisenberg DS. Amyloid seeding of transthyretin by ex vivo cardiac fibrils and its inhibition. Proc Natl Acad Sci U S A. 2018;115(29):E6741–50.
25. Yazaki M, Mitsuhashi S, Tokuda T, Kametani F, Takei Y-I, Koyama J, Kawamorita A, Kanno H, Ikeda S-I. Progressive wild-type transthyretin deposition after liver transplantation preferentially occurs onto myocardium in FAP patients. Am J Transplant. 2007;7(1):235–42.
26. Kumar S, et al. State-of-the-art review on management of end-stage heart failure in amyloidosis: transplant and beyond. Heart Fail Rev. 2022; https://doi.org/10.1007/s10741-021-10209-3.
27. Okamoto S, Zhao Y, Lindqvist P, Backman C, Ericzon B-G, Wijayatunga P, Henein MY, Suhr OB. Development of cardiomyopathy after liver transplantation in Swedish hereditary transthyretin amyloidosis (ATTR) patients. Amyloid. 2011;18(4):200–5.
28. Mathew V, Wang AK. Inotersen: new promise for the treatment of hereditary transthyretin amyloidosis. Drug Des Devel Ther. 2019;13:1515–25.
29. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med. 2018;379(1):22–31.
30. Brannagan TH, Wang AK, Coelho T, et al. Early data on long-term efficacy and safety on inotersen in patients with hereditary transthyretin amyloidosis: a 2-year update from the open-label extension of the NEURO-TTR trial. Eur J Neurol. 2020;27(8):1374–81.
31. US National Library of Medicine. ClinicalTrial.gov. https://www.clinicaltrials.gov/ct2/show/NCT05071300
32. US National Library of Medicine. ClinicalTrial.gov. https://www.clinicaltrials.gov/ct2/show/NCT04136171
33. Han H. RNA interference to Knock down gene expression. Methods Mol Biol. 2018;1706:293–302.
34. Zhang X, Goel V, Attarwala H, et al. Patisiran pharmacokinetics, pharmacodynamics, and exposure-response analyses in the phase 3 APOLLO trial in patients with hereditary transthyretin-mediated (hATTR) amyloidosis. J Clin Pharmacol. 2020;60(1):37–49.
35. Titze-de-Almeida SS, Brandão PRP, Faber I, et al. Leading RNA interference therapeutics part 1: silencing hereditary transthyretin amyloidosis, with a focus on Patisiran. Mol Diagn Ther. 2020;24(1):49–59.
36. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2018;379(1):11–21.
37. Yang J. Patisiran for the treatment of hereditary transthyretin-mediated amyloidosis. Expert Rev Clin Pharmacol. 2019;12(2):95–9.
38. Adams D, Polydefkis M, Gonzales-Duarte A, et al. Long-term safety and efficacy of Patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study. Lancet Neurol. 2021;20(1):49–59.
39. Solomon SD, Adams D, Kristen A, Grogan M, et al. Effects of Patisiran, an RNA interference therapeutic, on cardiac parameters in patients with hereditary transthyretin-mediated amyloidosis. Circulation. 2019;139(4):431–43.
40. US National Library of Medicine. ClinicalTrial.gov. https://www.clinicaltrials.gov/ct2/show/study/NCT03997383
41. Judge DP, Kristen AV, Grogan M, et al. Phase 3 Multicenter study of Revusiran in patients with hereditary transthyretin-mediated (hATTR) amyloidosis with cardiomyopathy (ENDEAVOUR). Cardiovasc Drugs Ther. 2020;34(3):357–70.

42. Adams D, Tournev IL, Taylor MS, Coelho T, Planté-Bordeneuve V, Berk JL, González-Duarte A, Gillmore JD, Low S-C, Sekijima Y, Obici L, Chen C, Badri P, Arum SM, Vest J, Polydefkis M, Collaborators THELIOS-A. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. Amyloid. 2022; https://doi.org/10.1080/13506129.2022.2091985.
43. Kelly JW. Alternative conformations of amyloidogenic proteins govern their behavior. Curr Opin Struct Biol. 1996;6:11–7.
44. Kelly JW, Colon W, Lai Z, Lashuel HA, McCulloch J, McCutchen SL, Miroy GJ, Peterson SA. Transthyretin quaternary and tertiary structural changes facilitate misassembly into amyloid. Adv Protein Chem. 1997;50:161–81.
45. Coelho T, Chorão R, Sousa A, Alves I, Torres MF, Saraiva MJM. Compound heterozygotes of transthyretin Met30 and transthyretin Met119 are protected from the devastating effects of familial amyloid polyneuropathy [abstract]. Neuromuscul Disord. 1996;6(Suppl 1):S20. https://doi.org/10.1016/0960-8966(96)88826-2.
46. Almeida MR, Damas AM, Lans MC, Brouwer A, Saraiva MJ. Thyroxine binding to transthyretin met 119. Comparative studies of different heterozygotic carriers and structural analysis. Endocrine. 1997;6:309–15.
47. Coelho T, Merlini G, Bulawa CE, Fleming JA, Judge DP, Kelly JW, Maurer MS, Planté-Bordeneuve V, Labaudinière R, Mundayat R, Riley S, Lombardo I, Huertas P. Mechanism of action and clinical application of tafamidis in hereditary transthyretin amyloidosis. Neurol Ther. 2016;5:1–25.
48. Park J, Egolum U, Parker S, Andrews E, Ombengi D, Ling H. Tafamidis: a first-in-class transthyretin stabilizer for transthyretin amyloid cardiomyopathy. Ann Pharmacother. 2020;54:470–7.
49. Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Planté-Bordeneuve V, Lozeron P, Suhr OB, Campistol JM, Conceicão IM, Schmidt HH, Trigo P, Kelly JW, Labaudinie're R, Chan J, Packman J, Wilson A, Grogan DR. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology. 2012;79(8):785–92.
50. Coelho T, Maia LF, da Silva AM, et al. Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy. J Neurol. 2013;260(11):2802–14. https://doi.org/10.1007/s00415-013-7051-7.
51. Barroso FA, Judge DP, Ebede B, et al. Long-term safety and efficacy of tafamidis for the treatment of hereditary transthyretin amyloid polyneuropathy: results up to 6 years. Amyloid. 2017;24(3):194–204. https://doi.org/10.1080/13506129.2017.1357545.
52. Merlini G, Coelho T, Waddington Cruz M, Li H, Stewart M, Ebede B. Evaluation of mortality during long-term treatment with tafamidis for transthyretin amyloidosis with polyneuropathy: clinical trial results up to 8.5 years. Neurol Ther. 2020;9(1):105–15. https://doi.org/10.1007/s40120-020-00180-w.
53. Mundayat R, Stewart M, Alvir J, et al. Positive effectiveness of tafamidis in delaying disease progression in transthyretin familial amyloid polyneuropathy up to 2 years: an analysis from the transthyretin amyloidosis outcomes survey (THAOS). Neurol Ther. 2018;7(1):87–101. https://doi.org/10.1007/s40120-018-0097-9.
54. Huber P, Flynn A, Sultan MB, et al. A comprehensive safety profile of tafamidis in patients with transthyretin amyloid polyneuropathy. Amyloid. 2019;26(4):203–9. https://doi.org/10.1080/13506129.2019.1643714.
55. Monteiro C, Mesgazardeh JS, Anselmo J, Fernandes J, Novais M, Rodrigues C, Brighty GJ, Powers DL, Powers ET, Coelho T, Kelly JW. Predictive model of response to tafamidis in hereditary ATTR polyneuropathy. JCI Insight. 2019;20:e126526.
56. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C, ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018;379:1007–16.

57. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, Patterson TA, Riley S, Schwartz JH, Sultan MB, Witteles R. Efficacy and safety of tafamidis doses in the Tafamidis in transthyretin cardiomyopathy clinical trial (ATTR-ACT) and long-term extension study. Eur J Heart Fail. 2021;23:277–85.
58. Elliot P, Drachman BM, Gottlieb SS, Hoffman JE, Hummel SL, Lenihan DJ, Ebede B, Gundapaneni B, Li B, Sultan MB, Shah SJ. Long-term survival with Tafamidis in patients with transthyretin amyloid cardiomyopathy. Circ Heart Fail. 2022;15:e008193. https://doi.org/10.1161/CIRCHEARTFAILURE.120.008193.
59. Kazi, D. S., Bellows, B. K., Baron, S. J., Shen, C., Cohen, D. J., Spertus, J. A…. & Shah, S. J. Cost-efectiveness of tafamidis therapy for transthyretin amyloid cardiomyopathy. Circulation 2020, 141(15), 1214–1224.
60. Liz MA, Mar FM, Franquinho F, Sousa MM. Aboard transthyretin: from transport to cleavage. IUBMB Life. 2010;62:429–35.
61. Sekijima Y, Dendle MA, Kelly JW. Orally administered diflunisal stabilizes transthyretin against dissociation required for amyloidogenesis. Amyloid. 2006;13(4):236–49.
62. Purkey HE, Dorrell MI, Kelly JW. Evaluating the binding selectivity of transthyretin amyloid fibril inhibitors in blood plasma. Proc Natl Acad Sci U S A. 2001;98(10):5566–71.
63. Miller SR, Sekijima Y, Kelly JW. Native state stabilization by NSAIDs inhibits transthyretin amyloidogenesis from the most common familial disease variants. Lab Investig. 2004;84(5):545–52. https://doi.org/10.1038/labinvest.3700059.
64. Green NS, Palaninathan SK, Sacchettini JC, et al. Synthesis and characterization of potent bivalent amyloidosis inhibitors that bind prior to transthyretin tetramerization. J Am Chem Soc. 2003;125(44):13404–14.
65. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. JAMA. 2013;310(24):2658–67.
66. Castano A, Helmke S, Alvarez J, et al. Diflunisal for ATTR cardiac amyloidosis. Congest Heart Fail. 2012;18(6):315–9.
67. Lohrmann G, Pipilas A, Mussinelli R, et al. Stabilization of cardiac function with diflunisal in transthyretin (ATTR) cardiac amyloidosis. J Card Fail. 2020;26(9):753–9.
68. Hanson JLS, Arvanitis M, Koch CM, et al. Use of serum transthyretin as a prognostic indicator and predictor of outcome in cardiac amyloid disease associated with wild-type transthyretin. Circ Heart Fail. 2018;11(2):e004000.
69. Rosenblum H, Castano A, Alvarez J, Goldsmith J, Helmke S, Maurer MS. TTR (transthyretin) stabilizers are associated with improved survival in patients with TTR cardiac amyloidosis. Circulation. Heart Failure. 2018;11(4):e004769.
70. Ibrahim M, Croix GRS, Lacy S, Fattouh M, Lara MIB, Behrooz L, Mechanic O. The use of diflunisal for transthyretin cardiac amyloidosis: a review. Heart Fail Rev. 2021; https://doi.org/10.1007/s10741-021-10143-4.
71. Siddiqia OK, Mintsb YY, Berka JL, Connorsa L, Dorose G, Gopala DM, Katarie S, Lohrmanc G, Pipilasb AR, Ruberga FL. Diflunisal treatment is associated with improved survival for patients with early stage wild-type transthyretin (ATTR) amyloid cardiomyopathy: The Boston University Amyloidosis Center experience. Amyloid. 2022;29(2):71–8. https://doi.org/10.1080/13506129.2021.2000388.
72. US National Library of Medicine. ClinicalTrial.gov. https://clinicaltrials.gov/ct2/show/study/NCT03860935
73. Gamez J, Salvadó M, Suñé P, Casasnovas C, Garcia RR. Transthyretin stabilization activity of the catechol-*O*-methyltransferase inhibitor tolcapone (SOM0226) in hereditary ATTR amyloidosis patients and asymptomatic carriers: proof-of-concept study. Amyloid. 2019;26(2). https://doi.org/10.1080/13506129.2019.1597702.
74. Cardoso I, Martins D, Ribeiro T, Merlini G, Saraiva MJ. Synergy of combined doxycycline/TUDCA treatment in lowering transthyretin deposition and associated biomarkers: studies in FAP mouse models. J Transl Med. 2010;8:74. Published online 2010 Jul 30. https://doi.org/10.1186/1479-5876-8-74.

75. Obici L, Cortese A, Lozza A, et al. Doxycycline plus tauroursodeoxycholic acid for transthyretin amyloidosis: a phase II study. Amyloid. 2012;19(Suppl 1):34–6. https://doi.org/10.3109/13506129.2012.678508.
76. Karlstedt E, Jimenez-Zepeda V, Howlett JG, White JA, Fine NM. Clinical experience with the use of doxycycline and Ursodeoxycholic acid for the treatment of transthyretin cardiac amyloidosis. J Card Fail. 2019;25(3):147–53. https://doi.org/10.1016/j.cardfail.2019.01.006.
77. ClinicalTrials.gov [Internet]. US National Library of Medicine. c2022. A study of Doxycycline and Tauroursodeoxycholic Acid (Doxy/TUDCA) plus standard supportive therapy versus standard supportive therapy alone in cardiac amyloidosis caused by transthyretin; 2020. https://ClinicalTrials.gov/show/NCT03481972
78. Ferreira N, Cardoso I, Domingues MR, Vitorino R, Bastos M, Bai G, Saraiva MJ, Almeida MR. Binding of epigallocatechin3-gallate to transthyretin modulates its amyloidogenicity. FEBS Lett. 2009;19(583):3569–76.
79. Bieschke J, Russ J, Friedrich RP, Ehrnhoefer DE, Wobst H, Neugebauer K, Wanker EE. EGCG remodels mature alpha-synuclein and amyloid-beta fibrils and reduces cellular toxicity. Proc Natl Acad Sci U S A. 2010;107:7710–5.
80. Miyata M, Sato T, Kugimiya M, Sho M, Nakamura T, et al. The crystal structure of the green tea polyphenol (2)-epigallocatechin gallate-transthyretin complex reveals a novel binding site distinct from the thyroxine binding site. Biochemistry. 2010;49(29):6104–14.
81. Ferreira N, Saraiva MJ, Almeida MR. Natural polyphenols inhibit different steps of the process of transthyretin (TTR) amyloid fibril formation. FEBS Lett. 2011;585(15):2424–30.
82. Ferreira N, Saraiva MJ, Almeida MR. Epigallocatechin-3gallate as a potential therapeutic drug for TTR-related amyloidosis: “in vivo” evidence from FAP mice models. PLoS One. 2012;7:e29933.
83. Kristen AV, Lehrke S, Buss S, et al. Green tea halts progression of cardiac transthyretin amyloidosis: an observational report. Clin Res Cardiol. 2012;101(10):805–13. https://doi.org/10.1007/s00392-012-0463-z.
84. Obici L, Mussinelli R. Current and emerging therapies for hereditary transthyretin amyloidosis: strides toward a brighter future. Neurotherapeutics. 2021;18(4):2286–302.
85. Gillmore JD, Gane E, Taubel J, Kao J, Fontana M, Maitland ML, Seitzer J, O’Connell D, Walsh KR, Wood K, Phillips J, Xu Y, Amaral A, Boyd AP, Cehelsky JE, McKee MD, Schiermeier A, Harari O, Murphy A, Kyratsous CA, Zambrowicz B, Soltys R, Gutstein DE, Leonard J, Sepp-Lorenzino L, Lebwohl D. CRISPR–Cas9 in vivo gene editing for transthyretin amyloidosis. N Engl J Med. 2021;385(6):493–502.
86. Richards DB, Cookson LM, Berges AC, Barton SV, Lane T, Ritter JM, Fontana M, Moon JC, Pinzani M, Gillmore JD, Hawkins PN, Pepys MB. Therapeutic clearance of amyloid by antibodies to serum amyloid P component. N Engl J Med. 2015;373:1106–14.
87. Wechalekar A, Antoni G, Al Azzam W, Bergström M, Biswas S, Chen C, Cheriyan J, Cleveland M, Cookson L, Galette P, Janiczek RL, Kwong RY, Lukas MA, Millns H, Richards D, Schneider I, Solomon SD, Sörensen J, Story J, Thompson D, van Dongen G, Vugts DJ, Wall A, Wikström G, Falk RH. Pharmacodynamic evaluation and safety assessment of treatment with antibodies to serum amyloid P component in patients with cardiac amyloidosis: an open-label phase 2 study and an adjunctive immuno-PET imaging study. BMC Cardiovasc Disord. 2022;22(1):49.
88. Falk RH, et al. Effect of Tafamidis on serum transthyretin levels in non-trial patients with transthyretin amyloid cardiomyopathy. JACC CardioOncol. 2021;3(4):580–6.
89. Judge DP, Heitner SB, Falk RH, Maurer MS, Shah SJ, Witteles RM, Grogan M, Selby VN, Jacoby D, Hanna M, Nativi-Nicolau J, Patel J, Rao S, Sinha U, Turtle CW, Fox JC. Transthyretin stabilization by AG10 in symptomatic transthyretin amyloid cardiomyopathy. J Am Coll Cardiol. 2019;74(3):285–95.
90. Fontana M, Martinez-Naharro A, Chacko L, Rowczenio D, Gilbertson JA, Whelan CJ, Strehina S, Lane T, Moon J, Hutt DF, Kellman P, Petrie A, Hawkins PN, Gillmore JD. Reduction in

CMR derived extracellular volume with Patisiran indicates cardiac amyloid regression. JACC Cardiovasc Imaging. 2021;14(1):189–99.
91. Rettl R, Mann C, Duca F, Dachs TM, Binder C, Ligios LC, Schrutka L, Dalos D, Koschutnik M, Donà C, Kammerlander A, Beitzke D, Loewe C, Charwat-Resl S, Hengstenberg C, Kastner J, Eslam RB, Bonderman D. Tafamidis treatment delays structural and functional changes of the left ventricle in patients with transthyretin amyloid cardiomyopathy. Eur Heart J Cardiovasc Imaging. 2021:jeab226. https://doi.org/10.1093/ehjci/jeab226. Epub ahead of print
92. Ticau S, Sridharan GV, Tsour S, Cantley WL, Chan A, Gilbert JA, Erbe D, Aldinc E, Reilly MM, Adams D, Polydefkis M, Fitzgerald K, Vaishnaw A, Nioi P. Neurofilament light chain as a biomarker of hereditary transthyretin-mediated amyloidosis. Neurology. 2021;96:e412–22. https://doi.org/10.1212/WNL.0000000000011090.
93. Castaño A, DeLuca A, Weinberg R, Pozniakoff T, Blaner WS, Pirmohamed A, Bettencourt B, Gollob J, Karsten V, Vest JA, et al. Serial scanning with technetium pyrophosphate (99 m Tc-PYP) in advanced ATTR cardiac amyloidosis. J Nucl Cardiol. 2016;23:1355–63. https://doi.org/10.1007/s12350-015-0261-x.
94. Duca F, Kammerlander AA, Panzenböck A, Binder C, Aschauer S, Loewe C, Agis H, Kain R, Hengstenberg C, Bonderman D, et al. Cardiac magnetic resonance T1 mapping in cardiac amyloidosis. JACC Cardiovasc Imaging. 2018;11:1924–6. https://doi.org/10.1016/j.jcmg.2018.06.010.
95. Garcia-Pavia P, Bengel F, Brito D, Damy T, Duca F, Dorbala S, Nativi-Nicolau J, Obici L, Rapezzi C, Sekijima Y, Elliott PM. Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy. Eur J Heart Fail. 2021;23(6):895–905.
96. Adams D, Algalarrondo PM, et al. Expert opinion on monytoring symptomatic hereditary transthyretin-mediated amyloidosis and assessment of disease progression. Orphanet J Rar Dis. 2021;16(1):411.
97. Conceição I, Coelho T, Rapezzi C, Parman Y, Obici L, Gálan L, et al. Assessment of patients with hereditary transthyretin amyloidosis- understanding the impact of management and disease progression. Amyloid. 2019;26(3):103–11.

Chapter 23
Treatment of AL Amyloidosis

Roberta Shcolnik Szor and Ashutosh Wechalekar

23.1 Treatment of Light Chain Amyloidosis: General Principles

Immunoglobulin light chain (AL) amyloidosis results from the excessive production of abnormal light chains by clonal plasma cells and, less frequently, clonal B cells, deposited as fibrillary protein aggregates in organs and tissues. This deposition of the precursor protein as amyloid material in the extracellular space of tissues leads to progressive organ damage, as occurs in other subtypes, but specifically in AL, the direct proteotoxic effect of circulating free light chains plays an important role, especially in cardiac injury, making the AL subtype more aggressive. Cardiac involvement may evolve rapidly into a life-threatening condition and is the most relevant prognostic factor in AL amyloidosis, determining overall survival and tolerability to treatment. For this reason, AL amyloidosis represents a medical emergency that requires immediate institution of treatment, which might be ideally initiated before severe organ damage has occurred. In theory, several stages in the pathophysiological process of AL amyloidosis can be therapeutic targets. However, agents capable of removing the deposited amyloid are still under study, and the current treatment is based on chemotherapeutic strategies to eradicate the underlying

R. S. Szor (✉)
DASA Group/Hospital 9 de Julho, São Paulo, SP, Brazil

A. Wechalekar
National Amyloidosis Centre, University College London, London, UK
e-mail: a.wechalekar@ucl.ac.uk

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_23

plasma cell clone and suppress light chain production [1–3]. Rapid and profound hematologic response (HR) should be the aim since this predicts improvement in organ function and overall survival. Therapeutic planning must be individualized to allow patients to receive the most effective treatment they can tolerate. Patients are stratified according to the extent of multiorgan involvement, particularly cardiac involvement, and comorbidities into different categories for a risk-adapted treatment approach that may vary from low-dose chemotherapy to autologous stem cell transplantation (ASCT).

23.2 Intensive Treatment Strategy: High-Dose Chemotherapy and Autologous Stem Cell Transplantation

High-dose chemotherapy followed by ASCT has been performed in AL amyloidosis for almost 30 years and is associated with deep and durable HR, leading to overall survival exceeding 10 years in responding patients [4–7]. However, the only randomized trial comparing ASCT with chemotherapy failed to show a benefit for the intensive strategy. Key issues in this study that may have compromised the results should be considered: the absence of stringent criteria for selecting patients for ASCT, the delay in starting therapy of approximately 1 month in this subgroup, disease progression leading some patients not to undergo transplantation, and the high transplant-related mortality (TRM) of 24% [8].

Given the multisystem character of AL amyloidosis and patient frailty, the establishment of stringent selection criteria and the growing experience of transplant centers have reduced TRM in recent decades from approximately 40% to less than 5%, and ASCT remains a standard treatment for medical fit patients [6, 9–11]. Approximately 20% of patients are considered eligible for ASCT at diagnosis, and eligibility criteria vary for each transplant center. In general, they include age $\leq$ 70–75 years, performance status $\leq$ 2, absence of severe organ dysfunction (especially cardiac), and systolic blood pressure $\geq$ 90 mmHg [4, 12, 13]. Refining the assessment of cardiac involvement through biomarker analysis may help predict TRM. A retrospective study showed that patients with NT-proBNP levels > 5000 pg/mL or troponin T > 0.06 ng/mL had a high risk of dying early after ASCT and are now considered important biomarkers in assessing eligibility for ASCT [14].

For ASCT ineligible patients, induction chemotherapy represents a possible strategy, as reducing free light chains and improving organ function can reverse some exclusion criteria, enabling ASCT. The benefit of induction before ASCT has been demonstrated in several studies, with improvement in hematological responses and survival. In high-risk AL amyloidosis (plasma cell clonal > 10% or associated multiple myeloma), induction therapy prior to transplant may be effective for rapidly controlling the involved light chain to avoid disease progression due to delays.

However, in patients eligible for high-intensity treatment, induction treatment is a double-edged sword, as some may lose their eligibility for ASCT due to treatment-related toxicities or progression of organ failure [15–21].

Mobilization and collection of stem cells are other points of attention in patients with AL amyloidosis, especially those with multiorgan and cardiac involvement. Complications such as capillary leak syndrome, volume overload, hypotension, arrhythmias, renal and cardiac decompensation, and deaths are reported. Again, patient selection is key to reducing these complications. More specifically, to reduce the risks of complications, granulocyte colony-stimulating factor should be used alone or in combination with plerixafor, and chemomobilization should be avoided. The optimal dose of progenitor cells might be at least 5 x 10^6 CD34+/kg to minimize delay in engraftment and complications related to aplasia [12, 22].

The most commonly used conditioning regimen is melphalan 200 mg/$m^{2,}$ but risk-adapted strategies with dose reductions have been reported and remain a point of debate in the literature. According to some authors, melphalan doses can be reduced to 100 or 140 mg/m^2 based on age and renal and cardiac function. This allows more patients to undergo transplantation, although at the expense of reduced HR and survival in most studies. This negative impact on outcomes makes this approach not recommended by other groups, making the need for melphalan reduction an exclusion criterion for performing ASCT [23–26].

As in multiple myeloma, consolidation therapy in AL amyloidosis should be considered in patients who do not achieve at least a very good partial response (VGPR) after ASCT, aiming to improve the depth of HR. It is well established in the literature that patients with profound HR (VGPR or better) have prolonged progression-free survival (PFS) and overall survival (OS) and better organ responses [27]. Regimens containing bortezomib and daratumumab have been studied and were associated with improved rates of CR and prolonged PFS. Consolidation with daratumumab also led to higher rates of negative minimal residual disease [28–30].

In the era of new drugs, the role of ASCT is being discussed, especially in patients achieving satisfactory HR after induction treatment with modern therapies. Whether ASCT improves long-term PFS and OS in patients with complete response remains an unanswered question. Some centers currently recommend the collection of stem cells based on individualized factors and the decision to perform or defer ASCT. A retrospective study comparing ASCT to bortezomib-based therapy found no differences in overall HR, OS in 2 years, PFS, or time to next treatment between the two strategies. Nevertheless, prospective studies are needed to better understand whether novel therapies will replace ASCT or change the role of ASCT in AL amyloidosis [31].

In summary, ASCT remains an effective treatment option for selected patients in experienced centers. Long-term results from referral centers show hematologic CR rates varying from 40 to 50%, with prolonged median overall survival, especially in patients attaining deep responses (median OS varying from 11 to 15 years in patients with CR or VGPR). Transplant-related mortality has progressively decreased over the decades, achieving less than 5% in recent years [4–6, 25].

23.3 Standard Chemotherapy Treatment in Patients Not Eligible for ASCT

The majority of patients diagnosed with AL amyloidosis are not eligible for ASCT and are treated with standard anti-plasma cell chemotherapy. Melphalan and dexamethasone (MD) have been the main regimen for decades, leading to HR rates of 45–75% of cases and a median OS of more than 7 years, with minimal toxicity. However, it is not considered to be less than adequate [32, 33]. From 2010 on, proteasome inhibitors became the mainstay of treatment based on several retrospective studies reporting encouraging results with the combination of bortezomib, cyclophosphamide, and dexamethasone (CyBorD). Deep and fast HR rates were reported (60–80% HR and 20–25% CR), and a median OS of 6 years was observed in the largest cohort treated with upfront bortezomib [34–40].

Recently, a phase 3 randomized trial confirmed the benefit of associating bortezomib with first-line treatment of patients ineligible for ASCT. The combination of bortezomib, melphalan, and dexamethasone (BMD) resulted in a significantly higher HR rate (VGPR/CR rate of 64% versus 39%), which translated to improved PFS and OS, with a twofold decrease in mortality rate, in relation to MD [41].

The largest randomized clinical trial in AL amyloidosis, which included almost 400 patients, brought another standard of care for patients not eligible for ASCT. The addition of the monoclonal antibody anti-CD38 daratumumab to CyBorD was associated with the best HR reported to date compared to CyBorD (94% versus 77%, CR 53% versus 18%). Interestingly, deep responses were rapidly achieved (median time of 17 days to reach at least VGPR) in the experimental group. Organ responses at 6 months were also in favor of the daratumumab arm, with cardiac and renal responses of 42% and 54% versus 22% and 27% in the CyBorD group, respectively. An endpoint combining survival free from both disease progression and organ deterioration was evaluated, favoring daratumumab treatment (HR of 0.58, 95% CI, 0.36–0.93; $p = 0.02$). It is important to note that patients in the experimental arm were treated with daratumumab until progression after the induction phase, whereas patients enrolled in the control group received a 6-month-long treatment.

In clinical practice, daratumumab-CyBorD, if daratumumab is accessible, is the treatment of choice for most patients with AL amyloidosis and is a key option for patients who may become eligible for ASCT, since this regimen does not impair stem cell collection in comparison with BMD. There is a suggestion that BMD might be preferred in patients carrying the 11;14 translocation, but data remain to be clearly validated [42]. Importantly, patients with IIIIB advanced cardiac involvement were excluded from both cited randomized trials, and treating this group of patients is still challenging [43]. Fig. 23.1 shows a treatment algorithm summarizing the initial approach of patients with AL amyloidosis.

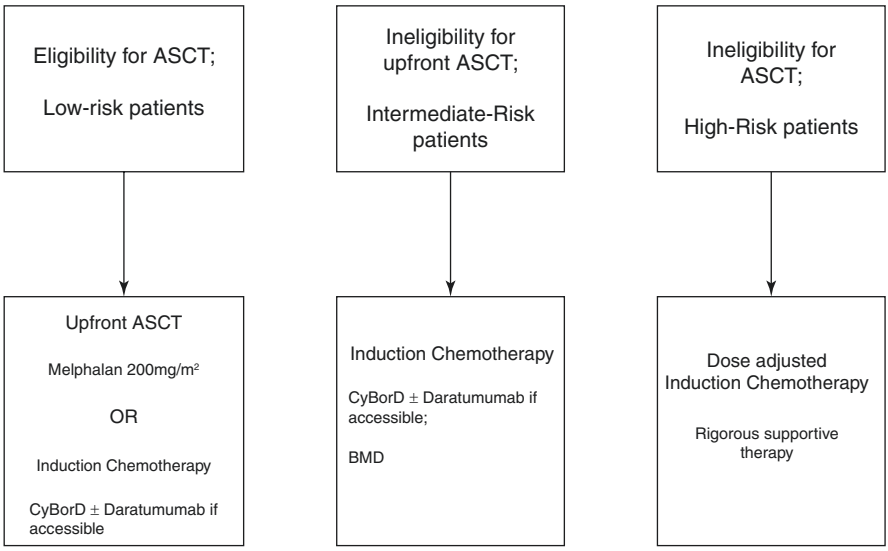


Fig. 23.1 Treatment algorithm for patients with AL amyloidosis. *ASCT* autologous stem cell transplantation, *CyBorD* cyclophosphamide, bortezomib, dexamethasone; *BMD* bortezomib, melphalan, dexamethasone

23.4 Response Assessment

Treatment in AL amyloidosis must promote deep and rapid HR, allowing the reversion of organ dysfunction and improvement in survival in the long term. Profound hematologic responses (at least VGPR) are associated with improved outcomes, and assessing minimal residual disease (MRD) seems to be relevant, since patients in CR with negative MRD have better organ responses than patients in CR but with positive MRD [44]. Responses to treatment should be assessed early to allow the identification of nonresponding patients and change therapy as soon as possible. Traditional hematologic response criteria have been used for decades (Table 23.1) [45, 46]]. However, new goals of treatment are being studied, and achieving a reduction of the involved free light chain to 20 mg/L or the difference between involved and noninvolved free light chains to <10 mg/L seems to better predict improved organ responses and survival [47]. Organ response criteria for the heart, kidney, and liver are well defined in the literature, and improvement in cardiac biomarkers is the mainstay of cardiac response assessment, whereas proteinuria and glomerular

Table 23.1 Response categories and response criteria in AL amyloidosis

Response Category	Response criteria
Hematologic Response	Complete response: Both criteria must be met: - Absence of amyloidogenic light chains (either free and/or as part of a complete immunoglobulin) defined by negative immunofixation electrophoresis of both serum and urine - Either a FLC ratio within the reference range or the uninvolved FLC concentration is greater than involved FLC concentration with or without an abnormal FLC ratio Very good partial response: dFLC concentration < 40 mg/L Partial response: dFLC decrease > 50% compared to baseline No response: all other patients
Organ Response	Heart (NT-proBNP): reduction of NT-proBNP of 30% and >300 ng/Lover the starting value. Baseline NT-proBNP has to be >650 ng/L to be measurable Heart (BNP): reduction of BNP of 30% and >50 ng/L over the starting value. Baseline BNP has to be ≥150 ng/L to be measurable Kidney: a 30% reduction in 24-h urine protein excretion or a drop of proteinuria below 0.5 g per 24 h in the absence of progressive renal insufficiency, defined as a decrease in GFR to 25% over baseline

FLC free light chains, *dFLC* difference between involved and noninvolved free light chains, *NT-proBNP* N-terminal pro B natriuretic peptide; *BNP* B natriuretic peptide

filtration rate are used to assess the reversal of renal involvement (Table 23.1) [45, 48, 49]. A combined model of evaluation of both hematologic and multiorganic responses has also been studied (CHOR model) and appears to early determine the benefit of treatment [50].

23.5 Treatment of Relapsed/Refractory AL Amyloidosis

Second-line treatment in the relapsed/refractory setting must be started early, ideally when hematologic parameters are altered, and before the occurrence of organ deterioration. Immunomodulatory agents (lenalidomide or pomalidomide) might be used, as they promote high HR rates (40–60%), with OS benefit in responding patients who were previously treated with alkylators and proteasome inhibitors. Toxicity is often an issue, and 41% of patients discontinued therapy with pomalidomide in a real-world study [51–56].

Proteasome inhibitors are also effective as second-line treatments. Carfilzomib either alone or in combination with other agents was studied and found to be feasible in relapsed patients. It has promoted an HR of approximately 60%, but with a high grade of toxicities. It was also studied in the upfront therapy in selected patients without severe cardiac or renal involvement, being associated with less neurotoxicity than bortezomib and should only be used with once weekly dosing [57].

Ixazomib, an oral proteasome inhibitor, in combination with dexamethasone was associated with a 56% HR in patients with relapsed amyloidosis. In the only phase 3 trial in relapsed/refractory amyloidosis, ixazomib and dexamethasone failed to meet the primary endpoint of HR rate compared to physicians' choice regimen. However, improved PFS, prolonged time to next treatment, and time to organ deterioration were demonstrated, favoring the ixazomib group [58, 59].

Daratumumab alone or in combination with other agents appears to be associated with the best responses, with elevated HR rates (55–90%) and a median time of 1 month to achieve any HR [60–64]. Daratumumab or a daratumumab-based combination regimen should be considered in daratumumab-naïve patients with relapsed disease.

23.6 Supportive Treatment

Management of patients with AL amyloidosis and multiorgan dysfunctions remains a challenge in clinical practice. In addition to starting anti-plasma cell treatment, rigorous supportive therapy must be provided to all patients. While waiting for HR, recommendations by a multispecialty team play a major role in sustaining vital organ functioning and improving quality of life. In patients presenting with cardiac and renal involvement, careful fluid balance, cautious use of diuretics, strict monitoring of blood pressure, and control of arrhythmias should be aimed, especially in dysautonomic patients. Nutritional support is also a main issue of supportive therapy, and solid organ transplantation must be considered in selected patients, mainly those achieving a deep HR.

References

1. Cohen OC, Wechalekar AD. Systemic amyloidosis: moving into the spotlight. Leukemia. 2020;34(5):1215–28. https://doi.org/10.1038/s41375-020-0802-4. PubMed PMID: 32269317
2. Palladini G, Milani P, Merlini G. Management of AL amyloidosis in 2020. Blood. 2020;136(23):2620–7. https://doi.org/10.1182/blood.2020006913. PubMed PMID: 33270858
3. Muchtar E, Dispenzieri A, Gertz MA, Kumar SK, Buadi FK, Leung N, et al. Treatment of AL amyloidosis: Mayo stratification of myeloma and risk-adapted therapy (mSMART) consensus statement 2020 update. Mayo Clin Proc. 2021;96(6):1546–77. https://doi.org/10.1016/j.mayocp.2021.03.012. PubMed PMID: 34088417
4. Sidiqi MH, Aljama MA, Buadi FK, Warsame RM, Lacy MQ, Dispenzieri A, et al. Stem cell transplantation for light chain amyloidosis: decreased early mortality over time. J Clin Oncol Off J Am Soc Clin Oncol. 2018;36(13):1323–9. https://doi.org/10.1200/JCO.2017.76.9554. PubMed PMID: 29558277
5. Sharpley FA, Petrie A, Mahmood S, Sachchithanantham S, Lachmann HJ, Gillmore JD, et al. A 24-year experience of autologous stem cell transplantation for light chain amyloidosis patients in the United Kingdom. Br J hematol. 2019;187(5):642–52. https://doi.org/10.1111/bjh.16143. PubMed PMID: 31410841

6. Sanchorawala V, Sun F, Quillen K, Sloan JM, Berk JL, Seldin DC. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem cell transplantation: 20-year experience. Blood. 2015;126(20):2345–7. https://doi.org/10.1182/blood-2015-08-662726. PubMed PMID: 26443620
7. Cibeira MT, Sanchorawala V, Seldin DC, Quillen K, Berk JL, Dember LM, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. Blood. 2011;118(16):4346–52. https://doi.org/10.1182/blood-2011-01-330738. PubMed PMID: 21828140; PubMed Central PMCID: PMC3204906
8. Jaccard A, Moreau P, Leblond V, Leleu X, Benboubker L, Hermine O, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med. 2007;357(11):1083–93. https://doi.org/10.1056/NEJMoa070484. PubMed PMID: 17855669
9. Nguyen VP, Landau H, Quillen K, Brauneis D, Shelton AC, Mendelson L, et al. Modified high-dose Melphalan and autologous stem cell transplantation for immunoglobulin light chain amyloidosis. Biol blood Marrow Transplant. 2018;24(9):1823–7. https://doi.org/10.1016/j.bbmt.2018.06.018. PubMed PMID: 29933072; PubMed Central PMCID: PMC7553205
10. Girnius S, Seldin DC, Meier-Ewert HK, Sloan JM, Quillen K, Ruberg FL, et al. Safety and efficacy of high-dose melphalan and autoSCT in patients with AL amyloidosis and cardiac involvement. Bone Marrow Transplant. 2014;49(3):434–9. https://doi.org/10.1038/bmt.2013.192. PubMed PMID: 24317129
11. Venner CP, Gillmore JD, Sachchithanantham S, Mahmood S, Lane T, Foard D, et al. Stringent patient selection improves outcomes in systemic light-chain amyloidosis after autologous stem cell transplantation in the upfront and relapsed setting. Hema. 2014;99(12):e260–3. https://doi.org/10.3324/hematol.2014.108191. PubMed PMID: 25193959; PubMed Central PMCID: PMC4258758
12. Sanchorawala V. High-dose Melphalan and autologous peripheral blood stem cell transplantation in AL amyloidosis. Acta hematol. 2020;143(4):381–7. https://doi.org/10.1159/000506498. PubMed PMID: 32248194
13. Varga C, Comenzo RL. High-dose melphalan and stem cell transplantation in systemic AL amyloidosis in the era of novel anti-plasma cell therapy: a comprehensive review. Bone Marrow Transplant. 2019;54(4):508–18. https://doi.org/10.1038/s41409-018-0284-4. PubMed PMID: 30089901
14. Gertz MA, Lacy MQ, Dispenzieri A, Kumar SK, Dingli D, Leung N, et al. Refinement in patient selection to reduce treatment-related mortality from autologous stem cell transplantation in amyloidosis. Bone Marrow Transplant. 2013;48(4):557–61. https://doi.org/10.1038/bmt.2012.170. PubMed PMID: 22964596
15. Kourelis TV, Kumar SK, Gertz MA, Lacy MQ, Buadi FK, Hayman SR, et al. Coexistent multiple myeloma or increased bone marrow plasma cells define equally high-risk populations in patients with immunoglobulin light chain amyloidosis. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(34):4319–24. https://doi.org/10.1200/JCO.2013.50.8499. PubMed PMID: 24145344; PubMed Central PMCID: PMC4881366
16. Cornell RF, Fraser R, Costa L, Goodman S, Estrada-Merly N, Lee C, et al. Bortezomib-based induction is associated with superior outcomes in light chain amyloidosis patients treated with autologous hematopoietic cell transplantation regardless of plasma cell burden. Transplant cell ther. 2021;27(3):264 e1–7. https://doi.org/10.1016/j.jtct.2020.11.018. PubMed PMID: 33781533; PubMed Central PMCID: PMC8010222
17. Huang X, Wang Q, Chen W, Zeng C, Chen Z, Gong D, et al. Induction therapy with bortezomib and dexamethasone followed by autologous stem cell transplantation versus autologous stem cell transplantation alone in the treatment of renal AL amyloidosis: a randomized controlled trial. BMC Med. 2014;12:2. https://doi.org/10.1186/1741-7015-12-2. PubMed PMID: 24386911; PubMed Central PMCID: PMC3895846
18. Minnema MC, Nasserinejad K, Hazenberg B, Hegenbart U, Vlummens P, Ypma PF, et al. Bortezomib-based induction followed by stem cell transplantation in light chain amyloidosis: results of the multicenter HOVON 104 trial. Hema. 2019;104(11):2274–82. https://doi.

org/10.3324/hematol.2018.213900. PubMed PMID: 30923094; PubMed Central PMCID: PMC6821610
19. Sanchorawala V, Brauneis D, Shelton AC, Lo S, Sun F, Sloan JM, et al. Induction therapy with Bortezomib followed by Bortezomib-high dose Melphalan and stem cell transplantation for light chain amyloidosis: results of a prospective clinical trial. Biol blood marrow transplant. 2015;21(8):1445–51. https://doi.org/10.1016/j.bbmt.2015.04.001. PubMed PMID: 25858810
20. Scott EC, Heitner SB, Dibb W, Meyers G, Smith SD, Abar F, et al. Induction bortezomib in Al amyloidosis followed by high dose melphalan and autologous stem cell transplantation: a single institution retrospective study. Clin Lymphoma Myeloma Leuk. 2014;14(5):424–30 e1. https://doi.org/10.1016/j.clml.2014.02.003. PubMed PMID: 24650974
21. Manwani R, Hegenbart U, Mahmood S, Sachchithanantham S, Kyriakou C, Yong K, et al. Deferred autologous stem cell transplantation in systemic AL amyloidosis. Blood Cancer J. 2018;8(11):101. https://doi.org/10.1038/s41408-018-0137-9. PubMed PMID: 30397193; PubMed Central PMCID: PMC6218452
22. Dhakal B, Strouse C, D'Souza A, Arce-Lara C, Esselman J, Eastwood D, et al. Plerixafor and abbreviated-course granulocyte colony-stimulating factor for mobilizing hematopoietic progenitor cells in light chain amyloidosis. Biol blood marrow transplant. 2014;20(12):1926–31. https://doi.org/10.1016/j.bbmt.2014.08.002. PubMed PMID: 25111581
23. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. Blood. 2002;99(12):4276–82. https://doi.org/10.1182/blood.v99.12.4276. PubMed PMID: 12036853
24. Landau H, Hassoun H, Rosenzweig MA, Maurer M, Liu J, Flombaum C, et al. Bortezomib and dexamethasone consolidation following risk-adapted melphalan and stem cell transplantation for patients with newly diagnosed light-chain amyloidosis. Leukemia. 2013;27(4):823–8. https://doi.org/10.1038/leu.2012.274. PubMed PMID: 23014566
25. D'Souza A, Dispenzieri A, Wirk B, Zhang MJ, Huang J, Gertz MA, et al. Improved outcomes after autologous hematopoietic cell transplantation for light chain amyloidosis: a Center for International Blood and Marrow Transplant Research Study. J Clin Oncol Off J Am Soc Clin Oncol. 2015;33(32):3741–9. https://doi.org/10.1200/JCO.2015.62.4015. PubMed PMID: 26371138; PubMed Central PMCID: PMC4737858
26. Gertz MA, Lacy MQ, Dispenzieri A, Ansell SM, Elliott MA, Gastineau DA, et al. Risk-adjusted manipulation of melphalan dose before stem cell transplantation in patients with amyloidosis is associated with a lower response rate. Bone Marrow Transplant. 2004;34(12):1025–31. https://doi.org/10.1038/sj.bmt.1704691. PubMed PMID: 15516945
27. Gertz MA, Lacy MQ, Dispenzieri A, Hayman SR, Kumar SK, Leung N, et al. Effect of hematologic response on outcome of patients undergoing transplantation for primary amyloidosis: importance of achieving a complete response. Hema. 2007;92(10):1415–8. https://doi.org/10.3324/hematol.11413. PubMed PMID: 17768110
28. Landau H, Smith M, Landry C, Chou JF, Devlin SM, Hassoun H, et al. Long-term event-free and overall survival after risk-adapted melphalan and SCT for systemic light chain amyloidosis. Leukemia. 2017;31(1):136–42. https://doi.org/10.1038/leu.2016.229. PubMed PMID: 27560108; PubMed Central PMCID: PMC5220129 received honoraria from Spectrum, Janssen and Prothena, and research funding from Onyx, Celgene, Millennium Pharmaceuticals, The Amyloidosis Research Fund, the Werner and Elaine Dannheiser Fund for Research on the Biology of Aging of the Lymphoma Foundation and Takeda. HH has received honoraria and research grant support from Celgene, Novartis and Takeda. RLC has received honoraria from Takeda-Millennium and Janssen and research support from Janssen, Takeda-Millennium, Prothena and Karyopharm
29. Kastritis E, Rousakis P, Kostopoulos IV, Gavriatopoulou M, Theodorakakou F, Fotiou D, et al. Consolidation with a short course of daratumumab in patients with AL amyloidosis or light chain deposition disease. Amyloid. 2021;28(4):259–66. https://doi.org/10.1080/13506129.2021.1971192. PubMed PMID: 34468250

30. Al Saleh AS, Sidiqi MH, Sidana S, Muchtar E, Dispenzieri A, Dingli D, et al. Impact of consolidation therapy post autologous stem cell transplant in patients with light chain amyloidosis. Am J Hematol. 2019;94(10):1066–71. https://doi.org/10.1002/ajh.25572. PubMed PMID: 31273808; PubMed Central PMCID: PMC7377298
31. Sharpley FA, Manwani R, Petrie A, Mahmood S, Sachchithanantham S, Lachmann HJ, et al. Autologous stem cell transplantation vs bortezomib based chemotheraphy for the first-line treatment of systemic light chain amyloidosis in the UK. Eur J Hematol. 2021;106(4):537–45. https://doi.org/10.1111/ejh.13582. PubMed PMID: 33460466
32. Palladini G, Perfetti V, Obici L, Caccialanza R, Semino A, Adami F, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. Blood. 2004;103(8):2936–8. https://doi.org/10.1182/blood-2003-08-2788. PubMed PMID: 15070667
33. Palladini G, Milani P, Foli A, Obici L, Lavatelli F, Nuvolone M, et al. Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach. Hema. 2014;99(4):743–50. https://doi.org/10.3324/hematol.2013.095463.
34. Venner CP, Lane T, Foard D, Rannigan L, Gibbs SD, Pinney JH, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood. 2012;119(19):4387–90. https://doi.org/10.1182/blood-2011-10-388462. PubMed PMID: 22331187
35. Mikhael JR, Schuster SR, Jimenez-Zepeda VH, Bello N, Spong J, Reeder CB, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood. 2012;119(19):4391–4. https://doi.org/10.1182/blood-2011-11-390930.
36. Palladini G, Sachchithanantham S, Milani P, Gillmore J, Foli A, Lachmann H, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood. 2015;126(5):612–5. https://doi.org/10.1182/blood-2015-01-620302. PubMed PMID: 25987656
37. Muchtar E, Gertz MA, Kumar SK, Lacy MQ, Dingli D, Buadi FK, et al. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: cracking the glass ceiling of early death. Blood. 2017;129(15):2111–9. https://doi.org/10.1182/blood-2016-11-751628.
38. Venner CP, Gillmore JD, Sachchithanantham S, Mahmood S, Lane T, Foard D, et al. A matched comparison of cyclophosphamide, bortezomib and dexamethasone (CVD) versus risk-adapted cyclophosphamide, thalidomide and dexamethasone (CTD) in AL amyloidosis. Leukemia. 2014;28(12):2304–10. https://doi.org/10.1038/leu.2014.218. PubMed PMID: 25027514
39. Jaccard A, Comenzo RL, Hari P, Hawkins PN, Roussel M, Morel P, et al. Efficacy of bortezomib, cyclophosphamide and dexamethasone in treatment-naive patients with high-risk cardiac AL amyloidosis (Mayo Clinic stage III). Hema. 2014;99(9):1479–85. https://doi.org/10.3324/hematol.2014.104109.
40. Kastritis E, Roussou M, Gavriatopoulou M, Migkou M, Kalapanida D, Pamboucas C, et al. Long-term outcomes of primary systemic light chain (AL) amyloidosis in patients treated upfront with bortezomib or lenalidomide and the importance of risk adapted strategies. Am J Hematol. 2015;90(4):E60–5. https://doi.org/10.1002/ajh.23936. PubMed PMID: 25580702
41. Kastritis E, Leleu X, Arnulf B, Zamagni E, Cibeira MT, Kwok F, et al. Bortezomib, Melphalan, and dexamethasone for light-chain amyloidosis. J Clin Oncol Off J Am Soc Clin Oncol. 2020;38(28):3252–60. https://doi.org/10.1200/JCO.20.01285. PubMed PMID: 32730181
42. Bochtler T, Hegenbart U, Kunz C, Granzow M, Benner A, Seckinger A, et al. Translocation t(11;14) is associated with adverse outcome in patients with newly diagnosed AL amyloidosis when treated with bortezomib-based regimens. J Clin Oncol Off J Am Soc Clin Oncol. 2015;33(12):1371–8. https://doi.org/10.1200/JCO.2014.57.4947. PubMed PMID: 25779559
43. Kastritis E, Palladini G, Minnema MC, Wechalekar AD, Jaccard A, Lee HC, et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. N Engl J Med. 2021;385(1):46–58. https://doi.org/10.1056/NEJMoa2028631. PubMed PMID: 34192431

44. Palladini G, Paiva B, Wechalekar A, Massa M, Milani P, Lasa M, et al. Minimal residual disease negativity by next-generation flow cytometry is associated with improved organ response in AL amyloidosis. Blood Cancer J. 2021;11(2):34. https://doi.org/10.1038/s41408-021-00428-0.
45. Palladini G, Dispenzieri A, Gertz MA, Kumar S, Wechalekar A, Hawkins PN, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30(36):4541–9. https://doi.org/10.1200/JCO.2011.37.7614. PubMed PMID: 23091105
46. Palladini G, Schonland SO, Sanchorawala V, Kumar S, Wechalekar A, Hegenbart U, et al. Clarification on the definition of complete hematologic response in light-chain (AL) amyloidosis. Amyloid. 2021;28(1):1–2. https://doi.org/10.1080/13506129.2020.1868810.
47. Muchtar E, Gertz MA, Lacy MQ, Leung N, Buadi FK, Dingli D, et al. Refining amyloid complete hematological response: quantitative serum free light chains superior to ratio. Am J Hematol. 2020;95(11):1280–7. https://doi.org/10.1002/ajh.25940. PubMed PMID: 32681737
48. Lilleness B, Doros G, Ruberg FL, Sanchorawala V. Establishment of brain natriuretic peptide - based criteria for evaluating cardiac response to treatment in light chain (AL) amyloidosis. Br J hematol. 2020;188(3):424–7. https://doi.org/10.1111/bjh.16198. PubMed PMID: 31515797
49. Palladini G, Hegenbart U, Milani P, Kimmich C, Foli A, Ho AD, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood. 2014;124(15):2325–32. https://doi.org/10.1182/blood-2014-04-570010. PubMed PMID: 25115890
50. Sidana S, Milani P, Binder M, Basset M, Tandon N, Foli A, et al. A validated composite organ and hematologic response model for early assessment of treatment outcomes in light chain amyloidosis. Blood Cancer J. 2020;10(4):41. https://doi.org/10.1038/s41408-020-0306-5.
51. Sanchorawala V, Wright DG, Rosenzweig M, Finn KT, Fennessey S, Zeldis JB, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. Blood. 2007;109(2):492–6. https://doi.org/10.1182/blood-2006-07-030544. PubMed PMID: 16960148
52. Kastritis E, Gavriatopoulou M, Roussou M, Bagratuni T, Migkou M, Fotiou D, et al. Efficacy of lenalidomide as salvage therapy for patients with AL amyloidosis. Amyloid. 2018;25(4):234–41. https://doi.org/10.1080/13506129.2018.1540410.
53. Dispenzieri A, Buadi F, Laumann K, LaPlant B, Hayman SR, Kumar SK, et al. Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis. Blood. 2012;119(23):5397–404. https://doi.org/10.1182/blood-2012-02-413161.
54. Sanchorawala V, Shelton AC, Lo S, Varga C, Sloan JM, Seldin DC. Pomalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 1 and 2 trial. Blood. 2016;128(8):1059–62. https://doi.org/10.1182/blood-2016-04-710822. PubMed PMID: 27381904
55. Palladini G, Milani P, Foli A, Basset M, Russo F, Perlini S, et al. A phase 2 trial of pomalidomide and dexamethasone rescue treatment in patients with AL amyloidosis. Blood. 2017;129(15):2120–3. https://doi.org/10.1182/blood-2016-12-756528. PubMed PMID: 28130212
56. Sharpley FA, Manwani R, Mahmood S, Sachchithanantham S, Lachmann H, Gilmore J, et al. Real world outcomes of pomalidomide for treatment of relapsed light chain amyloidosis. Br J hematol. 2018;183(4):557–63. https://doi.org/10.1111/bjh.15541. PubMed PMID: 30095161
57. Manwani R, Mahmood S, Sachchithanantham S, Lachmann HJ, Gillmore JD, Yong K, et al. Carfilzomib is an effective upfront treatment in AL amyloidosis patients with peripheral and autonomic neuropathy. Br J hematol. 2019;187(5):638–41. https://doi.org/10.1111/bjh.16122. PubMed PMID: 31388995
58. Sanchorawala V, Palladini G, Kukreti V, Zonder JA, Cohen AD, Seldin DC, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. Blood. 2017;130(5):597–605. https://doi.org/10.1182/blood-2017-03-771220.

59. Dispenzieri A, Kastritis E, Wechalekar AD, Schonland SO, Kim K, Sanchorawala V, et al. A randomized phase 3 study of ixazomib-dexamethasone versus physician's choice in relapsed or refractory AL amyloidosis. Leukemia. 2022;36(1):225–35. https://doi.org/10.1038/s41375-021-01317-y.
60. Palladini G, Kastritis E, Maurer MS, Zonder J, Minnema MC, Wechalekar AD, et al. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. Blood. 2020;136(1):71–80. https://doi.org/10.1182/blood.2019004460.
61. Roussel M, Merlini G, Chevret S, Arnulf B, Stoppa AM, Perrot A, et al. A prospective phase 2 trial of daratumumab in patients with previously treated systemic light-chain amyloidosis. Blood. 2020;135(18):1531–40. https://doi.org/10.1182/blood.2019004369. PubMed PMID: 32108228
62. Kimmich CR, Terzer T, Benner A, Dittrich T, Veelken K, Carpinteiro A, et al. Daratumumab for systemic AL amyloidosis: prognostic factors and adverse outcome with nephrotic-range albuminuria. Blood. 2020;135(18):1517–30. https://doi.org/10.1182/blood.2019003633. PubMed PMID: 32107537
63. Kaufman GP, Schrier SL, Lafayette RA, Arai S, Witteles RM, Liedtke M. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. Blood. 2017;130(7):900–2. https://doi.org/10.1182/blood-2017-01-763599. PubMed PMID: 28615223
64. Abeykoon JP, Zanwar S, Dispenzieri A, Gertz MA, Leung N, Kourelis T, et al. Daratumumab-based therapy in patients with heavily pretreated AL amyloidosis. Leukemia. 2019;33(2):531–6. https://doi.org/10.1038/s41375-018-0262-2. PubMed PMID: 30267007

Chapter 24
Ilustrative Cases in Amyloidosis

Diane Xavier de Ávila, Marcia Maria Jardim, Marcelo Imbroinise Bittencourt, Roberta Shcolnik Szor, Claudio Tinoco Mesquita, and Evandro Tinoco Mesquita

Abbreviations

AL	Light-chain amyloidosis
ATTR	Amyloid transthyretin
ECG	Electrocardiogram
LV	Left ventricular

D. X. de Ávila (✉)
Cardiovascular Science, Fluminense Federal University, Niteroi, Niterói, Rio de Janeiro, Brazil

Amyloidosis Center, Complexo Hospitalar de Niterói/DASA, Rio de Janeiro, Brazil
e-mail: dianeavilamed@cardiol.br

M. M. Jardim · M. I. Bittencourt
Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil
e-mail: mib@cardiol.br

R. S. Szor
Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, SP, Brazil

Grupo DASA, Barueri, Brazil

C. T. Mesquita
Nuclear Medicine and Molecular Imaging Department, Pró-Cardíaco Hospital, Rio de Janeiro, Brazil

Radiology Department, Fluminense Federal University, Niterói, Rio de Janeiro, Brazil

E. T. Mesquita
Cardiology, Complexo Hospitalar de Niterói–DASA, Niterói, RJ, Brazil

Cardiovascular Sciences, Fluminense Federal University, Niterói, RJ, Brazil

Interamerican Society of Cardiology (SIAC), Ciudad del Mexico, Mexico

PROCEPI, Niterói, RJ, Brazil

Sixth ward Cardiology, Santa Casa de Misericordia, Rio de Janeiro, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_24

LVH	Left ventricular hypertrophy
SA	Systemic amyloidosis
SPECT	Single-photon emission computed tomography
TTE	Transthoracic echocardiography

24.1 Case Report 01

24.1.1 Summary

Herein, we present the case of a 67-year-old male Brazilian patient who presented to the general practitioner with a 6-month history of diarrhea, weight loss, weakness, peripheral polyneuropathy, heart failure, and nephrotic syndrome. This case illustrates the multisystem presentation of AL amyloidosis, with a progressive course and multiorgan dysfunction, combined with involvement of the heart, kidney, gastrointestinal tract, and peripheral neuropathy.

24.1.2 Case Presentation

A 67-year-old male patient presented to the Internal Medicine Department of a public tertiary hospital in January 2015 with a history of chronic diarrhea that started 6 months ago, with progressive worsening. He had a weight loss of 14 kg, upper and lower limb weakness, lower limb edema, and fatigue. One year earlier, he had noticed tongue enlargement and voice changes.

24.1.3 Past Medical History

Gallstones, Smoking, Occasional alcohol consumption.

24.1.4 Physical Exam

Malnourished patient, with hyperchromic macules in the thorax and upper limbs, symmetrical edema in the lower limbs, and macroglossia.

Initial hypotheses were malignancy associated with a paraneoplastic cutaneous syndrome or an indolent infection such as tuberculosis or acquired immune deficiency syndrome.

24.1.5 Laboratory Analysis 1

Albumin 2.4 g/dL, proteinuria 10.2 g/24 h.

No alterations in complete blood count, creatinine clearance, hepatic or pancreatic tests, or negative serologic tests for HIV, hepatitis B or C virus were observed.

Antinuclear antibody, rheumatoid factor, and complement: negative/normal.

Stool analysis ruled out infections.

24.1.6 Imaging and Endoscopic Exams

Abdominal ultrasound showed cholelithiasis and normal-sized kidneys.

Colonoscopy: Friable mucosa with edema from the cecum to the rectum and erosions in the descending colon, sigmoid, and rectum (biopsied).

Biopsies: Colonic mucosa with a mild inflammatory infiltrate composed of neutrophils and lymphocytes, sometimes infiltrating crypt epithelium. Moderate edema in the lamina propria. *Ileum*: normal. Negative Ziel-Neelsen stain for Mycobacterium tuberculosis.

24.1.7 First Diagnosis

Inflammatory bowel disease and nephrotic syndrome as an extraintestinal manifestation.

24.1.8 First Treatment

Corticosteroids and mesalazine showed no improvement.

In October 2015, there was a worsening in diarrhea and edema, and new symptoms of nausea, vomiting, and abdominal pain arose. The patient had an episode of syncope and worsening of paresthesia in the upper and lower limbs. At this moment, his performance status by ECOG was 4.

24.1.9 Laboratory Analysis 2

Albumin 1.9 g/dL.

No changes in complete blood count, creatinine clearance, hepatic and pancreatic tests, coagulation tests, or thyroid function were observed.

24.1.10 Imaging Exams

Computed tomography scans revealed mild bilateral pleural effusion, a minimally dilated main pancreatic duct, and colonic distension without obstruction.

24.1.11 Second Diagnosis

Bacterial overgrowth syndrome and chronic pancreatitis.

24.1.12 Second Treatment

Antibiotics and pancreatic enzymes with no improvement.

One year and 3 months after the onset of symptoms, the diagnostic hypothesis of systemic amyloidosis was raised.

24.1.13 Upper Endoscopy

Mild enanthematic pangastritis. Erosive esophagitis. Esophageal moniliasis.

24.1.13.1 Gastric Biopsy

Pyloric and fundic mucosa with hyaline deposits in lamina propria.

Immunohistochemistry: Positive Congo Red stain (Fig. 24.1) with Positive Kappa and Lambda light chains.

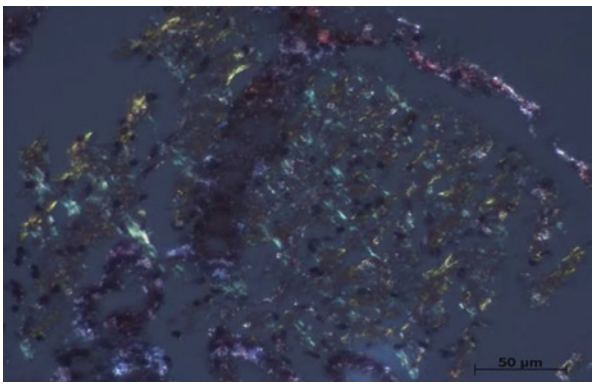


Fig. 24.1 Gastric biopsy showing in the immunohistochemistry a positive congo red stain, indicative of amyloidosis

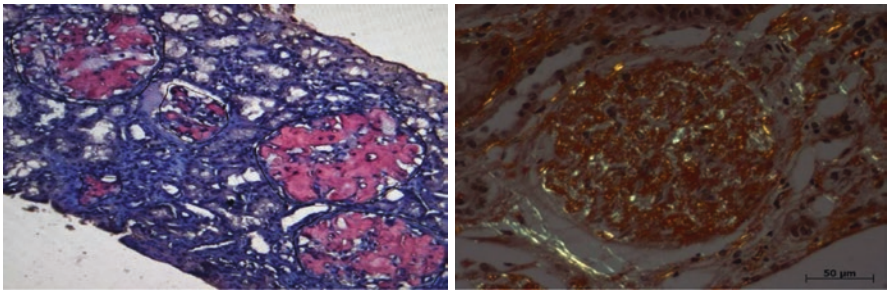


Fig. 24.2 Kidney biopsy showing diffuse amyloid deposits

24.1.13.2 Kidney Biopsy

Diffuse amyloid deposits (Congo Red +) in glomeruli, tubules, interstitium, and blood vessels (Fig. 24.2).

Immunofluorescence: IgA, IgG, IgM, C1q, C3, fibrinogen, Kappa, and lambda tested > > C3+.

24.1.14 Screening for Monoclonal Gammopathy

Absence of serum monoclonal component (immunofixation and serum protein electrophoresis).

Urinary IgA lambda monoclonal component (urinary immunofixation).

24 h urine protein electrophoresis: monoclonal component in beta region, not quantified, and 77% of albuminuria.

Free light chains were not available at that time.

Bone marrow biopsy showed 5–10% lambda clonal plasma cells and no evidence of amyloid deposits.

Cytogenetic: no metaphases/FISH unavailable.

Mass spectrometry (Research protocol): Lambda subtype.

NO CRAB criteria for associated multiple myeloma.

24.1.15 Cardiac Assessment: Imaging (Echo and MRI)

Moderate left ventricular (LV) hypertrophy, septal thickness 17 mm, mild LV diastolic dysfunction, subendocardial gadolinium late enhancement, LV ejection fraction = 69%.

24.1.16 Cardiac Assessment: Biomarkers

NTproBNP = 1200 pg/mL (reference < 125 pg/mL).
Troponine T = 0.4 ng/mL (reference < 0.014 ng/mL.

24.1.17 Neurologic Assessment

Electroneuromyography: Polyneuropathy affects sensory, motor, and autonomic nerve fibers with an axonal pattern.

24.1.18 Hepatic Assessment

Normal-sized liver (Ultrasound).
Normal alkaline phosphatase.

24.1.19 Conclusion

The final diagnosis was lambda light chain systemic amyloidosis, cardiac staging (Mayo Clinic Standard): III, and renal staging: II.

The patient was treated in the public health system. He was not eligible for intensive treatment with high-dose melphalan and hematopoietic stem cell transplantation. At that moment, in 2015, proteasome inhibitors were not available in the Brazilian public health system. Chemotherapy with oral melphalan and dexamethasone was the treatment offered at that time.

24.2 Case Report 02

24.2.1 Summary

Herein, an elderly woman, previously hypertensive, active, who is 86 years old, declines her quality of life, opening signs and symptoms of heart failure, and closes the diagnosis of wild-type amyloidosis.

24.2.2 History of Presentation

An 86-year-old female Brazilian patient sought outpatient care due to fatigue, discouragement, sporadic retrosternal discomfort, and dyspnea, and symptoms were significant after the death of her husband. Episodes of postural hypotension, hand paresthesia, and sporadic palpitations were also present. Electrocardiogram and Echocardiogram in Figs. 24.3 and 24.4.

24.2.3 Past Medical History

Systemic arterial hypertension using enalapril 20 mg BID and bisoprolol 1.25 mg. Dyslipidemia with the use of rosuvastatin 5 mg. She underwent tonsillectomy, subtotal hysterectomy, and trigger finger surgery. Bilateral carpal tunnel syndrome. No drugs, tobacco, or alcohol.

24.2.4 Laboratory Exams

Hemoglobin 13.4, 375.000 platelets, glucose 98, sodium 141, potassium 5.1, urea 63, creatinine 1.23—GFR 50 mL.min-1.1.73 m^2, ferritin 197, glycosylated hemoglobin 5.7%. Troponin T 0.032 ng/mL, NT-ProBNP 1995 pg/mL. Kappa light free

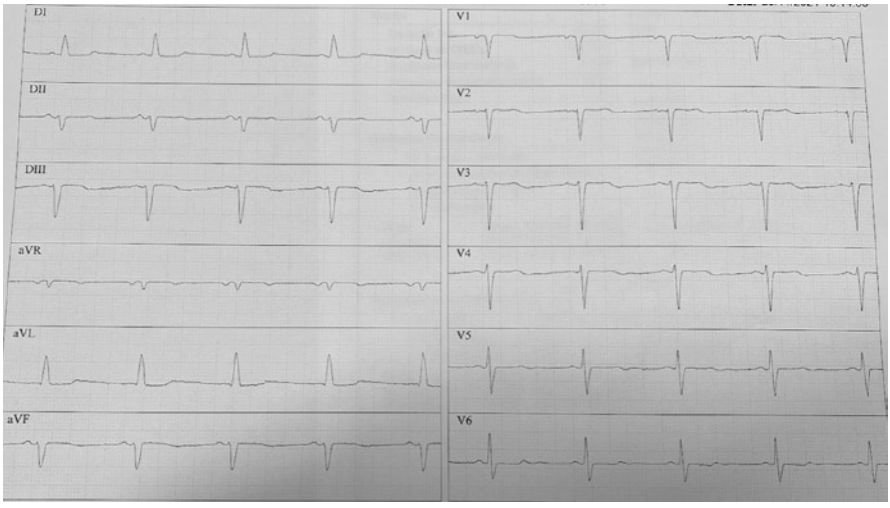


Fig. 24.3 Electrocardiogram in sinus rhythm, 56 beats per min, lower inactive zone, anteroseptal pseudoinfarction pattern, voltage within normal limits

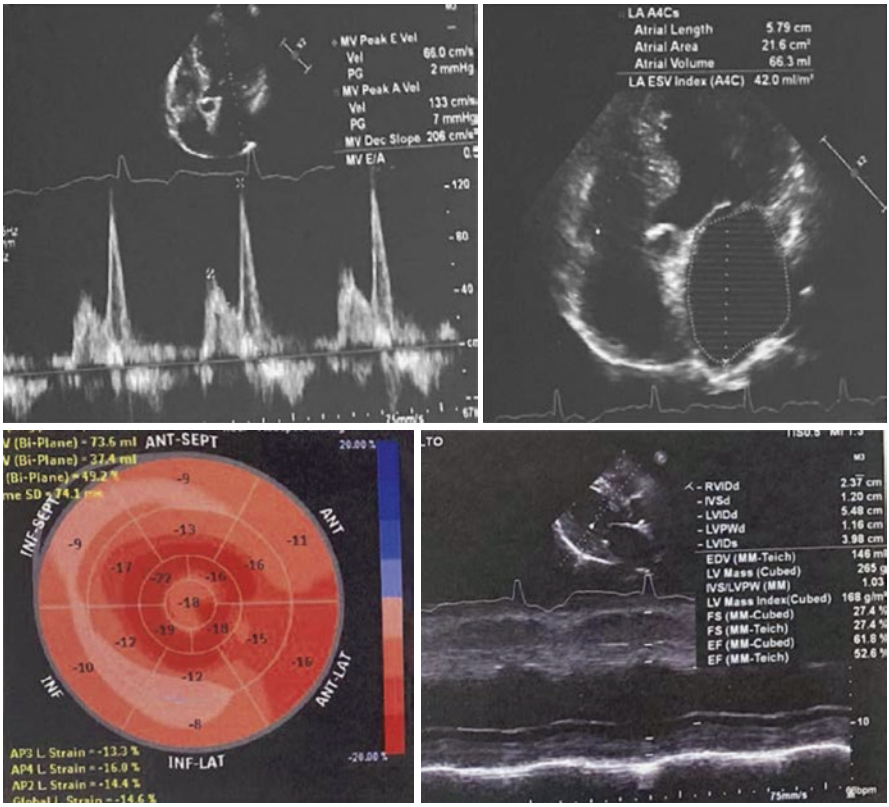


Fig. 24.4 Transthoracic echocardiogram showed systolic function with moderate global deficit, type I left ventricular diastolic dysfunction, mitral valve with moderate reflux, myocardial thickness with concentric increase, and enlarged left heart chambers. The septum and posterior wall were both 12 mm. Longitudinal global strain with more evident dysfunction in basal areas with apical preservation, GSL—14.6%, and two-dimensional ejection fraction of 52%

24.67 mg/L, lambda light free 13.93 mg/L, Kappa/Lambda ratio 1.77. Serum and urinary immunofixation—absence of monoclonal bands.

Myocardial scintigraphy with dipyridamole was performed without evidence of active ischemia, and ventricular function remained normal.

She was referred for myocardial resonance imaging at rest for screening for infiltrative disease (Figs. 24.5 and 24.6).

She was referred for genetic testing, which was negative for a mutation in the transthyretin gene. Myocardial scintigraphy marked with technetium pyrophosphate was performed.

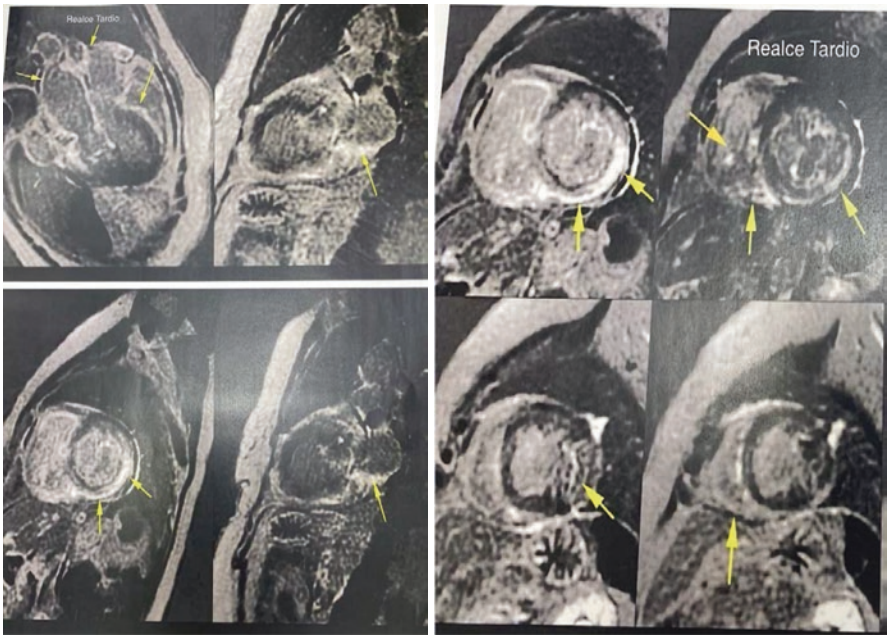


Fig. 24.5 MRI of the resting heart with diffuse late enhancement of the atrial and right ventricular walls, as well as heterogeneous late enhancement of the nonischemic left ventricular myocardium. There is an increase in the native T1 of the myocardium (approximately 1200 ms) and in the ECV (46%, considering a recent hematocrit of 37%) in the medial inferoseptal segment, which also suggests amyloidosis

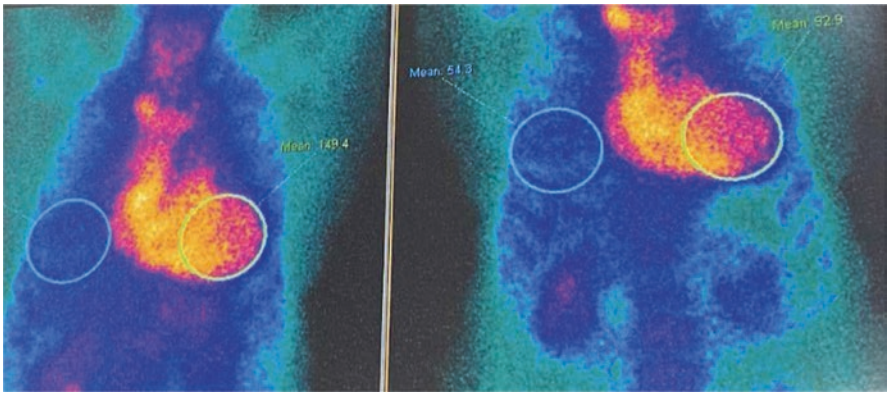


Fig. 24.6 99mTc-Pyrophosphate myocardial scintigraphy in which there was uptake in the cardiac projection Grade 3 Perugini, early heart/contralateral ratio 1.75, delayed heart/contralateral ratio 1.71, SPECT homogeneous capture, and strong intensity in the cardiac projection

24.2.5 Conclusion

This patient was diagnosed with wild-type amyloidosis and she is using 80 mg tafamidis, that is, 4 tablets of 20 mg daily in Brazil.

24.3 Case Report 03

24.3.1 Summary

Herein, we present the initial clinical picture of a 35-year-old woman who started with progressive peripheral polyneuropathy (Coutinho's stage II), heart failure, major dysautonomia, diarrhea, weight loss, blurred vision, convulsive syncope, and recent bradycardia. This case illustrates a clinical case of severe cardiomyopathy and neuropathy associated with amyloidosis.

24.3.2 History of Presentation

A 35-year-old Brazilian woman presented with progressive peripheral polyneuropathy (Coutinho's staging II) and recently developed progressive dyspnea, easy fatigability, orthopnea, and dry cough, with New York Heart Association functional class III/IV. She had major dysautonomia, diarrhea, significant weight loss, blurred vision, and convulsive syncope and then developed bradycardia. After 1 year of follow-up, left ventricular (LV) hypertrophy was detected with high levels of troponin and N-terminal pro–B-type natriuretic peptide.

24.3.3 Past Medical History

The patient was diagnosed with vitreitis and vasculitis 1 year before presentation. She also had a history of cholecystectomy and an uneventful pregnancy with cesarean delivery 8 years ago. The patient's family history was negative for features suggestive of genetic mutations; however, her paternal uncles died of similar conditions. She had no history of cigarette smoking or alcohol consumption, and she currently leads a sedentary lifestyle.

24.3.4 Differential Diagnoses

This clinical form of cardiomyopathy should be distinguished from other causes of heart failure (HF) with an LVEF of ≥50%, as these patients require different management. These include other cardiac diseases, such as valvular heart disease, pericardial disease, high-output HF, myocardial hypertrophy, and other hereditary causes of polyneuropathy and cardiomyopathy [1, 2].

24.3.5 Investigations

Laboratory investigations revealed 245 mg/dL kappa urinary light chains (normal: 170–370 mg/dL) and 124 mg/dL lambda chains (normal: 90–210 mg/dL). The kappa to lambda ratio was 1.98 (normal: 1.35–2.65). The concentration of serum light chains was 0.734 mg/dL for the kappa isotype (normal: <0.710 mg/dL) and 0.406 mg/dL for the lambda isotype (normal: <0.390 mg/dL). The cardiac troponin I level was 0.1 ng/mL (normal: <0.6 ng/mL), and the N-terminal pro–B-type natriuretic peptide (NT-proBNP) level was 1826 ng/L (normal: <125 ng/L).

The patient had peculiar electrocardiographic features of amyloidosis with cardiac involvement. These features included low-voltage limb leads and pseudoinfarction in the anterior precordial leads without LV hypertrophy voltage criteria despite increased wall thickness on transthoracic echocardiogram (TE) (Fig. 24.7a).

TE showed a mild increase in the LV wall thickness (the interventricular septum and posterior wall of the left ventricle were 13 mm thick) and infiltration of the interatrial septum and the free wall of the right ventricle, with normal LV function. The global longitudinal strain (GLS) pattern that is seen in cardiac amyloidosis typically spares the apex of the heart and is characterized by reduced LS in the basal segments with preserved or supranormal LS in the LV tip (Fig. 24.7b).

The neurophysiological findings were compatible with sensorimotor polyneuropathy with a primarily axonal pattern. She had reduced sensitivity and abolished reflexes in the lower limbs.

Myocardial scintigraphy with technetium-99 m-labeled pyrophosphate revealed an increased concentration of the radiotracer in the projection area of the heart against the costal margin, corresponding to a Perugini score of 3. Scores > 2 and a counting ratio between the heart and the contralateral region of >1.5 have a high probability of wild-type or hereditary transthyretin amyloidosis (Fig. 24.8).

The patient underwent genetic testing and was found to have a rare pathogenic mutation in the transthyretin gene, Glu54Lys (p.Glu74Lys).

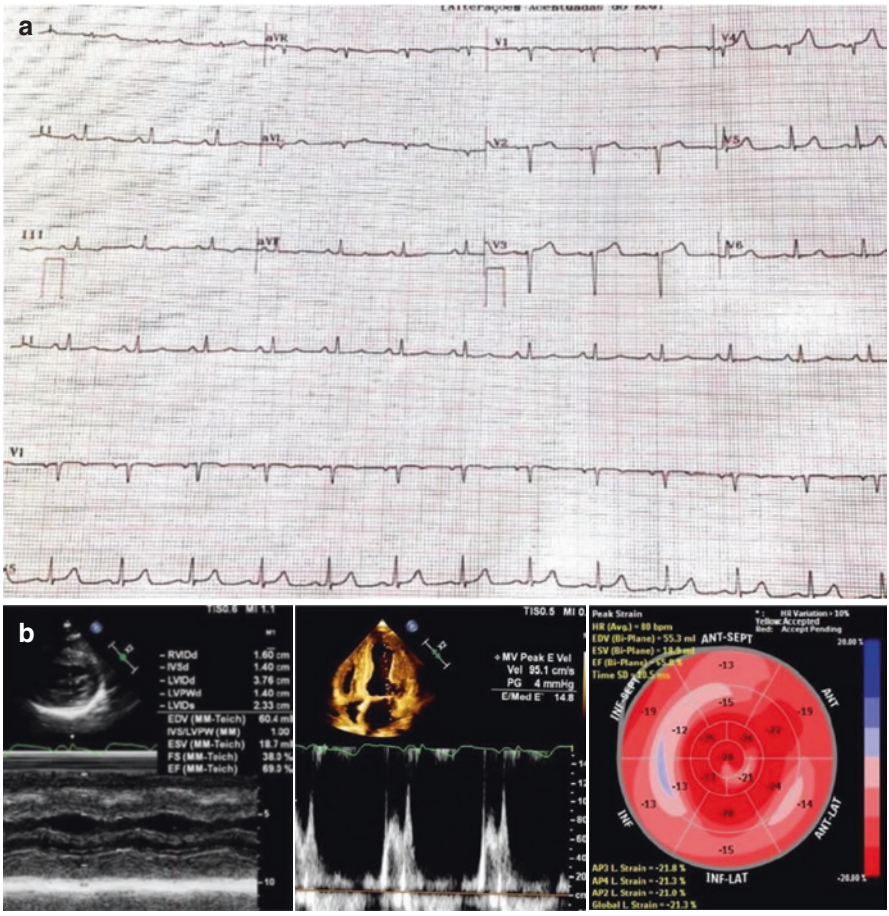


Fig. 24.7 (**a**) Low-voltage limb leads without left ventricular hypertrophy voltage criteria despite increased wall thickness on echocardiography and pseudoinfarction in anterior precordial leads. (**b**) Apical sparing describes a reduced longitudinal strain in the basal segments and preserves the supranormal longitudinal strain in the basal segments of the left ventricle

24.3.6 Discussion

Systemic amyloidosis is a progressive, severe, and infiltrative disease that results in amyloid deposition in several organs, including the heart. It can be a hereditary form associated with a mutation in the transthyretin gene with deposition of the malformed TTR proteins (ATTRv), due to degenerative processes related to age (wild or wild-type `ATTRwt]), or associated with deposition of light chain immunoglobulin secreted by plasma cells (AL) [3–7]. In this case, a rare and severe hereditary form was diagnosed in a young woman.

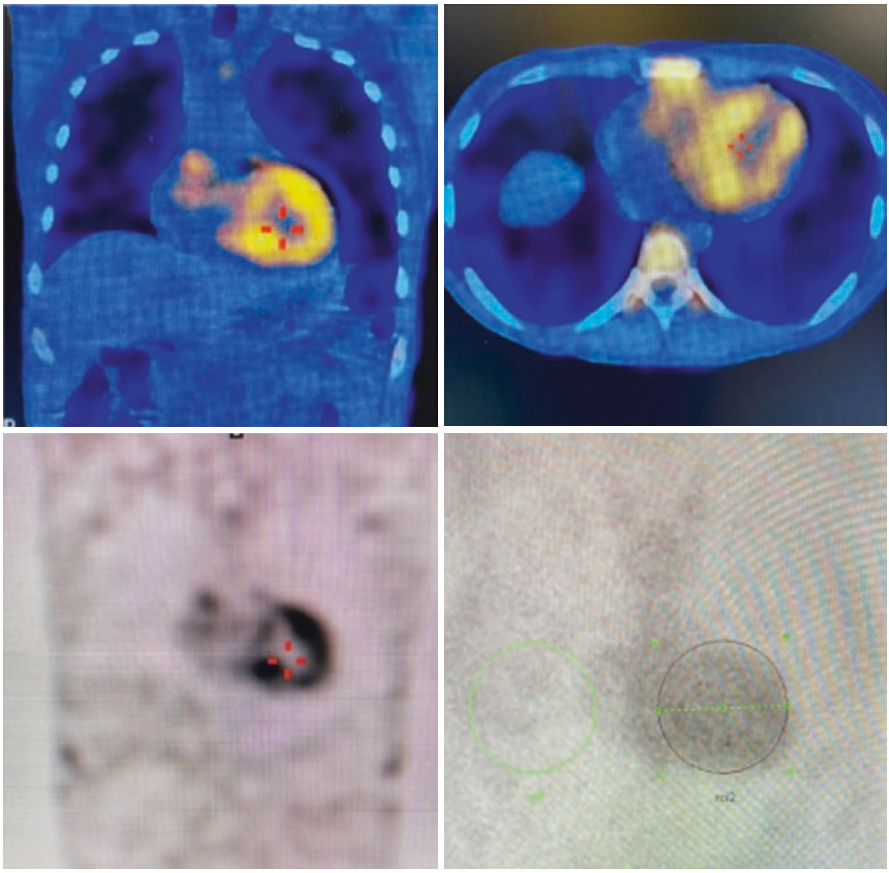


Fig. 24.8 Myocardial scintigraphy with technetium-99 m-labeled pyrophosphate. Increased radiotracer concentration in the projection area of the heart against the costal margin, corresponding to score 3 [10]

After the initial screening for light chain dosing and immunofixation, which demonstrated the absence of monoclonal proteins, the AL form was discarded, and we continued to investigate hereditary or wild-type forms of amyloidosis using non-invasive diagnostic modalities, such as scintigraphy imaging, that were positive for transthyretin amyloidosis. While analyzing possible mutations in the transthyretin gene, the presence of hereditary systemic amyloidosis was confirmed, Glu54Lys (p. Glu74Lys) [5–8].

The diagnosis was made through clinical and imaging features, such as electrocardiography and TE. CMR imaging helped differentiate it from other infiltrative or hypertrophic diseases, and myocardial scintigraphy with technetium pyrophosphate was performed. With a sensitivity of nearly 100%, myocardial scintigraphy with technetium pyrophosphate in grade 2 and 3 cases can confirm an amyloid infiltrate of transthyretin and does not require endomyocardial biopsy [3, 8].

This case had dramatic progression. Two years before the presentation, the patient started having numb and weak legs, persistent diarrhea, and episodes of vomiting after every meal. She also experienced loss of taste, loss of smell, progressive weight loss, vomiting, dry mouth, and urinary retention. In the middle of the last year, she started having blurred vision in her left eye, and in the last few months, the blurriness progressed to involve her right eye. A feeling of tiredness and swollen feet were consistent. She reported that she could not feel her feet, had lost weight from 94 to 47 kg in 6–12 months (Fig. 24.9), and sometimes had sudden fainting episodes.

Within 2 years, the polyneuropathy and cardiomyopathy progressed significantly, and the correct diagnosis was made. The duration between presentation and making the correct diagnosis can often be long. When the correct diagnosis is made, the disease is usually at an advanced stage, and available therapies are limited. Specialties are sought by such patients because of the systemic symptoms of the disease. The rare mutation Glu54Lys (p. Glu74Lys) was previously reported and described in a report from Costa Rica in a Turkish and a Japanese family whose members died before age 40 from HF [9].

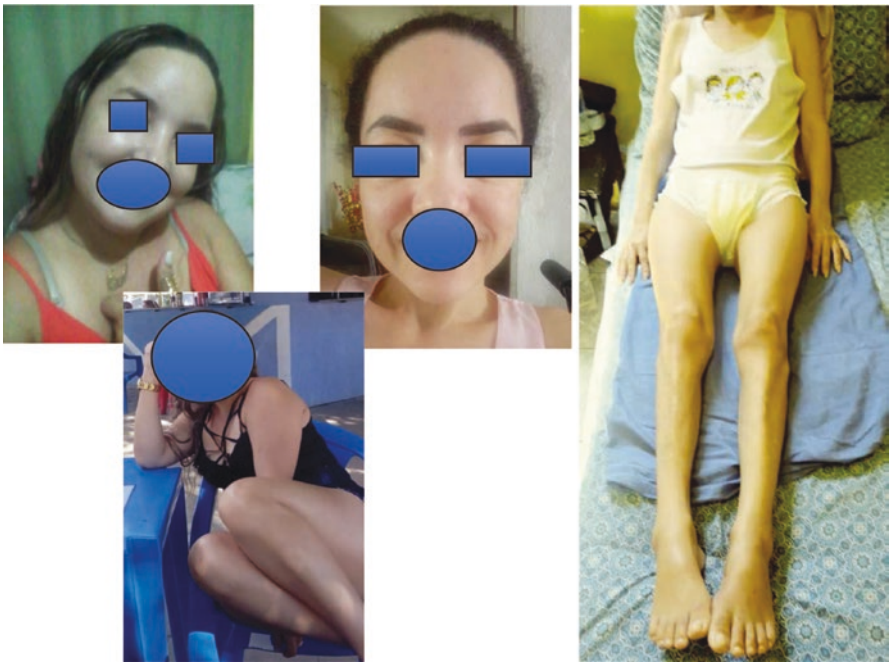


Fig. 24.9 Muscle loss and progressive limitation of the patient over 3 years

24.3.7 Management

As she had a late diagnosis and stage 2 polyneuropathy, patisiran was prescribed, and she is under this treatment. In patients with cardiomyopathy, tafamidis 80 mg daily is indicated. The patient currently receives furosemide and spironolactone for HF symptoms, but does not tolerate beta-blockers. She also does not tolerate low doses of enalapril due to dysautonomia and postural hypotension. The patient is undergoing respiratory and motor physiotherapy regularly.

24.3.8 Conclusion

This case highlights a patient with an atypical mutation who presented with imaging, electrocardiographic, and neurophysiological features typical in patients with ATTR amyloidosis who have both severe polyneuropathy and cardiomyopathy. This clinical case describes a long diagnostic journey, which is common in this patient population, and illustrates the warning signs that guided our investigations. On disease suspicion, the initial screening should include light chain dosage and immunofixation that excludes the AL form of amyloidosis, followed by myocardial scintigraphy with technetium pyrophosphate and genetic testing.

References

1. Reddy YN, Borlaug BA. Heart failure with preserved ejection fraction. Curr Probl Cardiol. 2016;41:145–88.
2. Rapezzi C, Quarta CC, Obici L, et al. Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective. Eur Heart J. 2013;34:520–8.
3. Donnelly JP, Hanna M. Cardiac amyloidosis: an update on diagnosis and treatment. Cleve Clin J Med. 2017;84:12–26.
4. Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. J Am Coll Cardiol. 2016;68:1014–20.
5. Conceição I, González-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2016;21:5–9.
6. Gertz MA, Benson MD, Dyck PJ, et al. Diagnosis, prognosis and therapy of transthyretin amyloidosis. J Am Coll Cardiol. 2015;66:2451–66.
7. Jorge AJ, de Ávila DX, Vilar EG, Ribeiro ML, Bruno KE, Pires AC. Cardiac amyloidosis with heart failure and middle range ejection fraction. Int J Cardio Sci. 2018;31:457–60.
8. Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. J Am Coll Cardiol Heart Fail. 2019;7:709–16.
9. Busse A, Sánchez MA, Monterroso V, Alvarado MV, León P. A severe form of amyloidotic polyneuropathy in a costa Rican family with a rare transthyretin mutation (Glu54Lys). Am J Med Genet A. 2004;128A:190–4.
10. Perugini E, Guidalotti PL, Salvi F, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-Diphosphono-1,2- propanodicarboxylic acid scintigraphy. J Am Coll Cardiol. 2005;46:1076–84.

Part II
Fabry Disease

Chapter 25
Neurological Manifestations of Fabry Disease

Marcondes C. França Jr and Maria Luiza Benevides

25.1 Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by pathogenic *GLA* variants. This leads to abnormal expression and/or function of the enzyme α-galactosidase A, resulting in the cellular accumulation of glycosphingolipids throughout the body. It is one of the most frequent metabolic disorders and is characterized by the involvement of multiple organs/systems throughout the disease course [1].

Neurological manifestations are relevant in affected individuals, both men and women. They are frequent, sometimes precocious, and may be intensely bothersome for affected individuals [2]. Moreover, they can impact overall patient survival [3]. In FD, glycosphingolipid accumulation extends to both the central (CNS) and peripheral nervous systems (PNS), which explains the heterogeneity of neurological symptoms and signs found in this disorder [1, 2].

In this chapter, we will revise the major neurological features in FD, stratified into PNS and CNS-related manifestations, in addition to cochleovestibular involvement. Emphasis will be given toward the typical clinical signs, the underlying pathophysiology, the diagnostic tests, and whenever available, specific therapies. Fig. 25.1 depicts the main neurological manifestations in Fabry disease.

M. C. França Jr (✉) · M. L. Benevides
Department of Neurology, School of Medical Sciences—University of Campinas (UNICAMP), Campinas, SP, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_25

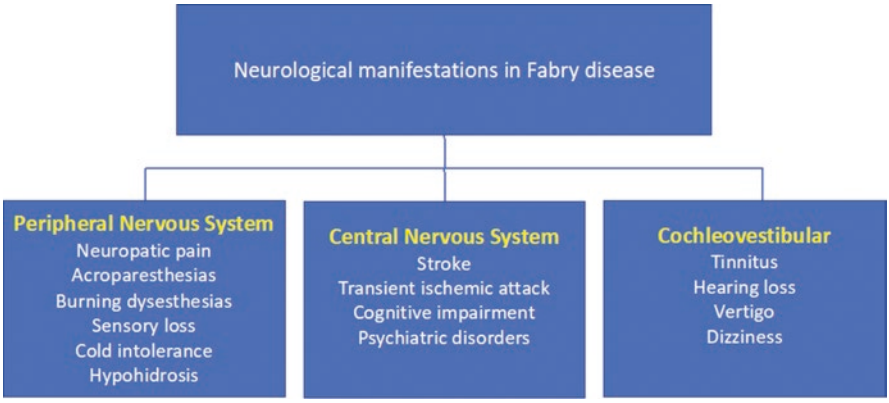


Fig. 25.1 Neurological manifestations in Fabry disease

25.2 PNS-Related Manifestations in FD

Small fiber neuropathy is a frequent counterpart in FD and is found in 80% of all affected subjects [4, 5]. In many patients, this is indeed the heralding manifestation of the disease. There is usually involvement of both sensory and autonomic fibers. In contrast to other neuropathies, one clearly identified preferential damage to A-delta fibers and relative sparing of C fibers [2]. Topographically, this is a classical length-dependent and symmetric axonopathy [6]. Even though both men and women may be affected, there are noteworthy sex-related differences [1]. The major one refers to the age of onset of PNS-related signs: men (who are hemizygous) first notice neuropathic pain in the first decade of life, whereas women (who are heterozygous) tend to perceive this symptom in the second decade of life.

Patients may have both somatic and autonomic manifestations, including acroparesthesias, cold intolerance, burning dysesthesias, and sensory loss that starts in the distal limbs (palms and soles). By far, the most frequent and relevant peripheral manifestation of FD is neuropathic pain [7]. In some individuals, it is so severe as to motivate suicidal attempts during intense crises. There are two neuropathic pain subtypes in FD: chronic and episodic. The first one manifests as constant burning, not so severe pain localized in the hands and feet. In contrast, episodic neuropathic pain—also known as "Fabry's crises"—presents as episodes lasting from hours to several days when patients suffer excruciating pain that starts in the hands and feet but then spreads centripetally to the proximal limb regions. Autonomic manifestations typically occur during these crises. Exercise, fever, and stress are well-known triggers for the episodes, but are not always reported by patients. Each crisis may have an acute onset and end, but recurrence is seen in many individuals over time. Later in the disease course, a subset of patients notice sustained pain improvement, which has been attributed to extensive peripheral nerve damage.

The mechanisms underlying neuropathic pain and small fiber dysfunction in FD are not yet fully understood [8]. Current evidence points to a combination of factors. One important mechanism is glycosphingolipid-mediated apoptosis of dorsal root

ganglia neurons, leading to secondary dying-forward degeneration of sensory axons. This was elegantly shown in vivo by Godel et al., who found dorsal root ganglia hypertrophy and increased blood flow in patients with FD undergoing an advanced spinal cord MRI protocol [9]. Endothelial involvement within the vasa nervorum due to glycosphingolipid accumulation seems to play a major role as well, causing nerve hypoxia and ischemia. Finally, abnormal expression of sodium channels in sensory fibers is another piece of the puzzle, which may contribute to pain because of the hyperexcitability of nociceptive neurons [10].

On the autonomic side, the major manifestations are cold intolerance and hypohidrosis [1, 2]. This may contribute to exercise intolerance, which is a conspicuous trait in FD. In addition to direct autonomic fiber damage, the deposition of lamellar intracytoplasmic inclusions in myoepithelial cells and small vessels around eccrine glands also contributes to abnormal sweating. Xerostomia, xerophthalmia, and gastrointestinal dysmotility are other dysautonomic symptoms common in FD [11].

Diagnosis of peripheral neuropathy in FD relies initially upon clinical suspicion, but should be confirmed with specific tools. Nerve conduction studies are the standard method to evaluate PNS disorders, but they are not useful here because they only assess large, myelinated fibers. Specific tests for SFN should be employed instead. One of them is quantitative sensory testing (QST), a psychophysical test that measures detection thresholds for warmth and cold in the hands and feet. These thresholds are extremely elevated in patients with FD [6]. Skin biopsy with intraepidermal nerve fiber density (IEND) quantification is considered the gold standard test to diagnose small fiber neuropathy in many centers. Some studies have indeed shown abnormally reduced IEND among patients with FD [12]. In our center, we have been using the quantitative sudomotor axonal reflex test (QSART), a technique that assesses the integrity of postganglionic cholinergic fibers responsible for sweat production [13]. Patients with FD typically present blunted QSART responses, remarkably different from controls.

Pain relief is one of the major goals in the clinical management of patients with FD and peripheral neuropathy. Nevertheless, there are no clinical trials specifically looking at the best drug and/or dosing regimen for this population. In practice, we consider general guidelines for neuropathic pain [14]. Gabapentin, pregabalin, carbamazepine, and amitriptyline all appear to be effective as preventive drugs. The choice between these drugs will be guided by the characteristics of each patient. Nevertheless, one should remember that gabapentin and pregabalin have exclusive renal clearance and should be used with caution in patients with or at risk for renal failure. Some authors recommend regular follow-up on renal function to ensure safe dosing.

25.3 CNS-Related Manifestations in FD

CNS manifestations in FD are also frequent, including tinnitus, hearing impairment, vertigo, psychiatric disorders, and cognitive impairment [15]. The most frequent and potentially life-threatening CNS manifestations are cerebrovascular events,

such as stroke and transient ischemic attack (TIA) [1, 15], showing an overall prevalence of 13% [15]. As happens with peripheral involvement, CNS symptoms are usually more prevalent and occur earlier in men than in women, since men are hemizygous, whereas women are heterozygous for FD [1]. The prevalence of CNS manifestations in FD is 12–31% among men and 5–18% among women [1]. The mean age of cerebrovascular events in men is 28.8–34 years, while in women, they usually arise at 40.3–50 years. Indeed, FD should be considered in young patients diagnosed with cryptogenic strokes [1, 16].

Strokes and TIA might manifest with paresis, ataxia, dysarthria, nausea, and dizziness [1]. Interestingly, despite cerebrovascular involvement being more frequent in men, TIA is more prevalent in women (16% vs. 11%) [17]. Cerebrovascular lesions affect white and gray matter and are more frequent in the posterior circulation [1, 2], especially related to vessel ectasia [2]. In addition to acute cerebrovascular events, chronic findings might be detected in magnetic resonance imaging (MRI), characterized by progressive white-matter lesions, which occur early in the course of FD [15].

Other CNS symptoms in FD are cognitive impairment and psychiatric symptoms [18]. Several studies have demonstrated that cognitive involvement mainly affects executive functioning, information processing speed, and attention [18]. Studies in younger patients are scarce, but it is possible that cognitive function is altered since childhood, especially involving executive functioning [19]. Cognitive impairment is believed to be associated with white matter pathology and depressive symptoms [18]. Among neuropsychiatric syndromes, depression is frequent, with rates that range from 15 to 62% [18]. Depression is directly related to chronic pain and, indirectly, to social and occupational consequences [18].

The mechanisms involved in CNS-related manifestations in FD are complex. The deficient activity of α-galactosidase A leads to the accumulation of globotriaosylceramide in vascular endothelial and smooth muscle cells, which alters vascular reactivity [15]. Therefore, patients with FD are susceptible to vessel occlusion and tissue ischemia [1, 2, 15]. Chronically, the increased interstitial pressure and hypoperfusion result in gliosis, demyelination, and white matter lesions [15]. Another peculiarity of ischemic lesions in FD is poststroke pain, which is described in 5–8% of patients after stroke [1]. Poststroke pain is likely related to glutamate levels and increased neuronal excitability [1].

Diagnostic suspicion of FD is usually made when peripheral symptoms occur since their onset often occurs earlier. However, cryptogenic stroke in young patients should give rise to the FD hypothesis [1, 15]. The prevalence of FD among those patients is approximately 1% and reaches 4.6% if small vessel disease is present [2]. Neuroimaging is helpful since some suggestive characteristics may be found, such as the pulvinar sign, stroke in posterior circulation, enlarged/tortuous basilar artery, and white matter lesions (Table 25.1) [2]. After FD diagnosis, in addition to cerebrovascular risks, patients should be monitored for neuropsychological impairments, since they might be bothersome and compromise quality of life [19].

Treatment of the cerebrovascular events in FD mainly concerns traditional management of stroke and TIA, using antiplatelet therapy, and avoiding other risk

Table 25.1 Brain MRI abnormalities in Fabry's disease

MRI sequence	Typical findings
T1	Hyperintensity in lateral pulvinar region
T2 and fluid-attenuated inversion recovery (FLAIR)	White matter lesions ischemic vascular lesions, mainly in posterior circulation
MR angiography	Dolichoectasia

factors (hypertension, hypercholesterolemia, smoking) [2, 15]. First-line therapy with enzyme replacement has not proven to be efficient in reducing stroke incidence or in mitigating white matter lesions [15]. CNS manifestations are usually late complications of FD, which may be the reason for the disappointing results of enzyme-replacement therapy for this purpose [15].

25.4 Cochleovestibular Manifestations in FD

Metabolic storage in FD also occurs in the cochleovestibular system and adjacent structures [15, 20, 21]. However, the exact incidence of otological symptoms is likely underestimated, since few patients are submitted to complete otological examination [20], and those symptoms might be subtler in comparison to other comorbidities related to FD. Some studies estimated this manifestation to be found in approximately 70% of patients [20, 21]. Tinnitus and hearing loss are the main presentations of cochlear impairment [20], whereas vestibular symptoms manifest as vertigo, dizziness, and instability [20]. Hearing loss is commonly bilateral, asymmetric, and sensorineural [20, 21].

A clinical clue to adequately monitoring otological impairments is the severity of renal and cardiac comorbidities, which is associated with the extent of hearing loss in FD patients [20]. In addition, hearing loss is associated with acroparesthesias and microalbuminuria levels [22]. Diagnostic tools that might enrich clinical evaluation and clarify cochleovestibular symptoms are pure-tone audiometry, speech audiometry, otoacoustic emissions, auditory brainstem response audiometry, and videonystagmography [20, 21]. Even when cochleovestibular manifestations related to FD are already diagnosed, possible confounders must be excluded, such as noise exposure, infections, and ototoxic medications [21].

The exact pathophysiology of cochleovestibular disorders in FD is not completely understood. Most likely, it involves the accumulation of globotriaosylceramides in cochlear structures, but mainly in endothelial cells and smooth muscle, leading to small vessel infarcts [21]. Further studies regarding the intrinsic mechanisms related to otological manifestations are needed. In addition, few studies have investigated the effects of enzyme replacement therapy on hearing loss, but the results are promising in stopping the progression [22].

In conclusion, despite being underdiagnosed, cochleovestibular disturbances should be regularly investigated since they are frequent and might compromise the quality of life of FD patients.

25.5 Enzyme Replacement Therapy and Neurological Manifestations

Enzyme replacement is now considered the mainstay of disease-modifying therapy in FD. Available data indicate that it may reduce the severity and/or progression of disease in the long term, but not all systems are impacted the same way by treatment. There is little information on the effects of enzyme replacement on neurological complications.

The results of an NIH-sponsored clinical trial were published in 2001 and favored the use of agalsidase alfa in the short term [23]. The authors recruited 26 adult men hemizygous for *GLA* variants and stratified them into 2 groups (placebo vs treatment). Individuals in the treatment arm received the medication (0.2 mg/kg) every 2 weeks and were followed for 24 weeks. At this point, the mean brief pain scores decreased significantly between baseline and follow-up among treated subjects (6.2 vs. 4.3, $p = 0.02$), but not in the placebo arm.

Some studies with long-term follow-up under treatment have reported neurological outcomes. They emphasized pain and TIA/stroke risk. One of those is the open label extension of the International Fabry Disease Study Group published in 2004 [24]. Wilcox et al. looked at the safety and efficacy results of agalsidase beta (1 mg/kg every other week) in a cohort of 58 patients with FD. After 36 months, pain remained under control (as shown by the scores on the McGill pain questionnaire). This was evident not only for those patients treated earlier (original treatment arm in the placebo-controlled phase), but also for those treated later (original placebo arm in the placebo-controlled phase). Regarding cerebrovascular complications, 8 out of 58 patients (8.6%) had either TIA or stroke in this period. Since there was no placebo group in the extension phase of the trial, one cannot ascertain whether enzymatic replacement indeed reduced stroke or TIA risk.

Similar positive effects on long-term pain improvement have been reported in the Fabry Outcome Survey based on data from 545 patients followed for up to 2 years [25]. In contrast, it is not yet clear whether enzyme replacement reduces stroke risk in FD patients. In some reports, the overall risk remains similar or even slightly higher than that found in natural history studies [26, 27].

25.6 Conclusions

Neurological complications are frequent, bothersome, and potentially life-threatening in patients with FD. Small fiber neuropathy and neuropathic pain are often the heralding manifestations in the disease, appearing in the first or second decades of life. In contrast, stroke or TIA appears later (typically in the third decade), but may lead to major handicap or even death. Recognition of neurological features in FD requires clinical expertise and specific confirmatory tests depending on the specific presentation. Both neuropathic pain and stroke are amenable to specific

pharmacological interventions aiming to alleviate or prevent these complications. Proper management may significantly improve the quality of life of affected patients. Currently, the long-term impact of disease-modifying therapies (particularly enzymatic replacement) on the neurological features of FD remains to be determined.

References

1. Møller AT, Jensen TS. Neurological manifestations in Fabry's disease. Nat Clin Pract Neurol. 2007;3:95–106.
2. Ranieri M, Bedini G, Parati EA, Bersano A. Fabry disease: recognition, diagnosis, and treatment of neurological features. Curr Treat Options Neurol. 2016;18:33.
3. Tomek A, Petra R, Paulasová Schwabová J, Olšerová A, Škorňa M, Nevšímalová M, Šimůnek L, Herzig R, Fafejtová Š, Mikulenka P, Táboříková A, Neumann J, Brzezny R, Sobolová H, Bartoník J, Václavík D, Vachová M, Bechyně K, Havlíková H, Prax T, Šaňák D, Černíková I, Ondečková I, Procházka P, Rajner J, Škoda M, Novák J, Škoda O, Bar M, Mikulík R, Dostálová G, Linhart A, National Stroke Research Network, part of Czech Clinical Research Infrastructure Network (CZECRIN) and Czech Neurological Society, Cerebrovascular Section. Nationwide screening for Fabry disease in unselected stroke patients. PLoS One. 2021;16:e0260601.
4. Schiffmann R. Natural history of Fabry disease in males: preliminary observations. J Inherit Metab Dis. 2001;24:15–7.
5. Kocen RS, Thomas PK. Peripheral nerve involvement in Fabry's disease. Arch Neurol. 1970;22:81–8.
6. Luciano CA, Russell JW, Banerjee TK, Quirk JM, Scott LJ, Dambrosia JM, Barton NW, Schiffmann R. Physiological characterization of neuropathy in Fabry's disease. Muscle Nerve. 2002;26:622–9.
7. Burand AJ Jr, Stucky CL. Fabry disease pain: patient and preclinical parallels. Pain. 2021;162:1305–21.
8. Miller JJ, Aoki K, Moehring F, Murphy CA, O'Hara CL, Tiemeyer M, Stucky CL, Dahms NM. Neuropathic pain in a Fabry disease rat model. JCI Insight. 2018;3:e99171.
9. Godel T, Bäumer P, Pham M, Köhn A, Muschol N, Kronlage M, Kollmer J, Heiland S, Bendszus M, Mautner VF. Human dorsal root ganglion in vivo morphometry and perfusion in Fabry painful neuropathy. Neurology. 2017;89:1274–82.
10. Schiffmann R, Scott LJC. Pathophysiology and assessment of neuropathic pain in Fabry disease. Acta Paediatr. 2002;439:S48–52.
11. Cable WJ, Kolodny EH, Adams RD. Fabry disease: impaired autonomic function. Neurology. 1982;32:498–502.
12. Scott LJ, Griffin JW, Luciano C, Barton NW, Banerjee T, Crawford T, McArthur JC, Tournay A, Schiffmann R. Quantitative analysis of epidermal innervation in Fabry disease. Neurology. 1999;52:1249–54.
13. Schiffmann R, Floeter MK, Dambrosia JM, Gupta S, Moore DF, Sharabi Y, et al. Enzyme replacement therapy improves peripheral nerve and sweat function in Fabry disease. Muscle Nerve. 2003;28:703–10.
14. Bates D, Schultheis BC, Hanes MC, Jolly SM, Chakravarthy KV, Deer TR, Levy RM, Hunter CW. A comprehensive algorithm for management of neuropathic pain. Pain Med. 2019;20(Suppl 1):S2–S12.
15. Fellgiebel A, Müller MJ, Ginsberg L. CNS manifestations of Fabry's disease. Lancet Neurol. 2006;5:791–5.

16. Mancuso M, Arnold M, Bersano A, Burlina A, Chabriat H, Debette S, et al. Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European academy of neurology. Eur J Neurol. 2020;27:909–27.
17. Mehta A, Ginsberg L. Natural history of the cerebrovascular complications of Fabry disease. Acta Paediatr Suppl. 2005;94:24–7.
18. Bolsover FE, Murphy E, Cipolotti L, Werring DJ, Lachmann RH. Cognitive dysfunction and depression in Fabry disease: a systematic review. J Inherit Metab Dis. 2014;37:177–87.
19. Bugescu N, Alioto A, Segal S, Cordova M, Packman W. The neurocognitive impact of Fabry disease on pediatric patients. Am J Med Genet Part B Neuropsychiatr Genet. 2015;168:204–10.
20. Asquier-Khati A, Mauhin W, Michel G, Gendre A, Durant C, Lavigne C, et al. Cochleovestibular involvement in patients with Fabry disease: data from the multicenter cohort FFABRY. Eur Arch Otorhinolaryngol. 2021;279:1–6.
21. Köping M, Shehata-Dieler W, Cebulla M, Rak K, Oder D, Müntze J, et al. Cardiac and renal dysfunction is associated with progressive hearing loss in patients with Fabry disease. PLoS One. 2017;12:e0188103.
22. Rodrigues J, Azevedo O, Sousa N, Cunha D, Mexedo A, Fonseca R. Inner ear involvement in Fabry disease: clinical and audiometric evaluation of a large cohort of patients followed in a reference center. Eur J Med Genet. 2018;61:341–7.
23. Schiffmann R, Kopp JB, Austin HA 3rd, Sabnis S, Moore DF, Weibel T, Balow JE, Brady RO. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA. 2001;285:2743–9.
24. Wilcox WR, Banikazemi M, Guffon N, Waldek S, Lee P, Linthorst GE, Desnick RJ, Germain DP. International Fabry disease study group. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. Am J Hum Genet. 2004;75:65–74.
25. Beck M, Ricci R, Widmer U, Dehout F, de Lorenzo AG, Kampmann C, Linhart A, Sunder-Plassmann G, Houge G, Ramaswami U, Gal A, Mehta A. Fabry disease: overall effects of agalsidase alfa treatment. Eur J Clin Investig. 2004;34:838–44.
26. Sirrs SM, Bichet DG, Casey R, Clarke JT, Lemoine K, Doucette S, West ML. CFDI investigators. Outcomes of patients treated through the Canadian Fabry disease initiative. Mol Genet Metab. 2014;111:499–506.
27. Germain DP, Charrow J, Desnick RJ, Guffon N, Kempf J, Lachmann RH, Lemay R, Linthorst GE, Packman S, Scott CR, Waldek S, Warnock DG, Weinreb NJ, Wilcox WR. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. J Med Genet. 2015;52:353–8.

Chapter 26
Cardiac Manifestations in Fabry Disease

Murillo de Oliveira Antunes

26.1 Introduction

FD is an X-linked genetic disorder of lysosomal storage, in which patients have deficient activity of the lysosomal enzyme α-galactosidase A (a-Gal A) [1]. a-GAL A deficiency leads to the accumulation of globotriaosylceramide and related globotriaosylsphingosine (lyso-Gb3) throughout the body. The degree of involvement varies greatly between different organ types due to the different production of a-GaL A, and Gb3 metabolism, present in the different cells and tissues of our body [2]. Cardiac involvement represents the main cause of impaired quality of life and death in patients with FD [3] and the early diagnosis is associated with improved prognosis, as it presents specific treatment through enzyme replacement that can delay the progression of the disease and its consequences [4–7].

26.2 Epidemiology

The reported incidence of FD is 1 in 40,000–117,000 individuals, although some neonatal screening surveys suggest that the incidence may be as high as 1 in 3100–8800 newborns [8, 9]. The reported prevalence of AFD with end-stage renal disease on hemodialysis ranges between 0.2 and 1.2%; in patients with cryptogenic stroke, the prevalence may be as high as 4.9% in men and 2.8% in women [10].

The distribution is equal between women and men and previous studies suggest that up to 50% of women with Fabry disease may be asymptomatic or unidentified [6].

M. de Oliveira Antunes (✉)
Clinical Research Center São Francisco, Hospital Universitário São Francisco, Bragança Paulista, São Paulo, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_26

26.3 Differential Diagnosis

The FD cardiac phenotype is left ventricular hypertrophy (LVH) and should be considered as a differential diagnosis of patients with unexplained myocardial hypertrophy of the left ventricle, or hypertrophic or restrictive cardiomyopathy [11]. It is crucial for the cardiologist who is treating a patient with hypertrophic cardiomyopathy to include FD in the differential diagnosis.

In patient hypertrophic cardiomyopathy or amyloidosis, some studies report that approximately 1–4% of these patients would have the diagnosis of FD [12–15].

26.4 Molecular Genetics

More than 1000 GLA variants have already been identified with descriptions of benign polymorphism mutations, variants of uncertain meaning, and pathogenic mutations [16, 17]. Among the pathogenic mutations, we find those that cause the absence or low activity of the a-Gal A enzyme and the classic phenotype of the disease; and variants that are associated with residual a-Gal A activity causing late-onset FD, which predominantly affects the heart or kidney (variant heart rate) [3]. Genetic variants associated with the cardiac variant include p.N215S (prevalent in North America and Europe), p.F113L (prevalent in Portugal), and IVS4 + 919G > A (prevalent in Taiwan) [18–20].

26.5 Pathophysiology of Cardiac Involvement in Fabry Diseases

The a-Gal A deficiency leads to the storage of Gb3 in many tissues and cell types and only 5–10% of residual enzyme activity appears to be sufficient to prevent clinically significant accumulation of globotriaosylceramide. In the heart, Gb3 deposits affect all types of cardiac cells and tissues, including myocytes, endothelial, and smooth muscle cells of intramyocardial vessels, endocardium, valvular fibroblasts, and conduction tissue [21]. The cardiac disorder includes unexplained left ventricular hypertrophy (LVH), valvular dysfunction, and conduction abnormalities. The progressive storage of these molecules eventually leads to cellular dysfunction, which can, in turn, trigger ischemia, inflammation, and fibrosis [22].

However, only the accumulation of Gb3 does not explain the entire spectrum of FD pathophysiology [23]. Along with the mechanical effects, the accumulation of Gb3 impairs endocytosis and autophagy, induces apoptosis, interferes with mitochondrial energy production [24], and triggers secondary processes, which lead to

tissue inflammation and biochemical and functional impairment of myocytes. In endomyocardial biopsies of patients with SCD, chronic inflammatory activity was observed [25].

Accumulation of Gb3 (and lyso-Gb3) can act as antigens that activate invariant natural killer T cells and lead to chronic inflammation and autoimmunity. The effects mediated by glycosphingolipids are abolished by anti-toll-like receptor-4 antibodies, suggesting a central role of this inflammatory pathway [26, 27], promoting extracellular matrix remodeling and fibrosis mediated by tumor growth factor [28]. Defective autophagy activates inflammasome and release of reactive oxidative species that are associated with microvascular dysfunction and perfusion abnormalities in early cardiac involvement contribute to inflammation [29].

Also, stored Gb3 can alter ion channel expression and/or cell membrane traffic, modifying the electrical properties of cardiomyocytes resulting in higher and lower spontaneous action potentials. Intracellular glycosphingolipids cause sarcomeric myofilament dysfunction and myofibrillolysis [30].

The appearance of myocardial fibrosis is common in Fabry's disease. In female patients, they may occur even before the presence of left ventricular hypertrophy. The pathophysiological mechanism of myocardial fibrosis is still not entirely clear. The most possible explanation is the presence of myocardial ischemia (secondary to microvascular endothelial dysfunction) associated with focal inflammatory diseases triggered by the storage of GL-3 in the cardiomyocyte [31]. Fig. 26.1 shows the main mechanisms by which Fabry disease compromises the heart.

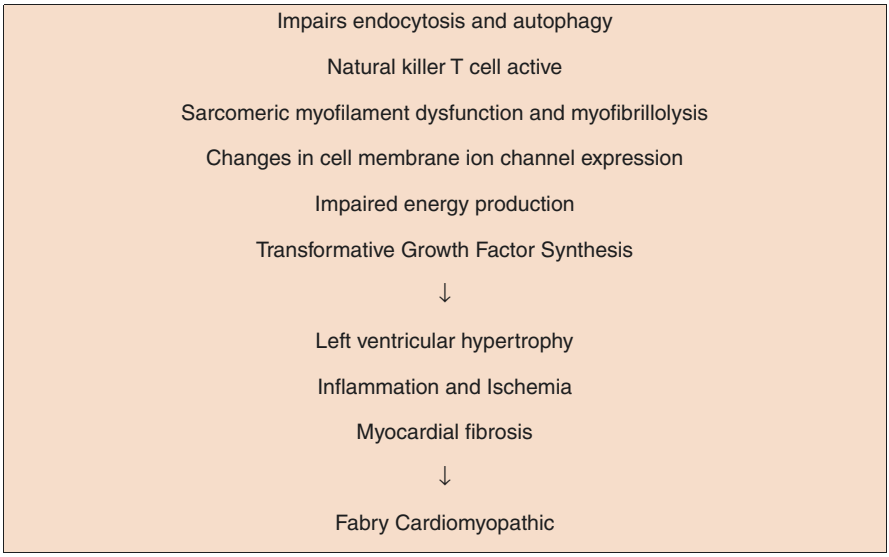


Fig. 26.1 Pathophysiology of FD

26.6 Clinical Presentation

Symptoms attributable to cardiac involvement in patients with Fabry disease include palpitations, angina pectoris, and dyspnea. However, the FD is rare and in the early stages the patients have nonspecific symptoms; frequently is poorly recognized by physicians and the diagnosis is often delayed. Data from the Fabry outcome Survey suggest that there is a delay of 13.7 years for men and 16.3 years for women from symptom onset to diagnosis [32].

Cardiac manifestations develop in the third or fourth decade of life in men and one decade later in women; the classic cardiac disease is characterized by progressive left ventricular hypertrophy, myocardial fibrosis, and diastolic.

Dyspnea and heart failure with preserved systolic function are the main clinical manifestations [11, 33].Chest pain or angina is a relatively common presentation in FD [8, 15, 16]. However, the coronary arteriography is normal in most patients and vascular Gb3 deposition causes endothelial dysfunction and coronary vasospasm [33–35].

Patients with AFD often complain of dysfunction palpitations. Most rhythm abnormalities are supraventricular tachycardias and atrial fibrillation or flutter [36]. Tachycardia, non-sustained ventricular tachycardia, fatal malignant arrhythmias (sudden cardiac death), and bradyarrhythmias requiring pacemaker and ICD implantation are reported [10]. Cardiac symptoms, ECG, and cardiac image findings are shown in Fig. 26.2.

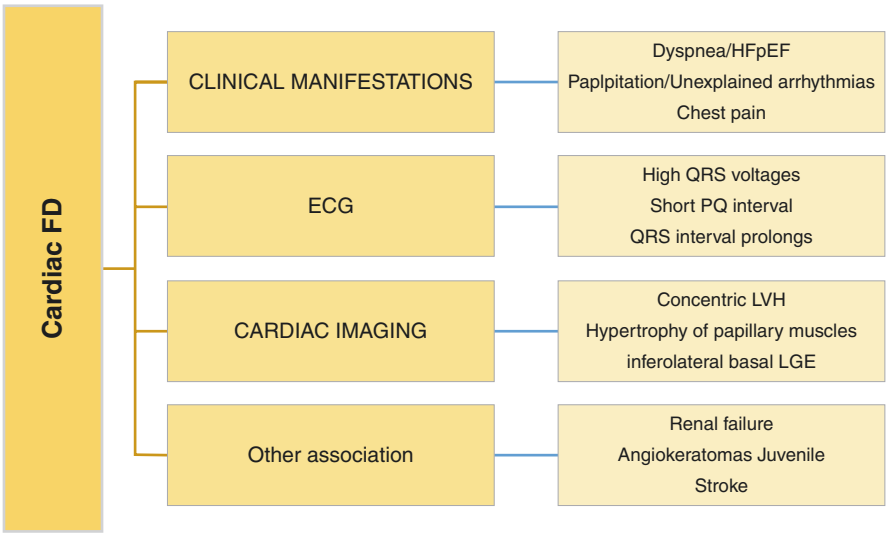


Fig. 26.2 Cardiac manifestations in Fabry disease. *HFpEF* heart failure with preserved ejection fraction. *LGE* late gadolinium

26.7 Cardiomyopathy

LVH is the main cardiac manifestation of Fabry disease [37–39]. Concentric remodeling is identified in the early stages, but with disease progression it can progress to eccentric hypertrophy. In up to 5% of cases, the hypertrophy may be only septal, being indistinguishable from that observed in sarcomeric cardiomyopathies. The occurrence of a dynamic obstructive gradient at the left ventricular outflow is rare [33, 40].

The right ventricle is frequently affected, but without functional or clinical repercussions.

The presence of visually prominent papillary muscles is reported. In a recent study it could be shown that the absolute papillary muscle area as well as the ratio of the papillary muscle area and the left ventricular circumference is enlarged in FD and can be used in the differential diagnosis [41].

Diastolic function is altered and relaxation and pseudonormalization abnormalities are frequently found; however, a restrictive pattern is extremely rare. The global left ventricular ejection fraction (EF) is typically preserved in Fabry disease.

Expansion of the cardiac interstitium and myocardial fibrosis are observed with the progression of the heart disease. In the end stage of Fabry cardiomyopathy, extensive areas of myocardial fibrosis are found, as well as severely impaired systolic and diastolic left ventricular function [42].

26.8 Electrophysiological Abnormalities

The ECG assessment can be used to identify Fabry disease at an earlier stage of the disease and the most adult patients with FD have an abnormal resting ECG. Commonly, electrocardiographic findings include criteria for LVH, repolarization changes, and PQ-interval shortening, due to shortening of the P-wave duration; one is the first signs of cardiac involvement. In patients with findings of short PQ, associated voltage criteria for diagnosing LVH should be investigated as FD.

Patients in early-stage FD have QRS interval shortening, but likely a result of enhanced conduction velocity, and with disease progression, the QRS interval prolongs AV conduction delay and progressive sinus node dysfunction [43]. Prior studies of FD patients have shown a correlation between prolonged QRS duration on ECG and LV mass on TTE and CMR [44, 45]. In FD, right bundle branch block is more common than left bundle branch block [41].

The ST- and T-alterations (ST-declines and T-wave inversion) can indicate myocardial fibrosis. These alterations are mainly found in the lateral leads V5 and V6 [43].

The most frequently encountered rhythm abnormalities are supraventricular tachycardias, atrial fibrillation, and atrial flutter [36].

ECG is a great tool in the differential diagnosis of myocardial hypertrophies and there is a high diagnostic performance by combining the corrected QT duration with the PQ interval minus the P wave duration in lead II [46]. Both abnormal ECG and echocardiogram of a female patient with FD are illustrated in Fig. 26.3.

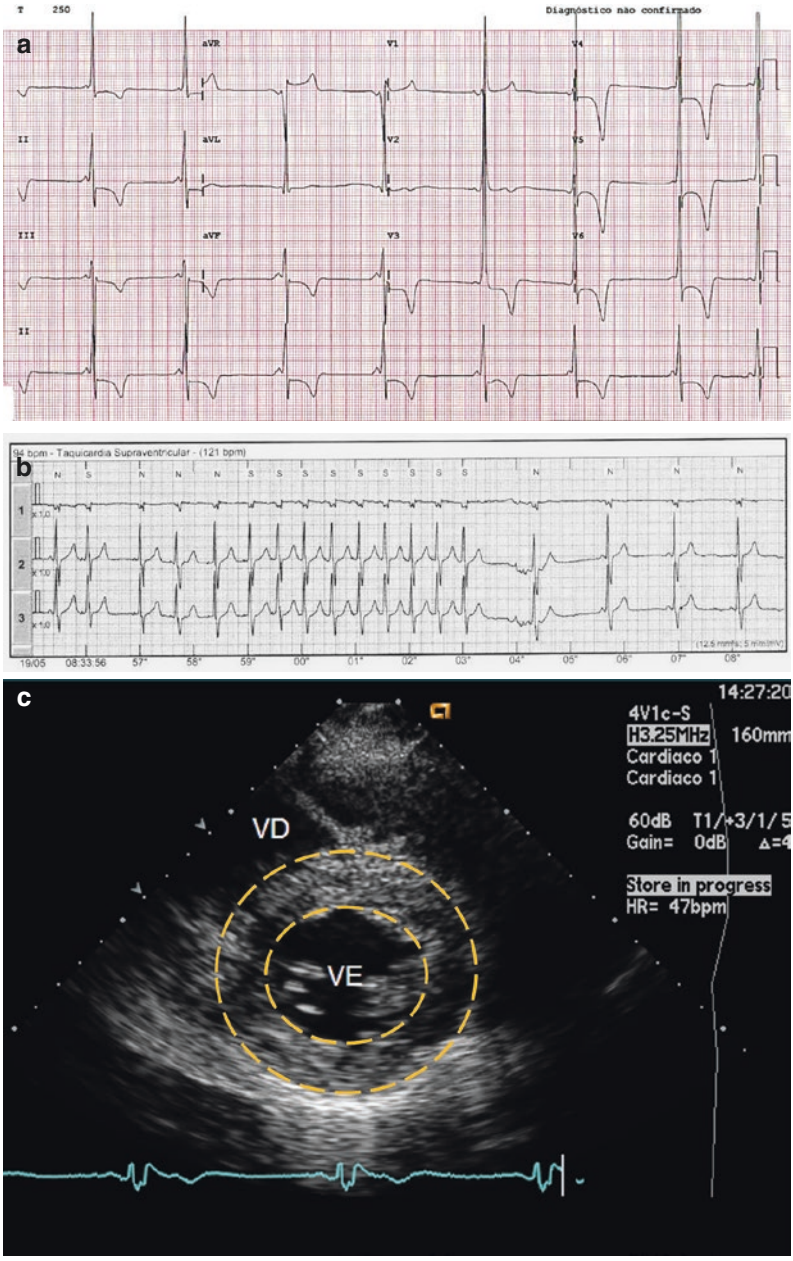


Fig. 26.3 45 years female with fabry disease. (**a**) Short PR interval associated with voltage criteria for the diagnosis of LVH in the ECG. (**b**) 24 h Holter recording showing a supraventricular tachycardia. (**c**) Echocardiogram demonstrates left ventricular hypertrophy and concentric remodeling. *VE* left ventricle, *VD* right ventricle

26.9 Valvular Disease

Valve disease in AFD is caused by infiltrative changes within valvular fibroblasts. Aortic and mitral valve involvement occurs in half of the patients [40], but the need for valve replacement due to severe valve disease is rare.

The most advanced stages of the disease may be associated with marked dilatation of the aortic root and may contribute to aortic valve insufficiency [39, 40].

26.10 Coronary Manifestations

Several mechanisms contribute to myocardial ischemia in DF. The presence of myocyte hypertrophy and fibrosis causes increased resistance and increased myocardial oxygen demand, precipitating the occurrence of ischemia due to an imbalance between supply and consumption [38, 47].

Also, the deposition of Gb3 vascular endothelium leads to microvascular dysfunction with nitric oxide pathway dysregulation and microvascular remodeling, causing vasospasm and angina with angiography; the epicardial coronary arteries described as structurally normal. Coronary microvascular function is markedly impaired in AFD patients irrespective of LVH and gender and may represent the only sign of cardiac involvement [47, 48].

26.11 Conclusion

The main cardiac manifestation found in Fabry disease is left ventricular hypertrophy. Patients with preserved heart failure and LVH should be investigated for the possibility of FD. Fabry cardiomyopathy has specific treatment through enzyme replacement therapy that stabilizes and prevents disease progression, especially in the early stages when extensive heart involvement and myocardial fibrosis are not yet observed.

References

1. Garman SC, Garboczi DN. The molecular defect leading to fabry disease: structure of human α-galactosidase. J Mol Biol. 2004;337:319–35. https://doi.org/10.1016/j.jmb.2004.01.035.
2. Ortiz A, Abiose A, Bichet DG, Cabrera G, Charrow J, Germain DP, et al. Time to treatment benefit for adult patients with Fabry disease receiving agalsidase β: data from the Fabry registry. J Med Genet. 2016;53:495–502. https://doi.org/10.1136/jmedgenet-2015-103486.

3. Pieroni M, Moon JC, Arbustini E, Barriales-Villa R, Camporeale A, Vujkovac AC, et al. Cardiac involvement in Fabry disease: JACC review topic of the week. J Am Coll Cardiol. 2021;77:922–36. https://doi.org/10.1016/j.jacc.2020.12.024.
4. Frustaci A, Chimenti C, Ricci R, Natale L, Russo MA, Pieroni M, et al. Improvement in cardiac function in the cardiac variant of Fabry's disease with galactose-infusion therapy. N Engl J Med. 2001;345:25–32. https://doi.org/10.1056/NEJM200107053450104.
5. Banikazemi M. Agalsidase-Beta therapy for advanced Fabry disease. Ann Intern Med. 2007;146:77. https://doi.org/10.7326/0003-4819-146-2-200701160-00148.
6. Imbriaco M, Pisani A, Spinelli L, Cuocolo A, Messalli G, Capuano E, et al. Effects of enzyme-replacement therapy in patients with Anderson-Fabry disease: a prospective long-term cardiac magnetic resonance imaging study. Heart. 2009;95:1103–7. https://doi.org/10.1136/hrt.2008.162800.
7. Weidemann F, Niemann M, Störk S, Breunig F, Beer M, Sommer C, et al. Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression towards serious complications. J Intern Med. 2013;274:331–41. https://doi.org/10.1111/joim.12077.
8. Burlina AB, Polo G, Salviati L, Duro G, Zizzo C, Dardis A, et al. Newborn screening for lysosomal storage disorders by tandem mass spectrometry in north East Italy. J Inherit Metab Dis. 2018;41:209–19. https://doi.org/10.1007/s10545-017-0098-3.
9. Poorthuis BJHM, Wevers RA, Kleijer WJ, Groener JEM, de Jong JGN, van Weely S, et al. The frequency of lysosomal storage diseases in the Netherlands. Hum Genet. 1999;105:151–6. https://doi.org/10.1007/s004399900075.
10. Linhart A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. Heart. 2007;93:528–35. https://doi.org/10.1136/hrt.2005.063818.
11. Fernandes F, Antunes MO, Hotta VT, Rochitte CE, Mady C. Deposit diseases as differential diagnosis of left ventricular hypertrophy in patients with heart failure and preserved systolic function. Arq Bras Cardiol. 2019;113:979–87. https://doi.org/10.36660/abc.20180370.
12. Elliott P, Baker R, Pasquale F, Quarta G, Ebrahim H, Mehta AB, et al. Prevalence of Anderson-Fabry disease in patients with hypertrophic cardiomyopathy: The European Anderson-Fabry disease survey. Heart. 2011;97:1957–60. https://doi.org/10.1136/heartjnl-2011-300364.
13. Maurizi N, Rella V, Fumagalli C, Salerno S, Castelletti S, Dagradi F, et al. Prevalence of cardiac amyloidosis among adult patients referred to tertiary centres with an initial diagnosis of hypertrophic cardiomyopathy. Int J Cardiol. 2020;300:191–5. https://doi.org/10.1016/j.ijcard.2019.07.051.
14. Seo J, Kim M, Hong G-R, Kim D-S, Son J-W, Cho IJ, et al. Fabry disease in patients with hypertrophic cardiomyopathy: a practical approach to diagnosis. J Hum Genet. 2016;61:775–80. https://doi.org/10.1038/jhg.2016.52.
15. Chimenti C, Pieroni M, Morgante E, Antuzzi D, Russo A, Russo MA, et al. Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. Circulation. 2004;110:1047–53. https://doi.org/10.1161/01.CIR.0000139847.74101.03.
16. Ortiz A, Germain DP, Desnick RJ, Politei J, Mauer M, Burlina A, et al. Fabry disease revisited: management and treatment recommendations for adult patients. Mol Genet Metab. 2018;123:416–27. https://doi.org/10.1016/j.ymgme.2018.02.014.
17. Fabry database. The Fabry mutants list. 2020. http://fabry-database.org/mutants.2020.
18. Hsu T-R, Hung S-C, Chang F-P, Yu W-C, Sung S-H, Hsu C-L, et al. Later onset Fabry disease, cardiac damage Progress in silence. J Am Coll Cardiol. 2016;68:2554–63. https://doi.org/10.1016/j.jacc.2016.09.943.
19. Azevedo O, Gal A, Faria R, Gaspar P, Miltenberger-Miltenyi G, Gago MF, et al. Founder effect of Fabry disease due to p.F113L mutation: clinical profile of a late-onset phenotype. Mol Genet Metab. 2020;129:150–60. https://doi.org/10.1016/j.ymgme.2019.07.012.
20. Germain DP, Brand E, Burlina A, Cecchi F, Garman SC, Kempf J, et al. Phenotypic characteristics of the p.Asn215Ser (p.N215S) *GLA* mutation in male and female patients with

Fabry disease: a multicenter Fabry registry study. Mol Genet Genomic Med. 2018;6:492–503. https://doi.org/10.1002/mgg3.389.
21. Clarke JTR. Narrative review: Fabry disease. Ann Intern Med. 2007;146:425. https://doi.org/10.7326/0003-4819-146-6-200703200-00007.
22. Desnick RJ, Blieden LC, Sharp HL, Hofschire PJ, Moller JH. Cardiac valvular anomalies in fabry disease clinical, morphologic, and biochemical studies. Circulation. 1976;54(5):818–25. https://doi.org/10.1161/01.cir.54.5.818.
23. Platt FM, d'Azzo A, Davidson BL, Neufeld EF, Tifft CJ. Lysosomal storage diseases. Nat Rev Dis Primers. 2018;4:27. https://doi.org/10.1038/s41572-018-0025-4.
24. Ivanova M. Altered sphingolipids metabolism damaged mitochondrial functions: lessons learned from Gaucher and Fabry diseases. J Clin Med. 2020;9:1116. https://doi.org/10.3390/jcm9041116.
25. Frustaci A, Verardo R, Grande C, Galea N, Piselli P, Carbone I, et al. Immune-mediated myocarditis in Fabry disease cardiomyopathy. J Am Heart Assoc. 2018;7:e009052. https://doi.org/10.1161/JAHA.118.009052.
26. Mauhin W, Lidove O, Masat E, Mingozzi F, Mariampillai K, Ziza J-M, et al. Innate and adaptive immune response in Fabry disease. JIMD Rep. 2015;22:1–10. https://doi.org/10.1007/8904_2014_371.
27. Rozenfeld P, Feriozzi S. Contribution of inflammatory pathways to Fabry disease pathogenesis. Mol Genet Metab. 2017;122:19–27. https://doi.org/10.1016/j.ymgme.2017.09.004.
28. Sanchez-Niño MD, Carpio D, Sanz AB, Ruiz-Ortega M, Mezzano S, Ortiz A. Lyso-Gb3 activates Notch1 in human podocytes. Hum Mol Genet. 2015;24(20):5720–32. https://doi.org/10.1093/hmg/ddv291.
29. Knott KD, Augusto JB, Nordin S, Kozor R, Camaioni C, Xue H, et al. Quantitative myocardial perfusion in Fabry disease. Circ Cardiovasc Imaging. 2019;12:8872. https://doi.org/10.1161/CIRCIMAGING.119.008872.
30. Chimenti C, Hamdani N, Boontje NM, DeCobelli F, Esposito A, Bronzwaer JGF, et al. Myofilament degradation and dysfunction of human cardiomyocytes in Fabry disease. Am J Pathol. 2008;172:1482–90. https://doi.org/10.2353/ajpath.2008.070576.
31. Cabrera G. Update on coronary involvement in Fabry disease. J Inborn Errors Metab Screen. 2016;4:232640981667942. https://doi.org/10.1177/2326409816679427.
32. Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest. 2004;34:236–42.
33. Wu JC, Ho CY, Skali H, Abichandani R, Wilcox WR, Banikazemi M, et al. Cardiovascular manifestations of fabry disease: relationships between left ventricular hypertrophy, disease severity, and-galactosidase a activity. Eur Heart J. 2010;31:1088–97. https://doi.org/10.1093/eurheartj/ehp588.
34. Kampmann C, Baehner F, Ries M, Beck M. Cardiac involvement in Anderson-Fabry disease. J Am Soc Nephrol. 2002;13(Suppl 2):S147–9.
35. Barbey F, Brakch N, Linhart A, Jeanrenaud X, Palecek T, Bultas J, et al. Increased carotid intima–media thickness in the absence of atherosclerotic plaques in an adult population with Fabry disease. Acta Paediatr. 2006;95:63–8. https://doi.org/10.1080/08035320600618924.
36. Shah JS, Hughes DA, Sachdev B, Tome M, Ward D, Lee P, et al. Prevalence and clinical significance of cardiac arrhythmia in Anderson-Fabry disease. Am J Cardiol. 2005;96:842–6. https://doi.org/10.1016/j.amjcard.2005.05.033.
37. Ferrans VJ, Hibbs RG, Burda CD. The heart in Fabry's disease. Am J Cardiol. 1969;24:95–110. https://doi.org/10.1016/0002-9149(69)90055-1.
38. Azevedo O, Cordeiro F, Gago MF, Miltenberger-Miltenyi G, Ferreira C, Sousa N, et al. Fabry disease and the heart: a comprehensive review. Int J Mol Sci. 2021;22:4434. https://doi.org/10.3390/ijms22094434.

39. Goldman ME, Cantor R, Schwartz MF, Baker M, Desnick RJ. Echocardiographic abnormalities and disease severity in Fabry's disease. J Am Coll Cardiol. 1986;7:1157–61. https://doi.org/10.1016/S0735-1097(86)80238-8.
40. Linhart A, Paleček T, Bultas J, Ferguson JJ, Hrudová J, Karetová D, et al. New insights in cardiac structural changes in patients with Fabry's disease. Am Heart J. 2000;139:1101–8. https://doi.org/10.1067/mhj.2000.105105.
41. Niemann M, Liu D, Hu K, Herrmann S, Breunig F, Strotmann J, et al. Prominent papillary muscles in Fabry disease: a diagnostic marker? Ultrasound Med Biol. 2011;37:37–43. https://doi.org/10.1016/j.ultrasmedbio.2010.10.017.
42. Anastasakis A, Sevdalis E. Anderson-Fabry Disease: a cardiomyopathy that can be cured. Hellenic J Cardiol. 2011;52:316–26.
43. Namdar M. Electrocardiographic changes and arrhythmia in Fabry disease. Frontiers in Cardiovascular Medicine. 2016;3. https://doi.org/10.3389/fcvm.2016.00007.
44. Kampmann C, Wiethoff C, Martin C, Wenzel A, Kampmann R, Whybra C, et al. Electrocardiographic signs of hypertrophy in Fabry disease-associated hypertrophic cardiomyopathy. Acta Paediatr. 2007;91:21–7. https://doi.org/10.1111/j.1651-2227.2002.tb03105.x.
45. Niemann M, Hartmann T, Namdar M, Breunig F, Beer M, Machann W, et al. Cross-sectional baseline analysis of electrocardiography in a large cohort of patients with untreated Fabry disease. J Inherit Metab Dis. 2013;36:873–9. https://doi.org/10.1007/s10545-012-9540-8.
46. Namdar M, Steffel J, Jetzer S, Schmied C, Hürlimann D, Camici GG, et al. Value of electrocardiogram in the differentiation of hypertensive heart disease, hypertrophic cardiomyopathy, aortic stenosis, amyloidosis, and Fabry disease. Am J Cardiol. 2012;109:587–93. https://doi.org/10.1016/j.amjcard.2011.09.052.
47. Tomberli B, Cecchi F, Sciagrà R, Berti V, Lisi F, Torricelli F, et al. Coronary microvascular dysfunction is an early feature of cardiac involvement in patients with Anderson-Fabry disease. Eur J Heart Fail. 2013;15:1363–73. https://doi.org/10.1093/eurjhf/hft104.
48. Elliott PM. Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with galactosidase A. Heart. 2005;92:357–60. https://doi.org/10.1136/hrt.2004.054015.

Chapter 27
Fabry Nephropathy

Maria Helena Vaisbich, Luis Gustavo Modelli de Andrade, Cassiano Augusto Braga Silva, Fellype Carvalho Barreto, and Marlene Antonia dos Reis

27.1 Introduction

Fabry disease (FD) is caused by mutations in the *GLA* gene, which encodes the lysosomal enzyme α-galactosidase A (α-Gal A), leading to the progressive accumulation of glycosphingolipids with terminal ⟨-D-galactosyl residues, particularly globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3) [1]. These lipids accumulate in lysosomes of different cells and can mainly affect the heart, kidneys, skin, eyes, central nervous system, and gastrointestinal system.

One of the main features of FD is insidious and progressive Fabry Nephropathy [2], which was recognized half a century after the first FD description as

M. H. Vaisbich (✉)
Pediatric Nephrology Unit, University of Sao Paulo, São Paulo, Brazil
e-mail: maria.vaisbich@hc.fm.usp.br

L. G. M. de Andrade
Departamento de Medicina Interna, Universidade Estadual Paulista, Botucatu, São Paulo, Brazil
e-mail: landrade@fmb.unesp.br

C. A. B. Silva
Nephrology Service, Senhor do Bonfim Group, Feira de Santana, BA, Brazil

F. C. Barreto
Nephrology Service, Departamento de Medicina Interna, Universidade Federal do Paraná, Curitiba, PR, Brazil
e-mail: fellype.barreto@ufpr.br

M. A. dos Reis
Nephropathology Service, General Pathology, Federal University of Triângulo Mineiro, Uberaba, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_27

angiokeratoma *corporis diffusum* [3]. Currently, it is known that kidney failure causes significant morbidity and mortality [4]. More than half of male and 20% of female adult patients eventually develop advanced renal disease [5]. Before the availability of a specific treatment, such as enzyme replacement therapy (ERT), the natural course of the disease was catastrophic, as described by Branton et al. in 2002. These authors found that only 25 of 105 classic male hemizygous patients survived until 50 years of age, and none survived beyond 60 years old [6]. Before the advent of ERT, the most common cause of death was uremica at approximately 41 years of age [7]. These data emphasize the burden of Fabry nephropathy and the need to avoid its progressive course.

The accumulation of Gb3 occurs in virtually all types of glomerular cells, including endothelial, mesangial, parietal epithelial cells, and podocytes, with a preference for the latter. Deposits are also detected in tubular cells (much less pronounced in the proximal tubule) and peritubular capillary endothelium [8]. Therefore, patients can present signs of tubular, vascular, and glomerular involvement.

At first, the disease was considered an adult disease, especially Fabry nephropathy. However, studies have shown that the renal pathogenic process begins early in life. Depositions of Gb3 start long before overt clinical renal disease. Moreover, kidney involvement was described even in fetal life. Early storage (characteristic zebra bodies on electronic microscopy) in the fetal part of the placenta was described for a male Fabry fetus by Elleder et al. in 1998 [9]. This study was supported by Vedder et al., who reported extensive storage and very low α-Gal A activity in the placental tissue of a mother heterozygous for FD who gave birth to a hemizygous male [10]. It is noteworthy that fetal corneal similar deposits were previously demonstrated by Tsutsumi et al. in 1984 [11], highlighting the precocity of Gb3 deposits in different tissues. Additionally, Tøndel et al. found severe accumulation of inclusions in podocytes and distal tubules in all study children. Most importantly, they demonstrated that glomerular, tubulointerstitial, and vascular changes are present before progression to overt proteinuria and a decrease in the glomerular filtration rate (GFR) [8]. In particular, these authors showed that arteriolopathy and/or interstitial fibrosis were present in more than half of the children, including those with no signs of renal disease, such as albuminuria. These findings were later supported by others, such as Wijburg et al.'s study, which showed that renal glomeruli undergo progressive changes that begin with mesangial widening, followed by focal fibrosis ending with a completely fibrotic and obsolescent glomerulus associated with tubular atrophy and interstitial fibrosis [4]. Therefore, based on these findings, the appropriate time to initiate specific treatment has been discussed in the literature. It has been demonstrated that patients may not fully benefit from specific treatment, such as ERT, if started when proteinuria is already established or GFR declines. Thus, early diagnosis and treatment of Fabry nephropathy, even in childhood, may be critical to preserve renal function [12]. Currently, the question is: How early is late?

Clinically, these histological findings have been translated by Riccio et al., 2018, who demonstrated glomerular hyperfiltration as an early marker of Fabry nephropathy. They showed a negative correlation between estimated GFR (eGFR) and age, proteinuria levels, cardiovascular involvement, and other manifestations of FD [13]. These data suggest that hyperfiltration in Fabry patients could be related predominantly to a predisease state. In this way, it is important to choose the appropriate GFR measurement methodology according to the patient's age [14]. If glomerular hyperfiltration is confirmed, the patient may benefit from a renal biopsy to verify histologic renal involvement as an indicator for specific treatment initiation.

Table 27.1 Studies reporting early renal involvement in pediatric Fabry patients

Author	Year	Patients	Mainly findings
Elleder et al. [9]	1998	Fetus	Gb3 inclusions, mainly in the podocytes
Todel et al. [8]	2008	9 children (7–18 years) with normal GFR and minimal or within normal range proteinuria	Gb3 inclusions in the podocytes and distal tubular epithelial cells along with effacement of the foot process of the podocytes in all cases, arteriolopahty in nearly 50% of the patients and focal and segmental glomerulosclerosis (FSGS) in adolescents
Ramaswami U et al. [4]	2010	Children	Renal histological abnormalities appear before the development of microlbuminuria/proteinuria
Najafian et al. [4]	2013	Children	The increase of the GB3 inclusions in the podocytes is correlated with both the effacement of the foot process of the podocytes and albuminuria
Branton et al. [6]	2002		Faster decline of the GFR in patients with higher proteinuria at baseline, strengthen the notion that proteinuria is a late surrogate marker of Fabry nephropathy
Riccio et al. [12]	2019	Children	The initial renal injury in young patients manifests through glomerular hyperfiltration which may be detected before the appearance of microalbuminuria and is, in general, associated with few or no renal symptoms Inverse relationship between GFR and age, proteinuria and cardiovascular abnormalities
Trimarchi et al. [15]	2015	Patients	Podocyturia in FD patients precedes microalbuminuria
Politei et al. [16]	2018	Children (4 a 9 years)	All patients had high plasmatic levels of LysoGb3 and podocyturia, but normal eGFR; microalbuminuria was present in half of the patients Renal histology analysis revealed glomerular, interstitial and vascular abnormalities

Evaluating the clinical and histologic studies shown in Table 27.1, it is possible to conclude that (1) Fabry nephropathy starts early in intrauterine life, and biomarkers such as microalbuminuria/proteinuria considered earlier in the past are in fact late [17]; (2) renal abnormalities start with Gb3 intralysosomal deposition and evolve sequentially with podocyte detachment from glomerular basal membrane (GBM) and podocyturia, glomerular hyperfiltration, and later microalbuminuria and proteinuria occur; (3) patients can also present with nephrogenic *diabetes insipidus*, hypokalemia, and/or renal tubular acidosis as a consequence of Gb3 deposition in the cells of the collect tubules [18]; and (4) reduction of GFR occurs in advanced stages of the disease.

With new information on the natural history of Fabry nephropathy, it is known that the pathophysiological process and organ damage start early in childhood and affect both boys and girls. Historically, there has been a paradigm change in FD. At first, the strategy was to detect patients with a clinical impact of the disease, such as by screening patients on dialysis for an unknown cause [19]; however, the objective is being expanded to detect younger, oligosymptomatic, or asymptomatic patients identified by family screening, in whom early diagnosis and treatment can mitigate or avoid the complications of the disease [20].

The possibility of a specific treatment such as ERT is modifying this evolution [21–23], although it is not a cure; however, there are some points that need to be clarified, such as which populations should be tested, which is the earliest marker of Fabry nephropathy, and what is the best protocol to monitor these patients and the time to start or stop specific treatment.

In this chapter, we intend to inform about the natural history of the disease, clinical manifestations, complementary exams to confirm diagnosis, and monitoring patients before or under specific and/or unspecific treatments, treatment options, and prognosis. We also show recent advances in diagnosis and therapy that have changed the patient's natural history and promoted a better evolution, especially in kidney involvement.

27.2 Pathophysiology

The failure to breakdown Gb3 and related glycosphingolipid substrates underlies the pathogenesis of FD. Gb3 accumulates in lysosomes and in other cellular compartments in almost every kidney cell, with massive deposits in podocytes, but also in mesangial, endothelial, tubular, and parietal epithelial cells. As podocytes are terminally differentiated and respond with a poor proliferation rate to injury and loss [24], a progressive accumulation has been observed in these cells. Najafian et al., using stereological electronic microscopy methods (quantitative morphometric method rather than a subjective scoring system), demonstrated that this podocyte progressive accumulation is age-dependent in young Fabry patients with normal

GFR and normal/low-grade proteinuria. In this study, foot process width correlated with fractional volume podocyte inclusions and proteinuria [25]. In 2020, Najafian et al. showed that there is a threshold for Gb3 inclusion volume fraction and/or podocyte size beyond which podocyte survival is compromised. These authors found that the podocyte Gb3 volume fraction correlated directly with age in patients under 27 years, but did not increase with age thereafter [26]. They demonstrated that the podocyte volume fraction reaches a plateau at approximately 27 years of age, while the mean podocyte volume and podocyte Gb3 volume continue increasing [26]. Although podocytes were enlarged, there was a significant progressive decline with age in the fraction of glomerular volume occupied by podocytes and in the number of podocytes per glomerulus, confirming podocyte loss with age [26]. In addition, podocyturia has been observed in these patients, confirming urinary podocyte loss from glomeruli [27–29]. Podocyturia has also been detected in other glomerular diseases and is described as one of the most precocious signs of glomerular damage [30].

The podocyte is critical to the maintenance of glomerular barrier selectivity, and its damage or loss is closely associated with proteinuria, a powerful predictor of progressive reduction in GFR [31]. Increased loss of podocytes and segmental foot process effacement, consistent with podocyte injury, have been described early in Fabry nephropathy, before the onset of proteinuria, and are related to focal segmental glomerulosclerosis (FSGS) and global glomerulosclerosis, an irreversible path to end-stage kidney disease (ESKD) [32]. The podocyte inclusion rate is supposed to have the main role in proteinuria, but the mesangial deposit rate was also found to be associated with foot process enlargement and proteinuria, but not with age or sex [25].

In addition to the role of podocytes in fibrosis pathogenesis, endothelial cells with sphingolipid overload might also contribute to fibrosis development, e.g., through luminal obstruction and ischemia [33]. Endothelial fenestration is reduced in Fabry patients' renal tissue, which could reflect the reduced nitric oxide bioavailability that was observed in endothelial cells of an FD mouse model [34].

Gb3 deposition can inhibit mTOR kinase activity (a negative regulator of the autophagy machinery), leading to autophagy dysregulation and contributing to renal damage in this disease [35].

In 2008, in addition to Gb3 deposits, lyso-Gb3 (the deacylated Gb3) increased deposits that were demonstrated as a characteristic feature of FD [36], and serum lyso-Gb3 levels were found to be significantly higher in patients than in healthy controls, mainly in males with the classic phenotype [37]. It has also been demonstrated that lyso-Gb3 is independently related to kidney dysfunction and other comorbidities [37]. Higher levels were found in patients with copy number variants than missense mutations, and it may also be employed as a marker of ERT response [38]. However, lyso-Gb3 is not only a diagnostic tool or a biomarker; it has an important role in FD pathology. Lyso-Gb3 directly inhibits α-Gal A activity and induces vascular smooth muscle cell proliferation, an element that may promote

increased intima-media thickness [36]. It promotes Notch1-mediated inflammatory and fibrogenic responses in podocytes, potentially contributing to Fabry nephropathy [39]. Lyso-Gb3 inhibition led to inhibition of proliferation and differentiation of fibroblasts into myofibroblasts, reducing collagen synthesis and thereby compromising vascular remodeling [40]. An in vitro study showed TGF-β1 and extracellular matrix protein production in normal podocytes exposed to lyso-Gb3 [41].

Prominent interstitial fibrosis was found in approximately 80% of Fabry kidney biopsies assayed by Rozenfeld et al., while glomerular sclerosis was found at a minor frequency [42]. This study showed that TGF-β1 is produced mainly in proximal tubular cells and activates FGF-2 in endothelial cells, leading to VEGF production [42]. They found VEGF expression in the glomerulus and blood vessel cells. As we already know from other nephropathies, these are important mediators involved with glomerulosclerosis, interstitial fibrosis, and GFR decline [43] and induce podocyte apoptosis [44]. Rozenfeld et al. [42] also demonstrated positive caspase-3 staining in Fabry patient renal tissues, confirming the high apoptotic state previously reported in peripheral blood mononuclear cells by De Francesco et al. [45]. These findings strongly support that Fabry renal cells undergo apoptosis. In addition, Rozenfeld et al. demonstrated positive staining for a marker of myofibroblasts (⟨SMA) in pericytes attached to interstitial peritubular capillaries, mesangial cells, and the periglomerular zone, confirming the presence of these profibrotic cells, which are induced by TGF-β1 and can explain both glomerular and tubulointerstitial fibrosis [42].

Increased markers of oxidative stress have also been found in Fabry patient tissues contributing to renal damage. Gb3 accumulation in the endothelium dysregulates nitric oxide synthase activity and leads to low nitric oxide synthesis and overproduction of reactive oxygen species [46, 47]. Endothelial fenestration is reduced in the renal tissue of Fabry patients, which could reflect the reduced nitric oxide bioavailability previously observed in an FD mouse model [34].

Gb3 deposition can inhibit mTOR kinase activity (a negative regulator of the autophagy mechanism), leading to autophagy dysregulation and contributing to renal damage in this disease [35]. Evidence of increased autophagy is confirmed by increased expression of autophagy markers (e.g., LC3) in both fibroblast cultures of Fabry patients [48] and in podocytes [35].

In tubular cells, Gb3 deposition may lead to focal tubular atrophy and interstitial fibrosis [49], and consequently, the corresponding upstream glomeruli may function poorly, stimulating neighboring glomeruli to hypertrophy. The subsequent hyperfiltration in these glomeruli triggers secondary FSGS. Angiotensin II probably also contributes to Fabry nephropathy by acting as a vasoconstrictor and propagating inflammation and fibrosis [50].

In conclusion, α-Gal A activity deficiency and consequently the accumulation of glycosphingolipids, mainly Gb3 and lyso-Gb3, induce the activation of numerous pathways, including inflammation, fibrosis, and increased oxidative stress, autophagy, and apoptosis rates [51, 52], leading to cell death and tissue fibrosis. Figure 27.1 shows the main pathogenic mechanisms involved in Fabry nephropathy.

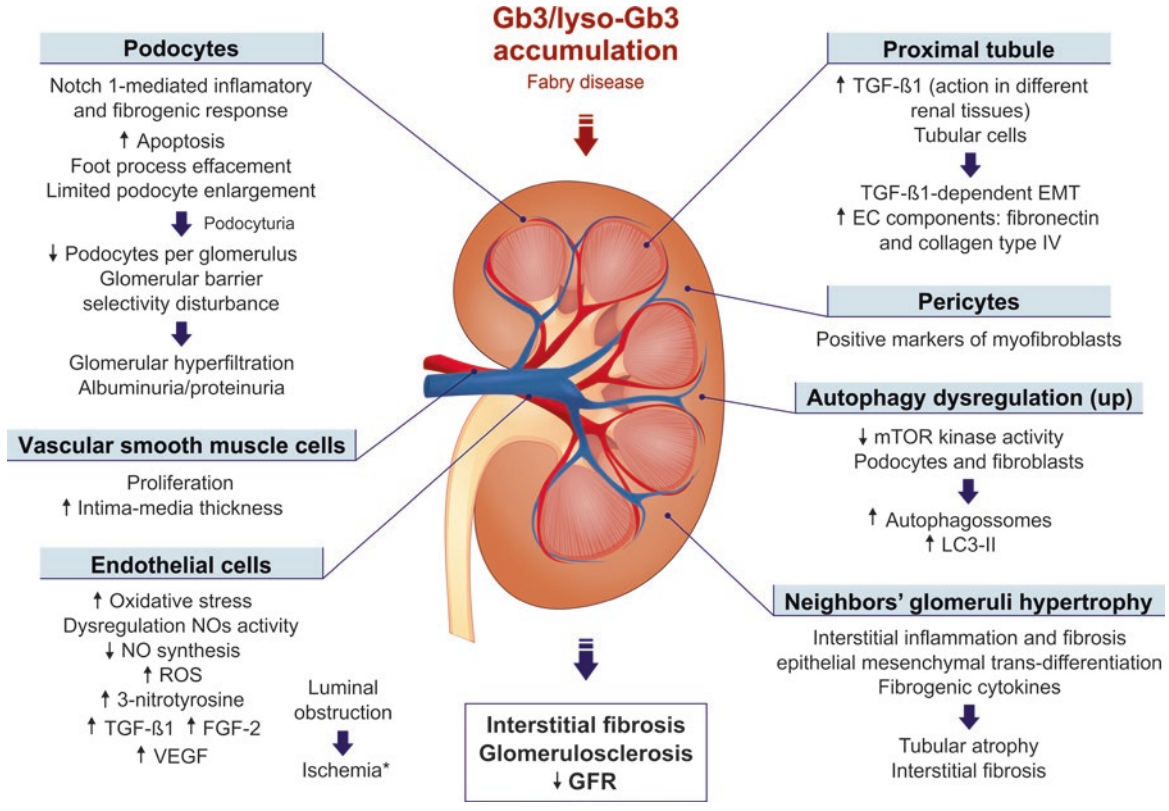


Fig. 27.1 Pathogenetic Mechanisms involved in Fabry Nephropathy. This figure shows the numerous pathways activated in Fabry Nephropathy as a consequence of Gb3/lyso-Gb3 deposits. All types of renal cells are involved and TGFβ1 along with other cytokines as well as increased oxidative stress, autophagy, and apoptosis rate have an important role to initiate the renal interstitial fibrosis and glomerulosclerosis which culminate with GFR decline

27.3 Clinical Manifestations and Natural History of Fabry Nephropathy

Kidney involvement in FD is responsible for one of the major clinical impacts in Fabry patients. Fabry nephropathy is characterized by progressive chronic kidney disease (CKD) that ultimately leads to ESKD and the necessity of renal replacement therapy (RRT) by the fourth decade of life [53].

Nonnephrotic proteinuria is usually present, whereas hematuria is uncommon [53]. Mild albuminuria has been recognized as an early manifestation of Fabry nephropathy, which may be present since childhood [8]. However, more recent studies have reported that podocyturia may be an earlier sign of Fabry nephropathy, appearing even before abnormal albuminuria [54, 55]. However, its applicability in daily clinical practice remains to be determined. Glomerular hyperfiltration has also been suggested as an early feature of kidney involvement in FD [13]. Both the lack of a single definition of glomerular hyperfiltration and the fact that its confirmation relies on performing nuclear medicine techniques are barriers that still need to be overcome [56, 57].

The natural history of Fabry nephropathy depends on the sex of the patient and the type of the disease-causing variant. In the classical phenotype, kidney involvement usually begins during childhood and may progress over time, eventually leading to the necessity of RRT [53]. The rate of GFR decline in untreated patients may vary substantially. A reduction in renal function is rare in children, but it can occur during adolescence [58]. Branton et al. reported a mean rate of loss of GFR in male patients with classic Fabry and CKD of −12.2 ± 8.1 mL/min/year, with progression from CKD onset to ESKD in 4 ± 3 years (range, 1–13 years) [6]. A retrospective study that included both males (n = 279) and females (n = 168) demonstrated a significantly greater progression rate in males than females as well as for those who had CKD at baseline. For males with eGFR ≥ 60 mL/min/1.73 m^2 and CKD, the annual GFR loss was −3.0 and −6.8 mL/min/1.73 m^2, respectively, while for females, the rate of GFR decline was −0.9 and − 2.1 mL/min/1.73 m^2/year, respectively [59].

Interestingly, a recent analysis restricted to female patients with classic *GLA* variants demonstrated a slight reduction in GFR over time (−0.83 mL/min/1.73 m^2), which is within the expected decline range of renal function for a healthy population [60]. Indeed, male patients with FD may progress to CKD 10 years sooner than females [61]. Even though female Fabry patients usually have a slower evolution of Fabry nephropathy, a small fraction of this population may be more seriously affected, requiring RRT at the same median age of males [61]. Finally, although a kidney late-onset variant has been described among ESKD patients [19], renal involvement in Fabry patients with a late onset phenotype seems to be rare and, most often, milder than in the classical phenotype [62].

Traditional risk factors for CKD progression, such as proteinuria, reduced renal function, and hypertension, have been associated with a faster progression of Fabry

nephropathy [59, 61]. As such, although the prevalence of hypertension among patients with FD is relatively low compared to other forms of CKD, it should not be overlooked [63].

Tubular dysfunction may also occur in FD patients. Distal convoluted tubules are particularly susceptible, resulting in impaired urinary concentration. Actually, the initial manifestation of kidney disease is often impaired urinary concentrating ability, more often in adolescence or young adulthood [64]. Proximal tubule dysfunction has been more rarely reported, which may cause Fanconi syndrome and incomplete renal tubular acidosis [64]. Furthermore, parapelvic cysts have also been recognized as a distinguishing manifestation of renal FD, with a higher prevalence in these patients than in those with other glomerulopathies [65, 66].

27.4 Morphological Alterations in Fabry Nephropathy

Alterations in renal morphology secondary to FD may be found in every microscopic technique: (1) embedded paraphing sample—light microscopy (Fig. 27.2a–e); (2) frozen sample—immunofluorescence (Fig. 27.2f); (3) resin-embedded sample, in semithin slide (Fig. 27.3); and (4) at the ultrastructural level—electron microscopy (Figs. 27.4 and 27.5) [53, 67]. Gb3 deposits may be found in all renal cells, particularly in the podocytes, which are highly specialized, terminally differentiated cells that are part of the glomerular filtration barrier. The formation of Gb3 deposits is still initiated during embryogenesis [68] and progressively accumulates over life. Due to their low capability of proliferation, podocytes usually present a greater amount of Gb3 deposits [27, 69, 70]. Podocyte injury may lead to proteinuria/albuminuria, sometimes in the nephrotic range.

The deposits of Gb3 may be present since the early stages of the disease, beginning in childhood. They are associated with effacement of the foot process of the podocytes and the level of proteinuria, having a central role in the development and progression of Fabry nephropathy [26, 27, 71]. Importantly, podocyte lesions have been detected even before the development of abnormal albuminuria and/or clinical manifestations [15, 70, 72] and may also be found in the later stages of Fabry nephropathy. Therefore, performing renal biopsy may be useful (1) for the diagnosis, (a) in different stages of the disease, (b) in cases without the classical pattern of the disease; (c) in heterozygous females who usually have a large spectrum of clinical presentation [73]; (d) to confirm (or to exclude) the pathogenicity of a *GLA* variant of unknown significance; (2) to rule out the diagnosis of other glomerulopathy, such as membranous glomerulopathy and lupus nephritis [74]; (3) to determine the prognosis, as the presence of chronic lesions may be evaluated in different renal compartments, such as glomerulosclerosis, thickness of the vascular wall, tubular atrophy, and interstitial fibrosis [69, 73]; and (4) to evaluate the efficacy of pathogenetic therapy during the follow-up of the patient [75, 76].

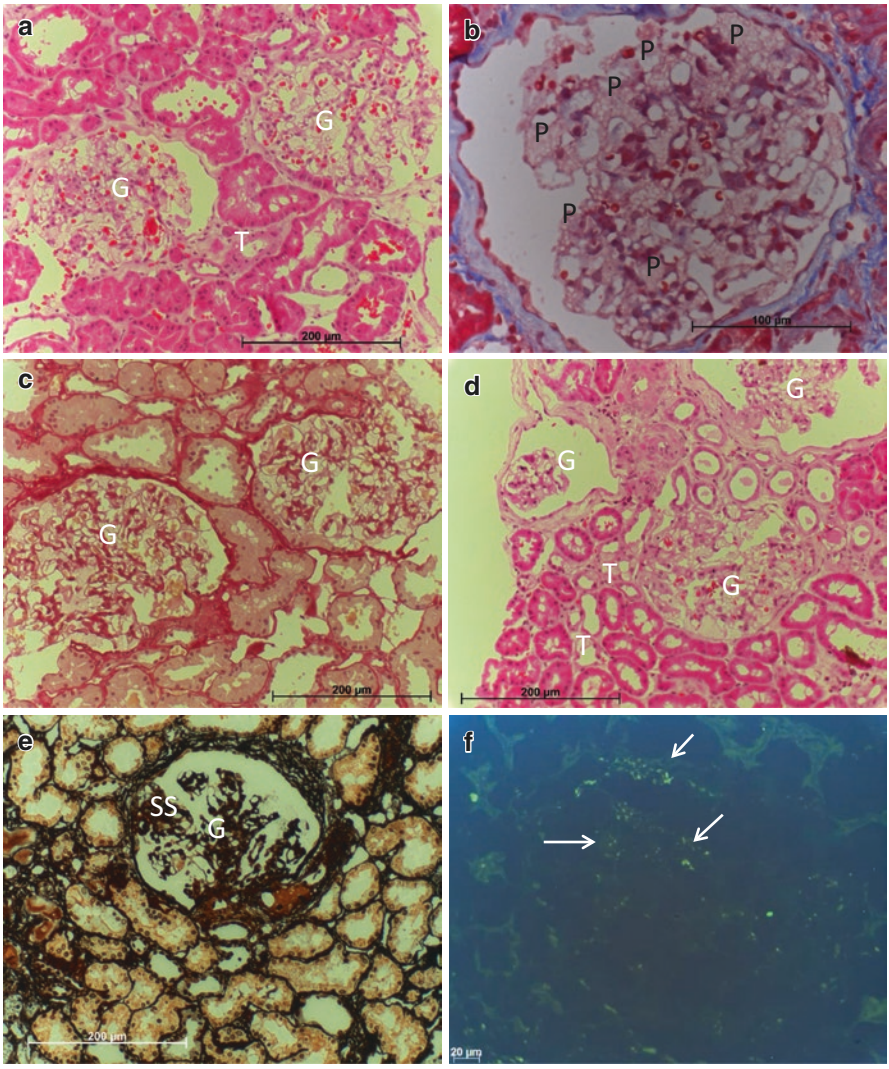


Fig. 27.2 kidney biopsy specimen under Light microscopy (**a**–**e**—Embedded in paraffin): The vacuoles seen in the cytoplasm of different cells: especially podocytes (P) in the glomerulus (G) and distal tubular cells (T). There is segmental sclerosis (SS) in glomerulus (e). (**a, d**) hematoxylin and eosin (**c**) Sirius red (**d**) Methenamine Silver Stain—magnification: 20× objective; 1.25× optovar; (**b**) Masson's trichrome (magnification 40× objective; 1.25× optovar). (**f**) yellowish green natural fluorescence of Gb3 in the glomerular and tubular cells (arrows) in frozen section under fluorescence microscopy (magnification: 40× objective; 1.0× optovar)

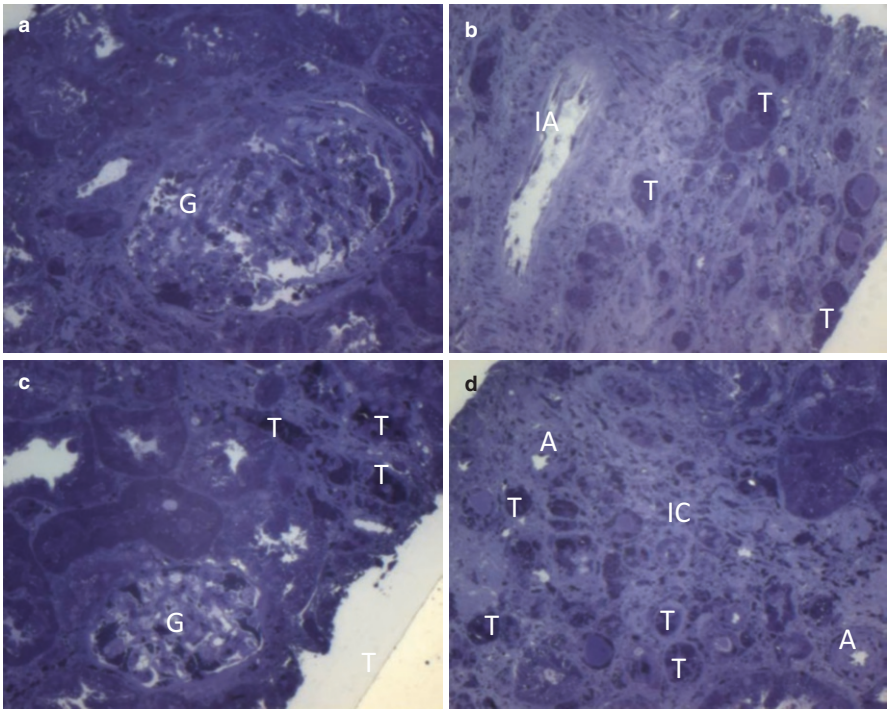


Fig. 27.3 Kidney biopsy specimen under Light microscopy—osmicated, epoxy-embedded tissue, stained with Toluidine blue. There are Gb3 deposits stained in dense, dark blue granules in the cytoplasm of different cells: especially in enlarges podocytes in glomerulus - G (**a, b**) and tubular cells -T (**b-d**), Endothelial Cells and smooth muscle cells in Arteriole – A (**d**); in Interlobular Arteria -IA (**b**) and in intersticial cells -IC (**d**). Magnification: 20× objective; 2.0× optovar

The deposits of Gb3 may be well-visualized by electron microscopy, for which the tissue sample is postfixed in osmium and embedded in resin. Lipids are osmiophilic, stained by toluidine blue (Fig. 27.3), and highly electrodense in electron microscopy (Figs. 27.4 and 27.5), characteristics that facilitate the visualization of the deposits [53, 67]. The deposits of Gb3 are highly electron-dense, concentric, multilamellar inclusions, with some electron lucid areas located within the lysosomes that give the aspect of myelin figure or "zebra bodies" (Figs. 27.4 and 27.5). At high magnification, 250.000×, multiple lamellae with periodicity of 3.5–4 nm can be seen [53, 67, 77].

The large deposits of Gb3 promote enlargement of the lysosomes and, consequently, of the cytoplasmic volume of the podocytes, with the enlargement of the foot process of the podocytes being a common finding (Fig. 27.4). Some medications, such as chloroquine, hydroxychloroquine, and amiodarone, may inhibit the activity of the enzyme ⟨-gal A, leading to the accumulation of Gb3, which

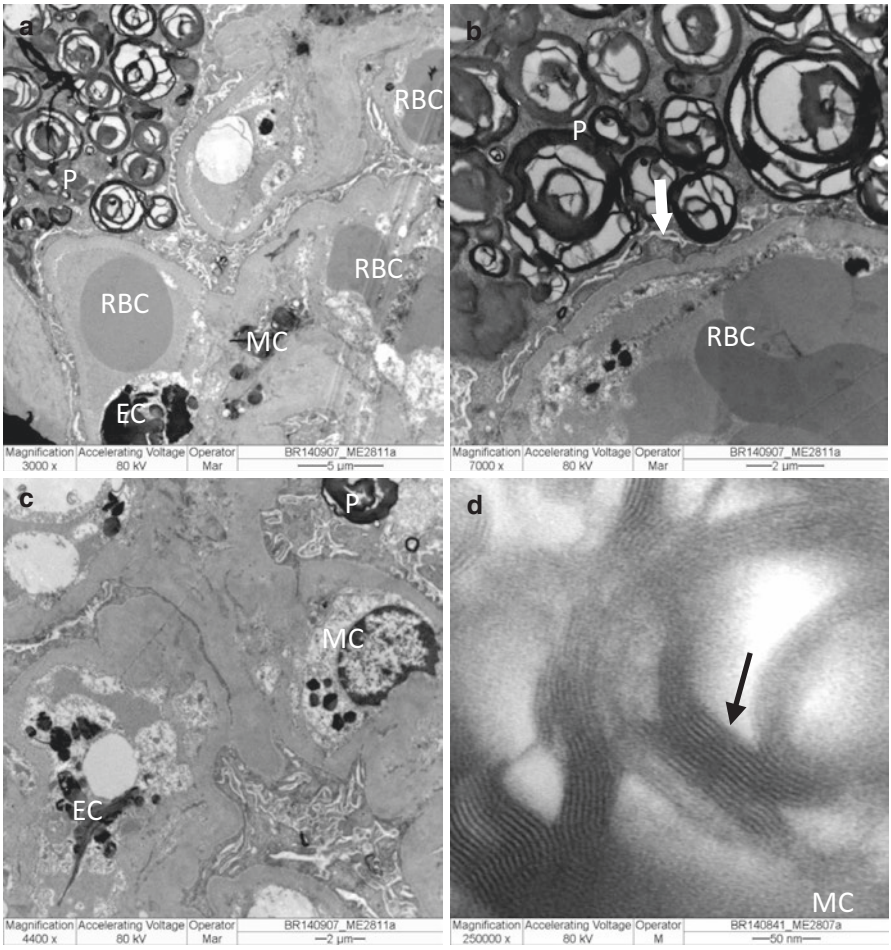


Fig. 27.4 Kidney biopsy specimen under Electron microscopy: (**a, b, c**) glomerulus with electron dense GL-3 deposits in Endothelial Cell (EC), Mesangial Cell (MC), and Podocyte (P), with effacement foot process (arrow). *RBC* red blood cells in capilar lumen. (**d**) In high magnification, Gb-3 deposits consist of electron-dense multi-lamellated concentric layers, with periodicity 3.5–5 nm (arrow). (Original magnification: (**a**) 3.000×; (**b**) 7.000; (**c**) 4.400×, and (**d**) 250.000×)

constitutes one of the main differential diagnoses of FD [78]. In other lipidoses, such as Niemann-Pick disease, Farber's disease, GM1 gangliosidosis, and Hurler syndrome, the morphology and localization of the deposits are different, and there are no prominent myelin bodies in the various renal cells, as occurs in FD. Renal lesions caused by silica have some similarities with Fabry nephropathy findings. However, other silica-specific renal lesions may help to support the diagnosis [53, 67].

In FD, the visualization of the renal tissue sample "*a fresco*", immediately after the biopsy procedure, by stereomicroscopy reveals large white glomeruli due to the

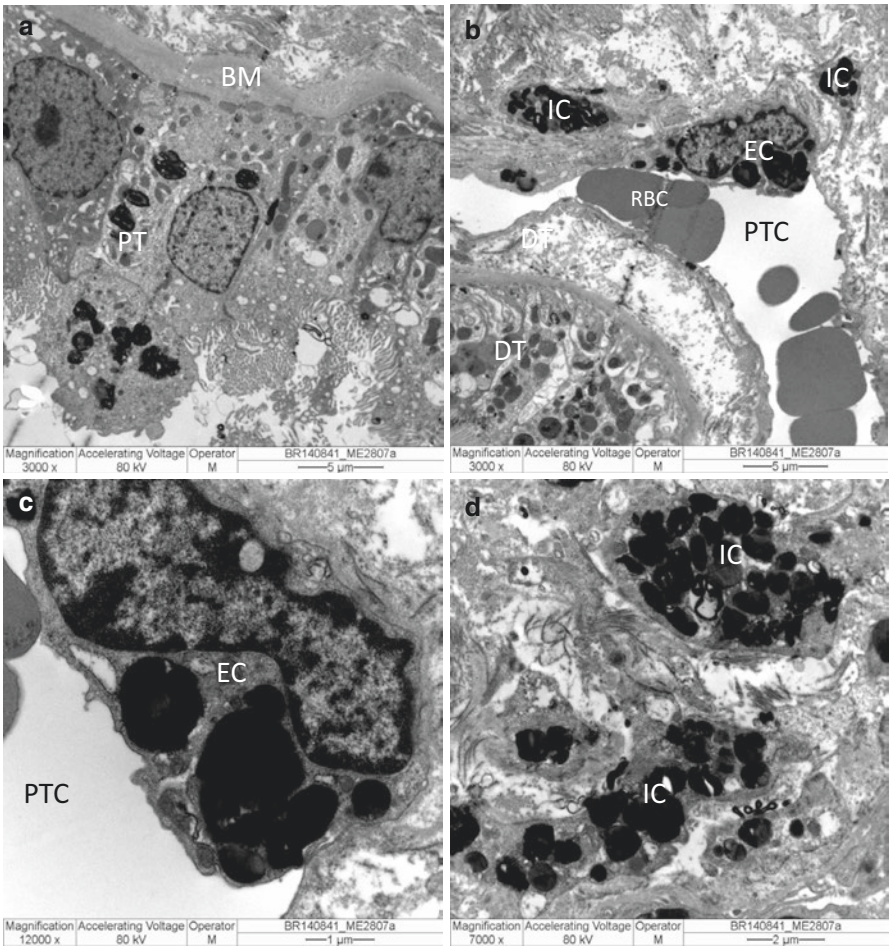


Fig. 27.5 Kidney biopsy specimen under Electron microscopy with electron dense Gb-3 deposits in lysosomes in different cells: (**a**) Proximal tubule (PT); (**b**) Distal tubule (DT) and in Endothelial cells (EC) of peritubular capillary (PTC); (**c**) Details of (b); and (**d**) cells in the interstitial compartment. *RBC* red blood cell; *BM* basal membrane (Original magnification: (**a**) and (**b**)–3.000×, (**c**)–12.000×, and (**d**)–7000×)

abundance of Gb3, whose burden of glomerular storage may be scored semiquantitatively [79]. A tissue sample should be frozen for immunofluorescence analysis. Immunofluorescence generally does not contribute, although some patients may have nonspecific deposits of IgM and C3 in areas of glomerulosclerosis and of thickness of the vascular wall due to arteriolar hyalinosis or intimal fibroelastic thickness of the arteries [53, 67, 77]. By using the frozen sample, the deposits of Gb3 may be identified by lipid staining, such as Sudan dye. Interestingly, the deposits of Gb3 have yellowish green natural fluorescence (Fig. 27.2f) and show a

birefringent Maltese cross pattern under polarized light, similar to the exfoliated urinary epithelial cells with Gb3 content seen by urine microscopy [71].

For light microscopy analysis (Fig. 27.2a–e), the sample is processed to be embedded in paraffin, passing through alcohol and xylol solutions, substances that dissolve the lipid content of the cells, generating an "empty" aspect. As such, after processing, the cells with Gb3 accumulation, particularly the podocytes, present the cytoplasm vacuolated in the different staining [53, 67]. Remnants of Gb3 may be identified by immunohistochemistry using specific anti-Gb3 antibodies [80].

The accumulation of Gb3 over time may cause abnormalities in all renal compartments [27, 71], ultimately leading to the development of chronic lesions, such as segmental (Fig. 27.2e) or global sclerosis of the glomeruli, arteriolar and arterial thickness, as well as tubular atrophy and interstitial fibrosis [53, 77]. These morphological abnormalities, including podocyte vacuolization (in paraffin-embedded tissue) and deposits of Gb3 (in resin-embedded tissue stained by toluidine blue dye), may be quantified by using the scoring system proposed by Fogo et al. [53, 67, 69]. This quantification is critical to evaluate the degree of glomerulosclerosis and interstitial damage, both relevant markers of chronicity and prognosis [73], and to evaluate the efficacy of pathogenetic therapy, for instance, when the presence of neutralizing anti-drug antibodies is suspected [73, 75]. Indeed, this standardized scoring system has been considered a helpful tool to assess the prognosis, the response to therapy for Fabry Nephropathy, and to investigate the pathogenic pathways that may lead to the progressive decline of renal function [53, 81].

27.5 Laboratory Findings

Regarding the laboratory findings in Fabry nephropathy, glomerular hyperfiltration may be one of the first signs of renal involvement, being generally more evident in young patients [57]. Subsequently, albuminuria, proteinuria, and a decrease in GFR occur [13]. The findings are similar to those observed in diabetic nephropathy. In general, microalbuminuria and proteinuria are already manifested in the second decade of life; however, based on new information, they have been considered late markers. Histological abnormalities preceding these markers have been demonstrated in renal biopsy studies performed in children showing deposits in almost all kidney cells leading to irreversible changes [33, 77]. Wijburg et al. showed that asymptomatic classic Fabry male patients present Gb3 accumulation and cell and vascular injury before albuminuria/proteinuria and other significant outcome detection [4].

Therefore, it is important to keep in mind that, although albuminuria/proteinuria are used in clinical practice, they are not sensitive enough to detect incipient disease. In addition, they do not correlate linearly with GFR, and it was demonstrated that they could be absent in advanced nephropathy [33].

The search efforts to identify earlier sensitive biomarkers have been a priority in Fabry nephropathy. Aguiar et al. found increased urinary levels of glomerular (transferrin and type IV collagen) and tubular (alpha1-microglobulin, N-acetyl-beta-glucosaminidase [NAG], and alanine aminopeptidase) dysfunction markers in Fabry patients with no albuminuria. The authors concluded that even though those markers are not currently employed in daily clinical practice, they confirmed the limitations of albuminuria [82]. Moreover, urinary type IV collagen and NAG correlated better with eGFR than albuminuria/proteinuria [82].

Renal distal tubular acidosis and isosthenuria caused by tubular deposits are less frequent, and Fanconi syndrome has even more rarely been observed [67]. Tubular dysfunction can be detected by the measurement of tubular function markers such as urinary low molecular weight proteins (e.g., urinary retinol binding-protein or β2-microglobulin) [67].

Urinary microscopy examination has been another way to investigate incipient Fabry nephropathy. Three main cell types have been identified as useful to recognize and evaluate the progression of Fabry nephropathy, although they are not specific for renal FD:

- *Urinary mulberry cells*: distal epithelial cells with Gb3 deposits with a lamellar appearance [53];
- *Maltese cross particles*: oval bodies with Maltese cross pattern under polarized light typically observed in nephrotic syndrome, and a lamellar pattern showing Gb3 deposits; under electron microscopy, it is possible to see the typical osmiophilic lamellar bodies in urinary cells (Gb3 characteristic deposits) [67, 83].
- *Podocyturia*: it has been correlated with podocyte injury and implicated as a potential sensitive diagnostic tool of renal involvement. Podocyturia has been detected earlier than albuminuria/proteinuria [84] and showed an inverse correlation with GFR in male classic patients [27], denoting the severity of Fabry nephropathy and with potential prognostic value [28, 54].

In female Fabry patients, random X chromosome inactivation and consequent mosaicism lead to heterogeneous renal involvement. However, in this group, it has been demonstrated that the relative number of podocytes without the FD phenotype increases with age, representing a disproportionate progressive loss of podocytes expressing the disease phenotype [83, 85].

Currently, many efforts have been made to find a reliable method to employ it in clinical practice, trying to avoid renal biopsy [77]. As Gb3 accumulation is the hallmark of FD, it was proposed that urinary and plasma Gb3 levels could reflect renal involvement; however, some studies have not found a correlation between these levels and other markers of renal function or symptomatology in both sexes [86, 87]. Furthermore, plasma Gb3 levels were found to be normal in late-onset Fabry male and female patients [87, 88].

On the other hand, lyso-Gb3 has been considered a useful diagnostic tool for differentiating classic FD and non-Fabry patients, but is also useful in males with nonclassical forms and females. Normal plasma lyso-Gb3 does not exclude the

disease in female suspected patients, but almost excludes the disease in males [89, 90]. In patients with genetic variants of unknown significance (VUS) and not usual phenotype and biochemical tests, an increased lyso-Gb3 plasma level >1.3 nmol/L can support the diagnosis. Lyso-GL3 can also be used for monitoring the effectiveness of the specific treatment [90].

Metabolomic approaches have revealed novel plasma lyso-Gb3 analogs with a role in FD pathogenesis and are potentially employable as diagnosis and monitoring tools [91, 92]. Lyso-Gb3 is significantly more abundant in plasma than its analogs; in contrast, it is less abundant in urine [93]. Urinary levels of these analogs were reduced in male Fabry patients under ERT, highlighting their utility as monitoring markers [91]. Furthermore, these analogs along with lyso-Gb3 have shown a role as biomarkers for the diagnosis of FD in patients with both classic and late-onset variants [94].

27.6 Fabry Nephropathy Diagnosis

Renal involvement may be supposed in the presence of albuminuria (>30 mg/g) or proteinuria (300 mg/g) in FD-confirmed patients without other concomitant pathologies, which could potentially determine these findings. Hematuria is not a characteristic feature. In addition, patients may already manifest GFR decline (eGFR < 90 mL/min) or hyperfiltration. Table 27.2 shows the main characteristic findings of Fabry nephropathy [73, 95]. It is important to keep in mind that in the presence of other renal pathologies, such as diabetes, SLE, or other glomerulopathy, a renal biopsy should be performed to establish the final diagnosis.

It is recommended to evaluate the albumin/protein ratio in 24-h samples or in isolated urine samples, observing the albumin/protein/creatinine ratio, mainly in the first morning sample. The GFR may be performed based on creatinine clearance calculation in 24-h urine collection or it may be estimated in adult patients based on the CKD-EPI equation and modified Schwartz formula in pediatric patients [96, 97].

Ideally, renal involvement monitoring should include periodic evaluation of GFR and albuminuria/proteinuria at least annually in low-risk to develop CKD patients, semiannually in patients with moderate risk, and every 3 months in high-risk patients [96]. In patients under ERT, renal histology analysis may be indicated in those patients with inappropriate response to treatment when there is a suspicion of antialgasidase antibody (ADA) presence [73].

Table 27.2 Diagnosis criteria of Fabry nephropathy

1. Fabry disease confirmed
2. eGFR < 90 mL/min
3. Albuminuria > 30 mg/g
4. Proteinuria > 300 mg/g
5. No concomitant renal pathologies (renal biopsy may be performed to rule out other pathologies and confirms the Fabry renal involvement)

27.7 Therapeutic Aspects of Fabry Nephropathy

The treatment of Fabry nephropathy aims to slow down the progression of the decline of renal function, which can be achieved by targeting proteinuria and blood pressure and controlling FD itself. As occurs in other proteinuria renal diseases, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are the first-line therapy to control albuminuria/hepaturia. The therapeutic goal is to achieve a urine albumin-to-creatinine ratio (ACR) < 30 mg/g in patients with albuminuria A2 or an ACR < 300 mg/g in patients with albuminuria A3 [96]. Blood pressure should be kept ≤130 × 80 mmHg.

First, one should bear in mind that the following laboratory and histological evidence of renal injury have been considered among the criteria to initiate ERT: decreased GFR (<90 mL/min/1.73 m^2 adjusted for age > 40 years); persistent albuminuria > 30 mg/g; podocyte foot process effacement or glomerulosclerosis on renal biopsy; moderate or severe Gb3 inclusions in a range of renal cell types [96]. Moreover, the Canadian Guidelines for the treatment of FD considered, among the minor criteria to start ERT, the presence of glomerular hyperfiltration (GFR > 135 mL/min/1.73 m^2) in at least 2, as measured by nuclear medicine techniques [98].

ERT, both agalsidase-alfa, 0.2 mg/kg every other week (eow), and agalsidase-beta, 1.0 mg/kg eow, have shown beneficial effects on the stabilization of kidney function and delay of progression to ESKD [22, 99, 100]. Treatment initiation at a younger age and before the presence of kidney damage, such as significant glomerulosclerosis and proteinuria, has been associated with greater benefits of ERT [22, 101]. A growing body of evidence suggests that a higher dose of ERT may have a potential benefit on preserving renal function and histology. Patients who had to reduce the dose of agalsidase-beta from 1.0 mg/kg eow to 0/3–0.5 mg/kg eow or to switch to agalsidase-alfa 0.2 mg/kg eow, due to the shortage of supply of agalsidase-beta, showed a greater decline in renal function [102] and reaccumulation of Gb3 in podocytes [103]. Patients who reswitched to the regular dose of agalsidase-beta after the end of the shortage period showed an attenuation of the decline in renal function [104]. Additionally, in patients with a progressive decrease in renal function despite using 0.2 mg/kg alpha eow, the switch to 0.2 mg/kg weekly significantly reduced the slope of eGFR [105, 106]. Dose-dependent clearing of podocyte Gb3 inclusions has been demonstrated by serial kidney biopsy-based studies in adult and pediatric patients with classic FD on long-term agalsidase on different dosing regimens [75, 107]. Otherwise, the limited removal of arterial/arteriolar Gb3 raised concerns about the long-term vascular effects of current therapy [107]. The formation of neutralizing ADA is an important issue that may interfere with the response to ERT, resulting in a worse disease course [108] aq2. Agalsidase-alpha seems to be associated with both lower infusion-associated reactions and lower formation of ADA and, consequently, might be a safer option for home infusion [52, 108].

Migalastat, an oral pharmacologic chaperone that increases endogenous α-Gal A activity, has been used to treat FD patients with amenable missense variants.

Migalastat treatment stabilizes renal function [109], similar to ERT [110], and reduces peritubular interstitial capillary and podocyte Gb3 inclusions [76]. Moreover, Migalastat has favorable effects on Fabry nephropathy, regarding stabilization of renal function and reduction of renal Gb3 inclusions, in patients with classic FD and amenable variants [111]. Otherwise, recent real-world studies have reported a moderate loss of eGFR in females and males over 24 months of treatment, which might be attributed to poor blood pressure control and/or insufficient amenability of *GLA* mutations [112].

In summary, patients with Fabry nephropathy should be offered the same general measures as all patients with proteinuric kidney disease, such as control of proteinuria and hypertension, salt restriction, and modification of lifestyle, in addition to specific therapy [113]. The choice of specific therapy should be individualized for each patient, whenever possible, in a sharing decision with the patient and his family. ERT is appropriate for all patients with FD, regardless of the type of the *GLA* variant [96]. Chaperone therapy is a choice only for patients with amenable variants and should not be used in patients with eGFR < 30 mL/min/1.73 m^2 and/or under 16 years old [16]. Finally, emerging therapies are under research, including next-generation ERT (pegunigalsidase alfa, moss-derived α-galactosidase A), substrate reduction therapy (lucerastat, venglustat), mRNA therapy, and gene therapy, which may provide better control of Fabry disease in the future [108].

References

1. Brady RO, Gal AE, Bradley RM, Martensson E, Warshaw AL, Laster L. Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficiency. N Engl J Med. 1967;276:1163–7.
2. Pompen AW, Ruiter M, Wyers HJ. Angiokeratoma corporis diffusum (universale) Fabry, as a sign of an unknown internal disease; two autopsy reports. Acta Med Scand. 1947;128:234–55.
3. Fabry J. Ein Beitrag Zur Kenntnis der Purpura hemorrhagica nodularis (Purpura papulosa haemorrhagica Hebrae). Arch Dermatol Syphilis. 1898;43:187–200.
4. Najafian B, Mauer M, Hopkin RJ, Svarstad E. Renal complications of Fabry disease in children. Pediatr Nephrol. 2013;28:679–87.
5. Wilcox WR, Oliveira JP, Hopkin RJ, Ortiz A, Banikazemi M, Feldt-Rasmussen U, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry registry. Mol Genet Metab. 2008;93:112–28.
6. Branton MH, Schiffmann R, Sabnis SG, Murray GJ, Quirk JM, Altarescu G, et al. Natural history of Fabry renal disease: influence of alpha- galactosidase a activity and genetic mutations on clinical course. Medicine (Baltimore). 2002;81:122–38.
7. Colombi A, Kostyal A, Bracher R, Gloor F, Mazzi R, Tho¨len H. Angiokeratoma corporis diffusum–Fabry's disease. Helv Med Acta. 1967;34:67–83.
8. Tøndel C, Bostad L, Hirth A, Svarstad E. Renal biopsy findings in children and adolescents with Fabry disease and minimal albuminuria. Am J Kidney Dis. 2008;51(5):767–76.
9. Elleder M, Poupetova H, Kozich V. Fetal pathology in Fabry's disease and mucopolysaccharidosis type I [in Czech]. Cesk Patol. 1998;34:7–12.
10. Vedder AC, Strijland A, Vd Bergh Weerman MA, Florquin S, JMFG A, CEM H. Manifestations of Fabry disease in placental tissue. J Inherit Dis. 2006;29:106–11.
11. Tsutsumi A, Uchida Y, Kanai T, Tsutsumi O, Satoh K, Sakamoto S. Corneal findings in a fetus with Fabry's disease. Acta Ophthalmol. 1984;62:923–31.

12. Riccio E, Sabbatini M, Bruzzese D, Annicchiarico Petruzzelli L, Pellegrino A, Spinelli L, On behalf of AFFIINITY Group, et al. Glomerular hyperfiltration: an early marker of nephropathy in Fabry disease. Nephron. 2019;141(1):10–7.
13. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20:629–37.
14. Pisani A, Visciano B, Imbriaco M, Di Nuzzi A, Mancini A, Marchetiello C, et al. The kidney in Fabry's disease. Clin Genet. 2014;86(4):301–9.
15. Trimarchi H, Canzonieri R, Muryan A, Schiel A, Araoz A, Forrester M, et al. Copious podocyturia without proteinuria and with normal renal function in a young adult with Fabry Disease. Case Rep Nephrol. 2015;2015:257628–4.
16. Politei J, Alberton V, Amoreo O, Antongiovanni N, Arán MN, Barán M, et al. Clinical parameters, LysoGb3, podocyturia, and kidney biopsy in children with Fabry disease: is a correlation possible? Pediatr Nephrol. 2018;33(11):2095–101.
17. Wornell P, Dyack S, Crocker J, Yu W, Acott P. Fabry disease and nephrogenic diabetes insipidus. Pediatr Nephrol. 2006;21(8):1185–8.
18. Nakao S, Kodama C, Takenaka T, Tanaka A, Yasumoto Y, Yoshida A, et al. Fabry disease: detection of undiagnosed hemodialysis patients and identification of a "renal variant" phenotype. Kidney Int. 2003;64:801–7.
19. Fervenza FC, Torra R, Warnock DG. Safety and efficacy of enzyme replacement therapy in the nephropathy of Fabry disease. Biologics. 2008;2(4):823–43.
20. Anderson LJ, Wyatt KM, Henley W, Nikolaou V, Waldek S, Hughes DA, et al. Long-term effectiveness of enzyme replacement therapy in Fabry disease: results from the NCS-LSD cohort study. J Inherit Metab Dis. 2014;37(6):969–78.
21. Germain DP, Charrow J, Desnick RJ, Guffon N, Kempf J, Lachmann RH, et al. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. J Med Genet. 2015;52(5):353–8.
22. Parini R, Pintos-Morell G, Hennermann JB, Hsu TR, Karabul N, Kalampoki V, FOS Study Group, et al. Analysis of renal and cardiac outcomes in male participants in the Fabry outcome survey starting Agalsidase alfa enzyme replacement therapy before and after 18 years of age. Drug Des Devel Ther. 2020;14:2149–58.
23. Shankland SJ. The podocyte's response to injury: role in proteinuria and glomerulosclerosis. Kidney Int. 2006;69:2131–47.
24. Najafian B, Svarstad E, Bostad L, Gubler MC, Tøndel C, Whitley C, et al. Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease. Kidney Int. 2011;79:663–70.
25. Najafian B, Tøndel C, Svarstad E, Gubler MC, Oliveira JP, Mauer M. Accumulation of Globotriaosylceramide in podocytes in Fabry nephropathy is associated with progressive podocyte loss. JASN. 2020;31:865–75.
26. Fall B, Scott CR, Mauer M, Shankland S, Pippin J, Jefferson JA, et al. Urinary podocyte loss is increased in patients with Fabry disease and correlates with clinical severity of Fabry nephropathy. PLoS One. 2016;11:e0168346.
27. Trimarchi H, Canzonieri R, Schiel A, Politei J, Stern A, Andrews J, et al. Podocyturia is significantly elevated in untreated vs treated Fabry adult patients. J Nephrol. 2016;29:791–7.
28. Liern M, Collazo A, Valencia M, Fainboin A, Isse L, Costales-Collaguazo C, et al. Podocyturia in paediatric patients with Fabry disease. Nefrologia. 2019;39:177–83.
29. Trimarchi H. Podocyturia: potential applications and current limitations. World J Nephrol. 2017;6(5):221–2.
30. Wanner C, Oliveira JP, Ortiz A, Mauer M, Germain DP, Linthorst GE, et al. Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry registry. Clin J Am Soc Nephrol. 2010;5:2220–8.
31. Kriz W, LeHir M. Pathways to nephron loss starting from glomerular diseases-insights from animal models. Kidney Int. 2005;67:404–19.

32. Weideman F, Sanchez-Niño MD, Politei J, Oliveira JP, Wanner C, Warnock DG, Ortiz A. Fibrosis: a key feature of Fabry disease with potential therapeutic implications. Orphanet J Rare Dis. 2013;8:116.
33. Shu L, Park JL, Byun J, Pennathur S, Kollmeyer J, Shayman JA. Decreased nitric oxide bioavailability in a mouse model of Fabry disease. J Am Soc Nephrol. 2009;20:1975–85.
34. Liebau MC, Braun F, Höpker K, Weitbrecht C, Bartels V, Müller RU, et al. Dysregulated autophagy contributes to podocyte damage in Fabry's disease. PlosOne. 2013;8:e63506.
35. Aerts JM, Groener JE, Kuiper S, Donker-Koopman WE, Strijland A, Ottenhoff R, et al. Elevated globotriaosylsphingosine is a hallmark of Fabry disease. Proc Natl Acad Sci U S A. 2008;105:2812–7.
36. Nowak A, Mechtler TP, Hornemann T, Gawinecka J, Theswet E, Hilz MJ, Kaster DC. Genotype, phenotype and disease severity reflected by serum LysoGb3 levels in patients with Fabry disease. Molecular Genet Metabol. 2018;123:148–53.
37. Lenders M, Stypmann J, Duning T, Schmitz B, Brand SM, Brand E. Serum-mediated inhibition of enzyme replacement therapy in Fabry disease. J Am Soc Nephrol. 2016;27:256–64.
38. Sanchez-Niño MD, Carpio D, Sanz AB, Ruiz-Ortega M, Mezzano S, Ortiz A. Lyso- Gb3 activates Notch1 in human podocytes. Hum Mol Genet. 2015;24:5720–32.
39. Choi JY, Shin MY, Suh SH, Park S. Lyso-globotriaosylceramide downregulates KCa3.1 channel expression to inhibit collagen synthesis in fibroblasts. Biochem Biophys Res Commun. 2015;468:883–8.
40. Sanchez-Niño MD, Sanz AB, Carrasco S, Saleem MA, Mathieson PW, Valdivielso JM, et al. Globotriaosylsphingosine actions on human glomerular podocytes: implications for Fabry nephropathy. Nephrol Dial Transplant. 2011;26:1797–802.
41. Rozenfeld PA, Bolla MA, Quieta P, Pisani A, Feriozzi S, Neuman P, Bondar C. Pathogenesis od Fabry nephropathy: the pathways leading to fibrosis. Mol Genet Metabol. 2020;129:132–41.
42. Chang AS, Hathaway CK, Smithies O, Kakoki M. Transforming growth factor-β1 and diabetic nephropathy. Am J Physiol Ren Physiol. 2016;201(310):F689–96.
43. Bai X, Geng J, Li X, Yang F, Tian J. VEGF-A inhibition ameliorates podocyte apoptosis via repression of activating protein 1 in diabetes. Am J Nephrol. 2014;40:523–34.
44. De Francesco PN, Mucci JM, Ceci R, Fossati CA, Rozenfeld PA. Higher apoptotic state in Fabry disease peripheral blood mononuclear cells: effect of globotriaosylceramide. Mol Genet Metab. 2011;104:319–24.
45. Joly DA, Grunfeld JP. 3-Nitrotyrosine as a biomarker for vascular involvement in Fabry disease. Kidney Int. 2014;86:5–7.
46. Biancini GB, Jacques CE, Hammerschmidt T, de Souza HM, Donida B, Deon M, et al. Biomolecules damage and redox status abnormalities in Fabry patients before and during enzyme replacement therapy. Clin Chim Acta. 2016;461:41.
47. Chevrier M, Brakch N, Celine L, Genty D, Ramdani Y, Moll S, et al. Autophagosome maturation is impaired in Fabry disease. Autophagy. 2010;6:589–99.
48. Alroy J, Sabnis S, Kopp JB. Renal pathology in Fabry disease. J Am Soc Nephrol. 2002;13(Suppl 2):S134–8.
49. Rockey DC, Bell PD, Hill JA. Fibrosis–a common pathway to organ injury and failure. N Engl J Med. 2015;373:96.
50. Meng X-L, Arning E, Wight-Carter M, Day TS, Jabbarzadeh-Tabrizi S, Chen S, et al. Priapism in a Fabry disease mouse model is associated with upregulated penile nNOS and eNOS expression. J Inherit Metab Dis. 2018;41(2):231–8.
51. Shu L, Vivekanandan-Giri A, Pennathur S, Smid BE, Aerts JMFG, Hollak CEM, et al. Establishing 3-nitrotyrosine as a biomarker for the vasculopathy of Fabry disease. Kidney Int. 2014;86(1):58–66.
52. Silva CAB, Moura-Neto JA, dos Reis MA, Vieira Neto OM, Barreto FC. Renal manifestations of Fabry disease: a narrative review. Can J Kidney Health Dis. 2021;8:1–14.
53. Trimarchi H, Canzonieri R, Costales-Collaguazo C, Politei J, Stern A, Paulero M, et al. Early decrease in the podocalyxin to synaptopodinratio in urinary Fabry podocytes. Clin Kidney J. 2019;12:53–60.

54. Pereira EM, Silva AS, Labilloy A, Monte Neto JT, Monte SJ. Podocyturia in Fabry disease. J Bras Nefrol. 2016;38(1):49–53.
55. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. Nat Rev Nephrol. 2012;8(5):293–300.
56. Riccio E, Sabbatini M, Capuano I, Pisani A. Early biomarkers of Fabry nephropathy: a review of the literature. Nephron. 2019;143(4):274–81.
57. Chimenz R, Chirico V, Cuppari C, Ceravolo G, Concolino D, Monardo P, Lacquaniti A. Fabry disease and kidney involvement: starting from childhood to understand the future. Pediatr Nephrol. 2021;37:95. https://doi.org/10.1007/s00467-021-05076-x.
58. Schiffmann R, Warnock DG, Banikazemi M, Bultas J, Linthorst GE, Packman S, et al. Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. Nephrol Dial Transplant. 2009;24(7):2102–11.
59. Wanner C, Feldt-Rasmussen U, Jovanovic A, Linhart A, Yang M, Ponce E, et al. Cardiomyopathy and kidney function in agalsidase beta-treated female patients: a pre-treatment vs. post-treatment analysis. ESC Heart Fail. 2020;7(3):825–34.
60. Ortiz A, Cianciaruso B, Cizmarik M, Germain DP, Mignani R, Oliveira JP, et al. End-stage renal disease in patients with Fabry disease: natural history data from the Fabry registry. Nephrol Dial Transplant. 2010;25(3):769–75.
61. Germain DP, Brand E, Burlina A, Cecchi F, Garman SC, Kempf J, et al. Phenotypic characteristics of the p.Asn215Ser (p.N215S) GLA mutation in male and female patients with Fabry disease: a multicenter Fabry registry study. Mol Genet Genomic Med. 2018;6(4):492–503.
62. Azevedo O, Gago MF, Miltenberger-Miltenyi G, Robles AR, Costa MA, Pereira O, et al. Natural history of the late-onset phenotype of Fabry disease due to the p.F113 L mutation. Mol Genet Metab Rep. 2020;22:100565.
63. Branton M, Schiffmann R, Kopp JB. Natural history and treatment of renal involvement in Fabry disease. J Am Soc Nephrol. 2002;13(Suppl 2):S139–43.
64. Ries M, Bettis KE, Chyke P, Kopp JB, Austin HA 3rd, Brady RO, Schiffmann R. Parapelvic kidney cysts: a distinguishing feature with high prevalence in Fabry disease. Kidney Int. 2004;66(3):978–82.
65. Pisani A, Petruzzelli Annicchiarico L, Pellegrino A, Bruzzese D, Feriozzi S, Imbriaco M, et al. Parapelvic cysts, a distinguishing feature of renal Fabry disease. Nephrol Dial Transplant. 2018;33(2):318–23.
66. Abensur H, Reis MA. Renal involvement in Fabry disease. J Bras Nefrol. 2016;38(2):245–54.
67. Brady RO, Uhlendorf BW, Jacobson CB. Fabry's disease: antenatal detection. Science. 1971;172(3979):174–5.
68. Fogo AB, Bostad L, Svarstad E, Cook WJ, Moll S, Barbey F, et al. Scoring system for renal pathology in Fabry disease: report of the international study Group of Fabry Nephropathy (ISGFN). Nephrol Dial Transplant. 2010;25(7):2168–77.
69. Tøndel C, Kanai T, Larsen KK, Ito S, Politei JM, Warnock DG, Svarstad E. Foot process effacement is an early marker of nephropathy in young classic Fabry patients without albuminuria. Nephron. 2015;129(1):16–21.
70. Levstek T, Vujkovac B, Podkrajsek KT. Biomarkeres of Fabry nephropathy: review and future perspective. Genes. 2020;11:1091.
71. Nakamichi T, Miyazaki M, Yamamoto T, Sato H, Ito S. Morphological details of renal lesions in late-onset normoalbuminuric Fabry disease. Nephron Clin Pract. 2015;130:86.
72. Waldek S, Feriozzi S. Fabry nephropathy: a review–how can we optimize the management of Fabry nephropathy? BMC Nephrol. 2014;15:72.
73. Monte Neto JT, Aldeman NLS, Chaves RV, Silva AS, Pereira EM, Brandão RMSS, et al. Coexistence of Fabry disease and immune complex glomerulonephritis: repost of two cases in a single family. REAS/EJCH. 2019;11(12):e503 1–9.
74. Tøndel C, Bostad L, Larsen KK, Hirth A, Vikse BE, Houge G, Svarstad E. Agalsidase benefits renal histology in young patients with Fabry disease. J Am Soc Nephrol. 2013;24(1):137–48.

75. Mauer M, Sokolovskiy A, Barth JA, Castelli JP, Williams HN, Benjamin ER, Najafian B. Reduction of podocyte globotriaosylceramide conten in adult male patients with Fabry disease with amenable GLA mutations following 6 months of migalastat treatment. J Med Genet. 2017;54:781–6.
76. Colpart P, Félix S. Fabry nephropathy. Arch Pathol Lab Med. 2017;141(8):1127–31.
77. de Menezes Neves PDM, Machado JR, Custodio FB, Monteiro MLGR, Iwamoto S, Freire M, et al. Ultrastructural deposits appearing as "zebra bodies" in renal biopsy: Fabry disease?–comparative case reports. BMC Nephrol. 2017;18(1):157.
78. Svarstad E, Leh S, Skrunes R, Larsen KK, Eikrem Ø, Tøndel C. bedside stereomicroscopy of Fabry kidney biopsies: an easily available method for diagnosis and assessment of sphingolipid deposits. Nephron. 2018;138:13–21.
79. Valbuena C, Leitão D, Carneiro F, Oliveira JP. Immunohistochemical diagnosis of Fabry nephropathy and localization of globotriaosylceramide deposits in paraffin-embedded kidney tissue sections. Virchows Arch. 2012;460:211–21.
80. Eikrem Ø, Skrunes R, Tøndel C, Leh S, Houge G, Svarstad E, Marti H-P. Pathomechanisms of renal Fabry disease. Cell Tissue Res. 2017;369(1):53–6.
81. Aguiar P, Azevedo O, Pinto R, Marino J, Baker R, Cardoso C, et al. New biomarkers defining a novel early stage of Fabry nephropathy: a diagnostic test study. Mol Genet Metab. 2017;121(2):162–9.
82. Shimohata H, Ogawa Y, Maruyama H, Hirayama K, Kobayashi M. A renal variant of Fabry disease diagnosed by the presence of urinary mulberry cells. Intern Med. 2016;55(23):3475–8.
83. Sanchez-Niño MD, Perez-Gomez MV, Valiño-Rivas L, Torra R, Ortiz A. Podocyturia: why it may have added value in rare diseases. Clin Kidney J. 2018;12(1):49–52.
84. Mauer M, Glynn E, Svarstad E, Tøndel C, Gubler M-C, West M, et al. Mosaicism of podocyte involvement is related to podocyte injury in females with Fabry disease. PLoS One. 2014;9(11):e112188.
85. Vedder AC, Linthorst GE, van Breemen MJ, Groener JE, Bemelman FJ, Strijland A, et al. The Dutch Fabry cohort: diversity of clinical manifestations and Gb3 levels. J Inherit Metab Dis. 2007;30(1):68–78.
86. Moura AP, Hammerschmidt T, Deon M, Giugliani R, Vargas CR. Investigation of correlation of urinary globotriaosylceramide (Gb3) levels with markers of renal function in patients with Fabry disease. Clin Chim Acta. 2018;478:62–7.
87. Smid BE, van der Tol L, Biegstraaten M, Linthorst GE, Hollak CE, Poorthuis BJ. Plasma globotriaosylsphingosine in relation to phenotypes of Fabry disease. J Med Genet. 2015;52(4):262–8.
88. Nowak A, Mechtler TP, Desnick RJ, Kasper DC. Plasma LysoGb3: a useful biomarker for the diagnosis and treatment. Mol Genet Metab. 2017;120:57–61.
89. Maruyama H, Miyata K, Mikame M, Taguchi A, Guili C, Shimura M, et al. Effectiveness of plasma lyso-Gb3 as a biomarker for selecting high-risk patients with Fabry disease from multispecialty clinics for genetic analysis. Genet Med. 2019;21(1):44–52.
90. Lavoie P, Boutin M, Auray-Blais C. Multiplex analysis of novel urinary lyso-Gb3-related biomarkers for Fabry disease by tandem mass spectrometry. Anal Chem. 2013;85(3):1743–52.
91. DuPont FO, Gagnon R, Boutin M, Auray-Blais C. A metabolomic study reveals novel plasma lyso-Gb3 analogs as Fabry disease biomarkers. Curr Med Chem. 2013;20(2):280–8.
92. Boutin M, Auray-Blais C. Multiplex tandem mass spectrometry analysis of novel plasma lyso-Gb3-related analogs in Fabry disease. Anal Chem. 2014;86(7):3476–83.
93. Alharbi FJ, Baig S, Rambhatla SB, Vijapurapu R, Auray-Blais C, Boutin M, et al. The clinical utility of total concentration of urinary globotriaosylsphingosine plus its analogs in the diagnosis of Fabry disease. Clin Chim Acta. 2020;500:120–7.
94. Ortiz A, Oliveira JP, Wanner C, Brenner BM, Waldek S, Warnock DG. Recommendations and guidelines for the diagnosis and treatment of Fabry nephropathy in adults. Nat Clin Pract Nephrol. 2008;4(6):327–36.

95. Ortiz A, Germain DP, Desnick RJ, Politei J, Mauer M, Burlina A, et al. Fabry disease revisited: management and treatment recommendations for adult patients. Mol Genet Metab. 2018;123(4):416–27.
96. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
97. https://www.garrod.ca/wp-conent/uploads/2019/04/Canadian-Fabry-Treatment-Guidelines-2018-final.pdf.
98. Mehta A, Beck M, Elliot P, Giugliani R, Linhart A, Sunder-Plassmann G, et al. Fabry outcome survey investigators. Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data. Lancet. 2009;374:1986–96.
99. Warnock DG, Ortiz A, Mauer M, Linthorst GE, Oliveira JP, Serra AL, et al. Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation. Nephrol Dial Transplant. 2012;27:1042–9.
100. Madsen CV, Granqvist H, Petersen JH, Rasmussen AK, Lund AM, Oturai P, et al. Age-related renal function decline in Fabry disease patients on enzyme replacement therapy: a longitudinal cohort study. Nephrol Dial Transplant. 2019;34(9):1525–33.
101. Lenders M, Canaan-Kuhl S, Kramer J, Duning T, Reiermann S, Sommer C, et al. Patients with Fabry disease after enzyme replacement therapy dose reduction and Switch-2-year follow-up. J Am Soc Nephrol. 2016;27(3):952–62.
102. Skrunes R, Svarstad E, Kampevold Larsen K, Leh S, Tøndel C. Reaccumulation of globo triaosylceramide in podocytes after agalsidase dose reduction in young Fabry patients. Nephrol Dial Transplant. 2017;32(5):807–13.
103. Krämer J, Lenders M, Canaan-Kühl S, Nordbeck P, Üçeyler N, Blaschke D, et al. Fabry disease under enzyme replacement therapy-new insights in efficacy of different dosages. Nephrol Dial Transplant. 2018;33(8):1362–72.
104. Schiffmann R, Askari H, Timmons M, Robinson C, Benko W, Brady RO, Ries M. Weekly enzyme replacement therapy may slow decline of renal function in patients with Fabry disease who are on long-term biweekly dosing. J Am Soc Nephrol. 2007;18(5):1576–8.
105. Schiffmann R, Swift C, Wang X, Blankenship D, Ries M. A prospective 10-year study of individualized, intensified enzyme replacement therapy in advanced Fabry disease. J Inherit Metab Dis. 2015;38(6):1129–36.
106. Skrunes R, Tøndel C, Leh S, Larsen KK, Houge G, Davidsen ES, et al. Long-term dose-dependent agalsidase effects on kidney histology in Fabry disease. Clin J Am Soc Nephrol. 2017;12(9):1470–9.
107. Lenders M, Brand E. Mechanisms of neutralizing anti-drug antibody formation and clinical relevance on therapeutic efficacy of enzyme replacement therapies in Fabry disease. Drugs. 2021;81(17):1969–81.
108. Azevedo O, Gago MF, Miltenberger-Miltenyi G, Sousa N, Cunha D. Fabry disease therapy: state-of-the-art and current challenges. Int J Mol Sci. 2020;22(1):206.
109. Hughes DA, Nicholls K, Shankar SP, Sunder-Plassmann G, Koeller D, Nedd K, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomized phase III ATTRACT study. J Med Genet. 2017;54(4):288–96.
110. Germain DP, Nicholls K, Giugliani R, Bichet DG, Hughes DA, Barisoni LM, et al. Efficacy of the pharmacologic chaperone migalastat in a subset of male patients with the classic phenotype of Fabry disease and migalastat-amenable variants: data from the phase 3 randomized, multicenter, double-blind clinical trial and extension study. Genet Med. 2019;21(9):1987–97.
111. Lenders M, Nordbeck P, Kurschat C, Eveslage M, Karabul N, Kaufeld J, Hennermann JB, et al. Treatment of Fabry disease with migalastat-outcome from a prospective 24 months observational multicenter study (FAMOUS). Eur Heart J Cardiovasc Pharmacother. 2021:211.
112. KDIGO. Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2012;2013(3):1–150.
113. McCafferty EH, Scott LJ. Migalastat. A review in Fabry disease. Drugs. 2019;79(5):543–54.

Chapter 28
Ophthalmological Manifestations of Fabry Disease

Adriana Muralha and Raul N. G. Vianna

28.1 Ophthalmological Manifestations of Fabry Disease

The ophthalmological manifestations of Fabry disease (FD) are inconsistent, but the most frequent and specific ocular finding is cornea *verticillata* (Fig. 28.1), resulting from Gb3 deposits between the basal membrane of the corneal epithelium and Bowman's membrane [1, 2]. Cornea *verticillata* presents an incidence of 76.9% in men and 73.1% in women with FD and was described almost as pathognomonic [1]. This appearance could be an isolated finding without other ocular abnormalities. Overall, there is no impairment in vision associated with this corneal alteration. The presence of corneal deposits should contribute to the diagnostic suspicion even in asymptomatic patients, once possible differential diagnoses, such as the chronic use of amiodarone and chloroquine, are excluded [2, 3].

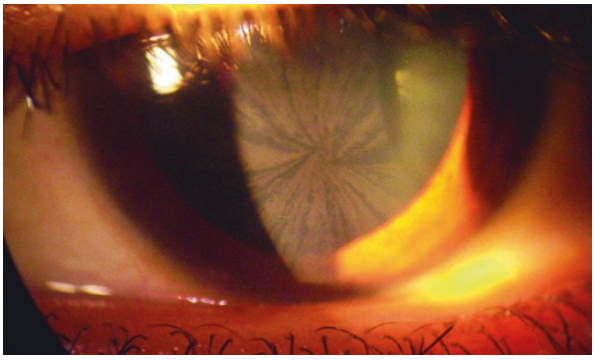


Fig. 28.1 *Cornea verticillata*. The brownish deposits are observed in a verticillate pattern at the level of the anterior layers of the cornea. (Courtesy of Burlini AP, MD)

A. Muralha (✉) · R. N. G. Vianna
Uveitis and Retina Unit, Department of Ophthalmology, Fluminense Federal University, Niterói, Rio de Janeiro, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_28

Vascular changes, periorbital edema, cataract, peripheral retinal pigmentation, papilledema, optic atrophy, nystagmus, and internuclear ophthalmoplegia are other described ophthalmologic findings [2].

Lens involvement consists of opacification of the posterior sutures that can evolve into a subcapsular cataract or may present as nonspecific lens opacities [2].

Conjunctival and retinal vascular changes are secondary to intracytoplasmic glycosphingolipid deposits in the vascular endothelium. In the retinal vasculature, abnormalities result in increased venous tortuosity, sectoral venous dilatation, arteriolar narrowing, and localized vessel constriction [2, 3].

There is evidence that correlates retinal findings with systemic vascular and cerebrovascular alterations. As such, clinical evaluation of retinal vessels may be an important marker of the state of the microvasculature [4, 5].

References

1. Bernardes TP, Foresto RD, Kirsztajn GM. Fabry disease: genetics, pathology, and treatment. Rev Assoc Med Bras. 2020;66:s10–6. http://www.scielo.br/j/ramb/a/KZVkfdZ7MDXvwjMjpm9nsLx/?lang=en
2. Rodriguez-Gonzalez-Herrero ME, Marín-sánchez JM, Gimeno JR, Molero-Izquierdo C, De-Casas-Fernández A, Rodríguez-González-Herrero B, et al. Ophthalmological manifestations in Fabry's disease. Four clinical cases showing deficient alpha-galactosidase-A activity. Arch Soc Esp Oftalmol. 2008;83(12):713–8. https://pubmed.ncbi.nlm.nih.gov/19085643/
3. Marques MG, Mira F, Ferreira E, Pinto H, Maia P, Mendes T, et al. Fabry's disease, an eye-kidney disease review. Port J Nephrol Hypert. 2015;29:15–20.
4. Bacherini D, Vicini G, Nicolosi C, Tanini I, Lenzetti C, Finocchio L, et al. Optical coherence tomography angiography for the evaluation of retinal vasculature in Fabry disease: our experience and review of current knowledge. Front Neurol. 2021;9:12. https://pubmed.ncbi.nlm.nih.gov/33767663/
5. Sivley MD, Benjamin WJ. Fabry keratopathy: manifestations and changes over time. Br J Ophthalmol. 2020;104(8):1148–55. https://pubmed.ncbi.nlm.nih.gov/31666224/

Chapter 29
Dermatological Manifestations in Fabry Disease

Samantha Vernaschi Kelmann

29.1 Introduction

The first descriptions of Fabry Disease (FD) in 1898, made by Johannes Fabry and Willliam Anderson [1, 2], emerged from the clinical observation of exacerbated dermatological manifestations of angiokeratomas distributed especially in the area of swimming trunks. Since then, several studies have been carried out to fully analyze the pathophysiology of the disease and its understanding.

29.2 Dermatological Manifestations

The main dermatological manifestations that occur in FD can be seen in the initial phase of the disease, guaranteeing the importance of its recognition to enable early diagnosis and speed up access to treatment.

29.2.1 Angiokeratomas

Angiokeratomas are vascular alterations characterized by dilatation of blood vessels found in the most superficial dermis and the anatomopathological presence of a thick or hyperkeratotic epidermis.

They can be found in multiple different conditions and are not exclusive to FD.

S. V. Kelmann (✉)
Institution Children's Institute, University of São Paulo, São Paulo, SP, Brazil
e-mail: dermatologist@samanthakelmann.com.br

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_29

They can be classified as localized or disseminated; however, regardless of their number or distribution, histologically, they share similarities: they present hyperkeratosis with epidermal interpapillary cones that surround dilated vessels that are found in the superficial or papillary dermis. Thrombi and dermal ectasia are usually present.

Angiokeratomas (Fig. 29.1) are often one of the earliest manifestations in FD. The number and size of these skin lesions progressively increase with age. They also tend to have a symmetrical distribution [3].

According to data from the Fabry Outcome Survey (FOS) in 2007 of 714 affected individuals (345 men and 369 women), angiokeratomas were present in 66% of men and 36% of women, with a mean age of onset of 19 years and 28 years, respectively [4]. These isolated, grouped, or generalized lesions may appear before the age of 16 [5], varying in distribution and intensity, but characteristically "in swimming trunks", that is, on the inner thighs, buttocks, navel, hypogastrium, scrotum, and female penis/genital [6].

These angiectasias may constitute the earliest manifestations and are capable of leading to the diagnosis of FD. On the other hand, in some patients, angiokeratomas may not be readily detected, requiring careful examination of the skin, especially in the scrotum and umbilicus, where isolated lesions may be present [7]. Angiokeratomas can also affect mucous membranes such as those of the conjunctiva, mouth, airways, and gastrointestinal and genitourinary tracts [8, 9].

Angiokeratomas records at the Hospital das Clínicas da Universidade de São Paulo from 1996–2002 found 3 patients with FD (10.3%). Other studies also point to the finding of patients with FD from the finding of angiokeratomas [10–12].

On the other hand, patients screened from cases on hemodialysis [13] and hypertrophic cardiomyopathy [14] and cryptogenic stroke [15] had less expressive results.

More knowledge on the subject and dissemination of the disease will allow more patients to be diagnosed, as well as their families from genetic counseling, and benefit from enzyme replacement treatment.

The systematic search for FD patients based on the presence of angiokeratomas is an important tool for early diagnosis.

It is necessary to educate physicians, especially dermatologists, so that they are aware that patients with angiokeratomas and their families should be investigated

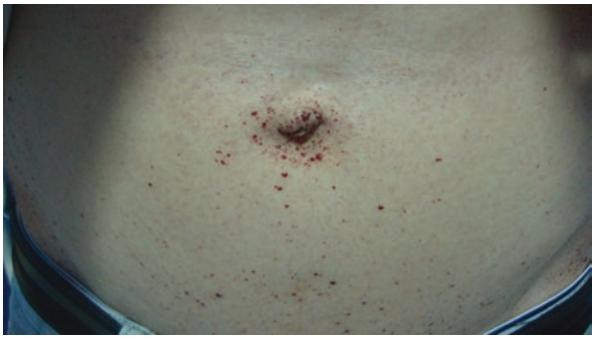


Fig. 29.1 Angiokeratomas in the umbilical region in a patient with FD

for the possibility of having FD. Despite not being pathognomonic, angiokeratoma is a good marker for finding and diagnosing FD.

It is important to clarify that there may be people with the classic form of FD without angiokeratomas or only with isolated lesions [16, 17].

29.2.1.1 Differential Diagnoses of Angiokeratomas

Some lesions are clinically similar to angiokeratomas and need to be differentiated. They are eruptive angioma, serpinous angioma, Kaposi's sarcoma, angiodysplastic syndrome, keratosis irritated seborrheic, pigmented basalioma, blue nevus, superficial malignant melanoma, melanoma metastases, and hereditary hemorrhagic telangiectasia [6].

Angiokeratomas can also be seen in other deposit diseases, including mannosidosis, fucosidosis, sialidosis, beta-galactosidosis deficiency, Schindler's disease [18–21], and isolated angiokeratomas without associated deposit material [22].

29.2.2 Sweating Changes

FD can lead to sweat gland infiltration and polyneuropathy. With this, there will be hypohidrosis or even anhidrosis with intolerance to heat and exercise.

There may also be a reduction in tears and saliva.

More rarely, but already described, there may also be hyperhidrosis.

29.2.2.1 Differential Diagnoses of Sweating Disorders

Hypohidrosis can be, among others, drug-related or caused by autoimmune diseases such as lupus or scleroderma.

In the case of reduced saliva and tears, the main differential diagnosis is Sjögren's Syndrome.

Hyperhidrosis, on the other hand, has differential diagnoses of its primary idiopathic and secondary forms (use of medications, neurological and endocrine diseases).

29.2.3 Acroparesthesias

The tingling and burning sensation in the extremities can lead to episodes of intense, limiting, and disabling pain in some cases.

They last from minutes to days and can generalize to the whole body. They are triggered by environmental factors such as heat, stress, flu, tiredness, and exercise.

29.2.3.1 Differential Diagnoses of Acroparesthesias

The main causes of acroparesthesia are rheumatological, endocrinological, and neurological diseases.

29.2.4 Lymphedema

Lymphedema occurs due to the accumulation of glycolipids in lymphatic vessels that ultimately lead to severe lymphatic microangiopathy with edema.

This edema appears especially in the legs and feet and can lead to the main complication, erysipelas.

29.2.4.1 Differential Diagnoses of Lymphedema Alterations

Postsurgical and chemotherapeutic lymphedema, congenic alterations of lymphatic vessels, or postelephantiasis-like infections.

29.2.5 Facial Dysmorphia

There is a list of facial changes characterized as being found in FD, but none of them would be completely pathognomonic.

- Fullness periorbital.
- Prominence of earlobes.
- Bushy eyebrows.
- Slightly broad forehead.
- Pronounced nasal angle.
- Prominent/bullous nose.
- Crests prominent supraorbitals.
- Midface hypoplasia.
- Full lips.
- Prominent nasal bridge.
- Broad wing base.
- Coarse features.
- Posteriorly rotated auricles.
- Prognathism.

29.3 Treatment

The treatment of dermatological changes can be divided into the following:

- Treatment of the manifestations themselves:
  - Angiokeratomas
    Lesions, which are most often asymptomatic, can be treated with electrocautery, liquid nitrogen, or ablative laser [23]. In more extensive lesions, local surgical resection may be performed. If scrotal angiokeratomas are associated with local changes that increase venous pressure, particularly varicocele, treatment of the underlying disease may lead to regression of the angiokeratomas [24]. Likewise, treatment with enzyme replacement therapy in FD also leads to the regression of angiokeratomas [25].
  - Hypohidrosis
    For cases of saliva or tear reduction, the use of medications that simulate the same, such as artificial tears and saliva, should be administered. Environmental care, such as staying in refrigerated places and avoiding exercise, especially in very hot places, especially for patients with anhidrosis, should be adopted.
  - Hyperhidrosis
    The treatment of hyperhidrosis can be done with the use of topical antiperspirant products in localized cases (hands, feet, armpits) or systemic (in case of hyperhidrosis disseminated) and use of injectable botulinum toxin in more resistant but also localized cases.
  - Acroparesthesias
    As triggers are responsible for acroparesthesias, environmental measures to reduce trigger points, such as avoiding extreme exercise, intense heat, and excessive tiredness, can help prevent acroparesthesias.
    For neuropathic pain, low doses of carbamazepine, gabapentin, phenytoin, nortriptyline, amitriptyline, and lamotrigine are used [26].
  - Lymphedema
    Compression stockings, lymphatic drainage, limb elevation.
- Treatment of the cause:
  - Enzyme replacement therapy in FD.
    Follow-up studies on enzyme replacement therapy demonstrated regression of angiokeratomas, adequacy of sweating, and reduction of heat intolerance and acroparesthesias [27].

References

1. Fabry J. Ein Beitrag Zur Kenntnis der Purpura haemorrhagica nodularis (Purpura papulosa hemorrhagica Hebrae). Arch Dermatol Syphilis. 1898;43:187–200.
2. Anderson WA. Angeio-keratoma. Br J Dermatol. 1898;10:113–7.
3. Lidove O, Jaussaud R, et al. Dermatological and soft-tissue manifestations of Fabry disease: characteristics and response to enzyme replacement therapy. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry disease: perspectives from 5 years of FOS. Oxford: Oxford PharmaGenesis; 2006.
4. Orteu CH, Jansen T, et al. Fabry disease and the skin: data from FOS, the Fabry outcome survey. Br J Dermatol. 2007;157(2):331–7.
5. Pintos Morell G. Enfermedad de Fabry: reconocimiento en la edad pediátrica. An Esp Pediatr. 2002;57(1):45–50.
6. Atherton, D. J., Moss, C. (2004). Naevi and other developmental defects. In: Burns T, Cox N, Breathnach S, Griffiths C. Rook's textbook of dermatology. Oxford, Blackwell Publishing. 1: 87–90.
7. Desnick RJ, Ioannou YA, Eng CM. Alpha-galactosidase a deficiency: Fabry disease. In: Beaudet AL, Scriver CR, Sly WS, Valle D, Childs B, Kinzler KW, Vogelstein B, editors. The metabolic and molecular bases of inherited disease, vol. 1. New York: McGraw-Hill; 2001. p. 3733–74.
8. Kanda A, Nakao S, et al. Fabry disease: ultrastructural lectin histochemical analyses of lysosomal deposits. Virchows Arch. 2000;436(1):36–42.
9. Larralde M, Boggio P, et al. Fabry disease: a study of 6 hemizygous men and 5 heterozygous women with emphasis on dermatologic manifestations. Arch Dermatol. 2004;140(12):1440–6.
10. Hogarth V, Dhoat S, et al. Late-onset Fabry disease associated with angiokeratoma of Fordyce and multiple cherry angiomas. Clin Exp Dermatol. 2011;36(5):506–8.
11. Zampetti A, Orteu CH, et al. Angiokeratoma: decision making methodology for the diagnosis of Fabry disease. Br J Dermatol. 2012;166(4):712–20.
12. Zampetti A, Orteu CH, et al. Angiokeratoma: decision-making aid for the diagnosis of Fabry disease. Br J Dermatol. 2012;166(4):712–20.
13. Merta M, Reiterova J, et al. A nationwide blood spot screening study for Fabry disease in the Czech Republic hemodialysis patient population. Nephrol Dial Transplant. 2007;22(1):179–86.
14. Monserrat L, Gimeno-Blanes JR, et al. Prevalence of Fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2007;50(25):2399–403.
15. Rolfs A, Bottcher T, et al. Prevalence of Fabry disease in patients with cryptogenic stroke: a prospective study. Lancet. 2005;366(9499):1794–6.
16. Mohrenschlager M, Ring J, et al. Skin manifestations of Fabry disease. JAMA. 2001;286(11):1315.
17. Mohrenschlager M, Henkel V, et al. Fabry disease: more than angiokeratomas. Arch Dermatol. 2004;140(12):1526–8.
18. Beratis NG, Varvarigou-Frimas A, et al. Angiokeratoma corporis diffusum in GM1 gangliosidosis, type 1. Clin Genet. 1989;36(1):59–64.
19. George S, Graham-Brown RA. Angiokeratoma corporis diffusum in fucosidosis. J R Soc Med. 1994;87(11):707.
20. Kawachi Y, Matsu-ura K, et al. Angiokeratoma corporis diffusum associated with galactosialidosis. Dermatology. 1998;197(1):52–4.
21. Suzuki N, Konohana I, et al. Beta-mannosidosis with angiokeratoma corporis diffusum. J Dermatol. 2004;31(11):931–5.
22. Fimiani M, Mazzatenta C, et al. Idiopathic angiokeratoma corporis diffusum. Clin Exp Dermatol. 1997;22(4):205–6.
23. Bechara FG, Huesmann M, Altmeyer P, Hoffmann K, Jansen T. Angiokeratoma of the glans penis: successful treatment with Nd: YAG laser. Acta Paediatr. 2002;Suppl(439):143.
24. Mohrenschlager M, Braun-Falco M, et al. Fabry disease: recognition and management of cutaneous manifestations. Am J Clin Dermatol. 2003;4(3):189–96.

25. Fauchais AL, Prey S, et al. Angiokeratoma regression in a Fabry disease after treatment with agalsidase-beta: clinical effectiveness marker? J Eur Acad Dermatol Venereol. 2010;24(6):737–8.
26. Schiffmann R, Kopp JB, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA. 2001;285(21):2743–9.
27. Desnick RJ, Brady R, et al. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. Ann Intern Med. 2003;138(4):338–46.

Chapter 30
Diagnostic Flowchart in Fabry Disease

Arsonval Lamounier Júnior

30.1 When to Suspect the Diagnosis of Fabry Disease?

Fabry disease (FD) diagnosis starts mainly when signs and symptoms suggestive of this disease are suspected, which we call red flags (Fig. 30.1). Clinical features of FD are dependent on the patient's sex due to the X-linked inheritance pattern and are also related to the patient's age as a consequence of the progressive lysosomal accumulation of globotriaosylceramide (Gb3) and its derivatives in the body's cells over time [1, 2]. These factors are important at the moment of phenotype evaluation of patients with a diagnosis suspicious for FD.

In male individuals, the most common early manifestations observed in children and adolescents (first and second decades of life) are angiokeratomas, acroparesthesias, gastrointestinal manifestations, hypohidrosis, and the characteristic corneal and lenticular opacities [1, 2]. Although kidney failure and left ventricular hypertrophy are late clinical findings (third and fourth decade of life), the presence of microalbuminuria and electrocardiographic changes can be found earlier, reflecting renal and cardiac involvement, respectively [1, 2]. Other clinical manifestations in FD are stroke, brain white matter changes on magnetic resonance imaging and lymphedema [1, 2]. In females, clinical manifestations are usually milder and observed later than in males [2]. Rarely, it is possible to identify completely asymptomatic women or to present clinical manifestations as severe as in males [2].

A. L. Júnior (✉)
Medicine School Universidade Vale do Rio Doce-UNIVALE, Governador Valadares, Brazil
e-mail: arsonval.junior@univale.br

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_30

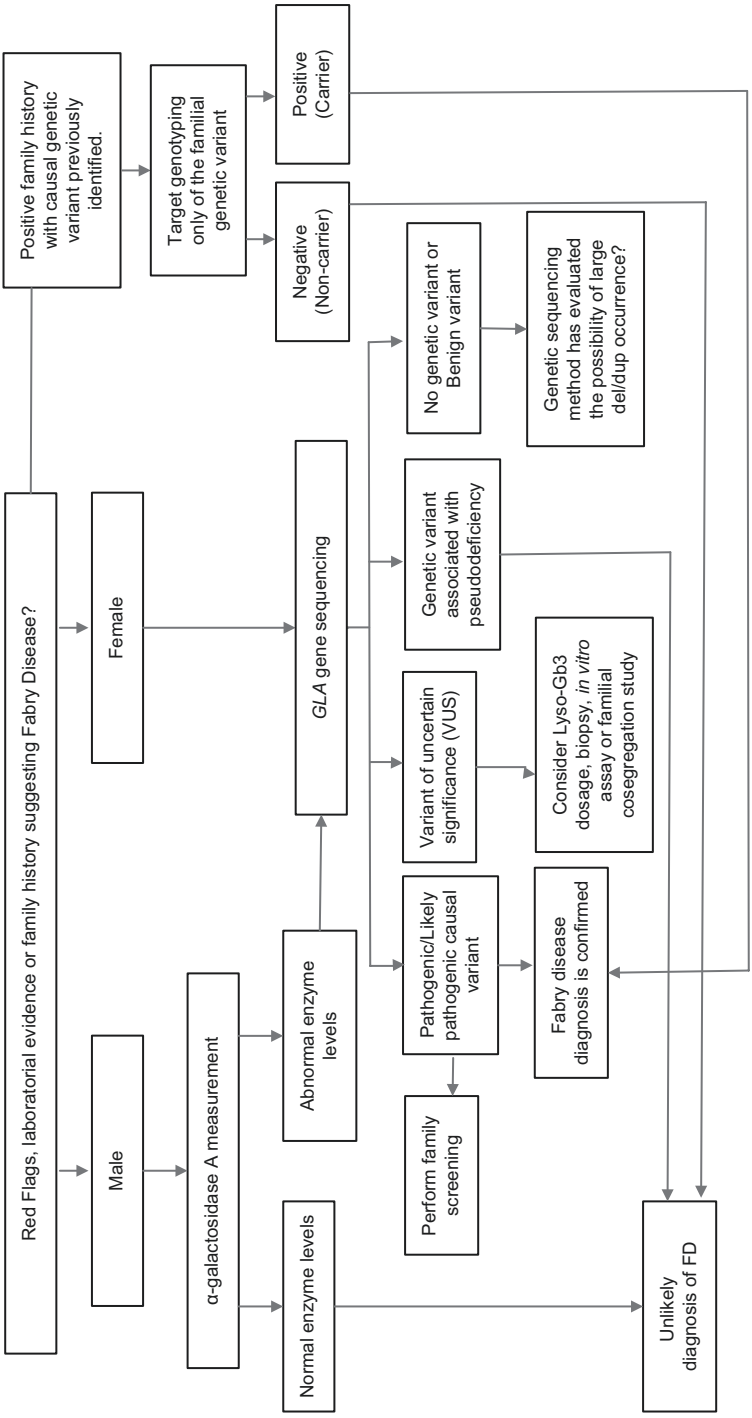


Fig. 30.1 Diagnostic flowchart in Fabry disease

30.2 What Is an Important Exam to Diagnose FD?

The dosage of the alpha-galactosidase A level plays a central role in the diagnosis of FD, especially in males. This can be performed in plasma, isolated leukocytes, and/or cell culture [2]. Enzyme dosage should always be requested in males. In male individuals with the classic FD phenotype, the enzyme dosage is usually less than 1%. In atypical presentations, enzymatic values higher than 1% are more frequent, with values below 30% being considered abnormal [3]. In females, the enzymatic dosage would not be recommended, as several women have levels of alpha-galactosidase A with values overlapping with control individuals. Therefore, genetic sequencing of the GLA gene is performed directly in female patients [2, 4, 5].

Family history in FD should be investigated considering the possible clinical heterogeneity of the disease among different individuals of the same family [6]. A pedigree of at least three generations should be constructed, and it would allow better visualization of the X-linked inheritance pattern suggesting the diagnosis and supporting the early diagnosis of other at-risk family members [4, 6–8]. Unspecific reports from distant relatives with renal failure, stroke, or heart disease should be considered in the family history [4]. In the case of positive family history with a causal genetic variant in the *GLA* gene previously identified, target sequencing only of the familial variant should be performed in the individual with suspicion of FD to confirm or exclude the diagnosis [4].

GLA gene full-sequencing or just specific familial variant genotyping should preferably be carried out in the context of genetic counseling, respecting the cultural aspects and psychological impact of this diagnosis on patients, and providing technical-medical information about genetic testing and FD [2, 4]. Some authors have suggested that the first step in family evaluation is to assess whether the identified genetic variant is de novo or familial. If it is familial, cascade screening should be performed [7]. Considering the distance that may exist between family members, active communication for possible carriers may require an interdisciplinary effort, with an average of up to five relatives diagnosed for each identified index case [6–8].

Genetic sequencing in FD can be performed through a unique analysis of the *GLA* gene. Genetic sequencing using the Sanger method is able to identify exonic variants, including small deletions/insertions and variants in splicing zones (usually positions −10 and + 10). However, Sanger sequencing does not detect more extensive deletions or duplications (which could account for up to 5% of the causal variants), such as those involving an entire exon, several exons, or even the entire gene [3]. In cases of strong clinical and laboratory suspicion of FD and genetic sequencing by Sanger with a negative result, additional genetic analysis using the MLPA method would be recommended to investigate the possibility of more extensive deletions or duplications [3]. Some laboratories have performed single sequencing of the *GLA* gene directly through the next-generation sequencing (NGS), which may include the analysis of copy number variations (CNVs). If the analysis of CNVs has been performed, the detection of more extensive deletions or duplications would be possible, making the MLPA technique unnecessary [3].

Genetic analysis by the NGS method also makes it possible to request a genetic panel that includes the *GLA* gene and other genes associated with the differential diagnosis of FD [3, 9–12]. These multigene NGS panels are generally focused on genes related to major FD clinical manifestations, such as genetic panels for hypertrophic cardiomyopathy or nephroglomerular diseases [9, 10]. The option of which multigene panel to order would be in accordance with the predominant phenotype of each patient and seems to be relevant in those atypical forms of FD, where the classic syndromic presentation is not observed. Other NGS multigene panels have been designed and validated containing genes related to several lysosomal storage diseases, although they have been more used for neonatal molecular screening and subsequent diagnosis [11, 12].

Genetic testing results can be conclusive, negative, or inconclusive. Variants considered pathogenic or likely pathogenic in the *GLA* gene can be used to confirm the diagnosis of FD and can be used with predictive value in family screening [1]. Molecular testing can be negative when the results show no identified genetic variant, benign variants, or genetic variants associated with alpha-galactosidase A pseudodeficiency [13]. The hypothesis of deep intronic variants affecting the splicing process is also another issue that should be addressed in patients with negative genetic results; however, available evidence in the literature for FD remains scarce.

When inconclusive, genetic sequencing identifies variants of uncertain significance (VUS) that cannot be used to establish the diagnosis. To "clarify" the pathogenicity of variants classified as VUS, the clinician can deepen the phenotype evaluation, taking into consideration four possible approaches: (a) measuring lyso-Gb3, (b) performing a tissue biopsy, and (c) in the case of an informative family (several individuals possibly affected), cosegregation study of the variant with the disease in family members may be considered [2, 13]. The gold standard test for evaluating the pathogenicity of a VUS, however, is (d) the in vitro assay of the variant's expression; nonetheless, it is performed only in a few laboratories [2].

Lyso-Gb3 measurement should not be routinely considered within the diagnostic approach of FD [3]. This biomarker may be increased in adult and pediatric patients of both sexes, and its use has been more used in the evaluation of the response to enzyme replacement therapy and the severity of the disease (disease progression stage) [2, 13]. Plasma or urine levels of normal lyso-Gb3 do not exclude the diagnosis of Fabry [2]. It has been established that patients carrying a VUS in the *GLA* gene with clinically relevant organ damage in FD (specifically heart disease) had a plasma lyso-Gb3 value $\geq$ 2.7 ng/mL, which could assist in reclassifying a VUS in patients with diagnostic suspicion of Fabry [14].

30.3 Is It Common to Use Tissue Biopsy to Aid the Diagnosis?

Tissue biopsy has also not been used routinely in the routine diagnosis of FD, but it could also be considered when genetic sequencing identifies a VUS in the *GLA* gene. This assessment could be raised mainly for FD atypical forms. Tissue

biopsy is most commonly applied and has diagnostic value in unexplained kidney failure, notably in those patients without a clear FD syndromic phenotype. Endomyocardial biopsy is rarely performed in the suspicion of Fabry in patients with left ventricular hypertrophy, as electrocardiographic and imaging markers can help to characterize the cardiac phenotype [1, 15, 16]. However, when an endomyocardial biopsy is requested, the presence of Gb3 in cardiac myocytes can establish the diagnosis of Fabry [1, 15]. A skin biopsy may show Gb3 accumulation in classic FD forms, and it also has diagnostic value, but it could be ineffective in atypical forms [3].

30.4 Are There Particularities for the Diagnosis of Atypical FD or Pediatric Forms?

It is important to emphasize that the atypical FD forms are related to late-onset genetic variants; the diagnosis is established after the fourth or fifth decade of life, and there is less neurological, dermatological, and/or ophthalmological involvement in general [3]. Most patients with suspected atypical forms of FD are those with a predominant phenotype of kidney failure or hypertrophic cardiomyopathy of unknown etiology and enzyme levels > 1% [3, 17].

Some particularities should be raised in the diagnosis of pediatric patients. FD diagnosis can be made in children from the first years of life, with the mean age of initial manifestations being lower in males [18]. The more common performance of clinical and genetic family screening has also been a factor responsible for a higher identification of FD individuals in pediatric age [6]. Diagnosis assessment in this age group and the use of genetic testing with predictive purposes in children are now especially accepted, as enzyme replacement therapy could prevent organ damage in adulthood [2, 18]. On the other hand, the timing of initiating treatment should be considered within a more detailed discussion, including whether the child is symptomatic and has clinically manifested disease. Proposals for neonatal screening with enzymatic and/or molecular testing have been carried out in several countries and are also implicated in the increase in diagnosis in children [4].

30.5 Is There a Genetic Diagnosis in FD Prenatal Care?

Prenatal genetic diagnosis has been offered in some European countries when the pregnancy is of a male fetus in families with an established diagnosis of FD [18]. It can be carried out in amniotic or villous-chorion cells [4]. For ethical reasons, prenatal diagnosis is not performed for female fetuses. Preimplantation diagnosis may be an option to be informed during genetic counseling of these families, although it is rarely used in clinical practice [18].

30.6 Conclusion

Although FD diagnosis is based on a clear propaedeutic sequence, it always requires a multidisciplinary approach because it is a multisystemic and progressive disease that begins in childhood and worsens throughout adult life. Phenotypic differences between the sexes and age-dependent clinical features are important factors at the time of the clinical evaluation of these patients. Diagnosis communication and family screening must also consider the social and emotional impact on these individuals, and it is important to be performed in a genetic counseling context. FD atypical forms and carriers of genetic variants of uncertain significance in the *GLA* gene can produce some uncertainties, and it could require the use of a greater number of tests to define or exclude the diagnosis. Advances in FD have been obtained in recent years, and the available therapies have increased the importance of this diagnostic flowchart. Its application may be essential for the early identification of patients and the reduction of morbidity and mortality in affected families.

References

1. Pieroni M, Moon JC, Arbustini E, Barriales-Villa R, Camporeale A, Vujkovac AC, Elliott PM, Hagege A, Kuusisto J, Linhart A, Nordbeck P, Olivotto I, Pietilä-Effati P, Namdar M. Cardiac involvement in Fabry disease: JACC review topic of the week. J Am Coll Cardiol. 2021;77(7):922–36.
2. Ortiz A, Germain DP, Desnick RJ, Politei J, Mauer M, Burlina A, Eng C, Hopkin RJ, Laney D, Linhart A, Waldek S, Wallace E, Weidemann F, Wilcox WR. Fabry disease revisited: management and treatment recommendations for adult patients. Mol Genet Metab. 2018;123:416–27.
3. Mehta A, Hughes DA. Fabry disease. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews® [internet]. Seattle (WA): University of Washington; 1993–2022. https://www.ncbi.nlm.nih.gov/books/NBK1292/
4. Laney DA, Bennett RL, Clarke V, Fox A, Hopkin RJ, Johnson J, O'Rourke E, Sims K, Walter G. Fabry disease practice guidelines: recommendations of the National Society of genetic Counselors. J Genet Couns. 2013;22(5):555–64.
5. Echevarria L, Benistan K, Toussaint A, Dubourg O, Hagege AA, Eladari D, Jabbour F, Beldjord C, De Mazancourt P, Germain DP. X-chromosome inactivation in female patients with Fabry disease. Clin Genet. 2016;89(1):44–54.
6. Laney DA, Fernhoff PM. Diagnosis of Fabry disease via analysis of family history. J Genet Counsel. 2008;17:79–83.
7. Rozenfeld PA, Masllorens FM, Roa N, Rodriguez F, Bonnano M, Yvorra C, Ceci R. Fabry pedigree analysis: a successful program for targeted genetic approach. Mol Genet Genomic Med. 2019;7(7):e00794.
8. Germain DP, Moiseev S, Suárez-Obando F, Al Ismaili F, Al Khawaja H, Altarescu G, Barreto FC, Haddoum F, Hadipour F, Maksimova I, Kramis M, Nampoothiri S, Nguyen KN, Niu DM, Politei J, Ro LS, Vu Chi D, Chen N, Kutsev S. The benefits and challenges of family genetic testing in rare genetic diseases-lessons from Fabry disease. Mol Genet Genomic Med. 2021;9(5):e1666.
9. Hoss S, Habib M, Silver J, Care M, Chan RH, Hanneman K, Morel CF, Iwanochko RM, Gollob MH, Rakowski H, Adler A. Genetic testing for diagnosis of hypertrophic cardiomyopathy mimics: yield and clinical significance. Circ Genom Precis Med. 2020;13(2):e002748.

10. Ars E, Torra R. Rare diseases, rare presentations: recognizing atypical inherited kidney disease phenotypes in the age of genomics. Clin Kidney J. 2017;10(5):586–93. https://doi.org/10.1093/ckj/sfx051. Epub 2017 Jul 19. PMID: 28980669; PMCID: PMC5622904
11. La Cognata V, Guarnaccia M, Morello G, Ruggieri M, Polizzi A, Cavallaro S. Design and validation of a custom NGS panel targeting a set of lysosomal storage diseases candidate for NBS applications. Int J Mol Sci. 2021;22(18):10064.
12. Málaga DR, Brusius-Facchin AC, Siebert M, Pasqualim G, Saraiva-Pereira ML, Souza CFM, Schwartz IVD, Matte U, Giugliani R. Sensitivity, advantages, limitations, and clinical utility of targeted next-generation sequencing panels for the diagnosis of selected lysosomal storage disorders. Genet Mol Biol. 2019;42(1 suppl 1):197–206. https://doi.org/10.1590/1678-4685-GMB-2018-0092. Epub 2019 Apr 11. PMID: 30985853; PMCID: PMC6687342
13. Germain DP, Levade T, Hachulla E, Knebelmann B, Lacombe D, Seguin VL, Nguyen K, Noël E, Rabès JP. Challenging the traditional approach for interpreting genetic variants: lessons from Fabry disease. Clin Genet 2021.
14. Niemann M, Rolfs A, Störk S, Bijnens B, Breunig F, Beer M, Ertl G, Wanner C, Weidemann F. Gene mutations versus clinically relevant phenotypes: lyso-Gb3 defines Fabry disease. Circ Cardiovasc Genet. 2014;7(1):8–16.
15. Linhart A, Germain DP, Olivotto I, Akhtar MM, Anastasakis A, Hughes D, Namdar M, Pieroni M, Hagège A, Cecchi F, Gimeno JR, Limongelli G, Elliott P. An expert consensus document on the management of cardiovascular manifestations of Fabry disease. Eur J Heart Fail. 2020;22(7):1076–96.
16. Smid BE, van der Tol L, Cecchi F, Elliott PM, Hughes DA, Linthorst GE, Timmermans J, Weidemann F, West ML, Biegstraaten M, Lekanne Deprez RH, Florquin S, Postema PG, Tomberli B, van der Wal AC, van den Bergh Weerman MA, Hollak CE. Uncertain diagnosis of Fabry disease: consensus recommendation on diagnosis in adults with left ventricular hypertrophy and genetic variants of unknown significance. Int J Cardiol. 2014;177(2):400–8.
17. van der Tol L, Svarstad E, Ortiz A, Tøndel C, Oliveira JP, Vogt L, Waldek S, Hughes DA, Lachmann RH, Terryn W, Hollak CE, Florquin S, van den Bergh Weerman MA, Wanner C, West ML, Biegstraaten M, Linthorst GE. Chronic kidney disease and an uncertain diagnosis of Fabry disease: approach to a correct diagnosis. Mol Genet Metab. 2015;114(2):242–7.
18. Germain DP, Fouilhoux A, Decramer S, Tardieu M, Pillet P, Fila M, Rivera S, Deschênes G, Lacombe D. Consensus recommendations for diagnosis, management and treatment of Fabry disease in pediatric patients. Clin Genet. 2019;96(2):107–17.

Chapter 31
Genetics in Fabry Disease

Charles Marques Lourenço

31.1 Introduction

Fabry disease (FD, OMIM 301500) is an X-linked inborn error of metabolism due to mutations in the gene encoding a-galactosidase A, a lysosomal enzyme [1].

Being inherited in an X-linked manner, the recurrence risk for heterozygous females of passing the mutated gene is 50% (both for male and female children) (Fig. 31.1a, b). On the other hand, daughters from hemizygous males (carriers of a GLA gene mutation) will always inherit the defective gene chance, while none of the sons of an affected male will inherit the mutation from the father since they receive the Y chromosome [2].

C. M. Lourenço (✉)
Neurogenetics Unit—Inborn Errors of Metabolism Clinics, National Reference Center for Rare Diseases, Faculdade de Medicina de São José do Rio Preto (FAMERP), São Paulo, Brazil
e-mail: charles.lourenco@edu.famerp.br

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_31

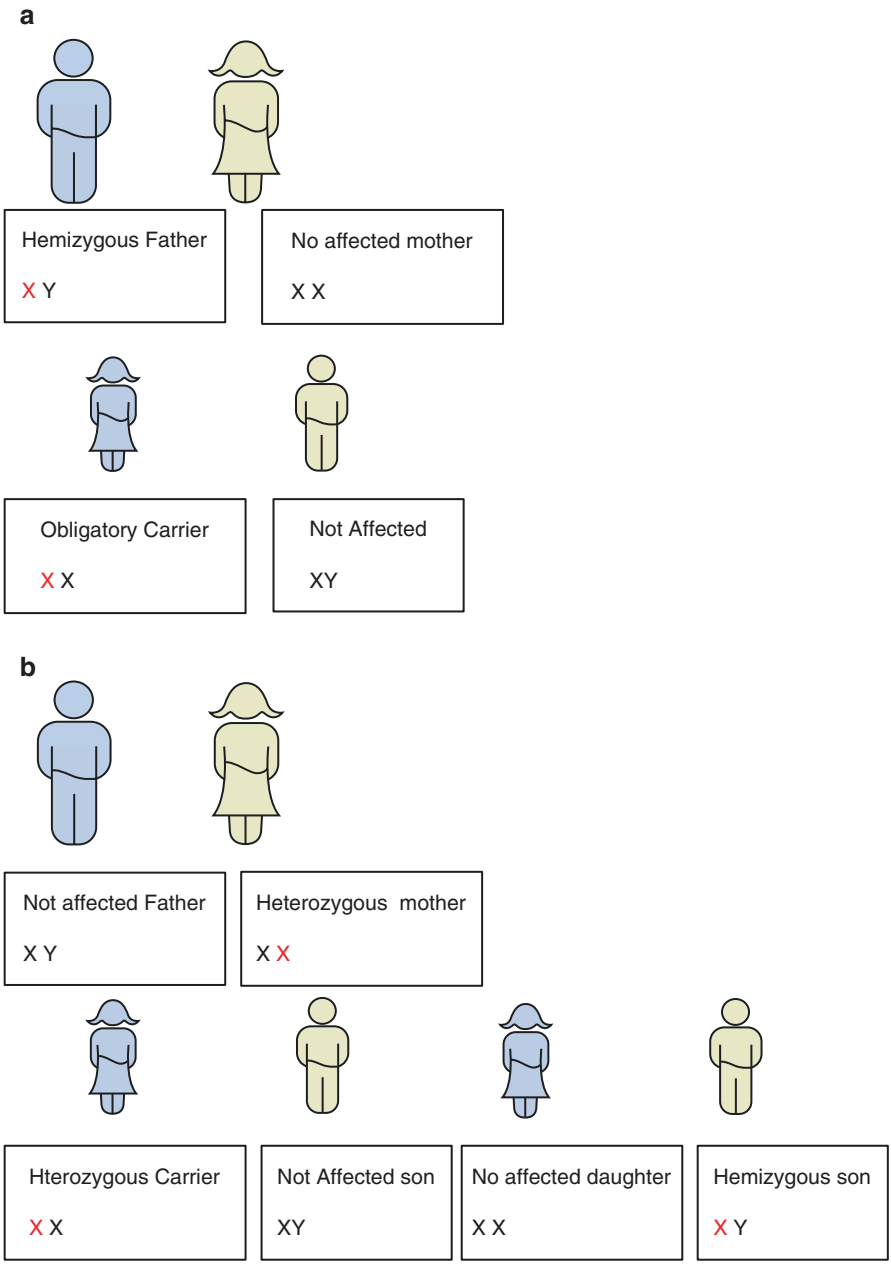


Fig. 31.1 (**a**) Heredogram/pedigree showing the recurrence risk of having affected children with FD when the father is a carrier of the GLA mutation in the X-chromosome (**b**) Heredogram/pedigree showing the recurrence risk of having affected children with FD when the mother is a heterozygous carrier of the GLA mutation in the X-chromosome. (From: Author's personal archive, 2022)

31.2 An X-Linked Recessive Disease?

In FD, the penetrance and the severity index of the phenotype are usually in males, whereas expressivity and severity index appear highly variable and often "intermediate" in many heterozygous females. In the past, heterozygous females were once thought to be only asymptomatic carriers; however, over the years, evidence has shown that the FD phenotype in women can present with great variability, developing disease manifestations from mild to severe [3].

Therefore, the former definition of FD as an X-linked recessive disorder (Fig. 31.2) has been abandoned since an increasing number of cohort and registry studies have shown that females are not just carriers, being affected in some instances the same way as hemizygous males. It was postulated that the disease could be classified as X-linked dominant or X-linked semidominant, but FD does not fit as an X-linked dominant/semidominant trait either [3, 4].

Classic definitions of X-linked recessive and dominant inheritance neither reflect the variable expressivity nor take into account the multiple mechanisms that can lead to disease expression in heterozygous females. Thus, terms such as X-linked recessive and dominant should probably be abandoned when addressing FD inheritance; instead, simply describing it as an "X-linked" disorder (Fig. 31.3) would avoid misconceptions regarding clinical expression in female patients [2].

Typically, a suggestive family history (e.g., unknown progressive kidney failure, recurrent "cryptogenic" strokes, or hypertrophic cardiomyopathy affecting several members,) is a strong indicator of FD; nevertheless, although rare, de novo mutations have been documented, so the absence of family history should not rule this diagnosis out [5, 6].

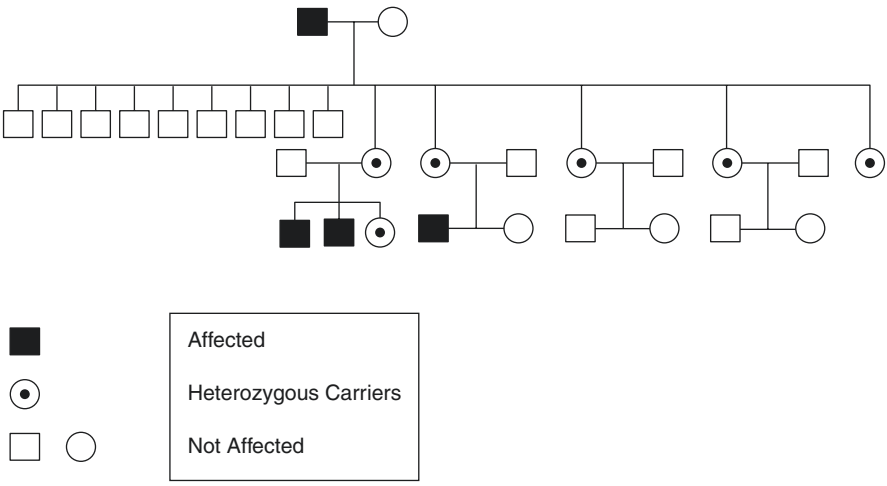


Fig. 31.2 A former typical "Fabry pedigree" presenting female patients as asymptomatic carriers. (From: Author's personal archive, 2022)

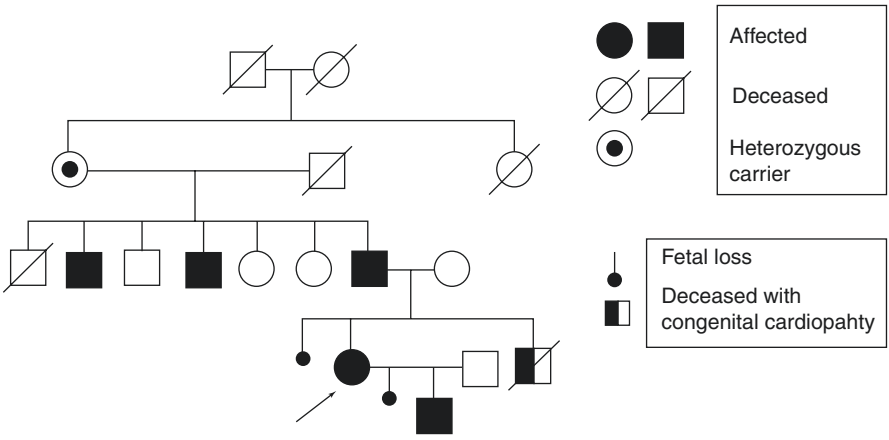


Fig. 31.3 A Fabry pedigree clearly differentiating asymptomatic female carriers from symptomatic female carriers. (From: Author's personal archive, 2022)

31.3 X-Chromosomal Inactivation and FD

X inactivation is one of the most important epigenetic gene regulations that operates in early embryogenesis in female mammals. Nevertheless, only in the 1960s, with the publication of the research work of the scientist Mary F. Lyon, did a unifying theory for X-linked disease manifestations emerge [7, 8]. In 1961, Dr. Lyon proposed that the heteropyknotic X chromosome was inactivated, citing as evidence her observations on the mosaic pattern of skin coloration seen in mice known to be heterozygous for X-linked genes that influence coat color. An example of this process is shown in Fig. 31.4a, b for female cats.

In her articles "Gene action in the X-chromosome of the mouse" and later with "Sex chromatin and gene action in the mammalian X-chromosome" in 1962, she also suggested that the inactivated chromosome X could be either paternal or maternal in origin in different cells of the same animal, and this process of inactivation occurred early in embryonic development [9, 10].

Subsequent events have confirmed the validity of Lyon's hypothesis, and in recognition of her foresight, the process of skewed X-chromosome inactivation (XCI) is often referred to as "Lyonization" [11]. This theory led to an immediate breakthrough in understanding the basic mechanisms responsible for X-linked diseases and solved many unexplained case studies. The majority of X-linked disorders cause disease manifestation only in hemizygous males [12].

The process of XCI occurs early in development at approximately 15–16 days of gestation [9]. Normally, either of the two X chromosomes can be inactivated in any particular cell. In human females, as in other female mammals, the choice of the active X chromosome is random, so that the X inherited from the father has the same possibility of being active as the X inherited from the mother. Thus, females exhibit mosaic expression of X-linked genes [10–12].

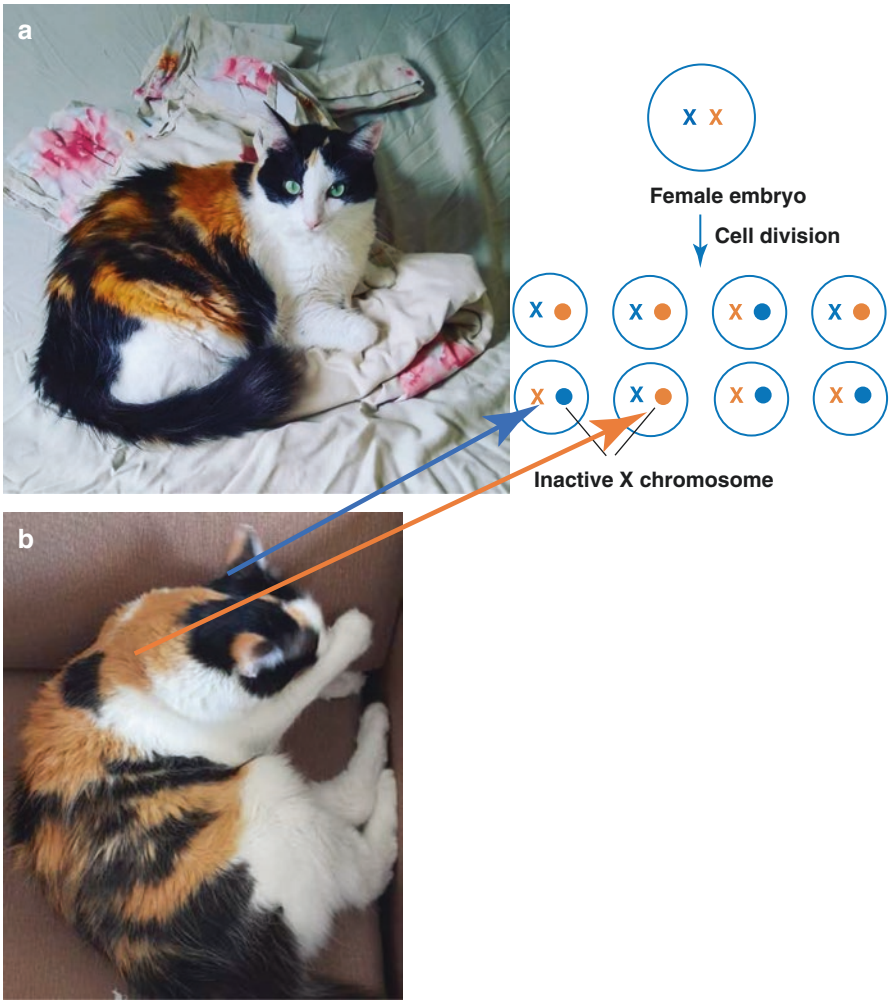


Fig. 31.4 (**a**, **b**) The process of skewed X-chromosome inactivation (XCI) occurs in each female cell, which can be seen clearly in the fur color disposition in female cats, displaying a mosaic expression of genes. Curiously, in female marsupials, the paternally derived X chromosome is consistently inactivated; in other mammals, this process is random. (From: Courtesy of Dr. Elizabeth Band, 2022)

Although there are many biological events other than skewed XCI that may influence the penetrance and expression in heterozygous females, skewed X inactivation plays a major role in the phenotypic expression of X-linked disorders [13], particularly in the FD somatic phenotype (Figs. 31.5 and 31.6).

Due to random X-chromosomal inactivation, enzymatic detection of carriers is often inconclusive [14–18]. Molecular testing of females at-risk to be carriers is therefore mandatory for accurate genetic counseling [19, 20].

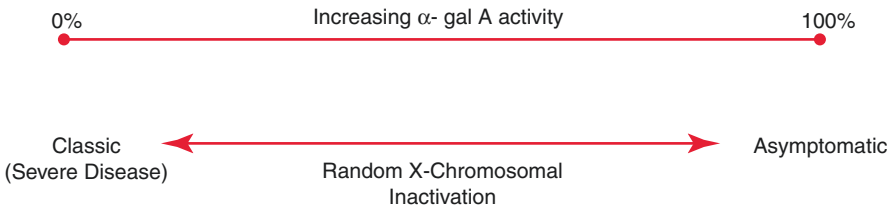


Fig. 31.5 In females affected by FD, there is a correlation between residual enzyme levels of α-galactosidase A and inactivation of the X-chromosome harboring the mutation in the *GLA* gene, although this relationship cannot always be verified in studying X-inactivation on leucocytes since every organ can have a different pattern of X skewing. (From: Courtesy of Dr. Robert Desnick, 2022)

Fig. 31.6 In hemizygous Fabry males with "classical mutations," it is possible to identify some coarsening of facial features over time, not as strinkly as in other lysosomal storage diseases, but clearly different from heterozygous female patients, even the symptomatic ones that do not show facial features of the disease. (From: Author's personal archive with Family consent, 2022)

31.4 *GLA* Mutations and Genetic Diagnosis of FD

The *GLA* gene has been cloned and identified as responsible for FD [21]. Disease-causing mutations are detected in the *GLA* gene, which is responsible for coding the AGAL enzyme. It is located on the long arm of the X chromosome (band q22), which is 12 kb in length and consists of seven exons and six introns [22].

Currently, more than 1000 different *GLA* mutations are known; although there are some common mutations, the majority of the affected patients carry "private" (family-specific) mutations (Figs. 31.7 and 31.8). This can be particularly difficult since an increasing number of genetic tests have become available due to the advances in next-generation sequencing (NGS). Currently, many FD patients have been identified through gene panels for cardiomyopathies, inherited kidney disorders, or even when undergoing whole-exome sequencing (WES) [23].

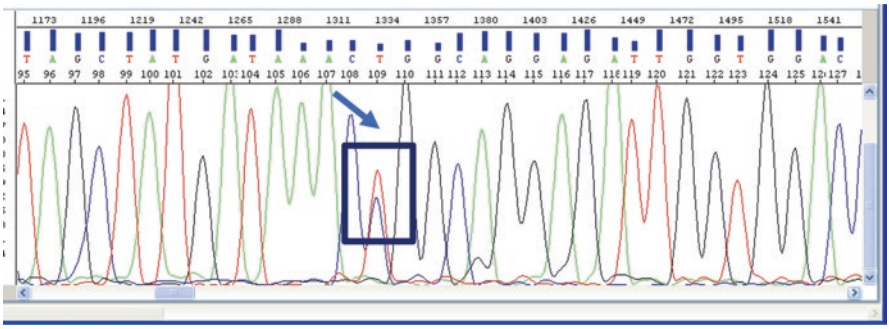


Fig. 31.7 Electropherogram showing a missense mutation in a heterozygous female patient affected with FD, identified with traditional Sanger sequencing. (From: Author's personal archive, 2022)

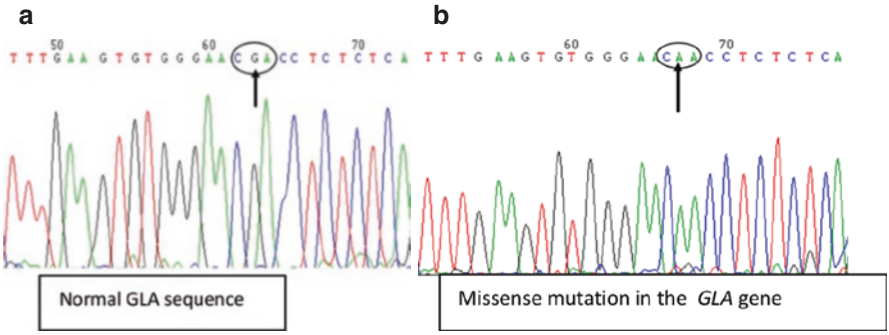


Fig. 31.8 (**a**, **b**) Electropherograms comparing normal *GLA* sequencing in a male patient with an affected male patient harboring the missense mutation p. Arg342Gln in the *GLA* gene, with a substitution of the nucleotide guanine by adenine, thus changing the enzyme sequencing, now presenting the amino acid glutamine instead of arginine at position 342 of the protein. (From: Author's personal archive, 2022)

31.4.1 Genetic Diagnosis in FD Male Patients

The diagnosis of classic FD males is straightforward: identification of *GLA* gene mutations encoding an absent or evidently dysfunctional α-galactosidase A enzyme. Extremely low α-GalA activity in leukocytes, fibroblasts, and dried blood spots (DBS) can be conveniently demonstrated using artificial water-soluble substrates, such as 4-methylumbelliferyl-α-galactoside [24]. More recently, DBS have become the method of choice for the investigation of patients since it can be used both for enzyme dosage and genetic molecular testing [25].

Nevertheless, with NGS becoming cheaper and allowing screening of many patients, it has not been unusual to identify male patients with a GLA mutation before performing enzyme testing (Fig. 31.9).

It is worth noting the fact that many *GLA* mutations found in male patients through genomic screening with NGS have not been reported previously, so in such cases, it is mandatory to perform enzyme assays for confirmation of deficient α-galactosidase A [26]. When the α-Gal levels are typically very reduced, there is no doubt in the diagnosis, and the variant of unknown significance (VOUS) seen in the *GLA* gene is validated by enzyme testing.

Unfortunately, in some instances, the diagnosis of FD even in male patients can be problematic. In particular, in those presenting with a not very specific symptom (such as albuminuria, left ventricular hypertrophy, or white matter lesions) in combination with a VOUS in the *GLA* gene accompanied by a relatively high residual enzyme activity in cells. In those cases, the detection of elevated concentrations of

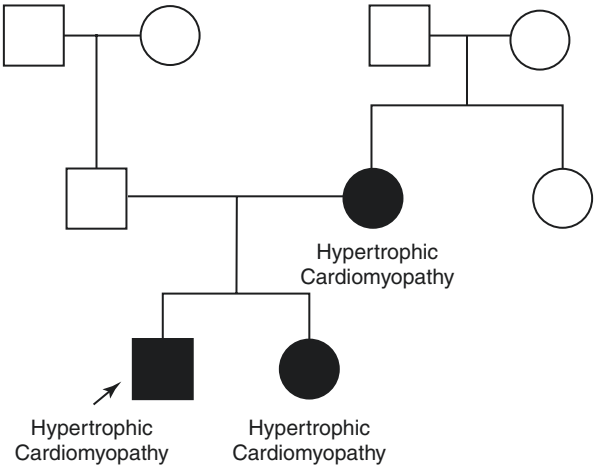


Fig. 31.9 Pedigree showing possible X-linked or autosomal dominant hypertrophic cardiomyopathy (HCM). The index case (arrow) was a 40-year-old male with episodes of syncope diagnosed with HCM after performing an echocardiogram. He underwent a gene panel for inherited cardiomyopathies and a missense mutation p. Gly373Ser (previously reported as pathogenic) was identified. (From: Author's personal archive, 2022)

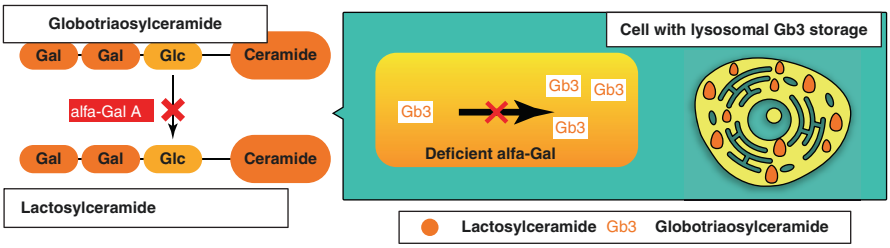


Fig. 31.10 Deficient α-Gal leads to Gb3 accumulation in tissues and can be identified through biopsies, especially when performing electron microscopy to show evidence of glycosphingolipid accumulation. (From: Author's personal archive, 2022)

plasma and urinary Gb3 and lysoGb3 can be used to further confirm the diagnosis and monitor patient response to therapy [27]. However, there are male patients who can carry a VOUS in the GLA gene with mild enzyme decrease and no clear abnormality in plasma or urinary Gb3 and lysoGb3 concentrations. In this regard, performing more invasive procedures (e.g., kidney biopsy, heart biopsy, electron microscopy of skin) can be helpful in showing glycosphingolipid storage burden (Fig. 31.10).

31.4.2 Genetic Diagnosis in FD Female Patients

Enzyme activity assays are not always informative for females affected by FD, particularly those with favorably skewed X-inactivation of the chromosome harboring the *GLA* mutation since they can have normal enzyme levels both in plasma and leucocytes. This is the reason that direct gene sequencing is the method of choice when investigating women with suspicion of FD [28, 29].

Detection of elevated lysoGb3 is very helpful to confirm FD diagnosis in females, particularly in those with VOUS in the GLA gene since enzyme assays will not be helpful in confirming the diagnosis, and the use of biomarkers can add to the evaluation of such patients. Analysis of biopsies and demonstration of deposits of Gb3 are considered, in more challenging cases, helpful to support diagnosis [29].

Women who are homozygous or compound heterozygotes have also been reported [30, 31]; this is a possible outcome for a daughter of a man with FD and his partner who is heterozygous for a *GLA* mutation.

31.5 Types of *GLA* Mutations

To date, more than 900 variants have been reported in the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=GLA). Most of the mutations reported are missense, followed by deletions, splicing site mutations, and

small insertions or duplications. Male patients with the "classical phenotype" usually carry null mutations, such as nonsense, frameshift, small deletions, and splice-site defects (Fig. 31.11). Nevertheless, patients with some missense mutations can also present with a classical phenotype and very reduced enzyme levels.

In affected male patients with FD, although not always, it is possible to establish a phenotype–genotype correlation. Usually, patients displaying a late-onset FD presentation (in the fourth or the fifth decade of life) have missense mutations with higher residual activity and normal/slightly increased biomarkers (Fig. 31.12).

Patients with more severe mutations tend to present earlier in life (many in childhood with acroparesthesias, abdominal pain, and recurrent febrile episodes). These patients have very low enzyme activity and increased lysoGb3 in plasma and Gb3 in urine [31].

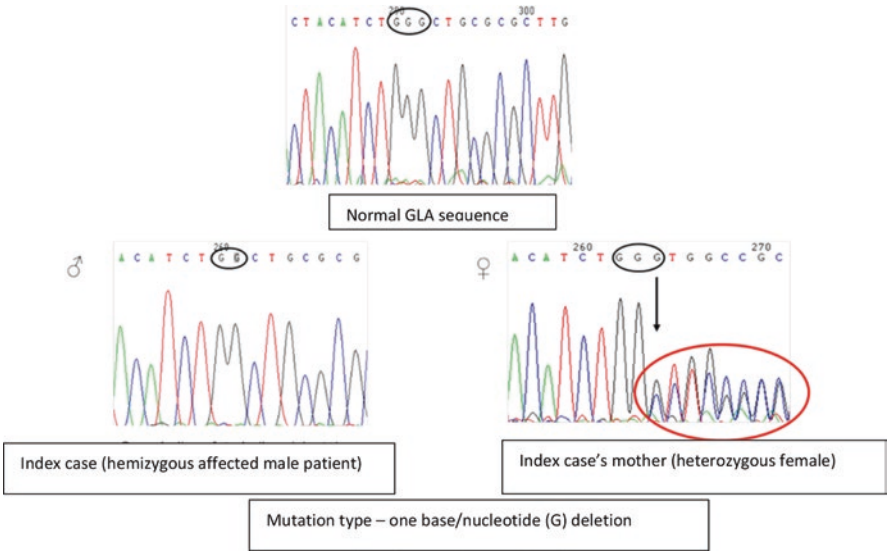


Fig. 31.11 Electropherograms comparing normal GLA sequences in a male patient with FD and male and female patients presenting a "null" mutation (nucleotide deletion) leading to a classical FD phenotype in both patients. (From: Author's personal archive, 2022)

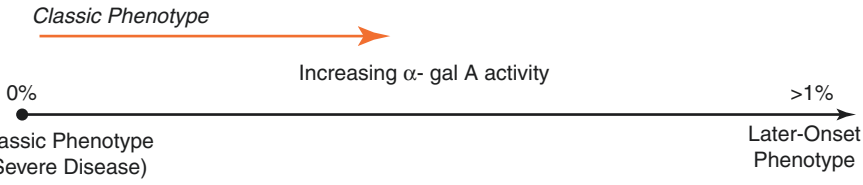


Fig. 31.12 Spectrum phenotype in FD male patients. The former renal and cardiac subtypes are in fact late-onset presentations. Thus, the term nonclassical FD or late-onset FD has been preferred. (From: Author's personal archive, 2022)

References

1. Lenders M, Brand E. Fabry disease: the current treatment landscape. Drugs. 2021;81(6):635–45. https://doi.org/10.1007/s40265-021-01486-1.
2. Viggiano E, Politano L. X chromosome inactivation in carriers of Fabry disease: review and meta-analysis. Int J Mol Sci. 2021;22(14):7663. https://doi.org/10.3390/ijms22147663.
3. Basta M, Pandya AM. Genetics, X-linked inheritance. Treasure Island: StatPearls Publishing; 2022. PMID: 32491315.
4. Dobyns WB, Filauro A, Tomson BN, Chan AS, Ho AW, Ting NT, Oosterwijk JC, Ober C. Inheritance of most X-linked traits is not dominant or recessive, just X-linked. Am J Med Genet A. 2004;129A(2):136–43.
5. Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW, Vogelstein B. The metabolic and molecular bases of inherited disease. 8th ed. New York: McGraw-Hill; 2001.
6. Ortiz A, Germain DP, Desnick RJ, Politei J, Mauer M, Burlina A, Eng C, Hopkin RJ, Laney D, Linhart A, Waldek S, Wallace E, Weidemann F, Wilcox WR. Fabry disease revisited: management and treatment recommendations for adult patients. Mol Genet Metab. 2018;123(4):416–27.
7. Chabás A, Happle R. Understanding the biology of X-linked diseases. Acta Paediatr Suppl. 2006;95(451):9–10. https://doi.org/10.1080/08035320600619104.
8. Dobyns WB. The pattern of inheritance of X-linked traits is not dominant or recessive, just X-linked. Acta Paediatr Suppl. 2006;95(451):11–5. https://doi.org/10.1080/08035320600618759.
9. Migeon BR. X inactivation, female mosaicism, and sex differences in renal diseases. J Am Soc Nephrol. 2008;19(11):2052–9. https://doi.org/10.1681/ASN.2008020198.
10. Lyon MF. X-chromosome inactivation and human genetic disease. Acta Paediatr Suppl. 2002;91(439):107–12.
11. Happle R. X-chromosome inactivation: role in skin disease expression. Acta Paediatr Suppl. 2006;95(451):16–23. https://doi.org/10.1080/08035320600618775.
12. Traupe H. Functional X-chromosomal mosaicism of the skin: Rudolf Happle and the lines of Alfred Blaschko. Am J Med Genet. 1999;85(4):324–9.
13. Deng X, Berletch JB, Nguyen DK, Disteche CM. X chromosome regulation: diverse patterns in development, tissues and disease. Nat Rev Genet. 2014;15(6):367–78. https://doi.org/10.1038/nrg3687.
14. Rossanti R, Nozu K, Fukunaga A, Nagano C, Horinouchi T, Yamamura T, Sakakibara N, Minamikawa S, Ishiko S, Aoto Y, Okada E, Ninchoji T, Kato N, Maruyama S, Kono K, Nishi S, Iijima K, Fujii H. X-chromosome inactivation patterns in females with Fabry disease examined by both ultradeep RNA sequencing and methylation-dependent assay. Clin Exp Nephrol. 2021;25(11):1224–30.
15. Juchniewicz P, Kloska A, Tylki-Szymańska A, Jakóbkiewicz-Banecka J, Węgrzyn G, Moskot M, Gabig-Cimińska M, Piotrowska E. Female Fabry disease patients and X-chromosome inactivation. Gene. 2018;641:259–64. https://doi.org/10.1016/j.gene.2017.10.064.
16. Ropers HH, Wienker TF, Grimm T, Schroetter K, Bender K. Evidence for preferential X-chromosome inactivation in a family with Fabry disease. Am J Hum Genet. 1977;29(4):361–70.
17. Navarro C, Teijeira S, Dominguez C, Fernandez JM, Rivas E, Fachal C, Barrera S, Rodriguez C, Iranzo P. Fabry disease: an ultrastructural comparative study of skin in hemizygous and heterozygous patients. Acta Neuropathol. 2006;111(2):178–85. https://doi.org/10.1007/s00401-005-0026-8.
18. Echevarria L, Benistan K, Toussaint A, Dubourg O, Hagege AA, Eladari D, Jabbour F, Beldjord C, De Mazancourt P, Germain DP. X-chromosome inactivation in female patients with Fabry disease. Clin Genet. 2016;89(1):44–54. https://doi.org/10.1111/cge.12613. Epub 2015 Jun 22.
19. Elstein D, Schachamorov E, Beeri R, Altarescu G. X-inactivation in Fabry disease. Gene. 2012;505(2):266–8.

20. Maier EM, Osterrieder S, Whybra C, Ries M, Gal A, Beck M, Roscher AA, Muntau AC. Disease manifestations and X inactivation in heterozygous females with Fabry disease. Acta Paediatr Suppl. 2006;95(451):30–8. https://doi.org/10.1080/08035320600618809.
21. Di Risi T, Vinciguerra R, Cuomo M, Della Monica R, Riccio E, Cocozza S, Imbriaco M, Duro G, Pisani A, Chiariotti L. DNA methylation impact on Fabry disease. Clin Epigenetics. 2021;13(1):24. https://doi.org/10.1186/s13148-021-01019-3.
22. Bernardes TP, Foresto RD, Kirsztajn GM. Fabry disease: genetics, pathology, and treatment. Rev Assoc Med Bras. 1992, 2020;66(Suppl 1):s10–6. https://doi.org/10.1590/1806-9282.66.S1.10.
23. Ezgu F, Alpsoy E, Bicik Bahcebasi Z, et al. Expert opinion on the recognition, diagnosis and management of children and adults with Fabry disease: a multidisciplinary Turkey perspective. Orphanet J Rare Dis. 2022;17(1):90. https://doi.org/10.1186/s13023-022-02215-x.
24. Michaud M, Mauhin W, Belmatoug N, Garnotel R, Bedreddine N, Catros F, Ancellin S, Lidove O, Gaches F. When and how to diagnose Fabry disease in clinical practice. Am J Med Sci. 2020;360(6):641–9. https://doi.org/10.1016/j.amjms.2020.07.011.
25. Simonetta I, Tuttolomondo A, Di Chiara T, Miceli S, Vogiatzis D, Corpora F, Pinto A. Genetics and gene therapy of Anderson-Fabry disease. Curr Gene Ther. 2018;18(2):96–106. https://doi.org/10.2174/1566523218666180404161315.
26. Miller JJ, Kanack AJ, Dahms NM. Progress in the understanding and treatment of Fabry disease. Biochim Biophys Acta Gen Subj. 2020;1864(1):129437. https://doi.org/10.1016/j.bbagen.2019.129437.
27. Simonetta I, Tuttolomondo A, Daidone M, Pinto A. Biomarkers in Anderson-Fabry disease. Int J Mol Sci. 2020;21(21):8080. https://doi.org/10.3390/ijms21218080.
28. Kok K, Zwiers KC, Boot RG, Overkleeft HS, Aerts JMFG, Artola M. Fabry disease: molecular basis, pathophysiology, diagnostics and potential therapeutic directions. Biomolecules. 2021;11(2):271. https://doi.org/10.3390/biom11020271.
29. Vardarli I, Rischpler C, Herrmann K, Weidemann F. Diagnosis and screening of patients with Fabry disease. Ther Clin Risk Manag. 2020;22(16):551–8. https://doi.org/10.2147/TCRM.S247814.
30. Mahmud HM. Fabry's disease—a comprehensive review on pathogenesis, diagnosis and treatment. J Pak Med Assoc. 2014;64(2):189–94.
31. Rodríguez-Marí A, Coll MJ, Chabás A. Molecular analysis in Fabry disease in Spain: fifteen novel GLA mutations and identification of a homozygous female. Hum Mutat. 2003;22(3):258. https://doi.org/10.1002/humu.9172.

Chapter 32
Echocardiography in Fabry

Sandra Marques e Silva and Gustavo Horacio Cabrera

Echocardiography is an effective, low-cost, widely available, noninvasive method to screen for Fabry cardiomyopathy. Moreover, it provides important information that helps in the differential diagnosis of other causes of ventricular hypertrophy as well as in the evaluation and monitoring of treatment effects [1]. A summary of the red flags for echocardiographic diagnosis of AFD cardiomyopathy is listed in Table 32.1.

The first hallmark feature of cardiomyopathy is left ventricular (LV) hypertrophy (Fig. 32.1). This abnormality happens without concomitant LV outflow tract obstruction or there abnormal loading conditions, such as systemic hypertension or aortic stenosis. Increased LV wall thickness above 11 mm for women and 12 mm for men are reasonable for the echocardiographic cutoff values accordingly to recent studies [2, 3]. It is important to highlight that Anderson–Fabry disease (AFD) is a sarcomeric cardiomyopathy photocopy. To understand, it does not have real myocyte hypertrophy but the enlargement of extracellular space mimicking due to globotriaosilceramide deposition together with the derived local inflammatory reaction [4, 5]. Accordingly, many AFD cardiomyopathies may be lost if the cutoff values to define the wall thickness in sarcomeric hypertrophy were applied. Although the concentric pattern is the predominant morphology, other geometries may occur leading to misdiagnosis, including asymmetric septal hypertrophy and isolated apical hypertrophy [6].

S. M. e Silva (✉)
Cardiologia e Ecocardiografia, Hospital de Base do Distrito Federal (HBDF), Brasília, Distrito Federal, Brazil

G. H. Cabrera
Coordinador del departamento de ecocardiografia en Santa Maria de la Salud, Miembro del Intenational Board de enfermedad de Fabry, San Isidro, Argentina

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_32

Table 32.1 Echocardiography red flags for the diagnosis of Anderson–Fabry disease cardiomyopathy

	ECHOCARDIOGRPHIC FINDINGS
LEFT VENTRICLE	increase wail thickness: concentric (most common), asymmetric septal, eccentric, apical Binary sign (neither sensitive nor specific for Fabry disease) Papillary muscle thickening and hyperechogenicity Systolic function generally preserved but can be reduced in advanced disease Diastolic function often impaired Abnormal TDI findings, including reduced strain, occur before increase in wall thickness Double-peak sign on strain rate imaging suggests segments of fibrosis Abnormal two-dimensional speckle-tracking results identify regional functional impairment and fibrosis Reduced strain often occurs in the basal posterior/lateral segments
RIGHT VENTRICLE	RVH Systolic function generally preserved, but severe dysfunction can occur Abnormal TDI findings, including reduced strain, can occur despite normal systolic function
ATRIA	Mild to moderate left atrial or biatrial enlargement Increased atrial reversal velocities suggest elevated left atrial pressures Abnormal TDI findings, including reduced strain, suggest atrial myopathy
VALVES	Leaflet thickening and redundancy, especially in mitral and aortic valves Valvular regurgitation often mild
AORTA	Often dilated at the sinus of Valsalva and ascending aorta but not at the descending thoracic aorta

TDI **tissue Doppler imaging**

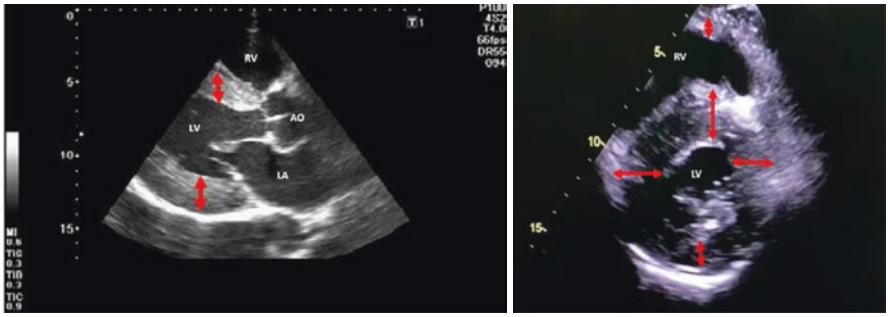


Fig. 32.1 Left ventricle hypertrophy (red flags) in a male patient with Anderson–Fabry disease cardiomyopathy. *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle, *Ao* aorta artery

Data from Fabry registries show that hypertrophy appears during the third decade of life in men and 10 years later in women and increases with disease progression, mainly among untreated patients and those with chronic kidney disease [7, 8]. There are no echocardiographic differences between patients with the classic phenotype and those with the late onset phenotype (cardiac variant). Furthermore, men with classical Fabry disease develop this at younger ages, with higher LV mass and higher plasma globotriaosylsphingosine concentrations and more cardiac events than men with late onset disease or women with either phenotype [9].

Right ventricular (RV) hypertrophy occurs in 31–71% accordantly to cohort studies. It is predominantly associated with LV disease, affects both sexes equally, and becomes increasingly common with advancing age. Data on the impact of AFD on RV systolic function are contradictory [10–13].

Papillary muscle is also hypertrophic in AFD cardiomyopathy and might serve as a marker to screen for this disease in patients with concentric LV hypertrophy. Despite its presence, there is no LV output flow obstruction or significant mitral regurgitation [14].

The second hallmark feature of AFD cardiomyopathy and the earliest sign of myocardial involvement is LV diastolic dysfunction (Fig. 32.2). Boyd et al. reported a prevalence of around 79% among AFD patients with most of the cases at mild to moderate laves. Although it can exist prior to the development of LV hypertrophy, most studies highlight it as a consequence of LVH and associated myocardial fibrosis [15]. A small proportion of patients have a pseudonormal filling pattern commonly associated with systolic dysfunction and with the end-stage disease. Restrictive physiology is uncommon among AFD patients [16, 17]. LV diastolic dysfunction also contributes to LA enlargement and may even precede LV hypertrophy. Increased left atrial stiffness index and reduced atrial compliance are due to an increase in LV filling pressures, and over a third of AFD patients have it [18, 19].

The third hallmark of AFD cardiomyopathy is the preserved systolic function throughout AFD patient's lifetime. Although most of the patients with Fabry cardiomyopathy have preserved LV ejection fraction, the use of more sophisticated echo techniques, such as strain-rate imaging, has shown regional longitudinal dysfunction early in the disease evolution. Even in patients without LV hypertrophy, the basal segments of the posterolateral wall may have impaired longitudinal strain. In more advanced stages of AFD cardiomyopathy, both regional longitudinal and radial functional parameters are markedly reduced [20]. Saccheri et al. by analyzing over 44 patients, 22 of those without LVH, observed that all patients from the first group and half of the second group had at least one segment with a strain value less than $\geq -15\%$. This demonstrates subclinical myocardial dysfunction in patients with preclinical FD and highlights the usefulness of longitudinal myocardial LV

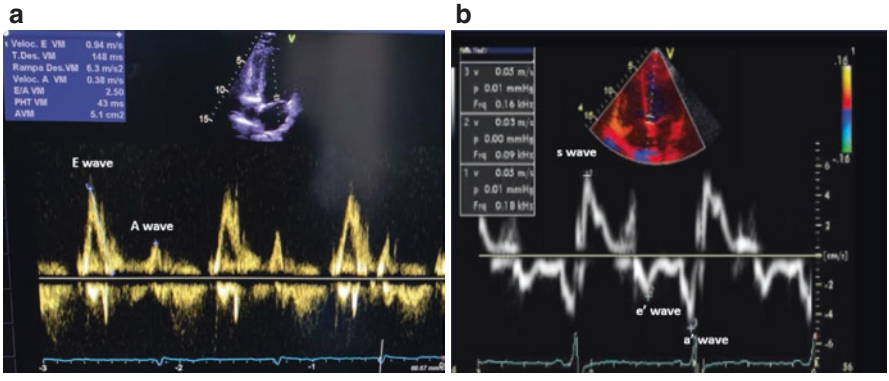


Fig. 32.2 Signs of diastolic dysfunction in a male patient with Anderson–Fabry disease cardiomyopathy. (**a**) Pulsed Doppler waves of the transmitral flow with $E/A = 2.5$, (**b**) Tissue Doppler waves of the medial mitral annulus with low-velocity values. $E/e' = 23.5$ (increased left ventricle's filling pressure) in an enlarged left atrium

strain measured with speckle tracking as an important tool to detect early myocardial involvement in young patients with FD [21].

Only a small percentage of patients develop LV and RV systolic dysfunction, which is a sign of end-stage disease. Its prevalence goes around 6–8%, and there is a strong correlation between reduced LV ejection fraction and the development of myocardial fibrosis as seen in cardiac magnetic resonance imaging studies [22, 23]. Interestingly, this anatomic change does not apply to the RV even when there is systolic dysfunction. All those complications happen more often among untreated-ERT patients and may lead to the development of heart failure symptoms and high disease mortality [24].

New echocardiographic techniques improved a lot the myocardial evaluation in AFD cardiomyopathy. The tissue doppler imaging (TDI) is an accepted method for identifying the early stages of several forms of inherited cardiomyopathy and so does to AFD. TDI has been reported to distinguish between patients with FD with and without LVH and relatives without the Fabry disease mutation [25–27] (Fig. 32.3).

Another new echocardiographic technique, the strain derived from the spackle-tracking, brought the method to a higher accuracy level (Fig. 32.3). The LV global longitudinal strain measurement provided a very important information on subclinical systolic dysfunction in patients with preserved EF. Several studies showed that the lower LV GLS values were due to the reduction in the regional strain of the basal

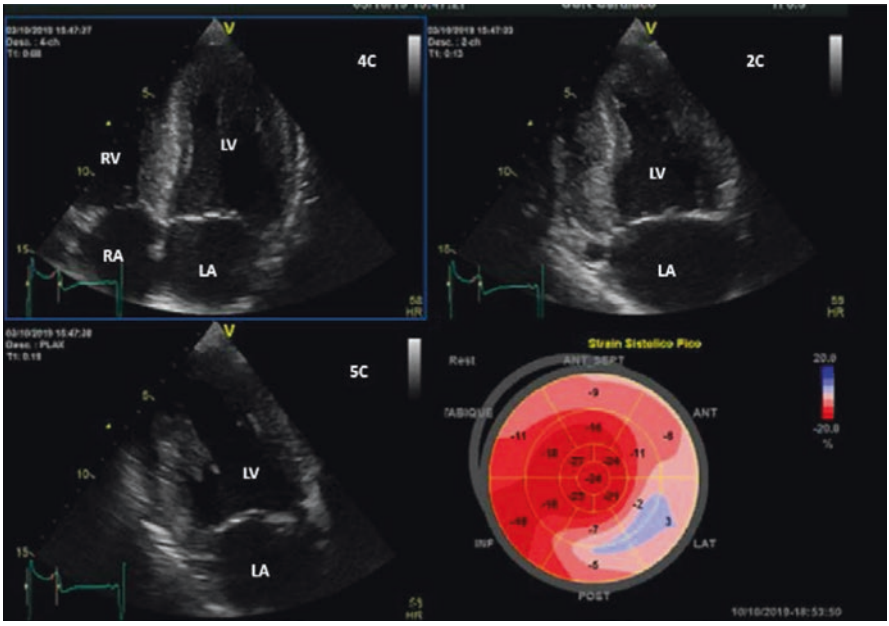


Fig. 32.3 Global longitudinal strain represented in the bull's eye graphic in a male patient with Anderson–Fabry disease cardiomyopathy. Reduced global longitudinal strain mainly due to low longitudinal strain at the posterior lateral wall (blue). *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

portion of the posterior-lateral wall [28–30]. Moreover, the association with magnetic resonance imaging showed that this abnormality is not always related to the presence of fibrotic tissue. Kramer et al. assessed 101 consecutive Fabry patients with strain echocardiographic imaging and gadolinium late enhancement (GLE) magnetic resonance imaging looking for a relationship between the presence of fibrotic tissue and a decrease in the GLS. The authors showed that the systolic strain of basal posterolateral segments was the most powerful predictor to distinguish between patients with and without LE with a sensitivity of 90% and a specificity of 97%. Patients with severe LE (>2%, $n = 22$) showed the lowest deformation values ($-5.9 \pm 8.4\%$) in basal posterolateral segments even with preserved left ventricle ejection fraction (LVEF) and normal LV diastolic diameter [31].

There are other important findings that may suggest AFD cardiomyopathy. The "binary sign," characterized by the hyperechogenicity of the endocardial layer (Fig. 32.4), is not pathognomonic of AFD and has low sensitivity and specificity in the diagnosis [32–34]. In general, significant hemodynamic valve insufficiency and stenosis are infrequent findings (Fig. 32.5). In a cohort of 111 patients from Germany, the most frequent findings were mild aortic ($n = 17$), mitral ($n = 57$), and tricuspid ($n = 38$) valve regurgitation. Only two patients showed mild aortic valve stenosis [35, 36].

To conclude, aortic remodeling is possible to occur at the root level leading to mild to moderate enlargement. Nevertheless, the risk of the development of important aortic regurgitation or dissection is very low unless when there is an association with other vascular diseases [37].

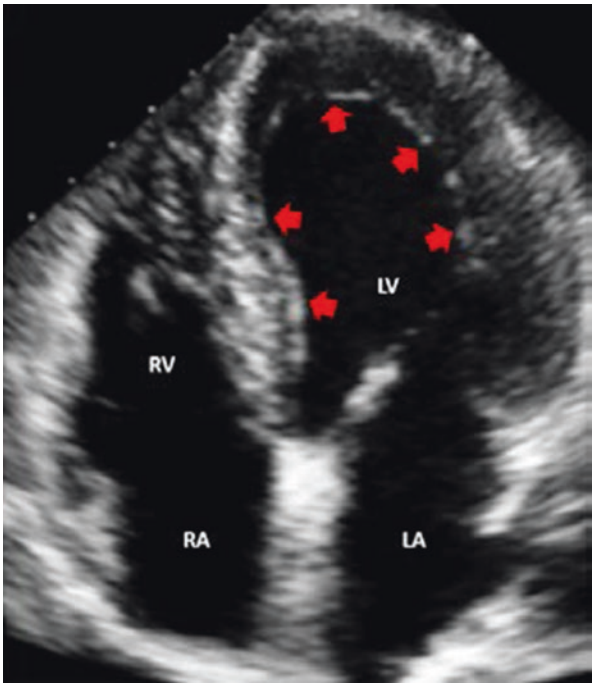


Fig. 32.4 Binary sign (red flags) in a male patient with Anderson–Fabry disease cardiomyopathy. *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

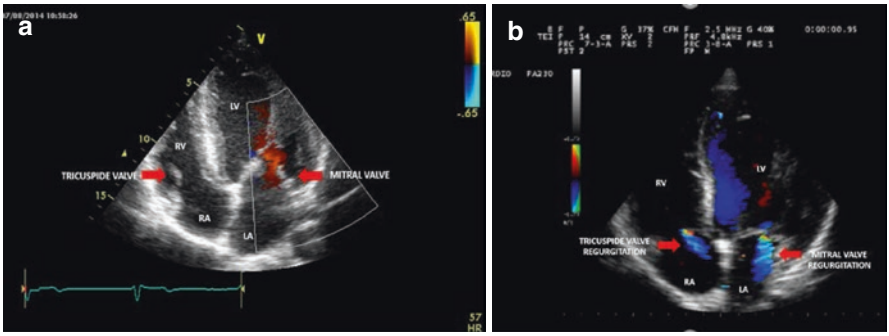


Fig. 32.5 Valve involvement (red flags) in a male patient with Anderson–Fabry disease cardiomyopathy. (**a**) Increased thickness of mitral and tricuspid valves (red flags). (**b**) Mild mitral and tricuspid valve regurgitation (red flags). *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

References

1. Niemann M, Weidemann F. Echocardiography in Fabry disease. Cardiogenetics. 2013;3:e3.
2. Sirrs S, et al. Canadian Fabry Disease Treatment Guidelines. Available at http://www.garrod.ca/wp-content/uploads/Canadian-FD-Treatment-Guidelines-2016.pdf; 2016.
3. Niemann M, Herrmann S, Hu K, Breunig F, Strotmann J, Beer M, Machann W, Voelker W, Ertl G, Wanner C, Weidemann F. Differences in Fabry cardiomyopathy between female and male patients: consequences for diagnostic assessment. JACC Cardiovasc Imaging. 2011;4:592–601.
4. Olivera-Gonzáleza S, Josa-Laordenb C, Torralba-Cabezaa MA. The pathophysiology of Fabry disease. Rev Clin Esp. 2018;218(1):22–8.
5. Rozenfelda P, Feriozzi S. Contribution of inflammatory pathways to Fabry disease pathogenesis. Mol Genet Metab. 2017;122:19–27.
6. Kampmann C, et al. Onset and progression of the Anderson–Fabry disease related cardiomyopathy. Int J Cardiol. 2008;130(3):367–73.
7. Mehta A, et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Investig. 2004;34(3):236–42.
8. Patel MR, Cecchi F, Cizmarik M, et al. Cardiovascular events in patients with Fabry disease natural history data from the Fabry registry. J Am Coll Cardiol. 2011;57(9):1093–9.
9. Arends M, Wanner C, Hughes D, Mehta A, Oder D, Watkinson OT, Elliott PM, Linthorst GE, Wijburg FA, Biegstraaten M, Hollak CE. Characterization of classical and nonclassical Fabry disease: a Multicenter Study. J Am Soc Nephrol. 2017;28(5):1631–41.
10. Kampmann C, Baehner FA, Whybra C, Bajbouj M, Baron K, Knuf M, et al. The right ventricle in Fabry disease. Acta Paediatr Suppl. 2005;94:15–8.
11. Palecek T, Dostalova G, Kuchynka P, et al. Right ventricular involvement in Fabry disease. J Am Soc Echocardiogr. 2008;21:1265–8.
12. Niemann M, Breunig F, Beer M, Herrmann S, Strotmann J, Hu K, et al. The right ventricle in Fabry disease: natural history and impact of enzyme replacement therapy. Heart. 2010;96:1915–9.
13. Graziani F, Laurito M, Pieroni M, Pennestri F, Lanza GA, Coluccia V, et al. Right ventricular hypertrophy, systolic function, and disease severity in Anderson-Fabry disease: an echocardiographic study. J Am Soc Echocardiogr. 2017;30:282–91.

14. Niemann M, Liu D, Hu K, Herrmann S, Breunig F, Strotmann J, Störk S, Voelker W, Ertl G, Wanner C, Weidemann F. Prominent papillary muscles in Fabry disease: a diagnostic marker? Ultrasound Med Biol. 2011;37(1):37–43.
15. Boyd AC, Lo Q, Devine K, et al. Left atrial enlargement and reduced atrial compliance occurs early in Fabry cardiomyopathy. J Am Soc Echocardiogr. 2013;26:1415–23.
16. Pieroni M, Chimenti C, Ricci R, et al. Early detection of Fabry cardiomyopathy by tissue Doppler imaging. Circulation. 2003;107:1978–84.
17. Liu D, et al. Association and diagnostic utility of diastolic dysfunction and myocardial fibrosis in patients with Fabry disease. Open Heart. 2018;5(2):e000803.
18. Pichette M, et al. Impaired left atrial function in Fabry disease: a longitudinal speckle-tracking echocardiography study. J Am Soc Echocardiogr. 2017;30(2):170–9.
19. Wu JC, et al. Cardiovascular manifestations of Fabry disease: relationships between left ventricular hypertrophy, disease severity, and alpha-galactosidase A activity. Eur Heart J. 2010;31(9):1088–97.
20. Weidemann F, Breunig F, Beer M, et al. The variation of morphological and functional cardiac manifestation in Fabry disease: potential implications for the time course of the disease. Eur Heart J. 2005;26(12):1221–7.
21. Saccheri MC, Cianciulli TF, Lax JA, Gagliardi JA, Cáceres GL, Quarin AE, Kisinovsky I, Rozenfeld PA, Reisin RC, AADELFA. Two-dimensional speckle tracking echocardiography for early detection of myocardial damage in young patients with Fabry disease. Echocardiography. 2013;30:1069–77.
22. Rosmini S, et al. Relationship between aetiology and left ventricular systolic dysfunction in hypertrophic cardiomyopathy. Heart. 2017;103(4):300–6.
23. Akhtar MM, Elliott PM. Anderson-Fabry disease in heart failure. Biophys Rev. 2018;10(4):1107–19.
24. Fernández A, Politei J. Cardiac manifestation of Fabry disease: from hypertrophic cardiomyopathy to early diagnosis and treatment in patients without left ventricular hypertrophy. J Inborn Errors Metab Screen. 2019:4.
25. Nagueh SF, Bachinski LL, Meyer D, Hill R, Zoghbi WA, Tam JW, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. Circulation. 2001;104:128–30.
26. De Backer J, Matthys D, Gillebert TC, De Paepe A, De Sutter J. The use of Tissue Doppler Imaging for the assessment of changes in myocardial structure and function in inherited cardiomyopathies. Eur J Echocardiogr. 2005;6:243–50. Epub 2004 Nov 5.
27. Zamorano J, Serra V, de Isla LP, Feltes G, Calli A, Barbado FJ, Torras J, Hernandez S, Herrera J, Herrero JA, Pintos G. Usefulness of tissue Doppler on early detection of cardiac disease in Fabry patients and potential role of enzyme replacement therapy (ERT) for avoiding progression of disease. Eur J Echocardiogr. 2011;12:671–7.
28. Vijapurapu R, Nordin S, Baig S, Liu B, Rosmini S, Augusto J, et al. Global longitudinal strain, myocardial storage and hypertrophy in Fabry disease. Heart. 2019;105(6):470–6.
29. Augusto JB, Johner N, Shah D, Nordin S, Knott KD, Rosmini S, et al. The myocardial phenotype of Fabry disease pre-hypertrophy and pre-detectable storage. Eur Heart J Cardiovasc Imaging. 2021;22(7):790–9.
30. Yeung DF, Sirrs S, Tsang MY, Gin K, Luong C, Jue J, et al. Echocardiographic assessment of patients with Fabry disease. J Am Soc Echocardiogr. 2018;31(6):639–49.
31. Kramer J, Niemann M, Liu D, et al. Two-dimensional speckle tracking as a non-invasive tool for identification of myocardial fibrosis in Fabry disease. Eur Heart J. 2013;34:1587–96.
32. Mundigler G, Gaggl M, Heinze G, Graf S, Zehetgruber M, Lajic N, Voigtlander T, Mannhalter C, Sunder-Plassmann R, Paschke E, Fauler G, Sunder-Plassmann G. The endocardial binary appearance ('binary sign') is an unreliable marker for echocardiographic detection of Fabry disease in patients with left ventricular hypertrophy. Eur J Echocardiogr. 2011;12:744–9.

33. Koskenvuo JW, Engblom E, Kantola IM, Hartiala JJ, Saraste A, Kiviniemi TO, Mononen I, Saraste M. Echocardiography in Fabry disease: diagnostic value of endocardial border binary appearance. Clin Physiol Funct Imaging. 2009;29:177–80.
34. Kounas S, Demetrescu C, Pantazis AA, Keren A, Lee PJ, Hughes D, Mehta A, Elliott PM. The binary endocardial appearance is a poor discriminator of Anderson-Fabry disease from familial hypertrophic cardiomyopathy. J Am Coll Cardiol. 2008;51:2058–61.
35. Weidemann F, Strotmann JM, Niemann M, et al. Heart valve involvement in Fabry cardiomyopathy. Ultrasound Med Biol. 2008;35:730–3.
36. Weidemann F, Breunig F, Beer M, Sandstede J, Stork S, Voelker W, et al. The variation of morphological and functional cardiac manifestation in Fabry disease: potential implications for the time course of the disease. Eur Heart J. 2005;26:1221–7.
37. Barbey F, Qanadli SD, Juli C, Brakch N, Palaček T, Rizzo E, et al. Aortic remodelling in Fabry disease. Eur Heart J. 2010;31(3):347–53.

Chapter 33
Cardiac Magnetic Resonance Imaging in Fabry Disease

Andréa Coy-Canguçu, Camila Nicolela Geraldo Martins, Adriana Aparecida Bau, Marly Uellendahl, and Otavio Rizzi Coelho-Filho

33.1 Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by pathogenic variants in the galactosidase alpha (GLA) gene, leading to deficient or undetectable α-galactosidase A (α-Gal A) enzyme activity. This results in progressive accumulation of globotriaosylceramide (Gb3) and its deacylated form, globotriaosylsphingosine (lyso-Gb3), within lysosomes, with potential neurological, renal, cutaneous, and cardiac involvement. It is possible that the previously reported prevalence of 1 in 40,000–117,000 may have been underestimated since neonatal screening programs have detected a surprisingly high incidence of pathogenic GLA mutations ranging from 1 in 1250 to 1 in 8800 [1–7].

To date, more than 1000 GLA variants have been identified, the majority of which are missense [8, 9]. Because the frequency of de novo mutations is less than 10%, most variants are either unique or confined to one or a few families, and even individuals with the same GLA variant may present different phenotypes [10–12].

A. Coy-Canguçu
Faculdade de Medicina—Pontifícia Universidade Católica de Campinas, São Paulo, Brazil

C. N. G. Martins · A. A. Bau
Faculdade de Ciências Médicas—Universidade Estadual de Campinas, São Paulo, Brazil

M. Uellendahl
Escola Paulista de Medicina—Universidade Federal de São Paulo, São Paulo, Brazil

O. R. Coelho-Filho (✉)
Faculdade de Ciências Médicas—Universidade Estadual de Campinas, São Paulo, Brazil

Discipline of Cardiology, Department of Internal Medicine, Hospital das Clínicas, State University of Campinas, Cidade Universitária "Zeferino Vaz", Campinas, Brazil
e-mail: orcfilho@unicamp.br

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_33

It is also worth mentioning that female carriers of pathogenic GLA mutations are susceptible to developing FD, with a heterogeneous clinical presentation that can vary from an asymptomatic or mild course with late-onset to a more severe phenotype resembling hemizygous males [13–18]. This wide variability of manifestations is partly explained by the process of random X-chromosome inactivation, after which a mosaic pattern of expression is established, with some cells expressing the normal GLA allele and others expressing the mutated allele [13, 19].

In addition to the mechanical effects that succeed tissue infiltration by Gb3 or lyso-Gb3, impaired degradation of these substrates causes cellular damage by hindering endocytosis, autophagy, and mitochondrial energy production, as well as promoting apoptosis [20, 21]. Furthermore, recent evidence has demonstrated that excessive Gb3 and lyso-Gb3 act as damage-associated molecular patterns, binding to toll-like receptor 4 in natural killer T cells and thus activating the nuclear factor κ B pathway [22, 23]. As a consequence, proinflammatory cytokines are released, and a systemic inflammatory response is elicited, eventually producing chronic and irreversible tissue injury, with subsequent fibrosis and organ failure [22, 23].

The classic early-onset FD phenotype, which mostly affects male patients, is characterized by multisystemic involvement due to absent or severely deficient α-Gal A activity (<1% of normal value) [1, 11, 24–26]. In children, typical manifestations include diffuse pain attacks, usually prompted by an increase in body temperature following physical exercise, fever, or a warm environment; sweating abnormalities, such as anhidrosis or hypohidrosis; and hearing loss [23]. Symptom severity and extent tend to progress with age, reflecting heart, kidney, and nervous system malfunction, especially during the third decade of life [1, 27]. Without adequate management, FD may lead to premature death from cardiomyopathy, renal failure, or stroke [1, 27].

Nonclassic late-onset FD, in turn, is marked by milder, slower-evolving symptoms often limited to a single organ as a result of reduced but still present enzyme activity (on average 30–35% of normal value) [28, 29]. Because this phenotype typically affects the heart, unexplained left ventricle hypertrophy (LVH) is a common first manifestation, especially in men and from the third decade of life [19, 27, 30, 31]. Other forms of cardiac involvement include heart failure with preserved ejection fraction (HFpEF), angina, arrhythmic events, hypertension, and valve regurgitation [19, 30, 31].

Cardiac involvement represents the leading cause of death in both men and women with classic or nonclassic FD [32]. Due to glycosphingolipids' recently discovered role as an inflammation trigger, FD has come to be interpreted as not only a storage disorder but also inflammatory cardiomyopathy [33]. Accordingly, a novel three-phase model for cardiac involvement in FD has been proposed, consisting of (1) Gb3 and lyso-Gb3 deposition, (2) cardiomyocyte hypertrophy and inflammation, and (3) fibrosis and impairment [34]. Since cardiac FD alterations develop long before symptom onset and are thought to be present in 0.5–1.0% of adult patients with unexplained LVH, it is recommended that those who meet this criterion are 40 years or older and have unknown family background be routinely screened for FD [11, 19, 35–48].

Diagnosis is established based on α-Gal A enzyme activity assessment and/or GLA sequencing [19]. Enzymatic testing is usually sufficient to confirm an FD diagnosis in male patients because most present α-Gal A activity values are far below normal standards, regardless of disease phenotype [25]. However, current recommendations encourage all diagnoses to be confirmed by genetic testing, considering that α-Gal A activity may be normal or slightly deficient in up to 60% of heterozygous female patients [12, 25, 49, 50]. Following diagnostic confirmation, cascade family genetic sequencing according to X-linked inheritance is strongly advised [12, 51].

As a potentially reversible disorder, it is essential that an early FD diagnosis be established to start adequate treatment that may include enzyme replacement therapy (ERT) to avoid disease-related complications. However, its relatively low prevalence rates, multiorgan manifestations, and similarities to other more commonly known LVH etiologies pose challenges to the timely recognition of FD and contribute to its underdiagnosis.

In this setting, cardiovascular magnetic resonance (CMR) has become an increasingly employed imaging modality in FD because of its greater accuracy and detail level compared to other noninvasive tools in detecting and characterizing tissue alterations, staging the degree of cardiac involvement, ruling out differential diagnoses, and monitoring patient response to ERT. Through CMR imaging, researchers were able to detect myocardial anomalies in up to 50% of GLA mutation carriers, even when LVH was mild, and no fibrosis was present [52].

For the detection, characterization, and staging of cardiac involvement, the following CMR features are applied: (1) cine imaging for cardiac morphology and function assessment; (2) parametric techniques (T1, T2, and T2* mapping) for identification of glycosphingolipid accumulation as well as myocardial inflammation; (3) late gadolinium enhancement (LGE) for identification of focal myocardial fibrosis; and (4) perfusion mapping for evaluation of perfusion integrity. Fig. 33.1 shows

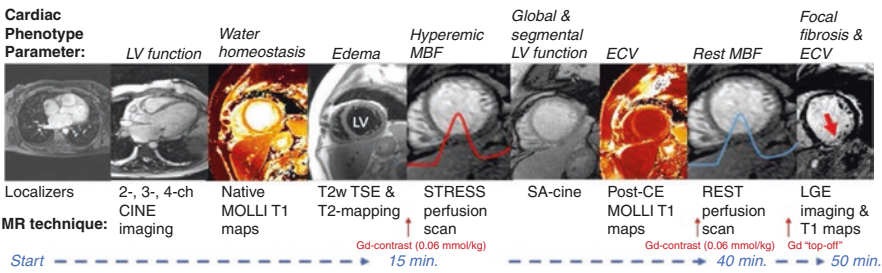


Fig. 33.1 An approximately 50-min CMR protocol assessing LV function, edema, hyperemic, and resting myocardial blood flow (MBF in mL/min/g), extracellular volume (ECV) expansion as a surrogate marker of diffuse fibrosis, and late gadolinium enhancement (LGE) to determine focal scar volume/extent. Stress perfusion is measured during maximal hyperemia with IV adenosine. All images in this schematic come from a recent CMR study of a patient with dilated cardiomyopathy, imaged by Dr. Coelho-Filho at UNICAMP in Campinas on the 3T scanner proposed for this study. *SA* short-axis, *4-ch* 4-chamber view, *T2w* T2-weighted, *MOLLI* modified Look-Locker

the typical CMR protocol to be applied in patients investigating cardiac involvement related to FD.

Key signs of FD detectible by cine imaging include progressive, concentric, and nonobstructive LVH, as well as papillary muscle thickening [23]. In later disease stages, right ventricle hypertrophy (RVH) and systolic dysfunction can also occur [23]. Regarding parametric techniques, low native T1 values due to intramyocardial glycosphingolipid accumulation may serve as a novel indicator of early cardiac involvement and as a predictor of worsening disease since a reduction in native T1 values has been reported in over 90% and 40% of FD patients with and without LVH, respectively [50]. As the disease progresses, a "pseudonormalization" in native T1 values may occur as a result of replacement fibrosis within the posterolateral LV wall [53]. An increase in T2 myocardial relaxation time, in turn, indicates myocardial inflammation and can be noted especially in the basal segment of the inferolateral LV wall, following a patchy distribution and correlating with LGE [54–56]. Finally, FD-related impaired perfusion is usually more evident in subendocardial layers and progressively worsens in segments with LVH, low native T1 values, and high LGE [23, 57].

Combined with the previously described features, strain imaging provides additional information to differentiate FD from other LVH etiologies, such as hypertrophic cardiomyopathy (HCM), cardiac amyloidosis, aortic stenosis, and hypertensive heart disease [23]. Unlike these clinical conditions, FD is characterized by abnormalities in the base-to-apex gradient (first in the circumferential strain [CS], then in the longitudinal strain [LS]), a reduction of regional LS in the basal inferolateral LV wall, and, in advanced stages, a decrease in global CS [58].

Last, LGE, T1, and T2 mapping may be valuable in estimating ERT efficacy and monitoring its effects. Previous studies have demonstrated that ERT is successful in reducing LV mass only in FD patients with little or no LGE at baseline, highlighting the importance of early diagnosis and treatment to reverse cardiac alterations and prevent disease progression [59–65]. LGE can also be used to clearly distinguish LV thinning as a result of fibrosis increase from that of ERT, preventing the wrongful assumption that LV mass is declining due to therapy when an increment in fibrosis is its underlying cause [23]. A reduction in T2 relaxation time, in turn, has been associated with LV mass regression after approximately 4 years of ERT [57]. No reports have yet been published on the use of T1 mapping in ERT monitoring.

This chapter aims to address potential challenges in the diagnosis of FD, emphasizing the importance of CMR for diagnostic accuracy, disease management, and therapy monitoring.

33.2 Fabry Diagnosis and Its Imposing Challenges

The diagnosis of FD is challenging, as it is a multisystemic disease with a relatively rare clinical prevalence. However, diagnosing FD early and correctly is essential so that ERT can be started as soon as possible.

Initial suspicion is commonly based on the various clinical manifestations that may involve neurological, dermatological, ophthalmological, renal, and cardiac symptoms. In previous FD studies, LVH has been reported in 53% of men and 33% of women after the third decade of life, with 60% of patients experiencing symptoms such as HFpEF, chest pain, and arrhythmias [19, 51]. Therefore, in cases of unexplained LVH associated with extracardiac "red flags" and characteristic family history, FD should be suspected [23].

Once FD is suspected, biochemical and genetic tests are necessary for diagnostic confirmation. In men, the diagnosis is established when α-Gal A activity is ≤30–35% compared to normal values. In women, sequencing of the GLA gene is habitually necessary since the activity of α-Gal A may be within the normal range in up to 60% of female patients due to random X-chromosome inactivation in heterozygous patients [12, 50].

In female patients, clinical presentation varies from asymptomatic patients to others suffering from a disease that is just as severe as in men. In addition, Echevarria et al. showed that in female carriers of pathogenic GLA mutations, FD progressively worsens with age, with the onset of LVH and renal dysfunction. The same authors reported an association between the expression of a wild-type GLA allele and a mild FD phenotype with little disease progression over time, as well as the relationship between a mutant GLA allele and early-onset FD, characterized by rapid evolution and poor prognosis [13].

However, it is important to note that patients with the same GLA mutation may present different phenotypes [12]. Considering the X-linked transmissibility of FD, three generations around a diagnosed individual should be screened for FD. According to Schiffman et al., FD-related clinical manifestations are mostly due to substrate accumulation rather than enzyme deficiency. Thus, detecting the accumulation of glycosphingolipids in a given organ is key to diagnosing FD and quantifying the risk of complications. In this scenario, a tissue biopsy may be necessary [29].

For blood markers, high-sensitivity troponin T (hs-TnT) correlates with fibrosis detected by CMR LGE. Therefore, hs-TnT is useful for predicting the progression of FD-related cardiomyopathy [66]. Regarding cardiovascular alterations, multimodality imaging is employed to identify LVH and provide evidence to support an FD diagnosis with cardiac involvement. It is clear that correct staging of cardiac involvement has important clinical repercussions. Once LVH is identified, careful assessment of additional manifestations suggestive of systemic disease, family history, electrocardiogram, and echocardiogram may offer clues to specific pathogenesis [67]. CMR, in turn, has become central to the diagnosis and staging of cardiac FD phenotypes. Typical characteristics include LGE (initially in the basal inferolateral wall) and low native T1 values, likely reflecting intramyocardial glycosphingolipid accumulation and preceding the development of significant LVH. For patients with a confirmed FD diagnosis, CMR can be used to assess the development of cardiac manifestations, to indicate ERT start, and to monitor those who are currently on ERT for stabilization or regression of cardiac disease [67].

33.2.1 Electrocardiogram

Many electrocardiographic alterations have been described in FD: LVH, T-wave inversion, and left atrial enlargement [68]. These findings are common in other diseases with a shared LVH phenotype [69]. Some patients may have ST-segment depression and T-wave inversion in the inferolateral wall, which is justified by the presence of fibrosis [70]. More specific changes to FD have been reported recently and have been useful in identifying FD. In the initial stages of the disease, a short PR interval is observed, probably due to changes in the conduction system by deposition of Gb3 [71], and an atrioventricular block can also be noted in more advanced stages of FD [72].

33.2.2 Echocardiogram

Patients with LVH face a diagnostic dilemma, as they fit into a phenotype that is common to many conditions. Hypertrophy can be either a physiological response to increased pressure in the left cardiac chambers, such as in athletes, or a consequence of primary or secondary cardiomyopathy [73]. Among these cardiomyopathies lies FD. Typically, FD patients present nonobstructive concentric LVH, but other findings are possible, such as asymmetric septal hypertrophy, LV outflow tract obstruction, or even apical hypertrophy [74]. It is noteworthy that LVH is a more common finding in men than in women with FD [75]. LV wall thickness and LV mass (LVM) should be determined and monitored over time [67]. Concomitant RVH has been described in 30–40% of FD patients, with RV function frequently unchanged despite hypertrophy [76]. This contrasts with cardiac amyloidosis patients, who have been shown to have impaired RV function even though their average RV wall thickness is similar to that of FD patients [76]. Unlike LVH, the presence of RVH is not sex-specific. It becomes more frequent with age, and its extent is associated with the degree of coexistent LVH [77]. Papillary muscle thickening and the ratio between the papillary muscle area and LV endocardium in the parasternal short-axis view are increased not only in FD but also in other disorders with the LVH phenotype, including cardiac amyloidosis, Friedreich's ataxia, and hypertensive heart disease [78]. Diastolic dysfunction is more prevalent in FD patients with LVH. Furthermore, decreased left atrial compliance was observed in FD patients compared to healthy controls by using tissue Doppler imaging (TDI), irrespective of LVH degree [55, 79].

33.3 Role of Cardiovascular Magnetic Resonance in Fabry

33.3.1 Traditional Methods for Tissue Characterization

CMR is a noninvasive imaging tool increasingly used in FD due to its ability to characterize the myocardial tissue, to determine ventricular volume, wall thickness,

and mass, and to identify pathological processes with great accuracy and at a detailed level. CMR has become essential in complementing echocardiography, as the former contributes to the determination of the extent of glycosphingolipid accumulation, edema, and interstitial fibrosis (evidenced by LGE), assisting in the diagnosis and follow-up of FD patients [24]. Fig. 33.2 shows the CMR findings of a patient with FD without LGE but with decreased T1 values due to glycosphingolipid accumulation.

The main cardiac manifestation in FD corresponds to LVH. Papillary muscles may also suffer hypertrophy and can thus add to the total LV mass [55]. By analyzing papillary muscle morphology, it is possible to differentiate FD from other LVH etiologies, such as HCM, cardiac amyloidosis, aortic stenosis, and hypertensive heart disease. In the absence of LVH, FD with papillary muscle hypertrophy may be suspected [80]. For the identification of myocardial hypertrophy, as well as the assessment of LV mass and ejection fraction, cine CMR steady-state free precession (SSFP) images should be obtained during breath-hold in the short-axis covering the entire LV and in multiple long-axes [55]. In this way, CMR has been able to identify cardiac alterations in up to 50% of patients with a positive genotype for FD, even when LVH is mild or not yet present [55]. According to Nordim et al., in a study involving 182 FD patients, LVH was more prevalent and more severe in men (66% vs 27% in women), with the LVH diagnosis occurring later in women [34]. Nonetheless, the prevalence of LVH increased with age in both sexes [34].

The key and perhaps the unique contribution of CMR to FD is its capacity to help identify glycosphingolipid accumulation in the myocardium, as well as edema and myocardial interstitial fibrosis, making it possible to assess changes in all stages of

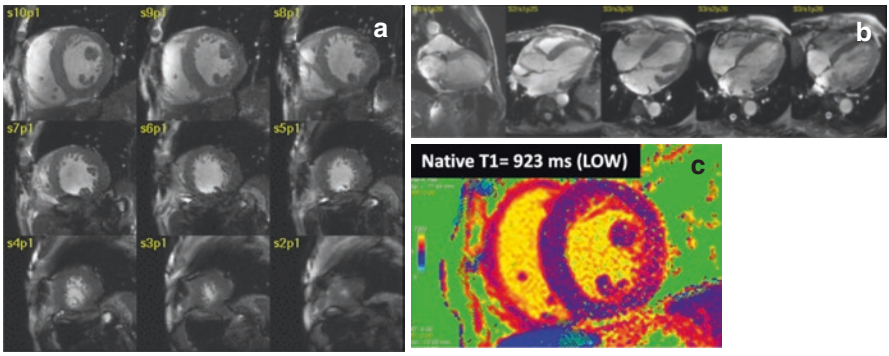


Fig. 33.2 A 59-year-old man with confirmed FD without any other cardiovascular disease. His past medical history was noticeable for peripheral neuropathic pain since childhood and heat and physical activity intolerance. His electrocardiogram (not shown here) revealed a short PR interval and complete RBB with signs of LVH. CMR showed concentric LVH with preserved LVEF without myocardial scarring assessed by LGE. Interestingly, the native T1 assessed by the MOLLI sequence was significantly low. (**a**) Short-axis view in diastole showing concentric LVH (septal wall 23 mm, posterior wall 18 mm). (**b**) Long axis view in diastole also highlighting concentric LVH. (**c**) T1 mapping with the MOLLI sequence demonstrating the low T1 value

the disease's evolution through native T1 mapping, quantification of ECV, and assessment of LGE [80].

33.3.1.1 Late Gadolinium Enhancement

CMR is essential for evaluating the evolution of FD, as it contributes to the detection of glycosphingolipid deposits that may progress into fibrotic areas. These are evaluated by the LGE technique.

LGE images are typically obtained using convectional inversion recovered sequences or with phase-sensitive inversion recovery (PSIR) 15 min after contrast administration. When PSIR is not available, it is important to set up the inversion time properly so that it cancels out myocardial signals without scarring. The emergence of LGE is more common among male patients with classic FD manifestations, especially LVH. In female patients, the occurrence of LGE is not necessarily associated with LVH and is present even in the absence of increased LV mass.

In FD patients with a typical or classical phenotype, LGE is most frequently found in the basal and middle regions of the inferolateral wall (an area of continuity with the mitral annulus) of the LV, following an epicardial pattern. This may be associated with its significant mobility (these regions are the most mobile of the basal segments during myocardial contraction), microvascular dysfunction, or even myocardial inflammation [55]. However, atypical patterns of LGE can also be identified in up to a quarter of patients and may be associated with asymmetric LV hypertrophy [80]. The progression of LGE has been shown to be an independent predictor for malignant ventricular arrhythmias and other arrhythmic events in FD patients. The assessment of LGE extent can also be pivotal in ERT indication since the presence of fibrosis can lead to an inefficient response to therapy [80]. Identifying FD patients with the most potential to respond to ERT is desirable, and LGE by CMR may be a useful tool for helping clinicians and cardiologists in this challenging task.

33.3.2 Advanced Methods for Tissue Characterization

33.3.2.1 T1 Mapping and Extracellular Volume Fraction

T1 mapping techniques acquired before and after gadolinium-based contrast administration (with subsequent ECV quantification) were developed and validated for the evaluation and quantification of myocardial interstitial fibrosis. Image acquisition for native T1 mapping is typically performed on short-axis views (commonly three slices: base, mid and apical) before and at least 5 min after the administration of gadolinium, with postcontrast images being used to calculate ECV [55, 81–83]. Native T1 mapping measurements are of particular interest in FD, as they reflect lipid deposition in both the intracellular and extracellular space [80]. The T1

relaxation time undergoes changes according to disease progression and glycosphingolipid accumulation, resulting in low native T1 values. Such a decrease can be identified in up to 90% of FD patients with LVH. Low native T1 values can also occur in up to 40% of FD patients without LVH but are associated with morphological and electrocardiographic alterations.

Additionally, native T1 reduction is strongly correlated with LV mass, making T1 mapping helpful in identifying early disease onset [55, 80]. With advancing age, it is common to find decreasing T1 values, especially in male patients and when LVH develops. In females, the reduction in T1 is more subtle and tends to remain stable with the progression of LVH [55]. Throughout FD progression, areas of fibrosis are formed in the same locations as glycosphingolipids are deposited, and as a result, there may be a pseudonormalization of native T1 values. In these cases, different values of native T1 are found in the myocardium, with lower values in the septum and higher values in the lateral walls [55].

33.3.2.2 Myocardial Strain

Alterations in the CS gradient may be an early marker for FD development. No differences in the CS gradient have been noted between sexes, and it has not been correlated with native T1 value, LVH, or LGE [55].

33.3.2.3 T2 and T2* Mapping

T2 and T2* mapping are techniques capable of identifying myocardial inflammation and assessing T2 relaxation time, influenced by the amount of water within tissues [55, 80]. T2 sequences are acquired in short axes from the apex to the base of the heart. The myocardial signal must be compared to the skeletal muscle signal to confirm the presence of relative edema and inflammation. In FD, myocardial edema increases with the development of LVH and disease progression. This edema increase, in turn, is related to a surge in troponin levels, demonstrating that inflammation plays a vital role in FD-related myocardial injury [55, 80].

33.4 Conclusions

In the current chapter, we briefly discuss the potential challenges in diagnosing FD, highlighting the role of CMR in FD. The multiparametric CMR protocol, incorporating not only the traditional sequences mainly used for myocardial morphology and function but also advanced techniques for tissue characterization, such as LGE, T1, and T2 mapping, provides unique and valuable information, improving not only the ability to detect glycosphingolipid accumulation within the myocardium but also offering meaningful insights about FD pathophysiology and its prognosis.

Compelling data also suggest that incorporating CMR in the diagnostic assessment of FD patients may identify individuals with more significant potential to respond to ERT.

Disclosures (including any relationship with industry) A.C.C., C.N.G. M, A.A.B., M.M.U.L., O.R.C.F. declare no conflict of interest.

References

1. Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, Linhart A, Sunder-Plassmann G, Ries M, Beck M. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest. 2004;34:236–42.
2. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA. 1999;281:249–54.
3. Lin HY, Chong KW, Hsu JH, et al. High incidence of the cardiac variant of Fabry disease revealed by newborn screening in the Taiwan Chinese population. Circ Cardiovasc Genet. 2009;2:450–6.
4. Spada M, Pagliardini S, Yasuda M, Tukel T, Thiagarajan G, Sakuraba H, Ponzone A, Desnick RJ. High incidence of later-onset Fabry disease revealed by newborn screening. Am J Hum Genet. 2006;79:31–40.
5. Gelb MH, Turecek F, Scott CR, Chamoles NA. Direct multiplex assay of enzymes in dried blood spots by tandem mass spectrometry for the newborn screening of lysosomal storage disorders. J Inherit Metab Dis. 2006;29:397–404.
6. Scott CR, Elliott S, Buroker N, Thomas LI, Keutzer J, Glass M, Gelb MH, Turecek F. Identification of infants at risk for developing Fabry, Pompe, or mucopolysaccharidosis-I from newborn blood spots by tandem mass spectrometry. J Pediatr. 2013;163:498–503.
7. Burlina AB, Polo G, Salviati L, et al. Newborn screening for lysosomal storage disorders by tandem mass spectrometry in North-East Italy. J Inherit Metab Dis. 2018;41:209–19.
8. Fabry Database. The Fabry mutants list. 2020. http://fabry-database.org/mutants. Accessed 10 Jan 2022.
9. Germain DP, Brand E, Burlina A, et al. Phenotypic characteristics of the p. Asn215Ser (p. N215S) GLA mutation in male and female patients with Fabry disease: a multicenter Fabry Registry study. Mol Genet Genomic Med. 2018;6(4):492–503.
10. Gal A, Beck M, Höppner W, Germain DP. Clinical utility gene card for Fabry disease—update 2016. Eur J Hum Genet. 2017;25:e1–3.
11. Doheny D, Srinivasan R, Pagant S, Chen B, Yasuda M, Desnick RJ. Fabry Disease: prevalence of affected males and heterozygotes with pathogenic GLA mutations identified by screening renal, cardiac, and stroke clinics, 1995–2017. J Med Genet. 2018;55:261–8.
12. Schiffmann R, Hughes DA, Linthorst GE, Ortiz A, Svarstad E, Warnock DG, West ML, Wanner C. Screening, diagnosis, and management of patients with Fabry disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2017;91:284–93.
13. Echevarria L, Benistan K, Toussaint A, Dubourg O, Hagege AA, Eladari D, Jabbour F, Beldjord C, De MP, Germain DP. X-chromosome inactivation in female patients with Fabry disease. Clin Genet. 2016;89:44–54.
14. Wilcox WR, Oliveira JP, Hopkin RJ, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. Mol Genet Metab. 2008;93:112–28.
15. Hopkin RJ, Cabrera G, Charrow J, et al. Risk factors for severe clinical events in male and female patients with Fabry disease treated with agalsidase beta enzyme replacement therapy: data from the Fabry Registry. Mol Genet Metab. 2016;119:151–9.

16. Whybra C, Kampmann C, Willers I, Davies J, Winchester B, Kriegsmann J, Brühl K, Gal A, Bunge S, Beck M. Anderson-Fabry disease: clinical manifestations of disease in female heterozygotes. J Inherit Metab Dis. 2001;24:715–24.
17. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med Genet. 2001;38:769–75.
18. Dobrovolny R, Dvorakova L, Ledvinova J, Magage S, Bultas J, Lubanda JC, Elleder M, Karetova D, Pavlikova M, Hrebicek M. Relationship between X-inactivation and clinical involvement in Fabry heterozygotes. Eleven novel mutations in the alpha-galactosidase A gene in the Czech and Slovak populations. J Mol Med (Berl). 2005;83:647–54.
19. Linhart A, Germain DP, Olivotto I, et al. An expert consensus document on the management of cardiovascular manifestations of Fabry disease. Eur J Heart Fail. 2020;22:1076–96.
20. Platt FM, d'Azzo A, Davidson BL, Neufeld EF, Tifft CJ. Lysosomal storage diseases. Nat Rev Dis Primers. 2018;4:27.
21. Ivanova M. Altered sphingolipids metabolism damaged mitochondrial functions: lessons learned from Gaucher and Fabry diseases. J Clin Med. 2020;9:1116.
22. Rozenfeld P, Feriozzi S. Contribution of inflammatory pathways to Fabry disease pathogenesis. Mol Genet Metab. 2017;122:19–27.
23. Caredda G, Bassareo PP, Cherchi MV, Pontone G, Suri JS, Saba L. Anderson-fabry disease: role of traditional and new cardiac MRI techniques. Br J Radiol. 2021;94:1124.
24. Hung CL, Wu YW, Lin CC, et al. 2021 TSOC expert consensus on the clinical features, diagnosis, and clinical management of cardiac manifestations of Fabry disease. Acta Cardiol Sin. 2021;37:337–54.
25. Favalli V, Disabella E, Molinaro M, et al. Genetic screening of Anderson-Fabry disease in probands referred from multispecialty clinics. J Am Coll Cardiol. 2016;68:1037–50.
26. Germain DP. Fabry disease. Orphanet J Rare Dis. 2010;5:30.
27. Zarate YA, Hopkin RJ. Fabry's disease. Lancet. 2008;372:1427–35.
28. Arends M, Wanner C, Hughes D, et al. Characterization of classical and nonclassical Fabry disease: a multicenter study. J Am Soc Nephrol. 2017;28:1631–41.
29. Schiffmann R, Fuller M, Clarke LA, Aerts JM. Is it Fabry disease? Genet Med. 2016;18:1181–5.
30. Hsu TR, Hung SC, Chang FP, et al. Later onset Fabry disease, cardiac damage progress in silence: experience with a highly prevalent mutation. J Am Coll Cardiol. 2016;68:2554–63.
31. Pieroni M, Moon JC, Arbustini E, et al. Cardiac involvement in Fabry disease: JACC review topic of the week. J Am Coll Cardiol. 2021;77:922–36.
32. Waldek S, Patel MR, Banikazemi M, Lemay R, Lee P. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. Genet Med. 2009;11:790–6.
33. Nordin S, Kozor R, Bulluck H, Castelletti S, Rosmini S, Abdel-Gadir A, Baig S, Mehta A, Hughes D, Moon JC. Cardiac Fabry disease with late gadolinium enhancement is a chronic inflammatory cardiomyopathy. J Am Coll Cardiol. 2016;68:1707–8.
34. Nordin S, Kozor R, Medina-Menacho K, et al. Proposed stages of myocardial phenotype development in Fabry disease. JACC Cardiovasc Imaging. 2019;12:1673–83.
35. Palecek T, Honzikova J, Poupetova H, Vlaskova H, Kuchynka P, Golan L, Magage S, Linhart A. Prevalence of Fabry disease in male patients with unexplained left ventricular hypertrophy in primary cardiology practice: prospective Fabry cardiomyopathy screening study (FACSS). J Inherit Metab Dis. 2014;37:455–60.
36. Monserrat L, Gimeno-Blanes JR, Marín F, et al. Prevalence of fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2007;50:2399–403.
37. Sachdev B, Takenaka T, Teraguchi H, Tei C, Lee P, McKenna WJ, Elliott PM. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. Circulation. 2002;105:1407–11.
38. Elliott P, Baker R, Pasquale F, Quarta G, Ebrahim H, Mehta AB, Hughes DA. Prevalence of Anderson-Fabry disease in patients with hypertrophic cardiomyopathy: The European Anderson-Fabry Disease survey. Heart. 2011;97:1957–60.

39. Gaggl M, Lajic N, Heinze G, Voigtländer T, Sunder-Plassmann R, Paschke E, Fauler G, Sunder-Plassmann G, Mundigler G. Screening for Fabry disease by urinary globotriaosylceramide isoforms measurement in patients with left ventricular hypertrophy. Int J Med Sci. 2016;13:340–6.
40. Maron MS, Xin W, Sims KB, Butler R, Haas TS, Rowin EJ, Desnick RJ, Maron BJ. Identification of Fabry disease in a tertiary referral cohort of patients with hypertrophic cardiomyopathy. Am J Med. 2018;131:200.e1–8.
41. Kubo T, Ochi Y, Baba Y, et al. Prevalence and clinical features of Fabry disease in Japanese male patients with diagnosis of hypertrophic cardiomyopathy. J Cardiol. 2017;69:302–7.
42. Nakao S, Takenaka T, Maeda M, Kodama C, Tanaka A, Tahara M, Yoshida A, Kuriyama M, Hayashibe H, Sakuraba H. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. N Engl J Med. 1995;333:288–93.
43. Arad M, Maron BJ, Gorham JM, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. N Engl J Med. 2005;352:362–72.
44. Chimenti C, Pieroni M, Morgante E, Antuzzi D, Russo A, Russo MA, Maseri A, Frustaci A. Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. Circulation. 2004;110:1047–53.
45. Havndrup O, Christiansen M, Stoevring B, et al. Fabry disease mimicking hypertrophic cardiomyopathy: genetic screening needed for establishing the diagnosis in women. Eur J Heart Fail. 2010;12:535–40.
46. Hagège AA, Caudron E, Damy T, et al. Screening patients with hypertrophic cardiomyopathy for Fabry disease using a filter-paper test: the FOCUS study. Heart. 2011;97:131–6.
47. Mawatari K, Yasukawa H, Oba T, et al. Screening for Fabry disease in patients with left ventricular hypertrophy. Int J Cardiol. 2013;167:1059–61.
48. Terryn W, Deschoenmakere G, De KJ, et al. Prevalence of Fabry disease in a predominantly hypertensive population with left ventricular hypertrophy. Int J Cardiol. 2013;167:2555–60.
49. Chien YH, Bodamer OA, Chiang SC, Mascher H, Hung C, Hwu WL. Lysoglobotriaosylsphingosine (lyso-Gb3) levels in neonates and adults with the Fabry disease later-onset GLA IVS4 + 919GA mutation. J Inherit Metab Dis. 2013;36:881–5.
50. Hagège A, Réant P, Habib G, Damy T, Barone-Rochette G, Soulat G, Donal E, Germain DP. Fabry disease in cardiology practice: literature review and expert point of view. Arch Cardiovasc Dis. 2019;112:278–87.
51. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: management and treatment recommendations for adult patients. Mol Genet Metab. 2018;123:416–27.
52. Kozor R, Grieve SM, Tchan MC, Callaghan F, Hamilton-Craig C, Denaro C, Moon JC, Figtree GA. Cardiac involvement in genotype-positive Fabry disease patients assessed by cardiovascular MR. Heart. 2016;102:298–302.
53. Sado DM, White SK, Piechnik SK, et al. Identification and assessment of Anderson-Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping. Circ Cardiovasc Imaging. 2013;6:392–8.
54. Moon JC, Sachdev B, Elkington AG, McKenna WJ, Mehta A, Pennell DJ, Leed PJ, Elliott PM. Gadolinium enhanced cardiovascular magnetic resonance in Anderson-Fabry disease. Evidence for a disease specific abnormality of the myocardial interstitium. Eur Heart J. 2003;24:2151–5.
55. Deva DP, Hanneman K, Li Q, Ng MY, Wasim S, Morel C, Iwanochko RM, Thavendiranathan P, Crean AM. Cardiovascular magnetic resonance demonstration of the spectrum of morphological phenotypes and patterns of myocardial scarring in Anderson-Fabry disease. J Cardiovasc Magn Reson. 2016;18:14.
56. Camporeale A, Pieroni M, Pieruzzi F, et al. Predictors of clinical evolution in prehypertrophic Fabry disease. Circ Cardiovasc Imaging. 2019;12:e008424.
57. Knott KD, Augusto JB, Nordin S, et al. Quantitative myocardial perfusion in Fabry disease. Circ Cardiovasc Imaging. 2019;12:e008872.

58. Mathur S, Dreisbach JG, Karur GR, Iwanochko RM, Morel CF, Wasim S, Nguyen ET, Wintersperger BJ, Hanneman K. Loss of base-to-apex CS gradient assessed by cardiovascular magnetic resonance in Fabry disease: relationship to T1 mapping, late gadolinium enhancement and hypertrophy. J Cardiovasc Magn Reson. 2019;21:45.
59. Desnick RJ, Brady R, Barranger J, Collins AJ, Germain DP, Goldman M, Grabowski G, Packman S, Wilcox WR. Fabry disease, an underrecognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. Ann Intern Med. 2003;138:338–46.
60. Motwani M, Banypersad S, Woolfson P, Waldek S. Enzyme replacement therapy improves cardiac features and severity of Fabry disease. Mol Genet Metab. 2012;107:197–202.
61. Arends M, Biegstraaten M, Hughes DA, et al. Retrospective study of long-term outcomes of enzyme replacement therapy in Fabry disease: analysis of prognostic factors. PLoS One. 2017;12:e0182379.
62. Koeppe S, Neubauer H, Breunig F, Weidemann F, Wanner C, Sandstede J, Machann W, Hahn D, Köstler H, Beer M. MR-based analysis of regional cardiac function in relation to cellular integrity in Fabry disease. Int J Cardiol. 2012;160:53–8.
63. Weidemann F, Niemann M, Breunig F, Herrmann S, Beer M, Störk S, Voelker W, Ertl G, Wanner C, Strotmann J. Long-term effects of enzyme replacement therapy on fabry cardiomyopathy: evidence for a better outcome with early treatment. Circulation. 2009;119:524–9.
64. Beer M, Weidemann F, Breunig F, Knoll A, Koeppe S, Machann W, Hahn D, Wanner C, Strotmann J, Sandstede J. Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy. Am J Cardiol. 2006;97:1515–8.
65. Hughes DA, Elliott PM, Shah J, Zuckerman J, Coghlan G, Brookes J, Mehta AB. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomized, double-blind, placebo-controlled clinical trial of agalsidase alfa. Heart. 2008;94:153–8.
66. Seydelmann N, Liu D, Krämer J, et al. High-sensitivity troponin: a clinical blood biomarker for staging cardiomyopathy in Fabry disease. J Am Heart Assoc. 2016;5:e002839.
67. Tower-Rader A, Jaber WA. Multimodality imaging assessment of Fabry disease. Circ Cardiovasc Imaging. 2019;12:e009013.
68. Namdar M, Steffel J, Jetzer S, et al. Value of electrocardiogram in the differentiation of hypertensive heart disease, hypertrophic cardiomyopathy, aortic stenosis, amyloidosis, and Fabry disease. Am J Cardiol. 2012;109:587–93.
69. Kampmann C, Wiethoff CM, Martin C, Wenzel A, Kampmann R, Whybra C, Miebach E, Beck M. Electrocardiographic signs of hypertrophy in fabry disease-associated hypertrophic cardiomyopathy. Acta Paediatr Suppl. 2002;91:21–7.
70. Namdar M. Electrocardiographic changes and arrhythmia in Fabry disease. Front Cardiovasc Med. 2016;3:7.
71. Namdar M, Steffel J, Vidovic M, Brunckhorst CB, Holzmeister J, Lüscher TF, Jenni R, Duru F. Electrocardiographic changes in early recognition of Fabry disease. Heart. 2011;97:485–90.
72. Ikari Y, Kuwako K, Yamaguchi T. Fabry's disease with complete atrioventricular block: histological evidence of involvement of the conduction system. Br Heart J. 1992;68:323–5.
73. Authors/Task Force Members, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. Eur Heart J. 2014;35:2733–79.
74. Linhart A, Palecek T, Bultas J, et al. New insights in cardiac structural changes in patients with Fabry's disease. Am Heart J. 2000;139:1101–8.
75. Linhart A, Kampmann C, Zamorano JL, Sunder-Plassmann G, Beck M, Mehta A, Elliott PM. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. Eur Heart J. 2007;28:1228–35.
76. Graziani F, Laurito M, Pieroni M, et al. Right ventricular hypertrophy, systolic function, and disease severity in Anderson-Fabry disease: an echocardiographic study. J Am Soc Echocardiogr. 2017;30:282–91.

77. Niemann M, Breunig F, Beer M, et al. The right ventricle in Fabry disease: natural history and impact of enzyme replacement therapy. Heart. 2010;96:1915–9.
78. Niemann M, Liu D, Hu K, et al. Prominent papillary muscles in Fabry disease: a diagnostic marker? Ultrasound Med Biol. 2011;37:37–43.
79. Boyd AC, Lo Q, Devine K, Tchan MC, Sillence DO, Sadick N, Richards DA, Thomas L. Left atrial enlargement and reduced atrial compliance occurs early in Fabry cardiomyopathy. J Am Soc Echocardiogr. 2013;26:1415–23.
80. Militaru S, Ginghina C, Popescu BA, Saftoiu A, Linhart A, Jurcut R. Multimodality imaging in Fabry cardiomyopathy: from early diagnosis to therapeutic targets. Eur Heart J Cardiovasc Imaging. 2018;19:1313–22.
81. Coelho-Filho OR, Mongeon F-P, Mitchell R, Moreno H, Nadruz W, Kwong R, Jerosch-Herold M. Role of transcytolemmal water-exchange in magnetic resonance measurements of diffuse myocardial fibrosis in hypertensive heart disease. Circ Cardiovasc Imaging. 2013;6:134–41.
82. Mongeon F-P, Jerosch-Herold M, Coelho-Filho OR, Blankstein R, Falk RH, Kwong RY. Quantification of extracellular matrix expansion by CMR in infiltrative heart disease. JACC Cardiovasc Imaging. 2012;5:897–907.
83. Neilan TG, Coelho-Filho OR, Shah RV, et al. Myocardial extracellular volume fraction from T1 measurements in healthy volunteers and mice. JACC Cardiovasc Imaging. 2013;6:672–83.

Chapter 34
Pharmacological Therapy in Fabry Disease

Joseph Bruno Bidin Brooks

34.1 Introduction

Fabry disease (FD) is a rare X-linked multisystemic lysosomal storage disorder caused by a deficiency of the lysosomal hydrolase α-galactosidase A (GLA), resulting in the storage of globotriaosylceramide (GB3) and globotriaosylsphingosine (lyso-GB3, deacylated form). FD estimated birth prevalence varies from 1:40,000 to 170,000. More than 1000 variants in the α-galactosidase A (GLA) gene have been described, most of which appear in late-onset form (nonclassic) families other than early-onset form (classic) families. In classic males, FD may present itself during childhood or adolescence with characteristic features such as acroparesthesia, abdominal pain, hypohidrosis, angiokeratoma, cornea verticillata, and microalbuminuria [1–6].

At a later age, progressive kidney disease, hypertrophic cardiomyopathy, and cerebrovascular disease can occur. Heterozygous females may also be affected and generally demonstrate a more variable phenotype. In both genders, life expectancy is diminished, although this is more apparent in males [7, 8]. Cardiac indicators of FD progression are listed in Table 34.1 [9].

Nonclassical FD patients and female patients have varied phenotypes, such as age of disease onset and disease progression. Gene variants and reduced GLA activity do not express the complete set of signs and symptoms. Patients with nonclassical FD may present with one single nonspecific symptom, such as chronic kidney disease (CKD), left ventricular hypertrophy (LVH), or cerebral vascular infarct (CVI) [10].

Once the diagnosis is confirmed, patients should be referred to a specialized, multidisciplinary Fabry center for initial examination, treatment planning, and

J. B. B. Brooks (✉)
Department of Function and Structure, Medical School, Universidade Metropolitana de Santos—UNIMES, São Paulo, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_34

Table 34.1 Cardiac indicators of FD progression. Adapted from Hughes et al.

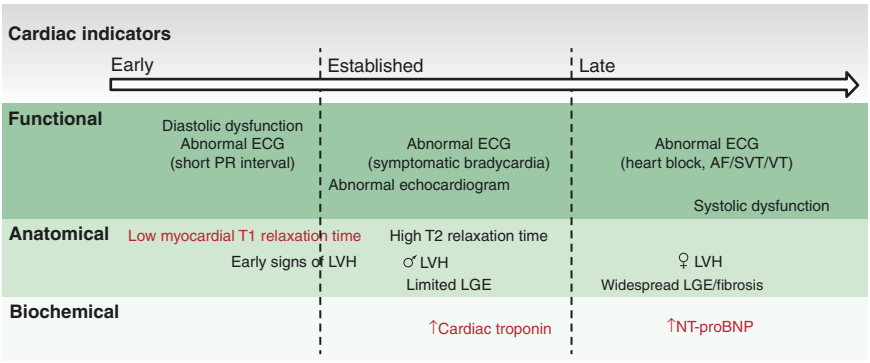
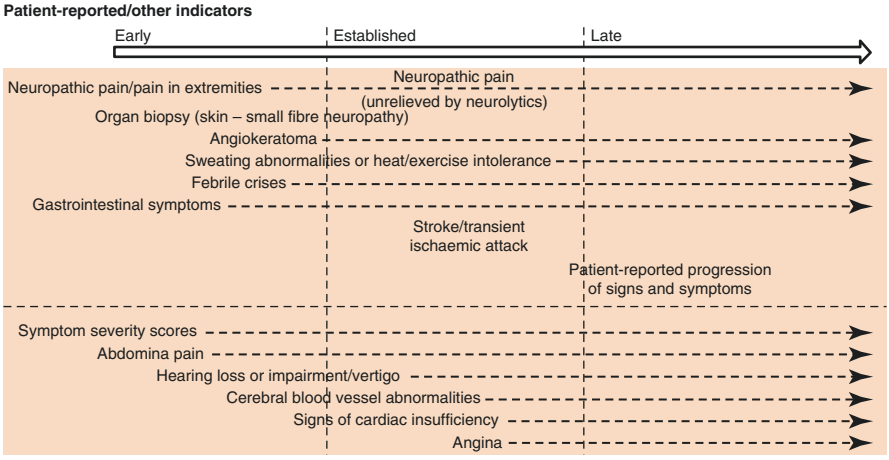


Table 34.2 Indicators for early therapy achieved. Modified from [10]



initiation of treatment. Indicators for early therapy based on symptoms are listed in Table 34.2. The following therapeutic goals should be achieved: reduction of complaints and symptoms, delay in the progression of organ manifestations, improvement in quality of life, and normalization of life expectancy.

Supportive therapy (symptoms or palliative treatment), that is, nonspecific therapy for FD patients, can improve symptoms. However, it does not treat the main cause (GLA deficiency), which, if left untreated, may lead to premature death.

Currently, there are two approved drugs for the specific treatment of FD, enzyme replacement therapy (ERT), and pharmacological chaperone therapy (migalastat). Both drugs ultimately aim to reduce the intracellular accumulation of GB3, replacing the deficient GLA function. Consequently, these therapies facilitate adequate transport and increase the enzymatic activity of GLA within the lysosome.

Table 34.3 Classes of recommendation

Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Recommended/ Indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIA	Weight of evidence/opinion is in favor of usefulness/efficacy	Should be considered
Class IIB	Usefulness/efficacy is less well established by evidence/ opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended

34.1.1 Classes of Recommendation

The usual class of recommendations for initiating a drug or performing a test or procedure is outlined in Table 34.3. This is the scale adopted by most guidelines in medicine [11].

34.2 Enzyme Replacement Therapy for FD Treatment

In 2001, the European Medicines Agency (EMA) authorized ERT to treat FD patients with two forms of the enzyme. Agalsidase alpha produced by gene activation in human fibroblasts is administered at a dose of 0.2 mg/kg intravenously every 2 weeks (Replagal®, Shire HGT, Inc., Cambridge, MA, USA) and is approved in many countries throughout the world, although not by the US Food and Drug Administration. Agalsidase beta is a recombinant product from Chinese hamster ovary cells at a dose of 1 mg/kg every 2 weeks (Fabrazyme®, Sanofi Genzyme, Cambridge, MA, USA) and is approved in Europe, the USA, and many other countries. In 2014, Fabagal®, and agalsidase beta manufactured by ISU Abxis (Seongnam-si, Gyeonggi-do, South Korea), ISU Global, was approved in South Korea only. After approximately two decades of experience, ERT has modified the natural history of the FD. ERT is indicated for patients with irreversible disease manifestations to stop or slow down the progression of damage due to Gb3 deposition. No studies to date have shown convincing evidence on clinical grounds for superiority or noninferiority of either of these enzymes in head-to-head comparative studies. ERT may decrease cardiac mass and reduce renal GB3 accumulation, while its effects on nervous system disease and renal function are less well established. Based upon these insights, early initiation of therapy is preferred. However, “early initiation of therapy” has not been defined until now. The response to ERT is rarely complete: not passing the blood–brain barrier; antidrug antibodies with neutralizing effect and tissue fibrosis (renal and cardiac). In addition, it may be questioned

whether patients with end-stage disease or comorbidities may still benefit from treatment. Several local and national guidelines and protocols exist with criteria to start ERT, and some also define stopping criteria for ERT [12–32].

34.2.1 Consensus Criteria for Initiation of ERT

The differentiation should be made between male and female patients and between patients with classical and nonclassical diseases. Target organ involvement-specific criteria for treatment initiation are listed in Table 34.3.

34.2.2 Consensus Criteria to Stop or Not Start ERT

The criteria to stop or not start ERT are summarized in Table 34.4 [33].

Recommendations for initiation of ERT by clinical involvement, such as in adult male and female patients with classic (early-onset) or nonclassical (later-onset) variants, are also listed in Table 34.5 [12].

Table 34.4 Recommendations for the initiation, not starting, and to stop enzyme replacement therapy

Evidence class and Recommendations	Classical FD, males	Nonclassical FD, males	Classical FD, females	Nonclassical FD, females
Renal				
– Microalbuminuria[a]	Class I		Class IIB	
– Proteinuria[a]	Class I		Class IIB	
– Renal insufficiency (GFR 60–90)[b]	Class I	Class IIA		Class IIB
– Renal insufficiency (GFR 45–60)[b]	All class IIB			
Cardiac				
– Cardiac hypertrophy (MWT > 12 mm) without (or only minimal signs of) fibrosis	All class I			
– Signs of cardiac rhythm disturbances[c]	All class I			
Central nervous system				
– White matter lesions	All class IIB			
– Transient ischemic attack/stroke	All class IIA			
– Hearing loss, corrected for age	All class IIB			

Table 34.4 (continued)

Evidence class and Recommendations	Classical FD, males	Nonclassical FD, males	Classical FD, females	Nonclassical FD, females
Pain				
– Neuropathic pain	All class IIA			
– Neuropathic pain even if completely controlled with pain medication	All class IIB			
Gastrointestinal				
– Gastrointestinal symptoms	All class IIA if <16 years of age All class IIB if >16 years of age			
Criteria for not starting ERT				*Class*
– Advanced cardiac disease with extensive fibrosis if the cardiac disease is the sole treatment indication[d]				I
– End-stage renal disease, without an option for renal transplantation, in combination with advanced heart failure (NYHA class IV)				IIA
– End-stage Fabry disease or other comorbidities with a life expectancy of <1 year				IIB
– Severe cognitive decline of any cause				IIB
Stop criteria				
– Noncompliance > 50% of infusions				I
– Failure to attend regularly (according to local guidelines) at follow-up visits				I
– Persistent life-threatening or severe infusion reactions that do not respond to prophylaxis, e.g., anaphylaxis				I
– Patient request				I
– End-stage renal disease, without an option for renal transplantation, in combination with advanced heart failure (NYHA class IV)				IIA
– End-stage Fabry disease or other comorbidities with a life expectancy of <1 year				IIB
– Severe cognitive decline of any cause				IIB
– Lack of response for 1 year when the sole indication for ERT is neuropathic pain while receiving maximum supportive care[e]				IIB

[a] According to international guidelines of kidney disease, KDIGO criteria.
[b] In mL/min/1.73 m^2 corrected for age (>40 years: −1 mL/min/1.73 m^2/year)
[c] Sinus bradycardia, AF, repolarization disorders, *GFR* glomerular filtration rate, *MWT* maximal wall thickness
[d] Consistent with Fabry disease and not fully explained by other pathology; *NYHA* New York Heart Association
[e] Does not apply to male patients with the classical phenotype

Table 34.5 Recommendations for ERT in adult male and female patients with classic (early-onset) or nonclassical (later-onset) variants. Adapted from Ortis et al.

Adult Fabry patient	Recommendation for initiation treatment
Classic (early-onset)	
Male, symptomatic or asymptomatic Female, symptomatic	ERT should be considered and is appropriate in all patients at any age of presentation Signs/symptoms suggesting major organ involvement – Neuropathic pain, – Proteinuria/albuminuria, evidence of renal impairment (may require renal biopsy) – Stroke or TIA – Symptomatic cardiac disease not due to other causes (dyspnea, palpitations, syncope, chest pain) – Recurrent diarrhea, chronic, disabling GI dysfunction – Exercise intolerance and impaired sweating
Female, asymptomatic	ERT should be considered if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or CNS – Renal disease: decreased GFR (<90 mL/min/1.73 m^2 adjusted for age > 40 years [GFR category ≥ G2], persistent albuminuria > 30 mg/g [albuminuria category A2 or A3]), podocyte foot process effacement or glomerulosclerosis on renal biopsy, moderate or severe GL-3 inclusions in a range of renal cell types – Silent strokes, cerebral white matter lesions (on brain MRI) – Asymptomatic cardiac disease (cardiomyopathy or arrhythmia, cardiac fibrosis on contrast cardiac MRI)
Nonclassic (later-onset)	
Male and female	ERT should be considered and is appropriate if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or CNS, even in the absence of typical symptoms. The abnormalities may require histological assessment or biochemical evidence of GB-3 accumulation

34.3 Chaperone Oral Therapy for FD

Currently, migalastat (Galafold™; Amicus Therapeutics, Cranbury, NJ, USA) is the only oral treatment molecule for Fabry disease, given 123 mg every other day. Migalastat was approved by the EMA in 2016 and the Food Drug Administration (FDA) USA in 2018 for the treatment of patients aged ≥12 years and estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 with susceptible GLA mutations. In Brazil, it was approved by ANVISA in 2019 for ≥16 years. Migalastat is not recommended in pregnant or breastfeeding patients [34].

Migalastat is a low molecular weight iminosugar analogous to the terminal galactose residue present in GL-3 that selectively and reversibly binds with high affinity to active sites of certain mutant forms of GLA. The binding of migalastat stabilizes these mutant forms of GLA in the endoplasmic reticulum and facilitates

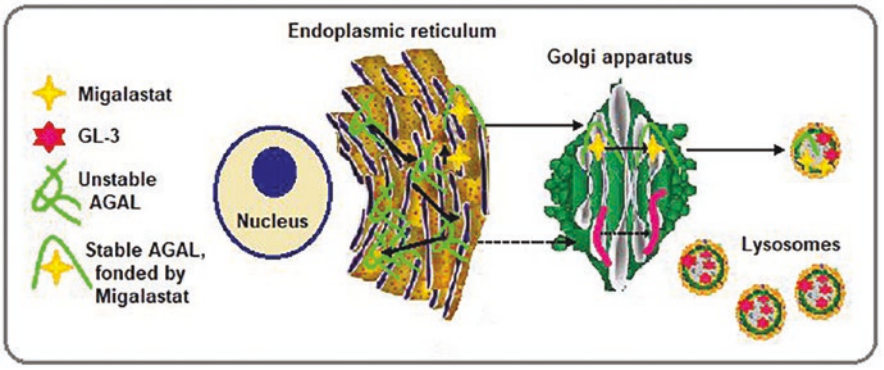


Fig. 34.1 Overview of migalastat's mechanism of action. *GLA* alpha-galactosidase A, *GB-3* globotriaosylceramide. (*) Synthesis of misfolded GLA. (**) Accumulation of misfolded GLA

their proper transport into lysosomes. Once in lysosomes, migalastat dissociates from the receptor (due to the more acidic pH) and restores the correct activity of the enzyme, which leads to the catabolism of GB3 and its substrates and prevents their intracellular accumulation. An overview of migalastat's mechanism of action is shown in Fig. 34.1 [34–37].

The susceptibility of GLA mutations to migalastat is determined by an "in vitro" good laboratory practice (GLP) pharmacogenetic assay, which has been clinically validated. This assay used human embryonic kidney 293 (HEK 293) cells that were transfected with DNA plasmids individually containing GLA to measure the increase in GLA activity in response to migalastat. Susceptible migalastat mutations are defined as mutations that translate into mutant forms of GLA that, in the presence of 10 μm/L migalastat, exhibit an increase in enzyme activity ≥1.2-fold above baseline and an absolute increase ≥3% of the enzymatic activity quantified as a percentage of the enzymatic activity of the "wild type" (wild type) α-galactosidase A. It is estimated that 35–50% of FD patients have mutations that are susceptible to treatment with migalastat. To check if the mutation is susceptible, just access the website https://www.galafoldamenabilitytable.com/hcp [13].

Migalastat was evaluated through two pivotal studies. The FACETS study evaluated the efficacy of migalastat compared to placebo in ERT-naïve patients who had migalastat-susceptible GLA mutations [38, 39]. In this study, patients were randomized to treatment with migalastat or placebo and assessed at the 6-month follow-up and 18-month follow-up. After the 18-month randomization period, patients in the placebo group started treatment with migalastat. Therefore, between 18 and 24 months, all patients were treated with migalastat. At 6 months of treatment, a statistically significant reduction in the inclusion of GB3 in renal interstitial

capillaries was observed. Treatment with migalastat also demonstrated a decrease in the mean total volume of GB3 inclusion in podocytes at baseline renal biopsies compared to 6 months, and this reduction is correlated with the reduction in the mean volume of podocytes. Renal dysfunction is present in most patients being treated for Fabry disease, progresses over time, and can lead to end-stage renal disease, as already mentioned in the text above; however, migalastat has the potential to stabilize or decrease the decline in kidney function, which is an important goal of treatment in Fabry disease. After 18 months, there was a significant reduction in the mean left ventricular mass index (LVMI) compared to baseline. These results were maintained up to 24 months of follow-up.

Gastrointestinal symptoms decreased in three domains (diarrhea, reflux, and indigestion) of five domains in the GSRS. An improvement in diarrhea was found after 6 months of migalastat therapy compared to placebo, and this benefit was sustained at 24 months. These results were also confirmed in the subgroup of men with classic phenotypes [38, 39].

In the ATTRACT study, ERT-experienced patients with susceptible GLA mutations were randomized to migalastat or to continue on ERT. In this study, renal function and plasma lyso-GB3 levels were maintained for 18 months in patients receiving migalastat or ERT. The mean change from baseline in 24-h proteinuria was approximately fourfold lower in patients on migalastat therapy than in those receiving ERT after 18 months [40].

Treatment with migalastat was associated with better cardiac outcomes than ERT. Migalastat significantly reduced the mean left ventricular mass index (LVMI) at 18 months. In open-label extension studies, iMVE decreased after 30 months in all participants (mean change, −3.8 g/m^2; 95% CI) and in participants with baseline LVH (mean change, −10.0 g/m^2; 95% CI). The reduction after 30 months among participants with baseline LVH was statistically significant [40]. The results demonstrated the durability of the iMVE response to long-term migalastat treatment.

In a study of seven male FD patients who switched from ERT to migalastat, a significant decrease in iMVE was also observed after 1 year of migalastat treatment, while plasma lyso-GB3 remained stable [41]. The estimated glomerular filtration rate (eGFR) was stable, and proteinuria decreased significantly. Two patients with pain at baseline reported an improvement in pain during ERT and further improvement during migalastat therapy. In conclusion, switching from ERT to migalastat is effective, safe, and well tolerated [13, 40, 42].

After a post hoc analysis, we evaluated long-term renal measures associated with migalastat therapy in treatment-naïve and ERT-experienced patients with Fabry disease and treatment-susceptible GLA variants. In conclusion, renal function was

stable during long-term treatment with migalastat (≤8.6 years), regardless of treatment status, sex, or phenotype. Early treatment should be encouraged to stabilize or delay the decline in renal function in patients with Fabry disease [41].

Compared to ERT, migalastat therapy has considerable advantages, making it a first-line therapy [34, 43, 44]:

1. Convenient oral regimen, thus eliminating the need for lifelong IV infusions and complications that have been associated with IV ERT.
2. The nonimmunogenic nature of migalastat prevents antibody-related adverse events, such as those observed with ERT.
3. Small molecule: migalastat has improved cellular and tissue distribution and a high potential to cross the blood–brain barrier (as evidenced in Fabry transgenic mice), which may aid in the treatment of nervous system-borne disease symptoms central.
4. The improved efficacy of migalastat compared to ERT in reducing iMVE suggests that migalastat may be more effective than ERT in penetrating cardiac tissue.
5. As an orally administered therapy, migalastat may also facilitate earlier intervention than ERT in patients with Fabry disease.
6. Migalastat allows for sustained and stable enzyme levels that more closely mimic those of endogenous enzymes, while ERT leads to fluctuating and intermittent enzyme activity.
7. Indicated for patients with classic or nonclassical presentations.

A summary of the eligibility for FD patient therapy with either ERT or migalastat is listed in Table 34.6.

Table 34.6 Summary of eligibility for FD patient therapy

ERT		Migalastat
	Confirmed diagnosis Clinical eligibility criteria	
Venous access GFR not specified Aged >8 years Considerations around childbearing Compliance if self-therapy		Amenability GFR>30 Aged >16 years ERT hypersensitivity Compliance
	First line or switch	

34.4 Symptomatic Therapies

Symptomatic treatment is a supportive intervention and helps the proper functioning of the target organs of the disease (renal, cardiac, and neurological), as well as relieving clinical symptoms if indicated, to clinically manage the other complications of Fabry disease-induced chronic tissue injury. Adjunctive support for the management of FD patients is listed in Table 34.7 [12]. Secondary prevention and lifestyle modification are also important for patient care and should be considered.

Table 34.7 Adjunctive support for the management of adult patients with Fabry disease. Adapted from Ortis et al.

Organ/system	Adjunctive/symptomatic therapy and preventative measures
General	Genetic counseling (at diagnosis and adolescence/prepregnancy, during pregnancy, or periodically for new issues)
Renal	The standard management approach for CKD – ACEI or ARB to target albuminuria level < 30 mg/g creatinine if baseline 30–300 mg/g or <300 mg/g if baseline > 300 mg/g (roughly equivalent to proteinuria > 500 mg/g); great care should be taken if the patient has baseline hypotension; dietary salt restriction – General management of CKD regarding statin indication and CKD-MBD prevention and management – Consider the assessment of 25 OH vitamin D levels and replacement therapy if deficient – Dialysis or kidney transplantation for patients entering renal failure (donor screened negative for Fabry disease if living-related)
Cardiac	Consider ACEI or ARB; beta-blockers should be used with caution and amiodarone avoided in patients receiving ERT • If symptomatic bradycardia/chronotropic incompetence or significant AV conduction impairment, consider permanent cardiac pacing • If evidence of atrial fibrillation, lifetime anticoagulation should be initiated, maintenance of sinus rhythm should be preferred while the use of amiodarone should be avoided, if possible • If evidence or strong suspicion of malignant arrhythmias, consider implantable cardioverter-defibrillator
Cerebral vascular	Stroke prophylaxis with antithrombotic agents (aspirin or clopidogrel) is indicated as secondary prevention; no data are currently available regarding primary prevention • Stroke prophylaxis with anticoagulants (warfarin or the new anticoagulant drugs in the absence of kidney failure), when needed, e.g., patients with atrial fibrillation
Peripheral nervous system	Individualize strategy for neuropathic pain management • First-line agents include anticonvulsants (e.g., carbamazepine, gabapentin, pregabalin); other drugs can be considered according to current international recommendations for neuropathic pain [19] • Pain crises: consider opioid agonists (care needed to avoid worsening GI disturbances) • Avoid pain triggers with lifestyle modifications (e.g., avoid temperature extremes, maintain proper hydration, use air conditioning, cooling vests, facial mist/spray)

Table 34.7 (continued)

Organ/system	Adjunctive/symptomatic therapy and preventative measures
Gastrointestinal	Delayed gastric emptying and dyspepsia symptoms may be successfully treated with metoclopramide and H-2 blockers, respectively; dysmotility and diarrhea may be treatable with dietary changes (increased fiber intake, more frequent and smaller meals) and pharmacotherapy
Pulmonary	Bronchodilators to provide relief of airway obstruction
Ophthalmological	Polarized glasses can help manage difficulty in driving at night (headlight splaying); artificial tears ointment
Auditory	Hearing aids, cochlear implants
Dermatological	Laser or surgical treatment for angiokeratomas; compression stockings may improve lymphedema

34.5 Monitoring FD Patients

Monitoring FD patients should start at diagnosis with appropriate intervals, incorporating measures that effectively capture the expected progression of the disease, if genotype and phenotype correlation data are available. Recommended assessments and schedules for monitoring organ involvement in FD patients are listed in Table 34.8 [12].

In conclusion, the clinical heterogeneity of FD requires an individualized approach to patient care. Genotype, phenotype, sex, family history, and specific clinical symptoms need to be taken into account when indicating therapy.

Long-term management in FD patients involves ERT and chaperone oral therapy in amenable gene variants and must be considered individually. Symptomatic treatment should be considered at each clinical evaluation to minimize target organ-specific complications and improve quality of life.

Table 34.8 Recommended assessments and schedule for monitoring organ involvement in FD patients. Adapted from Ortis et al.

Adult Fabry patient	Recommendation for initiation treatment
Classic (early-onset)	
Male, symptomatic or asymptomatic Female, symptomatic	ERT should be considered and is appropriate in all patients at any age of presentation Signs/symptoms suggesting major organ involvement – Neuropathic pain, – Proteinuria/albuminuria, evidence of renal impairment (may require renal biopsy) – Stroke or TIA – Symptomatic cardiac disease not due to other causes (dyspnea, palpitations, syncope, chest pain) – Recurrent diarrhea, chronic, disabling GI dysfunction – Exercise intolerance and impaired sweating
Female, asymptomatic	ERT should be considered if there is a laboratory, histological, or imaging evidence of injury to the kidney, heart, or the CNS – Renal disease: decreased GFR (<90 mL/min/1.73 m^2 adjusted for age > 40 years [GFR category ≥ G2], persistent albuminuria > 30 mg/g [albuminuria category A2 or A3]), podocyte foot process effacement or glomerulosclerosis on renal biopsy, moderate or severe GL-3 inclusions in a range of renal cell types – Silent strokes, cerebral white matter lesions (on brain MRI) – Asymptomatic cardiac disease (cardiomyopathy or arrhythmia, cardiac fibrosis on contrast cardiac MRI)
Non-classic (later-onset)	
Male and female	ERT should be considered and is appropriate if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or CNS, even in the absence of typical symptoms. The abnormalities may require histological assessment or biochemical evidence of GB-3 accumulation

References

1. Desnick RJ, Ioannou YA, Eng ME. α-Galactosidase A deficiency: Fabry disease. The online metabolic and molecular bases of inherited disease. 2007. p. 3733–74.
2. Meikle PJ, Hopwood JJ, Clague AE, Carey WF, et al. Prevalence of lysosomal storage disorders. JAMA. 1999;281(3):249–54.
3. Poorthuis BJ, Wevers RA, Kleijer WJ, Groener JE, de Jong JG, van Weely S, et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet. 1999;105(1–2):151–6.
4. Van der Tol L, Smid BE, Poorthuis BJHM, Biegstraaten M, Lekanne Deprez RH, Linthorst GE, et al. A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance. J Med Genet. 2014;51(1):1–9.
5. Brady RO, Gal AE, Bradley RM, Martensson E, Warshaw AL, Laster L, et al. Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficiency. N Engl J Med. 1967;276(21):1163–7.
6. Kint JA. Fabry's disease: alpha-galactosidase deficiency. Science. 1970;167(3922):1268–9.
7. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. J Med Genet. 2001;38(11):750–60.
8. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med Genet. 2001;38(11):769–75.

9. Hughes DA, Aguiar P, Deegan PB, Ezgu F, Frustaci A, Lidove O, et al. Early indications of disease progression in Fabry disease that may indicate the need for specific-disease treatment initiation: findings from the opinion-based PREDICT-FD modified Delphi consensus initiative. BMJ Open. 2020;10:e035182.
10. Desnick RJ, Brady R, Barranger J, Collins AJ, Germain DP, Goldman M, et al. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. Ann Intern Med. 2003;138(4):338–46.
11. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949–3003.
12. Ortiz A, Germain DP, Desnick RJ, Politei J, Mauer M, Burlina A, et al. Fabry disease revisited: management and treatment recommendations for adult patients. Mol Genet Metab. 2018;123:416–27.
13. Azevedo O, Gago MF, Miltenberger-Miltenyi G, Sousa N, Cunha D. Fabry disease therapy: state-of-the-art and current challenges. Int J Mol Sci. 2020;22(1):206. https://doi.org/10.3390/ijms22010206.
14. Lenders M, Brand E. Fabry disease: the current treatment landscape. Drugs. 2021;81(6):635–45.
15. Germain DP, Charrow J, Desnick RJ. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. J Med Genet. 2015;52(5):353–8.
16. Beck M, Hughes D, Kampmann C, et al. Long-term outcomes with agalsidase alfa enzyme replacement therapy: analysis using deconstructed composite events. Mol Genet Metab Rep. 2017;14:31–5.
17. Lidove O, Wets M, Pintos-Morell G. Effects of enzyme replacement therapy in Fabry disease—a comprehensive review of the medical literature. Genet Med. 2010;12(11):668–79.
18. Lenders M, Brand E. Effects of enzyme replacement therapy and antidrug antibodies in patients with Fabry disease. J Am soc Nephrol. 2018;29(9):2265–78.
19. Vedder AC, Linthorst GE, Houge G, Groener JE, Ormel EE, Bouma BJ, et al. Treatment of Fabry disease: outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg. PLoS One. 2007;2(7):e598.
20. Sirrs SM, Bichet DG, Casey R, Clarke JT, Lemoine K, Doucette S, et al. Outcomes of patients treated through the Canadian Fabry disease initiative. Mol Genet Metab. 2014;111(4):499–506.
21. Banikazemi M, Bultas J, Waldek S, Wilcox WR, Whitley CB, McDonald M, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann Intern Med. 2007;146(2):77–86.
22. Bierer G, Balfe D, Wilcox WR, Mosenifar Z, et al. Improvement in serial cardiopulmonary exercise testing following enzyme replacement therapy in Fabry disease. J Inherit Metab Dis. 2006;29(4):572–9.
23. Hughes DA, Elliot PM, Shah J, Zuckerman J, Coghlan G, Brookes J, et al. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomized, double-blind, placebo-controlled clinical trial of agalsidase alfa. Heart. 2008;94(2):153–8.
24. Rombach SM, Smid BE, Linthorst GE, Dijkgraaf MG, Hollak CEM, et al. Natural course of Fabry disease and the effectiveness of enzyme replacement therapy: a systematic review and meta-analysis: effectiveness of ERT in different disease stages. J Inherit Metab Dis. 2014;37(3):341–52.
25. Thurberg BL, Rennke H, Colvin RB, Dikman S, Gordon RE, Collins AB, et al. Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. Kidney Int. 2002;62(6):1933–46.
26. Germain DP, Waldek S, Banikazemi M, Bushinsky DA, Charrow J, Desnick RJ, et al. Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. J Am Soc Nephrol. 2007;18(5):1547–57.
27. Tøndel C, Bostad L, Larsen KK, Hirth A, Vikse BE, Houge G, et al. Agalsidase benefits renal histology in young patients with Fabry disease. J Am Soc Nephrol. 2013;24(1):137–48.

28. Rombach SM, Smid BE, Bouwman MG, Linthorst GE, Dijkgraaf MG, Hollak CE, et al. Long term enzyme replacement therapy for Fabry disease: effectiveness on kidney, heart and brain. Orphanet J Rare Dis. 2013;8:47. https://doi.org/10.1186/1750-1172-8-47.
29. Buechner S, Moretti M, Burlina A, Cei G, Manara R, Ricci R, et al. Central nervous system involvement in Anderson-Fabry disease: a clinical and MRI retrospective study. J Neurol Neurosurg Psychiatry. 2008;79(11):1249–54.
30. Jardim L, Vedolin L, Schwartz IV, Burin MG, Cecchin C, Kalakun L, et al. CNS involvement in Fabry disease: clinical and imaging studies before and after 12 months of enzyme replacement therapy. J Inherit Metab Dis. 2004;27(2):229–40.
31. Jardim LB, Aesse F, Vedolin L, Pitta-Pinheiro C, Marconato J, Burin MG, et al. White matter lesions in Fabry disease before and after enzyme replacement therapy: a 2-year follow-up. Arq Neuropsiquiatr. 2006;64(3B):711–7.
32. Weidemann F, Niemann M, Störk S, Breunig F, Beer M, Sommer C, et al. Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression toward serious complications. J Intern Med. 2013;274(4):331–41.
33. Biegstraaten M, Arngrímsson R, Barbey F, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. Orphanet J Rare Dis. 2015;10:36. https://doi.org/10.1186/s13023-015-0253-6.
34. Weidemann F, Jovanovic A, Herrmann K, Vardarli I. Chaperone therapy in Fabry disease. Int J Mol Sci. 2022;23(3):1887. https://doi.org/10.3390/ijms23031887.
35. Yam GH-F, Zuber C, Roth J. A synthetic chaperone corrects the trafficking defect and disease phenotype in a protein misfolding disorder. Faseb J. 2005;19:12–8.
36. Asano N, Ishii S, Kizu H, Ikeda K, Yasuda K, Kato A, Martin OR, Fan J-Q. In vitro inhibition and intracellular enhancement of lysosomal α-galactosidase A activity in Fabry lymphoblasts by 1-deoxygalactonojirimycin and its derivatives. J Biol Inorg Chem. 2000;267(13):4179–86.
37. Yam GH-F, Bosshard N, Zuber C, Steinmann B, Roth J. Pharmacological chaperone corrects lysosomal storage in Fabry disease caused by trafficking-incompetent variants. Am J Physiol Cell Physiol. 2006;290(4):C1076–82.
38. Germain DP, Hughes DA, Nicholls K, Bichet DG, Giugliani R, Wilcox WR, Feliciani C, Shankar SP, Ezgu F, Amartino H, et al. Treatment of Fabry's disease with the pharmacologic chaperone migalastat. N Engl J Med. 2016;375:545–55.
39. Schiffmann R, Bichet DG, Jovanovic A, Hughes DA, Giugliani R, Feldt-Rasmussen U, Shankar SP, Barisoni L, Colvin RB, Jennette JC, et al. Migalastat improves diarrhea in patients with Fabry disease: clinical-biomarker correlations from the phase 3 FACETS trial. Orphanet J Rare Dis. 2018;13(1):68. https://doi.org/10.1186/s13023-018-0813-7.
40. Feldt-Rasmussen U, Hughes D, Sunder-Plassmann G, Shankar S, Nedd K, Olivotto I, Ortiz D, Ohashi T, Hamazaki T, Skuban N, et al. Long-term efficacy and safety of migalastat treatment in Fabry disease: 30-month results from the open-label extension of the randomized, phase 3 ATTRACT study. Mol Genet Metab. 2020;131(1–2):219–28.
41. Bichet DG, Torra R, Wallace E, Hughes D, Giugliani R, Skuban N, Krusinska E, Feldt-Rasmussen U, Schiffmann R, Nicholls K. Long-term follow-up of renal function in patients treated with migalastat for Fabry disease. Mol Genet Metab Rep. 2021;28:100786. https://doi.org/10.1016/j.ymgmr.2021.100786.
42. Riccio E, Zanfardino M, Ferreri L, Santoro C, Cocozza S, Capuano I, Imbriaco M, AFFIINITY Group, et al. Switch from enzyme replacement therapy to oral chaperone migalastat for treating fabry disease: real-life data. Eur J Hum Genet. 2020;28:1662–8.
43. McCafferty EH, Scott LJ. Migalastat: a review in Fabry disease. Drugs. 2019;79(5):543–54.
44. Parenti G. Treating lysosomal storage diseases with pharmacological chaperones: from concept to clinics. EMBO Mol Med. 2009;1(5):268–79.

Chapter 35
A Case Report of Fabry Disease

Joseph Bruno Bidin Brooks and Humberto Villacorta Junior

35.1 Case Report of Fabry Disease

We report a case of a male patient, 28 years, Caucasian, with parents not consangued.

35.2 Main Complaint and Duration

Dizziness and imbalance are associated with numbness on the right side of the body for 3 years."

35.3 Previous History

The patient had a previous evaluation performed by another neurologist with a diagnosis of primary progressive multiple sclerosis. The patient's age at the time was 26 years.

J. B. B. Brooks
Department of Function and Structure, Medical School, Universidade Metropolitana de Santos–UNIMES, São Paulo, Brazil

H. Villacorta Junior (✉)
Cardiology Division, Fluminense Federal University, Niterói, Rio de Janeiro, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_35

35.4 Clinical Course

First Ictus at the age of 26 years; axial balance dysfunction and incoordination associated with right-sided paresthesia with acute installation and duration (3 min) with spontaneous improvement.

Second Ictus at the age of 27 years; axial balance dysfunction and incoordination. Left facial and right limb-sided paresthesia. Vertigo, diplopia, multidirectional nystagmus, dysphagia, dysarthria, dysphonia, with acute installation and no improvement.

During this attack, he was hospitalized. Analysis of cerebrospinal fluid, hematological tests, and urinalysis had normal results. Cerebral MRI was performed, showing white matter lesions (microangiopathy) and lateral medullary syndrome (Fig. 35.1).

At that time, a diagnosis of primary progressive multiple sclerosis was instituted, and interferon beta 1-b treatment was initiated. However, symptoms did not improve after hospitalization.

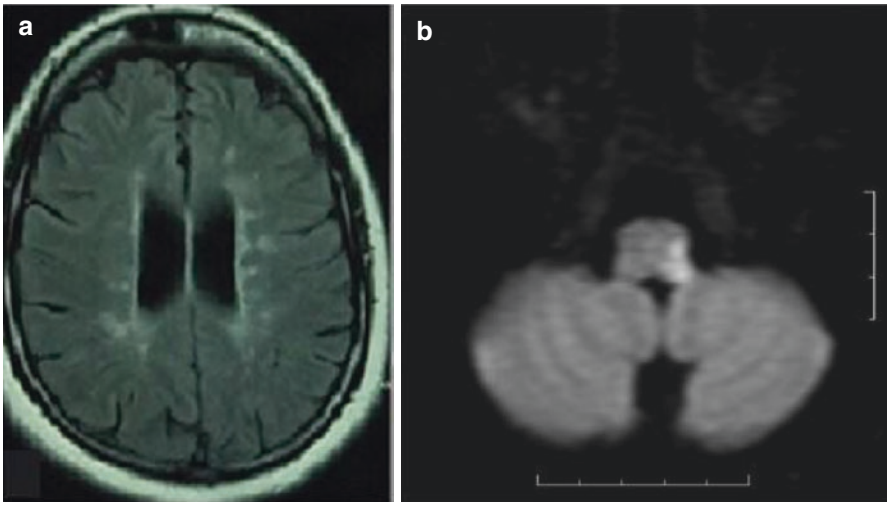


Fig. 35.1 Cerebral magnetic resonance imaging performed at the age of 27 years during hospitalization due to an episode of ictus. (**a**) Axial flair showing multiple punctate and confluent white matter hyperintensities in the periventricular area. (**b**) Diffusion restriction in the left lateral medulla oblongata

35.5 Evaluation at the Present Consultation

During his consultation with our service, he reported that when he was 10 years, he presented with acroparesthesia, heat intolerance, and abdominal pain. At the age of 20 years, he developed asymmetric neurosensory deafness, angiokeratoma, and non-nephrotic proteinuria (40 mg/24 h). On physical examination, an angiokeratoma was observed in the swimsuit area (Fig. 35.2a).

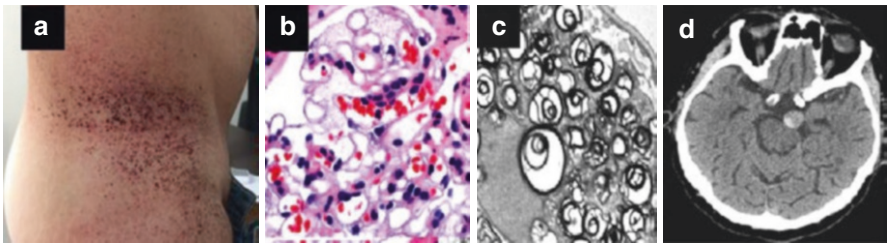


Fig. 35.2 (**a**) Angiokeratoma in swimsuit area, (**b**) kidney biopsy: light microscopy showing vague vacuolization of podocytes (H&E stain, ×400); (**c**) kidney biopsy: electron microscopy showing large lamellated lipid vacuoles (zebra bodies) within the podocytes; (**d**) axial contrast-enhanced CT scan showing basilar artery dolichoectasia

35.6 Family History

Early maternal death, at the age of 32 years, is presumably due to acute myocardial infarction. His mother also had angiokeratoma. His sister had angiokeratoma, acroparesthesia, abdominal pain, and a history of transient ischemic attack.

35.7 Cardiac Tests

Electrocardiogram: short PR interval, left ventricular hypertrophy; pre-excitation syndrome.

Echocardiogram: left ventricular hypertrophy; increased septum and posterior wall (15 mm).

35.8 Kidney Biopsy

Electron microscopy: large, lamellated lipid vacuoles (zebra bodies) within the podocytes (Fig. 35.2b, c).

35.9 CT Scan

Dilatation of the basilar artery (Fig. 35.2d).

The family pedigree is shown in Fig. 35.3.

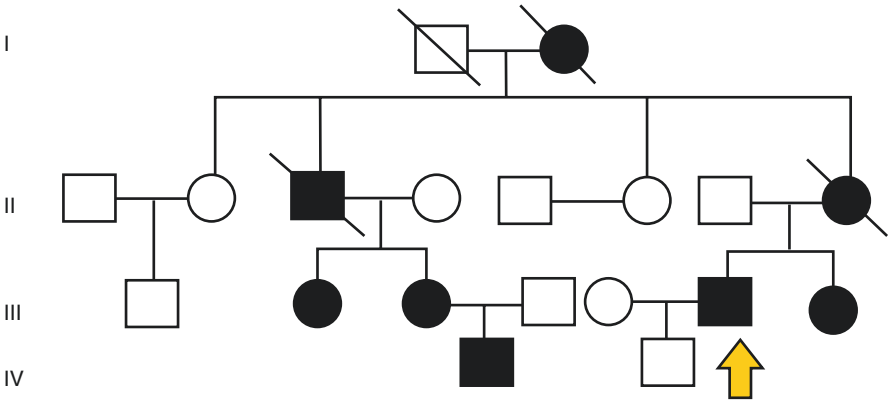


Fig. 35.3 Family pedigree. As shown above, the patient's grandmother was affected by the disease and transmitted the gene mutation to his mother. His sister was also affected

35.10 Genetic Analysis

Pathogenic variant: GLA hemizygous nonsense mutation (R220X).
Galactosidase Alpha gene: GLA Fabry Disease; X-linked disease.

35.11 Enzymatic Study

Lysosomal enzyme deficiency α galactosidase A: GLA—0.1 nmol/min/mg protein (normal 0.4–1.0).
Globotriaosylsphingosine (Lyso-GB3): 8.6 ng/mL (normal < 0.9).

35.12 Specific Treatment

Treatment with enzyme replacement therapy was initiated. There was no amenability to chaperone treatment. Agalsidase beta, at a dose of 1 mg/kg, was prescribed every 2 weeks.

35.13 Symptomatic Treatment

Pain crisis was treated with carbamazepine 200 mg TID. Antiplatelet aggregation and angiotensin converting enzyme inhibitors were also prescribed. Abdominal pain was attenuated with small meals spread throughout the day.

35.14 Follow-Up of Patients with Fabry Disease

Fabry disease is a systemic disease and involves manifestations from many specialties. Ideally, patients should be followed up by a multispecialty team, as shown in Fig. 35.4.

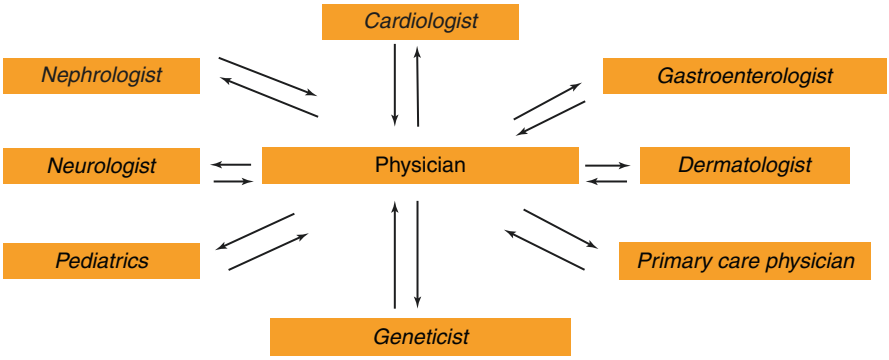


Fig. 35.4 After establishing the diagnosis of Fabry disease, patients should be enrolled in a multispecialty team for adequate follow-up and treatment

35.15 Conclusion

This case illustrates how easily the diagnosis of Fabry disease can be missed. A high degree of suspicion is necessary for the patient to have an early diagnosis and benefit the most from specific treatment.

Part III
Miscellany

Chapter 36
Clinical and Genetic Screening in ATTR and Fabry Disease in Children and Adolescents

Raquel Germer Toja Couto, Ana Flávia Malheiros Torbey, and Aurea Lucia Alves de Azevedo Grippa de Souza

36.1 Fabry Disease (FD)

Fabry disease (FD) is a debilitating progressive multisystem sphingolipid storage disorder resulting from the deficiency (partial or complete) of the lysosomal enzyme alpha-galactosidase A. FD is caused by pathogenic variants in the *GLA* gene. Unlike most other lysosomal diseases, the inheritance is X-linked [1]. It is generally believed that FD clinically affects only adult males; however, we currently know that FD is a burdensome condition in childhood, not only for males but also for females. Diagnostic delay is frequent, probably due both to the rarity of the disease and to the fact that the first complaints of the disease are only subjective symptoms difficult to understand and evaluate [2].

The incidence of FD has been estimated at 1 in 55,000 male births; however, it is probably underestimated [3]. A study carried out by Spada *at all* estimated a neonatal screening incidence of 1:3100–4600. The classic form, occurring in males, usually has an onset in childhood or adolescence. Females that are heterozygous typically have milder symptoms at a later age of onset than males [3, 4].

R. G. T. Couto
Antônio Pedro University Hospital of Universidade Federal Fluminense, Secretaria de Saúde do Distrito Federal, Niterói, Rio de Janeiro, Brazil

A. F. M. Torbey · A. L. A. de Azevedo Grippa de Souza (✉)
Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brazil
e-mail: anatorbey@id.uff.br; aureagrippa@id.uff.br

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_36

36.1.1 Pediatric Clinical Manifestation

Although FD is traditionally recognized as a disease of adults, pathophysiological processes and organ damage start in childhood with early symptoms in infants, affecting boys and girls [3]. Symptoms occur because of an enzyme deficiency that inhibits the ability of the lysosomes present in the body's cells to perform their normal function. The clinical picture is progressively shaped as the accumulation of nonmetabolized substrates in the cells induces cellular, tissue, and organ dysfunction [5]. In severe forms of disease, where enzyme activity is absent or very low, symptomatology appears at a young age compared to attenuated forms [6].

FD has a spectrum of phenotypes, whose predominant signs are neuropathic pain, which can manifest periodic crises of severe pain in the extremities (acroparesthesia), fatigue, gastrointestinal discomfort, hypohidrosis, angiokeratomas, corneal changes *(cornea verticillata)*, lenticular opacities, and hypoacusia. Subclinical kidney damage with albuminuria or proteinuria may be present in young individuals, but classic renal and cardiovascular manifestations (renal failure and ventricular hypertrophy) occur in adults. There is also an impact on quality of life with school absence, anxiety disorder, and depression [3].

Symptoms appear at a median age of 6 years in boys and 7–8 years in girls, but some children may have symptoms at a younger age [3]. Table 36.1 shows the symptoms in children and adolescents and the age of onset.

Table 36.1 Fabry disease: symptoms in children and adolescents and the average age of onset

System/Organ	Signal/Symptoms	Age of onset
Peripheral nervous system	Pain, crisis of pain, burning pain in feet or hands, Dysesthesia	2–4 years
Endocrine	Hypohidrosis or anhidrosis	2–5 years
Gastrointestinal	Abdominal pain, vomiting and nausea, diarrhea or constipation	1–17 years
Skin	Angiokeratomas	7–9 year (boys) 9–14 years (girls)
Oftalmologic	Corneal whorls/cornea verticillata	Newborn
Otolaryngologist	Hearing loss, tinnitus and vertigo	4 years
Kidney	Hyperfiltration, pathological albuminuria, proteinuria	13–16 years
Heart	Conduction abnormalities, valvular dysfunction, arrhythmias	8–10 years (boys) 9–14 years (girls)

36.1.2 Diagnosis

FD diagnosis requires a combination of clinical, biochemical, and molecular criteria. In many cases, it is challenging due to a variable phenotypic presentation. Phenotypic expression is highly variable depending on sex, as hemizygous males classically present with more severe symptoms than heterozygous females, whose symptoms may range from nonclinical to severe. As clinical symptoms can be nonspecific, diagnosis in childhood may be delayed, sometimes longer than a decade. In that way, FD is generally thought to be underdiagnosed [3, 7].

The main symptom that usually leads the children to the investigation is neuropathic pain, which usually has a burning character and is located in the extremities, most commonly in the palm, soles, and fingertips; neuropathic pain may be associated with diarrhea and abdominal pain [3].

The delay in diagnosis can be distressing for the child and family, since several visits to the pediatric emergency room are necessary and are usually misdiagnosed with rheumatologic disease [3]. These patients usually go through several medical specialties until they reach their diagnosis. Because FD affects multiple organ systems, a multidisciplinary team approach is useful [8]. Referrals to multiple subspecialists may be necessary to achieve optimal patient care. Case management can include specialists in medical genetics, pediatrics, or internal medicine, nephrology, ophthalmology, cardiology, dermatology, neurology, pain management, organ transplant, social work, and psychology/psychiatry [9].

The diagnosis of FD should also be considered when a family member has died before age 50 of cardiac arrhythmias, hypertrophic cardiomyopathy, stroke, and kidney failure [3].

Therefore, a high degree of clinical suspicion is necessary for the clinical diagnosis to be made in childhood, especially if the child is the index case and there is no family history of FD [3, 7].

Laboratory diagnosis of FD in boys, as recommended, is carried out by determination of aGalA activity. It can be measured in samples, such as dried blood spots, plasma, or leukocytes. The final diagnosis is accompanied by a genetic test establishing the presence of a pathogenic mutation in *GLA*. In girls, however, genetic testing is mandatory. FD should always be confirmed by the identification of a heterozygous *GLA* pathogenic variant, since enzymatic activity determination can be inconclusive [10].

The *GLA* gene is located on the Xq22 chromosome, and more than 1000 different *GLA* variants have been identified thus far in FD patients, most of which are private, including some variants of unknown significance (VUS). The phenotypes also depend on the nature of the *GLA* variant. Understanding variant pathogenicity is the key to accurate prevalence estimation, diagnosis, and management of the disease [11].

If the *GLA* pathogenic variant in the family is known, it can be specifically investigated in the individual who is manifesting the first symptoms. Therefore, children from affected families usually have a diagnosis established early before the onset of irreversible complications. It is essential to analyze the family history and confirm that the inheritance pattern is X-linked. That way there will not be a male-to-male transmission. It is also important to know that the absence of a known family history does not exclude the diagnosis [11].

Children who have at least one first-degree relative diagnosed with FD should be systematically screened. This is the best and fastest way to carry out the diagnosis.

Early childhood diagnosis is becoming more common for some variants of FD due to the implementation of newborn screening [12]. The greatest advantage is to determine the diagnosis before the onset of symptoms that usually present in childhood, but can be delayed to adulthood. In this way, it is possible to carry out clinical follow-up before irreversible lesions are installed, offering adequate treatment early [3, 12, 13].

However, neonatal screening is not performed routinely and does not always include screening for FD. It will depend on the experience of each country [3, 7, 13].

There are some barriers to performing genetic testing in family screening, such as high cost, difficulty in accessing genetic counseling and medical geneticists, reduced knowledge among other physicians about the disease and the benefits of early diagnosis and social and family issues such as fear of stigmatization [3, 7, 13].

The screening methods used in pediatric patients should be the same as those used for adults, being fundamental in boys to the measurement of α-GAL activity and genetic analysis in girls [3, 12].

Below are some scenarios where the diagnosis of FD can be made [3, 7]:

Genetic testing of children of parents with a known diagnosis of Fabry disease: offers the possibility of early diagnosis and treatment, if indicated. This is the recommendation of the European Society of Human Genetics.

Prenatal diagnosis: available in some countries, such as France for males but generally not for female fetuses.

Preimplantation diagnosis can be offered for families with known FD during assisted reproduction.

Renal and skin biopsy are tools that contribute to the diagnosis of FD in specific situations, such as the absence of family history and the detection of VUS.

36.1.3 Clinical Monitoring of Children Diagnosed with Fabry Disease

Asymptomatic children from families with FD: The investigation of organ involvement should start at 5 years of age for boys and approximately 12 years of age for girls. In addition, parents or guardians must be educated about the initial symptoms of the disease, so that they seek care if they appear. After the investi-

gation starts, it is followed by annual monitoring in boys and every 2–3 years in girls [3, 7].

Symptomatic children: the investigation of organ involvement should start immediately after diagnosis [3, 7].

Renal assessment: Screening for albuminuria and proteinuria should be performed in all patients. Renal biopsy already shows accumulation of globotriaosylceramide (Gb3) in kidney cells, even before the detection of albuminuria and proteinuria; however, renal biopsy is performed only in specific situations. In general, renal failure is not observed in children [7].

Assessment of glomerular renal function: in practice, it is recommended to measure the glomerular filtration rate calculated from 24-h urine at diagnosis and onset of treatment. Inability to collect urine timed, it is recommended to use the equations of pediatric tests to estimate renal function, which are more accurate than serum creatinine alone [3, 7].

Ultrasound is useful to measure the size of the kidneys at the baseline assessment [7].

Cardiac assessment: Cardiovascular screening should be performed with electrocardiogram and color Doppler echocardiography, preferably with the study of strain. The main cardiac finding is ventricular hypertrophy; however, conduction disturbances such as a short PR interval or sinus bradycardia may be observed. 24 h Holter monitoring should be performed only when guided by the presence of symptoms or positive findings on the electrocardiogram, and cardiac magnetic resonance will be performed only in selected patients [3, 7].

Oftalmologic assessment: Ophthalmologic examination including slit lamp examination: the presence of cornea verticillata (vortex keratopathy or whorls) strongly supports the diagnosis of a classic phenotype [3, 7].

Skin and gastrointestinal assessment: thorough physical examination and anamnesis, strict monitoring of growth curves [3, 7].

36.2 Hereditary Transthyretin Amyloidosis (ATTR Amyloidosis)

Cardiac amyloidosis (ATTR-CM) is a rare disease described as the leading cause of restrictive hypertrophic cardiomyopathy in elderly patients. ATTR-CM is known as an infiltrative disorder caused by myocardial deposition mainly of immunoglobulin light chain or transthyretin amyloidosis protein [14, 15].

As a long progressive and systemic disease, this deposition and infiltration of amyloid substances in the extracellular space leads to severe heart failure in adulthood [13]. There are three forms of ATTR-CM: (1) acquired monoclonal immunoglobulin light chain amyloidosis (AL-CM); (2) wild-type transthyretin amyloid cardiomyopathy (wtATTR-CM) with no mutation identified; and (3) hereditary transthyretin amyloid [14, 15].

36.2.1 Pediatric Manifestations

There are few literature references about childhood manifestations of ATTR in pediatric patients. To date, there has been only a reported case of ATTR-CM in children with clinical manifestations [14]. A 12-year-old boy was referred after a syncope episode, complaining of intermittent and nonspecific chest pain, fatigue, and shortness of breath in the prior month. His first tests showed a wandering atrial pacemaker (average 4 beats/min), normal intervals and no abnormal ST-T wave changes or hypertrophy signs on electrocardiogram, and transthoracic echocardiogram revealed marked left ventricle trabeculations. A ratio of noncompacted to compacted myocardium > 2:1 from the midbody to the apex with an LV ejection fraction measuring 52.13% was shown on cardiac MRI. After these findings, a genetic test was performed showing a mutation (Val122Ile) of hereditary transthyretin amyloidosis. Dual chamber implantable cardiac defibrillators and beta blockers were the therapeutics proposed, and after 6 years of follow-up, the patient was alive with only a few documented arrhythmic events.

Genetic testing can confirm a *TTR* gene mutation associated with hereditary ATTR-CM or ATTR-NP when we have the confirmed familial variant. As the clinical penetrance of pathogenic alleles is incomplete and with limited data, screening and management of asymptomatic carriers are still a challenge [15].

36.2.2 Genetic Counseling

As hereditary transthyretin amyloidosis has an autosomal dominant pattern of inheritance, children of heterozygous carriers of ATTR amyloidosis have a 50% chance of inheriting a pathogenic variant [16]. As the disease affects individuals after the fifth decade of life, genetic screening in childhood or prenatal care is not common. However, it is frequent for parents to want to know if their children will inherit the known pathogenic variant in the family and may request that the genetic evaluation be carried out.

Testing children for a disease with an adult onset, such as ATTR amyloidosis, before they are able to decide for themselves whether and when they wish to know about their inheritance can present with ethical, social, and legal challenges [17]. Genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality [18, 19].

References

1. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med Genet. 2001;38(11):769–75.
2. Ries M, Ramaswami U, Parini R, Lindblad B, Whybra C, Willers I, Gal A, Beck M. The early clinical phenotype of Fabry disease: a study on 35 European children and adolescents. Eur J Pediatr. 2003;162(11):767–72. https://doi.org/10.1007/s00431-003-1299-3. Epub 2003 Sep 20. PMID: 14505049.
3. Germain DP, Fouilhoux A, Decramer S, Tardieu M, Pillet P, Fila M, Rivera S, Deschênes G, Lacombe D. Consensus recommendations for diagnosis, management and treatment of Fabry disease in pediatric patients. Clin Genet. 2019;96(2):107–17.
4. Spada M, Pagliardini S, Yasuda M, Tukel T, Thiagarajan G, Sakuraba H, Ponzone A, Desnick RJ. High incidence of later-onset fabry disease revealed by newborn screening. Am J Hum Genet. 2006;79(1):31–40.
5. Ferreira CR, Gahl WA. Lysosomal storage diseases. Transl Sci Rare Dis. 2017;2(1–2):1–71.
6. Alkhzouz C, Miclea D, Bucerzan S, Lazea C, Nascu I, Sido PG. Early clinical signs in lysosomal diseases. Med Pharm Rep. 2021;94(Suppl 1):S43–6.
7. Vaisbich MH, Andrade LGM, Silva CAB, Barreto FC. Recommendations for the diagnosis and management of Fabry disease in pediatric patients: a document from the Rare Diseases Committee of the Brazilian Society of Nephrology (Comdora-SBN). J Bras Nefrol. 2022;44(2):268–80. https://doi.org/10.1590/2175-8239-JBN-2021-0216. PMID: 35238862.
8. Peters FP, Sommer A, Vermeulen A, Cheriex EC, Kho TL. Fabry's desease: a multidisciplinary disorder. Postgrad Med J. 1997;73(865):710–2.
9. Bennett RL, Hart KA, O'Rourke E, Barranger JA, Johnson J, MacDermot KD, Pastores GM, Steiner RD, Thadhani R. Fabry disease in genetic counseling practice: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2002;11(2):121–46.
10. Rozenfeld PA, Ceci R, Roa N, Kisinovsky I. The continuous challenge of diagnosing patients with Fabry disease in Argentina: genotype, experiences, anecdotes, and new learnings. J Inborn Errors Metab Screen. 2015;3:1–7.
11. Germain DP, Levade T, Hachulla E, Knebelmann B, Lacombe D, Seguin VL, Nguyen K, Noël E, Rabès JP. Challenging the traditional approach for interpreting genetic variants: lessons from Fabry disease. Clin Genet. 2022;101(4):390–402.
12. Hopkin RJ, Jefferies JL, Laney DA, Lawson VH, Mauer M, Taylor MR, Wilcox WR, Fabry Pediatric Expert Panel. The management and treatment of children with Fabry disease: a United States-based perspective. Mol Genet Metab. 2016;117(2):104–13.
13. Germain DP, Moiseev S, Suárez-Obando F, Al Ismaili F, Al Khawaja H, Altarescu G, Barreto FC, Haddoum F, Hadipour F, Maksimova I, Kramis M, Nampoothiri S, Nguyen KN, Niu DM, Politei J, Ro LS, Vu Chi D, Chen N, Kutsev S. The benefits and challenges of family genetic testing in rare genetic diseases-lessons from Fabry disease. Mol Genet Genom Med. 2021;9(5):e1666. https://doi.org/10.1002/mgg3.1666. Epub 2021 Apr 9. PMID: 33835733; PMCID: PMC8172211.
14. Griffin J, Rosenthal J, Grodin J, et al. ATTR amyloidosis: current and emerging management strategies. JACC CardioOncol. 2021;3(4):488–505. https://doi.org/10.1016/j.jaccao.2021.06.006.
15. Torpoco Rivera DM, Williams CT, Karpawich PP. Cardiac amyloidosis in a child presenting with syncope: the first reported case and a diagnostic dilemma. Pediatr Cardiol. 2022;43(3):700–3. https://doi.org/10.1007/s00246-021-02778-9. Epub 2021 Nov 16. PMID: 34783874.

16. Gillmore JD, Reilly MM, Coats CJ, Cooper R, Cox H, Coyne MRE, Green AJ, McGowan R, Moody WE, Hawkins PN. Clinical and genetic evaluation of people with or at risk of hereditary ATTR amyloidosis: an expert opinion and consensus on best practice in Ireland and the UK. Adv Ther. 2022;39(6):2292–301. https://doi.org/10.1007/s12325-022-02139-9. PMID: 35419651.
17. Fenwick A, Plantinga M, Dheensa S, Lucassen A. Predictive genetic testing of children for adult-onset conditions: negotiating requests with parents. J Genet Couns. 2017;26(2):244–50. https://doi.org/10.1007/s10897-016-0018-y. Epub 2016 Sep 28. PMID: 27680566; PMCID: PMC5382176.
18. COMMITTEE ON BIOETHICS; COMMITTEE ON GENETICS, AND; AMERICAN COLLEGE OF MEDICAL GENETICS AND; GENOMICS SOCIAL; ETHICAL; LEGAL ISSUES COMMITTEE. Ethical and policy issues in genetic testing and screening of children. Pediatrics. 2013;131(3):620–2. https://doi.org/10.1542/peds.2012-3680. Epub 2013 Feb 21. PMID: 23428972.
19. Maurer MS, Bokhari S, Damy T, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail. 2019;12(9):e006075. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006075.

Chapter 37
History and Clinical Research

Roberta Pereira dos Santos Coelho, Diane Xavier de Ávila, Nathalia Monerat Pinto Blazuti Barreto, Humberto Villacorta Junior, and Evandro Tinoco Mesquita

37.1 History of Amyloidosis

The signs and symptoms of amyloidosis have been known for over 200 years, but studies suggest that the first carrier individual in the hereditary form lived during the Late Middle Ages around the fifteenth century, and with population migration, it spread around the world. The timeline is described in Fig. 37.1 [1].

The number of mutation carriers in the transthyretin gene has increased worldwide, but it has been described that Val50met would have the highest incidence in

R. P. dos Santos Coelho (✉) · N. M. P. B. Barreto
Department of Pesquisa Clínica, Hospital Pro Cardiaco, Rio de Janeiro, Rio de Janeiro, Brazil
e-mail: roberta.santos@procardiaco.com.br

D. X. de Ávila
Cardiology, Complexo Hospitalar de Niterói–DASA, Rio de Janeiro, Brazil
e-mail: dianeavilamed@cardiol.br

H. Villacorta Junior
Cardiology Division, Fluminense Federal University, Niterói, Rio de Janeiro, Brazil

E. T. Mesquita
Cardiology, Complexo Hospitalar de Niterói–DASA, Rio de Janeiro, Brazil

Cardiology Division, Federal Fluminense University, Niterói, Rio de Janeiro, Brazil

Interamerican Society of Cardiology (SIAC), Cuidad de México, Mexico

PROCEPI, Niterói, RJ, Brazil

Cardiomyopathies Study Group DEIC/GEMIC, Rio de Janeiro, RJ, Brazil

Sixth ward Cardiology, Santa Casa de Misericórdia, Rio de Janeiro, RJ, Brazil

Cardiovascular Sciences, Federal Fluminense University, Niterói, RJ, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_37

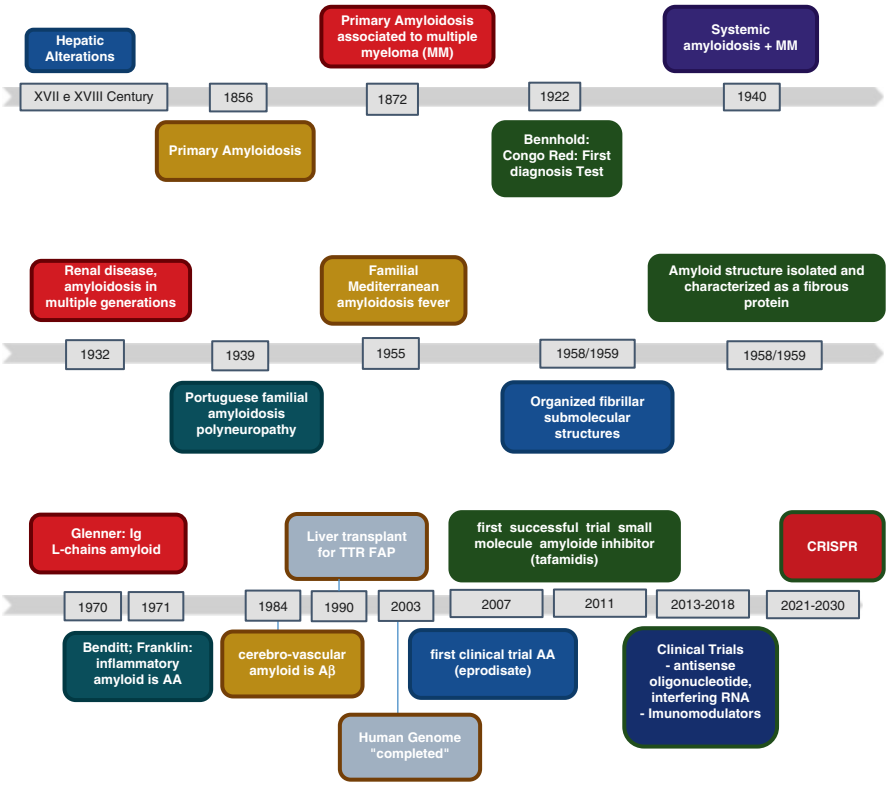


Fig. 37.1 Amyloidosis timeline

northern Portugal (cities of Póvoa do Varzim and Vila do Conde), where its prevalence reaches 1/1100, in addition to Sweden, Japan, and Brazil. It has been seen that the Val142Ie mutation in TTR is increasingly frequent in Afro-descendants, with a higher prevalence in the cardiac form of amyloidosis [2, 3].

A normal amylaceous constituent of plants was first described in 1838 by Matthias Schleiden. In 1854, Rudolph Virchow used this term because of the peculiar reaction of the corpora amylacea of the nervous system with iodine. Virchow defined amyloid as cellulose, and Friedreich and Kekule described amyloid as an albuminous or protein substance [4].

Primary amyloidosis was probably reported for the first time in 1856 when Samuel Wilks described lardaceous viscera in a patient who had no evidence of inflammatory or infectious disease. The first case of amyloidosis associated with multiple myeloma was reported by Weber 11 years later. In 1922, Bennhold introduced Congo red as an aniline dye that was used for staining textiles and could be the first diagnostic test [5, 6].

In 1958 and 1959, electron microscopy showed that all primary and secondary amyloidosis in animals had an organized fibrillar submolecular structure. In addition, studies have demonstrated a multiplicity of genes that determined amyloidosis in Japan, Sweden, Portugal, Italy, Iceland, Denmark, Greece, Germany and

elsewhere, reinforcing the importance of the numerous types of mutations in the transthyretin gene determining hereditary amyloidosis [7].

In 1940, Apitz noticed that in the association of myeloma with amyloidosis, there were deposits of a systemic form of the disease, including in the heart [6–7]. In 1952, Prof Corino Andrade brought attention to the type of peripheral neuropathy in Amyloidosis, and in 1974, the first TTR mutation was determined with the nucleotide sequence of the TTR gene [8]. Currently, there are more than 130 mutations.

In Brazil, according to DATASUS, there were 1886 deaths from all causes of amyloidosis between 2000 and 2019, but an increase in mortality has been reported, which reflects how underdiagnosed it was and how incidence has been rising in the last few years. With the prevalence of at least 1/100,000, Brazil is probably the second country with the highest number of amyloidosis cases, with Portugal being the first [9].

There are more proteins described as possible causes of amyloidosis, such as apolipoprotein A, mutations in fibrinogen Aa-chain cause familial amyloidosis, and mutations in apolipoprotein A-II. Recently, mutations in apolipoprotein C-2 and C-3 were associated with systemic amyloidosis, gelsolin, and cystatin-C, and hereditary amyloidosis was associated with a mutation in the immunoglobulin k-light chain constant region. New tools for studying these forms of hereditary amyloidosis and discovering other types of systemic amyloidosis have attracted the attention of the medical community [10].

37.2 History of Fabry Disease

The first case reports of Fabry disease were described almost simultaneously by two independent dermatologists in 1898 [11, 12]. The English dermatologist Willian Anderson described the case of a patient with angiokeratoma, and the German dermatologist Johannes Fabry reported a case of hemorrhagic nodular purpura. For this reason, the disease was first reported as Anderson–Fabry disease [13].

The mechanism of the disease was recognized to be abnormal storage of lipids in 1952, and the inheritance pattern of an X-linked disease, as well as the molecular defect responsible for the deposition, was established in 1960 [14]. Electron microscopic findings of Fabry disease were reported by Ken Hashimoto in 1965 [15], and the first specific treatment, enzyme replacement therapy, was approved in 2001.

37.3 Creation of Clinical Research Centers

All the knowledge that scientists have acquired is currently directed toward the goal of creating transformational therapies that allow people living with rare diseases to cope with the challenges of everyday life. Therefore, research institutions have been an important source of support for the treatment of these patients.

A Research Center or Clinical Research Institution is a public or private organization constituted and qualified to carry out clinical research. It may or may not be in a hospital or in a clinic, with highly specific activities, rules, and norms in conducting studies, in addition to high costs.

There must be some areas for (1) the service of research participants on an outpatient and day hospital basis, (2) inpatient care, (3) activities to support diagnosis and treatment, (4) logistical support, and (5) technical support and administrative support. The specificity of the test laboratories must be in accordance with the research activities to be carried out, as well as the complementary environments of these laboratories, such as a cold chamber, area for a laminar flow hood, and others. Some laboratories may be outsourced, but must comply with local regulations.

Some activities of the clinical research center can also be outsourced, such as material sterilization, clothing processing, food, clinical analysis laboratory, imaging, cleaning, and sanitizing; however, it is important to follow local regulations.

37.4 Clinical Research and Treatment of a Patient with Rare Disease

Research on rare diseases is a field still in development; the costs of medications are usually high, and the patient is often limited to using specific medications through clinical studies. Not all treatments are available in Brazil's public health system or through private practice. We must seek solutions for the financial toxicity that rare disease patients experience to improve their quality of life and survival.

Compassionate use is the availability of promising new drugs for personal use by patients and nonparticipants in an expanded access programme or clinical research programme not yet registered in the country, which is in the process of clinical development aimed at patients with debilitating conditions.

The expanded access program, on the other hand, is a way for making available a new drug, not yet registered in the country or not commercially available, which is in a phase III study, under development or completed, aimed at a group of patients with serious and/or life-threatening diseases and without a satisfactory therapeutic alternative with registered products [16].

All scientific research must respect ethical standards that will also characterize the proper conduct of the investigator, which will reflect on the integrity of the research. To guarantee the ethical guidelines of research, every Research Center must submit its research to a Research Ethics Committee before carrying out any procedure with the participant.

Studies on the incidence and prevalence of rare diseases should be encouraged, as this information is of high interest to professionals in the field, health authorities, patients, family associations, and pharmaceutical industries. A small proportion of rare diseases have a drug treatment approved or under development. There is a significant demand for investment in research for the treatment of these diseases, constituting a problem to be faced globally.

References

1. Sousa A, Coelho T, Barros J, Sequeiros J. Genetic epidemiology of familial amyloidotic polyneuropathy (FAP)-type I in Póvoa do Varzim and Vila do Conde (north of Portugal). Am J Med Genet. 1995;60(6):512–21. https://doi.org/10.1002/ajmg.1320600606. PMID: 8825887.
2. Buxbaum JN, Linke RP. A molecular history of the amyloidoses. J Mol Biol. 2012;421(2–3):142–59. https://doi.org/10.1016/j.jmb.2012.01.024. Epub 2012 Feb 1. PMID: 22321796.
3. Cohen AS. History of amyloidosis. J Intern Med. 1992;232(6):509–10. https://doi.org/10.1111/j.1365-2796.1992.tb00625.x. PMID: 1474352.
4. Kyle RA. Amyloidosis: a brief history. Amyloid. 2011;18(Suppl 1):6–7. https://doi.org/10.3109/13506129.2011.574354001. Erratum in: Amyloid 2011 Jun;18 Suppl 1:7. PMID: 21838413.
5. Kyle RA, Bayrd ED. Primary systemic amyloidosis and myeloma: discussion of relationship and review of 81 cases. Arch Intern Med. 1961;107:344–53.
6. Kyle RA. Historical review. Amyloidosis: a convoluted study. Brit J Hematol. 2001;114:529–38.
7. Magnus-Levy A. Bence-Jones-Eiweiss and amyloid. Zeitschrift fur Klinische Medizinische. 1931;116:510–31.
8. Apitz K. Die Paraproteinosen 306, 631-639. (Uber die Storundes Eiweisstoffwechsels bei Plasmoyctom). Virchows Archivfur Pathologische Anatomie und Physiologie (B). 1940;306:631–9.
9. Brasil, Ministério da Saúde. Banco de dados do Sistema Único de Saúde-DATASUS. http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sim/cnv/obt10uf.def. Acesso em 22 de novembro de 2021.
10. Benson MD. Transthyretin amyloidosis: a little history of hereditary amyloidosis. Amyloid. 2017;24(sup1):76–7. https://doi.org/10.1080/13506129.2017.1281116.
11. Anderson W. A case of angeiokeratoma. Br J Dermatol. 1898;10:113–7.
12. Fabry J. Ein beitrag zur kenntnis der purpura hemorrhagica nodularis (purpura papulosa hemorrhagica Hebrae). Arch Dermatol Syphilol (Berlin). 1898;43:187–200.
13. Werninghaus K, Raab R, Palko M, Bhawan J. Punctate and linear angiectases: Anderson-Fabry disease (angiokeratoma corporis diffusum). Arch Dermatol. 1995;131:85–6.
14. Schiffman R. Fabry disease. In: Neurocutaneous syndromes. Handbook of clinical neurology. Vol. 132. 2015. p. 231–48.
15. Mehta A, Beck M, Linhart A, Sunder-Plassmann G, Widmer U. History of lysosomal storage diseases: an overview. In: Fabry Disease: perspectives from five years of FOS. Oxford: Oxford Pharmagenesis; 2006. ISBN 978-1903539033, PMID 21290707.
16. Agência Nacional de Vigilância S. Resolução RDC n° 38, de 12 de agosto de 2013. Aprova o regulamento para os programas de acesso expandido, uso compassivo e fornecimento de medicamento pós-estudo. Diário Oficial da União. 2013.

Chapter 38
Misdiagnosis and Clinical Reasoning in Cardiac Amyloidosis

Mayara Gabriele Toledo, Diane Xavier de Ávila, Eduarda Corrêa Maia, and Evandro Tinoco Mesquita

38.1 Introduction

Recently, a Japanese study on rare diseases noted that the diagnosis of this type of disease is still of low alert from health professionals, particularly doctors. According to the World Health Organization, rare disease (RD) is defined as a disease with 1.3 cases per 2000 individuals. Currently, there are approximately 10,000 types of RDs in the world, with approximately 473 million people affected around the globe. However, many so-called RD are actually underdiagnosed. An underdiagnosed disease is one in which its frequency in the population is estimated to be lower than it actually is. In view of this, patients diagnosed with RD can be divided into two groups: "not yet diagnosed", which is composed of patients with RD but not yet diagnosed; and "not diagnosed", which is composed of patients whose diagnosis is unavailable, because there is no characterization of the disease or the causes have

M. G. Toledo · E. C. Maia
Department of Medical School, Hospital Universitário Antônio Pedro, Niterói, Rio de Janeiro, Brazil
e-mail: mayaratoledo@id.uff.br; eduardamaia@id.uff.br

D. X. de Ávila
Amyloidosis Center, Complexo Hospitalar de Niterói–DASA, Niterói, Rio de Janeiro, Brazil

Cardiovascular Sciences, Fluminense Federal University, Niterói, RJ, Brazil
e-mail: dianeavilamed@cardiol.br

E. T. Mesquita (✉)
Instituto Cardiovascular DASA-CHN, Niterói, Rio de Janeiro, Brazil

Interamerican Society of Cardiology, Ciudad de México, México

PROCEPI, Niterói, RJ, Brazil

Cardiomiopathies Study Group DEIC/GEMIC, Rio de Janeiro, Brazil

Sixth ward Cardiology, Santa Casa de Misericórdia, Rio de Janeiro, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_38

not been identified. Patients in the "not yet diagnosed" group take approximately 4–9 years to receive a correct diagnosis, even though the disease has already been described [1–3].

Many medical centers, faced with the problem of delayed diagnosis of RD, have become interested in better understanding this delay. To do this, quantitative and qualitative patient surveys were applied, in which it was shown that before the correct diagnosis was made, a number of diagnostic errors occurred [1–3].

Cardiac amyloidosis is a great example of a disease that, despite being considered rare, is actually more frequent than is usually recognized. The delay or misdiagnosis delays the start of treatment, which has better results in the earlier stages of cardiac involvement. Thus, when it is not diagnosed early, amyloidosis has a greater chance of complications, as do many rare and/or underdiagnosed diseases [4–6].

The patient's journey to a diagnosis of amyloidosis is a long one, a true diagnostic odyssey. Data from the literature show that the diagnosis of AL amyloidosis takes approximately 2 years, in general, requiring 5 clinicians before diagnosis: cardiology, hematology, oncology, nephrology, and neurology, with 19% only making the diagnosis. In TTR amyloidosis, on the other hand, diagnosis takes approximately 4 years, 39% after walking disability. In addition, 1/3 of the patients are asymptomatic. Thus, a large proportion of patients are left for years with progressing disease, untreated and without a closed diagnosis. As the disease progresses, the amyloidosis patient suffers deterioration of various organs, becomes vulnerable to various diseases, suffers reduced quality of life, and becomes dependent on caregivers. In addition, they become vulnerable to medications, which can impair the treatment of associated diseases and predispose them to increased drug reactions and adverse events. However, the natural history can be changed with early diagnosis and treatment (Fig. 38.1) [6–12].

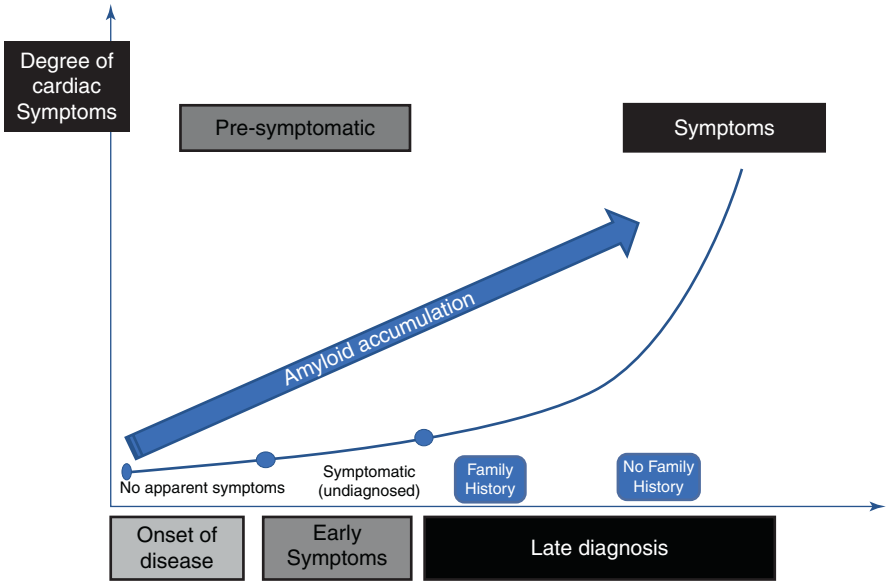


Fig. 38.1 Adaptado de Arbustini G. Merlini G. et al. JACC cardiovascular imaging in 2014

Clinical diagnosis started with Hippocrates 2500 years ago and is still a developing subject to this day. However, misdiagnosis is still very common and has many causes. Studies in outpatient clinics in the USA show a prevalence of diagnostic error of 5%. Thus, it is a public health and patient safety problem and has caused concern among physicians in many specialties, especially cardiology. Studies point out that it is difficult for physicians to reach assertive decisions. In regard to rare or uncommon diseases in practice, assertiveness in diagnosis is even more precarious [13, 14].

38.2 Understanding Misdiagnosis and Clinical Reasoning: Important Concepts

Clinical reasoning is the mental process used to arrive at possible diagnostic hypotheses and clinical decision-making in the face of disease. In the last two decades, its scientific basis has been studied. This process involves metacognition, memory, pattern recognition, perception, attention, reasoning, and problem solving [15–18].

Daniel Kahneman, a scholar of the psychology of judgment and decision making, has applied his knowledge in an attempt to discover how physicians think to arrive at a diagnosis. In his studies, he discovered 2 thinking systems used by doctors to reach a diagnosis, whose interaction determines thinking. These systems are based on the book Fast and Slow: Two Ways of Thinking [17, 19]. They are known as system 1 or general clinical reasoning and system 2 or clinical reasoning in particular. System 1 is implicit, instinctive, subconscious, fast, automatic, requires little effort, is based on pattern recognition and is subject to biases and interference. This system is based on heuristics, a term used in studies in the field of cognitive psychology. Heuristics is defined as a subconscious mental process that allows quick decisions; that is, when faced with a problem, one tends to simplify the solution, saving great effort. System 2 requires more effort and attention and is deliberative, slow, propositional, conscious, analytical, and less subject to biases. The latter system seeks to concentrate on the object of interest and avoid distractions to achieve a goal [19–22].

In general, after years of practice and study of observed cases, experienced physicians accumulate patterns, called scripts, and tend to use mainly system 1 to perform disease diagnosis, that is, heuristics. Beginning physicians and medical students tend to use mainly system 2 due to the smaller amount of accumulated scripts and less experience, thus raising more cognitive effort to reach the diagnosis. However, using system 2 does not mean inexperience, quite the contrary. The relationships between disease patterns and the way they manifest in patients are accumulated in the form of scripts from practical experiences and theoretical studies, but diseases often have atypical presentations, which naturally prompt the use of system 2 to reach the diagnosis. These disease patterns are stored in long-term memory [19, 21–24].

In the hypothetico-deductive reasoning model, which uses system 1, the solution to the problem is found through hypothesis, refutation, conjecture, and trial. In this case, the experience and disease scripts accumulated by the doctor are determinants of the probability of the correct diagnosis. The doctor tests the hypotheses until he finds the most likely one, which will be used to confirm the probability of the presented picture being the diagnosis thought and to exclude the other hypotheses.

Therefore, the assertiveness of the diagnosis in this model depends on the accuracy and quality of the hypotheses. The accumulated scripts depend on the frequency with which disease patterns are seen, discussed and studied, becoming increasingly refined [25].

As the physician's career progresses, he or she becomes faster and faster at formulating hypotheses for a diagnosis, since the presentation of a syndrome by the patient soon prompts reasoning for the scripts of pictures very similar to those seen before. However, every attempt at diagnosis comes with the chance of error because of this automatic way of functioning of the mind, based on system 1. The human brain turns much of the time to pattern recognition. When the pattern is not recognized, the brain turns to analytical reasoning (system 2). This fast and very intuitive process creates room for the occurrence of "cognitive biases," which are cognitive processes that lead to perceptual distortion and misinterpretation of data when using facilitative shortcuts. Biases are one of the main reasons for misdiagnosis, failure of information transmission among staff, and communication with the patient [26, 27]. There are several types of biases, with 5 main biases worth mentioning:

- Anchoring bias occurs when the physician anchors his/her thinking to an isolated characteristic or part of the information received in the decision-making process. For example: fixate on dyspnea and affirm that a patient has acute pulmonary edema [25, 26, 28].
- Confirmation bias: involves interpreting or seeking information in a way that confirms initial hypotheses [25, 26, 28].
- Availability bias: the tendency to consider a diagnosis to be the most likely based on the ease of remembering an example. For example, after the peaks of the COVID-19 pandemic, any cough would already prompt testing for confirmation of COVID-19 [25, 26, 28].
- Frame-effect bias: The way data are presented has an influence on our reasoning.
- Affective bias: the physician's own feelings promote distortions in the evaluation of patients [25, 26, 28].

In addition, contributing to the diagnostic error is "noise", a concept introduced in the book "Noise: A Flaw in Human Judgment", also by Daniel Kahneman. It is defined as "variability in judgments that should be identical". When biases and noise occur during the diagnostic reasoning process, complex and serious errors can occur [19, 20].

Two types of noise have been described: occasional and systemic. Occasional noise is generated when external elements influence the decisions of the individual or a team. Systemic noise refers to the unwanted variability when a group of individuals separately analyze similar events. Different opinions are extremely important for building knowledge and formulating hypotheses, but it becomes a problem when there is poor or no communication and dichotomous judgments, making the diagnostic reasoning process confusing and even more prone to error [19, 20].

Diagnostic error is a failure to establish an accurate and timely explanation for the patient's health problem or to communicate that explanation to the patient. Throughout medical training and in clinical practice, little is said about the

diagnostic error, a situation in which the medical training system makes a contribution. There are three main sources of errors in the diagnostic process:

- Errors without fault: lack of anamnesis information or very atypical presentation. For example, the patient arrives unconscious and without witnesses.
- System errors: waiting for an essential test result that takes too long to come out or is not available. This is an important factor in diagnostic delay and is usually related to the complementary system or to patients with poor access to health care.
- Cognitive errors: related to the physician's mental processes. Diagnosis is a combination of factors, and the fundamental process can be influenced by biases. For example, premature closure is when the reasoning of the diagnostic process is interrupted too early. It is the main error (70%) [17, 19, 20].

In regard to rare or uncommon diseases, doctors who rely heavily on system 1 thinking tend to make mistakes that delay diagnosis, since, due to low prevalence, there are few or no patterns accumulated in memory. From this begins the journey of patients with rare or uncommon diseases, marked by the search for several doctors of various specialties, multiple tests, and procedures. Many of these patients end up dying before the final diagnosis is discovered and take years to finally start treatment, as is the case with amyloidosis [2, 5].

38.3 Amyloidosis Patient Journey

Cardiac amyloidosis, although considered a rare disease, is actually an underdiagnosed disease. In general, it is estimated that it takes these patients approximately 2–4 years before cardiac amyloidosis is placed among the suspected diagnoses. By this time, most patients had been through at least five professionals from different specialties [1, 5–7].

This delay occurs for some reasons, such as the use of old criteria to initiate suspicion: clinical examination of diastolic restriction; low voltage ECG; the presence of sparkling on echocardiogram, abdominal fat biopsy considered to have high sensitivity, and failure to observe systemic manifestations together. Furthermore, the disease is rarely placed among the differential diagnoses. Because of the systemic presentation of the disease, several other diagnoses are commonly investigated. Other factors involved in this delay are the patient's own lack of knowledge about his disease and health status, as well as the physician's own lack of knowledge about amyloidosis and clinical reasoning. In this case, the physician's cognitive processes are easily affected by inadequate synthesis of the collected data and the influence of biases and noise. Added to all this is the lack of data integration, as many services still do not use electronic medical records. Thus, physical records are sometimes kept in a disorganized manner or even lost due to structural or organizational problems. With this, professionals lose the chance to recruit past data not reported by the patient and their families. Populations with greater difficulty in accessing specialized services are those most vulnerable to diagnostic delay [3, 6–10].

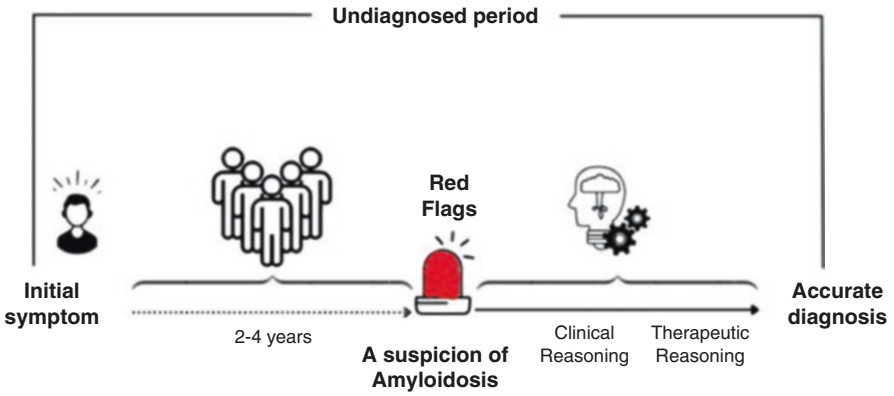


Fig. 38.2 Adapted diagram of the delay in the diagnosis of cardiac amyloidosis

Technological advances and expanded access to high-quality data have allowed new ways to aid the diagnostic process. Currently, diagnostic tools have contributed greatly to bringing to the physicians' minds some diagnostic suspicions that are little remembered on a daily basis. One important technology that has its use being expanded is Isabel Healthcare, a differential diagnosis tool. Isabel is used by physicians around the world to help create diagnostic hypotheses and differential diagnoses, i.e., it reduces clinical uncertainty. Its advantage is the ability to enter various characteristics of the patient's condition in free text, from which algorithms will be generated that contribute to clinical reasoning. This tool can be used on various handheld devices and has approximately 6000 diseases and 4000 drugs covered. The rejection of the adoption of technological support by physicians can also influence the delay and diagnostic error [5, 11, 12, 29].

This elapsed time is sometimes defined by uncertainty, frustration after several hospital visits, unnecessary tests and procedures, inadequate diagnosis and treatment, and worst of all, disease progression. Thus, this long journey has an emotional and economic cost to the patient, full of wasted time, effort, and resources until the treatment (Fig. 38.2) [3, 12].

38.4 Challenges in Diagnosing the Disease

In Brazil, faced with the complex pictures of the disease, in general, the diagnoses are made in services of high complexity in the public system. However, there is a lack of reference centers throughout the regions and structured public policies. This causes a great delay in diagnosis and the search for different centers of care, without success [8, 9].

In the last decade, different medical societies have developed guidelines and positions on cardiac amyloidosis to promote medical education and improve care. The Brazilian Society of Cardiology, 2021, developed an important document to guide the diagnostic reasoning stage. Two routes for the diagnosis of the disease were created: hematological and nonhematological. For this, attention to the RED FLAGS was reinforced. When applied, the reasoning becomes organized, and they aid the medical education process by facilitating the diagnostic reasoning of patients with amyloidosis [9, 12, 29, 30].

RED FLAGS—high suspicion of cardiac amyloidosis
Family history
HF with preserved FE, especially in men > 60 years
Functional class not compatible with ejection fraction
Patient with hypertrophic cardiomyopathy and presence of pericardial effusion, atrioventricular block, septal and valve thickening and granular appearance
Older man with symmetrical hypertrophic cardiomyopathy without other factors, such as systemic arterial hypertension
AF and conduction block in young people without comorbidities
Elevated Natriuretic Peptides disproportionate to the clinical picture
Bilateral carpal tunnel syndrome, especially in men with LVH
Erectile dysfunction, without comorbidities
Elevated troponins in the absence of coronary syndrome
Intolerance to ACEi, ARB II and beta-blockers
Macroglossia, shoulder pad and periorbital hematoma (AL form)
Bilateral carpal tunnel syndrome
Rupture of the biceps tendon
Unilateral or bilateral reduction of the pupillary reflex
Low-flow or low-gradient aortic stenosis with wall thickening
Unexplained progressive peripheral neuropathy (particularly if associated with autonomic dysfunction)
Echocardiography: biventricular hypertrophy, infiltrative phenotype, myocardial hyperrefringency, valve and/or interatrial septal thickening
Low voltage on ECG (20% without low voltage)
Concentric LV wall thickening with reduced QRS amplitude or no increase in proportion to the increased LV wall thickness

HF heart failure, *FE* ejection fraction, *AVB* atrioventricular block, *AF* atrial fibrillation, *LVH* left ventricular hypertrophy, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *ECG* electrocardiogram, *LV* left ventricular

Faced with findings suggestive of cardiac amyloidosis, further investigation of the disease begins. This is done with the measurement of the serum Kappa/lambda ratio, serum immunofixation and urinary immunofixation. If present, proceed via the hematological route, and if absent, proceed via the cardiological route. By the

hematologic route, evaluation by a hematologist and biopsy of peripheral tissues are urgently requested. If cardiac amyloidosis is found, the disease is confirmed and proceeds to amyloid protein typing by mass spectrometry or HI. If TTR is present, gene sequencing should be performed. Still in the hematological route, if cardiac amyloidosis is not found, perform cardiac scintigraphy with bone tracing, Pyrophosphate—Tc-99 m, if available [6, 10–12, 29, 31].

By the cardiac route, after dosage of the serum Kappa/lambda ratio, serum immunofixation, and urinary immunofixation with negative results, proceed with the performance of cardiac scintigraphy with bone tracing, Pyrophosphate—Tc-99 m, if available. In the case of cardiac uptake grade 2.3, heart/contralateral ratio ≥ 1.5, confirmed with SPECT, one has the confirmation of cardiac amyloidosis. In that case, one should proceed to genetic sequencing of the TTR form. If positive, hereditary aTTR. If negative, wild ATTR. If the scintigraphy has no findings consistent with amyloidosis, the amyloidosis is ruled out. If scintigraphy is not available, an endomyocardial biopsy with Congo red investigation is performed. If negative, amyloidosis is ruled out. If positive, proceed with amyloid protein typing by mass spectrometry or HI [10–12, 29–31].

38.5 Strategies for Reducing Diagnostic Error

There are several strategies that, if adopted routinely, contribute to the reduction of diagnostic error. One of these involves the physician's own training and method of diagnosis. Although the use of system 1 is convenient and commonly sufficient for diagnosis, the use of system 2 should be improved as well. Improved clinical reasoning and better knowledge of diagnostic errors are essential [15, 19].

At the first contact with the patient, regardless of the previous history of other visits, it is important to take a detailed history and perform a physical examination on the patient. This moment is also the key to establishing the doctor–patient relationship and gaining the patient's trust; after all, in the case of uncommon or rare diseases, patients have already exhaustively seen doctors [1–3].

From the data collected, the doctor must formulate a chart of signs and symptoms, starting by filtering the truly relevant information and organizing a problem list with a summary of the case. Always ask the patient if there is anything else to report. Then, the doctor must carefully analyze the data and even the patient's trajectory, what has been missed, and what else might be relevant. With this, one can formulate the hypotheses based on the learned knowledge and patterns and at least three differential diagnoses [20, 26, 28].

From these suspicions, if necessary, the investigation is started with complementary exams, always focused on the patient's condition. When the hypotheses are well formulated, the facilitated complementary exams are well-indicated. Especially in the case of uncommon diseases, which commonly call for specific and rarely

available exams, it is frequent to request an excess of exams that confuse the doctor even more. It is important to mention that this reasoning is dependent on the theoretical knowledge and scripts stored in the physician's memory. It is important to increase knowledge of related diagnoses to form robust heuristics that lead to the correct diagnosis, which requires in-depth study and discipline [24, 32].

When in doubt, it is not enough to close one's mind only to the syndromes that show some patterns of the disease presented by the patient and order a series of tests. At this moment, consulting other professionals, dedicating more time to reflect on the picture, researching reliable scientific sources, and asking the patient new questions are essential to better direct the formulation of hypotheses. Today, smart digital tools also support diagnostic reasoning, such as Isabel Healthcare. By putting together the problem list, the signs and symptoms, the hypotheses, the differential diagnoses, and the complementary tests, one can arrive at the final diagnosis. However, it is important to perform metacognition, even if there are no uncertainties or doubts. If these are still present, it will be even more essential. Metacognition is the self-reflection on the cognitive processes adopted in the reasoning and identification of points of failure and those that need correction. If necessary, the doctor must return to the data collection of the patient's history, generate new hypotheses, and/or request new complementary tests. It is always important to keep updating the problem list, the case summary, and the addition or exclusion of hypotheses and differential diagnoses. To do this, in addition to new tests and new data, the doctor can appeal to other expert opinions, diagnostic support applications, and staff involved in the care of the patient and his or her family [26, 33].

In the case of rare and uncommon diseases, metacognition is essential for detecting the doctor's own limitations, encouraging him to seek a second opinion and new knowledge. This step should not be neglected, since it is at this point that the most complex biases, errors, and noises are identified. Encouraging the practice of metacognition for diagnoses invariably involves the use of system 2 [1–3].

The error and delay in diagnosing cardiac amyloidosis are so relevant that, today, there are organizations formed to warn and contribute to the diagnosis of amyloidosis around the world. This is the case with the Amyloidosis Foundation, which emerged from the merger of two organizations interested in the problem of amyloidosis diagnosis, the Amyloidosis Research Foundation and the Amyloidosis Support Network, in 2007. This organization aims to raise awareness of earlier diagnosis among physicians and empower patients with the services offered by the organization itself. To this end, the Amyloidosis Foundation offers research grants for all types of amyloidosis, rounds, and participation in medical conferences to discuss the topic in addition to the Grand Rounds program, which educates physicians regarding diagnosis. This foundation becomes a great ally to the clinical reasoning to diagnose cardiac amyloidosis by providing education and awareness of the medical field as well as support and knowledge to the families under investigation [1–3, 5–7, 30].

In summary, one can put as key points to prevent diagnostic error:

Really listen to the patient and involve them in the diagnostic process
Detailed anamnesis and physical examination
Structured clinical data collection. Initially, without the influence of complementary tests to avoid quick decisions based on incomplete information.
Formulate a problem list and case summary—watch out for RED FLAGS
Think about the hypotheses and look for 3 differential diagnoses
Study and discuss cases, whether simple or complex, to refine the theoretical basis of scripting
Request and check the complementary exams based on the hypotheses, without exaggeration
Use metacognition in all clinical reasoning processes—use system 2!
Always keep a margin of doubt—recognize that every diagnostic process is subject to error.
Use the question: what else can it be?
Seek support with a second opinion, family, care team, doctors who have already seen you, and on diagnostic support apps like Isabel.
Learn the causes of errors, biases, and about clinical reasoning—cognitive debiasing.
The clinical reasoning process must be dynamic and team-based
Reflect on your diagnostic process, and detect errors and points for improvement.

It is also important to remember that patients with underdiagnosed diseases, after going through many doctors and appointments, become frustrated and may arrive discredited until the next doctor. An open and welcoming attitude will be important when collecting data [1–3].

Finally, being informed when a diagnosis is wrong is very important for improving clinical reasoning by allowing professional growth and improving the cognitive process involved in the diagnosis [15, 26, 27].

38.6 Conclusions

Stimulating the study of clinical reasoning, the diagnostic process, and related errors and biases is a golden rule for greater diagnostic assertiveness. The cognitive process of clinical reasoning should be stimulated in all stages of medical training. The diagnosis of cardiac amyloidosis still remains late. Cardiac amyloidosis should always be used in the differential diagnosis in clinical practice when encountering the Red Flags of the disease. New diagnostic methods and virtual tools facilitate the investigation. Early recognition of amyloidosis is the key to changing survival rates. Finally, many diseases that are considered rare are in fact underdiagnosed, often due to misdiagnosis.

References

1. Isono M, Kokado M, Kato K. Why does it take so long for rare disease patients to get an accurate diagnosis?—a qualitative investigation of patient experiences of hereditary angioedema. PLoS One. 2022;17:e0265847. https://doi.org/10.1371/journal.pone.0265847.
2. Svenstrup D, Jørgensen HL, Winther O. Rare disease diagnosis: a review of web search, social media and large-scale data-mining approaches. Rare Dis. 2015;3(1):e1083145. https://doi.org/10.1080/21675511.2015.1083145.
3. Lopes MT, Koch VH, Sarrubbi-Junior V, Gallo PR, Carneiro-Sampaio M. Difficulties in the diagnosis and treatment of rare diseases according to the perceptions of patients, relatives and health care professionals. Clinics. 2018;73:e68. https://doi.org/10.6061/clinics/2018/e68.
4. Isabel Health Care [homepage on the Internet]. The Isabel story. https://www.isabelhealthcare.com/. Accessed 6 May 2022.
5. Simões MV, Fernandes F, Marcondes-Braga FG, Scheinberg P, Correia EB, Rohde LEP, et al. Position statement on diagnosis and treatment of cardiac amyloidosis. Arq Bras Cardiol. 2021;117(3):561–98.
6. Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. Circulation. 2017;135(14):1357–77.
7. Waddington Cruz M, Amass L, Keohane D, et al. Early intervention with tafamidis provides long-term (5.5-year) delay of neurologic progression in transthyretin hereditary amyloid polyneuropathy. Amyloid. 2016;23:178–83.
8. Maurer MS, Elliot P, Comenzo R, Semigran M, Rapezzi C. Addressing common questions encountered in diagnosis and management of cardiac amyloidosis. Circulation. 2017;135(14):1357–77.
9. Mesquita ET, Jorge AJL, Souza Junior CV, Andrade TR. Cardiac amyloidosis and its new clinical phenotype: heart failure with preserved ejection fraction. Arq Bras Cardiol. 2017;109(01):71–80.
10. Rubin J, Alvarez J, Teruya S, et al. Hip and knee arthroplasty are common among patients with transthyretin cardiac amyloidosis, occurring years before cardiac amyloid diagnosis: can we identify affected patients earlier? Amyloid. 2017;24(4):226–30. https://doi.org/10.1080/13506129.2017.1375908.
11. Svenstrup D, Jørgensen HL, Winther O. Rare disease diagnosis: a review of web search, social media and large-scale data-mining approaches. Rare Dis. 2015;3:e1083145. PMID: 26442199.
12. Gertz M, Adams D, Ando Y, et al. Avoiding misdiagnosis: expert consensus recommendations for the suspicion and diagnosis of transthyretin amyloidosis for the general practitioner. BMC Fam Pract. 2020;21:198. https://doi.org/10.1186/s12875-020-01252-4.
13. Singh H, Meyer AND, Thomas EJ. The frequency of diagnostic errors in outpatient care: estimations from three large observational studies involving US adult populations. BMJ Qual Saf. 2014;23(9):727–31.
14. Giardina TD, Sarkar U, Gourley G, Modi V, Meyer AND, Singh H. Online public reactions to the frequency of diagnostic errors in US outpatient care. Diagnosis (Berl). 2016;3(1):17–22.
15. Melo M, Gusso GDF, Levites M, Amaro E Jr, Massad E, Lotufo PA, et al. How doctors diagnose diseases and prescribe treatments: a fMRI study of diagnostic salience. Sci Rep. 2017;7(1):1304.
16. Pelaccia T, Tardif J, Triby E, Charlin B. An analysis of clinical reasoning through a recent and comprehensive approach: the dual-process theory. Med Educ Online. 2011;16.
17. Higgs J, Jones M. Clinical decision making and multiple problem spaces. In: Higgs J, Jones MA, Loftus S, Christensen N, editors. Clinical reasoning in health professions. Amsterdam: Elsevier; 2008. p. 4–19.
18. Elstein AS. Thinking about diagnostic thinking: a 30-year perspective. Adv Health Sci Educ Theory Pract. 2009;14(S1):7–18.
19. Kahneman D. Fast and slow two ways of thinking. Objetiva. 2002. p. 9–497.

20. Kahneman D, Sibony O, Sunstein CR. Noise: a flaw in human judgment. 1st ed. New York: Little, Brown Spark; 2021.
21. Gurat MG, Medula CT Jr. Metacognitive strategy knowledge use through mathematical problem solving among preservice teachers. Am J Educ Res. 2016;4(2):170–89.
22. Mendonca VS, Gallagher TH, de Oliveira RA. The function of disclosing medical errors: new cultural challenges for physicians. HEC Forum. 2019;31(3):167–75.
23. Saposnik G, Redelmeier D, Ruff CC, Tobler PN. Cognitive biases associated with medical decisions: a systematic review. BMC Med Inform Decis Mak. 2016;16(1):138.
24. Réa-Neto A. Clinical reasoning—the diagnostic and therapeutic decision process. Rev Assoc Med Bras. 1998;44(4):301–11.
25. Wellbery C. Flaws in clinical reasoning: a common cause of the diagnostic error. Am Fam Physician. 2011;84(9):1042–8.
26. O'Sullivan ED, Schofield SJ. Cognitive bias in clinical medicine. J R Coll Physicians Edinb. 2018;48(3):225–32.
27. Singh H, Giardina TD, Meyer AND, Forjuoh SN, Reis MD, Thomas EJ. Types and origins of diagnostic errors in primary care settings. JAMA Intern Med. 2013;173(6):418–25.
28. Croskerry P, Singhal G, Mamede S. Cognitive debiasing 1: origins of bias and theory of debiasing. BMJ Qual Saf. 2013;22(Suppl 2):58–64.
29. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. Trends Cardiovasc Med. 2018;28(1):10–21.
30. Amyloidosis Foundation [homepage on the Internet]. Our history. https://amyloidosis.org/us/#our-history. Accessed 6 May 2022.
31. Singh V, Falk R, Di Carli MF, Kijewski M, Rapezzi C, Dorbala S. State-of-the-art radionuclide imaging in cardiac transthyretin amyloidosis. J Nucl Cardiol. 2019;26(1):158–73.
32. Charlin B, Boshuizen HPA, Custers EJ, Feltovich PJ. Scripts and clinical reasoning. Med Educ. 2007;41(12):1178–84.
33. Mamede S, van Gog T, van den Berge K, Rikers RMJP, van Saase JLCM, van Guldener C, et al. Effect of availability bias and reflective reasoning on diagnostic accuracy among internal medicine residents. JAMA. 2010;304(11):1198.

Chapter 39
Multidisciplinary Approach in Fabry Disease and Amyloidosis

Renata Adrielle Lima Vieira, Lidielle S.P.R. Pereira, Rejane Silva Rocha, Luciana Bastos Muniz, and Elaine Xavier de Ávila Almeida

39.1 Introduction

The various clinical and psychological disorders that these patients present require the involvement of a multidisciplinary health team, and the working of nurse, psychology, nutrition, physiotherapy, and speech therapy teams must be involved so that it is possible to attend the individual in a holistic way and expand the possibilities of treatments, mainly related to neuropathic changes in both diseases.

Neuropathic pain is disabling, causes a reduction in quality of life, impairs professional performance, and limits the social participation of patients who live with these pains. In this context, treatments aimed at minimizing pain and physical rehabilitation are facilitators of autonomy and mobility. From this perspective, it is important that health facilities adopt a coordinated approach to patient care, with the direction of doctors, for example, neurologists, cardiologists, nephrologists, and hematologists, to multidisciplinary professionals.

R. A. L. Vieira (✉)
Departamento de Nutrição Clínica e Social, Universidade Federal de Ouro Preto, Ouro Preto, Brazil
e-mail: renata.lima@ufop.edu.br

L. S.P.R. Pereira
Hospital Pró-Cardíaco, Rio de Janeiro, Brazil

R. S. Rocha
Instituto Oswaldo Cruz - FIOCRUZ, Rio de Janeiro, Brazil

L. B. Muniz
Centro Municipal de Reabilitação Professora Dilma Coutinho da Silva, Saquarema, Brazil

E. X. de Ávila Almeida
Centro Geriátrico Nilton Macedo Moreira, Iguaba Grande, Brazil

Hospital Municipal Naelma Monteiro, Rio das Ostras, RJ, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_39

These professionals are able to maintain a unique relationship with the patient and their family and thus manage to explore the patients' diverse needs, such as the psychological, social, and relationship conflicts that involve the life of the individual who lives with Fabry disease or amyloidosis.

39.2 Nutritional Approach in Fabry Disease

The clinical manifestations, arising from GL-3 accumulation, occur mainly in the vascular endothelium of the skin, heart, liver, kidneys, central nervous system, and gastrointestinal tract (nausea, vomiting, intermittent diarrhea, and constipation; abdominal pain and/or bloating). Gastrointestinal symptoms are some of the most frequent and early general complaints among patients with DF. In addition, they occur throughout the gastrointestinal tract, varying in intensity and frequency. The patient's presentation can vary with severe symptoms to a combination of multiple symptoms that affect daily functioning and health [1].

Significant gastrointestinal involvement has also been observed in children and may progress in severity with age, especially in children aged 1–4 years, with the most common complaint being abdominal pain and diarrhea with weight loss in childhood [1–3]. The body mass index (BMI) in boys with FD was lower than that in girls who had FD and healthy boys, probably due to the early onset of the disease and higher disease burden in boys than in girls [4, 5].

Although diarrhea presenting characteristic of watery stools, free of blood or mucus, is a common complaint, in female patients, constipation is more frequent [4, 5]. In addition, some patients with FD describe an interspersed cyclical pattern between diarrhea, constipation, and normal bowel movements, making diagnosis and management difficult. In most cases, gastrointestinal symptoms resemble irritable bowel syndrome (IBS) and inflammatory bowel diseases (IBD) [6].

Enzyme replacement therapy (ERT) improves the gastrointestinal symptoms associated with FD. However, more than half of patients treated with ERT continue to experience gastrointestinal symptoms, and others even develop new symptoms during use [7]. To date, no studies have been conducted on dietary interventions in patients with DF with gastrointestinal manifestations; therefore, the recommendations found in the scientific literature are similar to those for IBS and IBD [8].

There is little evidence for restricting particular foods in IBD [9, 10]. However, some foods, such as excessive amounts of dietary lipids, caffeine, lactose, fructose, sorbitol, alcohol, and spicy foods, may be poorly tolerated, especially for patients with diarrhea or mixed gastrointestinal manifestations (diarrhea and/or constipation) [8]. In addition, irregular and/or bulky food may affect colonic motility and therefore worsen symptoms. For this reason, patients should be advised to follow a regular pattern of meals (breakfast, lunch, and dinner with one or two snacks) and avoid waiting too long between meals or avoiding large meals, as well as eating late at night [8, 11].

In the presence of diarrhea, patients should be instructed to consume soluble fiber as tolerated. Metabolism of soluble fibers and resistant starches by intestinal bacteria leads to the production of short-chain fatty acids (SCFAs), which serve as substrates for colonocytes, facilitate the absorption of fluids and salts, and may help

Table 39.1 Sources of fiber

Soluble Fiber
Pectin (apple, citrus peel, vegetables, potatoes, fruit); Gums, mucilage, beta-glucans (oats, legumes); some Hemicelluloses (psyllium)
Fructool-oligosaccharides-FOS (garlic, onion, banana, tomato, artichoke, chicory)
Insoluble Fiber
Cellulose (whole wheat flour, beans, peas, apple, bran, cabbage, root vegetables); Type B hemicelluloses (bran, cereals, soybeans, whole grains); Lignin (mature vegetables, wheat)

Source: Adapted [14]

regulate gastrointestinal (GI) motility [12]. In the remission phase, the insoluble fiber content should be progressively increased [13].

For the treatment of constipation, a combination of soluble and insoluble fibers is of interest. However, increasing the amount of insoluble fiber in the diet, especially in patients without constipation, may worsen symptoms. Although increasing fiber intake is a usual component of initial therapy of gastrointestinal changes, patients may have ongoing symptoms possibly related to the type of fiber consumed (Table 39.1) [14].

Dietary fiber intake for adults is recommended to be 20–35 g/day. For children older than 2–20 years of age, 5 g plus age should be added to obtain the total daily fiber intake. There is no recommendation for children under 2 years of age because it is considered that breast milk is present in this age group. After 6 months of exclusive breastfeeding, a complete and varied diet is recommended [15, 16].

In addition, adequate fluid intake (30–35 mL/kg/day) is recommended, especially when powdered fiber supplements are used [13]. Adequate hydration should be remembered not only by increasing fiber intake, but also in situations of severe diarrhea, as it can result in dehydration and electrolyte depletion [9]. In this situation, restoring fluids and electrolytes is a priority. Electrolyte losses, especially of potassium and sodium, should be corrected soon by the use of oral electrolyte solutions and glucose with added potassium. Another strategy would be soups and broths, vegetable juices, and isotonic fluids [13].

The use of probiotics has also been suggested in cases of diarrhea in IBD and IBS [9, 17, 18]. Intake of 10^9 to 10^{11} bacteria through multistep probiotic supplementation has been associated with decreased incidence, duration, and severity of gastrointestinal diseases. Furthermore, it is related to reduced diarrhea and hospitalization times and induction and maintenance of IBD remission, with minimal adverse effects in adults and children [11, 19]. However, there are still no studies evaluating the use of probiotics in patients with FD.

Recent studies show that certain foods containing carbohydrates, such as those that are highly fermentable, in the presence of gut bacteria actually exacerbate gastrointestinal symptoms [13, 20]. This is because fermentable short-chain carbohydrates increase the water volume in the small intestine and colonic gas production. In this regard, reducing fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (low FODMAP diet) is proposed for improvements in bloating, pain, flatulence, diarrhea, and other symptoms [20].

In general, the low FODMAP diet consists of three stages: restriction, reintroduction, and FODMAP customization. In the first stage, it focuses on

comprehensive assessment of symptoms and diet, detailed description of FODMAPs and their association with symptom induction, followed by counseling on FODMAP restriction. In the case of persistent symptoms, the Low FODMAP diet should be stopped. However, if there is improvement in symptomatology, there should be education about reintroducing FODMAP-rich foods to assess individualized tolerance and identify the triggering symptoms of the foods. FODMAP-rich foods are added in increasing amounts every 3 days, while symptoms are monitored. Then, the patient can follow the FODMAP customization for which a less restrictive diet is consumed, which excludes their personal FODMAP triggers and allows for a more diverse dietary intake [21, 22]. It is essential that there is follow-up with a nutritionist, as it excludes many foods, so such a protocol is recommended for a short period (total duration of 4–6 weeks), being compromised mainly in the supply of carbohydrates and calcium [14, 21, 22].

In FD, some manifestations concerning the upper gastrointestinal tract are reported, although they are less common, such as dyspepsia, postprandial fullness, and early satiety. These symptoms may induce dietary restrictions and lead to weight loss [8]. In addition to medication management, dietary modifications are useful, such as low-fat meals, eating several smaller meals instead of a single main/voluminous meal, and avoiding foods known to trigger symptoms such as coffee, alcohol, chocolate, or fatty foods, although there is no evidence from randomized clinical trials to support such interventions [6, 23–25]. In the case of pancreatic dysfunction, supplementation with pancreatic enzymes alleviates various gastrointestinal symptoms [1]. Thus, gastrointestinal manifestations remain an important cause of morbidity that needs specific treatment [8].

In addition to gastrointestinal clinical manifestations, renal manifestations require specific nutritional management. Renal disease includes progressive proteinuria, followed by a reduction in the glomerular filtration rate, and may lead to failure with the need for dialysis and transplantation [25]. When glomerular damage occurs, the clinical picture is similar to that of diabetic nephropathy. However, along with ERT, several strategies are needed to prevent and treat FD nephropathy and its complications, such as cardiovascular events, hypertension, and bone disorders [26].

Dietary intervention is critical in treating most kidney disorders and preventing complications. In the case of chronic kidney disease (CKD), the goals of nutritional management are to preserve renal function, normalize body fluid composition, minimize hyperphosphatemia and renal osteodystrophy, counteract anorexia and nausea, provide energy and micronutrient needs, and promote optimal growth in children [8, 27].

Restriction of protein intake has been proposed to reduce glomerular hyperfiltration and slow the progression of renal failure (Table 39.2). These diets should be progressively installed to allow careful dietary counseling and adequate compliance. In adults with CKD at any stage or posttransplant, there is insufficient evidence to recommend a particular type of protein (plant vs animal) in terms of effects on nutritional status, calcium or phosphorus levels, or the blood lipid profile. However, reducing animal-based protein and moving toward more plant-based protein sources also reduces acid production and metabolic acidosis, which are

Table 39.2 Daily dietary protein recommendation for patients with chronic kidney disease

	Protein intake recommendation
CKD 3–5 patients not on dialysis and without diabetes, who are metabolically stable	• A low-protein diet providing 0.55–0.60 g dietary protein/kg body weight/day, or • A very low-protein diet providing 0.28–0.43 g dietary protein/kg body weight/day with additional keto acid/amino acid analogs to meet protein requirements (0.55–0.60 g/kg body weight/day)
CKD 3–5 patients not on dialysis and with diabetes, who are metabolically stable	• Protein intake of 0.6–0.8 g/kg body weight per day to maintain a stable nutritional status and optimize glycemic control
CKD 5D maintenance hemodialysis and peritoneal dialysis patients with/without diabetes who are metabolically stable	• Dietary protein intake of 1.0–1.2 g/kg body weight per day to maintain a stable nutritional status
Early posttransplantation	• In case of acute graft rejection, the protein recommendation is 1.3–1.5 g/kg of current or ideal weight
Late posttransplantation	• The recommendation is approximately 0.8 g/kg/day. A restriction of 0.6 g/kg/day may be considered in case of chronic rejection
Children with CKD2–5D	• Protein intake in children with CKD2–5D is at the upper end of the SDI to promote optimal growth • The protein intake at the lowest end of the range is considered the minimum safe amount and protein intake should not be reduced below this level
Children on dialysis	• Protein intake may need to be higher than the SDI for nondialysis patients to account for dialysate protein losses • In children with persistently high blood urea levels, we suggest that protein intake may be adjusted toward the lower end of the SDI, after excluding other causes of high blood urea levels

CKD Chronic kidney disease, *SDI* Suggested dietary intake
Source: Adapted [27–29]

common in CKD patients, especially for lower protein intakes (0.3–0.5 g/kg protein/kg/day) supplemented with ketoacids [27].

When edema is present or the patient is on renal replacement therapy (dialysis), sodium and fluid restriction (to less than approximately 1.5 L/day) is mandatory. In addition to its effects on edema, sodium restriction can slow the progression of kidney disease and albuminuria and mitigate hypertension, one of the main complications of CKD. Hypertension is not a common early finding in Fabry patients, but becomes more prevalent with disease progression [8, 30]. Dietary salt restriction (should be initiated, if tolerated, even in normotensive patients controlled with medication) of up to 5 g salt/day (NaCl) or less than 2 g sodium/day or <90 mmol sodium/day should be added to food in CKD patients. In addition, you should avoid processed and ultra-processed products, such as canned foods, French fries and cured meats, and industrialized ready-made seasonings [31].

Biochemical exams, including serum protein, albumin, folate, vitamin B12, calcium, and phosphate levels, are typically normal in DF. Therefore, if a patient has significantly abnormal levels, other diagnoses should be considered. However, anemia is a feature of Fabry patients, possibly because of underlying renal and cardiac problems [32]. Oral iron should be considered as first-line treatment in patients with mild anemia as a result of CKD who have not previously been intolerant to oral iron. The main disadvantages of oral iron include reduced efficacy compared to intravenous administration, poor gastrointestinal tolerance, malabsorption due to elevated hepcidin, and possible changes in the microbiome. Oral administration of a single dose of iron every other day versus every day increases fractional iron absorption and may be an effective strategy [33]. Intravenous iron should be considered for those with prior intolerance to oral iron, patients requiring erythropoiesis-stimulating agents, and those with hemoglobin below 10 g/dL [9].

Furthermore, monitoring 25 OH-vitamin D levels in patients with Fabry nephropathy should be part of routine management and should correct any nutritional vitamin D deficiency. This deficiency is associated with low bone mineral density, adverse cardiovascular outcomes, and worsening renal outcomes [1, 9, 23].

Other possible dietary interventions may modulate the inflammation and oxidative stress occurring in the pathophysiology of DF, which as a consequence leads to irreversible tissue damage with target organ fibrosis [34, 35]. Although there have been no specific studies on DF, diet is known to be one of the main environmental factors modulating both inflammation and oxidative stress. Isolated nutrients and nonnutritive food components, such as n-3 polyunsaturated fatty acids (PUFAs), polyphenols, prebiotics, and probiotics, can influence the inflammatory/oxidative stress response [36, 37].

Several lines of evidence support the beneficial effects of n-3 PUFAs with anti-inflammatory action [38–40]. In particular, it has been observed that eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA) partially inhibit the expression of adhesion molecules, leukocyte-endothelial adhesive interactions, and leukocyte chemotaxis synthesis of prostaglandins and leukotrienes [41], promoting improvement of the lipid profile (reducing triglycerides and LDL cholesterol and increasing HDL levels), reduction of blood pressure, and decreased risk of cardiovascular events in the presence or absence of CKD. Therefore, supplementation with 2–4 g/day EPA and DHA has been shown to be efficient and safe [27, 42]. Moreover, vegetable oils rich in α-linolenic (α-LA) and γ-LA, such as flaxseed oil and borage oil, respectively, exerted strong antiproliferative activity of fibroblasts in FD [43].

Polyphenols regulate immunity by interfering with immune cell regulation, the synthesis of proinflammatory cytokines, and gene expression and exhibit antioxidant activity. They inactivate NF-κB (nuclear factor kappa of activated B cells), modulate mitogen-activated protein kinase (MAPk) and arachidonic acid pathways, and suppress the expression of toll-like (TLR) and proinflammatory genes. They inhibit enzymes involved in the production of reactive oxygen species (ROS), such as xanthine oxidase and NADPH oxidase (NOX), while positively regulating other endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase,

and glutathione (GSH) peroxidase (Px). It is generally believed that polyphenol activity is mainly localized in the intestine, where its immunoprotective and anti-inflammatory activities are initiated, subsequently ensuring systemic anti-inflammatory effects. Therefore, the consumption of fruits and vegetables, legumes, cocoa, and green tea reduces oxidative stress and neutralizes inflammation [9, 44].

Associated with the consumption of polyphenols, the consumption of soluble fibers promotes anti-inflammatory action because they are fermented by intestinal bacteria, producing SCFAs, in particular butyrate [45]. In recent years, evidence has been growing that the microbiota plays a key role in human health for the immune system and inflammatory process by maintaining the barrier integrity of the gastrointestinal tract and preventing the passage of bacterial lipopolysaccharides (LPS), a potent low-grade systemic inflammatory stimulant [46].

Both food components (nutrients and nonnutrients) and dietary patterns have been shown to exert protective effects against inflammation and oxidative stress. Thus, the Mediterranean diet (DM) exerts beneficial effects on the primary and secondary prevention of cardiovascular disease, type 2 diabetes, CKD, and inflammatory status [8, 27, 47]. DM includes many foods with anti-inflammatory activity, such as extra virgin olive oil, tomatoes, leafy green vegetables, fruits, whole grains, nuts and legumes, moderate intake of fish, and other meats and nuts [48].

Therefore, finding nutritional strategies that aim to improve inflammation and oxidative stress and minimize the clinical manifestations present in FD should be considered to slow disease progression.

39.3 Nutritional Approach in Amyloidosis

The extracellular deposition of an abnormal fibrillar protein that occurs in amyloidosis disrupts tissue structure and function, either in a single organ or systemically. The different types of amyloidosis entail the most diverse organ changes, and clinical treatment is dependent on this variation [49].

Among patients with systemic amyloidosis, involvement of the gastrointestinal tract is common but often subclinical. Additionally, cardiac, hepatic, renal, and neurological changes may be present and are associated with evidence of oxidative stress injury and chronic inflammation [50, 51].

In addition to drug treatment, nutrition can help manage symptoms and prevent further protein production. Nutrition may also be helpful in treating the many complications that can arise. To date, no studies have been conducted on dietary interventions in patients with amyloidosis. Therefore, dietary modifications are usually based on symptoms, nutritional abnormalities, and which organs have been affected by the disease. Therefore, early diagnosis of amyloidosis and identification of these changes are extremely important in the treatment and management of the patient [52].

The presence and pattern of gastrointestinal symptoms vary substantially, not only among different types of amyloid but also within them. Gastrointestinal

presentations are often nonspecific, with involvement from mouth to large intestine, and include macroglossia, dyspepsia, hemorrhage, diarrhea, steatorrhea, intestinal obstruction, malabsorption, and consequently weight loss [53]. Diarrhea is associated with several mechanisms, including bacterial overgrowth, the degree of bile acid malabsorption, pancreatic exocrine insufficiency (PEI), and rapid intestinal transit related to autonomic neuropathy. This likely contributes to the malabsorption of proteins, fats, and fluids [54].

Dietary intervention in the presence of diarrhea should contain soluble fiber intake, as tolerated, to help regulate GI motility [12]. Historically, a low-fat diet has been recommended in PEI to reduce steatorrhea. This recommendation has been abandoned in modern dietary counseling due to the risk of exacerbating weight loss and fat-soluble vitamin deficiencies. Most patients with PEI will tolerate a normal fat diet, provided that the dose of pancreatic enzyme replacement and supportive treatment with proton pump inhibitors are optimized. The dietary consultation should also include advice for sufficient caloric intake and normal fat content. Small, frequent meals are generally better tolerated than large, high-calorie meals [55]. Deficiencies of fat-soluble vitamins are very common in patients with PEI, and vitamin supplementation therapy should be administered if necessary [53, 56].

Pancreatic enzyme replacement therapy (PERT) has an indisputable indication in the presence of steatorrhea and/or weight loss. Pancreatic digestive enzymes can be administered orally, along with meals, to compensate for the lack of endogenous enzyme secretion. Some studies have shown an improved fat absorption ratio, decreased symptoms related to poor digestion, and even improved quality of life [57–59]. PERT is now increasingly considered a treatment for poor digestion, rather than just a way to suppress diarrhea. Therefore, higher doses are needed for large, fat-rich meals, and lower doses are sufficient for snacks and small meals [55].

The optimal dose of pancreatic enzymes in amyloidosis has not been investigated. Recommendations for PEI range from 20 to 40,000 units of lipase per main meal, as recommended by the German Society for Digestive and Metabolic Diseases [60]. In general, half the dose is recommended for snacks and small meals. If signs or symptoms of maldigestion persist, the PERT dose can be increased, and proton pump inhibitors can be added [55]. In cases of severe malabsorption, total parenteral nutrition (PN) can be extremely helpful in patients with severe gastrointestinal involvement [52].

There are no nutritional recommendations in the literature for patients with obstructive GI symptoms with amyloidosis, so the recommendations are similar to those for IBD. In this situation, a textured adapted diet (pasty or liquid) or a distal (postobstruction) nasoenteral feeding tube (NFT) may be recommended. If oral feeding is not sufficient, enteral nutrition (EN) should be considered as supportive therapy. Formulaic or liquid EN should always be preferred over PN unless totally contraindicated. The formula used for primary nutritional therapy is polymeric, moderate fat content, with no specific supplements. PN is indicated when there is intestinal obstruction without the possibility of placement of the NFT beyond the obstruction or difficulty in passage or when other complications occur, such as high output intestinal fistula [9].

Another common initial finding is proteinuria (with predominant albuminuria), often associated with nephrotic syndrome and severe edema, foaming urine, or uremic signs [49]. In amyloidosis, renal alteration causes albuminuria in up to 80% of patients, with proteinuria in the nephrotic range in 30–50%. This alteration can occur in AL and AA amyloidosis. Massive proteinuria with generalized edema and hypoalbuminemia can occur with normal creatinine and blood urea nitrogen concentrations; however, evidence of mild renal dysfunction is often found. For those patients with renal failure, dialysis, and transplantation, the protein recommendations are the same as for CKD (Table 39.2). After transplantation, amyloid may eventually appear in the donor kidney if the abnormal protein source is not treated [49, 61].

Nutritional support is one of the main measures for the adequate control of clinical and laboratory complications of the nephrotic state. The greater the loss of protein in the urine, the greater the complications related to renal function, such as dyslipidemia, thromboembolic phenomena, and infections [62, 63]. There is no consensus regarding the amount of protein to be prescribed in nephrotic syndrome. However, in patients with a normal glomerular filtration rate, a normoprotein diet is recommended, usually 0.8–1.0 g/kg/day. A hyperprotein diet offers no benefit, as it does not increase the level of serum albumin and does not protect the individual from the complications of the nephrotic state [64].

Restriction of liquids is not always recommended, but should be done in the presence of hyponatremia and serum hyposmolarity and avoided when there are clinical signs of hypovolemia and renal hypoperfusion [63]. Daily weight control and 24-h urinary volume measurement are simple and very effective measures to assess the decrease in edema and response to treatment. The goal is a negative sodium balance and a controlled water balance [62].

Moreover, sodium restriction is fundamental for the control of edema, and the use of 2 g of sodium per day or 5 g of NaCl (kitchen salt) is recommended. This is possible by reducing the amount of salt in food preparation and avoiding the use of additional salt during meals. It is also advisable to avoid processed foods and sausages [31, 65].

Most diagnosed cases of primary amyloidosis (type AL, AH, ALH) are caused by a clinical picture of amyloid deposition in the bone marrow that has similarities to multiple myeloma. Chemotherapy combined with stem cell transplantation (SCT) is an indication for clinical treatment. With eradication of defective plasma cells, amyloid production is slowed or stopped, and the bone marrow can become healthy again, but only 20% of patients are eligible [49, 66].

Nutritional therapy is indicated when the SCT patient has insufficient oral intake. For patients with a functioning gastrointestinal tract, oral/enteral nutrition therapy is suggested. However, in cases where there is severe gastrointestinal involvement (severe mucositis, incoercible vomiting, paralytic ileus, severe malabsorption, prolonged diarrhea) or gastrointestinal symptoms related to graft-versus-host disease, the use of PN should be considered [52, 67, 68].

There is a low level of evidence to recommend parenteral glutamine supplementation in SCT [68]. However, a systematic review comparing NP with glutamine to

standard NP noted no reduction in length of stay, but showed a reduced incidence of positive blood cultures in patients receiving NP with glutamine than those on standard NP [67].

Other types of amyloidosis are associated with hormonal proteins, aging, or specific areas of the body. A special case of localized amyloidosis is cerebral amyloid angiopathy (CAA). Amyloid protein is deposited in the walls of the cerebral arteries, increasing the risk of stroke and dementia. This neurological clinical picture is mostly seen in older patients. Because of neurological involvement, it becomes highly disabling, painful, and degenerative. If left untreated, it affects the lower and upper limbs and leads to permanent disability. In addition to impaired mobility, dysphagia can lead to malnutrition and impact quality of life [69].

In the presence of dysphagia, the systematization of nutritional and phonoaudiological assistance is necessary. The nutritional treatment should involve the use of modified food textures, making the food pasty, and in more advanced degrees of dysphagia, it will be necessary to change the texture of liquids such as juices, milk, and water through thickeners. Some caveats should be made regarding the thickening of liquids according to the type of preparation. In dairy preparations, temperature influences dilution, and cooled (10 °C) preparations should be liquefied to homogenize them, while acidic juices hardly form lumps, unlike alkaline juices, which sometimes need to be liquefied [70]. When a patient fails a swallowing test and is unable to tolerate oral fluids or food safely, an NFT should be inserted [71].

Another important element of care when there is disabling neurological involvement is the increased risk of developing pressure injuries [71]. Nutritional care in this condition is also necessary. Providing and consuming adequate calories through carbohydrates and lipids supports collagen and nitrogen synthesis, thus promoting anabolism and sparing protein from being used as an energy source. The recommendation in a pressure injury situation is to provide 30–35 kcal/kg body weight per day for malnourished adults or those at risk of malnutrition. The recommendation for protein is 1.25–1.5 g/kg body weight/day [72].

Amyloid formation or postfibrillar modification in several types of amyloidosis is also involved in free radical-promoted injury, which results in oxidative stress. Therefore, n-3 PUFAs, polyphenols, prebiotics, and probiotics may be an interesting nutritional strategy in this disease, as they modulate the inflammatory/oxidative stress response [36, 37]. In a study with 20 patients, radical scavengers, such as N-acetylcysteine, vitamin E, and vitamin C, were used for 6 months, and the nutritional status index tended to increase, although no improvement was found in the amount of amyloid deposition in biopsy specimens, suggesting a therapeutic possibility for the treatment of amyloidosis [73].

Thus, it is observed that nutritional monitoring and appropriate nutritional strategies to slow the progression of comorbidities and improve clinical symptoms arising from Fabry disease and amyloidosis are necessary and thus contribute to a better quality of life of these patients.

39.4 Nurse Approach in Amyloidosis and Fabry Disease

In the context of nursing, recognizing the patient's needs and the risks to which they are exposed helps to plan care and the quality of care to be provided, in addition to the educational process, which is essential for a better understanding of patients and family members and for the successful implementation and continuity of treatment [74].

One of the ways for nurses to apply their knowledge and direct care to patients is through the Systematization of Nursing Care, using tools that guide and systematize the work to meet their work object effectively and efficiently in the search to guarantee the improvement of the quality of life of patients. For this, the nursing diagnosis—NANDA—North American Nursing Diagnosis Association (Table 39.3) is carried out for this purpose, shown in the following table with signs and symptoms, the diagnosis, and the nursing actions necessary for the treatment of the patient with Fabry Disease and amyloidosis [75, 76].

In the final phase of these diseases, with motor limitations and when bedridden, skin lesions resulting from decubitus and other consequences of systemic manifestations can occur, and the nursing action can consist either of preventing and maintaining the integrity of the skin of these patients and treating ulcers of the skin when needed.

Table 39.3 Example of nursing diagnosis and planning based on NANDA

Signs and Symptoms	Nursing Diagnosis	Nursing planning
Pain in hands and feet	Chronic pain	Perform pain survey, include location, characteristics (onset/duration/frequency)
Angiokeratomas in Fabry disease	Impaired skin integrity	Encourage daily skin hydration
Susceptibility to discomfort or damage to the oral mucosa due to reduced quantity or quality of saliva to hydrate the mucosa which can compromise health in Fabry disease	Risk of dry mouth	Carry out hydration of the oral mucosa
Dry eye	Risk of dry eye	Keep your eyes lubricated
Presence of liquid stools in three or more bowel movements in 24 h	Diarrhea	Facilitate the identification of eating behaviors to be modified; set realistic goals; inform about the health need for diet modification.
Emotional suffering and Suicide attempt	Unstable emotional control	Keep active listening

39.5 Physiotherapy Performance

The physiotherapists work mainly in the prescription and in the supervision of physical exercises, mainly in the prevention of signs and symptoms of neuromotor and osteomioarticular impairment, in the control of pain and in the improvement of functionality, generating an impact on the quality of life of these patients.

A program of individualized physical exercises directed to the training of muscular strength, balance, and coordination (kinesiotherapy) is able to improve the physical and functional performance of patients with chronic diseases such as Fabry Disease and Amyloidosis. This can be performed with dumbbells, shin guards, and exercises using one's own body weight or with elastic bands such as the theraband of different resistances, in addition to treadmills and/or stationary bicycles [77].

In this context, the role of the physiotherapist becomes essential in controlling pain through manual interventions, kinesiotherapy, and electrothermophototherapy resources such as ice or heat, laser, ultrasound, and transcutaneous electrical nerve stimulation (TENS), equipment used in the treatment of acute and chronic pain for over 20 years. TENS is capable of reducing pain and, consequently, the need for analgesics and anti-inflammatory drugs in patients with chronic pain, such as those with Fabry disease and amyloidosis [78–80].

Among the main clinical manifestations of amyloidosis of great importance for physical therapy, we have the loss of muscle mass that many patients end up presenting, leading to global muscle impairment, decreased aerobic capacity, and lower exercise tolerance [77].

When the patient still has preserved gait and functional independence, physiotherapy can act in a preventive way through exercises for muscle strengthening, kinesiotherapy, and cardiorespiratory conditioning of these individuals. Supportive treatment (nonpharmacological treatment), consisting of a rehabilitation service, supports groups in the clinic, psychiatric, and psychological care as fundamental in the treatment of pain, as well as the pharmacological [81].

In patients with Fabry disease, approximately 12–40% report disabling chronic pain in different regions of the body. Some authors postulate that pain in this case also consists of nociceptive or inflammatory components, as there are reports of improvement with the administration of nonsteroidal anti-inflammatory drugs (NSAIDs). In this case, we can also use resources such as laser and ultrasound, which are widely used in the treatment of pain associated with inflammatory processes with good results. In both diseases, functional decline and gait difficulty due to involvement of the motor roots may lead to the need to use gait aids (walkers, canes, or crutches), which will be important for maintaining the autonomy and independence of these patients. It is the role of the physical therapist to indicate the best device as well as to teach patients the correct way to use them [82–84].

In the final stage of these diseases, when the patient is possibly bedridden due to the progression of pain, joint deformities and other systemic manifestations, the physiotherapeutic action consists of maintaining the musculoskeletal integrity of these patients, reducing the chronic pain, and maintaining cardiorespiratory

capacity (minimizing the risk of respiratory infections by maintaining lung capacity) of these individuals.

It is important to emphasize that all treatments must be designed and conducted individually, even if the clinical manifestations are similar between patients. The patient with Fabry Disease and Amyloidosis must be looked at and treated in a holistic, multidisciplinary way, without, however, being considered as a singular being and, therefore, needs a treatment directed exclusively to their clinical and kinetic-functional condition.

References

1. Zar-Kessler C, Karaa A, Sims KB, Clarke V, Kuo B. Understanding the gastrointestinal manifestations of Fabry disease: promoting prompt diagnosis. Ther Adv Gastroenterol. 2016;9(4):626–34. https://doi.org/10.1177/1756283X16642936.
2. Germain DP, Fouilhoux A, Decramer S, Tardieu M, Pillet P, Fila M, Riviera S, Deschênes G, Lacombe D. Consensus recommendations for diagnosis, management and treatment of Fabry disease in pediatric patients. Clin Genet. 2019;96(2):107–17. https://doi.org/10.1111/cge.13546.
3. Laney D, Peck D, Atherton A, Manwaring L, Christensen K, Shankar S, et al. Fabry disease in infancy and early childhood: a systematic literature review. Genet Med. 2015;17:323–30. https://doi.org/10.1038/gim.2014.120.
4. Hoffmann B, Schwarz M, Mehta A, Keshav S. Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy. Clin Gastroenterol Hepatol. 2007;5:1447–53. https://doi.org/10.1016/j.cgh.2007.08.012.
5. Deegan P, Baehner A, Barba Romero M, Hughes D, Kampmann C, Beck M, et al. Natural history of Fabry disease in females in the Fabry outcome survey. J Med Genet. 2006;43:347–52. https://doi.org/10.1136/jmg.2005.036327.
6. Hilz MJ, Arbustini E, Dagna L, Gasbarrini A, Goizet C, Lacombe D, et al. Nonspecific gastrointestinal features: could it be Fabry disease? Dig Liver Dis. 2018;50:429–37. https://doi.org/10.1016/j.dld.2018.02.011.
7. Banikazemi M, Ullman T, Desnick RJ. Gastrointestinal manifestations of Fabry disease: clinical response to enzyme replacement therapy. Mol Genet Metab. 2005;85(4):255–9.
8. Francini-Pesenti F, Verdiana Ravarotto V, Bertoldi G, Spinella P, Calò LA. Could nutritional therapy take us further in our approaches to Fabry disease? Nutrition. 2020;72:110664. https://doi.org/10.1016/j.nut.2019.110664.
9. Bischoff SC, Escher J, Hébuterne X, Kłęk S, Krznaric Z. ESPEN practical guideline: Clinical Nutrition in inflammatory bowel disease. Clin Nutr. 2020;39(3):632–53. https://doi.org/10.1016/j.clnu.2019.11.002.
10. Cozma-Petrut A, Loghin F, Miere D, Dumitrascu DL. Diet in irritable bowel syndrome: what to recommend, not what to forbid to patients! World J Gastroenterol. 2017;23:3771–83. https://doi.org/10.3748/wjg.v23.i21.3771.
11. Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. Lancet. 2020;396:1675–88. https://doi.org/10.1016/S0140-6736(20)31548-8.
12. Venegas DP, De la Fuente MK, Landskron G, González MJ, Quero R, Dijkstra G, et al. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol. 2019;10:277. https://doi.org/10.3389/fimmu.2019.00277.
13. Mahan LK, Raymond JL. Alimentos, nutrição e dietoterapia. 14th ed. Rio de Janeiro: Guanabara Koogan; 2018.

14. Cuppari L. Nutrição Clínica no adulto. 4th ed. São Paulo: Editora Manole; 2018.
15. Marlett JA, McBurney MI, Slavin JL. Position of the American Dietetic Association: health implications of dietary fiber. J Am Diet Assoc. 2002;102(7):993–1000. https://doi.org/10.1016/s0002-8223(02)90228-2.
16. The National Academy Press. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients). Food and Nutrition Board; 2005. Disponível em: http://books.nap.edu/openbook.php?record_id=10490&page=339. Acessado em 31/01/22.
17. Dale HF, Rasmussen SH, Asiller ÖÖ, Lied GA. Probiotics in irritable bowel syndrome: an up-to-date systematic review. Nutrients. 2019;11(9):2048. https://doi.org/10.3390/nu11092048.
18. Naseer M, Poola S, Ali S, Samiullah S, Tahan V. Prebiotics and probiotics in inflammatory bowel disease: where are we now and where are we going? Curr Clin Pharmacol. 2020;15(3):216–33. https://doi.org/10.2174/1574884715666200312100237.
19. Yang B, Lu P, Li MX, Cai XL, Xiong WY, Hou HJ, Ha XQ, et al. A meta-analysis of the effects of probiotics and synbiotics in children with acute diarrhea. Medicine (Baltimore). 2019;98(37):e16618. https://doi.org/10.1097/MD.0000000000016618.
20. Altobelli E, Del Negro V, Angeletti PM, Latella G. Low-FODMAP diet improves irritable bowel syndrome symptoms: a meta-analysis. Nutrients. 2017;9(9):940. https://doi.org/10.3390/nu9090940.
21. Whelan K, Martin LD, Comer MC. The low FODMAP diet in the management of irritable bowel syndrome: an evidence-based review of FODMAP restriction, reintroduction and personalization in clinical practice. J Hum Nutr Diet. 2018;31(2):239–55. https://doi.org/10.1111/jhn.12530.
22. Liu J, Chey WD, Haller E, Eswaran S. Low-FODMAP diet for irritable bowel syndrome: what we know and what we have however, to learn. Annu Rev Med. 2020;71:303–14. https://doi.org/10.1146/annurev-med-050218-013625.
23. Ortiz A, Germain DP, Desnick RJ, Politei J, Mauer M, Burlina A, et al. Fabry disease revisited: management and treatment recommendations for adult patients. Mol Genet Metab. 2018;123(4):416–27. https://doi.org/10.1016/j.ymgme.2018.02.014.
24. Mahmud HM. Fabry's disease—a comprehensive review on pathogenesis, diagnosis and treatment. J Pak Med Assoc. 2014;64(2):189–94. Disponível em: https://jpma.org.pk/article-details/5948?article_id=5948 Acessado em 02/02/22.
25. Schiffmann R, Hughes DA, Linthorst GE, Ortiz A, Svarstad E, Warnock DG, et al. Screening, diagnosis, and management of patients with Fabry disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 2017;91(2):284–93. https://doi.org/10.1016/j.kint.2016.10.004.
26. Feriozzi S, Rozenfeld P. Pathology and pathogenic pathways in Fabry nephropathy. Clin Exp Nephrol. 2021;25(9):925–34. https://doi.org/10.1007/s10157-021-02058-z.
27. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. Am J Kidney Dis. 2020;76(3):S1–S107. https://doi.org/10.1053/j.ajkd.2020.05.006.
28. Shaw V, Polderman N, Renken-Terhaerdt J, Paglialonga F, Oosterveld M, Tuokkola J, et al. Energy and protein requirements for children with CKD stages 2-5 and on dialysis-clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. Pediatr Nephrol. 2020;35(3):519–31. https://doi.org/10.1007/s00467-019-04426-0.
29. Tantisattamo E, Kalantar-Zadeh K, Halleck F, Duettmann W, Naik M, Budde K. Novel approaches to sarcopenic obesity and weight management before and after kidney transplantation. Curr Opin Nephrol Hypertens. 2021;30(1):14–26. https://doi.org/10.1097/MNH.0000000000000673.
30. Del Pino M, Andrés A, Bernabéu AA, Juan-Rivera J, Fernández E, Díaz JDG. Fabry nephropathy: an evidence-based narrative review. Kidney Blood Press Res. 2018;43(2):406–21. https://doi.org/10.1159/000488121.

31. Nerbass FB, Calice-Silva V, Pecoits-Filho R. Sodium intake and blood pressure in patients with chronic kidney disease: a salty relationship. Blood Purif. 2018;45:166–72. https://doi.org/10.1159/000485154.
32. Kleinert J, Dehout F, Schwarting A, De Lorenzo A, Ricci R, Kampmann C, et al. Anemia is a new complication in Fabry disease: data from the Fabry Outcome Survey. Kidney Int. 2005;67:1955–60. https://doi.org/10.1111/j.1523-1755.2005.00294.x.
33. Babitt JL, Eisenga MF, Haase VH, Kshirsagar AV, Levin A, Locatelli F, et al. Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. Kidney Int. 2021;99:1280–95. https://doi.org/10.1016/j.kint.2021.03.020.
34. Orzechowski A, Cywińska A, Rostagno AA, Rizzi FM. Oxidative stress, chronic inflammation, and amyloidoses. Oxidative Med Cell Longev. 2019;8:6024975. https://doi.org/10.1155/2019/6024975.
35. Ravarotto V, Carraro G, Pagnin E, Bertoldi G, Simioni F, Maiolino G, et al. Oxidative stress and the altered reaction to it in Fabry disease: a possible target for cardiovascular-renal remodeling? PLoS One. 2018;13(9):e0204618. https://doi.org/10.1371/journal.pone.0204618.
36. Maleki SJ, Crespo JF, Cabanillas B. Anti-inflammatory effects of flavonoids. Food Chem. 2019;299:125124. https://doi.org/10.1016/j.foodchem.2019.125124.
37. Cristofori F, Dargenio VN, Dargenio C, Miniello VL, Barone M, Francavilla R. Anti-inflammatory and immunomodulatory effects of probiotics in gut inflammation: a door to the body. Front Immunol. 2021;12:578386. https://doi.org/10.3389/fimmu.2021.578386.
38. Sears B. Anti-inflammatory diets. J Am Coll Nutr. 2015;34:14–21. https://doi.org/10.1080/07315724.2015.1080105.
39. Allaire J, Couture P, Leclerc M, Charest A, Marin J, Lepine MC, et al. A randomized, crossover, head-to-head comparison of eicosapentaenoic acid and docosahexaenoic acid supplementation to reduce inflammation markers in men and women: the Comparing EPA to DHA (ComparED) Study. Am J Clin Nutr. 2016;104:280–7. https://doi.org/10.3945/ajcn.116.131896.
40. Li K, Huang T, Zheng J, Wu K, Li D. Effect of marine-derived n-3 polyunsaturated fatty acids on C-reactive protein, interleukin 6 and tumor necrosis factor alpha: a meta-analysis. PLoS One. 2014;9(2):e88103. https://doi.org/10.1371/journal.pone.0088103.
41. Daak AA, Elderdery AY, Elbashir LM, Katia Mariniello K, Mills J, Scarlett G, et al. Omega 3 (n-3) fatty acids downregulate nuclear factor-kappa B (NF-κB) gene and blood cell adhesion molecule expression in patients with homozygous sickle cell disease. Blood Cells Mol Dis. 2015;55:48–55. https://doi.org/10.1016/j.bcmd.2015.03.014.
42. Guo XF, Li KL, Li JM, Li D. Effects of EPA and DHA on blood pressure and inflammatory factors: a meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr. 2019;20:3380–93. https://doi.org/10.1080/10408398.2018.1492901.
43. Oliván-Viguera A, Lozano-Gerona J, Frutos LL, Cebolla JJ, Irún P, Edgar Abarca-Lachen E, et al. Inhibition of intermediate-conductance calcium-activated K channel (KCa3.1) and fibroblast mitogenesis by α-linolenic acid and alterations of channel expression in the lysosomal storage disorders, Fabry disease, and Niemann pick C. Front Physiol. 2017;8:39. https://doi.org/10.3389/fphys.2017.00039.
44. Yahfoufi N, Alsadi N, Jambi M, Matar C. The immunomodulatory and anti-inflammatory role of polyphenols. Nutrients. 2018;10(11):1618. https://doi.org/10.3390/nu10111618.
45. Bach Knudsen KE, Lærke HN, Hedemann MS, Nielsen TS, Ingerslev AK, Gundelund Nielsen DS, et al. Impact of diet-modulated butyrate production on intestinal barrier function and inflammation. Nutrients. 2018;10(10):1499. https://doi.org/10.3390/nu10101499.
46. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014;157:121–41. https://doi.org/10.1016/j.cell.2014.03.011.
47. Sureda A, Bibiloni MDM, Julibert A, Bouzas C, Argelich E, Llompart I, et al. Adherence to the Mediterranean diet and inflammatory markers. Nutrients. 2018;10:62. https://doi.org/10.3390/nu10010062.

48. Davis C, Bryan J, Hodgson J, Murphy K. Definition of the Mediterranean diet; a literature review. Nutrients. 2015;7(11):9139–53. https://doi.org/10.3390/nu7115459.
49. Ihne S, Morbach C, Sommer C, Geier A, Knop S, Störk S. Amyloidosis—the diagnosis and treatment of an underdiagnosed disease. Dtsch Arztebl Int. 2020;117(10):159–66. https://doi.org/10.3238/arztebl.2020.0159.
50. Wu JJ, Yao M, Ni J. Cerebral amyloid angiopathy-related inflammation: current status and future implications. Chin Med J (Engl). 2021;134(6):646–54. https://doi.org/10.1097/cm9.0000000000001427.
51. Blank N, Schönland SO. Chronic inflammation and AA amyloidosis. Dtsch Med Wochenschr. 2013;138(37):1835–8. https://doi.org/10.1055/s-0033-1349428.
52. Rosenzweig M, Comenzo RL. Liver and gastrointestinal involvement: update. Hematol Oncol Clin North Am. 2020;34:1081–90. https://doi.org/10.1016/j.hoc.2020.11.001.
53. Sattianayagam P, Hawkins P, Gillmore J. Amyloid and the GI tract. Expert Rev Gastroenterol Hepatol. 2009;3(6):615–30. https://doi.org/10.1586/egh.09.59.
54. Guirl MJ, Högenauer C, Santa Ana C, Porter JL, Katherine LH, Marvin JS, et al. Rapid intestinal transit as a primary cause of severe chronic diarrhea in patients with amyloidosis. Am J Gastroenterol. 2003;98(10):2219–25. https://doi.org/10.1111/j.1572-0241.2003.07695.x.
55. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. World J Gastroenterol. 2013;19(42):7258–66. https://doi.org/10.3748/wjg.v19.i42.7258.
56. Ebert EC, Nagar M. Gastrointestinal manifestations of amyloidosis. Am J Gastroenterol. 2008;103:776–87. https://doi.org/10.1111/j.1572-0241.2007.01669.x.
57. Toskes PP, Secci A, Thieroff-Ekerdt R. Efficacy of a novel pancreatic enzyme product, EUR-1008 (Zenpep), in patients with exocrine pancreatic insufficiency due to chronic pancreatitis. Pancreas. 2011;40:376–82. https://doi.org/10.1097/mpa.0b013e31820b971c.
58. Whitcomb DC, Lehman GA, Vasileva G, Malecka-Panas E, Gubergrits N, Shen Y, et al. Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: a double-blind randomized trial. Am J Gastroenterol. 2010;105:2276–86. https://doi.org/10.1038/ajg.2010.201.
59. Ramesh H, Reddy N, Bhatia S, Rajkumar JS, BaPaye A, Kini D, et al. A 51-week, open-label clinical trial in India to assess the efficacy and safety of pancreatin 40000 enteric-coated mini-microspheres in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. Pancreatology. 2013;13:133–9. https://doi.org/10.1016/j.pan.2013.01.009.
60. Hoffmeister A, Mayerle J, Beglinger C, Büchler MW, Bufler P, Dathe K, et al. S-3 Consensus guidelines on definition, etiology, diagnosis and medical, endoscopic and surgical management of chronic pancreatitis. German Society of Digestive and Metabolic Diseases (DGVS). Z Gastroenterol. 2012;50:1176–224. https://doi.org/10.1055/s-0032-1325479.
61. Cuddy SA, Falk RH. Amyloidosis as a systemic disease in context. Can J Cardiol. 2020;36(3):396–407. https://doi.org/10.1016/j.cjca.2019.12.033.
62. McCloskey O, Maxwell AP. Diagnosis and management of nephrotic syndrome. Practitioner. 2017;261(1801):11–5.
63. Mahalingasivam V, Booth J, Sheaff M, Yaqoob M. Nephrotic syndrome in adults. Acute Med. 2018;17(1):36–43.
64. Kodner C. Diagnosis and management of nephrotic syndrome in adults. Am Fam Physician. 2016;93(6):479–85.
65. Charlesworth JA, Gracey DM, Pussell BA. Adult nephrotic syndrome: nonspecific strategies for treatment. Nephrology. 2008;13(1):45–50. https://doi.org/10.1111/j.1440-1797.2007.00890.x.
66. Gertz MA. Immunoglobulin light chain amyloidosis: 2020 update on diagnosis, prognosis, and treatment. Am J Hematol. 2020;95(7):848–60. https://doi.org/10.1002/ajh.25819.
67. Murray SM, Pindoria S. WITHDRAWN: nutrition support for bone marrow transplant patients. Cochrane Database Syst Rev. 2017;3(3):CD002920. https://doi.org/10.1002/14651858.cd002920.pub4.
68. Horie LM, Barrére APN, Castro MG, Alencastro MG, Alves JTM, Dal Bello JP, et al. Diretriz BRASPEN de terapia nutricional no paciente com câncer. BRASPEN J. 2019;34(1):2–32.

69. Coulette S, Renard D, Lehmann S, Raposo N, Arquizan C, Charif M, et al. A clinico-radiological study of cerebral amyloid angiopathy-related inflammation. Cerebrovasc Dis. 2019;48:38–44. https://doi.org/10.1159/000502832.
70. Crary MA, Mann GD, Graner ME. Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. Arch Phys Med Rehabil. 2005;86(8):1516–20.
71. Ojo O, Joanne Brooke J. The use of enteral nutrition in the management of stroke. Nutrients. 2016;8(12):827. https://doi.org/10.3390/nu8120827.
72. Munoz N, Posthauer ME, Cereda E, Schols JMGA, Haesler E. The role of nutrition for pressure injury prevention and healing: the 2019 international clinical practice guideline recommendations. Adv Skin Wound Care. 2020;33(3):123–36. https://doi.org/10.1097/01.asw.0000653144.90739.ad.
73. Nakamura M, Ando Y. Amyloidosis and oxidative stress. Rinsho Byori. 2003;51(2):140–55.
74. Brokel JM, Avant K, Odenbreit M. The value of nursing diagnoses in electronic health records. In: Herdman TH, editor. Nanda International Nursing Diagnoses Kassel, definitions and classification 2012–2014. Oxford: Wiley; 2012. p. 99–113.
75. Ackley BJ, Ladwig GB. Nursing diagnosis handbook: an evidence based guide to planning care. 10th ed. St. Louis: Mosby/Elsevier; 2014.
76. Ackley BJ, Ladwig GB, Swan BA, Tucker SJ. Evidence-based nursing care guidelines: medical-surgical interventions. St. Louis: Mosby Elsevier; 2008.
77. Tomas MT, Clara HS, Bruno PM, Monteiro E, Carrolo M, Barroso E, et al. The impact of exercise training on liver familial amyloidotic polyneuropathy (FAP) patients. Transplantation. 2013;95(2):372–7.
78. Nangaku N, Miyata T, Kurokawa K. Pathogenesis and management of dialysis-related amyloid bone disease. Am J Med Sci. 1999;317(6):410–5.
79. Lampl C, Kreczi T, Klinger D. Transcutaneous electrical nerve stimulation in the treatment of chronic pain: predictive factors and evolution of the method. Clin J Pain. 1998;14(2):143–2.
80. Charbal C, Fishbain DA, Weaver MMA, Heine LW. Long-term transcutaneous electrical nerve stimulation (TENS) use: impact on medication utilization and physical therapy cost. Clin J Pain. 1998;14(1):66–73.
81. Rodrigues AC, Cunha AMR, Forni JEN, Dias LAC, Condi PR, Martins MRI. Fatores que influenciam a qualidade de vida em dor neuropática, musculoesquelética e oncológica. BrJP São Paulo. 2021;4(1):31–6.
82. Langley PC, Litsenburg CV, Cappelleri JC, Carroll D. The burden associated with neurophatic pain in western Europe. J Med Econ. 2013;16(1):85–95.
83. Davis KD, Flor H, Greely HT, Iannetti GD, Mackey S, Ploner M, Pustilnik A, et al. Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. Nat Rev Neurol. 2017;13:624–38.
84. Rajan JN, Ireland K, Johnson R, Stepien KM. Review of mechanisms, pharmacological management, psychosocial implications, and holistic treatment of pain in Fabry disease. J Clin Med. 2021;10:4168.

Chapter 40
Chronic Pain and Quality of Life

Valdênia P. de Souza, Marcelle Leitão Gomes Sá Pires, and Filipe T. Gusman

40.1 Introduction

The relief of human suffering is part of the doctor's training, and this is clear when there are acute conditions, but when faced with chronic pathologies, this mission often becomes frustrating. It is not uncommon in systemic diseases, such as amyloidosis and Fabry disease, which require greater attention and multidisciplinary care as the disease progresses.

Chronic pain is common, complex, and stressful, with an impact on the individual and society, a major cause of demand for health services as a result of an injury or illness, with physical and mental consequences such as insomnia, low self-esteem, and depression. The inability of full treatment to be achieved generates social isolation, depression, job loss, and nonadherence to treatment. Treatment and prevention strategies need to be understood in the context of social, biological, psychological, and physical factors, and integrative medicine is one of the strategies [1–5].

However, what is Integrative Medicine (IM)? Do we have in the final chapter of this book a new medicine? In 1990, in response to a demand from society, the concept of Alternative and Complementary Medicine (CAM) emerged at the University of Arizona, later called IM. It is a nonreductionist view of the whole, taking into account the body, mind, and vital force, also called by many spirituality and the influences of the community, not forgetting the principles of science. IM focuses on health and harmony and not only on diagnosis and disease; it is not an alternative

V. P. de Souza (✉) · M. L. G. S. Pires
Geriatrics Group—Clinic Care, Niterói, Rio de Janeiro, Brazil
e-mail: valdenia.souza@geriatrics.com.br; marcelle.pires@geriatrics.com.br

F. T. Gusman
Department of Palliative Care, Hospital Pro Cardiaco, Rio de Janeiro, Rio de Janeiro, Brazil

Brazilian Academy of Palliative Care, Rio de Janeiro, Brazil

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0_40

medicine because it is not an alternative to allopathy, but it integrates and complements and the integrative health team must understand the characteristics of the culture, community, spirituality, and lifestyle to place the patient at the center and make him/her coresponsible for the treatment. To achieve this goal, the team must make use of the principles of lifestyle medicine, traditional Chinese medicine, homeopathic medicine, anthroposophical medicine, and Ayurvedic medicine [5]. In 2009, between the Institute of Medicine—IOM USA and the Bravewell Collaborative, there was a meeting in which the conceptual basis of the MI that is disseminated until today and is implanted in the main American hospitals and universities, such as Duke University, Harvard, Cleveland Clinic, Mayo, among others, was disclosed, and from there, it was disseminated throughout the world, Europe and Latin American countries; for example, in Brazil, there has been a National Policy on Integrative and Complementary Practices in the public health system since 2006 [6–9].

Amyloidosis is a systemic disease, and depending on the amyloid type, some organs may be more affected than others, with different systemic presentations, as in Fabry disease, as already seen in literature. Through different pathophysiological bases, depression can be one of the focuses to consider in this patient. How can IM help?

40.1.1 Mind Body Therapies

Biomedical interventions alone do not address psychosocial factors, and the use of medications such as opioids as analgesia increases the risk of side effects, including hyperalgesia, abuse, and overdose [10]. Training with mind-body therapies had in one of its practices began in 1979 with Jon Kabat-Zinn, a physician and Professor Emeritus of Medicine at the University of Massachusetts who instituted the 8-week Mindfulness Based Stress Release (MBSR) program to address physical and emotional pain; focuses on the interactions between brain, body, mind, and behavior with the intention of using the mind to affect physical functioning and promote health using mindful breathing techniques, mindful eating, body scanning, movement, and compassion (first for yourself), all these without judgments [11].

The literature makes comparisons of both the classic and modified MBSR practice, with greater or lesser duration and changes in form, but without changing the essence—the scenario involved is chronic pain: lumbar, nonspecific, fibromyalgia, neck, cancer pain, musculoskeletal, and irritable bowel syndrome. Some investigators even report pain improvement of up to 30%, while others report improvement depending on pain intensity, for example, an improvement of 19% for daily pain and 13.7% for more severe pain in the last week [12, 13]. In this same study, a disability questionnaire was used, and the result in the group that had the 8-week intervention with the MBSR vs the control group was a decrease in disability (37 vs 22% p 0.01, respectively), allowing the start of new activities to maintain long-term functional capacity. There is difficulty in the quality of the work, but we can conclude that it

occurred due to fewer emergency visits and less use of allopathic analgesic medications. In addition, many patients associated the practice with a better quality of life. In studies where there was a pain scale, the use of mindfulness techniques was the same as the standard therapy used [14, 15].

Yoga is another mind-body technique studied for pain and quality of life. In 2017, Cochrane published a systematic review with 1080 participants with nonspecific low back pain and compared yoga added to standard exercise, and when comparing the patient without exercise, found favorable evidence of mild degree at 3 months and moderate degree at 6 months and again of slightly favorable degree with 12 months of Yoga practice [16]. A Canadian review analyzed the use of mindfulness and yoga in cases of noncancer pain and found beneficial data when compared with no treatment and positive data for negative feelings, sleep quality, fatigue, ability to work, concentration, more flexible personality, greater well-being, and even higher plasma serotonin concentrations [17].

Other mind-body therapies exist, such as biofeedback, Reikidian, hypnosis, Tai Chi Chuan, and Qigong, among others, but the literature on the treatment of chronic pain still has greater biases than previous studies, allowing a field for new studies.

40.1.2 Acupuncture

In traditional Chinese medicine (TCM), the human being is considered a complex of vital energy (Qi), and various systems in the body regulate the flow of this energy through many control points. Acupuncture is part of the TCM arsenal; it is an ancient technique classically characterized by the insertion of needles in certain specific points of the body, seeking to promote, restore, and balance the energetic functions of tissues and organs, improve blood circulation, increase immunity, and bring physical and mental well-being [18]. Studies involving chronic pain are carried out in scenarios similar to those of mindfulness, and within cancer pain, especially breast cancer patients, are highlighted with acupuncture [19, 20]. In 2020, Goldsmith et al. published a study with the US military in Veteran Affairs (VA) who, in addition to complaining of chronic pain, used opioids and integrative therapy; among them, acupuncture relieved pain, reduced or suspended the use of opioids, and improved quality of life [21]. This result is repeated, but the results are based on subjective data from the patients. A field in which there are several studies is peripheral neuropathy (PN), which occurs mainly in diabetic patients but also in other pathologies, for example, as a complication after chemotherapy and in amyloidosis and Fabry disease [22–24]. In diabetic patients with PN, Jiang published a meta-analysis comparing patients who received acupuncture versus vitamin B12. In all results, acupuncture was better in terms of pain and increased nerve conduction velocity, and adding vitamin b12 added the axonal repair effects and myelination treatment [25]. These positive effects can also be seen in patients with chemotherapy neuropathy, especially when dealing with fragile patients, where pain relief can be a unique opportunity [6, 25].

40.2 Other Options

Cannabidiol Among the indications of medicinal use, cannabidiol (CBD) is pain control. When looking at recent works in the literature, we still find a diversity of presentations, routes of administration (oral, spray, sublingal), doses and trials with small numbers of patients, and many randomized studies in progress still recruiting patients. There are compelling indications for the use of CBD in the context of chronic pain patients, for example, its use in severe insomnia [26].

Phytotherapy Very widespread in different populations in reference to acute pain and today gaining more adepts for the supplementation of different substances. It has books that are easy to acquire, but in many cases, it is difficult to guarantee the origin of the plants or extract, and the chronic use of most medications is not recommended, especially in those using chemotherapy and/or anticoagulants with the possibility of significant drug interaction.

Homeopathy, anthroposophical medicine, and hypnosis among others, need more studies in this chronic pain scenario.

Integrative medicine is present in the modern world to associate current techniques and benefit society, and it is up to each of us to question what we can do within scientific evidence to provide a better quality of life for our patients.

40.3 Palliative Care

Technological advances in medicine over the last 70 years have been extremely valuable for the treatment of various diseases that were previously at unapproachable stages, today proportionate to the needs of each person according to the stage and evolution of the disease. Treatments performed in intensive care centers should not be suitable for all patients, and establishing prognostic reasoning helps to avoid an artificial prolongation of life that adds suffering (dysthanasia) [27, 28].

The concept of modern palliative care was introduced in the mid-1960s in England by Dame Cecily Saunders who, when she founded the St. Christopher Hospice, described the philosophy of caring for all individuals diagnosed with serious and irreversible disease. It was understood that pain, like any other suffering the patient experienced, had four dimensions: physical, psychic (emotional), social, and spiritual. Health professionals should consider all these spheres to prevent and alleviate suffering. A very important point in this movement was to encourage all palliative measures to be instituted early, preferably from the diagnosis of the disease. Although the use of palliative care services in the advanced and terminal stages is still frequent, especially in the last days of life, Cicely made it clear that the sooner palliative measures are adopted, the better the quality of life will be [29–32]. In this way, palliative care enters as a multiprofessional and complementary approach to the modifying treatment of severe disease. The priority is the quality of life not only

of the patient, but also of their family members, including them in the so-called nucleus of care.

The World Health Organization (WHO), since 2002, has established important principles to recognize that palliative care has as a priority the value of the dignity of the individual; that is, it considers the person as a whole, not only from the point of view of the diagnosis of any clinical disease, but also oncological. Symptoms and care needs for patients with end-stage noncancer diseases present many situations and care needs that are similar to those of patients with advanced oncological disease [33, 34]. The principles of palliative care have been described as follows: promote relief from pain and other stressful symptoms; integrate psychological and spiritual aspects of care; provide multiprofessional assistance; recognize death as a natural process (orthothanasia); ensure that the patient lives as actively as possible until death; support for the family during the illness and grieving process [29, 32].

The practice of palliative care, whether by a specialist or not, provides dignity to the person (constitutional principle), allowing them not to be deprived of living their own death. It condemns the despotic obsession with healing and opposes euthanasia and dysthanasia, respecting people's autonomy. The awareness of society about palliative care is a humanitarian attitude and essential for the health system to change its approach to patients with chronic diseases. These diseases in which the diagnosis already makes them think that they threaten the continuity of their lives, such as amyloidosis and Fabry disease, need a palliative approach, from the initial to the advanced stages. These support will make them overcome with quality of life, regardless of the recommended and specific drug treatment [30–35].

References

1. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open. 2016;6(6):e010364. https://doi.org/10.1136/bmjopen-2015-010364. PMID: 27324708; PMCID: PMC4932255.
2. van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology—where do lifestyle factors fit in? Br J Pain. 2013;7(4):209–17. https://doi.org/10.1177/2049463713493264. PMID: 26516524; PMCID: PMC4590163.
3. Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth. 2019;123(2):e273–83. https://doi.org/10.1016/j.bja.2019.03.023. Epub 2019 May 10. PMID: 31079836; PMCID: PMC6676152.
4. Gardiner P, Luo M, D'Amico S, Gergen-Barnett K, White LF, Saper R, Mitchell S, Liebschutz JM. Effectiveness of integrative medicine group visits in chronic pain and depressive symptoms: a randomized controlled trial. PLoS One. 2019;14(12):e0225540. https://doi.org/10.1371/journal.pone.0225540. PMID: 31851666; PMCID: PMC6919581.
5. Otani MA, Barros NF. A Medicina Integrativa e a construção de um novo modelo na saúde [The Integrative Medicine and the construction of a new health model]. Cien Saude Colet. 2011;16(3):1801–11. https://doi.org/10.1590/s1413-81232011000300016. PMID: 21519670.
6. Deng G, et al. Integrative medicine research: context and priorities. Comissioned for the IOM Summit on Integrative Medicine and the Health of the Public; 2009.
7. LIMA PTR (Coord.). Medicina Integrativa. 1st ed. Barueri: Manole; 2015.
8. Rakel D. Integrative medicine. 4th ed. Philadelphia: Elsevier; 2018.

9. Brasil. Ministério da Saúde. Secretaria de Atenção a Saúde. Departamento de Atenção Básica. Política Nacional de Práticas Integrativas e Complementares no SUS—PNPIC-SUS. Brasília: Ministério da Saúde; 2006.
10. Brintz CE, Roth I, Faurot K, Rao S, Gaylord SA. Feasibility and acceptability of an abbreviated, four-week mindfulness program for chronic pain management. Pain Med. 2020;21(11):2799–810. https://doi.org/10.1093/pm/pnaa208. PMID: 32897319; PMCID: PMC7685688.
11. National Center for Complementary and Integrative Health. The science of mind and body therapies. https://nccih.nih.gov/video/series/mindbody. Accessed 2 Feb 2022.
12. McClintock AS, McCarrick SM, Garland EL, Zeidan F, Zgierska AE. Brief mindfulness-based interventions for acute and chronic pain: a systematic review. J Altern Complement Med. 2019;25(3):265–78. https://doi.org/10.1089/acm.2018.0351. Epub 2018 Dec 5. PMID: 30523705; PMCID: PMC6437625.
13. Morone NE. Not just mind over matter: reviewing with patients how mindfulness relieves chronic low back pain. J Evid Based Integr Med. 2019;24:2515690X19838490. https://doi.org/10.1177/2515690X19838490. PMID: 30942087; PMCID: PMC6448108.
14. Polaski AM, Phelps AL, Smith TJ, Helm ER, Morone NE, Szucs KA, Kostek MC, Kolber BJ. Integrated meditation and exercise therapy: a randomized controlled pilot of a combined nonpharmacological intervention focused on reducing disability and pain in patients with chronic low back pain. Pain Med. 2021;22(2):444–58. https://doi.org/10.1093/pm/pnaa403. PMID: 33621332; PMCID: PMC7901850.
15. Williams RM, Ehde DM, Day M, Turner AP, Hakimian S, Gertz K, Ciol M, McCall A, Kincaid C, Pettet MW, Patterson D, Suri P, Jensen MP. The chronic pain skills study: protocol for a randomized controlled trial comparing hypnosis, mindfulness meditation and pain education in Veterans. Contemp Clin Trials. 2020;90:105935. https://doi.org/10.1016/j.cct.2020.105935. Epub 2020 Jan 9. PMID: 31926321; PMCID: PMC7072005.
16. Wieland LS, Skoetz N, Pilkington K, Vempati R, D'Adamo CR, Berman BM. Yoga treatment for chronic nonspecific low back pain. Cochrane Database Syst Rev. 2017;1(1):CD010671. https://doi.org/10.1002/14651858.CD010671.pub2. PMID: 28076926; PMCID: PMC5294833.
17. Lachance CC, McCormack S. Mindfulness training and yoga for the management of chronic nonmalignant pain: a review of clinical effectiveness and cost-effectiveness [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2019. PMID: 31725209.
18. Chonghuo T. Tratado de Medicina Chinesa. 1st ed. Roca; 1993.
19. Vickers AJ, Vertosick EA, Lewith G, MacPherson H, Foster NE, Sherman KJ, Irnich D, Witt CM, Linde K, Acupuncture Trialists' Collaboration. Acupuncture for chronic pain: update of an individual patient data meta-analysis. J Pain. 2018;19(5):455–74. https://doi.org/10.1016/j.jpain.2017.11.005. Epub 2017 Dec 2. PMID: 29198932; PMCID: PMC5927830.
20. He Y, Guo X, May BH, Zhang AL, Liu Y, Lu C, Mao JJ, Xue CC, Zhang H. Clinical evidence for Association of Acupuncture and Acupressure with improved cancer pain: a systematic review and meta-analysis. JAMA Oncol. 2020;6(2):271–8. https://doi.org/10.1001/jamaoncol.2019.5233.
21. Goldsmith ES, MacLehose RF, Jensen AC, Clothier B, Noorbaloochi S, Martinson BC, Donaldson MT, Krebs EE. Complementary, integrative, and nondrug therapy use for pain among us military veterans on long-term opioids. Med Care. 2020;58(Suppl 2):S116–24. https://doi.org/10.1097/MLR.0000000000001333. PMID: 32826781; PMCID: PMC7444474.
22. Gertz MA, Dispenzieri A. Systemic amyloidosis recognition, prognosis, and therapy: a systematic review. JAMA. 2020;324(1):79–89. https://doi.org/10.1001/jama.2020.5493. PMID: 32633805.
23. Qureshi Z, Ali MN, Khalid M. An insight into potential pharmacotherapeutic agents for painful diabetic neuropathy. J Diabetes Res. 2022;27(2022):9989272. https://doi.org/10.1155/2022/9989272.
24. Molassiotis A, Suen LKP, Cheng HL, Mok TSK, Lee SCY, Wang CH, Lee P, Leung H, Chan V, Lau TKH, Yeo W. A randomized assessor-blinded wait-list-controlled trial to

assess the effectiveness of acupuncture in the management of chemotherapy-induced peripheral neuropathy. Integr Cancer Ther. 2019;18:1534735419836501. https://doi.org/10.1177/1534735419836501.
25. Jiang HL, Jia P, Fan YH, Li MD, Cao CC, Li Y, Du YZ. Manual acupuncture or combination with vitamin B to treat diabetic peripheral neuropathy: a systematic review and meta-analysis of randomized controlled trials. Biomed Res Int. 2020;2020:4809125. https://doi.org/10.1155/2020/4809125.
26. VanDolah HJ, Bauer BA, Mauck KF. Clinicians' guide to cannabidiol and hemp oils. Mayo Clin Proc. 2019;94(9):1840–51. https://doi.org/10.1016/j.mayocp.2019.01.003.
27. Matsumoto DY. Cuidados paliativos: conceito, fundamentos e princípios. In: Manual de cuidados paliativos. Academia Nacional de Cuidados Paliativos. 2nd ed. Rio de Janeiro: Diagraphic; 2009. p. 23–30.
28. Sociedade Brasileira de Geriatria e Gerontologia (SBGG) 2015. Vamos falar de Cuidados Paliativos. [acesso em 20 de setembro de 2020, citada em 20 de setembro de 2020]. Disponível em: https://sbgg.org.br/wp-content/uploads/2015/05/vamosfalar-decuidados-paliativos-vers%2D%2Do-online.pdf.
29. Slachevsky Ch A, Abusleme LMT, Arenas Massa Á. Cuidados paliativos en personas con demencia severa: reflexiones y desafíos [Palliative care of patients with severe dementia]. Rev Med Chil. 2016;144(1):94–101. https://doi.org/10.4067/S0034-98872016000100012.
30. Velasco-Sanz TR, Estella-García Á, Del Barrio-Linares M, Velasco-Bueno JM, Saralegui-Reta I, Rubio-Sanchiz O, Raurell-Torredà M. The importance of an interprofessional palliative approach for the critical patient. Enferm Intensiva (Engl Ed). 2019;30(1):1–3. https://doi.org/10.1016/j.enfi.2018.11.001.
31. De Blas Gómez I, Rodríguez García M. Gestión emocional y hábito reflexivo en la relación de Ayuda para el cuidado holístico del paciente paliativo [Emotional management and critical thinking in the aid relationship of the holistic care of palliative patients]. Rev Enferm. 2015;38(5):36–41.
32. Gómez-Batiste X, Espinosa J, Porta-Sales J, Benito E. Modelos de atención, organización y mejora de la calidad para la atención de los enfermos en fase terminal y su familia: aportación de los cuidados paliativos [Models of care, organization and quality improvement for the care of advanced and terminal patients and their families: the contribution of palliative care]. Med Clin (Barc). 2010;135(2):83–9. https://doi.org/10.1016/j.medcli.2010.02.015.
33. Cruz-Jentoft AJ, Rexach Cano L. Pronóstico vital en cuidados paliativos: ¿una realidad esquiva o un paradigma erróneo? [Prognosis of death in end of life care: an elusive fact or a flawed paradigm?]. Med Clin (Barc). 2013;140(6):260–2. https://doi.org/10.1016/j.medcli.2012.09.010.
34. Mounsey L, Ferres M, Eastman P. Palliative care for the patient without cancer. Aust J Gen Pract. 2018;47(11):765–9. https://doi.org/10.31128/AJGP-07-18-4625. PMID: 31207673.
35. Rajan JN, Ireland K, Johnson R, Stepien KM. Review of mechanisms, pharmacological management, psychosocial implications, and holistic treatment of pain in Fabry disease. J Clin Med. 2021;10(18):4168. https://doi.org/10.3390/jcm10184168. PMID: 34575277; PMCID: PMC8472766.

Index

D. Xavier de Ávila, H. Villacorta Junior (eds.), *Amyloidosis and Fabry Disease*,
https://doi.org/10.1007/978-3-031-17759-0