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Maria Adele Giamberardino
Paolo Martelletti
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Comorbidities in Headache Disorders

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Headache

Series editor
Paolo Martelletti
Roma, Italy

The purpose of this Series, endorsed by the European Headache Federation (EHF), is to describe in detail all aspects of headache disorders that are of importance in primary care and the hospital setting, including pathophysiology, diagnosis, management, comorbidities, and issues in particular patient groups. A key feature of the Series is its multidisciplinary approach, and it will have wide appeal to internists, rheumatologists, neurologists, pain doctors, general practitioners, primarycare givers, and pediatricians. Readers will find that the Series assists not only in understanding, recognizing, and treating the primary headache disorders, but also in identifying the potentially dangerous underlying causes of secondary headache disorders and avoiding mismanagement and overuse of medications for acute headache, which are major risk factors for disease aggravation. Each volume is designed to meet the needs of both more experienced professionals and medical students, residents, and trainees.

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Maria Adele Giamberardino • Paolo Martelletti
Editors

Comorbidities in Headache Disorders

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Editors
Maria Adele Giamberardino
Gabriele D'Annunzio
University of Chieti
Italy

Paolo Martelletti
Sapienza University of Rome
Clinical and Molecular Medicine Dept
Rome
Italy

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Foreword

The educational project developed within the European Headache Federation through the *Headache Book* series gives birth to its fourth product in just 2 years. The deeply studied topic of comorbidities requires today an organic systematization, and this is the fundamental message carried by this volume. Comorbidities in headache disorders represent the quintessence of clinical daily practice for experts and non-experts who face this area of clinical medicine. Nowadays medicine must be multidisciplinary, horizontally between different clinical disciplines and vertically between basic sciences and clinical sciences, connecting these latter to the latest pharmacological discoveries. It is here that the knowledge of the multiple intersections between headache disorders and comorbidities allows the most correct and safe therapeutic choice in terms of drug-drug interactions. Headache thus rightly falls within the modern conceptual model of *medicine of complexities* that requires a holistic approach to the clinical problem and faces patients' management in a multimodal perspective.

Paolo Martelletti
Sapienza University of Rome
Rome, Italy

Preface

Headache is recognized worldwide as a condition of high epidemiologic and medical relevance as well as of substantial personal and socioeconomic impact.

The complexity of the clinical picture in headache patients who present concurrent medical diseases is, instead, much less appreciated, in spite of the fact that comorbidities are rather the rule than the exception in this condition.

In its different forms, primary headache is, in fact, rarely present in isolation, but most often coexists with other painful or nonpainful diseases, a circumstance which enhances the disability of the patients and the burden to the medical system. Examples are pains arising from or expressed in musculoskeletal structures, such as myofascial pain syndromes from trigger points or fibromyalgia, other forms of orofacial pain and temporomandibular pain, or several visceral pains such as irritable bowel syndrome; dysmenorrhea, primary or secondary to endometriosis; or interstitial cystitis/painful bladder syndrome. Significant other comorbidities are cardiovascular and cerebrovascular diseases, particularly in the case of migraine, psychiatric diseases, obesity, and sleep disorders. Independently of possible common pathophysiological mechanisms at the basis of several of these clusters of conditions, which remain to be investigated in full, comorbidities in headache have numerous implications for diagnosis and treatment. Increasing evidence exists, in fact, that concurrent diseases may modify symptom presentation in headache: myofascial pain syndromes from trigger points and visceral pain episodes may exacerbate migraine pain, with epidemiological findings also suggesting that the presence of comorbid pain conditions may impact on the transition of episodic to chronic headache. On the other hand, headache can influence the disease progression of certain comorbidities, as shown, for instance, by the findings of a link between migraine frequency and high cholesterol levels, with consequent implications for cardiovascular risk. The repercussions on therapeutic decisions are even more important. A concurrent cardiovascular disease in migraine patients may, for example, deeply affect the therapeutic approach to the headache pain with vasoactive compounds. Comorbid obesity may impact significantly on the use of prophylactic agents whose main side effect is weight gain, such as calcium channel blockers, while psychiatric disorders – such as depression or anxiety – require careful

evaluation for diagnosis of their primary or secondary nature and for integrated treatment.

In spite of the frequency and relevance of comorbidities, most previous publications on headache primarily dealt with the condition per se. This book is instead aimed at putting headache into the wider perspective of its most frequent medical associated diseases, both painful and nonpainful. Epidemiology, possible shared pathophysiology, diagnostic challenges, and implications for management are discussed by recognized international experts in headache and numerous other disciplines. We hope this publication will be of interest and utility to the medical and scientific community at large, with the ultimate goal of improving understanding and treatment of the headache sufferers.

Chieti, Italy — Maria Adele Giamberardino
Rome, Italy — Paolo Martelletti

Contents

Contributors

Mario Amore Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genoa, Genoa, Italy

Lars Arendt-Nielsen Center for Sensory-Motor Interactions, Aalborg University, Aalborg, Denmark

Qasim Aziz Barts and The London School of Medicine and Dentistry, Queen Mary University, London, UK

Oliviero Bruni, MD Department of Developmental and Social Psychology, Sapienza University, Rome, Italy

C. Bushnell Department of Neurology, Wake Forest Baptist Health, Winston Salem, NC, USA

Stefano Caproni Struttura Complessa di Neurologia, Dipartimento di Neuroscienze, Azienda Ospedaliera "S. Maria" di Terni, Terni, Italy

Cindy N. Chai Veterans Affairs Hospital, Interventional Pain Medicine, Fresno, CA, USA

Cinzia Costa Clinica Neurologica, Università degli Studi di Perugia, Dipartimento di Medicina, Ospedale S. Maria della Misericordia, Perugia, Italy

Martina Curto Department of Psychiatry, Harvard Medical School, Boston, MA, USA

Department of Molecular Medicine, Sant'Andrea Medical Center, Sapienza University of Rome, Rome, Italy

Marina de Tommaso Neurophysiopathology of Pain SMBNOS Department, Bari Aldo Moro University, Policlinico General Hospital, Bari, Italy

Claudia Dosi, MD IRCCS Stella Maris, Scientific Institute of Child Neurology and Psychiatry, Calambrone, PI, Italy

Fernando Exposto Section of Orofacial Pain and Jaw Function, Institute for Odontology and Oral Health, Faculty of Health, Aarhus University, Aarhus, Denmark

César Fernández-de-las-Peñas, PT, MSc, PhD, DrScient Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain

Cátedra de Investigación y Docencia en Fisioterapia: Terapia Manual y Punción Seca, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain

Robert Gerwin, MD, FAAN Department of Neurology, Johns Hopkins School of Medicine, Johns Hopkins University, Baltimore, MD, USA

Pain and Rehabilitation Medicine, Bethesda, MD, USA

Maria Adele Giamberardino Department of Medicine and Science of Aging and CeSI-Met, "G. D'Annunzio" University of Chieti, Chieti, Italy

Paolo Girardi Department of Neuroscience, Suicide Prevention Center, Sant'Andrea Hospital, University of Rome, Rome, Italy

Dorian Lamis Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

Teresa Paiva, MD CENC, Sleep Medicine Center, Lisbon, Portugal

Lee B. Peterlin Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Maurizio Pompili, MD, PhD Department of Neuroscience, Suicide Prevention Center, Sant'Andrea Hospital, University of Rome, Rome, Italy

Paolo Prontera Centro di Riferimento Regionale di Genetica Medica, Dip. di Scienze Chirurgiche e Biomediche, Università di Perugia, Ospedale Santa Maria della Misericordia, Perugia, Italy

Luiz Paulo Queiroz Department of Neurology, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil

Simona Sacco Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, L'Aquila, Italy

Josemir W. Sander Department of Clinical and Experimental Epilepsy, NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, London, UK

Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, Netherlands

Paola Sarchielli Clinica Neurologica, Università degli Studi di Perugia, Dipartimento di Medicina, Ospedale S. Maria della Misericordia, Perugia, Italy

Ann I. Scher Uniformed Services University, Bethesda, MD, USA

Gianluca Serafini Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genoa, Genoa, Italy

Peter Svensson Aarhus University, Aarhus, Denmark

Department of Dental Medicine, KarolinskaInstitutet, Huddinge, Sweden

Noemi Tinetti, MD Headache in Childhood, Ceinsa Centro Integral Neurológico, Pcia de Buenos Aires, Argentina

Andrea Truini Sapienza University, Rome, Italy

Shuu-Jiun Wang Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan

Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan

Çiçek Wöber-Bingöl, MD Dr.GönülBingöl-Dr. MuammerBingölÇocukveErgenBaşağrısıDerneği, Society for Headache in Children and Adolescents, Suadiye, Istanbul, Turkey

Joanna M. Zakrzewska University College London (UCL), London, UK

Chapter 1
Cardio-cerebrovascular Comorbidity

S. Sacco and C. Bushnell

Abstract Migraine, particularly migraine with aura has been associated with an increased risk of vascular events including ischemic and hemorrhagic stroke, myocardial infarction, and angina. Data also indicated that migraineurs, as compared to non-migraineurs, have an increased burden of infarct-like lesions and white matter abnormalities at brain magnetic resonance. There are no tools to identify the migraineurs who will suffer vascular events. Recent onset of the migraine, active migraine, and frequent attacks are features associated with the increased stroke risk; combined oral contraceptives and cigarette smoking may further increase the risk of ischemic stroke in migraineurs. The mechanisms underlying this increased vascular risk are still unclear but experimental studies indicated an increased cellular excitability in migraineurs that may make the brain tissue more susceptible to ischemia. Additionally, clinical data supported an impairment of the vascular function in migraineurs at the systemic level. There is currently no direct evidence to support that a migraine prophylactic treatment can reduce future stroke risk; however, we cannot exclude that migraine prophylaxis, by raising the threshold for spreading depolarization, may lower stroke risk.

1.1 Epidemiological Evidence

Over the past decades numerous data have pointed to an association between migraine and cardiovascular diseases (CVD).

S. Sacco (✉)
Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, Institute of Neurology, L'Aquila, Italy
e-mail: simona.sacco@yahoo.com

C. Bushnell
Department of Neurology, Wake Forest Baptist Health, Winston Salem, NC, USA
e-mail: cbushnel@wakehealth.edu

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1.1.1 Migraine and Ischemic Stroke

The first study to demonstrate an association between migraine and stroke was a case–control study from the Collaborative Group which included 598 women with stroke aged from 15 to 44 years and a group of hospital and neighbor control participants [13]. The risk of ischemic stroke was increased by twofold in migraineurs who were oral contraceptives nonusers (relative risk [RR] 2.0; 95 % confidence interval [CI] 1.2–3.3) and by sixfold in migraineurs who used oral contraceptives (RR 5.9; 95 % CI 2.9–12.2) [13]. Subsequent studies [1, 8, 10, 12, 18, 26, 49, 50, 55, 58, 63, 90, 93, 101], with few exceptions [29, 102], further supported an increased stroke risk in migraineurs. Most of those studies included young women [10, 12, 13, 18, 49, 50, 55, 63, 90, 93, 101], some included also young men [10, 55, 90], and fewer included older subjects [1, 8, 26, 29, 58, 102]. Comparable studies [8, 10, 12, 13, 18, 26, 29, 49, 55, 58, 63, 90, 101, 102] were pooled in the first meta-analysis by Etminan et al. (Table 1.1) [21]. This meta-analysis indicated that subjects with migraine had a twofold increased risk of ischemic stroke as compared to non-migraineurs [21]. The risk was increased for both migraine aura and without aura [21]. After this meta-analysis, further studies [5, 27, 36–39, 51, 54, 62, 68, 97, 104] and two meta-analyses [91, 94] became available. Some of those studies included only young subjects [54, 62, 68], while most of them included older men and women [5, 27, 97, 104], older women [36, 37, 39, 51], or older men [38]. Data from comparable studies [10, 12, 26, 27, 29, 37, 38, 101, 102] pooled by Schürks et al. indicated that subjects with any migraine had a 1.7-fold increased risk of ischemic stroke (Table 1.1) [91]. The risk was increased for migraine with but not without aura (Table 1.1) [91]. Data from comparable studies [5, 8, 10, 12, 13, 18, 26, 27, 29, 37, 38, 49, 50, 58, 62, 63, 101, 102, 104] pooled by Spector et al. indicated that subjects with any migraine had a twofold increased risk of ischemic stroke (Table 1.1) [94]. The risk was increased for migraine with but not without aura (Table 1.1) [94]. After the publication of those meta-analyses, the American Migraine Prevalence and Prevention study (AMPP), a case–control study including more than 11,300 participants, further supported the increased overall stroke risk in those with migraine (OR 1.5; 95 % CI 1.2–2.1) [7]. The study confirmed that the association was driven by an increased risk mostly in migraineurs with (odds ratio [OR] 2.8; 95 % CI 2.0–3.8) rather than without aura [7]. More recently, the Northern Manhattan Study (NOMAS), a prospective population-based study including 1,292 participants with a mean age of 68 years followed for a mean of 11 years, evaluated the possible association between migraine and cardiovascular events including stroke [61]. The study was unable to demonstrate an association between migraine, either with or without aura, and stroke [61]. Notably, authors found that migraineurs as compared to non-migraineurs had an increased risk of stroke if they were also current smokers (hazard ratio [HR] 3.2; 95 % CI 1.1–8.9) [61]. Gelfand et al., in a further study including 1,566,952 children aged 2–17 years, were unable to demonstrate an association between migraine and ischemic stroke

Table 1.1 Meta-analyses evaluating the association between migraine and cardiovascular events

Outcome/ study	Search limit (year of publication)	Any migraine		Migraine with aura		Migraine without aura	
		Studies (*n*)	Effect estimates (95 % CI)	Studies (*n*)	Effect estimates (95 % CI)	Studies (*n*)	Effect estimates (95 % CI)
Ischemic stroke							
Etminan (2005) [21]	1996–2004	14	2.16 (1.89–2.48)	8	2.28 (1.89–4.39)	7	1.56 (1.03–2.36)
Schürks (2009) [91]	Up to 2009	9	1.73 (1.31–2.29)	8	2.16 (1.53–3.03)	8	1.23 (0.90–1.69)
Spector (2010) [94]	Up to 2009	19	2.04 (1.72–2.43)	8	2.25 (1.53–3.33)	7	1.24 (0.86–1.79)
Hemorrhagic stroke							
Sacco (2013) [84]	Up to 2013	8	1.48 (1.16–1.88)	3	1.62 (0.87–3.03)	3	1.39 (0.74–2.62)
Myocardial infarction							
Schürks (2009) [91]	Up to 2009	5	1.12 (0.95–1.32)	–	–	–	
Sacco (2015) [87]	Up to 2014	7	1..33 (1.08–1.64)	2	2.61 (1.86–3.65)	2	1.14 (0.81–2.45)
Angina							
Sacco (2015) [87, 88]	Up to 2014	5	1.29 (1.17–1.43)	3	2.94 (1.59–5.43)	3	1.45 (1.06–2.00)
Cardiovascular death							
Schürks (2009) [91]	Up to 2009	5	1.03 (0.79–1.34)	–	–	–	
Schürks (2011) [92]	Up to 2011	6	1.09 (0.89–1.32)	–	–	–	
Coronary heart disease mortality							
Schürks (2011) [92]	Up to 2011	3	0.95 (0.57–1.60)	–	–	–	

CI indicates confidence intervals

in this age group [24]. Notably, a post hoc analysis of adolescents (12–17 years) showed a threefold increased risk of ischemic stroke among those with migraine (incidence ratio [IR] 3.4; 95 % CI 1.2–9.5) [24]. A recent additional study by Albieri et al., using administrative coding data, of 49,711 patients hospitalized for

a first stroke, indicated an increase in the risk of ischemic stroke in migraineurs as compared to non-migraineurs (RR 1.1; 95 % CI 1.0–1.1) [1].

Notably, data also indicated that migraine may be associated with an increased stroke risk during pregnancy [9, 31, 105]. Data using administrative coding data from the United States Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality showed that a diagnosis of migraine was associated with an increased risk of ischemic stroke (OR 30.7; 95 % CI 17.4–34.1) [9].

Because of the low number of events in many of the available studies, we have little information on the frequency of the different types of ischemic stroke in migraineurs. Data from the Stroke Prevention in Young Women (SPYW) Study, a population-based, case–control study including 386 women aged 15–49 years with first ischemic stroke and 614 age- and ethnicity-matched controls, were unable to prove an association between migraine with aura and any of the main ischemic stroke subtypes (large-artery atherosclerosis, cardioembolic, lacunar, undetermined cause) [54]. In contrast, the Oxford Vascular Study (OXVASC), a population-based study including 1,810 participants with transient ischemic attack (TIA) or ischemic stroke, showed that as compared to events with determined etiology, patients with cryptogenic events most often had a history of migraine (OR 1.7; 95 % CI 1.4–2.2). The same association was seen for migraine with aura (OR 1.8; 95 % CI 1.4–2.3) and migraine without aura (OR 2.1; 95 % CI 1.4–3.0) in an analysis stratified by sex and vascular territory [48]. In this study, as expected, the frequency of migraine decreased with age in the overall cohort; however, the frequency of history of migraine did not fall with age in patients with cryptogenic TIA or stroke, such that with an analysis stratified by age, the association of migraine and cryptogenic events was strongest at older ages [48].

More recently, the Italian Project on Stroke in Young Adults (IPSYS) demonstrated that in young patients with ischemic stroke, migraine with aura represented an independent risk factor for overall recurrent vascular events and for recurrent ischemic stroke [69]. In this prospective study, including 1,867 patients with first-ever ischemic stroke aged 18–45 years, migraine with aura emerged as an independent marker of risk of recurrent vascular events (HR 2.0; 95 % CI 1.2–3.4), indicating the striking importance of this condition in young subjects with ischemic stroke.

With regard to functional outcome after ischemic stroke, the analysis of data from the Women's Health Study (WHS) cohort, a prospective study among 27,852 women aged ≥45 years, showed that migraine with aura was only linked with ischemic strokes of good functional outcome [73]. Compared with women without history of migraine and who did not experience a TIA or stroke, women who reported migraine with aura had an increased risk of TIA (RR 1.6; 95 % CI 1.0–2.4) and of non-disabling (modified Rankin Scale score 0–1) stroke (OR 2.3; 95 % CI 1.4–4.0), while the study was unable to demonstrate an association between migraine and the risk of disabling stroke or death [73]. More recently, the study by Albieri et al., further supported that migraine was associated with an increased risk of mild strokes [1].

Beyond the comparisons of migraine with aura rather than without aura, studies provided little knowledge about the other possible characteristics associated with increased stroke risk. Findings from the World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception indicated that migraine of more than 12 years duration (OR 4.6, 95 % CI 1.3–16.8) and migraine with aura with attacks more frequent than 12 times per year (OR 10.4; 95 % CI 2.18–49.4) were associated with an increased risk of ischemic stroke [18]. Data from the SPYW study indicated that women with a higher frequency of migraine with aura (>12 attacks per year) had higher odds of stroke (OR 1.7; 95 % CI 1.1–2.8), in addition to women with recent onset of migraine with aura (OR 8.3; 95 % CI 2.6–25.7). However, lower frequency, longer duration, and any severity of the attacks were not associated with a significant increase in the risk of ischemic stroke [54]. According to data from the WHS cohort, the association between migraine with aura and ischemic stroke appeared J-shaped. Specifically, there were increased risks for less than monthly (HR 1.9; 95 % CI 1.2–3.1) and greater or equal to weekly (HR 4.3; 95 % CI 1.4–13.3) attacks, but not for monthly migraine attacks [40].

Nonetheless, there was consistent evidence that oral contraceptives use substantially increased the risk of ischemic stroke among young women with migraine (Table 1.2) [12, 13, 54, 93, 101]. The meta-analysis by Etminan et al. showed that users of oral contraceptives had an approximately eightfold increase in the risk of ischemic stroke compared to those not using those agents (RR 8.7; 95 % CI 5.1–15.1) [21]. In addition, there is consistent evidence that smoking substantially increases the risk of ischemic stroke among subjects with migraine [12, 39, 54, 61, 101] and that the risk is even higher in smokers who additionally use oral contraceptives (Table 1.2) [12, 54]. With the exception of smoking most studies suggest that the association between migraine and stroke is only apparent among individuals without or with the lowest burden of cardiovascular risk factors [87].

1.1.2 Migraine and Hemorrhagic Stroke

Several studies have also addressed the possible association between migraine and hemorrhagic stroke [1, 8, 11–13, 23, 24, 27, 35, 41, 93]. The pooled analysis of comparable studies [8, 11–13, 27, 35, 41, 93] by Sacco et al. indicated that subjects with any migraine had a 1.5-fold increased risk of hemorrhagic (including intracerebral and subarachnoid hemorrhage) stroke (Table 1.1) [84]. Subgroup analyses showed that female migraineurs had a 1.6-fold increased risk of hemorrhagic stroke as compared with female non-migraineurs (pooled adjusted effect estimate [PAEE] 1.6; 95 % CI 1.2–2.1) as female migraineurs aged less than 45 years (PAEE 1.6; 95 % CI 1.1–2.2) when compared with female non-migraineurs in the same age group [84]. However, solid conclusions could not be made for the different migraine types (with and without aura) because of insufficient data as only three studies [12, 35, 41] collected data on the risk of hemorrhagic stroke according to migraine type (Table 1.1). Two of them [35, 41] showed an association between migraine with

Table 1.2 Risk of stroke in subjects with migraine according to oral contraceptive use and smoking status

	Study population	Outcome	Exposure	OC nonusers	OC users	Not smoking	Smoking	OC+ smoking
Collaborative Group (1975) [13]	Hospital-based case–control study on women with stroke aged 15–44 years	Ischemic stroke	Migraine vs no migraine	Risk estimate (95 % CI)				
Chang (2009) [12]	Hospital-based case–control study on women with stroke aged 20–44 years	Ischemic stroke	Migraine vs no migraine	2.0# (1.2–3.3)	5.9# (2.9–12.2)	–	–	–
Tzourio (1995) [101]	Hospital-based case–control study on women with stroke aged <45 years	Ischemic stroke	Migraine vs no migraine	2.3# (0.7–7.5)	16.9# (2.7–106)	1.6# (0.4–5.9)	7.39# (2.1–25.5)	34.4# (3.3–361)
Schwartz (1998) [93]	Hospital-based case–control study on women with stroke aged 18–44 years	Ischemic stroke	Migraine vs no migraine	3.7# (1.5–9.1)	13.9# (5.5–35.1)	5.8# (2.2–15.3)	10.2# (3.5–29.9)	
MacClellan (2007) [54]	Hospital-based case–control study on women with ischemic stroke aged 15–49 years	Ischemic stroke	Migraine with aura vs no migraine	–	2.1# (1.2–3.7)	–	–	–
Kurth (2008) [39]	Prospective cohort study on women aged ≥45 years participating in a clinical trial	Ischemic stroke	Active migraine with aura vs no migraine	1.5# (1.1–2.1)	–	–	1.5# (1.1–2.3)	[a]7.0# (1.4–22.8) [b]10.0# (1.4–73.7)
Monteith (2015) [61]	Prospective population-based cohort study	Stroke	Migraine vs no migraine	–	–	2.3§ (1.2–4.3)	2.10§ (0.8–5.3)	–
				–	–	0.5§ (0.2–1.3)	3.2§ (1.1–8.9)	–

Risk estimates represent odds ratios# or hazard ratios§

OC indicates oral contraceptives; *CI* indicates confidence interval

[a]Compared with women with migraine with aura who were nonsmokers and non-OC users

[b]Compared with women with no migraine who were nonsmokers and non-OC users

aura and hemorrhagic stroke, while only one showed an association between migraine without aura and hemorrhagic stroke [35]. Regarding hemorrhagic stroke type, available data suggested that the association between migraine and hemorrhagic stroke is driven by an increase of intracerebral but not subarachnoid events [11, 41]. Thereafter, Gaist et al. performed a case–control study using data from 1,797 subjects with intracerebral hemorrhage and 1,340 subjects with subarachnoid hemorrhage and frequency matched controls from a large epidemiological dataset, The Health Improvement Network (THIN) [23]. In this study authors were unable to demonstrate an increased risk of overall hemorrhagic stroke or of intracerebral hemorrhage or subarachnoid hemorrhage in subjects with migraine compared with non-migraineurs. Analysis according to migraine type showed that neither migraine with aura nor migraine without aura were associated with an increased risk of hemorrhagic stroke. Only subjects with a long history (≥20 years) of migraine had an increased risk of intracerebral hemorrhage as compared to control subjects. Gelfand et al., in a further study including 1,566,952 children aged 2–17 years, were unable to demonstrate an association between migraine and hemorrhagic stroke in this age group [24]. Recently, the study by Albieri et al., did not demonstrate an increased risk of hemorrhagic stroke in migraineurs; however, in this study subanalysis by gender suggested an increased risk for hemorrhagic stroke in women migraineurs (RR 1.4; CI 1.1–1.8) as compared to non-migraineurs but no difference by migraine status in men [1]. Notably, data from the Nationwide Inpatient Sample indicated also that, during pregnancy, a diagnosis of migraine was associated with an increased risk of intracerebral (OR 9.1; 95 % CI 3.0–27.8) but not subarachnoid hemorrhage [9].

1.1.3 Migraine and Cardiac Vascular Diseases

Some studies have identified migraine also as a possible risk factor for cardiac vascular events [37, 38, 59], while others were unable to prove this association [27, 98, 104]. The pooled analysis of available data [27, 37, 38, 98, 104] by Schürks et al. did not indicate an increased risk of myocardial infarction in subjects with any migraine versus no migraine (Table 1.1) [91], but subsequently, data has pointed to an association between any migraine with cardiac ischemic disease [107] and between migraine with and without aura and myocardial infarction [7]. A further meta-analysis by Schurks et al., by pooling data from comparable studies [14, 25, 51], showed that the presence of any migraine did not alter the risk of coronary artery disease mortality (Table 1.1) [92]. A more recent meta-analysis by Sacco et al., pooling data from comparable studies [7, 27, 37, 38, 59, 98, 104], indicated a 30 % increase in the risk of myocardial infarction in subjects with migraine as compared to non-migraineurs (Table 1.1) [87]. An analysis stratified according to aura status indicated an increased risk of myocardial infarction in subjects with migraine with aura as compared to non-migraineurs while the meta-analysis was unable to show an increased risk of myocardial infarction in subjects with migraine without

aura (Table 1.1) [87]. This same meta-analysis also indicated that migraineurs as compared with non-migraineurs had an increased risk of angina (Table 1.1) [87]. In the case of angina, the risk was increased in both migraineurs with migraine with and without aura (Table 1.1) [87]. Both for myocardial infarction and angina, the meta-analysis indicated that the overall increased risk was mostly driven by the association in women while the meta-analysis was unable to demonstrate the association in men [87]. Notably, data from the Nationwide Inpatient Sample indicated also that, during pregnancy, a diagnosis of migraine was associated with an increased risk of myocardial infarction (OR 4.9; 95 % CI 1.7–14.2) [9].

Data from the WHS cohort showed that the association with myocardial infarction was evident among women in the highest Framingham risk score group and this pattern of association was driven by a particularly increased risk of myocardial infarction in women with migraine with aura who had high total cholesterol levels [39]. In contrast to the findings for ischemic stroke, this same study reported and association between low migraine frequency (< monthly) and myocardial infarction (HR 2.4; 95 % CI 1.6–3.7) and angina (HR 1.9; 95 % CI 1.3–2.9) among women with active migraine with aura, while the study was unable to demonstrate an association between higher migraine frequency (monthly and ≥ weekly) and those same cardiac end points [40].

1.1.4 Migraine and Vascular Abnormalities at Brain Neuroimaging

Several studies have also indicated that compared to non-migraineurs, migraineurs have a higher burden of asymptomatic white matter brain lesions and, according to some studies, infarct-like lesions on brain magnetic resonance imaging (MRI) [4, 28, 42, 60]. Those lesions may suggest chronic ischemic disease, but their nature still remains elusive because of the lack of neuropathological correlation.

White matter abnormalities in migraineurs have an uncertain pathological significance and may correspond to gliosis, demyelination, and loss of axons; this set of findings has been attributed to microvascular damage. According to a systematic review of studies published up to January 2013, prevalence of white matter abnormalities in migraineurs ranged from 4 to 59 % [4]. A meta-analysis of studies published up to November 2003, of pooled data from 7 studies [16, 22, 30, 67, 74, 77, 109] suggested an increased risk of white matter hyperintensities in migraineurs (OR 3.9; 95 % CI 2.3–6.7) [99]. According to the Cerebral Abnormalities in Migraine an Epidemiological Risk Analysis (CAMERA) study, a population-based study including 134 migraineurs without aura, 161 migraineurs with aura, and 140 controls aged 30–60 years reported that migraine was associated with deep white matter abnormalities in women (OR, 2.1; 95 % CI, 1.0–4.1) [33]. This association was independent of the presence or absence of aura, and the risk increased with attack frequency (highest in those with ≥1 attack per month: OR, 2.6; 95 % CI, 1.2–5.7) [33]. A subsequent analysis from the CAMERA study indicated an

increased risk of infratentorial (mostly pontine) hyperintensities in migraine with and without aura [34]. By contrast, this same study showed that in men, deep white matter abnormalities were not influenced by the presence, subtype, or frequency of migraine. The Epidemiology of Vascular Ageing (EVA) study, a population-based cross-sectional study involving 780 participants, confirmed the association of migraine with white matter abnormalities (OR 1.8; 95 % CI 1.0–2.9) [42]. The association between migraine and white matter hyperintensities was evident only for deep located lesions and migraine with aura (OR 12.4; 95 % CI 1.6–99.4) but not for periventricular lesions and migraine without aura [42]. A meta-analysis by Bashir et al., pooling data from 4 comparable studies [17, 33, 42, 77] published up to January 2013, showed an increased risk of white matter abnormalities in subjects with migraine with aura (PAEE 1.7; 95 % CI 1.1–2.7) and no association with migraine without aura [4]. More recently, data from the NOMAS indicated no association between migraine with or without aura and white matter hyperintensity volume [60]. Recently, an analysis of data from a subset of 506 subjects included in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study, a placebo-controlled trial assessing effects by pravastatin on cardiovascular disease, was unable to demonstrate an association between migraine either with and without aura and white matter hyperintensities [2].

Two studies addressing the impact of migraine on white matter hyperintensities progression over time provided conflicting results [28, 66]. Data from the CAMERA study indicated that, after a mean follow-up of 8.5 years, migraine was associated with white matter hyperintensities progression (OR 2.1; 95 % CI 1.0–4.1) [66]. In contrast, data from the Atherosclerosis Risk in Communities (ARIC) cohort study involving 1,028 participants who received 2 magnetic resonance imaging 8–12 years apart was unable to demonstrate any difference in white matter hyperintensity progression over the time between individuals with and without migraine [28]. The available studies did not support the hypothesis that migraineurs with white matter abnormalities are at risk of cognitive impairment [42, 66, 73].

Infarct-like lesions appear as small infarcts on brain magnetic resonance imaging mostly in the absence of a clinical history of stroke. Their exact nature still remains elusive and they might be of a different nature rather than ischemic. Data from the CAMERA study indicated that migraine with aura was associated with an increased risk of posterior circulation (mostly cerebellar) infarcts (OR 13.7; 95 % CI 1.7–112), while the study was unable to demonstrate an association between migraine without aura and posterior circulation infarcts [33, 34]. Another population-based study in Reykjavik involving 4,689 participants indicated that subjects with migraine with aura had an increased risk of late-life infarct-like lesions (OR 1.4; 95 % CI 1.1–1.8) that specifically reflected an association with cerebellar lesions in women (OR 1.9; 95 % CI, 1.4–2.6) [89]. Migraine without aura and non-migraine headache were not associated with an increased risk. Data from the EVA study further supported an increased risk of infarct-like lesions in subjects with migraine with aura (OR 3.4; 95 % CI 1.2–9.3) [42]. However, in contrast to other studies, the results of the EVA study indicated that most of the infarcts were located outside of the cerebellum or the brain stem [42]. Data from the NOMAS indicated that those

reporting migraine overall had double the odds of infarct-like lesions (OR 2.1; 95 % CI 1.0–4.2) when compared with those reporting no migraine [60]. Recently, data from the PROSPER study showed no association between migraine either with or without aura and infarct-like lesions [2]. With regard to migraine progression, data from the CAMERA study also indicated that migraine was not associated with the progression of infarct-like lesions over time [66].

Recently, an analysis of data from the PROSPER study evaluated the possible association between migraine with cerebral microbleeds [2]. These authors were unable to demonstrate overall an association between overall migraine and cerebral microbleeds. However, analysis stratified by migraine type and microbleeds location (lobar, basal ganglia, infratentorial) indicated an association between migraine without aura with infratentorial microbleeds (OR 3.3; 95 % CI 1.0–11.0) [2].

1.2 Monogenic Diseases with Migraine and Stroke

Several monogenic diseases have been recognized that include both migraine and cerebrovascular disease in the disease spectrum, and this represents further evidence of shared mechanisms between the two conditions [81]. Those diseases are represented by cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial encephalopathy lactic acidosis with stroke-like episodes (MELAS), autosomal dominant retinal vasculopathy with cerebral leukodystrophy (AD-RVCL), and hereditary infantile hemiparesis, retinal arteriolar tortuosity and leukoencephalopathy (HIHRATL).

CADASIL is due to a mutation of the Notch3 gene on chromosome 19. It is characterized by migraine with or without aura, mood disturbances, TIA, or strokes (usually lacunar infarcts) and progressive cognitive decline; other less common clinical features are epilepsy, acute reversible encephalopathy, and myopathy. Migraine is very common in CADASIL and it is often the presenting symptom [103]. Subjects may have typical attacks of migraine with aura but atypical auras are particularly common [80].

MELAS is due to a mutation at position 3243 of the mitochondrial genome [95]. It is characterized by seizures, encephalopathy, stroke-like episodes, migraine mostly associated with vomiting and aura, short stature, cognitive impairment, depression, cardiomyopathy, cardiac conduction defects, and diabetes mellitus.

AD-RVCL is due to TREX1 mutation on chromosome 3 and is characterized by systemic microvasculopathy with adult-onset retinal vasculopathy and cerebrovascular disease variably associated with migraine, mainly without aura [32].

HIHRATL is due to a mutation in the COL4A1 gene on chromosome 13 [45]; the disease has some similarities with CADASIL and is characterized by features of cerebral small-vessel disease, including subcortical hemorrhagic and ischemic lacunar strokes and leukoaraiosis. Patients usually suffer also from migraine mostly with aura, seizures, infantile hemiparesis, developmental delay, neuropsychological abnormalities, and ocular, renal, and cardiac involvement.

1.3 Mechanisms Linking Migraine to Cardiovascular Diseases

The mechanisms underlying the relationship between migraine and cardiovascular events are still unclear and several hypotheses have been raised and extensively revised and discussed [6, 43, 56, 78, 79, 83, 86]. Current hypotheses mostly try to link vascular events in migraineurs to those mechanisms that usually cause the same vascular events in non-migraineurs subjects. Hypothesized mechanisms include the role of confounders such as pharmacological agents used to treat migraine (non-steroidal anti-inflammatory drugs, triptans, and ergotamine) or anxiety and depression; antiphospholipid antibodies and prothrombotic factors, including prothrombin factor, factor V of Leiden, elevations in von Willebrand factor antigen and activity, decreased platelet hemostasis time, clotting time, and collagen-induced thrombus formation time; MTHFR and ACE D/I polymorphisms; cervical arterial dissection; and patent foramen ovale. However, since none of those factors can entirely explain the cardiovascular risk of migraineurs, alternative hypotheses should also be considered and among them peculiar migraine-specific mechanisms.

Migraine headache depends on the activation and sensitization of the trigeminovascular pain pathway, while cortical spreading depression is considered the neurophysiologic correlate of migrainous aura [70]. The origin of the cortical spreading depression in human migraineurs remains unclear, but in animal models, cortical spreading depression has been triggered by ischemic phenomena, such as through infusions of endothelin-1, a powerful vasoconstrictor [19]. Other mechanisms include microembolization of the carotid circulation using tiny plastic spheres, cholesterol crystals, and microbubbles, following large reduction of local blood flow [64]. Cortical spreading depression may predispose to brain lesions by hypoperfusion (spreading oligemia), by activating a cascade of inflammatory events, and by a failure of neurovascular coupling to provide a sufficient increase in blood flow for the raised energy use in cortical spreading depression [3, 6, 43, 46]. The genetic mouse models expressing migraine mutations (e.g., familial hemiplegic migraine 1 and CADASIL) show a faster onset of ischemia-triggered spreading depolarization; an increased frequency of ischemic depolarization; enlarged infarcts with worse neurological outcomes (which could be prevented by anti-excitatory treatment); and more severe spreading of depolarization-induced oligemia [20]. As a result, the minimum critical level of blood flow required for tissue survival is elevated and infarction occurs, even in mildly ischemic tissues. Considering the above reported evidences, some authors have proposed that as cortical spreading depression may occur as a consequence of subclinical ischemia, thus aura may represent a variant of TIA [56]. The suggestion that a common alteration may cause both migraine and stroke is further supported by the existence of the above-reported monogenic diseases that are associated with both conditions. These conditions might serve as models to study migraine-vascular disease mechanisms [81, 108].

However, in migraineurs the risk of vascular events is increased even outside the brain. Even if it cannot be excluded that different mechanisms may be of importance

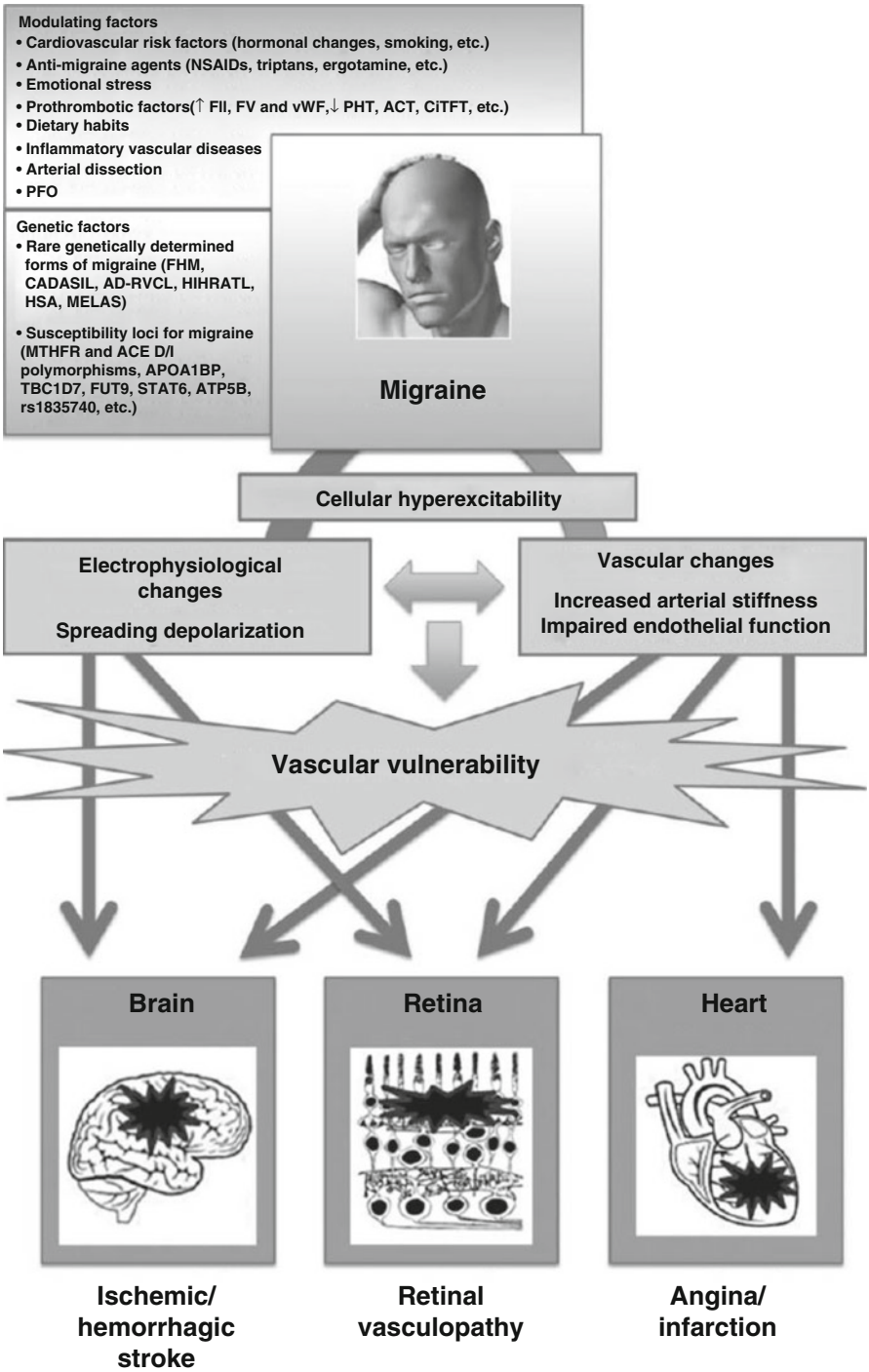
in cardiac and cerebral events, this possibility is unlikely and consequently the search for a cause for the association between migraine and vascular events should look at a general level. Electrophysiological changes could be present not only within the brain but also in other tissues (e.g., heart), and a complementary hypothesis may rely on a systemic peculiar vascular vulnerability of migraineurs that may contribute to the pathogenesis of migraine and over time, to the development of vascular events (Fig. 1.1) [71]. Numerous data suggest that in migraineurs the vascular system is impaired at a systemic level since migraineurs showed an alteration of arterial function (greater stiffness or impaired compliance of the arterial system) and according to some studies also of the endothelial function (altered flow-mediated dilation, reduced number of endothelial progenitor cells) compared to non-migraineurs [85]. Additionally, alteration of circulating factors linked to vascular dysfunction has been found in migraineurs [47, 52, 65, 76]. However, while in the general population markers of endothelial and arterial impairment represent precursors of atherothrombotic disease, evidence suggests that in migraine this may not be the case [96].

Recently, Mawet et al. investigated the hypothesis that a history of migraine predisposes to faster acute cerebral infarct growth [57]. They performed a case–control study of subjects with acute stroke (45 migraineurs and 27 controls), including chart documentation of migraine status and brain magnetic resonance imaging within 72 h of the stroke. In this study, migraine, particularly migraine with aura, more frequently showed the no-mismatch pattern with diffusion and perfusion magnetic resonance. This suggests accelerated loss of viable tissue at risk, as shown in the migraine mouse model [100].

1.4 Implications for Clinicians

While the evidence that links migraine to cardiovascular disease is robust, the overall increase in absolute risk of cardiovascular disease in migraineurs is rather small. Unfortunately, at the moment there are no reliable features that may indicate which subjects, across the overall migraine population, are at the highest risk of vascular events. The role that comorbid conventional vascular risk factors have on the risk

Fig. 1.1 Vascular vulnerability in migraine. *ACE* angiotensin-converting enzyme, *ACT* activated clotting time, *AD-RVCL* autosomal dominant retinal vasculopathy with cerebral leukodystrophy, *C-iTFT* collagen-induced thrombus formation time, *CADASIL* cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, *F II* prothrombin factor, *F V* Leiden factor, *FHM* familial hemiplegic migraine, *HIHRATL* hereditary infantile hemiparesis, retinal arteriolar tortuosity, and leukoencephalopathy, *HSA* hereditary systemic angiopathy, *MELAS* mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, *MTHFR* methylenetetrahydrofolate reductase, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PFO* patent foramen ovale, *PHT* platelet hemostasis time, *vWF* von Willebrand factor (From Ripa et al. [72])


Modulating factors
• Cardiovascular risk factors (hormonal changes, smoking, etc.)
• Anti-migraine agents (NSAIDs, triptans, ergotamine, etc.)
• Emotional stress
• Prothrombotic factors(↑ FII, FV and vWF,↓ PHT, ACT, CiTFT, etc.)
• Dietary habits
• Inflammatory vascular diseases
• Arterial dissection
• PFO
Genetic factors
• Rare genetically determined forms of migraine (FHM, CADASIL, AD-RVCL, HIHRATL, HSA, MELAS)
• Susceptibility loci for migraine (MTHFR and ACE D/I polymorphisms, APOA1BP, TBC1D7, FUT9, STAT6, ATP5B, rs1835740, etc.)
Migraine
Cellular hyperexcitability
Electrophysiological changes
Spreading depolarization
Vascular changes
Increased arterial stiffness
Impaired endothelial function
Vascular vulnerability
Brain
Retina
Heart
Ischemic/ hemorrhagic stroke
Retinal vasculopathy
Angina/ infarction

of cardiovascular events in migraineurs is controversial. While according to some studies the risk of ischemic stroke in migraineurs is magnified in the presence of some acknowledged vascular risk factors, according to other studies the risk is higher in those subjects not having comorbid vascular risk factors [88]. Data indicated that cigarette smoking is associated with three- to ninefold increased risk of ischemic stroke in migraineurs and oral contraceptive use with a four- to eightfold increased risk [12, 21, 101, 102]. The combination of smoking and oral contraceptive use in women is associated with a tenfold increase in the risk with respect to the presence of migraine alone [12]. According to those data, subjects with migraine with aura should be strongly advised to quit smoking and prescription of combined oral contraceptives deserves special caution [83]. Since migraine without aura is not a definite risk factor for stroke, no specific restrictions are warranted in women with this condition, especially in the absence of comorbidities. Oral contraceptive use should be carefully discussed in women with migraine with aura since they may contribute to an unacceptable increased vascular risk in particular if women smoke. Their prescription should be contraindicated in women with migraine with aura and other comorbid vascular risk factors or congenital or acquired thrombophilia [83].

So far, no drugs are currently recommended for the vascular prevention in migraineurs. Patients with migraine should not be prescribed aspirin or other antithrombotics for cardiovascular prevention unless other (i.e., non-migraine) clear indications are present. The same should be applied to migraineurs showing evidence of white matter hyperintensities or infarct-like lesions at brain magnetic resonance. Since patent foramen ovale has not been reliably associated with migraine nor with ischemic stroke in migraineurs [15], no specific strategies should be adopted in the presence of patent foramen ovale even in association with white matter hyperintensities and infarct-like lesions unless in some isolated cases showing proven additional markers of high vascular risk (e.g., thrombophilia). In general, the acute treatment and the secondary prevention measures of a patient with stroke who has a history of migraine do not differ from those of other stroke patients [44], regardless of the implications that migraineurs have a shorter therapeutic window during the course of an acute stroke [57, 100].

There is currently no direct evidence that a migraine prophylactic treatment can reduce future stroke risk [82]; however, we cannot exclude that migraine prophylaxis, by raising the threshold for spreading depolarization, may lower stroke risk [100]. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers that in some preliminary studies have shown some efficacy in migraine prevention have been also associated with reduction of cardiovascular risk independently of their blood pressure-lowering effect [71]. However, further evidence is needed to support their role as migraine preventive treatment in the absence of high blood pressure values and to demonstrate any possible benefit on the cardiovascular risk of migraineurs. On the contrary, β-blockers (propranolol, metoprolol, atenolol, bisoprolol) that are commonly used as migraine prophylactic agents have not been reliably associated with vascular preventive effects independently of blood pressure lowering.

Ergot alkaloids and triptans, two effective migraine acute treatments, may raise concerns regarding cardiovascular safety because of their vasoconstrictive effect. Data suggest that intense use of ergotamines is associated with a more than twofold increased risk of serious ischemic events; the risk may be even higher in subjects with comorbid cardiovascular disease [75, 104, 106]. Conversely, in the case of triptans, available studies and the resulting overall effect size estimate did not indicate an increased occurrence of cardiovascular events among intense users [53, 75, 104, 106]. Becker et al. found more than a twofold increased risk of stroke among migraineurs recently exposed to triptans and found more than a twofold increased risk for triptan users compared to unexposed migraineurs [5]. In addition, the fact that the migraine-stroke association is limited to migraine with aura argues against a strong influence of migraine treatment in stroke occurrence as patients with migraine with and without aura are similarly treated. In patients with a documented history of cardiovascular disease, use of ergot derivatives and triptans for acute migraine attacks is contraindicated as well as in patients with uncontrolled high blood pressure.

1.5 Gaps and Future Research

Currently, the evidence linking migraine with aura with stroke and other vascular events is so consistent that we can reliably consider this condition as a risk factor for vascular disease [7, 21, 91, 94]. In contrast, for migraine without aura data indicated only a trend toward an association that only in some studies reached the statistical significance [7, 21, 91, 94]. This may indicate that the risk of cerebrovascular disease for migraineurs without aura may be absent, but more likely it is just lower than the risk for migraineurs with aura; this possibility should be tested in larger studies.

Because most studies included women and young migraineurs, the role of age and gender needs to be better clarified in order to determine if migraine with aura can be considered a risk factor for vascular events in men and in older migraineurs. Some data indicated that recent onset migraine, active migraine with aura, and frequent attacks are associated with increased vascular risk [38, 40, 54], but this evidence needs to be further supported by additional studies. Additionally, most of the studies which showed an increased risk of stroke in migraineurs using oral contraceptives are not generalizable to newer drugs with new generation, low-dose estrogens compared with new formulations, or to progesterone-only contraceptives.

Migraine is a very common condition in the general population but only a limited number of subjects with migraine experience a vascular event. So far, we have no reliable features to identify those migraineurs at particularly increased risk, and future studies should establish laboratory, imaging, or other instrumental markers that can be reliably linked to future vascular event occurrence in migraineurs.

So far, cellular hyperexcitability, the postulated mechanism that links migraine to the increased vascular risk, has been demonstrated only in the mouse model [20]

and not in humans, whereas future studies will have to prove this mechanism even in human subjects. Additionally, studies should also try to explain why migraineurs have an increased risk of vascular events even outside the brain and the reasons for the impairment of the vascular function at a systemic level in migraineurs.

Currently, we do not know if migraine is a modifiable vascular risk factor. While we can suppose that migraine preventive drugs may reduce cellular hyperexcitability, we do not know if this may be associated with a reduced vascular risk. Studies involving mouse models of migraine are needed to provide some evidence about this possibility in the near future.

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Chapter 2
Psychiatric Comorbidity in Migraine and Chronic Headache

Gianluca Serafini, Shuu-Jiun Wang, Dorian Lamis, Martina Curto, Paolo Girardi, Mario Amore, and Maurizio Pompili

2.1 Introduction

Headache disorders are a public health priority as they are associated with significant disability and psychosocial impairment worldwide [64, 83]. Migraine is currently recognized as one of the major causes of lost days from work and school every year, and it is also responsible for severe lifestyle restrictions [84, 85]. Twice as common as tension-type headache, migraine is the most frequent primary headache and accounts for 22 % of all headache diagnoses, whereas other unspecified headache types may be observed in 18 % of cases [84, 85].

As reported by Lipton et al. [56], migraine is common in the United States (USA) with approximately 12 % of the general population suffering from a migraine in a given year. Moreover, it is usually associated with several comorbid psychiatric disorders such as depression, anxiety, and post-traumatic stress disorder [9, 45, 84]. Headache is often accompanied by both behavioral and somatic symptoms that may

G. Serafini • M. Amore
Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genoa, Genoa, Italy

S.-J. Wang
Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan

Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan

D. Lamis
Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

M. Curto
Department of Psychiatry, Harvard Medical School, Boston, MA, USA

Department of Molecular Medicine, Sant'Andrea Medical Center, Sapienza University of Rome, Rome, Italy

P. Girardi • M. Pompili, MD, PhD (✉)
Department of Neurosciences, Mental Health and Sensory Organs, Suicide Prevention Center, Sant'Andrea Hospital, University of Rome, Via di Grottarossa 1035–1039, Rome 00189, Italy
e-mail: maurizio.pompili@uniroma1.it

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be linked at multiple levels with psychiatric comorbidity [71]. Importantly, individuals with migraine and psychiatric comorbidity more frequently use healthcare services and experience a lower quality of life compared to those suffering from migraine without psychiatric comorbidity [70]. This comorbidity, especially when untreated, may have a negative impact on treatment outcomes, which enhance the risk of migraine chronicity as well as the evolution of episodic migraine into chronic migraine, strengthening the individual disability and psychosocial impairment [69].

Various studies examining the prevalence and impact of psychiatric disorders among patients with migraine and other types of headache have mainly focused on the impact of comorbid major depression, anxiety, substance abuse/dependence, and suicide behavior [8, 46, 121]. However, the association between headache and psychopathological conditions has been coarsely described from a clinical point of view rather than systematically analyzed [106]. Conversely, this association is strongly able to modify the illness outcome and may be considered a stimulating area for future headache research. In this review chapter, we aimed to explore the prevalence, impact, and clinical implications of psychiatric comorbidities related to migraine.

2.2 Psychiatric Comorbidities Associated with Migraine: Major Depression

One of the most relevant psychiatric comorbidities in individuals with migraine is major depression. Several studies [11, 58, 129] suggested that those with migraine were 2.5 times more likely to be depressed when compared with those without. Antonaci and colleagues [2] reported the existence of a high variability (from 8.6 to 47.9 %) of major depression in individuals with migraine according to their meta-analytic study. The comorbidity with major depression has been reported especially among individuals with migraine with aura and chronic migraine [3]. In addition, individuals with migraine and depression are more likely to be refractory to commonly available migraine treatments more frequently developing medication overuse and disability [78]. Based on existing evidence, a bidirectional relationship between migraine and major depression has been suggested [11, 84, 85].

Although there is no evidence, to our knowledge, showing that an improvement of major depression may reflect an improvement of migraine symptoms, some of the mechanisms associated with the efficacy of antidepressant medications in the prevention of migraine seem to be related to the shared causative mechanisms underlying both depression and migraine [12]. Specific pathophysiological hypotheses have been postulated in order to explain these shared causative mechanisms: serotonergic dysfunctions, periventricular white matter abnormalities, hormonal influences, and sensitization of the sensory/emotional neural networks [5, 103, 104]. These mechanisms were frequently mentioned in the effort to explain the commonly observed comorbidity between migraine and most of psychiatric conditions in clinical populations.

2.3 Bipolar Disorders and Migraine

Given that more studies about psychiatric comorbidity in migraine focused on unipolar depressive symptomatology, the exact prevalence of bipolar disorder spectrum in chronic headache patients is controversial. Based on available evidence, it has been suggested that bipolar disorder rates in chronic headache as well as in other headache disorders are largely underestimated. According to the findings of Robbins [94] who conducted their study in a sample of 287 total chronic headache subjects, bipolar disorder rates were 6.6 %, but a lifetime bipolar disorder rate in migraine was 8.6 % in the overall sample, 6.4 % in episodic chronic migraine patients, and 6.8 % in those experiencing chronic cluster headache were reported.

As for major depression, a bidirectional relationship has been also postulated between migraine and bipolar disorder. Several reports [8, 67, 68] found that the likelihood of being diagnosed with a bipolar disorder was three times higher in migraine patients with aura compared to the general population. It is also important to note that approximately 30 % of bipolar patients suffer from migraine. Recently, Fornaro and Stubbs [25] reported that those with a bipolar disorder type II were more likely to report migraine than those with bipolar disorder type I (54.17 % vs. 32.7 %). According to recent evidence [29, 31], subjects who suffered from a comorbidity with migraine had a type of bipolar disorder which is characterized by an earlier age of onset, a rapid cycling course, more frequent comorbid panic attacks, and increased prevalence in females than those without this migraine comorbidity. Dilsaver and colleagues [20] reported the existence of many similarities such as the episodic course, increased vulnerability to stress, family history of affective disorders, and a better response to valproate among those with bipolar disorder and comorbid migraine. Similarly to other psychiatric comorbidities, it has been hypothesized that even migraine and bipolar disorder may share common abnormalities (e.g., dysfunction of calcium channels) that play a fundamental role in the pathophysiology of both these conditions [31]. These conditions seem to also have a profound link with sleep disturbances as they share relevant neuroendocrine dysfunctions together with a significant response to lithium therapy as suggested by Costa et al. [18]. The importance of making the appropriate diagnosis may have a significant impact on headache care and suggests the utilization of more appropriate mood stabilizers conversely to what was commonly observed in clinical practice (e.g., bipolar disorder is often misdiagnosed, especially on initial presentation).

2.4 Anxiety Disorders and Migraine

Patients with migraine were also more likely (in more than 50 % of cases) to develop lifetime anxiety disorders. The prevalence of anxiety disorders is nearly 2–5 times higher in subjects with migraine when compared to the

general population and significantly higher in patients with chronic than episodic migraine [13]. Baskin and colleagues [4] noted that comorbidity between depression, anxiety disorders, and migraine is common. Migraine is also commonly associated with generalized anxiety disorder, obsessive compulsive disorder, and panic disorder [4].

As suggested by McWilliams et al. [66] and Smitherman et al. [107], a bidirectional association was found between migraine and anxiety disorders as the risk of experiencing migraine was 3.86 times higher in subjects with generalized anxiety disorder compared to those without. Moreover, individuals with migraine were 3.13 times more likely to develop generalized anxiety disorder than those without. According to recent reports [32], subjects with obsessive compulsive disorder were 4.57 times more likely to experience migraine with a frequency of 2–6 times per week. Moreover, Smitherman and colleagues [107] reported that patients with migraine, especially those affected by migraine with aura, were 3.76 times more at risk to have a panic disorder. Individuals with panic disorder usually experience a higher migraine frequency, an elevated psychosocial impairment and disability as well as an increased risk of medication overuse and chronicity [107]. There are many similarities such as the fear associated with illness episodes, autonomic and gastrointestinal symptoms, functional impairment, and overall burden of disease [107] between these groups. The strong relationship between migraine and panic disorder is also indirectly supported by the increased self-reported use of non-pharmacological treatments for headache in those with a family history of anxiety [69]. Baskin and colleagues [4] suggested that the correct management of anxiety in patients with migraine usually reflected the improvement of quality of life, a higher adherence and effectiveness of both pharmacological and non-pharmacological treatments for migraine.

Interestingly, Gonda and colleagues [30] reported that both subjects with anxiety and migraine showed a common genetic vulnerability to develop these conditions (e.g., higher frequency of the s-allele in a study about the 5HTTLPR polymorphism of the serotonin transporter gene). Several abnormalities have been postulated to play a role in the association between anxiety and migraine: serotonergic and hypothalamic-pituitary-adrenal (HPA) axis dysfunctions, hormonal abnormalities, pain-related cognition, and avoidance learning [59, 107].

2.5 Impulsivity, Aggression, and Migraine

Impulsivity and aggression may be commonly observed in patients with chronic headache since individuals with migraine often experience restlessness or agitation during headache episode [35]. Importantly, up of 90 % of patients with migraine demonstrated a variety of aggressive behaviors and impulsivity [117]. According to functional neuroimaging studies [41], the posterior hypothalamus is undoubtedly implicated in determining the occurrence of aggressive behavior throughout the chronic headache attacks.

It has been suggested that self-aggressive and depressive cognitions in chronic cluster headache correlated with depressive symptoms and impairment [60]. The authors evaluated 26 patients with chronic, 25 with active episodic, and 22 with episodic cluster headache outside the active period that have subsequently been compared to 24 migraine patients and 31 headache-free volunteers. Luerding and colleagues [60] reported that in chronic cluster headache and active episodic cluster headache patients, high levels of "self-aggression/depression" were all significantly associated with higher depressive symptoms and impairment measured at both an emotional and functional level. The authors stressed the notion that depression levels are associated with elevated self-aggression. Overall, aggressiveness and impulsivity represent complex phenomena that may be a frequent correlate of disabling conditions such as pain and major depression [1, 124].

2.6 Stress and Migraine

One of the most relevant migraine triggers may be identified with stressors. Subjects with chronic migraine usually presented with higher levels of stress [22] as well as more disabling life events in the year prior to their migraine chronicity when compared to those with episodic migraine [100]. These data have been also replicated by the longitudinal Brazilian study that demonstrated the association between higher migraine frequency and negative life events [98]. Several studies [36, 39, 40, 87, 88] showed the efficacy of relaxation therapies, biofeedback, and cognitive behavioral therapies in managing stress as well as in migraine prophylaxis. Both structural and functional impairments and even repeated migraines may be related to chronic stress exposure [7, 65]. It has been demonstrated that negative changes significantly influence the onset and maintenance of pain processing and central sensitivity, in conjunction with the same pain experience in migraine patients [7, 88]. fMRI studies also revealed that migraine patients exerted an increased activation of the perigenual cortex (associated with allostatic alterations in rats; [113]) relative to patients without migraine after a painful heat stimulus.

Important abnormalities have been also found in patients who suffered from analgesic or other headache medication abuse. For example, abnormal ACTH and cortisol release have been reported in individuals with chronic migraine and medication overuse [89]. A positive correlation between duration of chronic migraine and endocrine abnormalities has been observed [89]. Moreover, the fact that the decrease of stress usually reflects a subsequent higher risk of migraine attacks further enhances the existence of a biological link between migraine and stress [57]. It is important to note that both neuroendocrine and autonomic nervous systems are usually enhanced by stress with subsequent elevated production of glucocorticoids. The early exposure to stressful traumatic experiences might enhance the likelihood of developing major psychiatric disorders and is associated with the decrease in the expression of glucocorticoid receptors (GR) influencing gene function and response to future stressors [16].

2.7 Stress, Post-traumatic Stress Disorder, and Migraine

Tietjen and Peterlin [116] reported that those with a history of emotional, physical, and sexual abuse as well as physical neglect were more likely to develop migraines than the general population. Moreover, those who have been emotionally abused were more likely to develop chronic and more invalidating migraines as well as an earlier migraine onset relative to those who did not [114]. Tietjen and colleagues [115] observed that this correlation was independent of comorbidity with depression and anxiety.

Migraine frequency has been also linked to the number of childhood traumatic experiences [116]. A higher risk of migraine diagnosis rather than tension headaches has been reported in those with headache and a history of emotional abuse, emotional neglect, and sexual abuse [115]. Recent studies focused on cortisol dysfunctions and enhanced stress reactivity presumably related to past traumatic experiences in order to explain the association between abuse and migraine [53, 101]. Recently, it has been suggested that post-traumatic stress disorder, being a valid predictor of migraine, is able to mediate the association between migraine and childhood abuse [107]. Post-traumatic stress disorder among veterans, in particular men, is associated with enhanced headache drug utilization [102]. Post-traumatic stress disorder may also moderate the association between chronic pain and childhood abuse [92]. Raphael and Widom [93] hypothesized that the comorbidity with post-traumatic stress disorder is more relevant in these patients than the same burden related to childhood abuse in patients with chronic pain.

There are some psychological similarities between patients with post-traumatic stress disorder and those with chronic pain including fear avoidance and anxiety sensitivity [75, 105]. Xie and colleagues [126] stressed the presence in subjects with migraine and comorbid post-traumatic stress disorder of serotonin dysfunctions and 5HTTLPR polymorphisms of the serotonin transporter gene, whereas other reports [5, 34, 127] focused on the relevance of estrogen and the HPA axis in order to explain the comorbidity between migraine and post-traumatic stress disorder. As suggested by the study of Peterlin and colleagues [80], 4.5 % of patients without headache, 12.6 % of those with episodic non-migraine headache, 21.5 % of those with episodic migraine, and 19.2 % of those with chronic daily headache suffered from a lifetime post-traumatic stress disorder, respectively. It is also reasonable that major depressive disorder and post-traumatic stress disorder are able to reliably explain the more commonly observed medication abuse in headache individuals [79–82]. The comorbidity between major depressive disorder and post-traumatic stress disorder is undoubtedly more frequent in chronic daily headache than in episodic migraine [79, 82]. Patients with post-traumatic stress disorder were also more likely to show comorbid depressive and anxiety disorders [50], and thus post-traumatic stress disorder seems also able to account at least for the occurrence of some psychiatric comorbidities related to both episodic and chronic migraine. Importantly, targeting the multiple psychological implications related to post-traumatic stress disorder and depression may help to reduce the illness burden and attenuate the disability associated with migraine comorbidities.

Migraine subjects with post-traumatic stress disorder may be considered at greater risk of disability and experience more lost work days as they more frequently suffer from physical, mental health, and substance problems together with interpersonal difficulties when compared to migraine individuals without post-traumatic stress disorder [79, 82, 91]. Muse [72] and other recent authors have suggested that the disability of migraine individuals who suffered from a comorbid post-traumatic stress disorder may be significantly reduced using cognitive-behavioral therapy.

Overall, given the same frequency and prevalence exposure to stressful traumatic events, post-traumatic stress disorder is undoubtedly more common in those with chronic migraine relative to those with episodic migraine [51, 81, 99]. In summary, as suggested by Peterlin and colleagues [80], migraine subjects showed an increased lifetime and 1-year risk to develop post-traumatic stress disorder than the general population. But, relevantly, migraine subjects more commonly reported maladaptive stress responses that could enhance their vulnerability to develop a post-traumatic stress disorder [80]. Several neurobiological hypotheses have been formulated to explain the correlation between migraine and post-traumatic stress disorder such as serotonergic dysfunctions, HPA overactivity, and autonomic abnormalities. Since these abnormalities may be also found in subjects who were diagnosed with affective and anxiety disorders, this could be an interesting research area for the future in order to provide further explanations about the frequent comorbidity between post-traumatic stress disorder and migraine [47].

2.8 Sleeping Disorders and Migraine

Rains and Poceta [90] suggested that patients with migraine may commonly suffer from sleep disorders when compared to the general population. Similarly, a higher risk of disabling sleep disorders in patients with migraine has been reported by Odegard and colleagues [74]. Kelman and Rains [49] found that more than 50 % of migraine subjects showed occasional sleep disturbances but more than 30 % of them reported common and invalidating sleep disorders together with sleep duration of less than 6 h per night. More severe and disabling headaches may be associated with chronic short sleep [49], but patients with migraine usually reported a variety of sleep disorders including insomnia, restless leg syndrome, parasomnias, narcolepsy, and periodic limb movements during sleep [17].

Insomnia is a frequent comorbid condition in patients with migraine, depression, anxiety, and post-traumatic stress disorder. However, migraine and psychiatric conditions negatively influence sleep quality; however, poor sleep quality significantly predisposes one to migraine. Thus, sleep disturbances may be a very interesting indicator of psychiatric comorbidity in migraine patients helping to identify specific subgroups at risk for negative outcomes.

When compared to a placebo intervention, behavioral sleep modification is also able to both ameliorate headache frequency/severity and attenuate the illness burden

related to both chronic and episodic migraine based on a small randomized placebo-controlled trial [15]. Chronic migraine patients also reported significant benefits after managing sleep apnea and other sleep disturbances [90].

Similar to other psychiatric conditions, a bidirectional relationship has been postulated to explain the comorbidity between sleep disturbances and migraine: importantly, sleep disorders may be considered relevant risk (triggering) factors for migraine, but even migraine may significantly influence patients' quality of sleep [23]. Dodick and colleagues [21] suggested the existence of similar neurobiological mechanisms related to the occurrence of both sleep disturbances and migraine. Furthermore, major depressive and anxiety disorders are usually comorbid with both sleep disturbances and migraine.

Overall, the interaction between headache/migraine and sleep disturbances has been confirmed by several studies both in populations of adults and children. A detailed anamnesis for the presence of sleep disturbances should be conducted in order to carefully assess and manage either the disability or functional impairment of these conditions on migraine subjects [23].

2.9 Substance Abuse and Migraine

The association between substance abuse/dependence and migraine has been commonly reported [55, 97]. In 1982, Tennant and Rawson [112] demonstrated that more than 15 % of dependent patients first used opioids due to their headache, although not all subsequent studies confirmed these data [80, 111]. In particular, Peterlin and coworkers [80] did not find any association between substance abuse and migraine after controlling for depression and post-traumatic stress disorder.

Alcohol abuse/dependence does not seem to be correlated with migraine and chronic headache. According to the study of Jette and colleagues [45], a 12-month prevalence of alcohol dependence was not reported among those who suffered from migraine and healthy controls. Some researchers [76, 128] reported that the absence of a correlation between alcohol abuse/dependence and migraine may be explained by the fact that alcohol is an important triggering factor for the occurrence of headache/migraine attacks. Migraine subjects commonly reported that foods, alcohol, atmospheric changes, exposure to light, sounds, or odors are triggering or aggravating factors related to the occurrence of migraine attacks [38].

According to a pathophysiologic hypothesis, some specific environmental stimuli may affect the vulnerable brain leading to complex cellular and molecular changes, which have been shown to be significantly involved in the emergence of migraine attacks. Panconesi [76] suggested that the relationship between alcohol and headaches could be mediated by the 5-hydroxytryptamine system. Given this framework, some anticipatory symptoms, such as food craving, and abnormalities of the sleep-wake cycle may be correctly interpreted as relevant warning signs in preceding (at least 72 h before) the pain phase of the same migraine attack.

2.10 Suicidality and Migraine

Suicidality includes suicidal ideation, attempts, and death. The association between migraine aura and suicidality has been commonly described, and the shared pathophysiology between migraine, major depression, and suicidal behavior has been frequently reported [8, 77, 86]. Suicide attempts have been more commonly observed among patients with migraine relative to the general population, in particular among females and in those who suffered from migraine with aura [37]. The association between migraine and suicidal ideation has been investigated by Wang et al. [119] in 3963 adolescents where suicidal ideation has been reported in 8.5 % of the sample. Individuals with migraine, in particular patients affected by migraine with aura, exerted a higher suicidal ideation relative to healthy subjects. Only migraine with aura is correlated with the higher headache frequency after controlling for major depression scores and sociodemographic features. Only migraine with aura, but not headache frequency or the diagnosis of migraine per se, was significantly associated with suicide attempts even after adjusting for the presence of psychiatric conditions [8] in a sample of young adults with migraine.

Cluster headache has been renamed by clinicians as "suicide headache," but recent studies that focused on the occurrence of suicidal behavior in chronic headache patients criticized this terminology [63]. Rozen's survey found that 55 % of chronic headache subjects reported lifetime suicidal ideation and 2 % suicide attempts with no relevant differences between males and females [96]. When addressing impairment in chronic headache patients, Jürgens and colleagues [48] reported that suicide thoughts and suicidal tendencies were experienced by 22 % of chronic cluster headache patients, 15 % of episodic cluster headache patients in the active phase, 14 % of episodic cluster headache patients outside the active period, 4 % of migraine patients, and 3 % of healthy controls, respectively. Conversely, Robbins and colleagues [95] found that 6.3 % of subjects with episodic chronic headache patients and 5.9 % of those with chronic cluster headache patients had lower rates of active suicidal ideation, respectively.

Possible differences between migraine and non-migraine headache in suicide have been reported by Ilgen and colleagues [42]. The authors demonstrated in a 3-year follow-up study that suicide rates were increased in both migraine patients (OR = 1.68) and headache/tension headache (OR = 1.38). Based on their findings, migraine was the only significant predictor of suicide (OR = 1.34) even after controlling for age, sex, a medical comorbidity score, and psychiatric disorders. Chronic daily headache subtypes, headache frequencies, and medication overuse were not found to be correlated with suicidal behavior [120], whereas only headache severity, but not headache diagnosis, seems to predict the emergence of suicide attempts in a 2-year follow-up community-based study [10]. Other larger community-based studies such as the Epidemiological Catchment Area Study [111] and National Comorbidity Survey-Replication [43] showed the association between self-reported headache and suicidality.

The relationship between migraine with aura and major depression seems to be bidirectional [11], and common pathophysiological mechanism such as serotonergic dysfunctions and pain have been reported underlying both suicidal behavior and migraine [24, 119]. It is important to note that pain related to headache is a potential independent risk factor for suicide, especially for those with chronic headache or multiple pain locations [43]. Early and systematic suicide evaluation in the clinical practice should be carried out in migraine patients who suffer from chronic pain.

2.11 The Importance of Screening Instruments in the Detection of Psychiatric Comorbidity

As suggested by Maizels [62], an appropriate screening for comorbid psychiatric disorders in subjects with migraine and chronic headache should be performed. Many psychometric instruments are available to screen patients with psychiatric symptoms and specific disorders such as major depressive, anxiety, and bipolar disorders. The presence of comorbidity may significantly modify the illness outcome, worsen the quality of life and contribute to the psychosocial impairment of migraine patients; thus, the early and careful screening for psychiatric comorbidity is recommended [61, 62]. There are reports indicating the possibility to conduct verbal screening with unstructured questions [123], other studies supporting the appropriateness of four depression and anxiety questions included in the Patient Health Questionnaire [52, 125] and others assessing comorbidity using more articulated and detailed instruments which are also frequently used in psychiatric populations. As suggested by Smitherman and colleagues [108], a more accurate evaluation for the presence of psychiatric comorbidity seems to be necessary subgroups of patients who are unsuccessful with conventional treatment and/or show a partial response to the commonly available migraine medications.

The Italian Perceived Disability Scale [44] has been proposed as an additional screening instrument to identify the comorbidity with emotional distress/disturbances. This psychometric instrument has been shown to be valid and reliable with regard assessing suicidal intent and evaluating disability in those with chronic daily headache.

2.12 Discussion

Based on the main results of the studies which were mentioned within this review chapter, psychiatric comorbidity needs to be considered a common condition in patients with migraine and/or chronic headache. Consistent risk factors such as anxiety and depression, stressful life events, obesity, pain conditions, and medication overuse may be implicated in the emergence and maintenance of migraine/headache [3, 22, 100, 115].

The presence of psychiatric comorbidities may be more frequently observed in subjects with chronic migraine compared to those with episodic migraine [6, 14]. Among all psychiatric conditions, major depression seems to be one of the most relevant predictors associated with the onset of chronic migraine even after controlling for sociodemographic factors and headache features [3]. Moreover, a positive correlation has been demonstrated between the risk of developing a chronic migraine and the severity of depressive symptoms.

As previously mentioned, some neurobiological mechanisms such as serotonergic hyperactivity, HPA overactivity, hormonal abnormalities, inflammation, medication overuse, avoidance learning, and subjective beliefs that may enhance pain perception and emotional distress associated with migraine attacks have been hypothesized in the effort to understand whether anxiety and depression are implicated in the progression of migraine [109]. Common neurobiological characteristics including serotonergic dysfunctions, HPA hyperactivity, and inflammation might predispose patients to manifest both migraine and psychiatric comorbidities [2].

Concerning inflammation and inflammatory mediators, several reports [27, 118, 122] suggested the presence of abnormally increased levels of tumor necrosis factor-α, C-reactive protein, and specific interleukins in both depression and migraine [2].

In addition, there is a factor that might explain the impact of psychiatric comorbidities on migraine chronicity [73]. Based on the authors' suggestions, the dose-dependent association between chronic pain disorders such as migraine and affective symptoms such depressed mood, anxiety, irritability, and sleep disturbances that may impair the thalamocortical signal transmission of nociceptive signals together with the concentrations of specific neurotransmitters such as serotonin, noradrenalin, and dopamine in the same brain circuitries would be responsible of migraine chronicity in patients with psychiatric comorbidities.

However, there are a number of possible confounders that should be considered when trying to explain the occurrence of psychiatric comorbidity in patients with migraine/headache. Based on existing studies, current data concerning the nature of psychiatric comorbidity in patients with migraine may be biased by a number of variables such as the different types of substance which were abused, the differential traumatic experiences [54], as well as the different sleep disturbances [33] frequently coexisting with migraine [110]. The association between the history of childhood abuse and chronic headache has not been fully investigated, although it is well known that childhood traumatic events are a significant risk factor for the subsequent development of migraine [26, 116]. Another shortcoming that may confound the relation of psychiatric comorbidities in migraine populations is related to the frequent assumption of migraine medications (e.g., corticosteroids).

Moreover, whether psychiatric comorbidity is only present throughout the headache/migraine attacks or rather in other illness periods is really a matter of debate. Available studies are also predominantly cross-sectional in nature and commonly provide mixed results [48, 95]; thus, longitudinal follow-up studies are recommended. Importantly, although many reports focused on the bidirectional relationship between migraine and psychiatric comorbidity [11], the temporal course of

psychiatric comorbidity in patients with chronic headache is quite unclear. It is also important to report that a unidirectional relationship was proposed for some types of migraine such as the non-migraine severe headache disorders, as only non-migraine headache accounted for the new onset of depression, but depression did not account for the incident non-migraine headache. Therefore, a different neurobiological mechanism seems to be involved underlying this headache subtype. Finally, some psychometric instruments which are commonly used to assess psychiatric comorbidity have not been validated in headache populations, and this should be considered when analyzing data derived by available headache studies.

2.13 Conclusive Remarks and Future Perspectives

Migraine and chronic headache are major causes of disability and lost working days worldwide. Based on our findings, a strong correlation between primary headaches and psychiatric disorders has been reported by most studies. This type of association was identified for the first time in 1895 by Living who noted the emergence of affective symptoms such as depressed mood, anxiety, and irritability in patients with chronic headache [28]. Recent neurobiological mechanisms such as serotonergic hyperactivity, HPA overactivity, hormonal abnormalities, inflammation, medication overuse, avoidance learning, and subjective beliefs among patients that may enhance their pain perception and the emotional distress associated with migraine have been hypothesized in the effort to explain the association between migraine and psychiatric comorbidities. It is also important to note that patients with a diagnosis of chronic daily headache and migraine usually experience both severe hopelessness [19], which is a strong predictor of suicidal behavior, and perceived disability [44].

Our review suggests the critical need for the psychological assessment of patients with chronic migraine. We encourage future researchers to focus on other potential mechanisms, confounding variables, and unanswered questions that need to be carefully addressed. Prospective, longitudinal studies aimed to more thoroughly investigate the nature of the association between psychiatric comorbidity and migraine in samples of patients both in acute and chronic periods of illness are recommended. These reports that should focus on the interplay of factors actively involved in the associations among migraine, suicide risk, and psychiatric conditions.

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Chapter 3
Epilepsy Comorbidity

Cinzia Costa, Paola Sarchielli, Paolo Prontera, Stefano Caproni, and Josemir W. Sander

Abstract An association between migraine and epilepsy has been long prospected based on shared clinical and pathogenic characteristics. From epidemiological studies, the median prevalence of epilepsy in migraineurs appears to be about 6 %, compared with 0.5 % in the general population. Conversely, among epileptics, 8–23 % suffer from migraine headaches, compared with 12 % of the general population. However, only 1.7–3 % of epileptic patients experience seizures in close temporal relationship with migraine. The nature of the association between the two disorders is still debated. A common genetic, biochemical, and neurophysiological background facilitating the presentation of both disorders has been proposed, particularly when headache, especially migraine, is either part of seizures that occurs in the postictal phase or migraine with aura that triggers an epileptic crisis (the debated nosographic entity named migralepsy). Cortical hyperexcitability and spreading depression are believed to be shared between migraine and epilepsy. When migraine is an integral part of a genuine occipital epileptic seizure, cortical spreading depression initiated by the epileptic focus in the occipital lobes is believed to trigger migraine headache by activating trigeminal vascular system and other mechanisms mediated by brainstem nuclei. The relationship between migraine and epilepsy can be defined in two ways. First, the genetic mutations may be responsible for several channelopathies that induce changes in neuronal or glial ionic homeostasis. Second, mutations affecting

C. Costa (✉) • P. Sarchielli
Clinica Neurologica, Università degli Studi di Perugia, Dipartimento di Medicina, Ospedale S. Maria della Misericordia, Perugia, Italy
e-mail: cinzia.costa@unipg.it

P. Prontera
Centro di Riferimento Regionale di Genetica Medica, Dip. di Scienze Chirurgiche e Biomediche, Università di Perugia, Ospedale Santa Maria della Misericordia, Perugia, Italy

S. Caproni
Struttura Complessa di Neurologia, Dipartimento di Neuroscienze, Azienda Ospedaliera "S. Maria" di Terni, Terni, Italy

J.W. Sander
Department of Clinical and Experimental Epilepsy, NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, London, UK

Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, Netherlands

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GABAergic, glutamatergic systems or mitochondrial functions may be underlying. In particular, mutations in the familial hemiplegic migraine (FHM) 3 gene SCN1A (chromosome 2q24) have been associated with epilepsy. Other mutations involve SLC1A3, a member of the solute carrier family coding for transporter 1 of excitatory amino acids, and POLG and C10orF2, genes that code for mitochondrial DNA polymerase and Twinkle helicase, respectively. The comorbidity of migraine and epilepsy prompts the clinician to choose preventive drugs that are effective on both disorders. Antiepileptics that have been proven to achieve efficacy in these conditions include topiramate, valproate, and lamotrigine (migraine with aura).

Keywords Migraine and epilepsy comorbidity • Epidemiological evidence • Genetic background • Cortical spreading depression • Cortical hyperexcitability • Antiepileptic drugs

Abbreviations

AEDs	Antiepileptic drugs
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CBZ	Carbamazepine
CNP	Clonazepam
CSD	Cortical spreading depression
EA2	Episodic ataxia type 2
EEG	Electroencephalogram
EH	Epileptic headache
EPGP	Epilepsy phenome/genome project
FHM	Familial hemiplegic migraine
GABA	γ-Aminobutyric acid
GEFS+	Generalized epilepsy with febrile seizures plus
GPT	Gabapentin
IEH	Ictal epileptic headache
IH	Ictal headache
inter-IH	Interictal
LEV	Levetiracetam
LTG	Lamotrigine
MA	Migraine with aura
MO	Migraine without aura
MRI	Magnetic resonance imaging
OCX	Oxcarbazepine
PDS	Paroxysmal depolarizing shift
peri-IH	Peri-ictal
PGB	Pregabalin
PHT	Phenytoin

post-IH	Postictal
pre-IH	Pre-ictal
SMEI	Severe myoclonic epilepsy of infancy
TPM	Topiramate
TTH	Tension-type headache
VGB	Vigabatrin
VPA	Valproic acid
ZNS	Zonisamide

3.1 Introduction

Epilepsy and headaches are the two most common neurologic disorders, each with episodic attacks, affecting individuals of all ages worldwide. An overlapping of clinical, pathophysiological, and therapeutic aspects has been emphasized [1, 2]. Epilepsy and migraine are known to co-occur within individuals, but the contribution of shared genetic susceptibility to this comorbid association has long been considered unclear [3].

The prevalence of a history of migraine with aura (MA) (but not migraine without aura) was significantly increased in participants from the Epilepsy Phenome/Genome Project (EPGP) cohort with two or more additional affected first-degree relatives [4].

Several studies have pointed to common genetic and molecular substrates for migraine and epilepsy including phenotypic-genotypic correlations with mutations in the *CACNA1A*, *ATP1A2*, and *SCN1A* genes, as well as in syndromes due to mutations in *SLC1A3*, *POLG*, and *C10 or F2* [1, 5].

3.2 Prevalence of Epilepsy in People with Migraine

Overall, the prevalence of epilepsy in individuals with migraine has been reported to range from 1 to 17 % (median 5.9 %), which is higher than the population prevalence of about 0.5–1 % [6, 7]. Focal-onset and cryptogenic epilepsies are associated with higher rates of migraine than are generalized-onset seizures, but this increase is small (relative risk, 1.3) with the exception of cases of epilepsy caused by head trauma (relative risk, 1.8). This association between post-traumatic epilepsy and migraine can be attributed to the fact that head injury is a risk for both conditions [8].

Prior research has established an association with MA and epilepsy, but recent research suggests an increased incidence of epilepsy in subjects with migraine both with and without aura [9, 10]. A recent study involving 1,795 children with headache found that 56 (3.1 %) had idiopathic headache and idiopathic or cryptogenic epilepsy or unprovoked seizures and identified a strong association between migraine and epilepsy. The risk of epilepsy was 3.2 times higher in children with migraine

than in those with tension-type headache (TTH), with no significant difference between migraine with and without aura. Likewise, children with epilepsy had a 4.5-fold higher risk of developing migraine than TTH. In children with headaches, focal epilepsies prevailed (76.8 %). Three quarters of 36 children with migraine and focal epilepsy had cryptogenic epilepsy, with only one quarter having idiopathic epilepsy. In MA, epilepsy preceded migraine in 71 % of cases. Photosensitivity (7/56, 12.5 %) and positive family history for epilepsy (22/56, 39 %) were frequent in children with both headache and epilepsy [10]. A recent multicenter Italian study investigating headache and epilepsy comorbidity reported epilepsy in 1.6 % of individuals from headache centers and headache in 30.0 % from epilepsy centers [11].

3.3 Prevalence of Headache in Epileptic Patients

A relationship between epilepsy and migraine based on well-recognized shared pathogenic mechanisms, clinical characteristics (both conditions occur in attacks and sometimes may mimic each other), and risk factors was first hypothesized by William Gowers in 1907 [12]. Since then, the association has been debated; antiepileptic drugs (AEDs) are, however, effective as prophylactic agents for migraine.

Several studies have been conducted to verify the possible association between these two pathological conditions, but their findings have been inconsistent due to methodological limitations, including small numbers of patients, study design (prospective, retrospective), and inconsistent methods of case identification, as well as different classification criteria used for both headache (in particular migraine) and epilepsy.

Most studies have focused on the prevalence of migraine in people with epilepsy, whereas few studies have investigated the prevalence of other types of primary headaches such as TTH and cluster headache given that TTHs is very common in the general population and cluster headache rare [13]. In the general population, migraine occurs in approximately 6 % of adults with epilepsy younger than 64 years old [14]. Individuals with migraine and epilepsy may have a longer duration of epilepsy, higher seizure frequency, and higher rates of refractory epilepsy and polytherapy than those with epilepsy alone, irrespective of the severity of the migraine [15].

In an interview-based survey [16] involving 1,793 participants, the number of individuals with epilepsy was small, and a statistically significant association between migraine and epilepsy was not found. There was, however, a tendency for a higher prevalence of migraine in people with active epilepsy (5 of 11) than in those with epilepsy in remission (4 of 28) ($P = 0.09$), and a trend toward a more active epilepsy was observed in migraineurs (1.0 %, 5/524), particularly for MA (1.8 %, 3/168), compared with subjects without migraine (0.5 %, 6/1132).

A recent meta-analysis [17] investigated the lifetime co-prevalence of migraine and epilepsy using random effects models. Of the 3,640 abstracts and titles screened, ten eligible studies were identified, encompassing 1,548,967 subjects. An overall 52 % increase in the prevalence of migraine emerged among people with epilepsy versus those without epilepsy [PR, 1.52 (95 % CI, 1.29, 1.79)]. Conversely, an over-

all 79 % increase in the prevalence of epilepsy was detected among migraineurs versus subjects without migraine [PR, 1.79 (95 % CI, 1.43, 2.25)]. Subgroup analyses showed that the method of ascertaining the epilepsy or migraine status of subjects and inconsistent attempts to control for potential confounders are relevant sources of inter-study heterogeneity, suggesting the need for additional high-quality primary studies using validated and accurate methods of case ascertainment and control for confounders.

3.3.1 Temporal Relationship of Headache with Seizures

Considering the temporal relationship with epileptic seizures, headache can be classified as interictal (inter-IH) or peri-ictal (peri-IH). Inter-IH is not temporally related to seizures, and, according to ICHD-II criteria [18, 19], it is divided into migraine (with or without aura), probable migraine, TTH, probable TTH, cluster headache, and other primary headaches. Peri-IH occurs in temporal association with seizures and is divided into pre-ictal (pre-IH) and postictal (post-IH) headaches. Pre-IH is defined as appearing within the 24 h prior to a seizure [20–22], while ictal headache (IH) is present exclusively during a seizure [23]. Post-IH is defined according to ICHD-II as a "headache which develops within 3 h following a partial or generalized seizure and resolves within 72 h after the seizure" [18, 19].

The prevalence of inter-IHs ranges from 25 to 64 % [1, 24], and the risk of migraine has been estimated to be approximately twice that of the general population [25, 26]. In a recent study from Italian migraine and epilepsy centers including 388 people with epilepsy, 48.5 % had inter-IH, 26.3 % migraine, 19.1 % TTH, and 3.1 % other primary headaches. These findings are in line with previous literature for migraine, whereas the lower prevalence of TTH compared to the general population suggests that this mild condition could be underestimated in people with epilepsy [24] (Table 3.1). In the same study, peri-IH was observed in 23.7 % of individuals: pre-IH in 6.7 %, IH in 0.8 %, and post-IH in 19.1 %. Pre-IH was significantly presented only in migraineurs, both compared to patients without inter-IH (OR 3.54, 95 % CI 1.88–6.66, $P<0.001$) and to patients with TTH (OR 5.29, 95 % CI 1.50–18.68, $P=0.010$). Conversely, post-IH was significantly associated with both migraine (OR 2.60, 95 % CI 1.85–3.64, $P<0.001$) and TTH (OR 2.05, 95 % CI 1.41–2.98, $P<0.001$). Post-IH was also significantly associated with antiepileptic polytherapy ($P<0.001$), high seizure frequency ($P=0.002$), and tonic-clonic seizures ($P=0.043$).

Peri-IH headaches are common in children with epilepsy, affecting 41 % [34, 38]. This headache, including migraine without aura (MO), appears to be more often associated with focal epilepsy, both temporal and extra temporal lobe. Furthermore, peri-IH and in particular pre-IH may be related to the epileptic discharge and may have lateralizing value [22, 39].

Pre-IHs have been reported to occur in 5–15 % of people with epilepsy. The underlying mechanisms of migraine attack with or without aura followed by a typical epileptic seizure are subject to debate. Whereas IHs are rarer (3–5 %), post-IHs

Table 3.1 Prevalence of migraine in people with epilepsy

Authors	*N* of patients	M/F	Age	Method	Prevalence
Schon and Blau (1987) [27]	100	39/61	32 (mean)	Interview	18 %
Ottman and Lipton (1994) [25]	1,948	40 %/60 %	≥18	Structured telephone interviews + medical records review for 60 % of probands	24 %
Ito and Schachter (1996) [28]	162	82/80	19–65 (range)	Questionnaires mailed to the subjects + medical records review	NA[a]
Ito et al. (1999) [29]	109	36/73	38 ± 12[b]	Questionnaire + interview + medical records review	12.8 %
Velioglu and Ozmenoglu (1999) [18]	412	212/200	15–70 (range)	Interview with a standardized questionnaire	14 %
Leniger et al. (2001) [30]	341	154/187	40 ± 15 (mean)	Interview with a standardized questionnaire	18.2 %
Karaali-Savrun et al. (2002) [31]	135	80/55	≥10	Questionnaire administered to patients	14.8 %
Förderreuther et al. (2002) [32]	110	69/41	35.2 (mean)	Semi-standardized interview	10 %[b]
Ito et al. (2004) [33]	364	163/201	12–81 (range)	Structured interview with standardized questionnaire	8 %
Syvertsen et al. (2007) [34]	109	44/65	20–71 (range)	Questionnaire + semi-structured telephone interview	20 %
Kwan et al. (2008) [35]	227	98/129	36.0 ± 11.3 (mean)	Interview with standardized questionnaire + seizures and headache diary over the 3-month observation period + final interview	6.6%[b]
HELP Study Group (2010) [36]	597	348/249	≥13	Questionnaire at initial visit	12.4 %
Tonini et al. (2012) [11]	492[c]	154/338	≥18	Direct interview with questionnaire	18.3 %[b]
Duchaczek et al. (2013) [20]	201	106/95	≥18	Semi-structured interview	11 %
Winawer et al. (2013) [4]	730[d]	285/445	≥12	Telephone or in-person interview + medical record abstraction	25.2%[e]
Gameleira et al. (2013) [37]	304	141/163	4–88 range	Patients evaluated at the epilepsy clinic	32.9%[f]

Table 3.1 (continued)

Authors	*N* of patients	M/F	Age	Method	Prevalence
Wang et al. (2014) [23]	1,109	607/502	≥18	Self-administered questionnaire + standardized semi-structured telephone interview	12.53 %

From Mainieri et al. [24]
N number, *pts* patients, *M* males, *F* females, *yrs* years, *NA* not available
[a]A prevalence of interictal migraine is not clearly identifiable; the authors report a prevalence of inter-IH in 64 % of individuals, approximately half of them with a pounding quality and almost 70 % often accompanied by nausea and/or vomiting, photophobia, or phonophobia
[b]Calculated by the authors
[c]This multicenter study involved 1167 patients from epilepsy and headache centers, we considered only patients with epilepsy
[d]371 probands, 231 siblings, 128 parents: all with epilepsy
[e]23.5 % probands, 22.5 % siblings, 35.2 % parents
[f]The authors of the study does not distinguish between inter-ictal migraine and post-ictal headache with migrainous features

are more common (10–50 % of cases) [1, 24]. IH is more frequent in children than in adults due to different clinical features both in epilepsy and in headache. Children with epilepsy are more likely to have autonomic attacks with long-lasting ictal autonomic manifestations, while adults more often have other sensory or motor ictal signs. It has been speculated that in many children, seizures mimic migraine, which can be easily recognized by an EEG recording [10, 40, 41]. The main involvement of posterior regions emerged in people with ictal epileptic headache (IEH) who were affected by focal symptomatic epilepsies [42]. IH cannot, however, be diagnosed without an EEG recording. Few case reports on EEG-documented IEHs in focal or generalized idiopathic epilepsy have been published [43, 44]. Of these, one describes IEH associated with nonconvulsive status epilepticus in an individual with eyelid myoclonia plus absences [45].

Young adults with a history of inter-IH are more likely to develop post-IH [46]. Post-IHs also frequently occur after seizures in predisposed children, interrupting their daily activities [10, 40, 41]. Young age at onset and long duration of epilepsy, drug-resistant seizures, generalized tonic-clonic seizures, and, possibly, occipital epileptic focus are additional risk factors. Post-IH is estimated to have a significant impact on the quality of life of people with epilepsy, but it is frequently undertreated. Case reports suggest that post-IHs respond to simple analgesic as well as to triptans [47].

3.4 Classification Concerns and Some Definition Proposals

In the 1960s, the term “migralepsy” was introduced to describe a condition in which an MA attack is followed by symptoms characteristic of epilepsy. To make a diagnosis of migralepsy, a temporal relationship between the migraine aura and a

seizure event (within an hour) is necessary [48]. The definition of migraine-triggered epilepsy or migralepsy was included in the second edition of ICHD-II (under point 1.5.5) referring to epileptic seizures occurring during or within 1 h after a MA. Despite this, the term "migralepsy" has not been used uniformly in clinical practice, causing debate about the inadequacy of its definition in the current ICHD-II criteria [49–52]. People with IH are difficult to classify in ICHD-II and ICHD-3 beta and ILAE. The ICHD-II classification [19] defines "epileptic headache" as a headache with migraine features, while the individual also has a focal epileptic seizure. The term does not appear in the current ILAE and ICHD 3 beta classification [53]. In the ICDH-3 beta, code 1.4.4 refers to migraine aura-triggered seizure which is described as a seizure triggered by an attack of MA (Table 3.2).

The ILAE classification considers headache as a possible semiological ictal phenomenon among *non-motor* (point 2.0) features, describing it as a *cephalic* sensation (subclassified at sub-point 2.2.1.7) and not the only ictal expression of an epileptic seizure. Moreover, headache is not classified as a "pain" (among the "somatosensory" features at 2.2.1.1) or "autonomic" sensation (2.2.1.8), like signs of involvement of the autonomic nervous system, including cardiovascular, gastrointestinal, *vasomotor*, and thermoregulatory functions.

Over the last decade, IEH has been considered "a headache representing the only ictal phenomenon." In fact, IEH is recognized as a headache (only an ictal epileptic manifestation) lasting from minutes to days with evidence of ictal epileptiform EEG discharges, which resolve after intravenous antiepileptic medications. This can be an epileptic manifestation per se, with onset and cessation if isolated, correlating with the scalp or deep EEG pattern [21, 54]. It has been suggested that "migralepsy sequence" may not exist at all and that the initial part of the "migralepsy sequence" may be simply an "IEH" followed by other ictal autonomic, sensory, motor, or psychic features [54]. The term "IEH" was coined to describe episodes of migraine/headache of epileptic origin when confirmed by EEG recording.

It has been suggested that this condition be described as "pure" or "isolated" epileptic headache (EH), when the headache/migraine is the only epileptic manifestation (requiring differential diagnosis from other headache forms) [21]. According to ICD-II, "hemicrania epileptica" (if confirmed) is a very rare variant of EH, characterized by the ipsilateral location of headache and ictal EEG paroxysms.

Table 3.2 Migraine aura-triggered seizure definition from ICDH-3 beta

Diagnostic criteria include:
A. A seizure fulfilling diagnostic criteria for one type of epileptic attack and criterion B below
B. Occurring in a patient with 1.2 migraine with aura, and during, or within 1 h after, an attack of migraine with aura
C. Not better accounted for by another diagnosis
In the comments, it is reaffirmed that this phenomenon, sometimes referred to as migralepsy, is a rare event, originally described in patients with 1.2 migraine with aura and that evidence for association with 1.1 migraine without aura is still lacking

According to some authors, headache pain originates from trigeminal terminals in cerebral blood vessels; thus, headache should be classified as an "autonomic" sensation in the ILAE Glossary and Terminology. Headache should therefore be interpreted as the sole expression of an epileptic seizure and classified as an autonomic seizure. The debate continues and the matter needs further investigation [55].

3.5 Mechanisms Underlying Epilepsy and Migraine Comorbidity

Migraine attacks, in the same way as epileptic seizures, have been attributed to excessive neocortical cellular excitability. This state of brain hyperexcitability, which can be produced either by genetic factors or be acquired (due to head injury), increases the risk of both migraine and epilepsy, potentially leading to the comorbid association.

Cortical spreading depression (CSD) associated to migraine has been hypothesized as a link between headache (migraine) and epilepsy. CSD onset was described during the propagation of electrically provoked seizure discharges in the cerebral cortex and similarities in the ways in which CSD and seizures propagate were recorded [56]. CSD is characterized by a slowly self-propagating wave (2–6 mm/min) of sustained strong neuronal depolarization, responsible for transient (seconds), intense spike activity followed by neural suppression lasting for minutes [57].

Later, it was reported that seizures propagate rapidly, whereas the depolarization in CSD propagates slowly [58–60]. More specifically, evidence suggests that epileptiform activity associated with enhanced excitatory neurotransmission propagates at rates comparable to CSD, whereas epileptiform activity caused by reduced inhibition propagates much faster [61]. These two pathological phenomena were originally considered separate physiological events characterized by their different patterns of neuronal activities and characteristic ionic changes.

Despite these differences, both seizures and CSD are induced by similar mechanisms which include hypoxia, hypoglycemia, neural injury, high concentrations of K^+, or Na^+/K^+ pump inhibition [62]. More recently human studies have observed this depolarizing phenomenon in a variety of pathological states, including epilepsy [63]. Based on these observations, models of neuronal membrane biophysics have recently been developed which can include a broad range of experimental observations, from spikes to seizures, supporting the hypothesis that seizures and CSD lay along a dynamic continuum of the neuronal membranes [64].

CSD has been considered the pathophysiological correlate of MA [65]. Imaging studies of people with MA have also suggested that the presence of CSD in silent areas is an underlying mechanism [66–68]. Experimental findings [69, 70] as well as functional neuroradiological investigations in humans [71] have suggested the potential role of CSD in determining trigeminovascular activation,

describing it as the final common pathway responsible for the pain of migraine attacks. An increase in regional cerebral blood flow (rCBF) is associated with the depolarization phase, whereas a reduction in rCBF characterizes the phase of reduced neural activity [72]. In animal models, CSD can be triggered by focal stimulation (electrical, mechanical, high extracellular K+ or glutamate, persistent intracellular sodium influx, inhibition of the Na+−K+ ATPase pump) of the cerebral cortex, particularly occipital regions, while subcortical regions can also be involved [73, 74].

Experimental findings in 1990 had suggested that both seizure and CSD onset were due to the inability of the Na-K pump to regulate K^+ extracellular concentrations [75]. These experimental findings were supported several years later by the identification of novel mutations involving Na+, K+−ATPase pump gene ATP1A2 associated with FHM and benign familial infantile convulsions and the demonstration of a monogenic defect in familial occipital lobe epilepsy associated with MA [76, 77]. Other complementary mechanisms seem to be involved in the ionic diffusions of both events (i.e., epileptic depolarization and CSD onset). In particular, synchronization in CSD has been related to "gap junctional" [78]. The gap junctions in synchronizing the human neocortical network are also involved in epileptiform activity [79, 80]. The calcium-sensitive current is able to promote both seizure-like discharges and CSD in experimental models [81]. In addition, glutamate is believed to be a critical mediator of hyperexcitability which has been demonstrated to be present in both focal seizures and migraine [82–85].

In focal epilepsy, seizure generation and spread is mediated by synaptically released glutamate acting on AMPA receptors, whereas triggering of CSD depends on NMDA receptors and its spread does not require synaptic transmission [86–88]. Therefore, the difference between the physiology of CSD and focal seizure activity could be due to CSD non-synaptic glutamate release from glia and the synaptic glutamate release from neurons and perhaps glia in the case of epileptic discharges [89–92].

Clinical research confirms that CSD (migraine) and cortical focal discharges (seizures) can facilitate each other. Migraines occasionally trigger seizures, which often initiate post-IH similar to migraines. The most compelling evidence for a relationship comes from FHM, where migraine and epilepsy can be caused by monogenic mutations involving CACNA1A, ATP1A2, and SCN1A genes [93]. CSD facilitates synaptic excitability and efficacy in human neocortical tissues, contributing to hyperexcitability of neocortical tissues in people with migraine. This is supported by the efficacy of some AEDs in preventing the occurrence of migraine attacks [94]. Electrophysiological findings have demonstrated that CSD can trigger epileptiform field potentials prevented by γ-aminobutyric acid (GABA)-mediated inhibition, suggesting that CSD increases neuronal excitability and facilitates synchronization of neuronal discharges in the presence of partial disinhibition of the neuronal tissues. This process might explain the occurrence of seizures in neurological disorders with partial impairment of inhibitory tone, such as epilepsy and brain ischemia [95].

3.6 Genetic Aspects of the Migraine-Epilepsy Comorbidity

MA and MO are a common familial condition. Different linkage and association studies have shown wide genetic heterogeneity, identifying susceptibility genes (ESR1, TNF, KCNK18, etc.) [96–98]. The presence of familial aggregation suggests a genetic background and probably an oligogenic inheritance which is also present in the common form of primary epilepsy (idiopathic generalized epilepsy). The number of identified susceptibility genes is rapidly growing and currently includes CACNA1H, CASR, CACNB4, GABRD, CLCN2, SLC2A1, GABRA1, and SLC12A5 [99–101]. At the moment it seems that susceptibility genes identified in migraineurs are different from those of people with idiopathic generalized epilepsy. However, powerful genetic studies (through whole genome association and exome studies) have not yet been performed on large cohort of people with both migraine and epilepsy. Instead, several genes associated with specific, monogenic forms of migraine have been reported to be associated with epilepsy, thus suggesting the existence of at least a common pathogenetic mechanism. Migraine and epilepsy are shared comorbidities in some people and related to specific mutations: (1) FHM to CACNA1A, ATP1A2, SCN1A, and episodic ataxia type 6 (EA6), due to mutation in the SLC1A3 gene (channelopathy); (2) mitochondrial disease to MT-TL1, MT-ND5, POLG, C10, or F2; and (3) vascular disease to NOTCH3, responsible for CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) [1, 5, 102, 103].

FHM is a rare autosomal dominant syndrome characterized by hemiparesis during the aura phase of migraine and associated with mutation in one of three genes (CACNA1A, ATP1A2, SCN1A). A few studies have reported a prevalence of epilepsy about 7 % in FHM, but currently no conclusive data are available regarding a possible association between hemiplegic migraine and epilepsy. It is known that an increasing number of FHM with CACNA1A, ATPA1A2, and SCN1A mutations are associated with epilepsy.

CACNA1A gene encodes for the pore-forming α1 subunit of human voltage-gated Cav2.1 (P/Q type) calcium channels [104]. Mutations in this gene were first identified in people with episodic ataxia type 2 (EA2) and in different families with FHM1 [104]. In 1997, the expansion of a CAG repeat, which predicted a coding for polyglutamine in the C-terminal coding region of the CACNA1A gene was identified in families with slowly progressive spinocerebellar ataxia (SCA6) [105]. Apart from the SCA6, which is associated with a specific dynamic mutation, genotype-phenotype correlation studies have identified an association between EA2 and loss-of-function mutations. Mutations described to date in people with HM have been missense, leading to a gain-of-function effect with enhanced Cav2.1 channel activity and subsequent increased intracellular calcium concentrations, which in turn causes CSD. On the other hand, a number of non-truncating mutations have been observed to cluster in the S5–S6 linkers and their borders even in EA2 [106, 107].

Genotype-phenotype correlations seem to be dependent on the functional effects of the mutations as well as the positions of the modified amino acids. Since no clear loss-of-function mutation (e.g., stop codon, frameshift, deletion) has been identified in people with FHM1 epilepsy, it is plausible that the gain-of-function effect is a specific mechanism for this endophenotype.

Regarding shared pathogenetic mechanisms, since CACNA1A variants may be responsible for repeated CSD, they could trigger both HM and epilepsy [94]. S218L produces a shift in activation leading to a gain of function, especially in the case of small depolarization [108]. This condition has been further supported by the higher incidence of recurrent CSD in S218L knock-in mice [109]. It has been reported that neutralization of gating charges in I and II S4 transmembrane domains of the Cav1.2 calcium channel (encoded by the CACNA1C gene) only slightly affected the equilibrium constant of voltage sensor transition [109]. When the Cav2.1 channel (encoded by the CACNA1A gene) lies in the first two S4 segments, it is highly unlikely that it plays a relevant role in the development of epilepsy since epileptic phenotypes have been found to be strongly associated when the mutations are located in the III and IV S4 segments. Therefore, people with F/SHM1 harboring such variants need to be closely followed up and managed.

ATP1A2 gene encodes the α2 subunit of the Na^+, K^+-ATPase [110], an integral membrane protein responsible for establishing and maintaining the electrochemical gradients of Na^+ and K^+ across the plasma membrane. Mutations in this gene were first identified in a large Italian family with FHM2 [111]. The functional analysis of nine different pathogenic mutations in this gene has been reported, and, overall, the data suggest that the disturbance of clearance of extracellular K^+ by glial cells, thought to underlie FHM2, is due to a low turnover rate of the pump [112]. Other functional analyses have shown that some mutations cause total loss of function [111, 113, 114], while others reduce the catalytic turnover or change the kinetic characteristic of the pump [115, 116]. Glial and neuronal Na^+, K^+-ATPase play important roles in the clearance of extracellular K^+ to prevent depolarization of neurons during high neuronal activity. Malfunctioning of the Na^+, K^+-ATPase pump may lead to neuronal hyperexcitability and facilitate both paroxysmal depolarizing shift (PDS) causing seizures and CSD causing migraine. These may occur in three synergistic events: elevation of extracellular K^+ levels, accumulation of glutamate in the synaptic cleft, and an increase in intracellular Ca^{2+} concentration [117–119]. Missense mutations affecting the transmembrane domains can lead to both the perturbation of catalytic site functions and the modification of pump kinetic characteristics, and it is interesting to note that individuals carrying mutations within these domains are much more susceptible to developing epilepsy.

SCN1A gene encodes the α1 subunit of the voltage-gated Na^+ channel Nav 1.1. Mutations in this gene were first identified in people with familial epilepsy: generalized epilepsy with febrile seizures plus (GEFS+) [120] and Dravet syndrome, also known as severe myoclonic epilepsy of infancy (SMEI) [121]. A heterozygous

mutation in the SCN1A gene has been identified in affected members of three European families with FHM3 [122]. Mutations can affect the protein structure in the intracellular, extracellular, and transmembrane domains. The genotype-phenotype correlation seems to depend mainly on the functional effect of the mutation rather than its position through the canal protein. Mutations leading to loss of function are mainly associated with SMEI, whereas gain-of-function mutations are mainly associated with GEFS+ or FHM3 [123].

In the case of FHM3-epilepsy comorbidity, experimental evidence suggests that a single mutation can have double functional effects. A study of a family with the T1174S (c.3521 C>G) SCN1A mutation associated with seizures and/or HM, applying a genetic and functional approach, reported that this variant induced divergent functional effects, loss of function or gain of function, a finding consistent with both epilepsy and HM phenotypes [124].

These genetic studies seeking to identify the genetic background of multifactorial or oligogenic diseases (such as the common forms of migraine and epilepsy) often fail to produce valid results due to high heterogeneity and environmental influences. More powerful studies on a larger cohort of people with migraine alone, epilepsy alone, and migraine-epilepsy comorbidity are needed to elucidate fully the possible shared genetic substrates. Study results from channelopathies suggest that mutation in a single gene that impairs neuronal or glial ionic homeostasis (i.e., sodium, potassium, and calcium) or affects GABAergic or glutamatergic systems or mitochondrial functions can lead to a spectrum of nervous system diseases with frequent migraine/epilepsy comorbidity.

3.7 Therapeutic Implications

Some AEDs are effective in the prevention of migraine [125–127]. A rationale for their use is the hypothesis that migraine and epilepsy share several pathogenic mechanisms [126, 127].

Imbalanced activity between excitatory glutamatergic transmission and GABAergic inhibition could play a role in both migraine and epilepsy. Abnormal activation of voltage-gated channels has been implicated in increased neuronal cortical excitability common to both disorders.

In people with epilepsy and any type of headache, especially migraine, AEDs for both pathological conditions are ideal treatments [128], whereas tricyclic antidepressants and neuroleptic drugs should be avoided as they may lower the epileptogenic threshold.

It is thought that AEDs exert their anticonvulsant action by targeting most of these pathogenic steps [125, 127, 129–131], but the reasons why only a few AEDs are effective in migraine prophylaxis are still unknown. It can be speculated that AEDs acting on multiple mechanisms of actions, such as valproic acid (VPA), topiramate (TPM), and gabapentin (GPT), are the best candidates for migraine

prophylaxis. Accordingly, clear evidence in favor of an effective preventive action in migraine has been accumulated for both VPA and TPM. For GPT and lamotrigine (LTG), clinical data concerning their efficacy in migraine prophylaxis are still unclear.

TPM and VPA have been shown to be highly effective in preventing migraine, and both have been approved by the FDA for migraine prophylaxis [132]. Effective doses for migraine are generally lower than those for epilepsy, 880–1000 mg/day for VPA or 100 mg/day TPM.

The two drugs have also been shown to be effective for chronic migraine with and without medication overuse [133, 134]. LTG, a potent sodium channel blocker and glutamate receptor antagonist, has also been reported to be effective in people with MA (some of them with motor aura) but not in those affected by MO [135, 136]. Less robust evidence on efficacy is available for GPT and pregabalin (PGB) in episodic and chronic migraine forms. More promising results, which need to be confirmed, have been reported for levetiracetam (LEV) and zonisamide (ZNS). Other drugs such as phenytoin (PHT), oxcarbazepine (OCX), vigabatrin (VGB), and clonazepam (CNP) seem to be ineffective [137]. The findings of less headache in patients treated with carbamazepine (CBZ), recognized to be ineffective for migraine prophylaxis, in a study involving people with epilepsy and ictal and post-IH, may have been due to better controlled epilepsy in individuals who received this traditional first-choice treatment for partial epilepsy [34].

AEDs acting only via a single mechanism of action seem to be less effective in targeting migraine. Blockage of voltage-gated sodium channels alone, exerted by some AEDs (i.e., CBZ, PHT, OCX), seems to be insufficient to antagonize migraine crises, although this mechanism could be relevant in preventing epileptic crises. This does not imply that drugs such as VPA and TPM targeting Na^+ currents (but not exclusively) could exert their effectiveness in preventing migraine, including MA, by counteracting Na^+-dependent discharges and persistent Na^+ conductance. Other targets for both drugs could be relevant for their prophylactic effect in migraine. This could also be relevant for HM, with and without an association with epilepsy [138].

AEDs targeting many pathogenic steps involved in migraine and epilepsy have been reported to be more promising in preventing MA and MO [127]. AEDs modulating high-voltage-activated (HVA) $Ca^{(2+)}$ channels used in migraine prevention with different evidence of efficacy affect both cortical and PAG neurons with different potencies. LTG and LEV, but not VPA, appear to be equally effective and potent in inhibiting HVA $Ca^{(2+)}$ currents in both neuronal populations, whereas TPM is more effective in blocking these currents in PAG neurons than in cortical pyramidal cells.

Drugs more effective on cortical neuronal activity should therefore theoretically be more effective for migraine aura than those for epilepsy. This is true for LTG which specifically affects only migraine aura, whereas date are lacking on LEV[139]. Additional targets of AEDs relevant for MA and MO other than epilepsy are ligand-gated channels, including both ionotropic and metabotropic glutamate receptors.

Inhibition of excitatory synaptic currents has been demonstrated for TPM, VPA, and GPT in experimental models suggesting that they might have an effect on CSD in both MA and HM, particularly in the presence of epilepsy. Another target is GABAergic transmission, as shown for VPA. Its potentiation could play a role in modulating CSD, therefore intervening in preventing not only MO but also MA [127].

It has also been demonstrated that the suppression of CSD in rats by chronic daily administration of TPM, VPA, as well as propranolol, amitriptyline, and methysergide is dose dependent [140, 141]. Magnetoencephalographic findings confirmed the reduction of cortical excitability in people with and without aura following 30-day treatment with VPA [142].

Chronic treatment with LTG appears to exert a marked suppressive effect on experimental CSD, which correlates with its rather selective action on the MA [143]. Therefore, this class of drugs could be considered the first-choice therapy when migraine and epilepsy are comorbid.

30 % of people with migraine and epilepsy are unresponsive to treatment, and headache is a common side effect of some AEDs. VPA should not be prescribed to fertile women.

Among drugs used for symptomatic relief, both analgesics (from 66 to 80 % of patients) and triptans have been reported to be effective on post-IH, with triptans particularly effective for post-critical migraine-like headaches [47, 144–147].

An alternative non-pharmacological approach for preventing migraines in people with epilepsy is vagus stimulation. Two studies reported that 3/4 and 8/10 people with epilepsy and migraines had decreases in migraine frequency after stimulator implantation [146, 148].

3.8 Clinical and Instrumental Assessment

All people with epilepsy should be questioned regarding whether they experience headache/migraine. If present, its temporal relationship with seizures should be investigated. A careful clinical history should be recorded, and general and neurologic examinations should be performed, to exclude conditions that may present with both headache and epilepsy. MRI, sometimes with contrast or angio-MRI, as well as laboratory or instrumental investigations can be mandatory in some cases for establishing the diagnosis [149].

In the case of people with visual symptoms suggesting occipital seizures, differential diagnosis with visual migraine aura should be considered, based on the features of the two disorders [150].

MRI scans have shown transient cerebral anomalies in 6 % of people with migralepsy attributed to transient alteration in blood barrier integrity eliciting edema [50]. In a series of children with migralepsy, MRI yielded normal findings in 75 %, while the remaining 25 % showed brain abnormalities including neuronal migration disorder, leukoencephalopathy, periventricular gliosis, or hydrocephalus [51].

While electroencephalogram (EEG) is fundamental for a diagnosis of epilepsy, indications regarding its use for headache are lacking. EEG and especially 24-h video-EEG studies have shown abnormalities in electrical activity during migraine aura although these abnormalities were not typical of epileptiform activity [151, 152].

In IEH the EEG pattern is not unambiguous. A high-voltage rhythmic activity at 11–12 Hz with alternating spikes in the temporal-occipital regions has been found in some cases. Alternatively, abnormalities consisting of high-voltage theta wave activity alternating with acute waves, discharges of spikes, and continuous bilateral slow spike waves were observed in the occipital region or photoparoxysmal responses to intermittent light stimulation [51, 153–157].

Generally, surface EEG does not reveal abnormalities, which is often the case for focal epilepsy presenting with IH and originating in deep structures such as the orbitomedial frontal region or in Panayiotopoulos syndrome. This confirms that the absence of clear epileptic activity does not necessarily exclude a diagnosis of epilepsy; thus, in this case, deep electrodes can improve the diagnostic sensitivity [30, 158, 159].

3.9 Conclusions

Epidemiological studies suggest that epilepsy and migraine are comorbid conditions despite wide variation of prevalence rates between different studies. Evidence has shown that comorbid migraine affects the prognosis of epilepsy; in particular migraine co-occurrence has been associated with a longer duration of epilepsy, intractable seizure disorder, a later treatment response, and less chance of being seizure-free during a 10-year follow-up [15].

Epidemiological studies are needed to investigate further the association between epilepsy and headache/migraine in order to verify whether the chances of achieving remission of seizures, their intractability, and other outcome measures really differ between people with epilepsy with and without comorbid migraine.

Further studies should be population based to produce generalizable findings with lower risk of referral bias, should involve prospective data collection to reduce the risk of recall bias, and should use only validated screening and diagnostic methods to minimize the risk of misclassification bias. These instruments should be applied to all participants and all results recorded to avoid surveillance bias as well as publication bias [2]. Longitudinal studies should also be performed to ascertain the causal nature of the association between epilepsy and migraine and the direction of the relationship, investigating the temporal sequence of the two disorders. Consensus documents should be drafted on the most appropriate terminology to be used, particularly for “IEH” and “hemicrania epileptica,” in order to abandon the old term “migralepsy.” This could imply that both IHS and ILAE would be required to revise their international classifications of epilepsy and headache disorders.

Future research should be focused on common pathogenic mechanisms underlying increased brain excitability in both paroxysmal disorders, particularly when they have shared genetic backgrounds. Further insight into the molecular events involved in the association between headache/migraine and epilepsy is crucial to identifying additional treatment targets.

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Chapter 4
Visceral Pain Comorbidity in Headache

Qasim Aziz and Maria Adele Giamberardino

Abstract Primary headaches and visceral pain are both very frequent medical conditions in the general population. Epidemiologic studies indicate that they very often coexist. Particularly frequent is the comorbidity between migraine and cardiac ischemic pain and between migraine/tension-type headache and functional gastrointestinal disorders, particularly irritable bowel syndrome (IBS). In women, overlap exists between migraine, dysmenorrhea, primary or secondary to endometriosis and interstitial cystitis/painful bladder syndrome (IC/PBS). The pathophysiology of these frequent associations remains elusive. Comorbidity between cardiac pain and migraine is probably based on an endothelial dysfunction common to both migraine and atherosclerosis, the major cause of ischemic cardiac pain. For IBS, dysmenorrhea and IC/PBS, a common likely mechanism is that of central sensitization, present in all conditions, as testified clinically by a generalized increase in pain sensitivity not only in painful but also non-painful areas. This chapter addresses the general epidemiology of visceral pain-headache comorbidities focusing on the clinical characteristics and therapeutic challenges posed by the most frequently encountered associations.

Keywords Visceral pain • Migraine • Tension-type headache • Irritable bowel syndrome • Dysmenorrhea • Endometriosis • Myocardial infarction • Angina • Chronic pelvic pain • Painful bladder syndrome

4.1 Introduction

Visceral pain, especially recurrent or chronic, is a major health problem and one of the main reasons for medical consultation by the patients [85]. Primary headaches, particularly migraine and tension-type headache, also represent a significant

Q. Aziz
Barts and The London School of Medicine and Dentistry, Queen Mary University, London, UK

M.A. Giamberardino (✉)
Department of Medicine and Science of Aging and CeSI-Met, "G. D'Annunzio" University of Chieti, Centro Cefalee, Ospedale SS. Annunziata, via dei Vestini sn, Chieti 66100, Italy
e-mail: mag@unich.it

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epidemiologic problem, involving a high degree of disability [33, 37]. Comorbidity between several forms of visceral pain and headache is frequently observed, particularly with ischemic cardiac pain, irritable bowel syndrome (IBS), primary dysmenorrhea, pain from endometriosis as well as interstitial cystitis/painful bladder syndrome (IC/PBS), although the exact figures on these co-occurrences differ in the various studies [1, 5, 12, 18, 19, 25, 36, 40, 45–48, 53, 56, 58, 61, 66, 70, 78, 82, 84, 88, 91]. These associations may reflect common pathophysiological mechanisms especially as they often also involve other pain conditions, such as fibromyalgia [30, 94]. After a description of the general characteristics of visceral pain, this chapter will deal with the epidemiology of headache-visceral pain comorbidity and then focus on the available data on the most frequent of these comorbidities, highlighting for each the possible underlining mechanisms, diagnostic challenges and therapeutic implications.

4.2 Visceral Pain: Clinical Features and Pathophysiology

Visceral pain is a highly complex entity whose experience is variable in health and disease. It can occur in patients with organic disease and also in those without any readily identifiable structural or biochemical abnormality such as in the functional gastrointestinal disorders (FGID) [21].

Whether organic or functional, the features of visceral pain in the clinical setting are very specific and differ from those of pain arising from somatic structures [27, 28, 65]. Visceral pain also has a typical temporal evolution. In the very first phases of a visceral algogenic process, the symptom tends to be perceived along the midline of the thorax or abdomen, whatever the organ primarily involved. It is a vague and poorly localized sensation, accompanied by marked neurovegetative signs, such as nausea, vomiting, sweating or pallor and emotional reactions, such as anguish or a sense of impending death. In this phase, called “true visceral pain”, the accompanying symptoms are very similar to those commonly observed in migraine. *True visceral pain* is usually felt around the midline because most visceral organs are supplied with afferents bilaterally; the low density of sensory innervation of the viscera, together with the extensive functional divergence of the visceral input within the central nervous system, accounts for the poor localization and diffuse nature of the pain in this phase. The viscero-visceral convergence of sensory inputs documented among different organs at a central level also explains the relative non-specificity of visceral sensation in this phase (i.e. the difficulty in identifying its source).

At a later stage, either in the course of the same episode or in subsequent episodes, visceral pain becomes “referred” to somatic structures of the body wall, in areas that now differ according to the involved viscus, being represented by zones of the body which receive the same sensory innervation as the internal organ in question. In the phase of referral, the pain becomes sharper and better defined and

localized, no longer accompanied by emotional reactions and with notable attenuation of the neurovegetative signs. Referred pain from viscera can occur in the absence of any sensory change in the tissues where the symptom is perceived (referred pain without hyperalgesia) or be accompanied by superficial and/or deep pain hypersensitivity (referred pain with hyperalgesia) as revealed by decreased pain thresholds to different stimuli in the various tissues. Numerous controlled clinical studies in patients affected with different visceral pain conditions, such as renal and biliary colic, pelvic pain in women from either primary or secondary endometriosis and irritable bowel syndrome, have shown that the hyperalgesia mainly involves the muscle tissue, but can extend upwards to also affect the subcutis and skin in the most severe cases. The hyperalgesia also tends to accentuate in extent with the repetition of the visceral pain episodes and outlasts the phase of spontaneous pain, persisting for long outside the painful interval. In the area of pain referral, also sustained muscle contraction often takes place, and, in the long run, a dystrophic reaction of the muscle occurs, with reduced thickness and section area, while the subcutis undergoes thickening [10, 29, 32, 34]. *Referred pain without hyperalgesia* is explained by the convergence-projection phenomenon. Extensive experimental evidence documents the central convergence of visceral and somatic afferent fibres onto the same neurons, and the message from the viscera is thus interpreted by higher brain centres as coming from somatic structures because of mnemonic traces of previous experiences of somatic pain. Sensitization of convergent neurons, due to prolonged/repetitive nociceptive inputs from viscera, would be responsible for the development of somatic hyperalgesia in the referred area (convergence-facilitation theory) with consequent facilitation of sensory messages coming from the somatic area of referral. Reflex arc activations (afferent branch represented by sensory fibres from viscera, efferent branches represented by sympathetic efferents towards the skin/subcutis and somatic efferences towards the muscle) would also contribute to the referred phenomena [13, 73].

Some specific visceral pain conditions are also accompanied by generalized pain hypersensitivity, testifying central sensitization [94]. It is the case of primary dysmenorrhea, endometriosis, IBS and IC/PBS, where decreased pain thresholds, especially in deep tissues (muscle), have been found not only in the referred pain area but also outside this area, in distant control areas. In contrast, other forms of visceral pain, such as urinary or biliary colic, are not accompanied by generalized hyperalgesia [32]. Although with some exceptions, it is interesting to note that the forms of visceral pain most comorbid with headache are those characterized by a tendency towards a generalized increase in pain sensitivity. This fact, together with the observation that headache at a high frequency of attacks, whether migraine or tension-type headache, is also characterized by increased pain sensitivity also in non-painful areas, points to possible common pathogenetic mechanisms at the basis of some of the most common comorbidities, mainly rooted in central sensitization processes [30, 94].

The following sections will deal with specific visceral pain-headache comorbidities and their implications for diagnosis and treatment.

4.3 Cardiovascular Pain and Headache

Pain from the heart The most frequent cause of cardiac pain is coronary artery disease (CAD) [8, 51]. CAD represents the single highest cause of death in the USA [75]. It is prevalent in men until the age of 55, with mortality rates being fourfold to those of women. After menopause, CAD increases progressively in women [14], to reach equal distribution in the two sexes after age 65 [68]. The lower prevalence of coronary artery disease in women before menopause is commonly attributed to the protective effect of female sex hormones towards the atherosclerosis process. Numerous studies have investigated the relationship between cardiovascular events, among which cardiac pain from ischemic diseases, and headache, particularly migraine. Though the results are not always homogeneous, the overall outcome of these investigations is in favour of a specific association between migraine and ischemic cardiac pain [see 82]. In a large prospective cohort study on 27,840 USA women affected with migraine (aged 45 years or older) who were free of angina and cardiovascular disease (CVD) at study entry, Kurth et al. (2006) [47] reported 580 major CVD events during a mean follow-up of 10 years. Women affected with migraine with aura (MA) had multivariable-adjusted hazard ratios of 2.08 (95 % CI, 1.30–3.31; $P = .002$) for myocardial infarction and 1.71 (95 % CI, 1.16–2.53; $P = .007$) for angina, compared with non-migraine women. Migraine without aura (MO) was not associated with an increased risk of any CVD event. In contrast with previous data, in 2009 Schürks et al. [72] did not find an overall association between any migraine and myocardial infarction or coronary heart disease. In a prospective cohort study by Kurth et al. (2011) in men aged 40–84 years who were free of CVD at the beginning, 2,236 major CVD events were reported among 1,449 migraine sufferers during a mean follow-up of 15.7 years, with multivariable-adjusted hazard ratios (95 % confidence intervals) of 1.42 (1.15–1.77; $P < .001$) for myocardial infarction and 1.15 (0.99–1.33; $P = .068$) for angina, compared to non-migraine sufferers. This particular study points to the important role of migraine as a cardiovascular risk factor in men, in particular for myocardial infarction, although the study is limited by the fact that no data are available specifically for MA, and also by the circumstance that male gender represents, per se, a risk factor for CVD [46]. A post-hoc subgroup analysis of the Women's Health Study, which randomized 100 mg aspirin on alternate days in primary prevention of CVD among 39,876 women aged ≥45 years, showed that female patients with migraine and aura, who were assigned to aspirin, had an increased risk of myocardial infarction (RR 3.72, 95 % CI 1.39–9.95); this was evident only for nonsmokers or those affected with hypertension ($P < 0.01$) [45].

In 2015, Sacco et al. [70] published a meta-analysis of previous publications, performed through a PubMed and EMBASE search up to April 2014, for observational studies on the risk of any form of ischaemic heart disease in migraine sufferers, reporting in particular on the relationship between migraine and the risk of myocardial infarction. Using a random effects model to pool the effect sizes, out of 3,348 records, 15 studies (one case-control, one cross-sectional and 13 cohort studies) were identified and were included in the meta-analysis. The pooled analysis

indicated an increased risk of myocardial infarction (pooled adjusted effect estimate 1.33, 95 % confidence interval 1.08–1.64; $P = 0.007$) and of angina (pooled adjusted effect estimate 1.29, 95 % confidence interval 1.17–1.43; $P < 0.0001$) in migraine sufferers compared to non-migraine sufferers. The authors conclude that there is an association of migraine with myocardial infarction and angina.

While the association between migraine, particularly MO, and cardiac ischemic pain has been established, the possible explanation of the basis of this comorbidity remains controversial. A possible link between the two conditions has been identified in the detected higher concentrations of some serum markers in migraine sufferers vs controls, e.g. pro-brain natriuretic peptide (pro-BNP), which suggests a preclinical cardiac involvement in these patients and pro-inflammatory mediators such as IL-1beta and IL-6 [87]. A further element is represented by the fact that migraine patients, especially those with MA, present a significant reduction of number and function of circulating endothelial progenitor cells [50] (EPCs), which appear to be involved in repair and angiogenesis of ischemic tissues [57], compared to controls and patients with tension-type headache. Thus an altered endothelial function in migraine sufferers could represent the link between migraine and the increased risk of CV events, among which cardiac ischemic pain. This altered function in migraine was also confirmed by Rodríguez-Osorio et al. [69], who analysed flow-mediated dilation (FMD) in the dominant brachial artery, calcitonin gene-related peptide (CGRP), vascular endothelial growth factor (VEGF) levels, nitric oxide stable metabolites (NOx) and EPCs in peripheral blood samples of patients with episodic migraine vs controls, during interictal periods and migraine attacks. Migraine sufferers had significantly lower levels of EPCs and higher levels of NOx, VEGF and CGRP, with higher levels of these markers reported during attacks. Furthermore EPC counts decreased as migraine progressed in time. An adverse cardiovascular profile in patients with migraine has also been put in relationship with the detection of oxidative stress in the condition, in terms of both an increase in oxidizing substances and antioxidant mechanisms [74].

Metabolic factors promoting CV risk, such as cholesterol levels, could also represent a link between migraine and ischemic cardiac events, as suggested by the results of studies assessing the Framingham risk score in migraine sufferers. The Framingham risk score evaluates the risk of cardiovascular events by combining multiple traditional cardiovascular risk factors (such as age, sex, total cholesterol, HDL cholesterol, smoking, systolic blood pressure, antihypertensive medications) into a single quantitative estimate of risk which can be used to target preventive interventions [35]. In the cross-sectional population-based HUNT study [93], which enrolled 48,713 subjects (age $\geq$ 20 years), in 44,098 (90.5 %) of whom parameters were assessed such as blood pressure (BP), body mass index (BMI), serum total and high-density lipoprotein cholesterol to calculate the Framingham 10-year risk score for coronary death and myocardial infarction, an unfavourable cardiovascular risk profile (elevated Framingham risk score) was found in migraine with and without aura as well as in non-migrainous headache. The risk was higher in MA. A very interesting result was that the Framingham risk score consistently increased with a higher headache frequency. While for MO and non-migrainous headache, the increased risk

was accounted for by lifestyle factors such as low physical activity, smoking and a high body mass index, and these factors instead did not completely explain the elevated risk in MA. The specific relationship between lipid profile and migraine could account for these differences. A population-based study by Bigal et al. (2010) [7], for instance, found that all migraine sufferers were more likely to have a diagnosis of hypercholesterolemia than controls, the risk being highest in MA. After adjustments for CVD risk factors, gender, age, disability and treatment, migraine remained significantly associated with myocardial infarction. A significant elevation of total cholesterol and triglycerides was also found among migraine with aura patients enrolled in the cross-sectional Epidemiology of Vascular Ageing Study [67]. A further more recent study documented a significant positive association between migraine frequency and intensity with total and LDL cholesterol, in addition demonstrating for the first time a significant reduction of these lipid parameters after effective migraine prophylaxis. The study was retrospective and involved a small sample size; therefore, the results need to be confirmed in future prospective controlled trials. In spite of these limitations, however, it strongly suggests a link between cholesterol levels and migraine severity, underlining the importance of prevention of migraine chronification also in the light of reducing an important risk factor for atherosclerosis and, consequently, cardiovascular risk and cardiac visceral pain of ischemic origin [81].

While the bulk of the studies so far carried out on the relationship between CV risk and migraine has mainly evidenced a link between MA and CV, recently growing evidence exists about a link also with migraine without aura, as suggested by the results of a study on micro RNA profile in MO patients. MicroRNAs (miRNAs) are short, noncoding RNAs whose deregulation has been shown in several human diseases, including pain states and diseases associated with increased cardiovascular (CV) risk. This study in female patients affected exclusively with MO showed that the expression of four miRNAs was significantly different in MO patients versus controls. Specifically miR-27b was upregulated, while miR-181a, let-7b and miR-22 were downregulated. Remarkably, the same miRNAs are known to be modulated in the setting of atherosclerosis and stroke in humans. This study represents a first step towards further characterization of MO diagnosis/pathophysiology, also in relation to its link with cardiovascular risk [80].

The data so far available on migraine-cardiac pain comorbidity may have important implications for therapy. On one hand, evidence about an increased risk of cardiovascular events with the increasing severity of the condition strongly suggests that an early and effective preventative treatment of migraine is a measure to also prevent/reduce the risk of cardiac pain from ischemia. On the other hand, this association also reinforces the notion of great caution when prescribing symptomatics to migraine patients, whether triptans, because of their vasoconstrictive action (though preferential at cerebral rather than cardiac level), or non-steroidal anti-inflammatory drugs (NSAIDs), whose extensive employment is also associated with an increased risk of CV events. An accurate evaluation of the global health profile of the migraine patient, with particular attention to all the other CV risk factors (smoking habits, hypertension, obesity, hypercholesterolemia) is strongly recommended towards this aim [82].

An adequate prevention of chronic tension-type headache (TTH) is also crucial. Although no specific comorbidity data have been evidenced for tension-TTH and visceral pain of cardiac origin so far, it should be remembered, here again, the potential CV risk linked to NSAIDs, which represent the typical first-line symptomatic treatment for tension-type headache. Their excessive use should therefore be prevented also in the light of effectively preventing possible CV events at cardiac level [33].

4.4 Gastrointestinal Pain and Headache

The relationship between gastrointestinal and headache manifestations is particularly strict. Headache, especially migraine, presents with a number of associated symptoms also typical of the gastrointestinal tract, e.g. nausea or vomiting. In turn, abdominal gastrointestinal pain/disturbance can be part of the spectrum of headache conditions [37, 89].

4.4.1 Headache Conditions Associated with Gastrointestinal Pain Symptoms

Under the label of *Episodic syndromes that may be associated with migraine* (code 1.6), the most recent headache classification considers several conditions involving GI symptoms which can manifest in patients who also have migraine without and with aura or are at increased likelihood of developing either of these headache forms. Typically indicated as conditions occurring in childhood, they may also occur in adults. *Recurrent gastrointestinal disturbance* (code 1.6.1.) is described as "Recurrent episodic attacks of abdominal pain and/or discomfort, nausea and/or vomiting, occurring infrequently, chronically or at predictable intervals, that may be associated with migraine". The diagnostic criteria require at least five attacks with distinct episodes of abdominal pain and/or discomfort and/or nausea and/or vomiting; normal gastrointestinal examination and evaluation; absence of any other disorder which could account for these symptoms. A first subcategory is represented by *Cyclic vomiting syndrome* (CVS) (code 1.6.1.1), described as "Recurrent episodic attacks of intense nausea and vomiting, usually stereotypical in the individual and with predictable timing of episodes. Attacks may be associated with pallor and lethargy. There is complete resolution of symptoms between attacks". The cyclic nature is the hallmark, and is predictable; episodes usually start at the same time of day, have similar duration, intensity and type of associated symptoms and prodromal phenomena are often present. The attacks are very disabling. Triggering factors are often identifiable, such as menstruation, lack of sleep, certain foods, physical exertion and stress. The clinical features of this syndrome resemble those found in association with migraine headaches, and multiple threads of research over the last years

have suggested that cyclic vomiting syndrome is a condition related to migraine. Typically occurring in childhood, CVS also manifests in adults, though its prevalence in this population is at present unknown [38, 77]. Calhoun and Pruitt (2014) [11] performed an analysis of the literature, based on which they concluded that CVS likely represents a disorder on the migraine spectrum because CVS in adults is not only highly comorbid with migraine, but it responds to migraine preventives and in some cases to injectable sumatriptan even in the absence of headache. A second subcategory of recurrent gastrointestinal disturbance is *abdominal migraine* (code 1.6.1.2), described as "An idiopathic disorder seen mainly in children as recurrent attacks of moderate to severe midline abdominal pain, associated with vasomotor symptoms, nausea and vomiting, lasting 2–72 h and with normality between episodes. Headache does not occur during these episodes". Pain of abdominal migraine is severe enough to interfere with normal daily activities. In young children, the presence of headache is often overlooked, and in the headache classification, it is underlined how a careful history of presence or absence of headache must be taken in these cases, and, if headache or head pain during attacks is identified, a diagnosis of migraine without aura should be considered. Most children with abdominal migraine will develop migraine headache later in life [37].

4.4.2 Functional Gastrointestinal Diseases and Headache

The frequent association of headache, particularly migraine, with symptoms consistent with a diagnosis of functional gastrointestinal diseases (FGIDs) is revealed by numerous clinical observations and epidemiological studies [1, 12, 16, 48, 56]. The study by Aamodt, in particular (population-based, cross-sectional) [1], showed a higher prevalence of headache, including migraine, in subjects complaining of reflux symptoms, diarrhoea, constipation or nausea vs subjects not presenting with these symptoms. The paper by Cole et al. (2006) [16], reporting a large cohort study involving 97,593 patients with irritable bowel syndrome (IBS), showed a higher prevalence of migraine (6%) vs healthy controls (2.2%). However, a study of dyspeptic patients referred for upper gastrointestinal endoscopy failed to show a difference in migraine prevalence in patients with reflux-like/ulcer-like dyspepsia vs healthy controls, being higher only among those with dysmotility-like dyspepsia [56].

In 2011, Lackner et al. [49] published a study in which they evaluated 175 IBS patients (diagnosis according to Rome III criteria) (median age, 41 years; 78% women), referred to two specialty care clinics, for IBS symptom severity, comorbidities, psychiatric profile, abdominal pain intensity, health status and quality of life. There was an average of 5 comorbidities (1 mental, 4 physical) in IBS patients, the worst QOL occurring in those with more comorbidities. Comorbidity type was strongly associated with illness burden indicators. Tension-type headache was among the most frequent comorbidities, consistently associated with greater illness and symptom burdens (QOL, mental and physical function, distress, more severe

symptoms of IBS, pain). The authors conclude that comorbidities are common among patients with IBS and are associated with distress and reduced QOL. Specific comorbidities (among which tension-type headache) are associated with more severe symptoms of IBS.

More recently, Park et al. [62] evaluated the prevalence of functional symptoms (using Rome III criteria to classify FGID) in a prospective, systematically acquired cohort of migraine patients attending a teaching hospital in Korea. They aimed to clarify the relationship among these concomitant functional symptoms, psychological comorbidity and headache-related disability. In a prospective regimen, 109 migraine sufferers recruited from a headache clinic at a teaching hospital completed a self-administered survey that collected information on headache characteristics, functional gastrointestinal symptoms, anxiety, depression and headache-related disability. A total of 71 % of the patients met the Rome III criteria for at least one FGID. In patients with FGID, irritable bowel syndrome was the most common diagnosis (40.4 %), followed by nausea and vomiting syndrome (24.8 %) and functional dyspepsia (23.9 %). A specific difference among IBS subtypes in relation to the association with migraine was also found, with IBS-M (mixed, diarrhoea-constipation) being the most prevalent in migraine. Depression and anxiety scores were significantly higher in patients meeting the criteria for any FGID. The number of the symptoms consistent with FGID in individual patients correlated positively with depression and anxiety.

The authors conclude that FGID symptoms defined by the Rome III criteria are highly prevalent in migraine and that these symptoms correlate with psychological comorbidities, such as depression and anxiety.

The mechanisms beyond the frequent association between migraine and FGIDs still need to be clarified. Possible pathways common to both may involve the brain-gut axis, neuro-immunity and neuroendocrine interactions [58, 66]. Altered serotonin signalling is also a possibility together with a genetic predisposition, since IBS and migraine show strong familial aggregation [23, 24]. Polymorphisms in the promoter region of the serotonin reuptake transporter (SERT) gene (SERT deletion/deletion genotype) are associated with IBS, especially diarrhoea-predominant IBS [63], and SERT gene polymorphism of the variable number of tandem repeats is associated with migraine [64].

Among the various pathogenetic hypothesis for the comorbidity, however, the role of sensitization mechanisms seems particularly plausible. Although the pathophysiology of functional abdominal pain is incompletely understood, in fact, it has been postulated that peripheral sensitisation of visceral afferents, central sensitisation of the spinal dorsal horn and aberrancies within descending modulatory systems may have an important role [22]. Most patients with IBS present a generalized increase in pain sensitivity, the typical hallmark of central sensitization, similarly to patients with migraine and tension-type headache, especially with a high frequency of attacks/chronic [10, 59, 92].

The comorbidity between functional gastrointestinal disorders and headache has implications for therapy. The management of patients with functional abdominal pain requires a tailored multidisciplinary approach in a supportive and empathetic

environment in order to develop an effective therapeutic relationship. In the opinion of Farmer and Aziz [22], patient education directed towards an explanation of the pathophysiology of functional abdominal pain is a prerequisite step and provides the rationale for the introduction of interventions. A similar approach is also indispensable for headache patients as a premise towards the therapeutic measures. For functional visceral pain, interventions can usefully be categorized into general measures, pharmacotherapy, psychological interventions and "step-up" treatments. Pharmacotherapeutic/step-up options include tricyclic antidepressants, serotonin noradrenergic reuptake inhibitors and the gabapentinoids, the same class compounds used for prophylaxis in headache. Psychological treatments for FGIDs include cognitive behavioural therapy, recommended also in headache, and hypnotherapy. An integrated approach to both the headache problem and visceral pain condition in these patients is therefore highly advisable.

4.5 Urinary Pain and Headache

4.5.1 Interstitial Cystitis/Painful Bladder Syndrome and Migraine

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic visceral pain condition involving suprapubic pain and urinary symptoms such as urgency, nocturia and urinary frequency. Its prevalence rates in the general population range from 2 to 17.3 % (variability according to diagnostic criteria), with prevalence increasing in women and patients with one first-degree relative affected [43]. It is a typical example of urinary pelvic pain without an identifiable organic cause and, although its pathophysiology is probably complex and likely to involve multiple mechanisms, is believed to be largely contributed to by mechanisms of central sensitization, as reflected by a generalized increase in sensitivity to pain documented by several studies (see Giamberardino et al. [34]).

As recently examined by Fan et al. [19], IC/PBS has a spectrum of associations with other painful conditions, among which headache is particularly frequent. The authors examined 122 women with IC and 122 age-matched controls with stress urinary incontinence. All completed screening questionnaires for irritable bowel syndrome, temporomandibular disorder, multiple chemical sensitivities, tension and migraine headache, localized myofascial pain disorder and fibromyalgia. IC patients also completed questionnaires on interstitial cystitis/hypersensitive bladder syndrome symptom severity. IC patients vs controls proved to have a significantly higher probability to meet diagnostic criteria for irritable bowel syndrome (37.5 vs 11.5 %) and tension/migraine headache (38.7 vs 15.7 %; all $P < 0.001$).

The prevalence of the other examined disorders (temporomandibular disorder, multiple chemical sensitivities, localized myofascial pain disorders and fibromyalgia) did not reach a statistically significant difference between the two groups. In the multivariate model, associations were also observed for irritable bowel syndrome

(odds ratio 2.546; 95 % confidence interval 1.136–5.704) and tension/migraine headache (odds ratio 2.684; 95 % confidence interval 1.233–5.842). Patients with more comorbid conditions had more severe and bothersome interstitial cystitis/hypersensitive bladder syndrome symptoms as measured by the visual analog scale of pain ($P = 0.008$) and O'Leary-Sant bother index ($P = 0.035$). The authors conclude that IC patients have an increased probability to present with multiple non-bladder conditions, among which headache is particularly relevant, which correlate with the severity of IC symptoms.

Treatment of IC/PBS is still problematic and unsatisfactory. However, among pharmacologic measures adopted are tricyclic antidepressants (TCA; particularly amitriptyline), but also anticonvulsants, both of which are also commonly employed also for headache prophylaxis [20].

4.6 Pain from the Reproductive Organs and Headache

Primary dysmenorrhea/headache Primary dysmenorrhea is defined as cyclic pain associated with menses, not linked to any pelvic organic disease or structural abnormality of the female reproductive area. It affects over 50 % of all menstruating women and is caused by an excess prostaglandin production and increased contractility of the myometrium. Pain typically starts a few hours or days before bleeding, worsens as the menstrual flow begins and can last throughout the entire period of menses. The affected area is the lowest abdomen, but also the lower back and upper thighs can be involved. Usually cramplike, it is normally accompanied by neurovegetative signs and emotional reactions, i.e. nausea, vomiting, changes in heart rate, diarrhoea and anxiety [39]. The pain is accompanied by somatic hyperalgesia in the referred area, as shown by numerous psychophysical studies, this hyperalgesia particularly concerns the muscle; it is present throughout the cycle, but accentuates in the perimenstrual period. The degree of pain threshold lowering is a function of the number of years the patients have suffered from dysmenorrhea which, given the cyclic nature of this pain, corresponds to an accentuation of the hyperalgesia as a function of the number of perceived visceral pain episodes. Apart from hyperalgesia in the area of pain referral, however, dysmenorrheic women show a certain degree of muscle hypersensitivity also in other body regions (diffuse muscle hyperalgesia), similarly to the pattern observed in women affected with fibromyalgia [31].

The relationship between primary dysmenorrhea and headache is particularly strict. The most typical headache associated with menses is migraine. An association of migraine with the menstrual cycle is reported by about a half of all women migraine sufferers, though exclusively menstrual migraine affects only 5–8 % of women with migraine [37]. Although the mechanisms of menstrual-related pain conditions have not yet been fully clarified, menstrual-related overproduction of prostaglandins is implicated in the pathophysiology of both menstrual migraine and dysmenorrhea [60].

Nonsteroidal anti-inflammatory drugs (NSAIDs), indeed, represent the first-line treatment for the pain of dysmenorrhea, but they are also an important symptomatic option for migraine in the case triptans are not effective or contraindicated [33, 54]. In addition, hormone therapy is effective in many cases for treating dysmenorrhea and may be beneficial in the management of menstrual migraine. Thus, overlapping treatment regimens may be advantageous in treating the coexisting menstrual-related pain conditions of dysmenorrhea and migraine [53].

Endometriosis is the presence of endometrial tissue in abnormal locations in the abdominal/pelvic cavity, most often ovaries, uterine tubes, cul-de-sac, supporting ligaments of the uterus, pelvic peritoneum, rectovaginal septum, cervix and bowel surface. The disease is common, estimated to affect up to 10 % of women in their reproductive years and 25–35 % of infertile women. Typical symptoms of endometriosis are infertility or subfertility, vaginal hyperalgesia and dyschezia. Although there is no direct relationship between the extent of endometriosis lesions and the occurrence or degree of pain symptoms, pain is, indeed, a frequent manifestation of EM, either as secondary dysmenorrhea or as chronic pelvic pain, the latter being present in 15–24 % of fertile women, while active endometriosis is documented in around 33 % of women suffering from chronic pelvic pain [41, 55, 79]. Like women with primary dysmenorrhea, women with symptomatic endometriosis present abdomino/pelvic hyperalgesia, especially at muscle level, and also a generalized state of deep tissue hypersensitivity [6, 28]. The pathophysiology of endometriosis is still partly unknown. Hypotheses are retrograde menstruation, lymphatic system spread or hematogenous spread. The mechanisms of pain are also not completely known, but probably involve excess prostaglandin production, increased peritoneal sensitivity, chemical irritation of the peritoneum and bleeding in sites of endometriosis [79]. About 20 % of women with endometriosis present comorbidity with other chronic painful conditions: IBS, IC, vulvodynia, fibromyalgia and headache, particularly migraine [15, 84]. A significant association between endometriosis and headache was first suggested in 1975, when a study by Tervila et al. [83] documented that, among 125 women undergoing surgery due to pelvic pain, those who proved to have endometriosis externa (outside the uterine cavity) had significantly more headache in the menstrual period than those in whom pelvic pain was due to other causes, with headache being almost as common as pelvic pain. Ferrero et al. [25] also showed a significantly higher prevalence of headache among 133 women with endometriosis vs 166 controls (63.9 vs 36.1 %, $P<0.001$). This difference only regarded migraine (38.3 vs 15.2 %, $P<0.01$), being most marked for migraine with aura (13.5 vs 1.2 %, $P<0.001$), while no difference was found for tension-type headache (21 vs 22 %). In 2007 Tietjen et al. [84] published a study on the evaluation of 171 headache women and 104 healthy controls at the University of Toledo and Duke University over a period of 2 years, reporting a significantly higher frequency of endometriosis in migraine patients than in controls (22 vs 9.6 %, $P<0.01$). In addition, the frequency of chronic headache was significantly higher in patients with migraine plus endometriosis than in those with migraine only ($P=0.002$), with median headache-related disability scores also being significantly higher in the comorbid group ($P=0.025$). Patients with migraine and EM comorbidity complained

of more accentuated symptoms from the female reproductive organs (more menorrhagia, dysmenorrhea and infertility) but also had a higher frequency of other comorbidities, such as depression, anxiety, fibromyalgia and chronic fatigue syndrome and specifically more visceral pain from other districts, namely, the gastrointestinal tract (irritable bowel syndrome) and urinary tract (interstitial cystitis). Migraine sufferers had symptoms of premenstrual dysphoric disorder more frequently than control patients, although the difference between migraine sufferers with and those without EM was not significant. The authors conclude that the prevalence of EM is higher in women with migraine than in non-headache controls and that patients with migraine plus EM have more frequent and disabling headaches and more comorbid conditions, among which other forms of visceral pain, than migraine sufferers without EM. Migraine and endometriosis both share the feature of being influenced by ovarian hormones; however, the mechanisms beyond this frequent association are probably much more complex than a mere common hormonal basis and likely to involve multiple factors.

Migraine prevails in women during the reproductive years, often starting at the time of menarche and improving after menopause. Early menarche seems to be a risk factor for both headache [2] and endometriosis [55, 86]. Interestingly, for headache the age of menarche has been reported to influence the prevalence of the condition, not only among adolescents but throughout life [2]. Furthermore, migraine seems to start earlier in women with endometriosis [25]. Higher oestrogen levels or increased oestrogen sensitivity have been claimed as possible reasons for headache being more prevalent in women with early menarche. For endometriosis, if the theory of retrograde flow of menstrual blood is true, all conditions (including early menarche) that lead to more menstruations will produce a higher prevalence of endometriosis [78]. Gonadotropin-releasing hormone (GnRH) agonists (GnRH-a) have proven effective against pain from endometriosis, and a study specifically showed that their employment in endometriosis was also effective against the occurrence of migraine attacks [9, 52]. These observations further support the notion of the importance of the hormonal factor at the basis of both conditions, although the link is complex if one considers that headache is normally listed as a side effect of GnRH-a treatment. Genetic factors are also likely to contribute to the comorbidity. A large twin study published by Nyholt et al. in 2009 [61] suggested that the frequent co-occurrence of endometriosis and headache is to a large extent caused by shared genes. Other genetic studies are in favour of a genetic component for the comorbidity, e.g. the oestrogen receptor 1 gene has been implicated in migraine susceptibility [17, 42], and this same receptor has been reported to be associated with endometriosis [26, 44].

Another possible mechanism beyond comorbidity is that one disease is the cause of the other. In particular, since endometriosis has been shown to be associated with central sensitization (as revealed by decreased pain thresholds to various stimuli at somatic level not only in painful areas but also in non-painful control zones), it has been postulated that nociceptive impulses from regions other than the sites of the implants (and therefore also those from the cervicofacial area) are also facilitated. This facilitation mechanism would not be exclusive of endometriosis but also apply

to other conditions, such as chronic pelvic pain of other origins, as suggested by the results of a study by Karp et al. (2010) [40]. In women undergoing laparoscopy for pelvic pain, the authors showed a very high lifetime prevalence of migraine (67 %) within the group, but the difference between women with endometriosis compared to those with pelvic pain from other causes was not significant. Sensitization from endometriosis could thus facilitate headache occurrence, although this hypothesis needs confirmation. It has also been postulated [78] that if the increased sensitivity represents the link between endometriosis and headache, this effect could be mediated by prostaglandins or nitric oxide (NO), both involved in migraine and endometriosis pathophysiology. This possibility, however, is not supported by data so far available; in particular, no research has documented a correlation between prostaglandin and NO production by endometriosis implants and migraine attacks. Another possible mechanistic link between the two conditions is that migraine favours endometriosis diagnosis: as already reported above, migraine sufferers, especially at a high frequency of attacks, chronic, have a generalized lowering in pain thresholds, which persists in between the attacks [71], and this would involve the characteristic of migraine sufferers of being more susceptible to pain of any origin, thus also to pain from endometriosis, which would favour the diagnosis of EM. Here again, the hypothesis needs confirmation in controlled studies. It has also been discussed if the comorbidity may be explained by the use of estroprogestins (EPs) in both conditions. EPs are employed to relieve pain in endometriosis but at the same time the use of EPs has been shown to increase the risk of presenting endometriosis [76, 90]. EPs and hormonal replacement therapy are also associated with headache occurrence [3, 4]. So far, however, no systematic study has been able to demonstrate a direct causal link between an extensive use of EPs and endometriosis and/or headache occurrence, and therefore this hypothesis does not seem probable [78].

Treatments so far available for endometriosis are still variable and unsatisfactory. As for primary dysmenorrhea, however, symptomatic treatment with NSAIDs is frequently employed, which is also an effective therapeutic approach to headache [79].

4.7 Visceral Pain and Headache: More Than a Simple Co-occurrence

As reported in the previous sections, comorbidity is widely documented between headache and several forms of visceral pain. Clinical observations and preliminary clinical studies also suggest, however, that visceral pain and headache not only coexist in the same patients but may have a more “dynamic” interaction, with visceral pain expression influencing that of headache, at least in some instances. It has been shown, in fact, that headache attacks are often triggered by the visceral pain episodes in that they occur in strict temporal relationship with the pain from the internal organs. In comorbid patients, in fact, a significant number of both migraine and tension-type headache attacks have been shown to manifest preferentially within 24–48 h from crises of abdominal pain from IBS or suprapubic pain from

IC/PBS. This phenomenon probably occurs because of an exacerbation of the state of central neuronal excitability due to the nociceptive impulses from the visceral periphery, which would favour the triggering of the headache pain. Effective treatment of the visceral pain condition, even with measures not directly able to influence the headache pain, such as dietary treatment of IBS, has also been shown to improve the headache in the long run, reinforcing the notion of a complex and persistent interaction between the visceral and headache pain conditions in comorbid patients (Giamberardino M.A. et al., 2016). Visceral pain-headache comorbidity also needs to be looked at in the wider context of multiple comorbidities often affecting headache patients, whereby some of them present, for instance, IBS, painful bladder syndrome, pelvic pain and fibromyalgia, all conditions characterized by central sensitization. In the cases of these complex pictures, therapies primarily targeted at reducing CNS hyperexcitability have a chance to effectively address the global pain burden of the patient [94].

4.8 Conclusions

Comorbidity between headache and several forms of visceral pain is high, particularly between migraine and cardiac pain, IBS, IC/PBS, dysmenorrhea and pelvic pain from endometriosis. The pathophysiological mechanisms of these associations remain to be clarified in full. While the association between migraine and cardiovascular events, among which cardiac pain from atherosclerosis, is mainly attributed to the promotion of endothelial dysfunction by the migraine condition, for the other forms of visceral pain, all characterized by enhanced pain sensitivity, as in the case of migraine and tension-type headache especially at a high number of attacks/chronic, the possible link is represented by mechanisms of central sensitization. These central changes could be the expression of a common genetic predisposition due to which the affected individual is prone to develop multiple pains from different districts. Independently of pathophysiology, however, the visceral pain-headache co-occurrence is important clinically as it enhances the level of suffering and disability of the patients. A careful assessment and management of all visceral pain comorbidities is therefore mandatory in all headache cases, to effectively improve the overall well-being of the patients through integrated therapeutic interventions.

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Chapter 5
Fibromyalgia

Marina de Tommaso and Luiz Paulo Queiroz

Abstract Fibromyalgia (FM) is a common and disabling syndrome, characterized by widespread pain, fatigue, sleep disorders, and other associated symptoms such as cognitive dysfunction, irritable bowel, and headache.

FM is highly prevalent both in migraineurs and in patients with tension-type headache. The mean prevalence of FM in migraine patients is 19.4 %.

This comorbidity characterizes prevalently patients with chronic tension-type headache and chronic migraine. Frequency of headache, anxiety, pericranial tenderness, sleep disorders, and low physical quality of life were indicated as the main symptoms predisposing to FM comorbidity.

The common mechanism concurring in migraine, tension-type headache, and fibromyalgia is a dysfunction of pain modulation with enhanced expression of central sensitization symptoms.

Little evidence is available about the therapeutic approach to this comorbidity, amitriptyline being the sole drug indicated in FM, migraine, and tension-type headache. Duloxetine and pregabalin, used for FM, have limited evidence of efficacy in migraine and tension-type headache, as well as topiramate, flunarizine, sodium valproate, and beta-blockers in FM.

Non-pharmacological treatment, provided by transcranial magnetic and electrical stimulation, as well as other approaches, such as physical exercise and cognitive-behavioral therapy, should be the best choices to be tested in such critical patients.

Keywords Fibromyalgia • Migraine • Tension-type headache • Central sensitization • Pharmacological and not pharmacological treatment

M. de Tommaso (✉)
Neurophysiopathology of Pain SMBNOS Department, Bari Aldo Moro University, Policlinico General Hospital, Giovanni XXIII Building, Via Amendola 207 A, Bari, Italy
e-mail: marina.detommaso@uniba.it

L.P. Queiroz
Department of Neurology, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil

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5.1 Introduction

Fibromyalgia (FM) is a common and disabling syndrome, characterized by widespread pain, fatigue, sleep disorders, and other associated symptoms such as cognitive dysfunction, irritable bowel, and headache [1, 2]. The estimated prevalence in the general population is 4.2 % in females and 1.4 % in males (2.7 % in total population [2]). Diagnostic criteria for FM have changed in the last few years, from the ACR criteria published in 1990, defining FM as a chronic widespread pain including sleep disorders, fatigue, and positivity of at least 11 out of 18 tender points, to the most recent guidelines, which removed the tender point count criterion and emphasized the presence of associated symptoms and syndromes, including headache [3, 4]. In recent years, comorbidity between headache and FM has been reported in cohorts of primary headache or FM patients, all studies indicating this association as invalidating and worth full consideration in clinical management [5].

Recent evidence confirmed the involvement of both central and peripheral nervous system in the pathophysiology of this complex and still unexplained disorder, suggesting the presence of different FM phenotypes, some of these presenting with associated migraine [6].

In the present review, we will focalize on the diagnostic criteria for FM, prevalence of FM in primary headache, clinical features of primary headache patients presenting with diffuse pain, the pathophysiological hypothesis about this association, and main evidence and possible practical guidelines for clinical management and therapeutic approach.

5.2 Diagnosis of Fibromyalgia

The diagnosis of FM is eminently clinical, as there are no biomarkers (specific diagnostic tests or image findings) that confirm this disorder. The cardinal symptom of FM is chronic widespread pain (CWP), which is a manifestation of central nervous system sensitization. This hyperalgesic state is also evident by the presence of generalized tender point positivity. FM is, however, more than just a pain disorder; a constellation of associated symptoms may be present, including fatigue, sleep disturbances, difficulties with memory and concentration, irritable bowel syndrome, headache, and depression. The diagnosis of FM requires that organic diseases are not causing these symptoms.

In 1990, the American College of Rheumatology (ACR) published a set of criteria for the diagnosis of CWP and FM (ACR1990) [1]. The proposed criteria for FM were CWP in combination with tenderness in 11 or more of 18 specific tender point sites. CWP was defined as pain on the left and the right side of the body and pain above and below the waist. In 2010, the ACR introduced new preliminary diagnostic criteria that did not require tender point examination [3]. This would be more suitable for use by primary care physicians and nonspecialists, who may find it too

difficult to apply and to interpret tender point examination. This was also an impediment for doing large epidemiological studies on FM, as they required the examination of all CWP subjects by specialists. That is why an FM survey questionnaire was developed for epidemiological and clinical studies, published in 2011, modifying the ACR2010 criteria (ModACR2010) [4].

The ACR2010 consists of two scales: the widespread pain index (WPI) and the symptom severity scale (SSS). The ModACR2010 substituted the physicians' estimate of the extent of somatic symptoms by the sum of 6 specific self-reported symptoms and created a 0–31 FM symptom scale, by adding the WPI to the modified SSS (Table 5.1). The ACR2010 and the ModACR2010 reflect a conceptual change in the diagnosis of FM, from a predominantly pain syndrome to a multisymptom syndrome [7]. The ACR1990 criteria, however, are still valid and considered the "gold standard" for the diagnosis of FM in clinical practice.

In the Wolfe et al. 2011 publication [4], with an FM symptom scale score of ≥13, the sensitivity was 96.6 % and the specificity 91.8 %, allowing to differentiate FM from other rheumatologic diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and osteoarthritis, in 93.0 %. In a validation study of the ModACR2010 criteria, in 2014, Bennett at al. [8] reported a sensitivity of 83 %, a specificity of 67 %, and a correct classification of 74 %.

The evaluation of patients with probable FM comprises a complete physical examination, including palpation of tender points and a neurological examination, and ordering some tests, to exclude underling diseases that could be the cause of the FM symptoms. With respect to "routine" laboratory tests, they should be limited to a complete blood count, routine serum chemistries, thyroid-stimulating hormone,

Table 5.1 Modified 2010 American College of Rheumatology diagnostic criteria [3]

1. *Widespread pain index (WPI):* Note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19
Left shoulder girdle, right shoulder girdle, left upper arm, right upper arm, left lower arm, right lower arm, left hip (buttock, trochanter), right hip, left upper leg, right upper leg, left lower leg, right lower leg, left jaw, right jaw, chest, abdomen, upper back, lower back, neck
2. *Symptom severity score:* fatigue, waking unrefreshed, cognitive symptoms
For each of these 3 symptoms, indicate the level of severity over the past week using the following scale:
0 = no problem; 1 = slight or mild problems, generally mild or intermittent; 2 = moderate, considerable problems, often present and/or at a moderate level; 3 = severe, pervasive, continuous, life-disturbing problems
The symptom severity score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, and cognitive symptoms) plus the sum of the number of the following symptoms occurring during the previous 6 months: headaches, pain or cramps in lower abdomen, and depression (0–3). The final score is between 0 and 12

The diagnostic criteria for FM are satisfied if the following three conditions are met

1. The WPI is ≥7 and the SSS ≥5; or the WPI is 3–6 and the SSS ≥9
2. Symptoms have been present at a similar level for at least 3 months
3. The patient does not have a disorder that would otherwise explain the pain

and erythrocyte sedimentation rate and/or C-reactive protein [9]. Other tests may be ordered, depending on diagnostic hypothesis.

The main differential diagnoses of FM are rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, Sjögren syndrome, polymyalgia rheumatica, myofascial pain, myosites, myopathies, peripheral neuropathies, multiple sclerosis, entrapment syndromes, multiple myeloma, occult malignancy, hypothyroidism, adrenal dysfunction, systemic inflammation or infection, non-icteric hepatitis, Lyme disease, and anemia [9, 10].

5.3 Prevalence of Fibromyalgia in Primary Headache

The prevalence of FM has been evaluated in many studies around the world. The mean prevalence in the general population is 2.7 % (4.1 % in female and 1.4 % in male), with a female-to-male ratio of 3:1 [2]. In 2015, however, in a prevalence study comparing the three ACR criteria [1, 3, 4], Jones et al. [7] showed that FM prevalence rates vary with the different sets of classification criteria applied, being higher with the ModACR2010. In population studies, the mean 1-year prevalence of headache in general is 46 %, migraine 11 %, and tension-type headache (TTH) 42 % [11].

Some studies have estimated the prevalence of FM in patients with primary headache, especially migraine. The prevalence rates of FM in some primary headaches are shown in Table 5.2. FM is highly prevalent, both in migraineurs and in patients with TTH. The mean prevalence of FM in migraine patients in these nine studies is 19.4 % (Table 5.2).

The prevalence of headache in patients with FM has also been estimated. Marcus, Bernstein, and Rudy [21] reported that 76 % of FM patients complained of headache; 63 % of them had migraines. Vij et al. [22] found 55.8 % of migraine in FM sufferers.

5.4 Clinical Features of Headache Patients with FM Comorbidity

Recent studies in primary headache patients sharing FM comorbidity indicated that this comorbidity involves prevalently chronic tension-type headache and chronic migraine. Many studies focused on selected groups of migraine patients [12, 13], whereas in studies conducted on larger cohorts of primary headache patients, only migraine and tension-type headache seemed prone to this association, while other forms of primary headache, as cluster headache, did not show a relevant presence of patients with diffuse pain [15]. Among primary headache patients, frequency of headache, anxiety, pericranial tenderness, sleep disorders, and low physical quality of life were indicated as the main symptoms predisposing to FM comorbidity [15].

Table 5.2 Prevalence of fibromyalgia in primary headache patients

Author	*N*	Type of headache	Prevalence of fibromyalgia, %	Setting	Country
Peres et al. [12]	101	Transformed migraine	35.6	Headache clinic	Brazil
Ifergane et al. [13]	92	Episodic migraine	17.4	Headache clinic	Israel
de Tommaso et al. [14]	217	Primary headaches	36.4	Headache center	Italy
		Migraine	28.5		
		TTH	59.0		
de Tommaso et al. [15]	849	Primary headaches	19.6	Pain clinic	Italy
		Migraine	17.8		
		TTH	35.1		
Tietjen et al. [16]	1,413	Episodic and chronic migraine	6.9	Headache clinic	USA
Tietjen et al. [17]	223	Migraine	11.7	Headache clinic	USA
Le et al. [18]	8,044	Migraine	1.2	Twins cohort	Denmark
Küçüksen et al. [19]	118	Migraine	31.4	Headache clinic	Turkey
Marcus et al. [20]	1,439	Migraine	24.3	Online	Internet

In other studies on episodic migraine, high headache frequency was not indicated as a common feature of FM comorbidity [19], but evaluations were conducted in smaller case series not including chronic migraine. Moreover, also in those episodic migraine groups, severe headache intensity typified FM patients [19]. Another still unclear point is the low representation of FM symptoms among patients with migraine with aura [15]. In most of the studies, groups of migraine with aura included few patients [13, 14, 16, 19] in agreement with the lower frequency of this type of migraine in the general population. The reason why we did not find FM comorbidity in pure migraine with aura patients may be the low frequency of attacks in those patients, while patients with associated migraine without aura or evolving into chronic form showed FM-associated symptoms [15]. This observation, though worth further assessment in lager series, may confirm that frequency of headache is an important factor predisposing to FM comorbidity in migraine and tension-type headache groups. In other headache syndromes, such as chronic forms of TACs, FM was rarely represented, suggesting that these headache types probably do not have pathophysiological factors predisposing to widespread pain. Features of sleep were also described in a recent study of our group [23], showing that the reduced quantity of sleep as assessed by the MOS scale was associated with frequent and invalidating migraine, though patients with FM comorbidity presented with a more complex sleep disturbance, including deterioration of sleep quality and severe sleep disorders.

The general impression emerging from these studies is that the identification of features of FM comorbidity in primary headache patients includes the assessment of headache frequency, pericranial tenderness, quality of life, anxiety scores, and sleep features, which may be easily obtained in a routine clinical examination, as detailed below.

5.5 Pathophysiology of Fibromyalgia Comorbidity

The common mechanism concurring in migraine, tension-type headache, and fibromyalgia is a dysfunction of pain modulation with enhanced expression of central sensitization symptoms [24, 25].

Sensitization is a physiological phenomenon of the sensory system, which supports a progressive amplification of sensory neuron activation under repetitive stimulation, favoring the development of memory against potentially dangerous events by neuroplastic changes enabling a prompt defensive response. This phenomenon develops at both peripheral and central levels, given that increased excitability occurs in single neurons and at synaptic level. In neuropathic pain, where a lesion occurs at peripheral or central level [26], increased excitability of sensory neurons has a compensatory function and is determined as soon as the neuronal tissue is damaged. The natural evolution of any kind of persisting noxious stimulation leads to the progressive increase in sensory sensitization, contrasted by the modulation of the descending control, which is very complex and finalized to the adaptation of the subjective sufferance to the general context, cognitive and emotional status, and cultural trends [27]. In addition, brain structural or functional changes may influence the outcome of the descending modulation [27]. Allodynia, which determines an innocuous tactile and mechanoreceptive stimulus to be perceived as painful, is a clinical sign of central sensitization, indicating a change in the function of second-order wide-range sensory neurons in spinal cord and trigeminal nucleus. This symptom is present in both migraine and FM. Since many years, studies by Burstein group [28] ascertained an early development of allodynia during migraine attack, causing the skin and muscles to become painful in the pericranial and even somatic level. The spreading of pain outside the pericranial sites indicates sensitization at third-order thalamic-sensory neuron level [29]. In tension-type headache, pericranial tenderness is initially subtended by different causes, as postural problems, but symptoms persist for a central dysmodulation, which does not inhibit but rather enhances primary and secondary nociceptive neurons firing and the consequent muscular activation [30]. So far, allodynia and pericranial tenderness are symptoms of central sensitization which can predispose primary headache patients to diffuse somatic pain. In fact, in FM, pain at tender points is evoked by an innocuous mechanic stimulation and is provoked by sensitization of second-order nociceptive neurons in the spinal cord [25]. Migraine and FM are characterized by a predisposition to central sensitization as suggested by neurophysiological evidence. In fact, habituation of the sensory system, which is a physiological phenomenon occurring during repetitive stimulation to contrast the progressive increase of neuronal activation, is lacking in both migraine and FM syndrome, with special regard to nociceptive input processing [6, 31, 32]. New evidence about an involvement of the peripheral nervous system in the pathogenesis of pain in FM is opening a new scenario on this very complex syndrome and associated conditions. Skin biopsy findings suggested a dysfunction of small myelinated and unmyelinated afferents, which may be a phenotypical feature peculiar for FM [33, 34].

A neuronal dysfunction at both central and peripheral level in FM may thus be idiopathic and probably genetically determined. Complex and largely unexplored genetic disorders involving ionic channels may support both central dysfunction with associated clinical conditions as migraine and peripheral nerve involvement with a peculiar clinical phenotype of small fiber neuropathy [33, 34].

5.6 Possible Therapeutic Approach to Migraine and Tension-Type Headache Patients with FM Comorbidity

In migraine and tension-type headache patients, a correct symptomatic treatment may contribute to a reduction of the intensity and duration of the single episode, slowing the development of central sensitization. However, no study is available about the best symptomatic approach to prevent central sensitization. In migraine attacks, triptans may exert a modulation of 5HT receptors at the level of the peripheral trigeminal afferents, with a modulation of nociceptive inputs at central level [35]. Also the calcitonin gene-related peptide (CGRP), which is a neurotransmitter involved in sterile inflammation and trigeminal activation during migraine attack, is specifically inhibited by triptans [36]. However, no evidence is available regarding a possible protective effect of triptans on the development of central sensitization and its possible persistence outside the migraine attack. The timely interruption of a migraine attack may stop the evolution of central sensitization, so triptans may be the best choice, provided their early assumption. Few studies are available on the association between FM comorbidity and analgesic overuse, which contributes to the development of chronic migraine. Medication overuse was observed in only 8 % of 76 FM patients with migraine [20], but there is no sufficient evidence about the risk connected to an early symptomatic treatment in favoring drug abuse and headache worsening in patients with diffuse somatic pain. In regard to preventive treatment for migraine and tension-type headache, in patients with associated symptoms of FM, amitriptyline is the sole drug indicated in all of these conditions [24]. Duloxetine and pregabalin, used for FM, have limited evidence of efficacy in migraine and tension-type headache [5, 37], as well as topiramate, flunarizine, sodium valproate, and beta-blockers in FM [5]. Botulin toxin is a treatment of proven efficacy for chronic migraine [38] and symptoms of central sensitization [39]. Despite the lack of studies assessing the effects on associated FM, evidence of efficacy in FM is scarce. Cannabinoids may be a new opportunity for chronic migraine and FM, although recent meta-analyses indicated insufficient evidence of efficacy for management of chronic diffuse musculoskeletal pain [40] and migraine [41], even though the treatment is promising and worth confirmation and further evaluation. Transcranial magnetic and direct electric modulation of motor cortex have shown efficacy in FM, with a possibility to obtain long-lasting plastic changes of the nociceptive cortex [42–44]. Modulation of DLPF also seemed efficacious in controlling pain in FM patients [45, 46]. rTMS and TDCS efficacy was less studied in migraine [46–48], but interest in these non-pharmacological approaches is increasing [49]. An integrated and

individualized non-pharmacological approach is recommended in chronic headaches sharing FM. In FM, physical exercise and cognitive-behavioral therapy are first-line treatments, showing a high level of evidence [50]. Evidence is also growing in regard to a beneficial effect in chronic migraine [51].

In the treatment of migraine patients with associated FM, tai chi, yoga, meditation and mindfulness-based interventions, hypnosis or guided imagery, electromyogram biofeedback, and balneotherapy/hydrotherapy may be a choice also for diffuse pain, while qigong, acupuncture, chiropractic interventions, and electroencephalogram (EEG) biofeedback have shown low efficacy in FM [52].

5.7 Final Remarks

Fibromyalgia seems to be a relevant aspect in many patients suffering from primary headaches, potentially associated with increased invalidity. The standard clinical assessment of FM, according to the most recent criteria [3], together with the evaluation of pain at tender points [1], seems easy to perform and not significantly time consuming and useful in detecting complex patients, to be managed through an integrated therapeutic approach. Features of anxiety and depression as well as sleep disorders, allodynia, and pericranial tenderness are important factors predisposing to symptoms of diffuse pain, which can be evaluated in headache centers by standardized clinical scales [14]. Clinical assessment of the association between primary headaches, with special regard to migraine, and fibromyalgia, could also open up a new scenario on the genetic and environmental factors predisposing to these invalidating but still largely unexplained diseases.

Conflict of Interest The authors declare no conflict of interest.

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Chapter 6
Sleep Disorders Comorbidity

Oliviero Bruni, Claudia Dosi, and Teresa Paiva

Abstract The common structural and neurotransmitter pathways between headache and sleep accounted for the strict comorbidities between these two conditions, since it is mediated by the structural co-alteration of serotonergic and dopaminergic pathways that affect migraine and sleep.

Both an excess or a lack of sleep could be trigger for a migraine or headache attack, but also sleep could be a relieving factor for headache. Therefore, the link between sleep and headache or migraine is complex and could not be simply explained by the common neurotransmitters alterations. Different comorbid sleep disorders, like insomnia, parasomnias (sleepwalking, sleep terrors, enuresis), restless legs syndrome, periodic limb movements, and narcolepsy, could have distinctive pathogenetic causes. Alteration of sleep architecture, sleep fragmentation or hypoxia linked to sleep apnea are common recognized factors affecting headache or migraine. Often the treatment of a sleep disorder could resolve or improve headache and on the other hand the drugs used for migraine/headache prophylaxis could improve sleep.

Keywords Headache • Migraine • Sleep disorders • Parasomnias • Restless legs syndrome • Periodic limb movements • Sleep apnea • Narcolepsy • Colic

O. Bruni, MD (✉)
Department of Developmental and Social Psychology, Sapienza University,
Via dei Marsi 78, Rome 00185, Italy
e-mail: oliviero.bruni@uniroma1.it

C. Dosi, MD
IRCCS Stella Maris, Scientific Institute of Child Neurology and Psychiatry,
Calambrone, PI, Italy
e-mail: dosiclaudia@gmail.com

T. Paiva, MD
CENC, Sleep Medicine Center, Lisbon, Portugal
e-mail: teresapaiva0@gmail.com

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6.1 Introduction

Narcolepsy, restless legs syndrome, and sleep deprivation are the sleep pathologies considered among the recognized comorbidities of migraine [21, 150].

Depression and other psychiatric disorders together with pain disorders and stressful life events considered as headache comorbidities [133] are also risk factors or comorbidities for chronic sleep disorders.

Therefore the aim of this chapter is to stress the relevance of sleep in the framework of headache comorbidities.

Sleep represents the only well-documented behavioral state related to the occurrence of some headache syndromes, while headache may cause various degrees of sleep disruption. Different studies have shown a strong association between sleep and headache, which are related in a complex and not well-understood fashion [136].

Clinical observations and experimental data suggest that sleep and headache share common anatomical, physiological, and biochemical substrates.

An excess or lack of sleep [42, 70, 130], a bad quality and inadequate duration, can induce headache. Headache can be the result of abnormal sleep events, such as hypoxia or hypercapnia secondary to obstructive sleep apnea [3].

Headaches are known to occur during sleep, after sleep, and in relationship with various sleep stages [36, 117].

Many chronic headache patients, whatever their type, complain of insufficient and nonrestorative sleep, while sleep is effective in the relief the head pain [11, 46] probably through an autonomic reset [40].

Sleep disorders have been correlated with multiple diseases, but only few of them are linked by neuroanatomical and pathophysiological substrates. Headaches are the most frequent complaint showing this link with sleep disorders [44, 48].

Therefore, sleep disturbance and headache might represent the manifestations of a common underlying pathogenesis leading to migraine symptoms and sleep disturbances [106]. However, the findings are often controversial, and some of the relationships still remain unclear [40, 93, 108].

A model of interaction between headache and sleep has been proposed combining clinical data and experimental evidence [130]. Table 6.1 summarizes available data.

6.2 Pathophysiological Aspects

The pathophysiological links between headache and sleep can be defined and organized in the following aspects:

1. They share common anatomical pathways.
2. Their mechanisms depend on the same neurotransmitters.

Table 6.1 Relations between sleep and headache

Sleep
Trigger factor for headache (excessive, reduced or disrupted, increased deep sleep)
Relieving factor for headache
Cause of headache (e.g., sleep apnea)
Headache
Cause of sleep disruption (e.g., attacks occurring during sleep)
Comorbidity with sleep disorders (parasomnias, restless legs syndrome)
Headache/sleep association
Intrinsic origin (modulation through the same neurotransmitters)
Extrinsic origin (i.e., fibromyalgia syndrome)
Reinforcement (bad sleep hygiene)
Sleep related headache (during or after sleep)
Sleep stage relationship: REM sleep (migraine, cluster); slow-wave sleep (migraine)
Headache/sleep comorbidities
Insomnia
Restless legs syndrome and PLMS
Parasomnias
Narcolepsy
Sleep deprivation
Sleep habits

3. There are common genetic mechanisms.
4. They share chronobiological patterns and dysfunctions.
5. They may be caused by the same behavioral dysfunctions.
6. Early life alterations of sleep can induce headache latter in life.
7. Sleep is a headache trigger.
8. They have a bidirectional impact.
9. Several headache disorders have specific links with sleep dysfunctions.

6.2.1 Common Anatomical Pathways

The structural pathways involve the trigeminal nucleus caudalis in the pons and midbrain and the hypothalamus (emergence and spreading of the head pain), the hypothalamus with its connection to the pineal gland, the noradrenergic locus coeruleus, the antinociceptive system represented by the rostral ventromedial medulla oblongata, the serotonergic raphe nuclei, the noradrenergic locus coeruleus, and the periaqueductal gray (PAG) matter. All these structures are involved in the control of the sleep–wake cycle and in the modulation of pain through the action of the serotonergic and dopaminergic systems [41, 51, 124, 156].

6.2.2 Shared Neurotransmitters

The serotonergic system, in particular, might play an important role in the relationship between headache and sleep.

Serotonergic modulation of the sleep–wake cycle takes place through a multitude of postsynaptic receptors which mediate different or even opposite responses, such as facilitating sleep and inhibiting REM sleep; on the other hand, serotonin is important to the maintenance of behavioral sleep, which again depends on the complex interaction between the serotonergic and other neurotransmitter systems [125].

The direct role of the dopaminergic system in migraine pathogenesis has been linked to a dopaminergic receptor hypersensitivity or a dopaminergic imbalance that could account for increase of awakenings and wake during sleep and/or could lead to a decrease in activity and cortical activation [116]. In fact, individuals susceptible to migraine appear either to have genetic polymorphisms in the dopamine D2 gene, which increases responsiveness to dopamine, or to have defects in tyrosine hydroxylase, which inhibits dopamine metabolism. An imbalance of the dopaminergic system is responsible for some premonitory symptoms of migraine, such as nausea, yawning, and dizziness [96, 125].

Dopamine is also quite relevant in sleep: it is involved in several sleep disorders such as restless legs syndrome (RLS) and periodic leg movements of sleep (PLMS). Parkinson patients have important sleep dysfunctions and daytime sleepiness. Dopamine is involved in the circadian system by acting upon the pineal gland, and sleep deprivation in normal subjects increases dopamine levels in the brain.

6.2.3 Genetic Mechanism

Genetic association has been described between RLS and migraine, which seems to exhibit a polygenic inheritance pattern and at least seven genetic loci have been linked to RLS [21]. Such joint genetic origin is attributed to chromosome 14q21 [129]. In fact, there are occasional pedigrees in which RLS and migraine appear to co-segregate over several generations [87, 141].

6.2.4 Chronobiological Mechanisms

Several findings suggested a role for chronobiological factors in migraine, probably related to a hypothalamic involvement [42]. Clinical observations showed that migraine attacks have a seasonal, menstrual, and circadian timing, suggesting a role of chronobiological mechanisms and their alterations in the disease [5, 137]. It has been shown that migraine attacks exhibited a circadian periodicity with a peak during the first hours of waking (between 4 and 9 AM), a menstrual periodicity with a

peak after the onset of menses, and a weak seasonal periodicity with a mild over-representation during the summer months [56].

Furthermore, migraine patients are more frequently morning- and evening-type subjects than controls [62].

Several studies have shown a decrease in melatonin levels in subjects with migraine and cluster headache and a positive response to its therapeutic use in migraine, cluster, and hypnic headache [1, 14, 22, 28, 31, 32, 89, 90, 98, 101, 102, 113–115, 128, 148, 149, 154].

Peres [115] studied the plasma melatonin nocturnal profile: lower melatonin levels were observed in migraineurs with insomnia when compared with those without insomnia, together with a phase delay in the melatonin peak suggesting a chronobiological dysfunction in insomniac chronic migraineurs.

6.2.5 Induced by Common Behavioral Dysfunctions

Sleep hygiene has been defined as the conditions and practices that promote continuous and effective sleep: these include regularity of bedtime and arise time; conformity of time spent in bed to the time necessary sustained and individually adequate sleep, restriction of beverages, foods, and compounds (which tend to disrupt sleep) before bedtime; and regular exercise, nutrition, and environmental factors so that they enhance, not disturb, restful sleep [105].

In the first study published on sleep hygiene in adolescents with migraine, Bruni et al. [16] instructed 35 children and adolescents to follow directions to improve sleep hygiene, and the patients showed a significant decrease in the mean duration and frequency of migraine attacks, while the severity of the attacks did not change.

In adolescents, headaches are significantly related with sleep deprivation [107], sleep habits, and sleep disorders [17, 49, 50, 109].

The application of sleep hygiene guidelines could represent an alternative approach to the treatment of migraine by correcting an inappropriate sleep behavior, without recurring to pharmacological treatment. Melatonin in migraine might act also as a chronobiotic agent through a sleep hygiene effect [12].

On the other hand, excessive working hours, disruptive work schedules, daily stress, and stressful life events can provoke both headaches and sleep complaints, mainly insomnia.

6.2.6 Early Life Dysfunctions

A structural alteration of neurotransmitter pathways (serotonergic and dopaminergic) might act since the early period of life, predisposing to disorders of the sleep–wake rhythm in infancy and to the development of a headache disorder, as a result of this neurotransmitter imbalance.

Early-onset sleep disorders have been found to be predictive of headache persistence from infancy to childhood: they were reported in 78 % of children with enduring headache vs. 25 % of children showing headache remission [64].

6.2.7 Sleep as a Headache Trigger

Different studies in adults showed that lack of sleep was a most common factor to trigger headache together with emotional stress, physical strain, and particular foods [52].

An epidemiological study on 385 migraineurs and 313 non-migraine headache sufferers demonstrated that the most frequent precipitating factors were fatigue, sleep, stress, food and/or drinks, menstruation, heat/cold/weather, and infections in both groups. Sleep problems, rather than provoking migraine, can be premonitory symptoms similar to mood changes, food cravings, or surges of energy, which can occur many hours before the migraine attack [26].

6.2.8 Bidirectional Impact

The most frequent complaints of headache adult patients are represented by fatigue, tiredness, or sleepiness associated with insomnia [76].

Headache sufferers reported bad sleep more frequently than controls [33] and slept significantly shorter (6.7 h vs. 7.0 h); it took them longer to fall asleep (31.4 versus 21.1 min) and longer to fall back asleep after waking up at night (28.5 versus 14.6 min) [138].

More difficulty at sleep onset, more awakenings, more nocturnal symptoms (hypnagogic startles, restless legs syndrome, pain, respiratory problems, sweating, bruxism), and more awakening symptoms such as non-refreshing sleep, fatigue, paralysis, and daytime somnolence were reported in 75 adult chronic headache patients compared to 50 healthy controls [108].

In a recent study, 28,828 US citizens were scanned for severe headaches and sleep disturbances. Approximately 15.1 % of adults aged 18 years or older reported severe headaches in the past 3 months. Those reporting severe headaches were significantly more likely to have insomnia, excessive sleepiness, recurrent pain, and depression or anxiety symptoms during the preceding 12 months. Approximately 88 % of those with severe headaches also had at least one comorbid medical condition, compared to 67 % of those without severe headaches [140].

Headache also impacts upon sleep: Cluster headache patients and those with hypnic and sleep-related headaches may try not to fall asleep in order to prevent their headaches.

6.2.9 Headaches and Sleep Disorders

6.2.9.1 Insomnia and Headache

Insomnia is a common complaint, and like most headaches, it is more frequent in women. Different recent studies highlighted the strict relation between headache and insomnia. In a study of 50 insomniacs, 24 subjects (48 %) also complained of headache, mostly migraine without aura (37.5 %) or episodic tension-type headache (50 %) [3], but only 10 % had headache upon awakening.

A national survey in the United States recruited 5484 adults; it showed a significant association between frequent and severe headache, including migraine with and without aura, and insomnia, without differences between specific headache subtypes. Adults with headache were more likely than those without headache to report at least one of four insomnia symptoms: difficulty initiating sleep, maintaining sleep, waking up early, and daytime fatigue. Subjects with headache were more than twice as likely to report three or more of these symptoms than those without headache (1.83 % vs. 0.60 %; OR 2.5; CI 2.0–3.1) [88].

A Chinese study showed that the prevalence of DSM-IV insomnia was higher in women with headache than in those without headache (19.9 % vs. 5.3 %; $p < 0.01$). After adjusting for age and menopausal status, women with migraine, tension-type headache, and unspecified headache were significantly more likely than women without headache to report insomnia symptoms of difficulty in initiating and maintaining sleep and waking up early. Women with insomnia had a 4.0-fold increased risk of having headache at least once per week: in particular, a 3.2-fold increased risk of migraine, a 2.3-fold increased risk of tension-type headache, and a 2.2-fold increased risk of headache in general [152].

A population study in Norway showed that subjects with insomnia were significantly more likely, compared to those without insomnia, to suffer from headache in general (17.6 % vs. 11.8 %; OR 1.68; CI 1.58–1.79, $p < 0.001$) and migraine (16.8 % vs. 13.3 %; OR 1.41; CI 1.29–1.55, $p < 0.001$) [73].

A follow-up of the same study reported that, after adjusting for age, gender, and sleep medication, insomnia among headache-free subjects at baseline was associated with a significantly increased risk of headache 11 years later ($p < 0.001$). There was also a significant association between insomnia at baseline and headache frequency at follow-up, specifically for migraine ($p = 0.02$) and tension-type headache ($p < 0.001$) [104].

It is evident that headache and migraine are associated with insomnia, while only severe insomnia is associated with headache or migraine. In addition, it was found that insomnia is a risk factor for headache or migraine onset and for increased headache frequency, specifically for tension headache and migraine.

As insomnia appears to be a risk factor for headache or migraine onset, insomnia patients should probably be routinely evaluated for headache, and, on the other hand, tension headache and migraine patients should probably be routinely treated for insomnia, if present, as part of their overall management [142].

6.2.9.2 Snoring and Obstructive Sleep Apnea Syndrome (OSAS)

There is evidence that sleep-disordered breathing is associated with headaches. Self-reported snoring has been associated with morning and daytime headache [27, 103, 132, 144], and habitual snoring was more frequent in patients with chronic daily headaches (24 %) vs. controls (14 %) [131].

The prevalence of headache in a population of patients with OSAS has been evaluated by different authors [4, 13, 61, 63, 75, 103, 119, 131, 144] and ranged from 32.9 to 58.5 %. However, when evaluating in a headache clinic, the prevalence of OSAS was not different from that in the general population [77].

Guilleminault et al. [65] reported a 36 % incidence of morning headaches in 50 patients with sleep apnea. Dexter [37] reported 11 patients with chronic recurring headaches with a history suggestive of sleep apnea that was confirmed polysomnographically: ten of these patients had sleep apnea and one had mixed sleep apnea. Mathew et al. [97] also reported headache in patients with sleep apnea: 3 out of 18 patients with chronic headaches and 1 out of 4 patients with cluster headache had sleep apnea. Kudrow et al. [86] found a 60 % prevalence of sleep apnea among ten patients with cluster headaches: four of these patients had central apneas and two obstructive apneas.

The clinical presentation is a morning tension-type headache, mainly frontal, frontotemporal, or temporal (38.9 %) in location, tightening or pressing (78.9 %), and mild to moderate (84.2 %) [3]. Chronic headache was seven times more common among subjects with OSAS than in the general population, and treatment of sleep apnea (nCPAP) leads to headache improvement [47].

Several reports showed that migraine attacks in sleep apnea patients occur usually during nighttime or early morning [4, 13, 65]. Subjects with obstructive sleep apnea and other sleep disorders evaluated in a sleep laboratory had a higher headache frequency, mostly morning headaches, compared with healthy subjects [61].

In a population-based cohort study, the authors evaluated the effects of sleep-related breathing disorders (SBDs) on migraine development in patients aged 20 years or more and diagnosed with SBD. The cumulative incidence of migraine was significantly higher in the SBD cohort than in the control cohort. The risk of developing migraine was higher in men than in women with SBD; moreover, the incidence of migraine was higher in patients aged 20–44 years and 45–64 years. The findings indicated increased risk of developing migraine in adults, but not elderly, with SBD [66].

Jensen et al. [77] assessed the frequency of OSA in a population of headache patients. Seventy-five of 903 headache patients reported heavy snoring and episodes of interrupted nocturnal breathing (8 %). Among 43 patients examined with polysomnography (PSG), 14 (1.5 % of the total study population) had an apnea/hypopnea index (AHI) of 5/h or higher. Eleven of the patients reported morning headache. They concluded that OSA's prevalence is not higher than what is reported for the general population but that chronic daily headache appeared to be more frequent in patients with OSA. Idiman et al. [69] did not find a statistically significant relationship between headache and AHI or minimal oxygen saturation. Kallweit et al. [78]

reported that 11 (10.3 %, 8 % male) of 107 consecutive patients with OSA fulfilled diagnostic criteria for migraine (migraine with aura [MA] in four, migraine without aura [MO] in six, and CM in one). They did not find significant differences between patients with or without migraine. After 1 year, however, continuous positive airway pressure (CPAP) treatment was effective for sleep apnea, sleep quality, and migraine. Kristiansen et al. [85] concluded that migraine and OSA are unrelated in the general population. They investigated the relationship between migraine and OSA in a random age- and gender-stratified sample of 40,000 persons aged 20–80 years. Three hundred and seventy-six subjects with high risk and 157 with low risk of sleep apnea aged 30–65 years were identified based on screening questionnaires. They underwent clinical evaluation, a structured headache interview, and PSG. No relationship was found between MO or MA and OSA. This was true for moderate and severe OSA. Greenough et al. [63] found no relationship between the duration of nocturnal hypoxemia and headache complaints in patients with OSA.

Few data are available on the relationship between sleep apnea and migraine in children. Guilleminault et al. first reported that 18 of 50 OSA patients suffered from frontal or diffuse morning headache; afterward, several other reports supported this important relationship [65, 110].

A varied range of symptoms and signs are associated with OSAS in the pediatric population. In children and adolescents with OSAS, the most common clinical manifestation reported is snoring but also obesity, excessive daytime sleepiness, heavy habitual snoring, and neuropsychological disturbances [103]. Morning headaches and poor appetite may also present in OSAS, particularly in school-aged children, and it is one of the Diagnostic Criteria of Pediatric Obstructive Sleep Apnea by the American Academy of Sleep Medicine which may be due to carbon dioxide retention, sleep fragmentation, or gastroesophageal reflux [71].

A polysomnographic study in children with headaches indicated that sleep-disordered breathing was more frequent among children with migraine (56.6 %) and nonspecific headache (54 %) vs. chronic migraine (27 %) [44].

In synthesis, the prevalence of headaches is higher in OSA patients. The data concerning the higher prevalence of OSAS in migraine patients are controversial and point to an inexistent impact upon prevalence.

The association between headache and OSAS is probably based on a combination of factors: hypercarbia, hypoxemia, altered cerebral blood flow, increased intracranial pressure, alterations in sympathetic nerve activity and increases in blood pressure secondary to multiple arousals, and brainstem dysfunction. However, it has been hypothesized that migraine attacks could be secondary to sleep disruption rather than to sleep apnea by itself [142].

These findings revealed a strong relationship between migraine and sleep-disordered breathing, while chronic migraine was associated with more disrupted sleep and tension-type headache with bruxism. It is hypothesized that sleep-disordered breathing may predispose patients to sleep fragmentation, which in turn may exacerbate or aggravate preexisting signs of migraine, because sleep deprivation is known to trigger or worsen migraine attacks [40].

6.2.9.3 Restless Legs Syndrome

Restless legs syndrome (RLS) is commonly represented by an urge to move the legs, accompanied by unpleasant leg sensations, occurring at night, worsened by rest, and improved by movements [155].

There is evidence that restless legs syndrome (RLS) is another condition frequently reported by migraine patients [21]. RLS prevalence in migraine ranged from 8.7 to 39.0 % with no apparent differences based on gender and aura status, while migraine prevalence in RLS ranged from 15.1 to 62.6 % [54].

The first study suggesting an association between RLS and migraine in the pediatric population was conducted by Seidel et al. [134] and assessed the frequency of RLS in children and adolescents with migraine compared to headache-free controls. The authors included two control groups. The first group was recruited from an outpatient clinic of pediatrics and adolescent medicine (group 1). These children and adolescents were exclusively screened at follow-up after recovery from a minor illness and did not suffer from a significant medical, neurological, or psychiatric condition at the time they were included in this study. The second control group was recruited from primary school (group 2); the aim of the study and the objects of the questionnaires were explained to the children and teachers.

In 111 consecutive patients with a sole diagnosis of migraine with or without aura and 73 headache-free controls, the frequency of RLS in migraine patients was significantly higher (22 % vs. 5 % [$p < 0.001$] group 1 and 8 % [$p < 0.001$] group 2 [134]).

A common pathophysiological origin for migraine and RLS has been proposed [21], and a link involving a disturbance of iron metabolism has been considered. A recent study investigated daytime dysfunction in children with RLS and the effects of treatment primarily with iron supplements on RLS symptoms and daytime dysfunction in 25 children with RLS showing that after treatment, participants' daytime function had improved to levels similar to those of controls. Sixteen out of 23 cases were successfully treated primarily with iron supplement [57].

A link between RLS and a dysfunction within the dopaminergic system has also been suggested [21, 54, 155]. It is supported by the rapid improvement of RLS symptoms after treatment with dopaminergic agents. Dopamine is also involved in migraine pathophysiology. Dopaminergic symptoms (DPS) like yawning, irritability, and mood changes as well as nausea and vomiting occurring both during the premonitory and headache phases are present in 47.6 % migraine patients with RLS vs.13.1 % of those without RLS ($p < 0.001$). A further support to a "dopaminergic link" between migraine and RLS is the observation that antiemetics with antidopaminergic properties are effective in aborting migraine attacks [21].

The prevalence of both RLS and periodic limb movements in sleep (PLMS) increases with age. Complaints of morning or daytime headaches are three to five times more frequent in patients with RLS [145]. Fifty patients with severe headaches who qualified for the treatment with dopamine receptor-blocking agents had a prevalence of RLS of 34 %; this group had a higher risk of developing akathisia as a treatment side effect.

A recent study [146] investigated the prevalence, severity, and correlation between sleep quality and RLS in a large population of migraine patients and non-migraine controls as poor sleep presumably triggers migraine attacks. Restless legs syndrome prevalence in migraine was higher than in controls (16.9 % vs. 8.7 %; multivariable-adjusted odds ratio 1.83; 95 % confidence interval 1.18–2.86; $p = 0.008$) and more severe (adjusted severity score 14.5 ± 0.5 vs. 12.0 ± 1.1; $p = 0.036$). Moreover, poorer sleep quality was independently associated with RLS occurrence and RLS severity in migraine patients.

The hypotheses to explain the coexistence of RLS and migraine are based on a common genetic basis and brain structures involved (like the A11 dopaminergic nucleus of the dorsal posterior hypothalamus that lays a crucial role in RLS and trigeminovascular nociception). Furthermore, cerebral dopamine imbalance and altered iron metabolism were implicated; in fact, dopamine antagonists are effective in migraine attacks, and usually iron deficiency is associated with an increase in extracellular dopamine levels and in the changes in dopamine levels with circadian rhythm that could explain the appearance of RLS symptoms at night and the relationship with migraine because of a dopaminergic hyperfunction reached during the day after lower trough levels [96]. On the other hand, sleep deprivation or sleep instabilities caused by RLS could trigger migraine [54].

6.2.9.4 Periodic Limb Movements

There are only two case reports on increased periodic limb movements in adult headache patients: the first was a patient with hypnic headache syndrome [84] and the second was the case of a man with episodic cluster headache who suffered from severe obstructive sleep apnea and periodic limb movements during sleep [112].

To our knowledge, only one study investigated the presence of periodic limb movements in children with migraine [49]. The questionnaire survey showed that migraine children had a higher frequency of difficulty in falling asleep, non-rapid eye movement sleep parasomnias, and sleep-related movement disorders compared with the control group. In the migraine children group, the individuals with PLM pathological index ($PLMI \geq 5$) represent the 26.47 % of the sample and present higher frequency ($p < 0.001$), intensity ($p < 0.001$), duration ($p = 0.006$), and life impairment as scored in the PedMIDAS ($p < 0.001$) of headache and lower efficacy of prophylactic ($p = 0.001$) and acute ($p = 0.006$) pharmacological treatment than migraine children without PLM pathological index. These findings suggest that PLMS might influence the clinical presentation of migraine, increasing its severity, frequency, and all disabling aspects and also affecting treatment efficacy.

6.2.9.5 Narcolepsy

Narcolepsy is a rare neurological condition characterized by persistent, excessive daytime sleepiness, and generally it is underdiagnosed causing serious problems in patients.

Narcolepsy is considered as a comorbidity of migraine [150], but the association between narcolepsy and migraine is a matter of debate. The German Migraine and Headache Society Study Group [83] reported a similar prevalence of migraine in narcoleptics (21.9 %) and controls (19.8 %).

In this case control study of 96 narcoleptic patients, headache fulfilling the criteria for tension-type headache was significantly more often reported by narcolepsy patients than by the control group (60.3 % vs. 40.7 %) [83].

In another study, migraine prevalence had twofold to fourfold increase in the narcoleptic patients and amounted to 44.4 % in women and 28.3 % in men [34]. The onset of narcolepsy symptoms was 12.3 years before the onset of migraine symptoms. The increased prevalence of migraine was not due to pharmacological treatment for narcolepsy and did not depend on the severity of the narcolepsy symptoms [34].

No studies are available on the prevalence of migraine in children and adolescents with narcolepsy; headache has often been reported as a side effect of treatment in children with narcolepsy.

The relations between narcolepsy and migraine could be mediated by the orexinergic neurons of the posterior hypothalamus that are involved both in inhibition of analgesia and in narcolepsy. Dysfunctional hypothalamic activity might contribute to both altered REM function and altered pain processing via orexinergic neurons [91, 114].

6.2.9.6 Nocturnal Enuresis

Several studies also demonstrated a significant relationship between migraine and nocturnal enuresis. A study highlighted a strong correlation between the clinical history of nocturnal enuresis and the diagnosis of migraine, hypothesizing that nocturnal enuresis is a precursor of migraine and a migraine comorbid condition [92].

The presence of enuresis in migraine children has been previously incidentally reported in earlier studies [6, 55].

Patients with episodic migraine (EM) or chronic migraine (CM) had significantly more often a history of nocturnal enuresis vs. the control group (CG.12 %, EM.41 %, CM.49 %). A common pathophysiological substrate in the hypothalamus could explain this comorbidity through the inhibition of vasopressin secretion that leads to increased urinary frequency during the attack of migraine [111]. Recently, Carotenuto et al. [23] proposed that nocturnal enuresis and migraine could be linked to a dysfunction of the arousal system with primary nocturnal enuresis being considered as a migraine equivalent.

6.3 Specific Sleep Disturbances in Children

Children who suffer from headache have usually a high rate of sleep difficulties, including insufficient sleep, cosleeping, difficulties in falling asleep, anxiety related to sleep, restless sleep, night waking, nightmares, and fatigue during the day [8, 15, 20,

67, 99]. Different surveys in large pediatric populations have confirmed the strong association between headache and different sleep disorders, such as parasomnias, insomnia, sleep breathing disorders, and daytime sleepiness [2, 8, 10, 15, 94, 99].

The first survey on a pediatric population involving 283 headache sufferers, aged 5.0–14.3 years, confirmed the strong association between headache and different sleep disorders [15]: 164 with migraine (141 without aura and 23 with aura) and 119 with tension-type headache (84 episodic tension-type headache and 35 chronic tension-type headache), compared to an age-matched healthy control group.

Sleep duration and sleep latency: migraine and tension-type headache children presented a shorter sleep duration and a sleep latency >30 min. They also showed a higher prevalence of difficulty to fall asleep and of fears or anxiety when falling asleep. Headache children had a more interrupted sleep, with more than two awakenings per night.

Parasomnias: Sleeptalking, bruxism, and frightening dreams were more common in children with migraine, as reported in adults, especially for bruxism [25, 53, 143]. A higher frequency of sleepwalking was found in migraine with aura (13.04 %) confirming data reported in children and adults [7, 59, 121].

Sleep breathing disorders were more frequent in subjects with migraine vs. controls, while tension-type headache failed to show differences, confirming data already reported in children and in adults [8, 123].

Morning symptoms and daytime sleepiness: both groups of subjects with migraine (35.4 %) and tension-type headache (30.3 %) presented more restless sleep than controls (19.7 %); daytime sleepiness affected both headache groups in a higher percentage with respect to controls (12.2 % in migraine; 10.9 % in tension-type; 4.5 % in controls) and represented a worsening factor for the quality of life.

Twenty out of 283 (7.77 %) subjects presented recurrent nocturnal headache attacks and reported more sleep disorders than patients with diurnal attacks. The occurrence of nocturnal headache attacks deeply modifies the sleep pattern and affects the occurrence of night symptoms, confirming the involvement of common pathways in the pathogenesis of both conditions.

An older study evaluating the efficacy of L-5-hydroxytriptophan in 48 children with headache had reported the association of primary headache with sleep disorders: night waking (41.7 %), difficulty in falling asleep (20.8 %), sleep terrors and nightmares (14.6 %), enuresis (8.3 %), and somnambulism (6.3 %) [35].

More recent studies confirmed that children with migraine have an increased prevalence of sleep disturbances, such as bedtime resistance, insufficient and interrupted sleep, sleep-disordered breathing, disorders of arousal, sweating during sleep, difficulty waking up in the morning, and daytime sleepiness [49, 50, 127, 135].

Another study showed that headache characteristics independently predicted sleep anxiety ($p < 0.05$), parasomnias ($p < 0.03$), bedtime resistance ($p < 0.03$), sleepwalking ($p < 0.03$), and bruxism ($p < 0.01$); more specifically, the frequency of migraine predicted parasomnias, while duration of migraine predicted sleep anxiety and bedtime resistance. In this study, again a high rate of sleep disturbances in children, sleeping too little (42 %), bruxism (29 %), cosleeping with parents (25 %), and snoring (23 %), has been reported [99].

Other authors demonstrated that migraine without aura is a risk factor for disorders of initiating and maintaining sleep and chronic tension-type headache for sleep breathing disorders and excessive somnolence [24].

Snoring, parasomnias, sweating during sleep, and daytime sleepiness were more common among children with migraine compared with non-migraine and no headache groups with the odds ratio ranging from 1.97 to 2.17 for habitual snoring and daytime sleepiness [72].

Not all studies were in complete agreement; a recent investigation confirmed the higher prevalence of excessive daytime sleepiness, narcolepsy, and insomnia in children with headaches but not of sleep apnea, restlessness, and parasomnias [94].

6.3.1 Colic

Excessive crying in an otherwise healthy infant is commonly recognized as infant colic, affecting about 5–19 % of the babies. This condition of inconsolable crying in the evening increases in the first weeks of life and tapers off generally by 3–4 months of age [95].

Colicky infants are considered to be candidates for sleep disorders, and some reports revealed an association between infantile colic and migraine [74, 79].

The prevalence of colics in children with migraine is higher than in the control population: Bruni et al. [15] reported a positive history of colic in 38.4 % of subjects with migraine, significantly higher than controls (26.9 %) and subjects with tensive headache (25.2 %). This was further supported by another study showing a positive history of colic in children with migraine (52 % vs. 20 % in controls) [127].

A recent study on 208 consecutive migraine children aged 6–18 years reported infantile colic in 72.6 % vs. 26.5 % of children without migraine [74]. On the other hand, children with tension-type headache (TTH) showed a similar nonsignificant prevalence (35 % vs. 26.5 %), confirming that only migraine is linked with colic.

Colic is a common cause of inconsolable crying and pain in childhood; these two symptoms, in some genetically predisposed infants, could represent a form of infantile migraine with age-specific expression [79].

A case report of a colicky infant with irritability, head slapping with the hands, upper eyelid retraction, and family history of migraine suggested that the excessive crying may have resulted from headache or represent an abdominal migraine variant [74]. This hypothesis has been corroborated by the improvement of colic after the start of migraine therapy (cyproheptadine).

A recent meta-analysis showed that infant colic was associated with increased odds of migraine (OR 5.6, 95 % CI 3.3–9.5) [58]. The ICHD-III in the appendix included infant colic among the episodic syndromes that may be associated with migraine. If infant colic is a childhood periodic syndrome or a migrainous phenomenon, colicky infants could have an increased sensitivity to stimuli due to shared migraine genes. Further, the presence in the evening could be explained by the circadian biology and the fact that colic resolves around age 3 months linked to the

mature pattern of rhythmic excretion of endogenous melatonin [82]. Alternatively, it is possible that the association between infant colic and migraine is due to a shared genetic predisposition to both disorders, rather than infant colic being an early life expression of migraine genetics per se [58].

6.4 Polysomnographic Studies in Headaches

Several polysomnographic studies analyzed the sleep organization in headache and did not find any peculiar characteristics of sleep architecture in the adult population except for the strict relationship of some particular subgroups with specific sleep stages: (a) migraine attacks seem to be linked to REM stages and are associated with a large amount of deep sleep [36, 38]; (b) cluster headache is triggered by REM and NREM sleep particularly stage II [117]; and (c) chronic paroxysmal hemicrania is associated with a reduction of total sleep time and of REM phase, with an increase of awakenings during REM [80].

Headache is the presenting symptom of several sleep disorders that could be therefore misdiagnosed; Paiva et al. [106] demonstrated that, in several cases of adult migraine, after a polysomnographic study, the diagnosis was changed in half of the patients, and the treatment of the underlying clinical condition improved greatly the headache symptom. Among the 25 patients, 13 were misdiagnosed as headache: after the polysomnographic study, the diagnosis was changed in periodic limb movement of sleep in four cases, in fibromyalgia syndrome in six cases, and in obstructive sleep apnea syndrome in three cases.

In adults with migraine, the polysomnographic recording in attack-free periods showed a normal sleep pattern and muscular (EMG) activity in spite of a clear increase in REM sleep duration and latency [45]. Adult migraineurs showed, the day before the crisis, a decreased number of arousals, lower REM density and alpha power, suggesting a decrease in cortical activation [60]. In line with these findings, a decreased EEG complexity was observed in the first two NREM cycles in patients with spontaneous nocturnal attacks [139]. On the other hand, patients with tension-type headaches had persistently poor sleep with reduced sleep efficiency and slow-wave sleep [45].

6.4.1 Migraine

The first polysomnographic study of patients with sleep-related headache showed that awakening-related migraine attacks were associated with REM sleep in all patients: six awakenings from REM sleep; one within 3 min of the completion of a REM period; and one on awakening 9 min following the termination of a REM period [36]. The prevalence of REM-related attacks could be linked to the chrono-biology of migraine since the peak time of attack onset (4–9 AM) is during the hours of REM maximal representation [56]. However, even in a different sleep schedule (7 h sleep shift), the attacks continued to occur during REM sleep (even if

during daytime) demonstrating that migraine was related to sleep rather than to circadian rhythms [39].

Some relationships with NREM sleep have also been found: headache-related awakening occurred from non-REM sleep in two out of three patients with nocturnal headache [30].

Since the reduction of total sleep time and depth of sleep through sleep-rationing was effective in preventing migraine attacks it could be expected that migraine is somewhat related with NREM slow wave sleep (SWS). Dexter [38] confirmed this hypothesis showing that the morning arousals with headache were associated with sleep periods which had large amounts of SWS and REM sleep.

To our knowledge, only one polysomnographic study has been published on children with headaches [147]. This study reported the analysis of polysomnographic findings of 90 children with migraine (60), chronic migraine (11), tension headache (6), and nonspecific headache (13). Sleep-disordered breathing was more frequent among children with migraine (56.6 %) and nonspecific headache (54 %) vs. chronic migraine (27 %). Tension headache was not associated with sleep-disordered breathing. Fifty percent of children with tension headache manifested bruxism vs. 2.4 % of children with non-tension headache. Severe migraine and chronic migraine were associated with shorter sleep time, longer sleep latency, and shorter rapid eye movement and slow-wave sleep.

This study supports the notion that the evaluation of headache in children and adolescents should include an assessment of sleep disturbances and a polysomnographic analysis to confirm certain treatable sleep disorders.

The evaluation of the whole sleep cycle in children and adolescents has also been carried out with actigraphic studies showing that children and adolescents with headache had a poorer sleep quality than controls, with excessive daytime sleepiness, less time spent in quiet motionless sleep, and waking significantly earlier in the morning [19]. A previous study showed that during the interictal period, sleep parameters of children suffering from migraine did not differ from those of controls, but in the night preceding the migraine attack, there was a decrease in nocturnal motor activity, indicating a decrease in cortical activation during the sleep period preceding migraine attacks [18].

6.4.2 Cluster Headache and Chronic Paroxysmal Hemicrania

The description of Wolfe [151] of cluster headache (CH) attacks during sleep, in which patients jump out of the bed before being fully awake, suggested that there was a concurrent presence of a disorder of arousal that preceded or was the consequence of the pain attack. The onset of the nocturnal attacks in cluster headache was either from REM sleep [36] or NREM sleep [117].

Recently, it has been hypothesized that CH could be triggered in some cases by sleep-disordered breathing (SBD) that predicted the occurrence of CH in the first half of the night [29]. Consequently, in most cases of cluster headache, the treatment of the sleep apnea either with surgical interventions or with continuous

positive airway pressure solved or greatly improved the head pain [153]. An old report showed efficacy of melatonin as prophylactic agent in CH [122].

Chronic paroxysmal hemicrania is characterized by frequent nocturnal arousals with pain that occurs mainly from REM sleep and by marked fragmentation of sleep with an excessive number of sleep-stage shifts, a reduction of total sleep time and of REM [80]. This fragmentation of sleep is similar to what is seen in chronic cluster headache.

6.4.3 Hypnic Headache Syndrome

First described by Raskin in 1988, this is a rare recurrent, benign headache disorder occurring exclusively during sleep and in older subjects [126]. The common symptom is regular awakening from nocturnal sleep caused by headache attacks lasting 30–60 min. Recent polysomnographic studies of this syndrome showed conflicting results with a more consistent association with REM sleep in three cases [43] and with stage 3NREM in one case [100].

6.5 Conclusions

Several researches showed the existence of common structural and neurotransmitter pathways between headache and sleep and demonstrated that the pathogenesis of this comorbidity is linked to a structural co-alteration of serotonergic and dopaminergic pathways that affect migraine and sleep.

In the last few years, several studies converged in demonstrating that the link between sleep, headache, and migraine is complex. Comorbidities include insomnia, parasomnias (sleepwalking, sleep terrors, enuresis), RLS, PLMS, narcolepsy, and sleep deprivation. All these sleep disorders together with sleep habits/sleep hygiene represent comorbid, predisposing, predictive, or even prognostic features. In young children, colic should be considered as a putative comorbid symptom of migraine.

It is important for the clinicians to perform the clinical evaluation of headache with a careful analysis of sleep habits and patterns and the evaluation of the presence of sleep disturbances to adequately treat these conditions.

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Chapter 7
Obesity and Headache

Cindy N. Chai, B. Lee Peterlin, Ann I. Scher, and Simona Sacco

Abstract Obesity and headache are both highly prevalent conditions associated with substantial personal and societal impact. Population studies have consistently identified an association between obesity and headache in general and specifically in migraine. Age and sex substantially modify this risk, with obese individuals <50 years of age and women having the greatest risk. While the causal relationship is not known, obesity and migraine share overlapping central and peripheral mechanisms that may contribute to this relationship. In addition, factors such as medications which modulate weight and lifestyle behaviors of migraineurs supply additional complexity to the obesity-migraine relationship. Currently there are no substantial data supporting a specific diet for overweight and obese migraineurs; and only limited research suggests bariatric surgery in obese episodic migraineurs that may be associated with reduced headache frequency and severity. Overall, clinicians treating migraine patients should take particular care in their choices of medications prescribed to their patients, given that many migraine drugs can modulate weight, and promote healthy lifestyle choices in regard to diet and exercise.

7.1 Introduction

Obesity and headache are both highly prevalent conditions associated with substantial personal and societal impact. In the current chapter, we first briefly review the epidemiology of common primary headache disorders and obesity, individually

C.N. Chai
Veterans Affairs Hospital, Interventional Pain Medicine, Fresno, CA, USA

B.L. Peterlin (✉)
Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: lpeterlin@jhmi.edu

A.I. Scher
Uniformed Services University, Bethesda, MD, USA

S. Sacco
Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, L'Aquila, Italy

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and in association. We then discuss potential mechanisms for this association, focusing on the central and peripheral pathophysiological pathways of migraine that overlap with the pathways driving feeding and the regulation of adiposity. We close by discussing treatment considerations for overweight and obese headache sufferers.

7.2 Epidemiology of Primary Headache Disorders

Headache in general is very common, with a global lifetime prevalence of 66 % (male 65 %, female 69 %) and 1-year prevalence of approximately 47 % (male 37 %, female 52 %) [95]. The most common primary headache disorder is tension-type headache (TTH), with a lifetime prevalence of approximately 46 % globally [95]. The 1-year prevalence of TTH overall has been estimated to be 38 % [95] and varies widely from less than 10 % to more than 80 % depending on the region studied [27, 33, 88, 95]. The 1-year incidence for TTH is between 14 and 44 per 1000 person-years [53, 62]. There is a female predilection for TTH, with a female to male ratio between 1.2:1 and 3:1 [27, 86].

Migraine, while less common than TTH in the general population, is the most common primary headache disorder presenting to a physician's office [98]. The lifetime prevalence of migraine is 14 % globally [95]. The 1-year prevalence of migraine is 12–15 % [61, 95]. Migraine incidence has been estimated between 3 and 18 cases per 1000 person-years [53, 62]. As with TTH, migraine is more common in women (17.6 %) than men (6.5 %) and in both sexes most common in those of reproductive age (between 20 and 50 years of age) [61, 95].

7.3 Epidemiology of Obesity

Obesity, a common condition worldwide, is associated with significant individual and societal burdens [20, 38, 39]. The World Health Organization (WHO) classifies obesity as having body fat percentage greater than 35 % in women and 25 % in men (physical status: the use and interpretation of anthropometry. Report of a WHO expert committee [81]). However, due to ease of use and cost-effectiveness, most epidemiologic studies use the body mass index (BMI) to establish the threshold for obesity. BMI is an estimate of obesity that is calculated based on an individual's height and weight. A BMI $\geq$30 kg/m^2 is classified as general or total body obesity (TBO) (Clinical guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health [24]) (see Tables 7.1a and 7.1b). In addition to BMI, body fat distribution has also been found to be an important predictor of health outcome; therefore abdominal obesity (abd-O), as estimated based on the waist circumference (WC), has also

Table 7.1a WHO BMI designations

Women and men			
Non-Asian populations	Asian populations[a]		
BMI < 18.5	BMI < 18.5	Underweight	
BMI 18.5–24.9	BMI 18.5–22.9	Normal weight	
BMI 25–29.9	BMI 23–24.9	Grade I obesity	Overweight
BMI 30–39.9	BMI 25–30	Grade II obesity	Severe overweight/obese
BMI ≥ 40	BMI ≥ 30	Grade III obesity	Morbid obesity

[a]In 2000 the World Health Organization, the International Association for the Study of Obesity, and the International Obesity Task Force recommended that the BMI value ≥23 represents overweight status and a BMI ≥25 represents obesity in Asian populations. In 2004 the World Health Organization identified potential public health action points for a BMI between 23.0 and 27.5 in Asian populations. However, formal recommendations for BMI cutoffs for obesity status were not made, and the WHO proposed that each country make decisions regarding BMI definitions at increased risk for its population

Table 7.1b WHO WC designations

Men		
WC < 94	Normal weight	
WC 94–102	Action level 1	Overweight
WC > 102 cm	Action level 2	Abdominal obesity
Women		
WC < 80	Normal weight	
WC 80–88	Action level 1	Overweight
WC > 88 cm	Action level 2	Abdominal obesity

emerged as an additional cost-effective method to estimate and study obesity in nonclinical populations [58, 71].

Globally approximately 13 % of adults aged 18 and older are obese (WHO Global Health Observatory (GHO) data [111]). In the United States, 35 % of women and 32 % of men have been estimated to have TBO [35]. In addition to sex, the prevalence of obesity, as well as its association with adverse health outcomes, varies by age and race. For example, while obesity is a risk factor for cardiovascular disease in younger individuals, the risk is attenuated or absent with advancing age [3, 5, 67, 103]. Further, as compared to Caucasians, Asians have greater and blacks have less body fat at the same BMI [82, 110]. Because of this, studies from China use different definitions and references for defining normal weight and obesity status which makes it challenging to compare the disease risk of obesity from different regions [23]. In 2000 the World Health Organization, the International Association for the Study of Obesity and the International Obesity Task Force recommended that the BMI value ≥23 represents overweight status and a BMI ≥25 represents obesity in Asian populations (*The Asia-Pacific Perspective*: *Redefining Obesity and Its Treatment* [4, 50]). Subsequently, in 2004 the World Health Organization identi-

fied potential public health action points for a BMI between 23.0 and 27.5 in Asian populations. However, formal recommendations for BMI cutoffs for obesity status were not made, and the WHO proposed that each country make decisions regarding BMI definitions at increased risk for its population [110].

Both TBO and abd-O are comorbid with a variety of medical disorders and are associated with worse disease outcomes [1, 18]. Specifically, as has migraine, obesity has been shown to be associated with several cardiovascular and cerebrovascular risk factors, including hypertension, insulin resistance, hyperlipidemia, and pain [8, 22, 70, 84].

7.4 The Epidemiological Association Between Obesity and Headache Disorders

A body of literature supports an association between headache and obesity. In the following sections, we first discuss the existing literature examining the association between obesity and headache in general. We then separately discuss the relationship between obesity and episodic migraine, chronic migraine, and TTH.

7.4.1 General Population Studies Evaluating Obesity and Headache in General

In 2003, Scher et al. conducted the first longitudinal general population study which established a relationship between obesity and headache [92]. Scher's study evaluated a cohort of obese and nonobese participants with episodic headaches (defined as 2–104 headaches/year, $n = 1134$, ages 18–65, 71 % women) as compared to those with chronic daily headaches (defined as 180 or more headaches/year, $n = 798$, ages 18–65, 80 % women) at baseline and again 11 months later. At baseline, obesity (sr-BMI ≥30) was 34 % more common in chronic daily headache (CDH) participants than those with episodic headache (OR 1.34, CI 1.0–1.8). Additionally, episodic headache participants with obesity were over five times more likely to transform into CDH at the 11-month follow-up visit than nonobese (sr-BMI <25) episodic headache participants (OR 5.28, CI 1.3–21.1) [92].

Subsequently, a cross-sectional analysis of 11 large general population databases (including National Health Interview Survey (NHIS), National Health Examination and Nutrition Survey, Alameda County Health Study (ACHS), Tecumseh Community Health Study (TCHS), and Women's Health Initiative (WHI)) that included over 200,000 women 16–90+ in age demonstrated that participants with obesity (BMI 30–39.9) had an approximately 35 % increased odds of reporting headache as compared to those women with BMI = 20. Those with morbid obesity (BMI ≥ 40) were associated with an approximately 80 % increase in the odds of reporting headache [52].

7.4.2 General Population Studies Evaluating Obesity and Migraine

The first cross-sectional general population study demonstrating an association between migraine and obesity was conducted by Brown et al. utilizing the Australian Longitudinal Study on Women's Health (ALSWH) database [17]. The ALSWH study included nearly 13,000 reproductive-aged women between 18 and 23 years and found that obese women (BMI > 30) had a 47 % (OR 1.47, 95 % CI 1.25–1.73) increased risk of having migraine or headache compared to woman of normal weight (BMI 25–29.9) [17].

Following the Brown et al. and Scher et al. studies [17, 92], Bigal et al. conducted a population-based cross-sectional analysis evaluating the relationship between obesity and episodic migraine (EM). Notably, the control group in this study included those with no headache, non-migraine headache, and possibly chronic daily headache (CDH). In this study ($n = 30{,}215$, ages 18–60+, 65 % women, obesity based on sr-BMI), those with increasing BMI were found to have increasing odds of high-frequency episodic migraine (defined as those with 10–14 headache days/month) compared to normal-weighted episodic migraineurs (BMI 30–34.9, OR 2.9, 95 % CI 1.9–4.4, BMI ≥ 35, OR 5.7, 95 % CI 3.6–8.8). However, those with obesity were not reported to be more likely to have lower frequencies of EM (i.e., ≤9 HA days/month) [10]. A second cross-sectional study by Bigal et al. in 2007 also supported an association between high-frequency EM and obesity [11].

Overall, the epidemiological literature has consistently demonstrated the importance of age and sex as modifiers of the obesity-migraine association, with data supporting the strongest association in those of predominantly reproductive age (<50–55 years; the age when migraine is most prevalent) [11, 17, 34, 79, 80, 85, 92, 108, 112, 116], [10], [78], [107] (Table 7.2), with an attenuated risk or no risk in older populations (50–55+ years) [52, 79, 80, 112, 114], [64], [113], [78] (Table 7.3). Specifically, the disease risk modification by age has been demonstrated in three separate general population cohorts (including the National Health and Nutrition Examination Survey [NHANES], the Nord-Trondelag Health Study in Norway [HUNT], and the National Comorbidity Survey Replication [NCS-R]). In the first of these studies from the NHANES ($n = 21{,}783$), men and women with migraine who were under the age of 55 showed an increase risk of migraine or severe headaches as compared to those who were nonobese (men: OR 1.38; CI 1.20–1.59; women: OR 1.39; CI 1.25–1.56). However in individuals older than 55, this risk was absent [78]. The second study to support a disease risk modification by age utilized the HUNT general population database ($n = 27.945$) [112]. Although age-specific cutoffs for the risk of migraine in those with obesity were not reported, the lead author (BW) was able to provide age-specific data upon request for a subsequent meta-analysis. Notably, after adjustments including age and sex, in those <50 the risk of migraine was increased by 35 % (OR 1.35, CI 1.18–1.55) in those with obesity as compared to those of normal weight; however in those 50 years or older, this risk was not present (OR 0.90, CI 0.728–1.12, data

Table 7.2 Epidemiologic studies on migraine and obesity in predominantly reproductive-aged subjects

Author (year) Study design (Database)	Population inclusion	Sex Race Mean age (range)	HA DX BMI Dx (SR vs M)	Findings
Brown (2000) [17] CS-GP (ALSWH)	Those with: 1. No HA/Mig 2. HA/Mig $n=12,855$ (HA/Mig 7229)	Women only Not reported 88.6 % Australian 20 (18–23)	Non-ICHD BMI: SR	The OR of HA or Mig was increased in those women who were overweight (BMI 25–29.9) or obese (BMI 30). (Overweight: OR 1.12, CI 1.00–1.25; obese: OR 1.47, CI 1.25–1.73)
Scher (2003) [92] Long-GP	Those with: 1. 2–104 HA/year 2. CDH: 180+ HA/year $n=1932$ (EH 798, CDH 1134)	Combined sexes White 73 % Nonwhite 25 % 40 (18–65)	Non-ICHD BMI: SR	1. The odds of CDH were increased in headache subjects (*EH + CDH*) who were overweight (BMI 25–29.9: OR 1.26; CI 1.0–1.7) or who were obese (BMI 30: OR 1.34; CI 1.0–1.8) 2. The odds of new-onset CDH was fivefold greater in those EH subjects who were obese (OR 5.28, CI 1.3–21.1) compared to normal-weighted subjects (sr-BMI 18.5–24.9)
Bigal (2006) [10] CS-GP (AMS)	Those with: 1. 14 or < non-migraine HA days/month 2. EM 3. CDH $n=30,215$ (EM, 3791)	Combined and stratified sex White 72 % Black 25 % 39 (18–89)	ICHD BMI: SR	The odds of low frequency EM (including those groups with <3 HA days/month and those with 3–9 HA days/month) were not increased in those with obesity versus those with normal weight The odds of high-frequency EM (i.e., 10–14 headache days/month) were increased in overweight (BMI 25–29.9: OR 1.3, CI 1.1–1.9), obese (BMI 30–35: OR 2.9, CI 1.9–4.4), and morbidly obese groups (BMI ≥35: OR 5.7, CI 3.6–8.8) compared to those with normal weight (BMI 18.5–24.9)

Table 7.2 (continued)

Author (year) Study design (Database)	Population inclusion	Sex Race Mean age (range)	HA DX BMI Dx (SR vs M)	Findings
Bigal (2007) [11] CS-GP (AMPP)	Those with: 1. EM and probable Mig 2. SETTH 3. Other EH 4. No HA (unknown if CDH was included or excluded) $n=162,576$ (EM, 18,968)	Combined and stratified sex White 87.5 % Black 6.2 % Others 3.4 % Unknown 3.0 % 40–49 (12–70+)	ICHD2 BMI: SR	The odds of high-frequency EM (i.e.,10–14 headache days/month) were increased in overweight (BMI 25–29.9: OR 1.15, CI 0.98, 1.13), obese (BMI 30: OR 1.3, CI 1.1, 1.5), and morbidly obese groups (OR 1.7, CI 1.4, 1.9) as compared to EM participants of normal weight (BMI 18.5–24.9)
Ford (2008) [34] CS-GP (NHANES)	Those with: 1. Severe HA or Mig 2. No severe HA or Mig $n=7601$ (EM, 1649)	Combined and stratified sex White 50 % Black 18 % Mex-Am 24 % 46 (20–85)	Non-ICHD BMI: M	The odds of migraine or severe headaches were increased in those with obesity (BMI $\geq$ 30) as compared to normal-weighted (BMI 18.5–25) episodic migraineurs (OR 1.37, CI 1.09, 172)
Peterlin (2010) [78] CS-GP (NHANES)	Those with: 1. Severe HA or Mig 2. No severe HA or Mig $n=15,631$ ($\leq$55 years) (EM, 3915)	Stratified White 70–82 % Black 8–11 % 38 (20–55)	Non-ICHD BMI: M	1. The odds of migraine or severe headaches were increased in obese women (BMI 30, OR 1.39, CI 1.25, 1.56) and obese men (BMI 30, OR 1.38, CI 1.20, 1.59) as compared to nonobese (BMI $<$ 30) women and men 2. The odds of migraine or severe headaches were increased in abd-O women (OR 1.26, CI 1.1–1/45) and abd-O men (OR 1.3, CI 1.13–1.49) as compared to women and men without abd-O
Robberstad (2010) [85] CS-GP (HEAD-HUNT YOUTH)	Those with: 1. Mig 2. TTH 3. Non-classifiable HA 4. No HA in past 12 months $n=5847$ (EM, 392)	Combined and stratified White 98 % Nonwhite $<$3 % $\leq$18 (13–18)	Non-ICHD BMI: M	The odds of migraine were increased in adolescent and young adults who were overweight or obese (OR 1.6, CI 1.4, 2.2) as compared to those of normal weight Note: obesity status was defined based on pediatric cutoff points

(continued)

Table 7.2 (continued)

Author (year) Study design (Database)	Population inclusion	Sex Race Mean age (range)	HA DX BMI Dx (SR vs M)	Findings
Vo (2011) [107] CS-GP (OMEGA)	Those who: 1. Received a Mig Dx 2. Never Dx with Mig $n=3733$ (EM, 672)	Women White 86 % Others 14 % <40 (18–40s)	Non-ICHD BMI: SR	The odds of migraine were increased in obese (BMI ≥ 30) premenopausal women as compared to those of normal weight (BMI 18.5–24.9) and which increased with increasing obesity status (BMI 30–34.9: OR = 1.48; CI 1.12, 1.96; BMI 35–39.9: OR 2.07; CI 1.27, 3.39; BMI ≥40: OR 2.75; CI1.60, 4.70)
Winsvold[a] (2011) [112] CS-GP (HUNT)	Those with: 1. Mig 2. No Mig $n=16,319$ (Mig, 2728)	Combined Not reported 20–<50	ICHD BMI: SR	The odds of migraine were increased in obese (BMI ≥ 30) participants as compared to those of normal weight (BMI 18.5–24.9: OR 1.29, CI 1.14, 1.46) and remained significant after adjustment for age, sex, and education (OR 1.35, CI 1.18, 1.55)
Yu (2012) [116] CS-GP	Those with: 1. EM (<15 HA days/month) 2. No EM (excluded those with headache ≥15 days/month) $n=5029$ (EM, 467)	Combined Han Chinese 94 % Others 6 % 43 (18–65)	ICHD2 BMI: M	The odds of EM were increased in Asians with morbid obesity (BMI ≥ 30; OR 2.10, CI 1.39–3.12) as compared to Asian individuals of normal weight (BMI 18.5–23) Note: in Asian populations normal weight is estimated as a BMI of 18.5–23, obesity a BMI ≥25, and morbid obesity a BMI ≥30. See Tables 7.1a and 7.1b for complete BMI categories for obesity status in Asian populations
Peterlin (2013) [79] CS-GP (NCS-R)	Those with: 1. Active EM (≤168 HA days/year) 2. Never had HA or Mig $n=2265$ (EM, 149)	Combined and stratified White 85.5 % Black 14.5 % <50 (18–50)	ICHD2 BMI: SR	The odds of EM were increased in those who were obese (OR 1.86, CI 1.20, 2.89) as compared to individuals of normal weight (BMI 18.5–24.9) The odds of EM increased with increasing obesity status from normal weight to overweight to obese ($p=0.001$)

Table 7.2 (continued)

Author (year) Study design (Database)	Population inclusion	Sex Race Mean age (range)	HA DX BMI Dx (SR vs M)	Findings
Wang (2015) [108] CS-GP	Those with: 1. Migraine (<15 HA days/month) 2. TTH 3. CDH (≥15 HA days/month) 4. No headache $n=1023$ (EM, 152)	Women only Han Chinese 95.3 % Non-Han 4.7 % 20–29 (20->40)	ICHD3-beta BMI: SR	The unadjusted odds of EM were increased in those who were obese (BMI ≥ 25) as compared to individuals of normal weight (BMI 18.5–22.9), OR 1.86, CI 1.04, 3.34, $p<0.05$. However, this was no longer significant after adjustments including age, seniority, and nursing specialty Note: in Asian populations normal weight is estimated as a BMI of 18.5–23, obesity a BMI ≥25, and morbid obesity a BMI ≥30. See Tables 7.1a and 7.1b for complete BMI categories for obesity status in Asian populations

Abd-O abdominal obesity (defined as WC ≥102 cm in men; WC ≥88 cm in women), *CI* confidence interval, *CS* cross-sectional. *Long* longitudinal, *EH* episodic headache, *EM* episodic migraine, *GP* general population study, *HA* headache, *Mex-Am* Mexican American, *OR* odds ratio, *M* measured, *SR* self-reported, *Mig* migraine, *SETTH* severe episodic tension-type headache
[a]Data unpublished, personal communication

unpublished, personal communication) [112]. The third study supporting age modification of the migraine-obesity association came from the NCS-R. An almost twofold greater odds of EM in obese individuals as compared to those of normal weight (OR 1.81, CI 1.27, 2.57; $p=0.001$) was demonstrated [79, 80]. This increased risk of EM in obese participants was strongest in participants who were younger than 50 years of age and women (OR 1.95, CI 1.38, 2.76; $p=0.0002$) [79, 80]. Subsequently to these three studies, a meta-analysis exploring the association between migraine and BMI categories found that in obese women, the risk of having migraine was increased (PAEE 1.44, 95 % CI 1.05–1.97) as compared to normal weight women [72]. In men, considering the only two available studies, the meta-analysis was unable to find an association between migraine and obesity [72].

In addition to age and sex, race likely has a relevant role in the association between migraine and obesity as well. Two studies investigated the possible association between migraine and obesity in Asian subjects, both of which used a BMI ≥ 25 as the cutoff for obesity. (Note: Obesity in Asian populations is accepted as BMI ≥25, whereas morbid obesity is classified as BMI ≥30; see Table 7.1a.) The first of those two studies included more than 5000 participants aged 18–65 years in China.

Table 7.3 Epidemiologic studies on migraine and obesity in predominantly peri-postmenopausal-aged subjects

Author (year) Study design (Database)	Population Inclusion	Sex Race Mean age (range)	HA BMI Dx (SR vs M)	Findings
Mattsson (2007) [64] CS-GP (Swedish database)	Total: 684 EM: 130	Women only Not reported 54 (40–74 years)	IHS BMI: M	Obesity was not associated with migraine in older women
Keith (2008) [52] CS-GP (WHI) [a]	Total: >220,370 EM: not reported	Women only White 83 % >50 (50–79 years)	Non-ICHD BMI: M	Obesity was not associated with migraine in older women
Winter (2009) [113] CS-GP (WHS)	Total: 63,467 EM: 9195	Women only Not reported 54 (≥45 years)	Non-ICHD BMI: SR	Obesity was not associated with active migraine or prior history of migraine in older women
Peterlin (2010) [78] CS-GP (NHANES)	Total: 6152 (>55 years) EM: 749	Both Men: white 81.8 % Black 8.2 % Women: white 79.8 % Black 9.1 % 68 (≥55 years)	Non-ICHD BMI: M	Obesity was not associated with migraine in older women or men
Winsvold[b] (2011) [112] CS-GP (HUNT)	Total: 15,031 Mig: 677	Both Not reported ≥50	ICHD BMI: SR	Obesity was not associated with migraine in older women or men
Winter (2012) [114] Long-GP (WHS)	Total: 19,162 EM: 3483	Women only White 95 % 54 (≥45 years)	Non-ICHD BMI: SR	Neither obesity nor weight gain was associated with migraine in older women
Peterlin (2013) [79, 80] CS-GP (NCS-R)	Total: 1356 (aged > 50) EM: 39	M 49.7 % F 50.3 % White 85.5 % Black 14.5 % >50 (50–98 years)	ICHD2 BMI: SR	Obesity was not associated with episodic migraine in older women or men

CS cross-sectional, *EM* episodic migraine, *Long* longitudinal, *GP* general population, *m-BMI* measured BMI, *sr-BMI* self-reported BMI

[a]This study was a meta-analysis evaluating the association between headache in general and obesity; however only the WHI database was used when evaluating the association between obesity and migraine specifically

[b]Data unpublished, personal communication

Although not in Chinese individuals with grade I obesity (BMI 25–29.9), those with morbid obesity (BMI ≥ 30) had a twofold increase in the risk of migraine (OR 2.1, 95 CI 1.4–3.2) as compared to those classified as normal weight participants (BMI 18.5–23.0 kg/m^2) [116]. A second study in China, involving around 1100 female nurses ages > 20, found that those with obesity (BMI ≥ 25) had an 86 % increased risk of migraine (OR 1.86, 95 % CI 1.04–3.34, $p < 0.05$) compared to those of normal weight (BMI 18.5–22.9). However, this did not remain significant after adjustments for age, seniority, and nursing specialty (OR 1.5, 95 % CI 0.8–2.8) [108].

Only one general population study has attempted to look at the disease modification of the migraine and obesity association in whites versus blacks. In the general population study utilizing the National Comorbidity Survey Replication, while the odds of EM were increased by 81 % (OR 1.81, 95 % CI 1.27–2.57; $p < 0.001$) in those with obesity when including both black and white participants, the odds of EM were twofold higher when analyses were limited to only white participants (OR 2.06, CI 1.41–3.010) [79, 80].

7.4.3 General Population Studies Evaluating Obesity and Chronic Migraine

In addition to episodic migraine, there is also an association between chronic migraine and obesity. After Scher et al. demonstrated an increased risk for obese individuals to develop chronic headache [92], Bigal and Lipton further confirmed this relationship with a large population-based cross-sectional study of more than 30,000 participants (ages 18–89, female 62 %, headache diagnosis based on ICHD, obesity based on sr-BMI) [10]. As in the Scher study, investigators noted a significant association between increasing categories of sr-BMI and increasing odds of chronic migraine [10]. Specifically, there was a 1.5-fold increased odds for having chronic migraine in those with BMI between 30 and 34.9 (OR 1.5, CI 1.2–1.8) and a twofold increased odds for having chronic migraine in those with BMI > 35 (OR 2.0, CI 1.4–2.4) compared to those of normal weight (BMI 18.5–24.9) [10]. In addition, a recent large general population cross-sectional study based on the German Headache Consortium cohort ($n = 6992$, ages 18–65, 50 % women, headache diagnosis based on ICHD2, obesity based on sr-BMI) showed that chronic migraine participants were more likely to be obese (sr-BMI >30) compared to those without headache (OR 1.72, 95 % CI 1.02–2.92) [93]. However, this did not remain significant after adjustments for pain medication use (OR 1.85, 95 % CI 0.54–6.27) [93]. In the most recent study including more than 15,000 participants aged 35–74 years, investigators showed an increased risk of daily migraine in obese as compared to normal weight participants (OR 1.9, 95 % CI 1.1–3.1) [89]. The pooled analysis of the two comparable studies [10, 89] indicated that overweight was associated with 40 % increase in the risk of chronic migraine (PAEE 1.4, 95 % CI 1.1–1.7), and obesity was associated with 80 % increase in the risk of chronic migraine (PAEE 1.8, 95 % CI 1.3–2.3) [72].

7.4.4 General Population Studies Evaluating Obesity and Tension-Type Headache (TTH)

The association of obesity with TTH is not as clear as that between obesity and migraine, with some data suggesting a connection [108, 112], while other studies unable to prove the association [11, 93, 114]. Winsvold et al. in a cohort of nearly 50,000 subjects aged ≥20 years found a 20 % increased risk of non-migrainous headache among obese participants as compared to normal weight participants (OR 1.2, 95 % CI 1.1–1.3) [112], though it did not specify TTH by ICHD diagnosis. However, in [11] study, while CTTH has been found to be more prevalent in those morbidly obese compared to those normal weight (4.3 %, OR 1.4, CI 1.1–1.9), episodic tension-type headache has not been found to be significantly associated with obesity (sr-BMI) [11]. Finally, Robberstad et al. reported a 40 % increased risk of TTH (episodic and chronic together) in adolescents 13–18 years of age who were overweight or obese (OR 1.4, 95 % CI 1.1–1.6) [85].

7.5 Central and Peripheral Associations Between Migraine and Obesity

As discussed above, obesity has been reported to be a risk factor for headache in general, as well as in both episodic migraine and chronic migraine. The obesity-migraine association is greater in women as compared to men and younger as compared to older individuals [22]. There is only a weak association between tension-type headache and obesity. The current epidemiological literature on this association does not allow us to identify the direction of the association, as only two separate databases have been utilized to examine this association longitudinally, one which did not include non-headache controls [92] and the second only examined older women (age ≥45, from the WHS) [114].

While the directionality of the migraine-obesity association has not yet been clarified, factors such as medication side effects and exercise likely contribute to or modify this relationship. Weight gain is a common side effect of many frequently used migraine prophylactic medications [96]. It is conceivable that medication-related weight gain is at least in part contributing to the prevalence of obesity among migraineurs. Additionally, lack of physical activity has been linked with increased migraine attacks. More specifically, lack of exercise has been demonstrated to be associated with a 21 % increased risk of headache attacks in adult migraineurs (HR 1.209; $p < .01$) [115] and a 50 % increased risk of migraine in adolescents (OR 1.5, 95 % CI 1.0–2.2) [85]. Additionally, obese migraineurs were found to spend less time engaging in physical activity than obese participants without migraine [14]. Therefore a more sedentary lifestyle may be a common link between obesity and worsening headache in migraineurs.

Alternatively, or in addition, there are several plausible shared mechanisms between the regulations of feeding/adiposity and that of pain/migraine pathogenesis, which may also help to explain the obesity-migraine association. Adipose tissue is an active endocrine organ with roles in energy homeostasis, reproduction, as well as inflammation [99]. In the following section, we review the central and peripheral pathways regulating feeding and adipose tissue function and discuss the extensive overlap of pathways implicated in both obesity and migraine.

7.5.1 Central Regulation of Feeding and Its Overlap with Migraine Pathophysiology

The regulation of feeding is controlled by the "melanocortin system." The melanocortin system is composed of the arcuate nucleus (ARC) of the hypothalamus and its connections [16]. The ARC contains orexigenic and anorexigenic neuropeptides [25, 26]. Signals from the ARC neurons are transmitted to several other hypothalamic nuclei, including the paraventricular nucleus (PVN), which express adiponectin and leptin receptors, as well as to the ventromedial (VM) and lateral hypothalamus (LH) nuclei [16, 25, 26, 99]. In the LH, there are two groups of neurons, the orexin neurons, which stimulate feeding, and the melanin-concentrating hormone (MCH) neurons, which inhibit food intake. These neurons subsequently project to the brainstem nuclei, the nucleus tractus solitarius (NTS), and the dorsomotor nucleus of the vagus (DMV), where the descending hypothalamic inputs are integrated with the peripheral inputs from the liver and gastrointestinal tract [16, 25, 26].

The hypothalamus, in addition to regulating the drive to feed or not feed, has also been implicated in migraine. This was initially suggested based on the observations of hypothalamic premonitory and postdromal symptoms in migraineurs, such as changes in thirst, food cravings, mood, and sleep disturbances [13]. More recently, functional imaging has demonstrated hypothalamic activation during acute migraine attacks [29]. Further, several hypothalamic peptides, proteins, and neurotransmitters involved in feeding have been implicated in migraine pathophysiology. Notably, these include serotonin, orexin, and adipokines such as adiponectin and resistin (below).

7.5.1.1 Serotonin

Serotonin is a neurotransmitter synthesized from the essential amino acid tryptophan. Interictal levels of plasma serotonin have been shown to be low in migraineurs [77]. If migraine is a syndrome of chronically low serotonin, there is likely a decreased activation of serotonin receptors in migraineurs. Serotonin receptors, specifically the postsynaptic 5-HT_{1B} and 5-HT_{2C}, are directly involved in satiety [56]. Mice with a disruption of the 5-HT_{2C} receptor exhibit increased feeding and develop late-onset obesity and diabetes [68]. The low serotonin state in migraineurs interictally may thus promote an increased drive for feeding.

Acute migraine attacks are associated with a 60 % increase in 5-HT plasma levels [77]. With the sudden raise in 5-HT release, hypophagia may ensue [43], further demonstrating the close link between serotonin and both migraine and feeding drive. Several drugs that modulate serotonin and its receptors, including those receptors most directly implicated in satiety, the 5-HT_{1B} and 5-HT_{2C}, are also used in the management of migraine ([42, 77]).

Finally, serotonergic neurons in the dorsal raphe nucleus express orexin receptors and are excited by orexin A [42], which we will discuss next.

7.5.1.2 Orexin

As with serotonin, orexin has been linked to migraine and feeding. Specifically, orexin OXA and OXB are peptides with neuronal cell bodies primarily localized in the LH. These orexins containing neurons have been shown to project to the cortex, thalamus, hypothalamus, brainstem (including the locus coeruleus and the raphe nucleus), as well as gastrointestinal tract [102]. Orexin acts on two G-protein-coupled receptors, OXR1 and OXR2, which have been shown to stimulate feeding and contribute to arousal and pain [12, 47, 102].

In animal studies, centrally administered orexin increases food intake and has also been shown to reverse the cholecystokinin-induced loss of appetite. In addition, in visceral adipose tissue, orexin has been shown to decrease the expression of hormone-sensitive lipase, which suggests that orexin may also modulate adipose tissue metabolism by inhibiting lipolysis [47].

In addition to their role in feeding, orexins have also been implicated in pain and headache. Specifically, OXA levels have been shown to be elevated in the cerebrospinal fluid of chronic daily headache sufferers [91]. Further, intrathecally administered OXA in rats has been shown to inhibit heat-evoked hyperalgesia as well as to reduce mechanical allodynia [65]. This anti-hyperalgesic property is inhibited when pretreated with the orexin receptor antagonist [32, 51]. OXA has also been shown to inhibit neurogenic vasodilation as well as TNC neuronal nociceptive responses to electrical stimulation of the dura mater in rats [48, 49]. The full role of the orexins and their receptors in migraine is still being determined.

7.5.1.3 Adipocytokines

In addition to peptides and neurotransmitters, adipocytokines participate in energy homeostasis and the regulation of feeding. Adiponectin and leptin are two such adipocytokines which we discuss next.

7.5.1.4 Adiponectin

Adiponectin (ADP) is a protein primarily secreted from adipocytes, with receptors expressed in the brain, the endothelium of blood vessels, as well as in the liver and muscle [54, 76]. Women have been reported to have higher ADP levels than men by

puberty [100, 101]. In addition, ADP levels increase with age. Human ADP can exist in the blood in a full-length form or as a fragment globular form. While ADP has been shown to be primarily pro-inflammatory, Tsatsanis et al. found that adiponectin-mediated induction of macrophages can form tolerance and cause an "anti-inflammatory" effect when there is high enough circulating levels [101]. In addition, adiponectin can exist as one of the several characteristic oligomers or multimers. The different multimers can exert either pro- or anti-inflammatory properties depending on the multimer involved [76, 100]. The low molecular weight (LMW) multimer of ADP has been shown to have anti-inflammatory properties through reduction of interleukin (IL)-6 secretion, while high molecular weight (HMW) ADP has been shown to activate nuclear factor kappa-β (NFkβ) pathways and induce IL-6 secretion in humans [46, 74].

The first study to evaluate ADP and its multimers was a clinical trial of 37 participants by Peterlin et al. [75]. Investigators found elevated levels of total ADP in chronic and transformed migraineurs at baseline level of pain, as compared to non-migraine controls and to episodic migraineurs when pain-free. This elevation in total adiponectin in chronic migraineurs was largely due to the increase in the HMW multimer of ADP [75]. More recently Duarte et al. demonstrated that total ADP was increased in migraineurs ($n = 133$) as compared to non-headache controls, and there was no significant difference in ADP levels between those with episodic versus chronic migraine [31].

Changes in adiponectin have also been evaluated ictally [21, 79, 80]. In the largest longitudinal ictal migraine study to date, Chai et al. conducted a double-blind, placebo-controlled trial evaluating peripheral blood specimens from episodic migraineurs at acute pain onset and up to 120 min after treatment with sumatriptan/naproxen sodium vs placebo in a total of 34 participants [21]. In all participants, pretreatment pain severity increased with every quartile increase in the HMW/T-ADP ratio (CV 0.51, 95 % CI 0.08, 0.93; $p = 0.019$). Further in treatment responders, and not in nonresponders, T-ADP levels decreased (CV −0.98, 95 % CI −1.88, −0.08; $p = 0.031$), and the LMW/T-ADP ratio increased (CV 0.04, 95 % CI 0.01, 0.07; $p = 0.043$) at 120 min after treatment as compared to before treatment [21].

Finally, the association between adiponectin and migraine may be stronger in men than women. Based on a study with 981 participants, crude, mean total adiponectin levels were found to be greater in men and women with migraine (8.1 μg/mL, SE 0.5) as compared to those without migraine (7.0 μg/mL, SE 0.2) ($p = 0.031$). After adjustments, the odds of migraine were increased by 88 % with each SD increase in total adiponectin in men (odds ratio [OR] 1.86, 95 % confidence interval [CI] 1.15, 3.01; $p = 0.011$), but not in women (OR 1.05, 95 % CI 0.80, 1.37; $p = 0.728$; p interaction = 0.029) [28].

7.5.1.5 Leptin

Leptin has been implicated in the modulation of inflammation and its deficiency leads to obesity [25, 57]. Like adiponectin, leptin is primarily produced by adipocytes, but also by several other tissues including the brain. Leptin is inhibited

by testosterone and increased by ovarian sex steroids, with women exhibiting levels which are 2–3 times higher than men even when matched for age and BMI [60, 97].

Studies evaluating interictal leptin levels in migraineurs have been variable, with the majority of studies suggesting no difference in interictal leptin levels in migraineurs as compared to controls [28, 40, 74, 117]. In one study where leptin levels were found to vary between migraineurs and non-migraineurs, Bernecker et al. found higher fasting leptin levels in 40 nonobese female migraineurs (15.07 ± 9.63) compared to controls (9.99 ± 5.62; $p < 0.01$) after adjustment for age and BMI [7]. In studies where no difference was found in leptin levels between migraineurs and non-migraineurs, one did not adjust for age, sex, or glucose levels when they were significantly different across groups [40], one utilized a predominantly older (age 45+) population [28], and one did not report or adjust for insulin, glucose levels, and diabetes [59].

Only one study thus far evaluated ictal leptin levels in those with EM and did not find alterations in leptin levels in migraineurs based on treatment response [21]. However, in analyses including pain severity across all time points (pre- and post-treatment), pain severity decreased with increasing quartiles of leptin levels after adjustments, suggesting that leptin may have an inverse relationship with acute migraine pain severity [21].

Studies have also shown variable results when evaluating leptin levels pre- and post-medication. One study which evaluated serum leptin levels in migraineurs before and after preventive treatment with amitriptyline reported increased leptin levels after treatment (pre-tx 7.15 ± 1.12, post-tx 16.85 ± 2.38, $p < 0.01$) [6]. However, one small case series of six migraine patients reported that leptin was decreased by $39.2 \pm 6.5\,\%$ from baseline following 20 weeks of topiramate treatment (leptin level change $-39.2 \pm 6.5\,\%$, p 0.013) [94].

Although no clear trend can be determined regarding interictal and ictal leptin levels in those with migraine as compared to controls based on current available data, future studies are warranted with careful consideration of the migraine state at the time samples are drawn as well as of important covariates such as age, sex, glucose, and body mass index.

7.5.2 Peripheral Regulation of Adiposity and Its Overlap with Migraine Pathophysiology

Expansion of adipose tissue during weight gain leads to the recruitment of macrophages and T cells and directly results in the induction of adipocytokines and expression of several pro-inflammatory cytokines [99, 109], including IL-1, IL-6, and TNF-α. In fact, one third of the IL-6 concentration in the circulation of obese individuals comes from adipocytes [16, 100]. TNF-α has also been shown to induce insulin resistance and inhibit adipocyte differentiation, further contributing to this vicious cycle [76].

Several alterations in cytokines have been reported in patients with migraine. Specifically, serum TNF-α and IL-6 have been shown to be increased ictally in episodic migraineurs, while cerebrospinal fluid TNF-α has been shown to be increased in chronic daily headache sufferers [87, 91]. In addition, serum levels of the anti-inflammatory cytokine, IL-10, have also been shown to be lower following treatment of acute attacks with sumatriptan, suggesting elevated levels of IL-10 during acute attacks [66]. Adiponectin and leptin have been shown to have reciprocal relationships with several of these cytokines. Thus future studies evaluating the effect of cytokines on adipocytokines and of adipocytokines on cytokines in migraineurs would be of interest.

7.6 Treatment Considerations for Obese Headache Patients

Obesity, as a potentially modifiable risk factor for migraine, deserves special attention by clinicians treating migraineurs. In the following section, we will discuss the evidence and precautions associated with both surgical and nonsurgical weight loss options and their efficacy in improving headache.

7.6.1 Nonsurgical Weight Loss Strategies in Obese Headache Patients

Physical exercise is a key weight loss strategy and is often recommended to migraine patients. Lack of physical activity has been demonstrated to be associated with increased headache attacks in both adolescents and adult migraineurs [85, 115]. However, activity has also been reported by migraineurs to be a headache trigger, raising concern among some migraineurs that exercise may exacerbate their migraine [44]. This concern has been addressed by multiple studies that ultimately support moderate exercise in migraineurs [37, 55, 104]. One study of migraineurs assigned to a moderate-intensity exercise program (40 min per day, including warm-up and cooldown periods, three times/week, for 12 weeks) found improvement of maximal oxygen uptake without worsening migraine status. In fact, there was a decrease in both the number of migraine attacks and the severity of headaches by the third month of the program [104]. However, this study did not specify if exercise itself improved migraine symptoms or if it is the weight reduction as a result of exercise which accounted for the improvement. One study in the adolescent population (ages 14–18) showed that lowering BMI was significantly associated with better migraine outcomes 12 months after an interdisciplinary intervention program for weight loss [105]. Subsequent data also found that those who did not become migraine-free after the intervention program had higher adiposity [106]. Larger randomized control studies are underway to further evaluate the efficacy of a standardized weight loss intervention for reducing migraine frequency in the adult population [27].

Diet is an integral aspect of a successful and healthy weight loss plan. However, there has been conflicting theories regarding the role of dietary fat and protein in the genesis or alleviation of head pain in migraineurs [73]. While some argue that a low-fat or a low-protein diet may improve migraine [9, 19, 45], others have tried the ketogenic diet and the modified Atkins diet as possible migraine treatments [30, 36, 63]. More recently, Ramsden et al. conducted a randomized, single-blinded, parallel-group trial involving 67 adult patients with chronic daily headache comparing the effect of a combined high omega-3 and low omega-6 fatty acid diet versus a diet with reduction of omega-6 fatty acids alone. After 12 weeks, participants on the high omega-3 and low omega-6 diet had greater reduction in headache days per month (−8.8 vs −4.0; $p=0.02$) and headache hours per day (−4.6 vs −1.2, $p=0.01$) compared to participants on the reduced omega-6 diet [83]. Overall, definitive scientific evidence substantiating the efficacy of any particular diet as part of migraine therapy is still lacking, and further research is warranted.

Medications used for migraine often carry weight-related side effect profiles [96] (Table 7.4), and weight gain is among the most common reasons for a patient to reject a migraine prophylactic medication (Table 7.4) [56]. Some of the most common migraine prophylactic medications that can induce weight gain include tricyclic antidepressants (amitriptyline) and anticonvulsant medications (valproic acid) [63]. Alternatively, a favorable side effect of topiramate, a common migraine prophylactic medication, is weight loss [2, 94, 96]. This has made topiramate a particularly good choice for migraine prophylaxis in obese migraineurs. Migraineurs

Table 7.4 Potential migraine preventative medications and weight considerations

Drug class/drug	Weight change
Antidepressants	
Amitriptyline	↑↑↑
Paroxetine	↑↑
Nortriptyline	↑↑
Fluoxetine	↑
Venlafaxine	↔↓
Duloxetine	↔↓
Protriptyline	↓
Anticonvulsants	
Divalproex sodium	↑↑↑
Gabapentin	↑
Lamotrigine	↔
Topiramate	↓↓
Beta blockers	↑
Serotonin (5-HT) antagonists	
Methysergide	↑↑↑
Cyproheptadine	↑↑↑
Calcium channel blockers	
Flunarizine	↑↑↑
Verapamil	↔

with higher BMI may also respond differently to migraine medications than migraineurs with normal BMI. In a retrospective study involving around 350 migraineurs, investigators found that when treated with a triptan, those individuals with BMI 18.5–24.9 were more likely to achieve pain relief at 2 h compared to those with BMI > 25 (frovatriptan: 30 % vs 24 %, $p < 0.05$; rizatriptan or zolmitriptan or almotriptan: 34 % vs 27 %, $p < 0.05$) [90].

7.6.2 Surgical Weight Loss in Obese Headache Patients

One of the first studies to evaluate the effect of bariatric surgery on headache frequency and severity in morbidly obese episodic migraineurs was by Bond et al. It was a 2-year prospective observational study of obese patients presenting for bariatric surgery [15]. Headache frequency was evaluated in 24 morbidly obese participants (88 % women, mean age 39.3). With an average reduction of BMI from 46.6 to 34.6 at 6 months postsurgery, Bond et al. found that headache frequency declined from an average of 3.7 headache days per month before surgery to 2.2 headache days per month at the 6-month follow-up visit ($p = 0.013$) [15]. There was also a decrease of headache severity and headache-related disability (MIDAS) at the 6-month post-surgery follow-up in these participants.

Subsequently, Novack et al. conducted a second prospective clinic-based study of 29 morbidly obese, reproductive-aged women fulfilling migraine criteria before and after bariatric surgery (mean age 33.2, all women) [69]. Their findings echoed Bond's results, again suggesting that improvement in headache frequency and disability occurs as early as 3 months following bariatric surgery (mean BMI 37) and is maintained at 6 months after surgery (mean BMI 34). Of the 23 episodic migraineurs included in the study, the median monthly headache frequency declined from four headache days/month at baseline to two headache days/month 3 months following bariatric surgery, which further improved to just one headache day/month, 6 months after surgery. In addition, the authors reported improved headache-related disability (both the MIDAS and HIT-6), decreased headache duration, and improved headache-associated symptoms following bariatric surgery [69].

Most recently Gunay et al. evaluated data from 81 morbidly obese patients (mean age 40, 90 % women) with preoperative diagnosis of episodic migraine who underwent Roux-en-Y gastric bypass in a retrospective study [41]. After surgical weight loss (mean BMI decreasing from 48 to 33), migraine symptoms were improved in 89 % of patients within 5.6 ± .9 months (range 1–36; $p < .01$, chi-square test). This improvement was independent of the improvement in migraine-associated comorbidities, such as sleep apnea, menstrual dysfunction, depression, and anxiety. Interestingly, this study also compared patients who developed migraine after obesity onset ($n = 51$) with those who had migraine before obesity ($n = 24$). Those who developed migraine after obesity onset showed higher likelihood of complete resolution of migraine compared to those who developed migraine prior to the onset of obesity ($p < .01$) [41].

One limitation of the above surgical weight loss studies includes the retrospective documentation of changes in headache frequency and related parameters vs a prospective headache diary. Thus, larger controlled studies that include assessment of potential mediators and prospective measures of monthly headache frequency are needed to substantiate these findings. Moreover, although the above studies suggest that weight loss could be a principal mechanism underlying the potential benefits of bariatric surgery, it is also possible that several downstream mechanisms may also be at play, such as favorable changes in inflammatory cytokines and adipokines or behavioral activity (e.g., dietary changes including decreased exposure to migraine food triggers as a result of postoperative dietary restrictions, increased engagement in physical activity due to weight loss, improved physical function, etc.). Additionally, given that many obese and overweight migraineurs may not choose or may be ineligible for bariatric surgery, it is important to evaluate whether weight loss achieved via nonsurgical approaches (i.e., lifestyle interventions such as diet and exercise) produces similar improvements in headache frequency and severity in controlled trials before formal recommendations are able to be made.

7.7 Conclusion

Population studies have consistently identified an association between obesity and headache in general and specifically in migraine. Age and sex substantially modify this risk, with obese individuals <50 years of age and women having the greatest risk. While the causal relationship is not known, obesity and migraine share overlapping central and peripheral mechanisms that may contribute to this relationship. In addition, factors such as medications which modulate weight and lifestyle behaviors of migraineurs supply additional complexity to the obesity-migraine relationship. Currently there are no substantial data supporting a specific diet for overweight and obese migraineurs, and only limited research suggests bariatric surgery in obese episodic migraineurs that may be associated with reduced headache frequency and severity. Overall, clinicians treating migraine patients should take particular care in their choices of medications prescribed to their patients, given that many migraine drugs can modulate weight, and promote healthy lifestyle choices in regard to diet and exercise.

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Chapter 8
Comorbidity in Paediatric Headaches

Çiçek Wöber-Bingöl and Noemi Tinetti

Abstract Headache and migraine may be associated with a broad variety of comorbid disorders in children and adolescents. In this chapter, we review evidence from population-based and clinic-based studies including somatic as well as psychiatric disorders.

Keywords Headache • Migraine • Comorbidity • Asthma • Allergy • Cardiovascular disorders • Stroke • Epilepsy • Learning disabilities • Sleep disorders • Attention deficit hyperactivity disorder • Tourette syndrome • Depression • Anxiety

8.1 Introduction

Headache and migraine in children and adolescents show an estimated overall mean prevalence of 54.4 and 9.1 % and cause significant burden [1, 2]. Accordingly adequate treatment is mandatory [3–5]. Managing headache in young patients requires a comprehensive view of the problem, not focusing on headache itself but also considering comorbidity, psychosocial aspects and the patients' environments affecting headache frequency [3, 5]. In this chapter, we will review the comorbidity of headache and migraine in children and adolescents and summarize the scientific evidence.

'Comorbidity' is a general medical term that implies an association, more than casual, but probably not causal, between an index disease and one or more coexisting physical or psychiatric disorders [6]. The epidemiology of the comorbidities in children and adolescents with recurrent headache is largely unknown. The majority of the reports on comorbidities are based on observations within headache centres

Ç. Wöber-Bingöl, MD (✉)
Dr. Gönül Bingöl – Dr. Muammer Bingöl Çocuk ve Ergen Başağrısı Derneği – Society for Headache in Children and Adolescents, Tan Sokak 2/7, Suadiye, Istanbul, Turkey
e-mail: yasar.woeber-bingoel@meduniwien.ac.at

N. Tinetti, MD
Headache in Childhood, Ceinsa Centro Integral Neurológico, Tucumán 967, 6500-9 de Julio, Pcia de Buenos Aires, Argentina

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and thus have a referral bias. They do provide an estimate of these conditions in patients with frequent or disabling headaches. The pathophysiology of the comorbidities should be expected to be similar to adults with the same conditions. For many of these conditions the exact interrelationship is not known and may be due to a general biological stressor that can be broadly applied, while others may have a more defined aetiology.

8.2 Asthma and Atopic Disorders

Asthma and related allergic disorders including sinusitis are a common problem in children and adolescents. Approximately, 9 % of children and adolescents have asthma, and this increases to 32 % for any allergic condition [7]. Migraine itself has a neuroinflammatory component, and it could be expected that in patients with immunologic or inflammatory conditions, there may be an increased risk of migraine. In two population-based studies from the USA [8, 9], asthma and hay fever were more common in children with headache than in those without headache and asthma, as well as seasonal allergies were more common in adolescents with migraine than in those with 'nonspecific headache'. Two clinic-based studies showed conflicting results. In one study there was no association between primary headaches and atopic disorders [10], whereas in another study, the risk of atopic disorders was significantly increased in migraine compared to tension-type headache (TTH) and in migraine with aura compared to migraine without aura and TTH [11].

The underlying aetiology of a possible comorbidity of migraine and atopic disorders might be due to an inflammatory disorder or due to the stress of two chronic conditions and therefore be a generic comorbid response. Regarding pharmacological treatment of migraine in patients with comorbid asthma or atopic disorders, the risk of sensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) must be considered, and beta-blockers should not be used for migraine prophylaxis to avoid exacerbation of asthma.

8.3 Cardiovascular Disease

In adults there may be a relationship between cardiovascular disease and migraine. This has not been well described in children. As many of the cardiovascular syndromes in children are due to congenital heart defects, there may be a degree of compensation by the time the patients begin to express their migraine. The correlation between migraine and patent foramen ovale (PFO) is debatable. In a review published in 2008 [12], the authors identified 134 articles and included 18 which met a priori selection criteria. The estimated strength of association between PFO and migraine, reflected by summary odds ratios (ORs), was 5.13 [95 % confidence interval (CI) = 4.67–5.59], and between PFO and migraine with aura, the OR was

3.21 (95 % CI = 2.38–4.17). The grade of evidence was low. The association between migraine and PFO was OR 2.54 (95 % CI = 2.01–3.08). The grade of evidence was low to moderate. Six studies of PFO closure suggested improvement in migraine, but had a very low grade of evidence. In a review from 2016 [13] including the only two studies in children [14, 15], the authors suggest to close the debate on PFO and migraine and they emphasize the low quality of the studies. According to this review, in patients with PFO, the prevalence of migraine ranged between 16 and 64 %, and in patients with migraine, the prevalence of PFO ranged between 15 and 90 %. Observational studies that examined the effect of PFO closure on migraine showed a wide range of outcomes and all three randomized controlled trials failed to meet the primary endpoint. The authors conclude that 'there is no good quality evidence to support a link between migraine and PFO and, that patients and providers should adhere to guidelines-recommended pharmacological, physical, and behavioural therapy for patients with migraine, even if a PFO is identified on echocardiography'.

With respect to other cardiac comorbidities, Jacobs et al. [6] identified in their review only one over other potential findings, i.e. QTc prolongation during a migraine attack in three of 13 children seen in an emergency department [16].

8.4 Stroke

An increased risk for stroke in teenage girls and young women with probable migraine with aura has been noticed, particularly for those who smoke or use oral contraceptives, compared with women who do not have migraines.

In 2007, a study by MacClellan et al. assessed the link between probable migraine with visual aura (PMVA) and probable migraine without visual aura with ischemic stroke among groups of women [17]. Using data from a population-based, case-control study, they studied 386 women aged 15–49 years with first ischemic stroke and 614 age- and ethnicity-matched controls. Based on their responses to a questionnaire on headache symptoms, subjects were classified as having no migraine, probable migraine without visual aura or probable migraine with visual aura(PMVA) according to various factors including headache characteristics and various clinical features. The results showed that young women with PMVA had 1.5 greater odds of ischemic stroke (95 % CI = 1.1–2.0); the risk was highest in those with no history of hypertension, diabetes or myocardial infarction compared to women with no migraine. Women with PMVA who were current cigarette smokers and current users of oral contraceptives had 7.0-fold higher odds of stroke (95 % CI = 1.3–22.8) than did women with PMVA who were non-smokers and not users of oral contraceptives. Women with onset of PMVA within the previous year had 6.9-fold higher adjusted odds of stroke (95 % CI = 2.3–21.2) compared to women with no history of migraine. Their conclusion was that PMVA was associated with an increased risk of stroke, particularly among young women and teenage girls without other medical conditions associated with stroke. Behavioural risk factors, specifically smoking

and oral contraceptive use, markedly increased the risk of PMVA, as did recent onset of PMVA. PMVA may be a risk factor for stroke or these patients may be genetically predisposed for both, with the migraine or the stroke being a comorbidity.

In 2015, Gelfand et al. published the first population-based study on the association between migraine and stroke in children and adolescents [18]. The authors included more than 1.5 million subjects aged 2–17 years. All of them were members of a health care delivery system that provides care to approximately 30 % of the population of northern California. Children and adolescents were classified as having migraine, if they had an ICD-9 code for migraine from any encounter, if migraine was mentioned in a significant health problem list or if pharmacy records showed a prescription of a migraine-specific medication. A stroke had occurred in eight of 88,164 migraineurs and in 80 of 1.3 million children and adolescents without headache. The ischemic stroke incidence rate was 0.9/100,000 person-years in migraineurs and 0.4/100,000 person-years in children and adolescents without headache. This difference was statistically not significant (incidence rate ratio (IR) 2.0, 95 % CI0.8–5.2). Similarly, the hemorrhagic stroke incidence rate (0.5/100,000 person-years in migraineurs and 0.9/100,000 person-years in subjects without headache) did not show a statistically significant difference between migraineurs and subjects without headache (IR 0.6, 95 % CI 0.2–2.0). In contrast, a post hoc analysis of adolescents aged 12–17 years showed an increased risk of ischemic stroke among those with migraine (IR 3.4, 95 % CI 1.2–9.5). Further studies are needed to confirm this finding.

8.5 Epilepsy

In a population-based study, the prevalence of epilepsy was higher in children with headache than in headache-free children epilepsy (OR, 2.02; 95 % CI, 1.04–3.94) [8]. In a clinic-based study of paediatric epilepsy patients, it has been observed that a larger than expected proportion of these patients and their families have a history of migraine. This relationship appeared to be even higher for children who had migraine with aura [19]. Migraine and epilepsy are related with each other in various ways and share aspects of genetics, pathophysiology, semiology and treatment [20]. Winawer and Connors found a shared genetic susceptibility to migraine with aura in many types of nonacquired focal and generalized epilepsies [21]. Furthermore linkage studies in families with rolandic epilepsy and other types of epilepsy showed associations with genes related to familial hemiplegic migraine [19]. The precise mechanisms underlying the association of migraine and epilepsy remain unclear. Several studies have suggested an excessive neocortical hyperexcitability together with similar molecular and genetic substrates [20]. In epilepsy, neocortical hyperexcitability, abnormal hypersynchronous electrical discharges in neuronal cells and subsequent alterations of ion metabolism

lead to recurrent seizures. In migraine, however, cortical spreading depression, rather than hypersynchronous discharges the basis for migraine aura and the trigger for headache [20].

Regarding the differential diagnosis of migraine aura and occipital epilepsy, it was suggested that elementary visual hallucinations cannot be anything else but visual seizures. They were found to be entirely different from migraine visual aura in colour, shape, size, location, movement, duration and development. In distinction, migraine visual aura with or without headache usually starts with predominantly flickering black and white, linear and zigzag patterns in the centre of the visual field, gradually expanding over minutes toward the periphery of the hemifield and often leaving a scotoma [20].

According to the beta version of the third edition of the International Classification of Headache Disorders (ICHD-3 beta) [22], headache related to epileptic seizures may be classified as migraine aura-triggered seizure (ICHD-3 beta 1.4.4), hemicrania epileptica (ICHD-3 beta 7.6.1) and post-ictal headache (ICHD-3 beta 7.6.2) with the latter being by far the most common [20].

Antiepileptic drugs (AEDs) which have been demonstrated to be safe and effective in the treatment of migraine include in particular divalproate and topiramate. The choice of AED in comorbid epilepsy and migraine should be guided by the underlying epilepsy syndrome and should consider a medication with prospective migraine preventive properties. The goals of treatment vary; for migraine the aim is reduction in frequency by at least 50 % and treatment is administered for 4–6 months, whereas for epilepsy the goal is seizure freedom for 2 years. Thus the epilepsy treatment dictates the duration of AED use.

8.6 Obesity

Obesity is an area of growing concern in children and adolescents. Worldwide the incidence of obesity in childhood and adolescence is increasing. In obese children, there is an effect on both headache frequency and disability [6, 8, 23]. Pathophysiologically, serotonin, orexin, adiponectin and leptin have been suggested to have roles in both feeding and migraine [24]. The increased risk of headache and migraine related to obesity needs to be addressed in the overall treatment plan, as it appears that those children who can lower their BMI percentile have a greater improvement than those who don't lose weight [24].

In a prospective study investigating the impact of a weight loss treatment on headache in 135 obese adolescent migraineurs participating in a 12-month programme including dietary education, physical training and behavioural treatment, the authors assessed decreases in weight, body mass index (BMI), waist circumference, headache frequency and intensity, use of acute medications and disability. Both lower baseline BMI and amount of weight loss were associated with better outcomes [25].

8.7 Sleep Disorders

Disturbances in sleep can have both a biological and a behavioural basis. Sleep deprivation is one of the most common triggers of migraine in children and adolescents. This is complicated by the biological changes affecting sleep that occur during puberty, causing adolescents to have delayed sleep onset, which is hormonally controlled, in conflict with many school systems that require these children to wake earlier than is biologically natural.

Headaches may occur during sleep; they may be related to certain sleep stages or they may be noticed on awakening. Nocturnal headaches can be a result of disrupted sleep or may cause sleep disruption. However, headaches wakening a child from sleep may also be red flag and call for further diagnostic workup including magnetic resonance imaging. In addition, there may be specific sleep disturbances in children and adolescents [24]. Children who suffer from headache may have a high rate of sleep difficulties, such as insufficient sleep, co-sleeping with parents, difficulties falling asleep, anxiety related to sleep, restless sleep, night waking, nightmares and fatigue during the day [24]. Migraine in children and adolescents was related to sleepwalking, bedwetting, pavor nocturnus and restless legs syndrome [24, 26]. Epidemiologic studies on the relation of headache and migraine to sleep disturbances in children and adolescents are lacking.

With respect to treatment education and lifestyle modification, including sleep hygiene has been suggested, and sleep conditions should be screened obligatorily in children and adolescents with migraine in order to improve patient management and to choose the most appropriate treatment [27].

8.8 Learning Disabilities

The term learning disabilities (LD) comprises difficulties in a broad range of academic and functional skills such as listening, speaking, reading, writing, reasoning, mathematics, coordination, spatial adaptation and memorization. These difficulties can occur alone or in varying combinations and can range from mild to severe. The causes of LD are not well understood, and sometimes there is no apparent cause. In some cases LD are related to heredity, problems during pregnancy and birth, head injuries, malnutrition, toxic exposure or behavioural or social factors [28]. By using data from the National Survey of Children's Health, the overall lifetime prevalence of LD in US children in 2003 was calculated to be 9.7 %(95 % CI = 9.4–10.1), meaning that an estimated 6 million US children aged below 18 years had LD at some stage in their life [29]. From experience in a tertiary headache centre, LD are more frequently seen in children with migraine. In an epidemiologic study, LD were more frequently reported in children with frequent or severe headaches (OR, 1.59; 95 % CI = 1.26–2.02) [8]. Although LD are considered to be lifelong disorders, academic skills themselves can be improved with targeted interventions. Practice is a particularly important component in developing competence. Specialized instructions are

designed to make improvements in the weak areas. In addition, adjustments and equipment such as electronic dictionaries or word spellers are intended to accommodate or help compensate for the disabilities. In children with migraine experiencing a significant increase in attack frequency afterschool entry, LD should be considered as an underlying cause, even though evidence from controlled trials is lacking.

8.9 Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder in children. Eight to twelve percent of children are affected worldwide. The onset is before 7 years of age. ADHD is characterized by a persistent pattern of inattention, hyperactivity and impulsiveness. At least half of children with the disorder will have impairing symptoms in adulthood. Twin, adoption and molecular genetic studies show ADHD to be highly heritable, and other findings have recorded obstetric complications and psychosocial adversity as predisposing risk factors [29]. In an epidemiologic study [8] including subjects aged 4–18 years, the prevalence of attention deficit disorder was significantly higher in individuals with frequent or severe headache (OR, 2.02; 95 % CI = 1.56–2.64). In contrast, other studies found an association between migraine and hyperactivity symptoms, but not with symptoms of inattention. Studies showing an association of childhood migraine with inattention symptoms were questioned because of methodological limitations [24]. In one study, ADHD was more common in patients with tension-type headache than in migraineurs, but this was not confirmed in other studies [6]. With respect to the management of children and adolescents with recurrent headaches, physicians should be aware of symptoms of ADHD, as they might have a negative impact on frequency or severity of comorbid migraine or TTH.

8.10 Gilles de la Tourette Syndrome

Tourette syndrome (TS) is one of the most common childhood genetic movement disorders, with a reported frequency in children as high as 3 %. The condition is characterized by motor and phonic tics that fluctuate in distribution, severity and frequency. TS is associated with attention deficit with or without hyperactivity, obsessive-compulsive traits and other neurobehavioral comorbidities, such as poor impulse control, self-injurious behaviour, anxiety and mood disorders. The frequency of migraine headache in a clinic sample of TS subjects including 62 children and 38 adults was nearly fourfold more than the frequency of migraines reported in the general population [30]. In a prospective questionnaire-based study [31], the incidence of migraine was four times higher, and the incidence of TTH was five times higher in children with TS than in the age-matched general population.

8.11 Depression and Anxiety Disorders

Depression is a common disorder in children and adolescents. A lifetime prevalence of serious depression is found in approximately 5 % of subjects younger than 18 years of age. The prevalence of depression increases with age, especially after the onset of puberty. There is no gender-related difference in children. Onset of puberty, however, is associated with a marked increase in the rate of depression among females, with a female-to-male ratio of 2:1. The prevalence of depression may be higher in children with other psychiatric disorders, such as ADHD or anxiety disorders, and in those with general medical conditions such as diabetes, asthma or cancer. Anxiety disorders comprise generalized anxiety disorder, panic disorder, phobias, obsessive-compulsive disorder, post-traumatic stress disorder and separation anxiety.

The comorbidity of migraine and psychiatric disorders has been investigated frequently and carefully in adults [32]. In contrast, there is far less evidence in children and adolescents [24, 33–35]. In 2008, Amouroux and Rousseau-Salvador [33] reviewed studies on the relation between migraine, anxiety and depression and selected those specifying the diagnostic criteria of migraine and using validated measures for anxiety and depression. Of 11 articles, 10 used a control group matched for age and sex. Only three of the studies used a representative sample of the general population. The studies included do not provide conclusive findings for the comorbidity of migraine, anxiety and depression in children. The majority of the studies with clinical populations show slightly higher scores on at least one of the anxiety or depression scales in the migraine group as compared to the control group. However, in all 11 studies, the average score on the anxiety and depression scales in children with migraine did not reach a pathological level, according to the norms established by the validated scales. Findings point to above-average levels of anxiety or depression, rather than diagnosed psychopathologies. None of the three studies carried out in the general population revealed differences between the anxiety and depression scores in children with migraine as opposed to children in the control group. In recent a review, Gelfand et al. concluded that the majority of children and adolescents with migraine do not have a comorbid psychiatric disorder and they point out that depression was associated with chronic migraine in one study [35].

Longitudinal studies suggest that psychiatric disorders in children and adolescents have an impact on pre-existing primary headaches and increase the risk of subsequent development of recurrent headache. In a clinic-based follow-up study, Guidetti et al. [36] assessed the relation between migraine, tension-type headache and various psychiatric disorders including anxiety disorders, sleep disorders, adjustment disorder, elimination disorders, eating disorders, mood disorders and school disorders. Generalized anxiety disorder was the most frequent psychiatric diagnosis, and anxiety disorder at baseline was related to enduring headache and migraine. In an epidemiologic study on ‘functionally impairing headache’, Pine et al. [37] found headache to be twice as common in depressed adolescents than in non-depressed adolescents. Major depression in adolescents, without current or past

headache, prospectively predicted the new onset of headaches in young adulthood. Among adolescents without a history of chronic impairing headache, those with current major depression faced a nearly tenfold increased risk of developing such headaches at some time during the next 7 years. Similarly, results from the Young HUNT follow-up study suggest that symptoms of anxiety and depression in early adolescence may be associated with subsequent occurrence of recurrent headache and the authors suggest that early identification of depression and anxiety in young headache patients may lead to improved headache management [38].

Studying the relationship between migraine and suicidal ideation in a non-referred sample of adolescents, Wang et al. [39] found that suicidal ideation was reported more frequently by subjects with migraine compared to non-migraine subjects (16.1 % vs 6.2 %; OR 2.9; 95 % CI = 2.3–3.6; $p = 0.001$). After controlling for depression score and sociodemographic characteristics, the association remained for migraine with aura (adjusted OR 1.79; 95 % CI = 1.07–2.99; $p = 0.025$) and high headache frequency (>7 days/month; adjusted OR 1.69; 95 % CI = 1.12–2.56; $p = 0.013$) but not for migraine without aura or probable migraine.

8.12 Conclusions

Recurrent headache and migraine in childhood and adolescence may be associated with and influenced by various comorbidities. Evidence is still limited. Statistically significant associations between migraine and other disorders were found more often in clinic-based than in population-based studies. Considering possible comorbid disorders in the management of headache and migraine is a prerequisite for establishing effective treatment strategies.

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Chapter 9
Temporomandibular Disorder Comorbidity

Fernando Exposto, Peter Svensson, and Lars Arendt-Nielsen

Abstract Temporomandibular disorders (TMD) are conceptualized as a group of diverse conditions related to the jaw muscles, temporomandibular joint (TMJ) and related tissues and may be associated with pain, limitations in jaw movements and noises in the TMJ. It is generally agreed that TMD just represents an umbrella term, and intensive work has been devoted to establish specific criteria for subsets of TMDs which are both reliable and valid. This has been achieved with the Diagnostic Criteria for TMD (DC/TMD) (Schiffman et al., J Oral Facial Pain Headache 28(1):6–27, 2014), and all main diagnoses now have known reliability, sensitivity and specificity values which are unique for any pain classification system. One of the new diagnoses in the DC/TMD is headache attributed to TMD (HATMD) (Schiffman et al., Cephalalgia 32(9):683–692, 2012; Schiffman et al., J Oral Facial Pain Headache 28(1):6–27, 2014) which clearly indicates that there is a close overlap between some of the many headache types and some of the painful TMDs. It may be useful from a clinical perspective to recognize some of the similarities in clinical presentation but also to try to identify potential differences in symptomatology as well as underlying pain mechanisms and management. This chapter will first provide an overview of the clinical presentations and overlaps between TMD and headache. Some of the basic mechanisms related to nociception from musculoskeletal tissues, peripheral and central sensitization and endogenous inhibitory controls will then be discussed with particular reference to TMDs.

F. Exposto
Section of Orofacial Pain and Jaw Function, Institute for Odontology and Oral Health, Faculty of Health, Aarhus University, Aarhus, Denmark
e-mail: fernando.exposto@odont.au.dk

P. Svensson (✉)
Section of Orofacial Pain and Jaw Function, Institute for Odontology and Oral Health, Faculty of Health, Aarhus University, Aarhus, Denmark

Department of Dental Medicine, Karolinska Institutet, Huddinge, Sweden
e-mail: peter.svensson@odont.au.dk

L. Arendt-Nielsen
Center for Sensory-Motor Interactions, Aalborg University, Aalborg, Denmark
e-mail: Denmarklan@hst.aau.dk

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9.1 Overview of Clinical Classifications of TMD and Headache

The international standard for headache classification is the International Classification of Headache Disorders (ICHD) which has been extensively field tested and used [1]. The DC/TMD can now be considered the international standard of clinical TMD classification together with the expanded TMD taxonomy [83]. One important point to realize is that not all TMDs are associated with pain; in fact, many of the TMDs are related to clicking or popping sounds from the TMJs or deviations in jaw movement patterns which are not painful or do not even bother the patient. This is particularly important when comorbidity between TMDs and headaches is considered. The painful TMDs are now grouped into jaw muscle pain (myalgia, myofascial pain with referrals), TMJ pain (arthralgia) and HATMD. It should be noted that the degenerative TMJ disorders (i.e. osteoarthrosis) are not necessarily associated with pain, but if so, the diagnosis should be combined with TMJ arthralgia. Furthermore, it should be noted that the painful TMDs all have good-to-excellent sensitivity and specificity values (>0.85), whereas the non-painful ones (structural TMDs like disc displacements with/without reduction, degenerative TMJ disorders) all have poor sensitivity values but good-to-excellent specificity values. Notwithstanding the importance and significance of the ICHD classification, no systematic information seems available for reliability or validity measures of different subsets of headaches. Table 9.1 lists the criteria for the painful TMDs according to the DC/TMD, whereas the specific criteria for the most common types of headaches (tension-type headache (TTH), migraine) can be found in the original ICHD publication [1].

From a purely anatomical perspective, all types of painful TMDs are obviously "headaches" as the jaw and orofacial region are part of the head. Therefore, merely based on this fact, it is perhaps unsurprising that painful TMDs and headaches frequently overlap. However, a more careful examination of the specific criteria for painful TMDs per the DC/TMD reveals that these diagnoses are only justified if patients outline their pain in specific parts of the jaws/temple and if this can be verified by the examiner based on further questions to the patients. Moreover, the pain complaints need to be reproduced by either jaw movements or standardized palpation of the jaw muscles or TMJs, i.e. emphasis is devoted to the clinical feature of "familiar pain". In contrast to the DC/TMD specifications, no particular emphasis is given to pain distribution in TTH except that it is usually bilateral, affects the temple and that the quality may be "pressing". TTH is mainly subdivided according to the temporal characteristics into infrequent episodic, frequent episodic and chronic types. Furthermore, there are subsets of TTH which are associated with pericranial tenderness. In the DC/TMD, specific recommendations for clinical palpation of muscles with 1 kg and the TMJ with 0.5 kg are provided, whereas the ICHD criteria give no two such specifications, and the evoked response includes "tenderness" and not only "pain". Such differences in criteria may indeed be important when the overlap between conditions is examined.

Table 9.1 Overview on specific criteria for painful TMDs and headaches attributed to TMDs according to two major classification systems (DC/TMD and ICHD-3)

	Local myalgia	Myofascial pain with referral	Arthralgia	Headache attributed to TMD (DC/TMD)	Headache attributed to TMD (ICHD – 3)
Description	Pain of muscle origin as described for myalgia with localization of pain only at the site of palpation when using the myofascial examination or protocol	Pain of muscle origin as described for myalgia with referral of pain beyond the boundary of the muscle being palpated when using the myofascial examination protocol. Spreading pain may also be present	Pain of joint origin that is affected by jaw movement, function, or parafunction, and replication of this pain occurs with provocation testing of the TMJ	Headache in the temple area secondary to pain-related TMD (see Note) that is affected by jaw movement, function, or parafunction, and replication of this headache occurs with provocation testing of the masticatory system	Headache caused by a disorder involving structures in the temporomandibular region
History	Positive for both of the following: 1. Pain in the jaw, temple, in the ear, or in front of ear 2. Pain modified with jaw movement, function, or parafunction	Positive for both of the following: 1. Pain in the jaw, temple, in the ear, or in front of ear 2. Pain modified with jaw movement, function, or parafunction	Positive for both of the following: 1. Pain in the jaw, temple, in the ear, or in front of ear 2. Pain modified with jaw movement, function, or parafunction	Positive for both of the following: 1. Headache of any type in the temple 2. Headache modified with jaw movement, function, or parafunction	A. Any headache fulfilling criterion C B. Clinical and/or imaging evidence of a pathological process affecting the temporomandibular joint (TMJ), muscles of mastication, and/or or associated structures C. Evidence of causation demonstrated by at least two of the following: 1. Headache has developed in temporal relation to the onset of the temporomandibular disorder 2. Either or both of the following: (a) Headache has significantly worsened in parallel with progression of the temporomandibular disorder

(continued)

Table 9.1 (continued)

	Local myalgia	Myofascial pain with referral	Arthralgia	Headache attributed to TMD (DC/TMD)	Headache attributed to TMD (ICHD – 3)
					(b) Headache has significantly improved or resolved in parallel with improvement in or resolution of the temporomandibular disorder 3. The headache is produced or exacerbated by active jaw movements, passive movements through the range of motion of the jaw, and/or provocative manoeuvres applied to temporomandibular structures such as pressure on the TMJ and surrounding muscles of mastication 4. Headache, when unilateral, is ipsilateral to the side of the temporomandibular disorder
Exam	Positive for all of the following: 1. Confirmation of pain location(s) in the temporalis or masseter muscle(s) 2. Report of familiar pain with palpation of the temporalisor masseter muscle(s) 3. Report of pain localized to the site of palpation	Positive for all of the following: 1. Confirmation of pain location(s) in the temporalis or masseter muscle(s) 2. Report of familiar pain with palpation of the temporalisor masseter muscle(s) 3. Report of pain at a site beyond the boundary of the muscle being palpated	Positive for both of the following: 1. Confirmation of pain location in the area of TMJ(s) 2. Report of familiar pain in the TMJ with at least one of the following provocation tests: (a) Palpation of the lateral pole or around the lateral pole	Positive for both of the following: 1. Confirmation of headache location in the area of the temporalis muscle(s) 2. Report of familiar headache in the temple area with at least one of the following provocation test: (a) Palpation of the temproalis muscle(s)	Not available

			(b) Maximum unassisted or assisted opening, right or left lateral, or protrusive movement(s)	(b) Maximum unassisted or assisted opening, right or left lateral, or protrusive movement(s)	
Comments	The pain is not better accounted for by another pain diagnosis. Other masticatory muscles may be examined as dictated by clinical circumstances, but the sensitivity and specificity for this diagnosis based on these findings have not been established	The pain is not better accounted for by another pain diagnosis. Other masticatory muscles may be examined as dictated by clinical circumstances, but the sensitivity and specificity for this diagnosis based on these findings have not been established	The pain is not better accounted for by another pain diagnosis	The headache is not better accounted for by another headache diagnosis	Not better accounted for by another ICHD-3 diagnosis

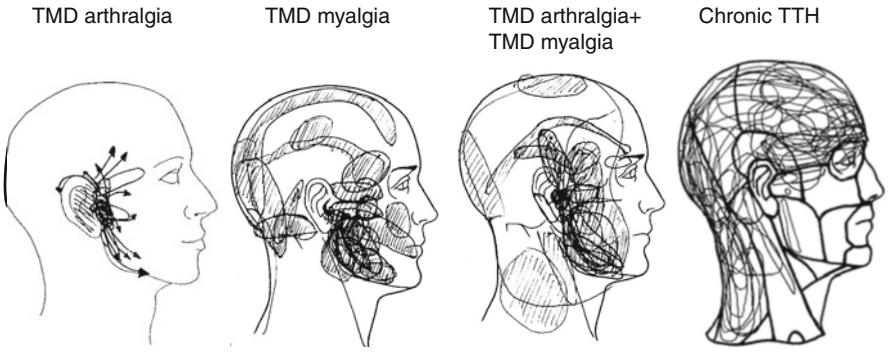

Fig. 9.1 Superimposition of individual patient-based drawings of perceived areas of pain. Temporomandibular joint (*TMJ*) arthralgia ($n = 10$), temporomandibular disorder (*TMD*) myalgia ($n = 13$), mixed TMJ arthralgia and TMD myalgia ($n = 13$), and patients with chronic tension-type headache (*TTH*) ($n = 22$). The three TMD drawings are from Svensson (unpublished); the TTH drawing is from Schmidt-Hansen et al. 2005

When patients with different clinical TMD and headache diagnoses are asked to draw their painful areas on figures of the head, a close inspection, in addition to a more quantitative analysis, indicates that the location/specific sites differ between, e.g. myalgic TMDs, TMJ arthralgias, chronic tension-type headaches (CTTH) and migraine patients (Fig. 9.1). The possibility of the frequently observed overlap and comorbidity between painful TMDs and headaches being due to pure chance should be considered, since both conditions are highly prevalent and manifest in the head. Most studies describing this overlap are, in fact, cross-sectional and based on slightly different criteria for TMD and headaches, and keeping in mind some of the potential weaknesses of the ICHD to pinpoint location and amount of pressure for palpation, this, in addition to lack of blinding of examiners, may perhaps explain part of this overlap. Studies with concise and operationalized criteria for both TMD and headache will be needed together with sufficient blinding of examiners for clinical diagnosis.

With these caveats in mind, more recent and longitudinal studies have looked into the comorbidity between painful TMDs and headaches. One study found that first-onset TMD pain (not subdivided into muscle or TMJ pain) was significantly associated with reports of headache and headache severity [102]. It should be noted that first-onset TMD pain was also associated with pain in one or more bodily sites. However, this could lead to the challenging suggestion that the TMDs were attributed to headache in contrast to the DC/TMD and ICHD diagnoses of HATMD. So could there be a bidirectional relationship between painful TMDs and headaches, perhaps related to more basic characteristics of the nociceptive system? In the following, an overview on basic pain mechanisms from musculoskeletal tissues is provided, and the implications for TMD and headache are discussed.

9.2 Basic Pain Mechanisms

Both peripheral and central sensitization processes have been implicated in the pathophysiology of painful TMDs [24, 25] and headaches [7, 13, 14, 17, 21, 60, 68]. It should be noted that there is currently no accurate electrophysiological or imaging test of either peripheral or central sensitization of the nociceptive pathways in the human trigeminal system but rather a number of clinical "proxies" of these mechanisms, such as quantitative sensory testing (standardized application of thermal, mechanical, chemical or electrical stimuli and recording of patient-based responses or evoked physiological measures).

9.2.1 Peripheral Sensitization

In TMD, peripheral sensitization can occur through either activation of muscle or joint nociceptors [23, 99]. Several substances have been shown to activate peripheral muscle nociceptors [73, 74]. It is thought that the two most important factors in causing muscle pain are the release of adenosine triphosphate (ATP) and protons (H+). These substances activate receptors on free nerve endings causing depolarization of the nociceptive neuron. This activation in turn causes the release of neuropeptides from the free nerve endings such as substance P (SP), bradykinin (BK), calcitonin gene-related peptide (CGRP), serotonin and prostaglandin E2 (PGE2), what is termed neurogenic inflammation [122]. There are also other substances, such as tumour necrosis factor alpha (TNF-α) and nerve growth factor (NGF), that are released and can further stimulate nociceptors [74]. Because of this cascade of events, the sensitivity of the muscle nociceptors is increased causing hyperalgesia, and they are more susceptible to stimuli such as normal jaw function. In the case of the TMJ, inflammation is probably the most common driver of pain. It is thought that inflammation caused by increased loading and remodelling results in the release of pro-inflammatory substances such as TNF-α and interleukins [3, 111]. The release of these substances will, as with muscle pain, cause the release of more inflammatory substances, such as SP, BK, PGE2 and CGRP. This neurogenic inflammation will result in the hallmarks of inflammation such as redness, oedema, increase in temperature and pain [112]. It has also been shown in experimental models of headache as well as myalgic and arthralgic TMD that there is an increase in peripheral glial cells [22, 69, 118, 127] that may contribute to the peripheral sensitization that may be seen in the different types of TMD and headaches.

In the context of headaches and TMDs, it is significant that these changes in the normal conduction of somatosensory information from the joint and muscle structures may contribute to a spread and referral of pain that could be perceived as a "headache" by the patients due to the close anatomical relationship between the TMJs, masticatory muscles and the usual sites where headaches are felt such as the temple, frontal and occipital areas.

Despite this, clinically, the concentrations of ATP, PGE2, glutamate and other inflammatory mediators have not been shown to differ in tender points of patients with CTTH when compared to healthy controls [5]. The authors concluded that tender points are not sites of ongoing inflammation. On the other hand, Shah et al. found that there was inflammation in active trigger points (TrPs) in the trapezius of neck pain subjects as well as a remote site and that these were substantially different from controls [100]. However, such studies need to be replicated in larger sample sizes and with blinded observers.

In patients with myalgic TMD and in experimental models of myalgia, lower mechanical and thermal thresholds have been shown in the painful area when compared to controls [49, 70, 89, 103, 107–109, 116]. In patients with TTH, such signs or "proxies" of peripheral sensitization have also been demonstrated. Studies assessing pressure pain threshold (PPT) in patients with TTH have found, with some exceptions, that PPTs in the cranial region are lower in patients with episodic TTH (ETTH) when compared to controls, and these same thresholds are more robustly decreased in patients with CTTH [2, 6, 42, 98]. Furthermore, it is clinically evident that TTH consists of various subgroups where muscle triggers such as TrPs may play a role. No studies have so far addressed the question of how TrPs may help stratifying different populations, but a number of papers have shown an association between the number of trigger points and the severity of TTH attacks [38–40, 43]. Interventional studies (needling, toxins, local analgesics) targeting the TrPs have resulted in very different outcomes, and many of these studies lack controls and proper patient profiling.

Regarding arthralgic TMD, it is thought that the process of peripheral sensitization can occur much in the same way as with myalgic TMD. Despite this, arthralgic TMD appears to have low prevalence among headache sufferers [48, 51]. Gonçalves et al. reported that a muscular component seems to be needed to cause mixed TMD or myalgic TMD and that both of these were more associated with chronic daily headache and migraine than with ETTH [51]. This could be due to the fact that most of the time if arthralgic TMD is severe enough, it may cause a protective reflex of the jaw muscles (e.g. a splinting effect) and could eventually lead to myalgic TMD as well [119]. More research will be needed to demonstrate the importance of such possible reflex mechanisms in TMD pain and HATMD.

In summary, peripheral sensitization is believed to be an important mechanism in both TMDs and headaches. In general it is shown that peripheral sensitization may play a role in decreasing somatosensory thresholds (mechanical, thermal). The increased tenderness upon palpation of muscles for both TMD and headaches is thought to be due to sensitization of muscle nociceptors although more studies are needed.

9.2.2 Central Sensitization

Strong excitation of nociceptive-specific fibres such as C fibres, and in particular those from deep tissues such as muscles and joints, can in turn lead to prolonged excitability of neurons in central nociceptive pathways that is referred to as central

sensitization, and this phenomenon may be responsible for allodynia [120]. If central sensitization is limited to the trigeminal second-order neurons, pain will be limited to the areas innervated by the trigeminal nerve [21]. On the other hand, if this sensitization advances to the third-order neurons in the thalamus, the phenomenon could be responsible for the widespread pain that is reported in some subgroups of painful TMDs and headaches [21, 62]. As a result of widespread hypersensitivity, there are many comorbidities among different pain syndromes with a high prevalence of, for example, TMD in fibromyalgia [63] and chronic low back pain [9] as well as TTH [29] and migraine [117]. The more widespread a musculoskeletal pain problem becomes, the more somatosensory signs of generalized hypersensitivity are found [26].

Clinically, this widespread hypersensitivity has been shown both through patient report of pain [115] and also through lowered pain thresholds both cranially and extracranially [20, 45, 70, 84, 116]. For example, patients with myalgic TMD pain have generally lower pain thresholds to mechanical stimuli applied to the painful area when compared to control subjects [70, 107, 110, 116]. However, it has also been shown that myalgic TMD patients have decreased pain thresholds outside the painful area and have a greater temporal summation (TS) of nociceptive cutaneous input [44, 70, 116]. These latter observations are difficult to explain with peripheral sensitization and clearly implicate the central nociceptive pathways. A generalized hyperexcitability of central nociceptive processing in TMD patients has been indicated by the finding of more pronounced TS of pain and greater after-sensations following repetitive painful mechanical stimulation of the fingers versus control subjects [94], and similarly widespread mechanical pain hypersensitivity has been reported in both myalgic TMD [44] and TMJ arthralgia patients [8]. It has also been shown that specific subgroups of TMD patients with widespread tender points present with lowered pressure and thermal pain thresholds both in trigeminal and extra-trigeminal areas when compared to TMD patients with less widespread tender points [84].

The same evidence of central sensitization has been found in patients with TTH even though, similarly to TMD, specific subgroups of patients present with different findings. These studies have found, with some exceptions, that PPT are lower in patients with ETTH when compared to controls [2], and these same thresholds are more robustly decreased in patients with CTTH, both in cephalic and extra-cephalic regions [2, 98]. Regarding TS studies, the results are fickle as they either show a small increase in TS of CTTH patients or no difference between these and controls [7, 95]. Taken together, these findings suggest that central sensitization may play a role in patients with CTTH but not to the same extent in ETTH [12]. Furthermore, evidence of central sensitization has also been found in migraine [19, 67] and cluster headache [45] both in cephalic and extra-cephalic regions.

These findings of central sensitization have been confirmed in both human and animal experimental studies. Activation of subnucleus caudalis neurons has been found in experimental animal models of both myalgic and joint TMD [28, 61, 90] as well as headache [16, 20]. In human experimental models, intramuscular injection of hypertonic saline into the masseter muscles causes localized pain around the

injection site as well as spread and referral of pain to the temple, teeth and ear both in patients with myalgic TMD pain and healthy controls. Moreover, patients with myalgic TMD reported a larger pain area and more pain intensity than controls [110]. A similar study was done in frequent ETTH and CTTH patients. Both groups showed increased pain levels and larger pain areas when compared to healthy controls. Furthermore, and differently from the TMD study, increased sensitization of extra-trigeminal sites was also found [98]. This is in line with another recent study on CTTH patients showing a generalized hyperalgesia to single and repetitive electrical stimuli [7]. An important finding is that since the distinction between infrequent episodic (IETTH) and frequent episodic (FETTH) TTH, it has been reported that pain thresholds in FETTH are lowered when compared to the IETTH but do not differ from CTTH [98]. These findings imply that FETTH and CTTH are part of a continuum and not separate entities and that central sensitization is perhaps necessary for chronification [17, 18].

In summary, both myalgic TMD and headache patients have several clinical features which are compatible with both peripheral and central sensitization of the nociceptive pathways. This increased sensitivity is reflected into different pain conditions such as fibromyalgia, TMD and headache, and thus it is important for the clinician to be aware of this overlap between conditions [126].

9.3 Endogenous Pain Modulatory Systems

There is increasing evidence that the balance between the descending pain inhibition and facilitation may be disturbed in some chronic pain conditions and that this phenomenon has a role in maintaining central sensitization and spontaneous pain [86, 106, 125]. It has been observed for some time now that wide dynamic range neurons (convergent neurons) are inhibited by nociceptive stimuli applied to a segment remote from the excitatory receptive fields [59]. This phenomenon of diffuse noxious inhibitory control-like effects can also be triggered in humans and is termed conditioned pain modulation (CPM) [124]. CPM can be assessed as the analgesic effect to a given painful test stimulus when applied together with a tonic painful stimulus (the conditioning stimulus). CPM is assumed to be the net sum of the descending pain inhibition and pain facilitation, and this net sum is shown to result in reduced pain inhibition in many chronic pain conditions [105, 123].

Regarding patients with painful TMD, the results have been equivocal as some studies have shown that the endogenous pain modulatory system (EPMS) is not compromised [47, 59]. The results may however depend on the technique used to assess CPM as other studies with different types of conditioning stimuli have shown impaired CPM in painful TMD [56, 81] as well as the heterogeneity of the TMD group that can include patients with arthralgia, myalgia or with both. Other findings indicate that CPM could be impaired in TMD pain patients especially at sites with chronic pain but not at pain-free sites and that the clinical pain characteristics do not influence CPM [59]. Similar deficiencies in CPM have been shown in patients with

TTH and migraine [27, 35, 85, 93]. Again this may have implications for the overlap between painful TMDs and headache as impaired endogenous control systems may contribute to the spreading and referral of pain. Another consideration is whether the pain condition occurs due to a deficient EPMS or if the pain condition causes the deficiency in the EPMS. It has been shown that CPM can change over time and that these changes may be related to the absence or presence of pain as well as sleep disturbances [53, 58, 64]. With this in mind, the interaction between painful TMD and headaches becomes even more complex as it could be argued that a deficient EPMS could facilitate both conditions but also that the presence of one or the other could weaken the EPMS and thus contribute to the presence of the other. Clearly there is a need for developing more sophisticated CPM techniques to better understand the potential contribution of EPMS in painful TMDs and headaches.

9.4 Genetics

Recently, it has been shown that different functional polymorphisms and haplotypes can cause differences in pain perception and sensitivity [34, 87]. The most promising avenue of research in the field of TMD is the variation in coding of the catechol O-methyltransferase (COMT). This enzyme metabolizes catecholamines such as epinephrine, norepinephrine and dopamine that play a critical role in pain perception, cognitive function and affective mood [34]. An association has been found between COMT haplotypes and sensitivity to experimental painful stimuli [33]; it has also been shown that carriers of the low pain sensitivity haplotype of the COMT gene have a 2.3 times lower risk of developing myalgic TMD when compared to individuals carrying the high pain sensitivity haplotype [34]. Furthermore, it has been shown that individuals carrying specific polymorphisms are also at a higher risk of developing TMD [75]. Finally, it has been demonstrated that the influence of COMT activity on pain sensitivity is, in part, mediated through adrenergic receptors beta 2 and 3 (ADRB2 and 3) [76] and that individuals who carry one haplotype coding for high and one coding for low ADRB expression display high positive psychological traits, have higher levels of resting arterial pressure and are about ten times less likely to develop TMD [32]. The activation of ADRB leads to the release of nitric oxide (NO) as well as several cytokines such as TNF-α, IL-1β and IL-6 [55], all of which have been implicated in painful TMD and TTH [4, 31, 57, 82, 101]. Moreover, selective treatment with an ADRB antagonist (propranolol) has been shown to decrease pain depending on the number of low pain sensitivity (LPS) alleles of the COMT gene [113]. However, numerous other genes coding for neurotransmitters and neuromodulators may obviously also have implications for pain sensitivity [113] and TMD [79, 104].

Regarding headaches, the genetic contribution to familial hemiplegic migraine (FHM) is well established [114], and some studies have shown a genetic contribution to regular migraine as well [37, 88]. Another recent study on twins concluded that genetic factors play a role in FETTH, while IETTH appears to be caused

primarily by environmental factors [91]. Most studies regarding TTH have failed to show a relationship with specific genetic traits [41, 54], but most of these studies have not distinguished among the different types of TTH.

Furthermore, it has been shown that both dopamine receptor D3 (DRD3) and serotonin transporter gene polymorphisms can predict the efficacy of CPM [66, 87]. Considering that several studies have indicated that a less efficient CPM may be implicated in TMD [56, 81], migraine [77, 93], TTH [85, 93] and chronic post-traumatic headache [30], it would be important to consider that these genes may be indirectly involved in the development of TMD and headaches.

In summary, there is emerging evidence to support the notion of a genetic component involved in both myalgic TMD and TTH, and more studies may help to further identify vulnerable genes that interact with environmental factors, such as physical and emotional stress, to produce pain-prone phenotypes at risk for developing myalgic TMD pain and/or headache. These studies highlight the importance of individually tailored treatment plans for both TMD and headaches and further emphasize the idea that similar presenting conditions may have a different pathophysiology [11].

9.5 Clinical Evidence of Comorbidity Between TMD and Headaches

Several studies have looked at the association between TMD and headache with evidence of significant overlap between these conditions [51, 52, 65, 78]. A higher prevalence of TMD has been found in both episodic and chronic migraine patients when compared to controls [52]. Another study found that the presence of TMD increases the risk of chronic daily headache (CDH), migraine and ETTH. Furthermore, this increased risk was found for myalgic and mixed TMD but not for arthralgic TMD [51]. A study that investigated the frequency of TMD in 99 headache patients showed that the prevalence of TMD in the headache population is 56.1 % [10]. Moreover, the highest percentage of TMD was found in patients with a combination of migraine and TTH (75 %), followed by migraine alone (53.3 %) and TTH alone (45.4 %) [10]. Finally, several studies have shown that headaches are more severe and frequent as TMD pain increases [51] but also that TMDs are more severe in patients with headache [72]. Taken together these findings support our notion of a bidirectional relationship between painful TMDs and headache. At present, a temporal relationship between these two conditions cannot be inferred as most studies are cross-sectional. Despite this caveat one cross-sectional study showed that when asked through a questionnaire, adolescents reported that the onset of headache preceded the TMD pain [78]. On the other hand, a longitudinal study that followed the development of trigeminal and spinal pain for a period of 2 years showed that the baseline presence of spinal pain or TMD signs was more likely to cause headache occurrence than in subjects where these features were not present at baseline [71].

The fact that the severity of TMD and headaches increases when both conditions are present has recently been confirmed in a study where PPTs of masticatory muscles were shown to be lower in patients with both migraine and TMD, followed by migraine only, TMD only and finally healthy controls [92]. Furthermore, it has been shown that when TMD and migraine present in the same patient, the best therapeutic results are obtained when directing therapy to both conditions [15, 50]. Several studies have looked into the effects of treatment of TMD on headache with positive but varied results, and the studies have not always distinguished between the different types of headache [36, 46, 121]. For example, Ekberg et al. have shown that the use of an oral appliance in patients with concomitant TMD and TTH resulted in improvement of both frequency of headache and tenderness to palpation in the masticatory muscles when compared to a control appliance group [36]. The specificity of the different treatment modalities in painful TMD may however not be very high, and their mechanistic action on complex pain processes has not been established.

Finally, the diagnosis HATMD has been included in both the ICHD [1] as a secondary headache and the DC/TMD [96, 97]. In this type of headache, the pain needs to be felt in the temples and has to be modified by jaw function, and finally it either has to get worse as the TMD gets worse or it has to improve as the TMD gets better (Table 9.1). The diagnostic criteria for secondary headaches [80] state that for a disorder to qualify as a secondary headache, it has to fulfil two criteria: evidence of causation and the headache which is not better accounted for by another headache diagnosis. There are, we feel, some issues with these criteria in regard to HATMD. Firstly, evidence of causation between headaches and TMD, as has been discussed above, is still lacking, and the evidence actually points more towards a reciprocal relationship [51]. Secondly, if the headache is produced or exacerbated by jaw movement, then it could be argued that in fact this fits into one of the categories of the DC/TMD such as local myalgia if the headache is felt in the temple and is exacerbated by palpation of the temporalis muscle and myofascial pain with referral if, for example, palpation of the masseter muscle exacerbates a headache felt in the temple. Furthermore, if the headache is caused by TMJ pain and movement, it could also be argued that this is merely referred pain from the TMJ. This is not accounted for in the ICHD or the DC/TMD as in these criteria headache can only be better accounted for by other headaches and not by other pain conditions such as local myalgia and referred pain.

9.6 Conclusions and Future Directions

There is overwhelming evidence in the clinical literature on substantial overlaps between painful TMDs and headache. Nevertheless, it may be premature to conclude that headaches are attributed to TMDs or that TMDs are attributed to headaches; rather they may be associated with each other and perhaps in a bidirectional manner. Some of the underlying pain mechanisms from joints and muscle tissue may help to understand that the (trigeminal) nociceptive system undergoes

profound neuroplastic changes that could contribute to poor localization and identification of the source of pain. Furthermore, such neuroplastic switches in nociceptive transmission may, through complex cellular changes both at the peripheral level, but also involving central sensitization and impairment of EPMS, help explain chronification of TMD pain and headache. There is an urgent need for more research into the basic trigeminal pain mechanisms lacking behind the general field of spinal pain mechanisms in addition to clinical sound and well-characterized studies on overlaps between painful TMDs and headache.

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Chapter 10
Orofacial Pain Comorbidity

Andrea Truini and Joanna M. Zakrzewska

10.1 Trigeminal Neuralgia

TN is a relatively rare condition defined as "a sudden unilateral severe, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial nerve" IASP [1].

10.1.1 Epidemiological Studies

In a recent survey of UK GP practices, it was estimated that it has an incidence of 26.8 per 100,000 person years [2], but the disorder is often misdiagnosed, and in a similar study done in Holland, where the neurologist validated the diagnosis, the incidence rate was 12.6 per 100,000 person years (CI 10.5–15.1) [3]. A systematic review of the epidemiology and diagnosis of this condition shows that there are no papers which would provide data on the long-term prognosis of this condition and there is little on comorbidity [4]. The condition is well known to induce natural periods of pain remission and these seem to be extremely variable in length [5], and fewer patients undergo surgery than has been estimated [6].

The early epidemiological studies in the USA attempted to look for risk factors. Rothman and Monson [5] compared 500 patients who had been admitted to hospital for surgical management of their TN over a 16-year period with 528 controls who had been admitted for cervical disc problems. In their initial analysis, they identified multiple sclerosis as a risk factor but then also identified that the following factors were more commonly seen in TN patients: they smoked and drank less, had fewer tonsillectomies and were less likely to be Jewish or be immigrants. They also noted that TN patients were less likely to have other systemic diseases. In a further paper

A. Truini
Sapienza University, Rome, Italy
e-mail: andrea.truini@uniroma1.it

J.M. Zakrzewska (✉)
University College London (UCL), London, UK
e-mail: j.zakrzewska@ucl.ac.uk

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using the same population, Rothman and Beckman [7] found that patients with lower face pain (mandibular division) were more likely to be younger at onset and this was more marked in men. Right-sided pain was more common. Non-smoking and non-drinking were associated with upper face pain, whereas non-Jewish origin was associated with increased risk for lower face pain. They suggest that this could be due to selective injury of cells, but no other explanations are provided.

10.1.2 Multiple Sclerosis

The most frequent comorbidity is multiple sclerosis (MS), and this had already been noted by Harris in 1926, who also observed that TN MS patients were more likely to be bilateral cases [8]. It has, however, been suggested that Oppenheim had noted this connection on autopsy in 1894. Hospital-based studies have estimated that MS patients are 20 times more likely to present with TN symptoms than non-MS patients [9]. TN prevalence among MS patients ranges from 1.9 to 7.9 %, with the most recent systematic review and meta-analysis putting it at 3.8 % (95 % confidence interval 2–6 %) [10]. In most series more females are affected. In the majority of instances, MS occurs prior to TN developing [11], and patients with more severe MS are more likely to develop neuropathic pain including TN. TN tends to occur later than other neuropathic pains. Boneschi et al. (2008) found that the overall prevalence of TN was the same in relapsing/remitting and progressive forms, but if broken down in subgroups, there were some differences, with progressive being more common than relapsing/remitting.

TN is more likely to be bilateral than in other TN cases [12–14]. The age of onset of TN may be earlier among the MS patients compared to patients with TN alone [15, 16], but this finding is not consistent across all studies [11, 17]. Osterberg et al. [14] postulate that MS patients with TN may differ from those with TN alone in that they may also have central pain, which is aching, burning and more constant, and this pain is superimposed on the pain from the TN. This is supported by Cruccu et al. [11] who show damage to second-order neurons in the spinal trigeminal complex, an area not typically involved with TN alone. However, not all other researchers have confirmed these patterns. Some have found more bilateral TN in MS patients, as seen in Table 10.1, but others have not shown this difference [16]. O'Connor et al. reviewed the association of pain with MS and showed that risk factors for increased likelihood of pain were older age, longer disease duration and greater disease severity [15].

Neurosurgeons have been reporting results of surgical procedures in patients with TN and MS and have shown lower efficacy, relating this to complex pathophysiology of the condition, as some patients also have neurovascular compression [28]. Interestingly, Ariai et al. [29] noted from their database of 350 TN patients who had a microvascular decompression (MVD) that 10 had ipsilateral brainstem T2-MRI hyperintensity but only 5 had potential clinical features of MS and only one has since had MS confirmed. Previous studies have suggested that MRI findings correlated

Table 10.1 Some data from neurology and MS clinics and a few from the neurosurgical units

Publication	TN number	Setting number	Frequency	Gender	Age onset	Number MS first disease	Interval between MS TN years	Bilateral cases number
Rushton and Olafson (1965) [18]	35	Neurology 1735	2					4
Chakravorty (1966) [19]	10	Neurology 124	8	6 F 4 M	Mean 51	0	Mean 21	0
Jensen et al. (1982) [20]	22	Neurology 900	2.4	12 F 10 M	13 below 50	19	Mean 12	7
Vermote et al. (1986) [12]	3	Neurology 83 MS	3.6					
Moulin et al. (1988) [21]	7	Neurology ms 159	4.4					
Katusic et al. (1990) [9]	3	Neurology 75	4					
Hooge and Redekop (1995) [13]	35	MS clinic 1882	1.9	24 F 11 M	Mean 51	30	Mean 11.8	5
Eriksson et al. (2002) [22]	5	Neurology ms 255	2					
Solaro et al. (2004) [23]	36	Neurology ms 364	2.2					
Osterberg et al. (2005) [14]	18	Neurology ms 429	4.9	13 F 5 M	Mean 49	17	Mean 19	2
Cruccu et al. (2009) [11]	50	MS neuropathic pain clinics 139		32 F 18 M	Mean 43 sd 11			4
Montano et al. (2012) [24]	21	Neurosurgery		11 F 10 M		5	Mean 13.8 SD 8.4	
Mohammad-Mohammadi et al. (2013) [25]	96	Neurosurgery			Median 50	86	Median 10 years	10
Bender et al. (2013) [26]	63	Neurosurgery 822	8	29 F: 46 M	Mean 52	51		9
Lummel et al. (2014) [27]	12	Neuroradiology		9 F: 3 M	Mean 46	7	Mean 15	
Foley et al. (2013) [10]	1755	Meta-analysis 7101						

with clinical findings at surgery where demyelination of the central portion of the trigeminal nerve is noted [30, 31]. Cruccu et al. [11] also showed a strong correlation between T2 hyperintensity in patients with TN and MS but also found these findings in other MS patients who did not have TN. Diffusion tensor imaging in 12 patients with TN MS shows microstructural changes not just on the side of the TN as compared to 12 matched TN with neurovascular contact and 123 controls [27]. Ariai et al. suggest therefore that MVDs should not be done in patients with T2 hyperintensity even if they have neurovascular compression. This is not borne out by Montano et al. [28] who reviewed all surgical procedures in TN MS patients, and noted that the best results are obtained with MVD, although the results are not as good as for classic TN.

10.1.3 Hypertension, Cardiovascular

Given that neurovascular compression plays a role in some forms of TN, it would seem probable that arterial tortuosity and hypertension could increase the risk of having TN. In a small cohort of 36 patients in Minnesota, Yoshimasu et al. [32] reported a possible association with hypertension, with an odds ratio of 1.96 (95 % confidence interval 1.2–3.1). There are, however, conflicting reports in the literature. Teruel [33] used a hospital population of 84 classic TN with and without hypertension (diagnosed and treated with antihypertensives by physicians) and compared them to 252 age- and gender-matched controls. They found a prevalence of 37 % in TN and 32 % in the control group with an odds ratio of 1.24 (95 % confidence interval 0.7–2) which was not statistically significant when compared to the controls. It needs to be noted that this was a retrospective study, the duration of hypertension may be important and it could be that both populations are older. A population study based on insurance claims which cover 97 % of the population in Taiwan showed that patients with hypertension have an increased risk of getting TN [34]. Pan et al. [34] identified 138,492 people with at least two visits of ICD9-coded hypertensive diagnosis and then found 2 age- and sex-matched subjects for each, thus making 276,984 patients. A diagnosis of TN had to be recorded at least twice, and they also ascertained the presence of diabetes and hyperlipidaemia as comorbidities over a 3-year period. They identified 121 patients who developed TN in the hypertensive group and 167 in the non-hypertensive group and when corrected for the comorbidities had an adjusted hazard ratio of 1.5 (95 % CI 1.19–1.9). The follow-up was only 3 years, so the effect of duration of hypertension was not evaluated. A longer-term follow-up would ascertain whether hypertension results in increased tortuosity of vessels, which could then produce demyelination of the trigeminal nerve if in close contact. An epidemiological study in a city of Egypt looking for TN in >30-year-olds found 4 cases among 13,541 and noted comorbid depression and hypertension [35]. The cases were diagnosed by experienced neurologists.

In a prospective cohort of 158 patients, a history of hypertension was found in 32 % (95 % confidence intervals, 25–40 %), and 17 % had some form of cardiovascular disease, but this data was not compared to controls or national data [36].

Using the same insurance database in Taiwan as described for hypertension, Pan et al. [37] looked for increased susceptibility to stroke. They identified 1453 TN patients (based on at least 3 visits over a 2-year period) and then for the same time period examined a non-TN age- and gender-matched group of 5812 individuals. They reported an increased risk of stroke after TN was diagnosed (TN cohort, 73 developed a stroke), and so the adjusted (controlled for other cardiovascular disorders and diabetes) hazard ratio was 1.76 (95 % CI 1.33–2.33). However, other risk factors are not accounted for, the study only lasted 2 years and there are no details of how the diagnosis was made.

10.1.4 Headaches, Other Facial Pain

It would be expected that these patients may have other forms of headache, and in the 158 patients reported by Maarbjerg [36], the following were noted: tension-type headache 13 %, migraine without aura 9 %, post-traumatic headache 3 %, idiopathic stabbing headache 1 % and cluster headache 1 %. Association of cluster headache and TN has been described by several headache neurologists and termed Cluster-tic [38]. Haviv et al. [39] in their study of 81 TN patients reported no significant association with muscle pain but did note disturbance of sleep. Although most patients report that sleep provides a welcome relief from TN, Wu et al. have shown that sleep disturbance is more likely in TN and other studies have confirmed this finding [39, 40]. Glossopharyngeal neuralgia and TN can coexist. Gaul et al. reported 2 cases in 19 patients [41] and Ferroli reported 6 out of 31 [42].

10.1.5 Psychological Disturbances

As with all chronic pains, psychological factors need to be considered, and it is often difficult to differentiate between pre-existing psychiatric and psychological problems and those arising as a result of the pain itself or due to the medications. Several anticonvulsants are also used in psychiatric practice and so could possibly mask some psychiatric disorders [43].

The largest study to date looking at the relationship between TN and mental health was reported by Wu et al. in 2015 [43]. Using the national database over a period of 10 years, they compared newly diagnosed TN patients with no previous psychiatric problems (*n*. 3273), with a matched control group of 13,092. The diagnosis of TN had been made by a neurologist based on at least two visits and the mental health diagnosis by a psychiatrist. They found TN patients had increased depression, anxiety and sleep disturbance but no other psychosis. Previous smaller studies have suggested similar findings, but in those studies, TN patients were compared to other facial pain patients. Castro et al. [44] compared 15 TN patients with 15 temporomandibular patients in a secondary care setting using semi-directed

interviews and the Hospital Anxiety and Depression Scale (HADS). Both groups showed mild anxiety and depression with high limitations in activities of daily living, although it was only the TN patients that reported high pain intensity. Patients with TN appeared to have better coping strategies and were more positive about outcomes. Graff-Radford et al. [45] highlighted that there was higher psychological dysfunction (Minnesota Multiphasic Inventory and Chronic Illness Problem Inventory) in 21 patients with postherpetic neuralgia than 15 TN. They postulate that despite TN pain being of greater severity, it was intermittent, so providing a period of respite.

A group of 30 TN and TN+ concomitant pain patients were compared to 30 persistent idiopathic facial pain using the following measures: Sheehan Disability Scale (assessment of the patients' functional impairment in three domains: work/school, social life/leisure activities and family life/home responsibilities score >5 impairment), Covi Anxiety Scale and Beck Depression Inventory (BDI). The TN group showed significantly higher scores for physical disability, anxiety and depression than the persistent idiopathic facial pain group [46]. Unlike the Castro study, anxiety and depression were linked with pain severity, especially in those with TN and concomitant pain [46]. This could support Graff-Radford's theory that it is the continuous nature of chronic pain that is more likely to result in psychological morbidity. This is further supported by Komiyama et al. study [47], which compared 282 burning mouth syndrome patients and 83 TN. In this study patients in both groups were divided into those with acute (<6 months) and chronic (>6 months) symptoms, and they used the questionnaires from the Research Diagnostic Criteria for Temporomandibular Disorders (RDC-TMD) Axis II section. Pain severity was higher in both acute and chronic TN than in burning mouth syndrome patients, but somatization and depression were lower.

Zakrzewska and Thomas [48], using the Hospital Anxiety and Depression Scale (HADS), showed that depression reduced significantly after surgical management with radiofrequency thermocoagulation, whereas there was a less significant reduction of anxiety.

More formal neuropsychological assessments do show that patients with TN have deficits in psychomotor speed, reaction time, complex attention and cognitive flexibility as well as cognitive memory and general cognitive functioning, but it is difficult to determine what accounts for this, pain, medications or disease-specific features [49]. A recent study looking at adverse effects of antiepileptics in TN using questionnaires shows that cognitive function is significantly affected [50]. As Meskal et al. propose, these tests need to be carried out again after successful surgery when patients are off all medications and pain-free. Fear of pain and especially its unpredictability can make patients with TN more hypervigilant and therefore result in more pain [51, 52].

Tolle et al. [53], using psychometric measures in 82 TN patients, and Allsop et al. [54], using one-to-one interviews with 16 TN patients, showed that TN has a considerable impact on quality of life which affects not only the patient but the community where they live.

There are 8 case reports of TN and connective tissue disorders, but the TN is atypical (e.g. bilateral, continuous background pain) and so does not fulfil the criteria for classic TN [55].

10.1.6 Conclusion

Overall the most important comorbidity for TN is MS. Other comorbidities include hypertension and TN patients may be at higher risk of strokes. No psychiatric morbidities other than depression and anxiety have been identified, and these may change after successful surgical management.

10.2 Persistent Idiopathic Facial Pain

The International Headache Society defines persistent idiopathic facial pain as a "persistent facial and/or oral pain, with varying presentations but recurring daily for more than 2 h per day over more than 3 months, in the absence of clinical neurological deficit" (http://www.ihs-headache.org/ichd-guidelines).

Although previous studies reported a prevalence of persistent idiopathic facial pain of 0.3–0.4 % [3, 56], the unclear case definition of these studies and the lack of widely agreed diagnostic criteria might hamper the reliability of these findings. Persistent idiopathic facial pain, previously defined as atypical facial pain, is a diagnosis of exclusion. Often the onset of pain is preceded by minor operation or injury to the face, maxillae, teeth or gums, but pain persists after healing of the initial noxious event and without any demonstrable local cause. Pain is usually aching, dull, throbbing or pressing and fluctuates in intensity. It is poorly localized; it does not have the characteristics of cranial neuralgia and is not associated with identified lesions affecting the trigeminal system or the facial tissues [57, 58]. Pain may be described as either deep or superficial. With time, it may spread to a wider area of the craniocervical region.

Although a few studies using quantitative sensory testing and neurophysiological examination showed that some patients might have minor somatosensory abnormalities [59], usually persistent idiopathic facial pain is not associated with trigeminal sensory loss or other physical signs, and standard diagnostic tests, such as trigeminal reflex recordings, do not disclose any noteworthy abnormalities of trigeminal afferents [60]. Conversely, functional neuroimaging studies have reported a decrease in striatal dopamine in patients with persistent facial pain [61], thus supporting the recent evidence on the basal ganglia importance in somatosensory system function [62].

Given that neurological examination is normal and no somatosensory afferent pathway damage can be reliably demonstrated, persistent idiopathic facial pain cannot be identified as a neuropathic pain condition [63].

10.2.1 Psychological Disturbances

Mental health plays an important role in maintaining or aggravating chronic pain [64]. Although in earlier studies persistent idiopathic facial pain was considered either a hysterical conversion symptom or a symptom of underlying psychiatric disorders, more recent findings suggested that the relationship between persistent idiopathic facial pain and psychological disturbances might be bidirectional [65]. According to most studies, the prevalence of psychological disturbances reaches up to 50 % [57, 66, 67].

Clinical studies showed that while stress, depression and anxiety increase the risk of chronic facial pain [68, 69], optimism is inversely related to facial pain [70]. Personal illness belief also influences treatment outcomes and the disease course. In patients with persistent idiopathic facial pain, perceived negative consequences of the illness, beliefs in strong illness identity and in a long illness timeline are associated with poorer outcome [71]. All these observations emphasize the importance of psychosocial factors for facial pain chronification.

A case series study [72] reported that the most common psychiatric disorders were the major depressive disorder, social phobia and obsessive–compulsive personality disorder. Although the association between these psychiatric disorders and persistent idiopathic facial pain is still far from being completely understood, it is worth mentioning that major depressive disorder, social phobia and obsessive–compulsive personality disorder have been associated with dopamine system dysfunction [73]. Accordingly, psychiatric disorders and facial pain could both originate from low brain dopamine activity, and thus patients with persistent idiopathic facial pain have a shared vulnerability for chronic pain conditions and psychiatric and personality disorders, most likely mediated by dysfunctional brain dopamine activity [72].

Many studies, however, have also indicated that suffering caused by pain further exposes a patient to psychiatric disorders and might even initiate personality changes [73]. Hence it is still difficult to disentangle the close relationship between persistent idiopathic facial pain and psychological disturbances.

10.2.2 Sleep Disorders

Sleep disorders impair the quality of life and are frequent comorbid conditions in chronic pain patients [74]. The most frequent sleep disorders in patients with pain consist of delayed sleep onset, restless sleep, frequent awakenings and nonrestorative sleep. Although the association between pain and sleep is often considered to be bidirectional (poor sleep enhances pain and greater pain negatively influences sleep), the observation showing that presleep pain did not predict subsequent sleep quality argues against this view [75]. This study showed that while sleep quality consistently predicts pain, presleep cognitive arousal, rather than pain, predicts sleep quality. While several studies have investigated sleep disturbances in patients with temporomandibular disorders, the problem of sleep disorders in patients with persistent idiopathic facial pain has been poorly addressed. Some observations

report that over 50 % of patients with facial pain complain of sleep disorders. Sleep disorders in patients with facial pain are similar to those in patients with other chronic pains and consist of primary insomnia and nonrestorative sleep [74, 76, 77].

10.3 Burning Mouth Syndrome

The International Headache Society defines the burning mouth syndrome as an "intraoral burning or dysaesthetic sensation, recurring daily for more than 2 h per day over more than 3 months, without clinically evident causative lesions" (http://www.ihs-headache.org/ichd-guidelines).

Reported prevalence of burning mouth syndrome in general populations varies from 1 to 15 % [78, 79]. An epidemiological study, investigating 1500 participants, reported a prevalence rate of burning mouth syndrome of 3.7 % (5.5 % in women and 1.6 % in men). The burning mouth syndrome prevalence increases with age, with the highest prevalence (12 %) in women aged 60–69 years [80, 81]. The pain is usually localized in the anterior part of the tongue, the anterior hard palate and the lips. Although burning mouth syndrome is most usually bilateral and symmetrical, some patients report unilateral pain. In most patients pain increases over the day, being most intense in the evening. Most patients also report dry mouth (despite spared saliva secretion) and changes in taste and smell. Burning mouth syndrome is a diagnosis of exclusion. Given that a normal oral mucosa is a prerequisite for the diagnosis, a careful examination of the oral cavity is necessary to confirm the absence of intraoral lesions [82, 83].

Although burning mouth syndrome has for long been attributed to psychogenic factors, several studies have demonstrated abnormalities of both nociceptive and non-nociceptive trigeminal afferent pathways [84, 85]. A skin biopsy study showing abnormal tongue innervation has further supported the possibility that burning mouth syndrome is related to somatosensory system damage [86]. Although this study supports the possibility that burning mouth syndrome is a neuropathic pain condition, wide agreement is still lacking.

Besides studies investigating damage to the peripheral nervous system, functional neuroimaging studies have shown dopamine deficits in patients with burning mouth syndrome, thus raising the possibility that like persistent idiopathic facial pain, burning mouth syndrome is associated with basal ganglia dysfunction [61]. Conversely, a voxel-based morphometry MRI study has shown modifications of the grey matter concentration in most pain-related brain areas, thus suggesting that deficiency in the control of pain might contribute to burning mouth syndrome [87].

10.3.1 Psychological Disturbances

Similar to persistent idiopathic facial pain, psychological disturbances have been associated with burning mouth syndrome, but their role in the pathogenesis remains unclear [88, 89]. Most patients with burning mouth syndrome suffer from psychological disturbances, predominantly consisting of depression, anxiety and high level

of somatization [81]; some studies have also indicated that cancerophobia and hypochondria are frequent complaints and might also represent a bad prognostic index [90]. Whether anxiety and depression influence the severity of symptoms is still an open matter. While some studies identified that anxiety correlates with taste abnormalities and pain, others showed that the severity of psychological disturbances did not correlate with symptoms and the depression and anxiety did not differ in patients with more severe pain than in those with less severe pain [80, 90]. Some observations have also indicated that alexithymia might be a relatively common problem in patients with burning mouth syndrome. Alexithymia might increase the probability of somatization; this personality trait disorder has been described also in other idiopathic pain conditions [91, 92].

Although many studies have demonstrated peripheral somatosensory nervous system abnormalities and central nervous system dysfunction as possible mechanisms underlying burning mouth syndrome, some studies nevertheless reported that this condition seems to be directly related to the preceding psychological disturbances. According to these studies, depressive symptoms could contribute to pain, which could be a somatic feature of depression in patients with burning mouth syndrome [93]. The relationship between pain and psychological disturbances is further supported by the observation that the mere reassurance can be an effective treatment, resulting in a reduction of symptoms in many patients, and that improvement of psychological status often relates directly to a reduction in symptoms [89, 94]. However, arguing against the view that psychological disturbances precede and concur to burning mouth syndrome, some clinical studies showed that in several patients burning mouth symptoms precede the onset of the psychological disturbances and cause "reactive depression". In these patients psychological disturbances remit upon pain relief. These findings suggest that in some cases burning mouth syndrome could be the cause rather a mere consequence of psychological disturbances [95].

10.3.2 Sleep Disorders

As well as other chronic pain conditions, burning mouth syndrome is associated with sleep disorders. Poor sleep quality has been reported in up to 67 % of patients with burning mouth syndrome [96]. Although it could be reasonably expected that the poor sleep is a mere consequence of pain, a retrospective population-based cohort study indicated that sleep disorders increased the risk of burning mouth syndrome [97].

10.4 Trigeminal Neuropathic Pain

Trigeminal neuropathic pain is a heterogeneous condition including different diseases such as iatrogenic damage of trigeminal nerve branches (e.g. injury of the inferior alveolar, lingual nerves for dental procedures or root canal therapy) [98] and zoster-related trigeminal damage [99].

Although iatrogenic damage of trigeminal nerve branches and zoster-related trigeminal damage are frequently encountered clinical problems, only a few studies have addressed comorbidities in patients with these conditions.

Trigeminal neuropathic pain hampers social functioning due to interference with the daily activities, thus ultimately leading to psychological disturbances [100, 101]. An observational, cross-sectional study [101] showed that pain due to inferior alveolar or lingual nerve injury is significantly associated with depression and anxiety; in this study, enrolling eighty-nine patients with iatrogenic trigeminal nerve damage, about two-thirds of patients suffered from mood disturbances.

Herpes zoster has a lifetime prevalence of 10–20 % [102], and cranial herpes zoster (especially involving the ophthalmic division) accounts for 10–20 % of cases [103]. Retrospective epidemiological studies based on help-seeking behaviour report that about 10 % of the patients with herpes zoster have pain after the rash has healed, 5 % of the patients have pain at 3 months and 2 % at 1 year [103]. Although it is widely agreed that herpes zoster and postherpetic neuralgia are commonly associated with psychological disturbances [104], no study has directly investigated this problem in patients with zoster-related trigeminal damage. A longitudinal observational study conducted in primary care and enrolling more than 1000 patients with zoster eruption [105] showed that patients with pain have lower mental health than patients without pain, and those with more severe pain are more likely to report symptoms of anxiety and depression. A clinical and quantitative sensory testing study [106] showed that in patients with postherpetic neuralgia, depression and anxiety correlated with the pain severity.

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Chapter 11
Myofascial Trigger Points Comorbidity in Headache

Robert Gerwin and César Fernández-de-las-Peñas

Abstract Headache is a common problem that results in considerable suffering and disability. Treatment of headache is directed to prevention of headache as well as to alleviating a pain attack. In this regard identification of trigger factors that both contribute to the development of headache and that contribute to the suffering and pain associated with headache can lead to more effective treatment strategies. Myofascial trigger points (TrPs, hypersensitive spots in taut bands of skeletal muscles) are triggers of both migraine and tension-type headache, play a role in temporomandibular-related headache disorders and contribute to pain and suffering associated with headaches. Conditions such as sleep disorders, fibromyalgia and hypermobility syndromes, in which TrPs are generally found, can also play a role in some headaches. Treatment directed toward these conditions plays an adjunctive role in headache management.

Keywords Migraine • Tension-type headache • Myofascial pain • Trigger points • Referred pain • Fibromyalgia • Temporomandibular disorders • Sleep disorders

R. Gerwin, MD, FAAN (✉)
Department of Neurology, Johns Hopkins School of Medicine, Johns Hopkins University, Baltimore, MD 21205, USA

Pain and Rehabilitation Medicine, Bethesda, MD, USA
e-mail: gerwin@painpoints.com

C. Fernández-de-las-Peñas, PT, MSc, PhD, DrScient
Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain

Cátedra de Investigación y Docencia en Fisioterapia: Terapia Manual y Punción Seca, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain
e-mail: cesar.fernandez@urjc.es

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11.1 Migraine Headache Myofascial Comorbidities

Migraine comorbidities are common and encompass far more than myofascial pain syndromes that are the specific interest of this section. Studies of migraine comorbidities look at the issue of both conditions that are comorbid with migraine and of other conditions for which migraine itself is a significant comorbidity. Migraine as a significant comorbid condition of another disorder does not mean that the other disorder is a significant comorbidity of migraine, especially if the disorder is uncommon. However, in this chapter we will consider such an association as significant and such conditions as important comorbidities. To illustrate this, we know that migraine occurs in as much as 20–30 % of a number of disorders, including epilepsy, asthma, stroke, kidney stones, psoriasis, rheumatoid arthritis and fibromyalgia [1]. By the same token, comorbid disorders occur in 56.7 % of 982 migraine patients [2]. This does not mean that any one of these disorders is a significant comorbidity of migraine, for if a specific condition occurs in only 1–2 % of migraine patients, it is not a significant in terms of frequency. However, there are more studies of migraine as a comorbid condition of other disorders than there are of specific conditions being comorbid with migraine. Hence, we will look at the association of migraine with a variety of conditions without regard to the prevalence of migraine in these conditions.

Migraine comorbidities occur in distinct clusters or constellations of patients. One group is characterized by hypertension, hyperlipidemia, diabetes mellitus and hypothyroidism. A second constellation is patients with depression, anxiety and fibromyalgia, and sexual abuse. A third group has no defining comorbidities [3]. However, this classification of migraine sufferers has never been applied to the comorbidity of interest here. Nevertheless, in the studies mentioned, fibromyalgia syndrome is a common comorbid condition that is of particular interest because of the overwhelming occurrence of myofascial trigger point pain [4, 5]. In addition to the conditions mentioned, migraine with cutaneous allodynia is more common in patients with irritable bowel syndrome, chronic fatigue syndrome, depression and anxiety, and fibromyalgia than in persons without any of these disorders [6].

Migraine comorbidities can be direct or indirect. We define direct comorbidities as those that are associated with migraine and indirect comorbidities as those that are secondary to a direct comorbidity. Thus, sleep disorders are directly associated with migraine headache, but sleep disorders also are a provocative factor for muscle pain and myofascial trigger points (TrPs). In this section, we talk about myofascial comorbidities of migraine, either as direct or primary comorbidities, and we discuss additional secondary migraine comorbidities that themselves are comorbid with myofascial TrPs.

11.1.1 Myofascial Trigger Points (TrPs)

Myofascial TrPs are associated with migraine headache to a significant degree, as we shall see. This association by itself begs the question as to whether TrPs in the head, neck and shoulder muscles are derivative to the headache, occurring as a

consequence of migraine, or causative, contributing to the initiation of headache, or both. Myofascial TrPs cause local pain at the site of the spot, but also cause pain at distant sites, a phenomenon known as referred pain [7, 8]. Referred pain is central to the concept of a myofascial TrP, because the hallmark of myofascial TrP pain is tenderness and pain in the referred pain distribution of the point, something not unique to muscle, but found in most somatic pain syndromes whether the pain originates in muscle, joint or elsewhere. It is also a well-described entity in visceral pain, as is commonly seen in gall bladder pain referred to the shoulder and cardiac angina pain referred to the neck or the arm. Referred pain is the result of central sensitization and neuroplastic changes in the central nervous system [8, 9]. TrP referral patterns are important because the muscle of the head, neck, and shoulders, usually refers pain to common headache areas. Referral patterns are most often unilateral. The upper trapezius muscle in the shoulder refers pain to the neck, the parietal area and the temple. The sternocleidomastoid muscle, sternal head, commonly refers pain to the forehead, the temple, to the retro-aural and vertex areas. The clavicular head of the sternocleidomastoid muscle refers pain to the forehead, but in this case, the referral can be bilateral. Posterior cervical muscle TrPs in the splenii, in the oblique capitis inferior and in the semispinalis muscles refer pain to the parietal area, to a band-like distribution low over the ear to the temple and to the eye (Fig. 11.1). Thus, the headache pattern in migraine is reproduced by myofascial TrP referred pain to a large extent.

Myofascial TrP pain referral patterns in the head, neck and shoulder muscles are to the occipital, parietal, temporal, frontal and vertex regions of the head, in other words, to every part of the head that can be described as painful in headache, whether tension-type headache or migraine [7]. This includes pain referred to the eye, a common site of headache pain. The association of TrPs specifically in migraine headache is well described. Calandre et al. found that 93.9 % of migraineurs have trigger points in relevant muscles compared to 29 % of controls [10]. The number of TrPs in a patient with migraine headaches is directly related to the intensity and duration of the headaches. Migraineurs who had more numerous TrPs had more severe and longer-duration migraine headaches. Active TrPs, defined as TrPs that spontaneously produce pain, are more common in migraineurs with unilateral headache than in non-headache control subjects and are ipsilateral to the headache more than contralateral or bilateral, except for the suboccipital muscles [11, 12]. In the author's clinic, 54 consecutive headache patients were evaluated for active TrPs that reproduced all or part of their headache pain. Thirty-six (67 %) met the criteria for migraine headaches, of whom 40 % had 15 or more headache days a month. Active TrPs relevant to their headache complaints were found in 100 % of these migraine sufferers, most commonly in the upper trapezius muscles in the shoulders (Gerwin RD, unpublished data 1995). Active myofascial TrPs relevant to the headache complaint are likely to be found in migraine patients when they are properly examined. Active and latent TrPs in the sternocleidomastoid muscle and in the trapezius muscle are more common in migraineurs than in control subjects [13].

The association of myofascial TrPs with migraine is of interest etiologically as TrPs can be considered either as a consequence of migraine headache, unrelated epiphenomena or causative in the sense that they can be one of the many triggers

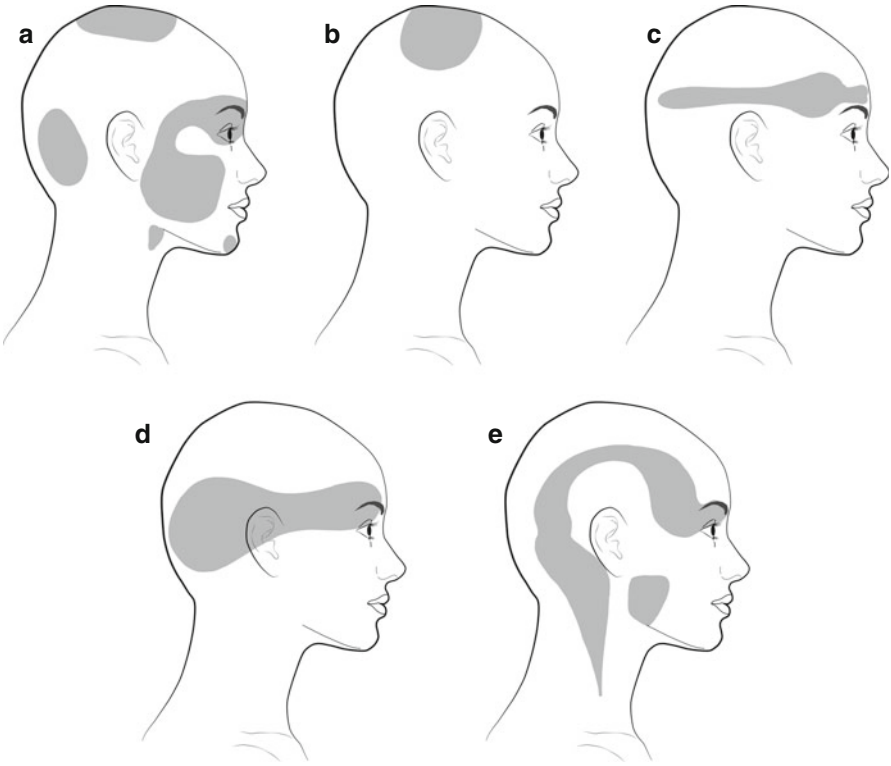

Fig. 11.1 Referred pain elicited by TrPs in the cervical muscles: (**a**) sternocleidomastoid, (**b**) splenius capitis, (**c**) semispinalis capitis, (**d**) suboccipital and (**e**) upper trapezius

that activate the trigeminovascular cascade that initiates a migraine attack [14]. This issue is of importance, because if they are either unrelated or are secondary to migraine, they do not necessarily need to be treated. However, if they are a potential trigger of migraine, then treatment of these TrPs might well diminish the frequency and intensity of migraine. An early exploration of this question showed that activation of TrPs in the neck and shoulder muscles of migraineurs elicited referred pain to the head in 73 % of subjects. Inactivation of myofascial trigger sites in the neck and shoulder muscles by injection of either lidocaine or saline eliminated headache pain (symptom-free) in 26 of 48 subjects (54 %) at 70 min. This was significantly better than medical therapy [15]. A more recent, landmark study showed that treatment of active TrPs in the neck that referred pain to migraine headache pain sites in the head, in other words, that reproduced migraine headache pain, reduced local pain, decreased the sensitivity of referred pain areas and reduced the number and maximal intensity of migraine headaches [16]. Local TrPs in the neck and in the referred pain areas in the head were evaluated at days 0, 3, 10, 30 and 60 for their electrical pain threshold. The cervical triggers were injected with lidocaine on day 0 after obtaining baseline measurements. The electrical pain thresholds in the skin,

subcutaneous tissue and muscle in the TrP sites in the neck and in the referred pain areas in the head were reduced at baseline in the migraine subjects compared to the values in the normal control subjects, meaning that they were more sensitive in the migraineurs. The sensitivity (electrical pain threshold) of all three tissue layers, as measured by their electrical pain threshold, returned to normal in the treated group compared to controls over the treatment period, but did not change in the untreated migraine subjects. The number of migraine attacks in the treated subjects decreased by 46.8 %, and the maximal intensity of migraine headaches was reduced by 17.6 %, compared to pretreatment, a significant change [16]. Thus, proper management of cervical myofascial TrPs can reduce not only local cervical pain sensitivity but can also reduce pain sensitivity in related headache regions and also reduce headache frequency and intensity. This strongly suggests that cervical myofascial TrPs can operate either as triggers of the migraine-inducing trigeminovascular cascade or that myofascial TrPs are potent activators of central sensitization that can make migraine headache more likely. A more recent study further confirms this hypothesis since migraine patients receiving drug treatment combined with TrP therapy experienced greater reduction in migraine intensity and frequency than those patients who received drug treatment alone [17].

11.1.2 Temporomandibular Joint Dysfunction, Trigger Points and Migraine

Temporomandibular joint dysfunction is a disorder of the facial muscles associated with mastication. Temporomandibular disorder (TMD) and migraine are associated as a common comorbidity [18]. Tomaz-Morais reported that 71.4 % of migraineurs had comorbid TMD (OR, 4.1, $P = 0.03$) and that the prevalence of more than six signs and symptoms of TMD were present in 54.8 % of subjects with primary headache (migraine or tension-type headache) [19]. Moreover, patients with both TMD and migraine tend to have hypertrophy of the lateral pterygoid muscle (58.7 %), and abnormal mandibular movements (61.2 %) and temporomandibular joint disc displacement (70 %) [20]. Muscle hyperactivity may be a result of migraine, a result of TMD or an aggravating factor in both conditions. Twin studies in women with both migraine and TMD showed that additive genetic effects contributed 27 % of the variance in TMD pain and 49 % of the variance in migraine headache. The model revealed that 12 % of the genetic component of TMD pain is shared with migraine [21]. The authors suggest that the association between TMD and migraine in women may be partially due to modest shared risk for both conditions. This idea has greater implications than shared genetic risk, because a number of conditions that coexist or that are comorbid with migraine are more common in women than men. Migraine itself is more frequent in women than men. TMD, fibromyalgia, irritable bowel syndrome, fibromyalgia and hypothyroidism are all more common in women than in men. Treatment of both conditions, TMD and migraine, at the same time, is more effective than treating either condition alone [22].

11.1.3 Otalgia

Otalgia is also associated with migraine. Subjects with chronic otalgia of more than 3 months duration, and who had no identifiable cause of their otalgia, were treated with migraine therapies. Sixty-five per cent of the 29 patients studied met the International Headache Society criteria for migraine. Improvement in symptom intensity, frequency and duration was reported in 92 % of subjects. This association is notable because TrPs in both the clavicular head of the sternocleidomastoid muscle and the deep masseter muscle refer pain deep into the ipsilateral ear and TrPs in the clavicular head of the sternocleidomastoid muscle can cause tinnitus [7]. In fact, inactivation of TrPs in the cervical muscles was effective for tinnitus [23]. Although TrPs are more common in the sternocleidomastoid muscle in migraineurs than in non-headache controls [13], the authors did not investigate this possible relationship, but given the frequency with which we see TrPs in these muscles in TMD and in migraine patients, the association could explain this association.

11.1.4 Fibromyalgia Syndrome

Fibromyalgia syndrome has already been mentioned as a condition in which migraine is a common comorbidity. Myofascial TrPs are common in fibromyalgia patients [4, 5]. Thus, one expects to find TrPs in patients with both fibromyalgia and migraine. This possibility has not been studied specifically, but the possible association is consistent with what we see in our patients with both migraine and fibromyalgia.

11.1.5 Sleep Disorders

Sleep disorders are well known as provocative factors for muscle pain [24, 25]. Persons with chronic myofascial pain often have sleep disorders that result in insomnia, or reduced stage 3 and stage 4 sleep, resulting in non-restful or non-restorative sleep. These conditions have certainly been described in fibromyalgia, a condition known to be comorbid with myofascial pain. The adjusted hazard ratio for persons with a sleep-related breathing disorder developing migraine was 2.34 (95 %CI 1.72–3.44) and interestingly was higher in men than in women [26], even though migraine is more common in women than in men.

Restless leg syndrome (RLS) is another condition that both causes sleep disturbance and is a comorbid condition of migraine. Restless leg syndrome was found in 1.4 % of migraine patients [27]. Migraine patients with RLS had a poorer sleep quality than migraineurs without RLS. There is a bidirectional relationship between migraine and RLS, with each capable of triggering the other [27]. The association

between the two conditions is more common in younger persons aged 19–29 than in older persons aged 50–59 [28]. Restless leg syndrome is related to iron deficiency in some subjects. Iron deficiency is also a predisposing factor for headache. This aspect of the relationship was not explored in the cited studies. However, RLS is certainly a cause for sleep disturbance. The association between migraine and sleep disturbance has already been noted. The relationship between sleep disturbance and muscle pain has likewise already been noted [24, 25].

11.1.6 Hypermobility Syndromes

Ehlers-Danlos syndrome (EDS) is a connective tissue disorder in which there is a hypermobile form that is associated with migraine. Migraine is the most common headache type in the hypermobile form of EDS [29]. Headache is complex in EDS patients and may be due to many different mechanisms, including posterior fossa compression syndrome, intracranial hypertension and intracranial hypotension, and cervical and temporomandibular joint instability. The latter two conditions, instability of the temporomandibular joint and cervical spine instability, are both associated with myofascial TrPs that can contribute to the headache picture and that can trigger migraine headache in these patients.

In conclusion, clinicians should be aware that there is an established relationship of migraine headache and myofascial TrPs. Current evidence strongly suggests that myofascial TrPs play a role in triggering migraine attacks, either directly by nociceptive input to the trigeminal nerve or through the mechanism of central sensitization. Examination of the migraine patient for myofascial TrPs in the muscles of the head, neck and shoulders can lead to productive therapeutic measures that address both myofascial pain and migraine. Moreover, there are conditions associated with migraine, enumerated in this chapter, that are also associated with myofascial TrPs. Therefore, it is productive to evaluate patients for these conditions as well when managing patients with migraine. The approach to migraine headache must be comprehensive and extend beyond considering the important, commonly investigated issues of diet, allergy, stress and familial basis of migraine.

11.2 Trigger Point Comorbidity in Temporomandibular Disorders

Temporomandibular pain disorder (TMD) is a term including different pain conditions involving the temporomandibular joint (TMJ), the masticatory muscles and their associated tissues, e.g. ligaments, or disc. Diagnostic criteria of TMD have been recently updated (DC/TMD) including group I (myofascial TMD) and group II (disc displacement) [30]. The overall prevalence of TMD pain is 4.6%, with 6.3% for women and 2.8% for men (ratio 2:1) [31]. A meta-analysis including a

total of 3,463 subjects with orofacial pain concluded that the overall prevalence for myofascial TMD (group I muscle disorder-DC/TMD criteria) was 45.3 % and the prevalence of disc displacement (group II-DC/TMD criteria) was 41.1 % [32].

The most common clinical features of TMD include spontaneous face pain or pain with mandibular motion. Patient-based drawings show symptoms concentrated around the masseter muscle, the mouth, including the teeth, and spread up to the temporalis muscle [33]. The pain is felt to be deep. "Spreading pain" is a descriptive phrase commonly used by the patients. This constellation of pain symptoms is a cardinal symptom complex in patients presenting with myofascial TMD pain, although not exclusive of this condition. The words describing the pain of patients suspected to have myofascial TMD resemble the pain features of muscle pain and TrPs in general, as described by Simons et al. [7]. Another typical clinical sign of myofascial TMD is tenderness or pain on muscle palpation particularly of the masticatory muscles.

The clinical signs taken altogether suggest that TrPs may be clinically related to TMD pain. Several experimental pain models have demonstrated that injection of an irritant substance in the masseter muscle mimics the symptoms experienced by individuals with TMD [34–36]. Any of the masticatory muscles, including the masseter, temporalis, lateral pterygoid, medial pterygoid and hyoid muscles, can refer pain to the orofacial region (Fig. 11.2) and can contribute to TMD pain symptoms. Clinical evidence to support this referral pattern is scarce, although scientific data from human pain models clearly support the notion that referred pain from masticatory muscles is involved in myofascial TMD [37]. An early study reported that myofascial pain from head and neck muscles was the most prevalent diagnosis in a sample of 164 patients [38]. The referred pain pattern following manual examination of TrPs in the masticatory muscles in one non-blinded study was similar to the pain pattern experienced by subjects with TMD [39]. The lateral pterygoid and masseter muscles were the most common sources of referred pain to the craniofacial region in a sample of 230 patients with TMD pain in this study. In a blinded-controlled study, Fernández-de-las-Peñas et al. reported the existence of multiple active TrPs in the masticatory and neck-shoulder musculature in women with myofascial TMD [40]. Local and referred pain, elicited from manual palpation of active TrPs, together reproduced the symptoms in all TMD patients. Temporalis and masseter muscles were the most affected by active TrPs in women with TMD; but it is noticeable that they also exhibited TrPs in the upper trapezius and sternocleidomastoid muscles [40].

It has been suggested that different muscles may be involved in TMD and tension-type headache (TTH), since TMD pain is clinically more similar to the pain patterns produced by stimulation of the masseter muscle, whereas TTH is more similar to the pain patterns evoked by stimulation of cervical muscles, e.g. upper trapezius [41]. This assumption is supported by another study comparing the prevalence of TrPs between women with TMD and fibromyalgia [42]. This study revealed that women with TMD had greater number of active TrPs in head/neck muscles than women with fibromyalgia and that the neck muscles were more affected in fibromyalgia whereas the masticatory muscles were more affected in TMD pain [42].

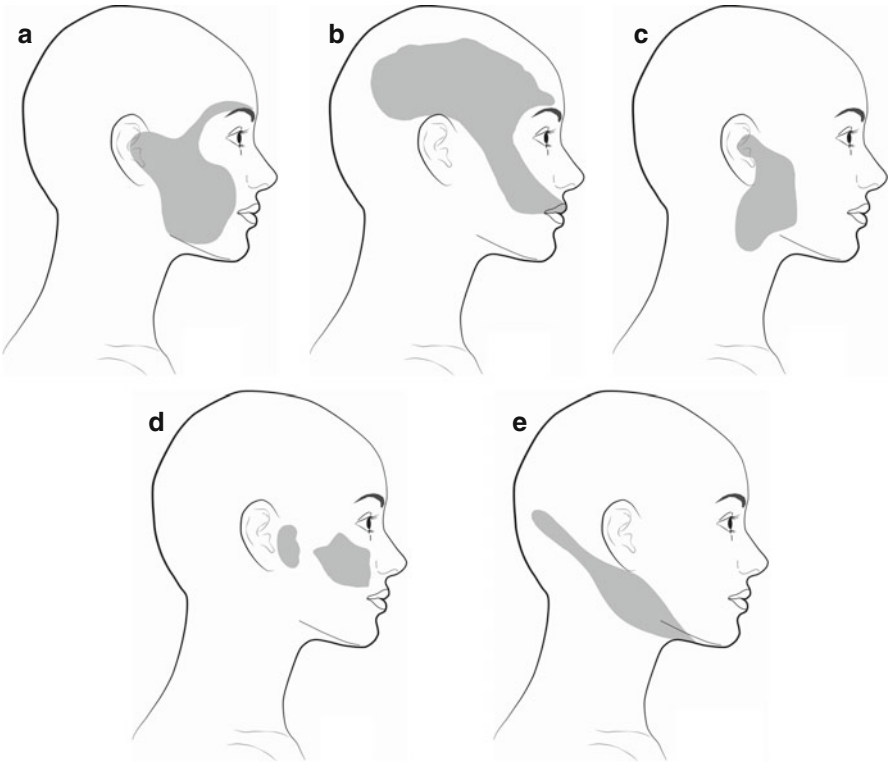

Fig. 11.2 Referred pain elicited by TrPs within the masticatory muscles: (**a**) masseter, (**b**) temporalis, (**c**) lateral pterygoid, (**d**) medial pterygoid and (**e**) hyoids

Patients with TMD exhibit multiple TrPs supporting the assumption that spatial summation plays a significant role in this condition. Each patient showed at least five active TrPs in the neck/head musculature [41, 42]. It is likely that nociceptive activity from active TrPs contributes to central sensitization mechanisms seen in subjects experiencing TMD pain. We postulate that ongoing nociceptive input originating from active muscle TrPs [43, 44] perpetuates or promotes sensitization of central pathways in TMD. This hypothesis agrees with a study reporting lower pressure pain thresholds, i.e. higher pressure pain sensitivity, at the referred pain area in TrPs in the masticatory muscles [45] and other studies in which dry needling of active TrPs within the masseter muscle induced significant increases in pressure pain thresholds when compared to sham dry needling in myofascial TMD [46, 47]. Finally, the role of active TrPs in TMD pain is also supported by some studies suggesting that treatment of active TrPs with dry needling in the masticatory muscles (Fig. 11.3) is effective in the management of these patients [48, 49]. Other authors proposed that manual therapies targeting the masticatory muscles are also effective in the management of TMD pain (Fig. 11.4) [50].

Fig. 11.3 Dry needling of masseter muscle TrPs (Copyright, David G Simons Academy™, Switzerland©, with permission)

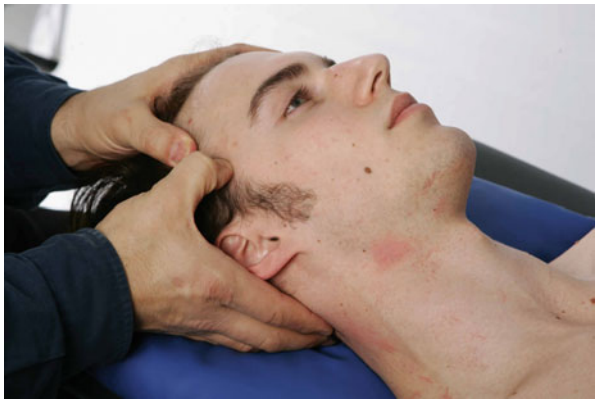

Fig. 11.4 Manual therapy applied over temporalis muscle TrPs (Copyright, David G Simons Academy™, Switzerland©, with permission)

11.3 Trigger Points in Tension-Type Headache

There has been an increasing interest in the pathogenic mechanism of headache disorders since they constitute a serious health problem [51]. Tension-type headache (TTH) has a prevalence of almost 60 % in the general population [52] and is one of the most common headaches, but it is also the most neglected [53]. It is accepted that TTH has a muscular origin and that peripheral and central nervous system factors play a crucial role in its development and persistence [54, 55].

Pain features of TTH (deep, pressing, tightening or dull pain) resemble the descriptions of referred pain originating in TrPs. In fact, TTH is considered as the prototype of headache where the main factor responsible for the pain is TrP referred pain [56]. Additionally, headaches involving a significant component of pain referred from TrPs have been called myogenic headaches, to indicate the role of muscle pain in the genesis of the headache [57], although this term in not widely accepted in the literature.

Simons et al. [7] described several neck and shoulder muscles from which referred pain can mimic TTH, including the upper trapezius, sternocleidomastoid, splenius capitis, splenius cervicis, semispinalis capitis, semispinalis cervicis or suboccipital (see Fig. 11.1). There was little scientific evidence before this century about the association between TrPs and TTH. Some early studies found active TrPs in neck and shoulder muscles in subjects with TTH, particularly in the splenius capitis, semispinalis capitis, upper trapezius and suboccipital muscles [58, 59]. However, these were noncontrolled and non-blinded studies. An updated series of blinded-controlled clinical studies observed that active TrPs in the suboccipital [60], upper trapezius [61, 62], sternocleidomastoid [63] and temporalis [64] muscles and extraocular muscles such as the superior oblique [65] and lateral rectus [66] are highly prevalent in subjects with TTH and reproduce the headache pain pattern. In addition, the presence of active TrPs in these muscles was associated with headaches of greater intensity, frequency and duration and also to greater pressure pain hypersensitivity [60–64]. The fact that patients with chronic TTH who had active TrPs had more severe headache characteristics than those with latent TrPs is evidence of temporal integration of signals from TrPs [67]. This suggests temporal integration of nociceptive inputs from active TrPs by central nociceptive neurons, leading to sensitization of central pathways in patients with TTH. Nevertheless, it has been questioned if active TrPs are consequence and not a causative factor of central sensitization in chronic pain conditions (see "The Exchange Between Dodick and Gerwin in Letters to the Editor", *N Eng J Med* 2006;354:1958). The data supports peripheral sensitization associated with elevated levels of chemical mediators that have been found in active TrPs regions, as well as central sensitization produced by active TrPs [68, 69]. In fact, there is good evidence that TrPs cause peripheral and central sensitization, but there is no evidence that central sensitization predisposes to the development of TrPs. This is an important point, because the two concepts are diametrically opposed and are central to two mutually exclusive ways of looking at the role of TrPs in TTH.

It is also important to note that active TrPs in the same neck and shoulder muscles reproduce the headache in children with TTH [70]. Alonso-Blanco et al. showed that the referred pain elicited from active TrPs shared similar pain patterns as spontaneous headache in both adults and children with TTH, but slight differences in TrP prevalence and location of the referred pain areas could be observed between adults and children [71]. Current evidence clearly supports a relevant role of TrPs in the pathogenesis of TTH. Abboud et al. assert that understanding TrP mechanisms, in association with other musculoskeletal disorders, provides insight into TTH pathophysiology, diagnosis and interdisciplinary patient care [72].

TrPs have been postulated to play a pathogenic role in TTH in an updated pain model for this condition [73]. The updated model is based on previous models considering that the main problem in TTH is the sensitization of central pain pathways due to prolonged peripheral nociceptive inputs. The peripheral nociceptive inputs are provoked by the liberation of algogenic substances and chemical mediator at the periphery in pericranial tender tissues [74]. Fernández-de-las-Peñas et al. postulated that TTH could be explained by referred pain from active TrPs that is mediated

through the spinal cord and trigeminocervical nucleus caudalis [73]. Thus, active TrPs located in muscles innervated by C1–C3 or by the trigeminal nerve would initiate the peripheral nociceptive input and could produce a continuous afferent negative barrage into the trigeminal nerve nucleus caudalis. Sensitization of nociceptive pain pathways in the central nervous system due to prolonged nociceptive stimuli from TrPs is likely to be responsible for the conversion of episodic to chronic TTH [75]. According to this updated model, referred pain elicited by TrPs would be one (but not the only one) of the main causes of the headache experienced by patients with TTH. Needless to say, this updated model needs further confirmation and verification.

Studies of the effect of treatment of TrPs should help to clarify the role of TrPs in TTH. However, few studies have explored the effects of TrP management in individuals with TTH, and most of the studies were uncontrolled [76]. The only randomized, controlled trial investigating this issue found that TrP release massage that focused on the cervical musculature was effective for reducing headache frequency. The authors of this study also observed a significant placebo effect [77]. Another controlled study found that application of positional release manual therapy on active TrPs was effective for reducing the frequency and duration of the headache and of medication intake [78]. Other controlled studies using multimodal manual therapy, including TrP approaches, reported that this treatment was effective for reducing headache pain parameters in individuals with chronic TTH [79, 80]. Similar to manual therapies, the effect of TrP injections, dry needling and botulinum toxin A for inactivating TrPs in patients with headache remains controversial [81, 82]. Discrepancies between studies may be related to the fact that subgroups of TTH patients may exist where TrP management may be more or less beneficial. This concept is supported by two studies of women with TTH to identify those who would likely experience short-term favourable outcomes after receiving manual therapy to inactivate TrPs [83, 84]. Individuals with TTH who have active TrPs in the neck and shoulder muscles and a lower degree of central sensitization respond more quickly to manual TrP than those persons without these features, supporting the concept of relevant subgroups of headache patients [83, 84].

In conclusion, there is clear clinical and scientific evidence supporting the role of TrPs in headache syndromes, including temporomandibular pain. Clinicians should proper explore the patients for these TrPs to improve their therapeutic strategies.

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