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Series Editor: Olga Golubnitschaja

Olga Golubnitschaja *Editor*

Flammer Syndrome

From Phenotype to Associated Pathologies, Prediction, Prevention and Personalisation

EPMA European Association for Predictive Preventive & Personalised Medicine

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What This Book Series Is About…

Current Healthcare: What Is Behind the Issue?

For many acute and chronic disorders, the current healthcare outcomes are considered as being inadequate: global figures cry for preventive measures and personalised treatments. In fact, severe chronic pathologies such as cardiovascular disorders, diabetes and cancer are treated after onset of the disease, frequently at near end-stages. Pessimistic prognosis considers pandemic scenario for type 2 diabetes mellitus, neurodegenerative disorders and some types of cancer over the next 10–20 years followed by the economic disaster of healthcare systems in a global scale.

Advanced Healthcare Tailored to the Person: What Is Beyond the Issue?

Advanced healthcare promotes the paradigm change from delayed interventional to predictive medicine tailored to the person, from reactive to preventive medicine and from disease to wellness. The innovative predictive, preventive and personalised medicine (PPPM) is emerging as the focal point of efforts in healthcare aimed at curbing the prevalence of both communicable and non-communicable diseases such as diabetes, cardiovascular diseases, chronic respiratory diseases, cancer and dental pathologies. The cost-effective management of diseases and the critical role of PPPM in modernisation of healthcare have been acknowledged as priorities by global and regional organisations and health-related institutions such as the Organisation of the United Nations, the European Union and the National Institutes of Health.

Why Integrative Medical Approach by PPPM as the Medicine of the Future?

PPPM is the new integrative concept in healthcare sector that enables to predict individual predisposition before onset of the disease, to provide targeted preventive measures and create personalised treatment algorithms tailored to the person. The expected outcomes are conducive to more effective population screening, prevention early in childhood, identification of persons at risk, stratification of patients for the optimal therapy planning and prediction and reduction of adverse drug-drug or drug-disease interactions relying on emerging technologies, such as pharmacogenetics, pathology-specific molecular patterns, subcellular/cellular imaging, disease modelling, individual patient profiles, etc. Integrative approach by PPPM is considered as the medicine of the future. Being at the forefront of the global efforts, the European Association for Predictive, Preventive and Personalised Medicine (EPMA, http://www.epmanet.eu/) promotes the integrative concept of PPPM among healthcare stakeholders, governmental institutions, educators, funding bodies and patient organisations and in the public domain.

The current book series, published by Springer in collaboration with EPMA, overviews multidisciplinary aspects of advanced biomedical/medical approaches and innovative technologies. Integration of individual professional groups into the overall concept of PPPM is a particular advantage of this book series. Expert recommendations focus on the cost-effective management tailored to the person in health and disease. Innovative strategies are considered for standardisation of healthcare services. New guidelines are proposed for medical ethics, treatment of rare diseases, innovative approaches to early and predictive diagnostics, patient stratification and targeted prevention in healthy individuals, persons at risk, individual patient groups, subpopulations/populations, institutions, healthcare economy and marketing.

Bonn, Germany Olga Golubnitschaja

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About the Book Series Editor

Prof. Dr. Olga Golubnitschaja Department of Radiology, Medical Faculty of Rheinische Friedrich-Wilhelms-University in Bonn, Germany, has studied journalism, biotechnology and medicine and has been awarded research fellowships in Austria, Russia, UK, Germany, the Netherlands and Switzerland (early and predictive diagnostics in paediatrics, neurosciences and cancer). Dr. Golubnitschaja is the author of more than 400 well-cited international publications (research and review articles, position papers, books and book contributions) in the innovative field of predictive, preventive and personalised medicine (PPPM) with the main research focussing on pre- and perinatal diagnostics, diagnostics of cardiovascular disease and neurodegenerative pathologies and predictive diagnostics in cancer and diabetes.

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Since 2009, Dr. Golubnitschaja is the Secretary-General of the "European Association for Predictive, Preventive and Personalised Medicine" (EPMA, Brussels) networking over 50 countries worldwide, www.epmanet.eu; Book Series Editor of *Advances in Predictive, Preventive and Personalised Medicine*, Springer Nature; Book Editor of *Predictive Diagnostics and Personalised Treatment: Dream or Reality*, Nova Science Publishers, New York 2009; Book Co-editor *Personalisierte Medizin*, Health Academy, Dresden 2010.

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Dr. Golubnitschaja is a Regular Reviewer for over 30 clinical and scientific journals and serves as a Grant Reviewer for the national (Ministries of Health in several European countries) and international funding bodies.

Since 2007 until the present, she works as the European Commission evaluation expert for FP7, Horizon 2020, IMI-1 (Innovative Medical Initiatives) and IMI-2. In years 2010–2013, she was involved in creating the PPPM-related contents of the European Programme "Horizon 2020".

Currently, Dr. Golubnitschaja is the Vice-Chair of the Evaluation Panel for Marie Curie Mobility Actions at the European Commission in Brussels.

Flammer Syndrome in the Global Context – The "U-Shape" of Health Risks

Olga Golubnitschaja

Abstract Unmet healthcare needs of young populations are the key issue of currently observed epidemics of non-communicable disorders. Moreover, an unprecedented decrease in the average age of onset of these disorders is recorded. The majority of non-communicable disorders carry a chronic character by progressing over a couple of years from a reversible suboptimal health condition to irreversible pathology with collateral complications. The time-frame between both conditions is the operational area for predictive diagnosis and identification of persons at risk by innovative screening programmes followed by the most cost-effective personalised treatment possible, namely primary prevention tailored to the person. Particularly in young people, both abnormally low and high BMI play an important role with long-term adverse health effects. Monitoring both underweight and overweight trends across the European countries and worldwide using data objectively measured and obtained with comparable methods, thoroughly performed analysis of the trends causality as well as follow-up mitigating programmes are essential measures which should be considered a public health priority.

In contrast to the overweight subpopulations, the causality, risks and associated pathologies linked to the underweight subpopulations are much less understood. Actual studies clearly demonstrate that thinness is an overlooked phenomenon with wide variation in prevalence and trends across developed countries. The matter deserves longitudinal studies in multinational context to understand risk factors and to contribute to targeted preventive programmes focused on thinness and follow-up. The causality is complex. The book highlights the most recent knowledge collected in the

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area providing facts and hypothesis for the follow-up investigations. Flammer syndrome phenotype typical for young slim persons is in the focus providing insights into characteristic symptoms and deficits functionally liked to mechanisms which may underlie the development of associated pathologies. Corresponding health-threating conditions are exemplified in the book utilising an up-to-date multi-professional expertise considering cardiovascular, ophthalmologic, neurologic, psychologic, psychiatric, gynaecologic, otorhinolaryngologic, dental and nutritional aspects, several syndromes, disordered eating, eating disorders, microbiome, sleep medicine, wound healing, and application of innovative technologies, amongst others.

Keywords Flammer syndrome · BMI · Overweight · Underweight · Health risks · Major pathologies · Non-communicable diseases · Cardiovascular · Cancer · Mental behavioural disorder · Respiratory diseases · Epidemic · Teenager age · Adolescence · Predictive preventive personalised medicine · Phenotyping · Genotyping · Multilevel diagnostics · Strategy · Ophthalmology · Neurology · Psychology · Psychiatry · Gynaecology · Oncology · Otorhinolaryngology · Dentistry · Nutrition · Disordered eating · Eating disorders · Microbiome · Sleep medicine · Wound healing · Innovative technologies · Paradigm change · Holistic approach · Health economy · European platform

1 Unmet Healthcare Needs of Young Populations Is the Key Issue of the "Reactive" Medicine: The Paradigm Shift to PPPM Is Crucial

Unmet healthcare needs of young populations is the key issue of currently observed epidemics of non-communicable disorders. Moreover, an unprecedented decrease in the average age of onset of these disorders is recorded as characteristic for the early twenty-first century: teenagers diseased on diabetes type 2, depression and suicide in youth, frequent vascular dysregulation and "young" strokes with unknown aetiology, reproductive dysfunction, aggressive mestastasing cancer subtypes in 20+ years old patients with particularly poor outcomes, significantly increasing prevalence of preventable high myopia in high school students, in young people – increasing prevalence of impaired wound healing, allergic reactions and autoimmunity as well as respiratory disorders, amongst others [1–11].

Paradox is that specifically in adolescents the adverse health effects by suboptimal health conditions are reversible in most cases. This unique capacity is, however, not adequately utilised by current concepts of healthcare: still the clinical manifestation of the disease is the acknowledged indicator for conventional medical services. However, the majority of non-communicable disorders carry a chronic character by progressing over a couple of years from a reversible suboptimal health condition to irreversible pathology with collateral complications. The time-frame between both conditions is the operational area for predictive diagnosis and identification of persons at risk by innovative screening programmes followed by the most cost-effective personalised treatment possible, namely primary prevention tailored to the person.

2 Opposed Trends in Adolescents

Specifically in adolescents, physical and mental health linked to the body shape plays the central role for major aspects in their life such as optimal health condition, sexual life and long-term partnering, successful career development as discussed in the chapter 3 "Flammer syndrome-affected individuals are predisposed to associated pathologies early in life: Psychological and psychiatric aspects". However, complex and challenging educational efforts, much time spent with computer, due to unavoidable computerisation of a daily life, amongst others, strongly promote sedentary life-style resulting in physical inactivity, overweight, obesity, and early diabetes type 2 with a cascade of collateral pathologies. For example, in Germany in average from 100 teenagers aged 12–16 years, 11 are overweight and 9 obese. Similar statistics are recorded for many European countries as well as worldwide [12, 13].

On the other hand, recognition of this actuality gave rise to the opposed trends: 50% of female teenagers and 25% of male teenagers with normal weight in Germany believe that they are overweight and start unsupervised dieting early in life. Consequently, "disordered eating" followed by clinical manifestation of eating and mental disorders in adolescence such as anorexia nervosa and depression become highly prevalent in young populations. Table 1 summarises global statistics for the prevalence of abnormal body-weight; risks associated with both trends are listed [12–16].

3 Association Between Abnormal Weight and Increased Mortality: The "U-Shape" of Risks

A potential association of the abnormal BMI and increased risks to die from one of the most common pathologies has been recently analysed by a large-scale population-based cohort study which considered 3.6 million adults in the UK [17]. The results are well in consensus with our consideration of both – overweight and underweight subpopulations as particularly risky for increased pathology incidence and mortality rates. Figure 1 graphically summarises clear "U-shape" trends in association between the all-case mortality risks and corresponding BMI values. Noteworthy, with very few exceptions, the lowest risks have been demonstrated by 22–25 kg/m^2 for the absolute majority of pathologies considered [17]. Noteworthy, smoking as otherwise considered a strong risk factor has rather minor influence on the BMI/all-case mortality association. Finally, depending on the type of pathology, either right wing (low BMI, e.g. neurological dementia and mental/behavioural cause of death) or left one (high BMI, e.g. hypertensive heart disease as the cause of death) or both – low and high BMI equally (e.g. respiratory disease as the cause of death) might be particularly risky for the affected person. Even accidental death – both transport-related and non-related ones demonstrate the "U-shape" with low and high BMI as risky for an increased mortality.

Table 1 Prevalence of abnormal body-weight and associated risks

Prevalence	Associated risks
Overweight/pre-obesity	
Female: BMI 25–30; male: BMI 26–30	
Obesity	
Class I: BMI 30–35; class II: BMI 35–40; class III: BMI > 40	
50 million girls and 74 million boys are obese worldwide as registered in 2016.	Significantly increased risks of chronic diseases are reported such as
Weight problems increase rapidly in most of the EU Member States, with 51.6% of the overweight EU population aged >18 years.	Type 2 diabetes
WHO recorded: behind the Americans, Europe had the 2nd highest level of overweight and/or obese people in 2014	Psychiatric, neurologic, cardiovascular, ophthalmic, gynaecologic, otorhinolaryngologic, dental, and oncologic diseases, amongst others.
WHO-COSI recorded: around 33% European children aged 6–9 years were overweight or obese in 2010 that is increased as compared with 2008 (25%)	Once manifested, these pathologies create substantial direct and indirect costs to healthcare and society at large.
Underweight	
Grade 1: females BMI < 19, males BMI <20; grade 2: BMI ≤ 17; grade 3: BMI ≤ 16	
75 million girls and 117 million boys were moderately or severely underweight in 2016.	Being underweight in adolescence is associated with adverse health consequences though-out the life-course.
The distribution is strongly heterogeneous as exemplified below.	Following risks are reported:
Intercontinental analysis demonstrates that American girls were less likely to be thin in 2006 than in 1998; while a noteworthy increment was observed for French girls with a 41% increase in the likelihood to be thin in 2006 than in 1998.	Becoming overweight in a long-term perspective
	Psychiatric, neurologic, cardiovascular, ophthalmic, gynaecologic, otorhinolaryngologic, dental, and oncologic diseases, amongst others.

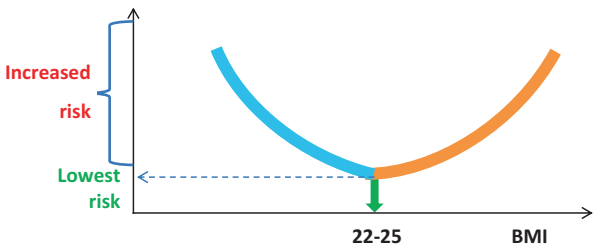

Fig. 1 The "U-shape" is characteristic for the association between BMI and "all-case mortality" risks including both communicable and non-communicable diseases (several types of cancer, neurological, mental and behavioural disorders, cardiovascular disease, and respiratory diseases, amongst others); the figure generalises the results published by Bhaskaran K. with coauthors presenting a population-based cohort study of 3.6 million adults in the UK [17]

4 Innovative Screening Programmes Focused on Phenotype Are Due

In the above provided context, monitoring both underweight and overweight trends across the European countries and worldwide using data objectively measured and obtained with comparable methods, thoroughly performed analysis of the trends causality as well as follow-up mitigating programmes are essential measures which should be considered a public health priority.

Considering the overweight subpopulations, in March 2005, the European Commission has launched a European platform for action on diet, physical activity and health with more than 300 initiatives designed to promote better nutrition and physical activity in the EU [16].

The causality, risks and associated pathologies linked to the underweight subpopulations are much less explored. Actual studies clearly demonstrate that thinness is an overlooked phenomenon with wide variation in prevalence and trends across both developing and developed countries. The matter deserves longitudinal studies in the multinational context to understand the causality and risk factors and to contribute to targeted preventive programmes [14, 15].

Syndromes and pathologies linked to obese versus anorexic phenotypes (both used to generalise abnormally high and low BMI, respectively) are schematically demonstrated in Fig. 2. Flammer syndrome symptoms and signs can be more frequently observed in individuals with a slim body shape than in other phenotypes. The causality is complex. Therefore, the book utilises an up-to-date multiprofessional expertise considering cardiovascular, ophthalmologic, neurologic, psychologic, psychiatric, gynaecologic, oncologic, otorhinolaryngologic, dental, nutritional aspects, several syndromes, disordered eating, eating disorders, microbiome, sleep medicine, wound healing, and application of innovative technologies, amongst others. Applying a holistic approach to the human health, the book highlights facts and hypothesis for the relevance of the Flammer syndrome phenotype for a number of common health conditions such as suboptimal health, disease predisposition and clinically manifested associated pathologies. Corresponding life-threating health conditions are exemplified in the book.

The book clearly demonstrates that additionally to the diagnostic approach dedicated to the signs and symptoms characteristic for the FS phenotype, identification of the condition-specific molecular signature, multi-level biomarker panels, and, finally, the creation of the individualised patient profile is essential for the correct risk assessment and predictive diagnosis followed by targeted preventive measures and creation of treatments tailored to the affected person – altogether representing a really personalised medical approach.

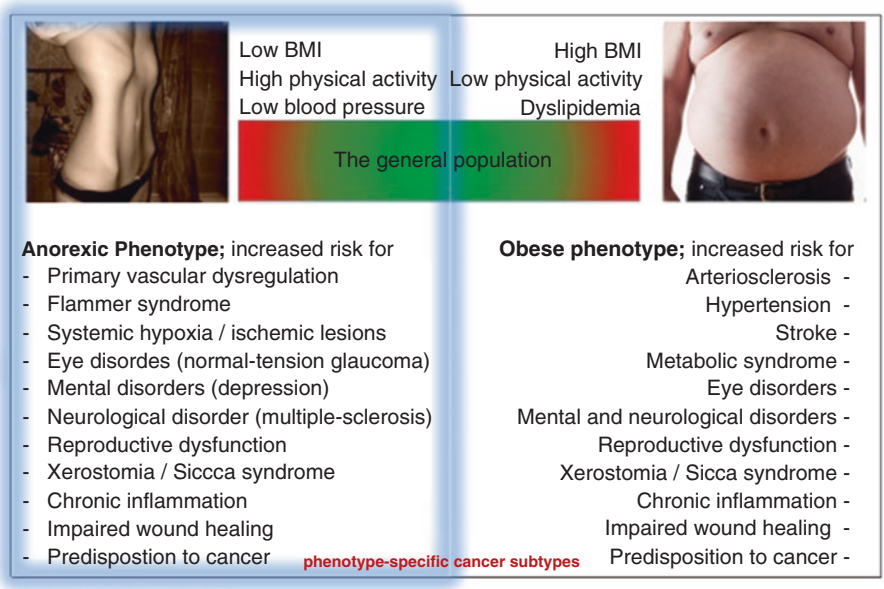

Fig. 2 Phenotyping and associated risks: two opposite phenotypes (anorexic versus obese) demonstrate a lot of similarities when a strong predisposition to severe pathologies is considered; however, personalised patient profiling is crucial to predict and prevent potential risks individually
Current book volume analyses risks specifically associated with Flammer syndrome (FS); Thinness is characteristic for the FS-affected individuals. The association between Flammer syndrome and thinness (anorexic phenotype as an extreme case of the FS is marked in Fig. 2) as well as increased health risks, individualised prediction and prevention are discussed in the book

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General Lessons Learned from Flammer Syndrome

Josef Flammer and Katarzyna Konieczka

Abstract There are modern trends in medical research, such as molecular biology, molecular genetics and animal experiments. This is taking an ever greater role in industrial research, but also at universities, with consequences for the filling of positions and the distribution of funds. This is also reflected in the number of publications. While this undoubtedly has many advantages and has also brought much medical progress, there are important aspects in medicine for which other approaches are needed. By means of the discovery of Flammer Syndrome, we would like to show that alternative research methods are also important and have a right to exist. Important on the long road to the discovery of Flammer Syndrome were the observations on individual patients, a holistic approach and interdisciplinary cooperation.

Keywords Flammer syndrome · Discovery · Holistic approach · Interdisciplinary cooperation · Phenotype · Ophthalmology · Symptoms · Normal-tension glaucoma · Cold hands · Education requirements · General practitioner · Blood pressure · Vascular dysregulation · Concepts · Predictive preventive personalized medicine · Generalists · Plasma endothelin · Thirst · Individualized patient profiles · Glaucomatous neuropathy · Risks · Pathomechanism · Retinal vein occlusion · Emotional stress · Personality

1 Flammer Syndrome

Flammer syndrome (FS) describes a certain phenotype of people with an innate tendency to react differently with their blood vessels to stimuli such as the cold or emotional stress. People with FS present certain signs and symptoms, such as cold hands, low blood pressure, or low body mass index, much more frequently than do

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people without FS. The syndrome itself is not a disease, and it can be found even in completely healthy and efficient people. The life expectancy of those with FS seems to be even above average, although some of those affected do suffer from their symptoms. The medical significance lies, however, in the fact that FS predisposes those who have it to certain diseases.

Because the various important aspects of the syndrome have already been reviewed in open access journals, we will not repeat them here. We instead recommend papers that have already been published on the following aspects of FS: a description of the core element of the syndrome, the primary vascular dysregulation [1]; a summary of the phenomenology of the FS [2]; a historical overview of its discovery [3]; and a short description of the diseases known to be associated with it [4].

This book article describes some very general aspects that we can learn from the discovery and history of FS.

2 The Downsides of Medical Specialization

Biological reaction patterns are essentially the same throughout the body. There are many more parallels between the different organs [5] than we normally perceive. It is therefore not surprising that a predisposition such as FS can potentially affect several organs at the same time or one after the other.

However, in recent years and decades, medicine has increasingly been divided into smaller and smaller areas. Accordingly, the specialists have more and more knowledge in an ever-diminishing sub-area. Of course, this has many advantages, both for the physicians and for the patients concerned. However, it also has a price. We would like to illustrate the possible disadvantages and dangers of such specialization, using the example of FS.

The very first step that led to the discovery of the syndrome and its medical significance was the observation that patients with normal-tension glaucoma (NTG) often have remarkably cold hands [3]. Ophthalmologists not concentrating exclusively on the eye could only detect such a relationship. Even within ophthalmology, specialization went so far that glaucoma specialists focused their attention extensively on the optic nerve head, overlooking the glinting spots on the retina, which are caused by the increased back scatter of activated astrocytes [6]. Even less noticed was the connection between the activation of the astrocytes with the FS [7].

3 The Intellectual Processing of Results

Research produces many individual results, and there is often a lack of experts who have the necessary range of knowledge and intellectual power to collect, weigh, and integrate this information and make it available to everyone in a review. Let us explain this using an example: Many researchers have studied the relationship between glaucoma and blood circulation. One group describes increased oxygen saturation in the retinal veins and concludes that a relative overperfusion occurs in glaucoma. Another group studies vascular density using optical coherence tomography angiography

(OCTA) and concludes that vascular density is decreased in glaucoma. Still another group finds that, in patients with glaucoma, a slower flow velocity with an increased flow resistance can be seen through color Doppler imaging. All these results seem to contradict each other. However, if they are viewed in conjunction with one another, then the slower flow velocity explains the seemingly reduced vessel density. This is because a minimum velocity of the blood column is required for a vessel to be detected in the OCTA. The reduced velocity leads to a moderate hypoxia. However, because the astrocytes are activated, the oxygen transport from the blood vessels to the axons is reduced and, despite hypoxia in the axons, increased oxygen saturation in the retinal veins occurs [3]. As can be seen through this example, writing good reviews can therefore be as important as doing good experimental work.

4 The Need for Interdisciplinary Cooperation

Interdisciplinary cooperation can make up for some of the disadvantages of high specialization. However, this only works if the communication between the specialists is good and if each specialist has at least minimal knowledge of neighboring fields in order to understand the questions and concerns of other specialist. Consider the following example: When it became clear that low blood pressure was an important risk factor for glaucomatous neuropathy [8], ophthalmologists began to refer their glaucoma patients to internists for blood pressure evaluation. We saw patients for a second opinion with the information from the referring ophthalmologist that the blood pressure was, according to internist, completely normal. Then we often found a very low blood pressure. What had happened? The internist, not knowing that systemic hypotension is relevant for glaucoma, had simply excluded systemic hypertension. The fact that a patient had low blood pressure had not even been noticed.

5 Education Requirements

At universities and medical schools, medical students are mainly taught by specialists. In order to understand interdisciplinary contexts—such as the context that is so relevant to managing FS—and to put them into practice later, it is important also to offer topic-centered training and to further strengthen students' general medical education.

6 The Role of the General Practitioner (GP)

We have often seen patients who have been in the care of several specialists in parallel because of different complaints, such as NTG at the ophthalmologist, tinnitus or a sudden loss of hearing at the ear specialist, and headaches at the neurologist. Moreover, in such cases, the internist has noticed that the patient is "difficult," not tolerating certain drugs. By viewing the full scope of symptoms, we could tell these patients that all this is connected, that they do not suffer from several different and

independent diseases but rather from one syndrome: FS. We could also explain that the hypersensitivity to certain drugs is not an expression of neurotic behavior but rather part of the FS and that it only demands a reduction of the dose of the corresponding drugs. As such, the GP has a larger overview of a patient's full medical situation and is in a better position to recognize such connections. We therefore need more well-trained generalists who can summarize and integrate all information coming from different specialists. In addition, as well as knowledge of a specific field, specialists require at least a minimal knowledge of other fields. This indicates that broad theoretical and practical training should precede specialization. In addition, research teams would ideally be composed of different specialists.

7 The Power of Habit

Humans do not like to change habits. This also applies to our clinical activities. As mentioned above, it has become increasingly clear that low blood pressure is a crucial risk factor for glaucoma. Nevertheless, ophthalmologists who measure blood pressure in their practice are still very rare. Of course, change tends to arrive much faster when a new development is financially interesting for the physician.

8 The Role of Opinion Leaders

The flood of new medical information is never-ending. This makes it more and more difficult for physicians to maintain a good overall knowledge and to be able to separate the wheat from the chaff. It is therefore understandable that many physicians orient themselves around opinion leaders. Such leading experts, however, often remain in their own thought patterns and have difficulty opening themselves up to ideas that fall outside their own doctrines; this can indirectly hamper progress. This can also be illustrated by our experience doing research on FS. When we first demonstrated the relationship between finger blood flow and visual field behavior [9], certain experts mocked it and declared that such connections, if not impossible, were at least insignificant. Why should an eye disease have anything to do with fingers? This has made it very difficult for us to continue our research in this field and to request financial support. However, our urge to pursue this question was fortunately stronger than this headwind we faced. Nevertheless, some results were only fully accepted by the scientific community after American research centers found the same connections, decades later [10].

9 The Power of the Textbook, A Double-Edged Sword

Points of entry into a new subject area mostly occur through textbooks. Textbooks summarize complex literature and present the knowledge in a didactic format. If you follow textbooks related to a certain topic over a long period of time,

it becomes apparent how much content the authors simply distill from former authors. This has major consequences, as doctrines shape the thinking of entire generations. This can be illustrated through the doctrine on the pathomechanism of retinal vein occlusions. Over decades, textbooks described the cause of retinal vein occlusion to be a thrombus formation. Although this has never been proven and although the therapy based on this assumption did not work, it was not questioned. We then observed patients with FS developing retinal vein occlusion when they experienced great emotional stress. This caused us to question the traditional conception of retinal vein occlusions. Based on observations of patients and relevant literature, we concluded that such occlusions might also be caused by the constriction of a retinal vein [11]. We and others have subsequently shown that retinal veins can indeed constrict actively, especially when stimulated by the vasoconstrictor endothelin [12]. This increases the retinal venous pressure and, in extreme cases, leads to a clinical picture of retinal vein occlusion [13]. We learn from this that textbooks are helpful, but they must always be questioned critically.

10 Leadership

It is a good tradition that the academic staff of a clinic at a university hospital simultaneously conducts teaching, research, and clinical activities. In this way, the different disciplines are automatically linked, research is oriented towards the needs of patients, new scientific knowledge is quickly transferred to the clinic, and teaching is both patient-related and up to date. However, this requires an extremely high commitment of time and energy on the part of the physicians concerned. Therefore, there is now a tendency to separate research and clinical activity. As a consequence, a clinic is managed in parallel by a scientific and a clinical chief physician. In such a structure, it would have been very unlikely that FS could be detected. For example, when a patient told us that she almost never felt thirsty, we were able to check whether other patients had made similar observations and whether this symptom was linked to other signs or symptoms, such as an increase in the plasma concentration of endothelin.

Further, although there are many excellent learning tools at students' disposal, such as journal, books, and videos, they nevertheless learn best from teachers as role models. This indicates—for hospitals and, particularly, university hospitals—that staff and heads of departments should see patients regularly and in parallel to carry out scientific studies. Only by the exact observation of patients do researchers develop ideas for studies. When research fellows also see patients, we have observed that they automatically become motivated to carry out studies.

11 The Link Between Basic Science and Clinical Science

In recent decades, more and more labs have been running using very sophisticated methodologies, keeping hundreds of mice. Realizing that the transfer to clinical science is often insufficient, the field of translational research has been introduced.

Although the intention behind its introduction is sound, we have observed in daily life that the real exchange between basic researchers and clinicians is insufficient. Basic researchers should know more about real patient situations, and clinicians should have a fundamental knowledge of basic research. One way to achieve this is holding regular common research meetings; through these, in time, the barrier between the two areas shrinks and a mutual learning process begins. This was also a prerequisite for the discovery of FS. If, however, researchers working in labs dominate such meetings, clinicians feel quickly lost; this can be avoided if the meetings are chaired or co-chaired by good clinicians.

12 Animal Studies

There is a firm belief throughout the scientific community that we can study diseases primarily in animals and then transfer knowledge gained about pathophysiology and treatment to humans. However, the transfer of successful treatments in animals often leads to very frustrating results in humans. For example, some human diseases do not occur in animals; for some, one part of the disease can be imitated to some extent in an animal model, but for others, such as NTG, no animal model exists. If animal models were exclusively focused on, it would have never been possible to discover FS. Therefore, certain types of research need to be done primarily through studies of humans.

13 The Pressure of Academic Selection

Many universities have defined expectations for the careers of young academics. This is usually based on the number of original papers they publish in journals with high impact factors. This has many advantages, such as promoting transparency and fairness. However, it also has downsides. Often, papers are considered original even if they are not innovative and simply repeat known aspects in a slightly different way. In addition, publishing in a high impact journal does not automatically mean that the findings will have a major impact in medicine and for patients. The development of the findings about FS, for example, was primarily based on clinical observations and experience. Such findings cannot immediately be hedged with a p-value and, therefore, are much more difficult to publish.

14 Conclusion

Although many modern research trends certainly have many advantages, in this article, we tried to promote tolerance towards alternative structures and approaches, which, from our point of view, are just as important and successful as many the more commonly established methods.

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1987–2013	Professor and Head of the Department of Ophthalmology, University of Basel
1995–1996	Dean of the Faculty of Medicine, University of Basel
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Awards and Honors

1984	International Chibret Award, Helsinki (Finland)
1985	Alfred Vogt Award, St. Moritz (Switzerland)
1986	Invited Professor, University of Harbin (China)
1986	Invited Professor, Dalhousie University, Halifax (Canada)
1990	Honorary Member and Medal of the Sicilian Ophthalmological Society (Italy)
1990	Promotion Award Vogt Foundation, Crans Montana (Switzerland)
1991	Honorary Guest of the Argentinian Ophthalmological Society, Buenos Aires
1992	Alcon Award, Fort Worth, Texas (USA)
1993	Invited Professor of the University of California, San Francisco (USA)
1996	Honorary Guest of the Japanese Glaucoma Society, Tokyo (Japan)
1996	Honorary Guest, Meeting of the Nobel Prize Laureates, Lindau (Germany)
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2002	Poster Award, SOG (Swiss Ophthalmological Society), Lucerne (Switzerland)
2003	Invited Professor, University of Varna (Bulgaria)
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"Regulation of receptor expression through delivery of artificial transcription factors"

Flammer Syndrome-Affected Individuals May Be Predisposed to Associated Pathologies Early in Life: Psychological and Psychiatric Aspects

Olga Golubnitschaja, Detlef E. Dietrich, Dieter Felbel, and Vincenzo Costigliola

Abstract Symptoms and signs of Flammer Syndrome (FS) usually appear in puberty. Appearance of the FS symptoms early in life is an extremely important indication for predictive and preventive measures to be considered by innovative concepts of predictive, preventive and personalised medicine (PPPM) and applied individually according to the patient profile of the affected person. This chapter provides the room for an

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opinion of experienced psychiatrists to consider facts and to demonstrate their vision in the area, at which time point the FS phenotype is getting evident and how innovative PPPM concepts might be applied to daily medical practice by

– selecting FS affected individuals at early stage of the phenotype development in teenagers
– optimising the environmental influence on development of the personality profile (family and school)
– and avoiding unhealthy behavioural habits such as "disordered eating" and clinical onset of the associated pathologies such as eating disorders (anorexia nervosa, bulimia) and mood and mental disorders (depression as an example).

Keywords Flammer syndrome · Obsessive personality · Perfectionism · Teenagers · Environment · Risk factors · Patient stratification · Psychology · Psychiatry · Disordered eating · Eating disorders · Anorexia nervosa · Bulimia · Leanness · Mood disorders · Depression · Predictive diagnostics · Primary and secondary prevention · Personalisation of medical services · Treatment tailored to the person

1 FS Symptoms and Signs Appear in Puberty – Predisposition to Anorexic Phenotype Early in Life

The introductory chapter "Flammer Syndrome in the Global Context – The "U-Shape" of Health Risks" provides the global overview of current trends in young populations demonstrating huge and permanently increasing numbers of individuals with both – obese and anorexic phenotypes strongly predisposed to a cascade of pathologies developed later on in life. These actualities prompt researchers and caregivers to consider more precisely the causality and adverse health effects of both phenotypes. To this end, a noticeable thinness (particularly slim body shape) has been demonstrated as being characteristic for the FS-affected individuals [1]. Finally, particularly in females signs and symptoms of FS appear early in life, frequently in puberty, since the hormonal regulation and therefore, changes in a hormonal profile, for example, during the pubertal maturation and in menopause play a crucial role in the expression of the FS phenotype. Consequently, early appearance of the FS symptoms is an extremely important indication for predictive and preventive measures to be considered by innovative concepts of predictive, preventive and personalised medicine (PPPM) and applied individually according to the patient profile of the affected person. This chapter provides the room for an opinion of experienced psychiatrists to consider facts and to demonstrate their vision in the area, at which time point the FS phenotype is getting evident and how innovative PPPM concepts might be applied to daily medical practice by

– selecting FS affected individuals at early stage of the phenotype development in teenagers
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– and avoiding unhealthy behavioural habits such as “disordered eating” and clinical onset of the associated pathologies such as eating disorders (anorexia nervosa, bulimia) and mood and mental disorders (depression as an example).

2 “Disordered Eating” and “Eating Disorders” – Relationship to FS Phenotype in Teenagers

Amongst reported eating disorders the absolute majority of cases is represented by anorexia nervosa and bulimia. Noteworthy, a great portion of bulimia cases originates from treated anorexia nervosa that the current section is focused on.

Experienced psychiatrists report on two characteristic picks in onset of anorexia nervosa amongst teenagers, namely the first one around the puberty begin by the age of 14 years and the second one by 18 years of age. An absolute majority of cases occur in female subpopulations compared to the male ones; the clinical pictures of each pick differ from each other dramatically. On the other hand all anorexic females around 14 years of age demonstrate very similar behavioural profiles and symptomatic development. The main attributes and contributing factors are described in detail below.

2.1 The Pubertal Changes Begin

The pubertal changes increase awareness of the adolescents of their body shape particularities. Therewith the life-phase begins when young girls and boys consider their bodies with enormous self-criticism. This process can have particularly strong impacts and long-term consequences, if anybody expresses a negative opinion about their shape.

2.2 The Most Frequently Discussed Parameter Is a Low Body Weight as the Symbol of Beauty

When considering an individual body shape, the most frequently discussed parameter is the body weight, that leads to the concepts of thinness as the symbol of beauty, strong dieting and obligatory weight loss. This is the conceptual begin for the “disordered eating”.

2.3 Risk Factors by the Familial Environment

Frequently Dieting Mothers

Beauty symbol by thinness is strongly supported by the familiar environment, for example, in case the mother is talking about or undergoes dieting frequently. It is then very likely that her daughter(s) will follow this behavioural pattern. The particular problem reported by psychiatrists is that even after the mother stops dieting, the daughter(s) frequently continues uncontrolled starvation till her anorexic condition might be diagnosed as an "eating disorder".

Children of Academics

Noteworthy, as particular systematic and perfectionistic in dieting and developing anorexic condition the adolescents growing up in academic families have been demonstrated, for example the children of teachers.

Overprotected Children

Another risk factor is created by overprotecting parents, who are hyperactive in developing their initiatives strongly focused on their child. This attitude may significantly suppress an adequate development of own interests, activities and competences by children inside and outside the family motivating the young generation to follow the behavioural patterns of their parents.

"Stiff" Families

Similarly to the above described familial risk factor, also the prioritised traditional behaviour in the family may create enormous psychological pressure acting against normal development of a teenager. Consequently, any change of the "tradition" is considered as damaging the family and may lead to development of disordered behaviour of affected children as well as eating and mental disorders in a long-term manner.

"Conflict-Mitigating" Behavioural Pattern in the Family

Another typical risk factor which may be created by familial environment is the so-called "conflict-mitigating" behavioural pattern. In this special case either one or both parents put special efforts to avoid opinion differences in the family as potentially "destabilising" their family. Therefore, the conformity is strongly cultivated in those families with all consequences essentially belonging to this behavioural pattern.

Psychiatrists report on the above described familial constellations as representing the frequent risks for developing behavioural disorders at the teenager age such as disordered eating. Noteworthy, particularly affected might be teenagers with meticulous personality and tendency to perfectionism, who grow up in academic families. Further, whereas anorexic teenagers around 14 years of age are rarely predisposed to suicidal thoughts, anorexic adolescents aged 18 years demonstrate highly increased risk for suicide. Obviously mood disorders such as depression go hand-in-hand with eating disorders. Below presented paragraphs highlight the most relevant features of mood disorders and provide overview towards innovative PPPM related strategies in predictive diagnostics, preventive and personalised treatments.

3 Mood Disorders: Paradigm Change in Diagnostics and Treatment Approaches

Mood disorders strongly predispose affected individuals to suicidal thoughts and consequent active measures. In the context of the presented book, it is important to mention that the "U"-shaped risks to die on one of the most frequent pathologies (see the introductory chapter "Flammer Syndrome in the Global Context – The "U-Shape" of Health Risks") is predominantly shifted to the individuals specifically demonstrating low BMI, who are at high risk for mortality, due to mood disorders, in contrast to persons with normal weight and/or overweight [2].

The aetiology of mood disorders is generally very complex. Besides a genetic predisposition, there is a range of possible aetiopathogenic risk factors such as altered epigenetic (post-genomic) regulation [3, 4] linked to familial and other constellations described above, developmental experiences, external and internal risk factors [5–7], clinically manifested different types of illness and disabilities, medication, drug use, both – acute and chronic stress exposure, sorts of traumata, conflict situations, social discomfort, bereavement, sleep disturbances, and female gender (due to the fact that depression is more prevalent in women) [8–10]. For over, many of the contributing factors are synergistically interactive [3, 11] resulting in a great multifactorial aetiopathogenic variability (subtypes) of mood disorders. Furthermore, the resilience and coping factors as well as the presence versus absence of support by family, relatives, friends and others – all varying between individuals – may significantly influence the development and course of a mood disorder. Consequently, the diversity of aetiopathogenic and protective factors is the subject for individualised patient profiling, early and predictive diagnostics and therapeutic algorithms tailored to the person. The advanced personalised psychiatric approach towards understanding and treatment of mood disorders is requested to reflect all these aspects presented below.

3.1 Diagnosis

A mood disorder is diagnosed based mainly on three essential components, namely the current psychopathology, the course of the disease and on the exclusion of an organic origin.

1. In most patients, the psychopathology itself varies strongly from individual to individual not always reflecting a mono-disorder but rather a group of diseases with overlapping symptoms and aetiopathogenic links [9, 12–14]. Diagnoses made by considering specific clinical syndromes and by application of diagnostic tools such as MRI, often remain case-unspecific that evidently demands a novel holistic approach. Disease and subtype-specific biomaker panels may significantly improve the diagnostic power and enhance overall specificity and sensitivity of corresponding approaches [15–19] essentially leading to the treatment algorithms tailored to the patient and resulting in improved treatment response.
2. The course of disease should be precisely recorded for providing a correct diagnosis and an optimal follow-up treatment. To this end, the exact evaluation of the individual patient history is crucial being also relevant for secondary prevention strategies. Consequently, there is a need in detailed interview strategies.
3. An exclusion of the organic origin of a syndrome became more reliable, mainly due to routine application of imaging technologies such as MRI and nuclear medicine techniques which are extremely helpful in identifying somatic reasons for mood disturbances [20].

3.2 Treatment

Treatment options for mood disorders demand more individualised services as specified below.

1. Regarding antidepressant medication, it is well known that currently not more than 30–40% of the affected patients respond adequately; the absolute majority of the patients respond only partially towards antidepressants or do not respond at all. Consequently, this difference reflects a great variety of subtypes of mood disorders, and a mean value recorded for highly heterogeneous group of patients provides usually conclusions which are not specific for the individual. Non-responsive patients need a therapy adapted to the individualised patient profile; personalised approaches utilising comprehensive biomarker panels would allow for more precise assessment and more effective antidepressant therapy [15, 16].
2. Individualised therapy monitoring is essential to avoid ineffective treatments and adverse side-effects. Patients self-reports towards medication is a useful instrument for evaluating the therapy effectiveness and for creating more consequent follow-up recommendations [21].

3. Psychotherapeutic approaches appear to be more specific than drug therapy. Several successful psychotherapeutic strategies are evidence-based (e.g. Cognitive Behavioural Therapy, Interpersonal Psychotherapy and the Cognitive Behavioural Analysis System of Psychotherapy (CBASP) as well as Psychodynamic Therapy). Most of them are based on interviews with patients as a diagnostic tool analysing the disease onset, development and contributing factors for affected persons individually.
4. Personal empathy between the patient and their psychotherapist (e.g. psychologist, physician) plays a crucial role in the therapy efficacy. Furthermore, modern psychoanalysis applies aspects of transference and counter-transference within the psychotherapeutic context that is a highly individual approach. To this end, some efforts are made to implement prediction tools to enhance an individual therapeutic efficacy [22].
5. Finally psychoanalysis is in the mission to understand internal and external risk factors and individual contributors: an initial triggering factor for the depression onset might be, for example, the loss of an intimate person such as the partner or a child or friend. This may induce the pathological process by a strong stress reaction, feeling of insufficiency, helplessness and guilt. The subsequent depression may evolve through neurobiological changes including imbalance of the CRH-Cortisol-hormone-axis and alterations in released neurotransmitters (serotonin, noradrenaline and dopamine), amongst others. In such a depressive state the introspection into the "self" and the interaction with the subjects' social environment (e.g. being confronted with helplessness, anger and conflicts) may further potentiate the severity of depression. Contributing internal and external (environmental) factors and potentiating mechanisms may keep the depression going, that is the matter for individualised psychoanalysis making the follow-up treatment successful, once the contributing factors are well identified. Individualised patient profiling is the robust platform for successful preventive strategies [23, 24].

3.3 Prevention

Personalised prevention strategies should be based on known general risk factors for depression [5–7] and the interview of the subject to assess the personal resources and the social support or social stress. In addition, information about evidence-based secondary preventive strategies is useful, if an affective disorder is current. All strategies should be established in a primary healthcare strategy, in most cases by the responsible general practitioner, and supported by public relation activities. It appears useful to include knowledge from childhood and adolescence psychiatry [18], long-term studies of affective disorders and evidence-based information from genomics and multiomics. All information has to be dealt very sensitively with, and should be an obligatory part of personalised interaction between the therapist (physician, psychotherapist) and the patient.

4 Outlook and Expert Recommendations

Per evidence, psychiatry and psychotherapy require a new paradigm applied to the overall management that would implement predictive approaches, targeted prevention and personalisation of medical services positively impacting on individual outcomes and healthcare as a whole. What is recommended to reach this goal?

The paradigm shift from reactive to predictive medical services should be implemented reconsidering current strategies of "disease care" in favour of predictive medical approach as the platform for the cost-effective "health care" [25].

Individualised patient profiling is essential for the effective patient stratification, characterisation of the individual predisposition and creation of treatments tailored to the person [26].

Multi-level diagnostics is a robust platform for PPPM strategies which includes specialised questionnaires, patient history, medical imaging and precise molecular biological characterisation of the patient and/or predisposed individual [25]. An innovative PPPM approach for the overall management of mood disorders has been recently described in the literature [15].

Professional interactome amongst relevant professional groups should be designed in order to create a multi-professional approach in the area [25].

Innovative screening programmes should be developed to select and to treat persons at risk in a suboptimal health condition, in order to avoid clinical manifestation of the disease.

New educational programmes are required to improve knowledge of professionals and general population in the area. The programmes should provide detailed information about the above listed points explaining why the paradigm shift is needed, what are the instruments for reaching that, why the multi-level diagnostics is more advanced compared to the currently available approaches, how the professional interactome can be designed in the most optimal way, and what are the benefits of the patients and healthcare-givers by the realised concepts of PPPM. More information regarding interrelations between Flammer syndrome, disordered eating, mood disorders, complexity of risks, and microbiome is provided in the book chapter "Flammer Syndrome, Disordered Eating and Microbiome: Interrelations, Complexity of Risks and Individual Outcomes" by Rostyslav Bubnov and Olga Golubnitschaja.

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Flammer Syndrome: Psychological Causes and Consequences of Visual Impairment

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Abstract About 285 million people are estimated to be visually impaired worldwide, amongst them 39 million are blind. In contrast to refractive deficits caused by diseases of the cornea or lens which can be corrected by optic means or surgery, diseases affecting the visual nervous system (retina, optic nerve, brain) are widely assumed to be irreversible. If patients are informed of such a grim diagnosis and poor prognosis, they typically experience anxiety and fear of becoming blind. This creates a psychological double-burden: not only do they experience fear-inducing difficulties in daily life with reading, orienting or mobility, but a negative prognosis typically has a severe emotional impact, leading to worries, anxiety, fear, depression, and social isolation. Therefore, vision loss and emotional responses go hand-in-hand, creating a long lasting psychosocial and socioeconomic burden to the affected individuals and society at large.

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The aim of this chapter is to summarize the literature with the goal to untangle the relationship between vision loss and psychological factors related to the Flammer Syndrome phenotype – both in research and in the clinical context from a holistic point of view. We conclude that stress is both *consequence* and *cause* of vision loss. This creates a vicious cycle of a downward spiral, in which initial vision loss creates stress which further accelerates vision loss, creating even more stress and so forth. We propose that optimized stress management in Flammer Syndrome affected individuals can help activate residual vision and restoration, augmenting current approaches to prevent further vision loss and to enhance rehabilitative efforts such as vision training and brain stimulation.

Keywords Flammer syndrome · Personality · Vascular dysregulation · Vascular endotheliopathy · Autoregulation · Visual impairment · Eye disorders · Blindness · Psychology · Psychosomatic medicine · Relaxation · Restoration · Stress response · Epigenetic regulation · Predictive preventive personalised medicine

Abbreviations

AMD	age-related macular degeneration
FS	Flammer Syndrome
GON	glaucomatous optic neuropathy
HTG	high-tension glaucoma
IOP	intraocular pressure
NTG	normal-tension glaucoma
POAG	primary open-angle glaucoma
QOL	quality of life
RP	retinitis pigmentosa
ANS	anatomic nervous system
AION	anterior ischemic optic neuropathy
SAM	sympathetic adrenomedullary system
HPA	hypothalamic-pituitary-adrenal axis
CRH	corticotropin releasing hormone
AVP	arginine vasopressin
ACTH	adrenocorticotropic hormone
PFC	prefrontal cortex
NO	nitric oxide
eNOS	endothelial nitric oxide synthase
CT	computed tomography
MRI	magnetic resonance imaging
PACG	primary angle closure glaucoma
DES	dry eye
SAS	Self Rating Anxiety Scales
SDS	Self Rating Depression Scales

OSDI	Ocular Surface Disease Index.
NOVL	non-organic vision loss or functional vision loss
VF	visual fields
VA	visual acuity
CS	contrast sensitivity
AVL	Age-Related Vision Loss Scale
NEI-VFQ-25	National Eye Institute 25-Point Visual Functioning Questionnaire
PHQ-9	Patient Health Questionnaire -9
SF-36	36-Item Short Form Survey
GAD-7	Generalized Anxiety Disorder 7-item
SCL-90	Symptom Checklist-90-Revised
BDI	Beck-Depressions-Inventory

1 Stress and Vision Loss: What Is First – "The Hen or The Egg"?

The concept of the deficient mental health as linked to the vision loss dates back to ancient times. In a Sanskrit book entitled "SUSRUTA SAMHITA", believed to be written as early as 1.300 BC [1], i.e. over 3.000 years ago, a famous Indian surgeon named Susruta, practicing the ancient Indian traditional Ayurveda medicine, lists 18 different causes of vision loss (see first chapter on "Basics of Eye Diseases" with an excerpt shown in Fig. 1). Among them, six "causes" or signs of bodily or emotional stress are listed: improper sleeping habits like day time sleeping, awakening at night etc. (SWAPNA VIPARYAASCHA), continuous weeping (PRASAKTA SAMRODHANA), excessive anger (KOPA), Grief (SHOKA), Stress suffering -pain, physical and mental exhaustion (KLESHA) and suppression of tears (BHASHPA GRAHATH).

Our hypothesis that visual impairment has, at least in part, a psychosomatic component, is based on two considerations: Firstly, patients suffering from impaired vision (for example due to glaucoma or optic neuritis) often report that their vision loss happened at the time of massive and/or prolonged mental stress (or shortly thereafter). The source of massive mental stress could be significant life events such as financial, marital, employment (retirement) or severe health problems. When asked about it, patients often mention that their vision loss might have been triggered by stress.

The second consideration is related to the fact that the biological response chain follows continuously (or acutely) elevated stress hormone levels in blood vessels (such as cortisol, adrenalin, endothelin). They cause vascular dysregulation which leads to insufficient amounts of oxygen supply in the eye (and possibly brain) tissue with widespread consequences at biochemical, physiological and psychological levels. The "Flammer Syndrome" (FS) is a good example for that, when endothelial cell dysfunction, which occurs possibly due to epi/genetic abnormalities in combination with an increased stress hormone exposure collectively lead to vascular autoregulation problems [2] (see below).

Stress: *cause* of vision loss

Psychology lessons from ancient India

(1.500 - 600 B.C.)

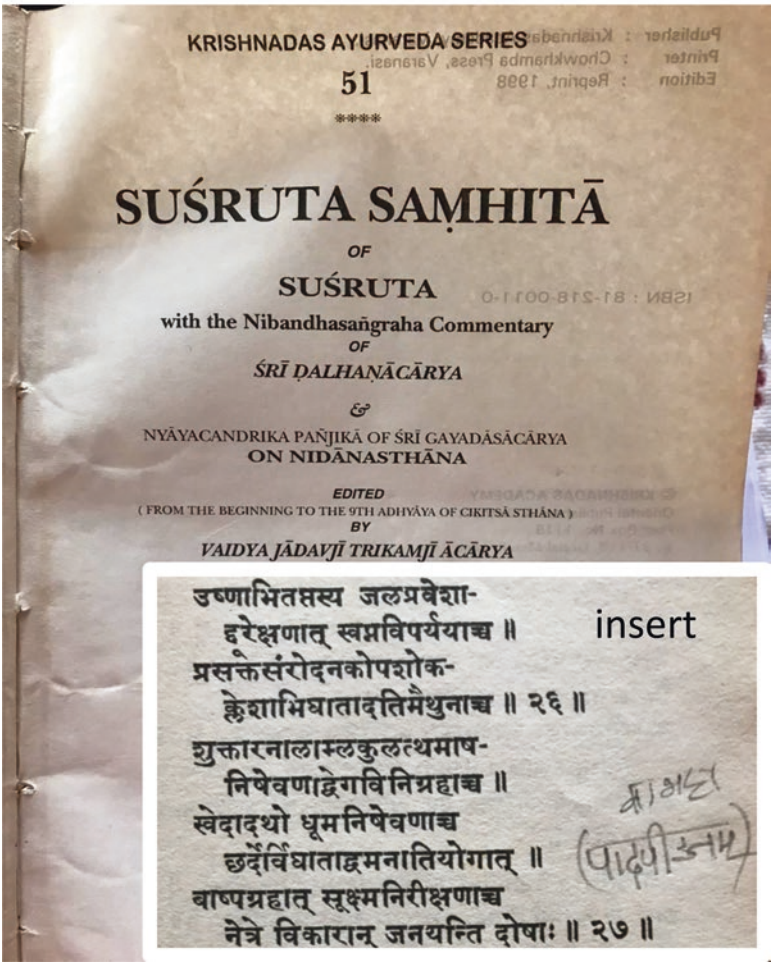

Fig. 1 Causes of vision loss taken from "SUSRUTA SAMHITA"[1], first chapter of "BASICS OF EYE DISEASES". The figure shows the original Sanskrit text passage. The transformation to Roman lettering and the respective English translation shows six causes of vision loss (printed in bold) which are related to emotional stress: (1. USNABHITAPTASYA JALAPRAVESHATH – Drinking or exposing to cool water after exposing to heat. 2. DOOREKSHANATH – Looking at the very distant objects regularly for a long time, may be without blinking. 3. **SWAPNA VIPARYAASCHA – Improper sleeping habits like daytime sleeping, awakening at night etc.** 4. **PRASAKTA SAMRODHANA – Continuous weeping**. 5. **KOPA – Excessive anger**. 6. **SHOKA – Grief**. 7. **KLESHA – Stress – suffering -pain, physical and mental exhaustion**. 8. ABIGHAATA – Minute irritative injuries or contusion injuries or perforating injuries. 9. ATI MAITHUNNA – Indulgence in excessive sexual intercourse. 10. SHUKTHA ARANALA AMLA – Vinegar and alcoholic beverages. 11. KULUTTA -Intake of horse gram excessively. 12. MASHA – Intake of black gram excessively. 13. ATISWEDA – Excessive sweating. 14. DHOOMA NISEVANATH – Exposing to smoke or tobacco smoking. 15. CHARDHIR VIGHATATH – Suppressing the vomit. 16. VAMANATHI YOGATH – Excessively indulging in inducing vomiting. 17. **BHASHPA GRAHATH – Suppressing tears**. 18. SUKSHMA NIREEKSHANATH – Observing the minute things or seeing too tiny objects)

Indeed, the association between an excessive stress and glaucoma pathomechanisms has already been proposed [3, 4]. On the other hand, mental stress is rather considered as the *consequence* of vision loss reducing quality of life (QOL) [5]. Constant anxiety and worries plague many patients, as they anticipate a grim future of a progressing blindness. This fear severely impacts their quality of life (QOL) and life-style [6], due to increased risks of losing employment, greater dependence on others and declining self-esteem [7]. This is particularly relevant to acquired visual impairment but less so for blindness since birth [8].

Despite a compelling body of rationale, stress is still of little concern to clinical ophthalmogy because opthalmologists are neither trained, nor financially rewarded for helping fix psychological problems; in contrast, usually they are not provided with psychological and/or psychiatric training. Indeed, if clinicians would accept the fact that excessive stress is causal for vision loss, they would acknowledge the considerable risk of using negative statements in their communication such as "you are going to be blind", "there is nothing to do against the cause of your blindness", or "blind stays blind".

In agreement with our clinical experience amalgamated with a thorough literature review [2, 9], we now wish to propose that psychological stress is not only a *consequence* but also a meaningful *risk factor* for visual impairments. If confirmed, new understanding could lead to early and even predictive diagnosis and more effective treatment options tailored to the "person behind the eye". Before discussing the scientific aspects of the issue in more detail let us introduce an example from daily medical practice by the case report provided now:

Case Report

W.G., a 78 year old woman, is happily married for 55 years. As a former business manager who worked 50+ h/week all her life as supervisor in a bank's IT department, she presented herself at SAVIR-Center in Magdeburg to receive treatment for her severe vision loss on both eyes.

Case history: W.G. had cataract surgery on both eyes in 2001 with excellent outcome and clear vision thereafter. In January 2013, she lost vision on her left eye immediately after having undergone gynecological surgery under general anesthesia. In the morning of surgery, she received a tranquilizer to prepare her for general anesthesia. But because the surgery was delayed, she received additional injections of the tranquilizer throughout the day. The surgery finally started in the late afternoon and lasted more than 2 h. As she woke up, it was already dark outside. She slept well through the night, but next morning she noted that her left eye was completely blind and she had to vomit, which she never did before. She suspected that the blindness occurred as a result of the surgery, but she had not noticed it due to the darkness in the evening. Her vision recovered a bit spontaneously but remained severely impaired. The vision loss worried her a lot as she wondered how to manage her life with only one eye and how she could

(continued)

continue to take care of her frail husband who suffered from heart problems. Three years later, in 2016, her husband's health suddenly deteriorated requiring immediate by-pass surgery. She worried not only about her vision problem but also that her husband might die and what her future would be like after 55 years of a happy marriage. On the day after her husband's surgery, her vision suddenly deteriorated also on the right eye and she suspected that the 3 years of continuous stress plus her acute worries were suddenly "discharged" in her vision loss. Though other factors might have contributed to her condition, obviously stress was the main trigger for her acute vision loss. However, when asking her ophthalmologist, whether the vision loss might be related to stress, she was informed that stress had absolutely nothing to do with the vision loss, though a cause has not been clearly identified by the ophthalmologist. Asking what her prognosis would be, she was told that "once it is damaged, it will stay damaged forever". Finally, an assistant doctor made a remark without any sense of empathy: "whatever you try, you will go blind".

Medical: The ophthalmological report indicates a history of Sicca syndrome for both eyes; left eye optic nerve atrophy due to NAION in 2013, and right eye NAION in 2016, normal IOP, no fundus pathology except for a nasal vasoconstriction OD. Brain CT and lab values were normal, except for indication of hyperlipoproteinemia. No treatment recommendation for vision loss was given.

Vision testing: Vision testing in October 2017 revealed an OD Humphrey visual field index of 12% (mean deviation −25.97 dB). OS could not be measured due to fixation problems. Supra-threshold stimulus detection (High Resolution Perimetry, HRP) to measure residual vision showed detection rates of 43% OD (fixation of 100%) and 59% OS (fixation 99%) with reaction times of 600/500 ms, respectively. The discrepancy between near-threshold and super-threshold testing was surprisingly large. OD/OS visual acuity was 0.25/0 and contrast sensitivity 1.0 monocular on both eyes and 1.24 binocularly (see Fig. 3).

Subjective vision: W.G. reported her vision to be reduced in both eyes; OD was worse as she could see only course shapes but no details. OS could recognize course shapes in temporal visual field sectors and shadows in the nasal half of the visual field which she perceived as grey ("foggy") vision. She could no longer read newspapers of her bank account statements, had problems recognizing faces, frequently bumped into people or objects, had painful glare with bright lights, adaptation problems from dark to light, dry eyes and problems with black-white contrast; color perception was subjectively intact. Her eyes could move in all directions, but she had occasional extra-saccades while fixating.

Psychological Assessment: She was cognitively normal, understood and responded to questions adequately and was intellectually quite alert.

(continued)

However, mental stress and worries in the past and at present were dominant. She showed signs reminiscent of the Flammer syndrome (FS) (see below): cold hands and fluctuations towards low blood pressure, slim body shape, tendency to worry a lot, ambitious and perfectionist attitude both at work and at home, problems falling asleep, lack of the feeling of thirst, and very pale skin in her face and extremities. In addition, she reported her thinking to be dominated by the wish to fulfill the expectations of others but ignoring her own desires, wishes and needs. She was quite aware that stress has been – and still was – a problem, but she did not know what to do about it and was quite anxious to be ending up blind.

Case summary and conclusions: It is likely that the vision loss on the left eye after her 2013 surgery may have been caused by the lengthy tranquilizer/anesthesia and might be explainable by closed angle glaucoma or perfusion problems (apparently not directly related to stress) as described by Flammer [10]. The subsequent loss on the right eye 3 years later, in all probability, is stress-related because of anxiety and worries about her own vision loss plus her husband's health problems, in conjunction with her tendency to neglect her own emotional needs. This might have induced a vasospasm as a consequence of her chronic (3-years) stress plus the acute stress due to her husband's heart surgery. It is conceivable that the earlier negative experience and stress induced by the pessimistic prediction of the assistant doctor ("you will be blind") did not help the situation but rather potentiated the stress, increasing the probability of vision loss.

Treatment: The patient was treated with the aim to improve blood circulation and brain synchronization to activate residual vision [11] by daily administration of alternating current stimulation [12–15], relaxation and eye yoga exercises. In addition, she received psychological consulting with the aim to develop greater stress resilience and improve coping by emotionally accepting the vision loss. Though we do not know which therapeutic module was most effective, the combination of all treatments she received during a two-week period improved her vision both objectively and subjectively (for further descriptions of these methods, [16]).

Treatment outcome: After the 2 week treatment in the SAVIR-Center in Magdeburg, W.G. subjectively noted that her vision had improved: half way through the treatment she could see at far distance again and her "grey" vision became brighter ("white") in the upper visual field sector. She was also able to see more details again. For example, she could see parts of her face again when looking into a mirror and her eyes and hair again for the first time. She reported being able to read street signs again, but her central visual field still felt problematic. These subjective reports were confirmed by Humphrey visual fields which improved from 12% to 21% visual field index with no fixation losses or false positives at both time points (Fig. 3).

(continued)

Another case, also shown in Fig. 3 presents 52 years old woman, suffered from normal tension glaucoma. As she came for treatment to the office of the first author (B.S.) for 10 days, she did not improve much. She was a rather agitated and energetic woman with strong tendency to worry and perfectionism. As she returned for a second course of treatment about 12 months later, the psychological consulting from the first visit, together with a second course of 10-day treatment and psychological consulting had a remarkable benefit for her vision which improved from 19% to 63% visual field index.

Both clinical cases are clear examples of the Flammer Syndrome (FS) phenotype. Contextually, another representative patient case has been recently described in the literature [17] indicating an evident lack of the dedicated healthcare. It demonstrates the urgent necessity to pay attention to symptoms and signs of FS phenotype for early diagnosis and treatments tailored to the person, in order to improve individual outcomes. We now consider specific FS signs and symptoms relevant for mental stress in patients who are predisposed to and suffering from the eye disorders.

2 Flammer Syndrome and Stress

FS and the science behind it is a starting point for our discussion of the concept that some diseases of impaired vision may be considered psychosomatic in nature. Specifically amongst eye disorders, FS is found mostly in cases with the normal-tension glaucoma (NTG) first described by Dr. Josef Flammer at the University Eye Clinic in Basel, Switzerland, who provided insights into how closely the mind and the body interact [9, 18, 19]. NTG often leads to visual field impairments but almost never to blindness. According to Flammer's proposal, stress hormone release in persons with endothelial dysfunction leads to vascular dysregulation. This, in turn, is a key mechanism of vision impairment in NTG but not in high-tension glaucoma which is characterized by an increased intra-ocular pressure. The discovery of the Flammer Syndrome (FS) is a key advance in our understanding of the role of stress in certain forms of vision impairment. It establishes a link between human psychology (state of mind), pathophysiological susceptibility (endothelial integrity) and biological stress response (stress hormone release signature), the combination of which may lead (or at least predisposes) to vision loss. Noteworthy, FS is most obvious in younger patients suffering from NTG, but the principles learned from FS may be well applicable to some other diseases of the visual system.

According to Flammer, the FS might be inherited and its objective symptoms and signs (such as endothelial dysfunction, capillary reaction to cold stress, altered gene expression, etc) are detectable across the life span (although more pronounced in premenopausal compared to postmenopausal women), with or without specific stress conditions. But FS persons (FS+) react differently to stress than those without

Flammer syndrome signs (FS−). FS+ individuals response to emotional stress by vasoconstriction, whereas FS− subjects react with an imbalance of the ANS, which lead to tachycardia, high blood pressure, IOP rise, stomach pain, gastrointestinal upset, etc.

Stress, especially in young patients with FS+, can provoke acute diseases such as AION or retinal venous vasoconstrictions because of vascular endotheliopathy. This vasoconstriction does not seem to be the result of stress hormone exposure alone. Rather, persons with vascular endotheliopathy are more susceptible to stress, i.e. with an altered responsiveness to stress hormones (mainly adrenalin and endothelin), to cold provocation, low atmospheric pressure at high altitudes and mechanical insults. FS is thus the result of an interaction of a specific epi/genetic regulation and psychology (stress perception). Endothelial mitochondrial dysfunction seems to be the subcellular contributor to FS [20]; this dysfunction is decisive for regulation of the smooth muscles in the retina vessels, which are not controlled by the ANS.

These observations suggest that glaucomatous optic neuropathy (GON) is not only the result of some sort of "mechanical insult" due to elevated IOP on the optic nerve head (ONH) with subsequent degeneration of the inner layer of retina and optic nerve. As the FS demonstrates, this "mechanical" view of glaucoma is too simplistic. GON pathology is much more complex: GON (i) involves not only the eye but the entire optic pathway including other parts of the brain, (ii) GON can develop at either elevated or normal IOP levels, and (iii) ocular blood flow (OBF) is reduced which affects not only the eye but also other body parts such as the nail fold capillaries [21] and possibly the brain.

However, not everyone with FS-phenotype develops glaucoma, which is a multifactorial disease. This means that multiple contributors play a role in clinical manifestation of the disorder such as triggering factors, excessive oxidative stress, reduced "repair" capacities and a personality-based insufficient stress resilience (coping). FS is more prevalent in women (70%), and FS patients tend to be slender, have typically indoor rather than outdoor jobs, and they are more likely academics than blue collar workers [22]. Further, FS patients tend to have prolonged sleep onset time, prolonged blood flow cessation in the finger capillaries after cooling, autoregulation problems of ocular blood flow, increased retinal venous pressure, stiffness of retinal vessels, and increased oxidative stress, which altogether are likely to contribute to the FS associated pathologies. FS+ individuals have also generally increased sensitivities to certain drugs, high altitudes (lower atmospheric pressure) changes, vibration, and pain sensation [22].

Finally, individuals with FS-phenotype demonstrate specific psychological characteristics. FS+ patients are often worrisome and remarkably assiduous, sportive, and ambitious, with a tendency towards perfectionism. Such patients seem to have an urge to be good to everyone (like "angles") and fulfill first and foremost the needs of others like their spouses, family, friends, and coworkers. By being so good to others, they frequently neglect their own emotional needs and desires. Their brain is more focused towards the social fabric in the outside world, neglecting their own self. Such persons tend to be ruled by self-denial and – to use psychoanalytic terms – their "super-ego" (strictly observing duties, rules and satisfying expectations) domi-

nates their "It" (pleasure, joy, emotional satisfaction). This super-ego domination, however, leads to long-lasting self-deprivation, increasing the level of anxiety and fear with risk of depression. Contextually, FS+ shares certain similarities with the Takotsubo syndrome, a stress-induced cardiomyopathy, which also affects mostly women demonstrating similar psychological characteristics [23].

Because of these personality traits, FS-individuals do experience chronic mental stress, often without knowing or acknowledging it. The origin of this trait might differ among FS-individuals, but most likely certain negative experiences stamped the personality in childhood which is stabilized or reinforced by programmed stress sensitivity as a shared cause. Indeed, some FS+ patients consulted by the authors do report sexual abuse during their childhood; this trauma may lead to programmed stress sensitivity. These actualities lead to the conclusion that FS associated pathologies are at least in part of psychosomatic origin.

Concerning eye diseases, FS association is found in normal tension glaucoma, retinitis pigmentosa [24], increased retinal venous due to a dysregulation of venous outflow from the eye [19, 25], retinal vein occlusion [26], optic nerve compartment syndrome [22], and preoperative ischemic optic neuropathy [27]. However, from both – the clinical and scientific perspective, a systemic vascular dysregulation does not impact solely the eye function in the human body. Other organs described in the literature as being affected by FS are inner ear with diseases such as tinnitus or sudden hearing loss [22], and the brain. FS also plays a role in pathology of other diseases such as multiple sclerosis [28], predisposition to cancer [29–32] and particularly poor individual outcomes of oncological diseases [33–36] – **see corresponding chapters in the book.**

In conclusion, the Flammer Syndrome carries a *holistic character* and, therefore, demands multi-level analyses including molecular, cellular, physiological and behavioral (psychological) levels.

3 Mental Stress and Personality: Psychological Aspects of Coping with Impaired Vision and Blindness

Psychology is the science of mind and behavior, including all aspects of conscious and unconscious experiences as well as thought (cognition) [37]. When a person suffers from prolonged psychological (mental) stress, this reduces QOL and is a burden not only to him/her, but also to their social environment [38]. People have different mechanisms for coping with stress, i.e. being able to react to stress in an adaptive manner. But if stress is too high or lasts too long, or if the person does not have sufficient resilience capacities or copying skills because of his/her personality disposition, then mental fatigue, burnout, anxiety/fear or depression may ensue. This can go hand-in-hand with organic/somatic problems like feeling non-organic pain or non-organic vision loss [39–41], especially if such persons have a predisposing genotype. There are many diseases dealt with in medicine characterized by both somatic and psychological aspects (so-called "psychosomatic medicine"). Its task is

to help reducing the impact of psychological problems to improve patient's well-being and providing coping resources for their physical diseases or disabilities [21, 42–48]. Since diseases of the visual system have traditionally been viewed as an exclusive affair of biology and physics (optics), an interaction between ophthalmology and psychosomatic medicine is evidently underdeveloped.

Whether an individual is resilient or susceptible to stressors depends largely on their personality. Maladaptive coping strategies and specific personality patterns are often found in patients with glaucoma [49–51]. For example, Mabuchi [52] observed that PAOG patients have significantly higher mean neuroticism scores (N); further, agreeableness (A) and conscientiousness (C) are significantly lower in male POAG patients. The mean extraversion score (E) was significantly lower in female POAG patients. Freeman et al. [49] observed that those patients that use denial when confronted with their first POAG diagnosis had a faster progression of the visual field loss.

Individuals, who are blind or have low vision, face the constant challenge of psychologically and socially adjusting to their disability [53]. A person's personality determines, whether their coping strategy is sufficient to handle stressful events or not. Meta-analyses [54] link optimism, extraversion, conscientiousness, openness and agreeableness to more engagement in coping; so does, in contrast, neuroticism which leads to less disengagement in coping [55]. Benn [56] studied two personality traits: neuroticism and optimism and five coping strategies: distancing, accepting responsibility, escape avoidance, effective problem solving and positive reappraisal. The result indicated that personality and coping (primarily distancing and escape-avoidance) appears to exert their effects directly on adaptation. Neuroticism and escape-avoidance are associated with reduced adaptation, and optimism and distancing are related to greater adaptation. It is well known that adaptation through coping is a psychological defense mechanism. Tolman et al. [57] used the "Adaptation to Vision Loss Scale" and tested 144 patients with AMD. The study suggested that blind older adults with AMD who were more adapted to their vision reported fewer depressive symptoms.

This puts the studies by Flammer in context. He observed that the FS happens more frequently in females (70%); FS women tend to be characterized by stereotypic feminine traditional gender socialization, which is an important determinant for anger suppression and all the signs attributed to FS+ [58].

To summarize, since personality traits determine how a person reacts to everyday stressors and because many patients with vision loss (especially glaucoma) are poorly adapted to stress, we argue that patients with specific personality traits related to negative coping styles are more prone to vision loss and its progression. If it is agreed that prolonged mental stress can be a major (though not only) cause of vision loss, then ophthalmologists, psychologists, psychiatrists and other related professionals should be encouraged to offer stress management interventions to vision loss patients with the goal to reduce stress and thus prevent or halt the progression of vision loss. Furthermore, if such stress reduction methods are successful, then conclusive evidence is needed for the proposition that stress is *causal*, and not just the consequence of vision loss. The study that meditation can normalize

IOP is one such study [59], and many several other observation show how stress reduction can help in the management of vision loss.

4 The Stress Response

Acute as well as chronic stressors can elicit the onset or worsen the course of vision loss. Understanding the physiological mechanisms of the stress response is, therefore, a pursuit of pertinent and pragmatic interest.

4.1 Stress Response Systems

The brain has two outflow systems to control the adaptation of the body to stress: firstly, the neuronal sympathetic adrenomedullary system (SAM) which is part of the autonomic nervous system (ANS), and secondly a neuroendocrine stress response system, i.e. hypothalamic-pituitary-adrenal axis (HPA). Both are activated during stress, and both are controlled by neural brain networks which are involved in the control of stress and emotion. Critical brain regions are the brain stem, hypothalamus, prefrontal cortex, amygdala, and hippocampus.

The Sympathetic Adreno-Medullary System

Walter Cannon suggested already in 1932 [60], that acute responses to threat involve activation of the sympathetic nervous system via autonomic centers in the brain stem, resulting in peripheral catecholamine release from the adrenal medulla. This sympathetic activation prepares the organism for increased activity by constricting blood vessels to redistribute blood flow to muscles and by increasing heart rate and pulmonary function, in order to maintain homeostasis under conditions of increased demand [61]. Sympathetic activation simultaneously also shuts down other bodily functions that are not needed at that moment such as feeding, reproduction or sleep. Stomach and upper intestinal functions are inhibited so that digestion is slowed down. Thus, the stress response is adaptive for a “fight and flight” response, which is of great relevance for the survival of the individual and survival of the species in evolution. It increases metabolism for this action via glycogenolysis in the liver to raise glucose levels, and modulates brain function to increase vigilance, attention and arousal. Here, central norepinephrine helps activating the HPA axis [62].

As the Flammer Syndrome implies, repeated or chronic activation of this system can elicit vascular system dysfunction in patients, which have genetically suscepti-

ble endothelial cells that can promote development of vision loss. In addition, a sensitized system due to early-life adversity could represent a risk factor for developing vision loss in response to acute stressors [63]. This might be particularly true for genetically predisposed individuals [64].

Hypothalamic-Pituitary-Adrenal Axis

While the SAM is rather a fast-reaction system, the HPA axis has a slower reaction to internal and/or external stress. The HPA axis is controlled by the CA3 region of the hippocampus, and corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) neurons originating in the paraventricular nucleus of the hypothalamus. Activation of these neurons is elicited by combined input from cortical limbic and brain stem circuits. The prefrontal cortex and hippocampus inhibit the HPA axis and input from amygdala and noradrenergic brain stem nuclei activate it (see next section). Axons of CRH neurons (and co-secreted AVP) terminate in the median eminence onto small blood vessels (neuroendocrine transmission). Here, the neuronal signal is "translated" into a hormone "blood-borne" signal by releasing neuropeptides into the portal circulation of the pituitary gland from where they reach the anterior pituitary corticotrophic cells to stimulate the secretion of adrenocorticotropic hormone (ACTH). ACTH, in turn, stimulates the synthesis and release of glucocorticoids (e.g. cortisol in humans) from the adrenal gland into the blood circulation. Glucocorticoids then lead to increasing blood sugar through gluconeogenesis and provide the energy resources for the organism to flee or to fight. Because glucocorticoids modulate transcription of certain genes in the cell nuclei, the hormonal response to stress is slower and longer lasting than the faster SAM actions [65].

While the release of glucocorticoids during stress is good news for its adaptation to survive generally, it is bad news under conditions of severe or chronic stress, such as early childhood trauma or patients receiving a negative medical prognosis, such as "you are going blind". The overexposure of the brain to glucocorticoids can then become toxic to neurons, e.g. in the hippocampus and prefrontal cortex, and glucocorticoids can even be toxic to retinal tissues [65, 66]. Because of various feedback loops, glucocorticoid increase progressively damage the hippocampus, leading to further glucocorticoid release, then to even more damage of the brain; a vicious cycle.

Lower than normal levels of glucocorticoid release are also detrimental as this can have adverse effects on the proper regulation of hormones to control central stress responses and activation of the immune system [67, 68]. Hence, an optimal balance of glucocorticoid release during stress is critical for a healthy adaptation response to stress.

4.2 Brain Circuits Implicated in the Stress Response

Besides the systemic stressors and homeostatic imbalances, the response to psychological or emotional stressors is key, but this requires appraisal and processing activities by higher brain regions.

While brain stem nuclei regulate the activation of SAM and the HPA with ascending ("bottom-up") projections, several "top-down" processes are involved in eliciting the stress response. These brain structures include limbic forebrain structures, including the amygdala, the hippocampus, as well as the prefrontal cortex (PFC). While hippocampus and PFC atrophy in conditions of chronic stress, the amygdala volume increases. It is involved in autonomic regulation and fear learning [69–72], and its volume enlargement is found in glaucoma patients [73]. But how the brain's visual and emotional system interacts in cases of low vision is a yet unexplored issue of ardent importance.

4.3 Stress and Inflammation

In addition to the HPA axis and the SAM, the immune system is another regulatory framework that is activated in response to stress. There are complex interactions between these three regulatory systems. For example, psychosocial stress can activate inflammatory responses, by neural activation of signalling pathways in immune cells, resulting in increased NFκB production, which induces the secretion of inflammatory mediators [68, 74]. Inflammatory mediators in turn can activate central stress responses. Concerning vision loss the role of inflammation is a topic long known to be critical for a variety of ocular maladies. A detailed overview of this field is, nonetheless, beyond the scope of this paper and we prompt the reader to read important reviews by others [74–80].

5 Stress and Vision Loss in Glaucoma

Glaucoma is an appropriate example of how an eye disease can be influenced or caused by mental stress. The biological response to mental stress and the pathogenesis of glaucoma share numerous common features sufficient to justify the mental stress based aetiology (see also Fig. 2). The principle mechanisms are intraocular pressure elevation, vascular dysregulation, an imbalance of autonomic nervous system regulation and immunological aspects [42, 43].

With the premise of above introductory remarks, we suggest that vascular dysregulation is a key mechanism of normal tension glaucoma (NTG) pathogenesis [18, 81, 82]. It may arguably be caused by stress hormones circulating in the vascular system, which – in turn – are controlled by brain cognition and emotional

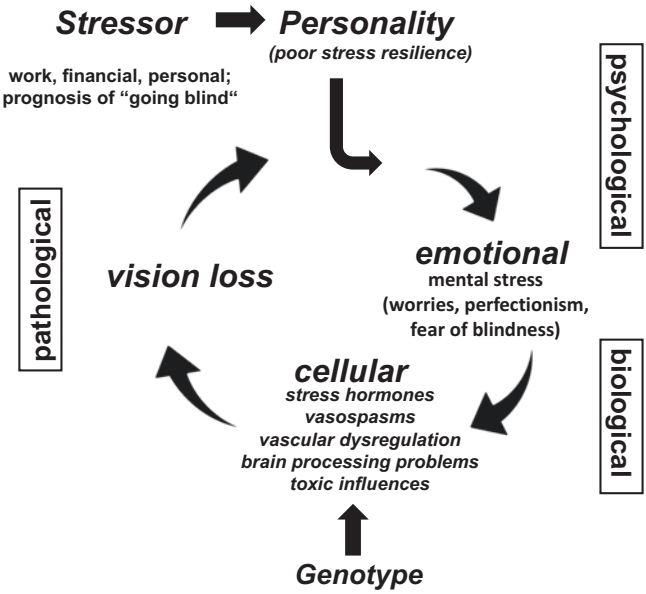

Fig. 2 Diagram of Stressors (chronic or acute) and their effects showing the vicious cycle of mental stress and vision loss and the cause-effect relationship of stress and vision loss. According to this concept, low vision is both, *cause* and *consequence* of vision loss. Note: the disease is involving different levels of analysis, psychological, biological and pathological (ophthalmological)

response to stressors. Stress hormones influence vascular tone, particularly in and around the optic nerve and thereby impair vascular autoregulation. It is therefore conceivable that the patient's individual emotional response to stressors determines whether or not the brain induces the release of stress hormones. In this case psychological factors would contribute to the development of NTG. While such a physiological hormonal state might be a necessary condition, it is not a sufficient cause as not everyone with emotional stress ends up with glaucoma. Therefore, other factors must underlie the ethiopathogenic picture to make the difference whether or not a stressed person develops NTG. Such factors could range anywhere from genetic susceptibility, stress sensitization to a disturbed stress resilience system. As we will discuss below, such factors may contribute to the pathology of the ocular blood vessel endothelial cells. In other words, we could look upon the brain and patient's individual experiences as starting points for the pathogenesis of glaucoma, and presumably other vision problems as well (genetic/pathological conditions being the second rung in the ladder). Neither of the two factors alone should be considered sufficient to cause NTG, but it is rather the combined effect of both. This can be described by the following causal chain of events which is slightly different from high tension glaucoma: (see also Fig. 2).

Normal tension glaucoma:

Stressors (chronic or acute) - > brain's cognitive interpretation - > emotional response- > stress-related biological responses (hormonal, vascular dysregulation)- > retinal and optic nerve pathology - > visual field loss.

High tension glaucoma:

Stressors (chronic or acute) - > brain's cognitive interpretation - > emotional response- > autonomic imbalance - > rising intraocular pressure (IOP) - > retinal and optic nerve pathology - > visual field loss.

Below provided paragraphs of the subchapter analyze the proposed mechanism in detail.

5.1 Stress and Intraocular Pressure

The main cause and the only currently known modifiable risk factor for glaucoma is elevated intraocular pressure (IOP). This reduces blood flow in the eye due to physical pressure on the choroidal vascular system. The standard of care is lowering IOP by topical drugs or performing surgery with the aim to relieve the physical pressure and thus normalize blood flow. Several publications indicate that mental stress is associated with IOP elevation which is confirmed by molecular studies (see below) [83]. In patients who already have glaucoma, both acute and chronic stress raise IOP; when lasting for longer duration, stress may raise IOP even in those not having glaucoma [83, 84]. But 33–57% of all glaucoma cases [85] have normal-tension glaucoma (NTG). This shows that besides the physical influence of IOP there are other causes of glaucoma as well: vascular dysregulation [19, 22, 86] and an imbalance of the brain and eye pressure [73] are two possible mechanisms which are either directly or indirectly controlled by the brain.

5.2 Blood Flow, Vascular Dysregulation and Stress Hormones

Besides IOP, primary vascular dysregulation is particularly relevant for both, POAG pathogenesis and NTG [87]. The connection between the ocular perfusion pressure and primary vascular dysregulation has been explicated in NTG by Flammer [19, 22].

Both POAG and NTG are caused, or accelerated by, stress hormones in the vascular system such as glucocorticoids, pro-inflammatory cytokines, and endothelin-1. They influence vascular tone, particularly in and round the optic nerve and thereby impair vascular autoregulation. Stress hormones all contribute to endothelial dysfunction (loss of autoregulation) possibly via downregulation of endothelial nitric oxide synthase (eNOS) expression, eNOS inactivation, decreased

nitric oxide (NO) actions, and increased NO degradation, together with vasoconstriction counteracting against NO-induced vasodilatation. NO is a known regulator of ocular blood flow and the reduction of NO metabolites is known to be associated with glaucoma [88]. NO is involved in the control of basal blood flow in the choroid, optic nerve and the retina via the maintenance of the autoregulation of ocular blood flow [89].

5.3 Autonomic Nervous System Imbalance

Stress being one of the main causes of sympathetic nervous system activation is an axiomatic fundamental of medical science. The evolutionary function of stress is to prepare the body and mind for the "fight-and-flight" response. In contrast, parasympathetic influences are predominant during relaxation states. The autonomic nervous system is also a factor keeping the blood flow in synch with metabolic demand of nerve cells. It controls autoregulation of the vasculature which is the intrinsic capacity to maintain constant flow despite changes in perfusion pressure. But if autoregulation fails in the ocular blood vessels, this can have a dramatic impact on ocular blood flow homeostasis thereby aggravating vision impairment. Hence, blood flow regulation may not match the metabolic demands of the retinal nerve cells which then fail to fire action potentials at the needed activity level or at the right point in time. It is to be noted that, similar to blood flow in the retina, blood flow in the brain is also autoregulated.

Na and Riccadonna [42, 43] showed that dysfunction of autonomic control is associated with NTG which they discovered by analyzing heart rate variability; autonomic dysfunction may, in fact, induce chronic ischemia of the optic nerve. The study of Heart Rate Variability (HRV) under conditions of the cold provocation test confirmed the predominance of the sympathetic nervous system activity in NTG.

5.4 Inflammation

Psychological stress is also a major provocative factor in chronic inflammatory conditions which increases TNF-α (an anti-inflammatory myokine) and IL6, a pro-inflammatory cytokine [90]. As an example, elevated levels of IL6 are found in the aqueous humour of glaucoma patients, suggesting their contribution to glaucoma pathogenesis.

TNF-α is a cell signaling protein (cytokine) involved in systemic inflammation. Its levels are elevated in glaucoma patients and major depressive disorders revealing a tri-faceted link between TNF-α, psychological stress, and glaucoma. Levels of pro-inflammatory mediators TNF-α as well as IL6 and IL8 are elevated in glaucoma and downregulated by meditation, which is associated with a normalization of IOP

[59]. For further details about the relationship of psychological stress and the immune system, please refer to Segerstrom and Miller [75].

6 Psychosomatic Aspects in Other Pathologies Related to Vision Loss

The available literature on this topic is summarized in Table 1. Though it is still unclear whether stress alone is sufficient enough to induce visual loss, it is at least a well-recognized key player, when other pathology-relevant contributors are involved, such as arteriosclerosis, inflammation, or, as in the case of FS, an endothelial dysfunction.

6.1 Non-organic Vision Loss

One rather frequent observation is quite revealing: vision loss can happen without any indication of pathological abnormalities as examined with blood tests, electrophysiological evaluation, retina imaging, computed tomography (CT) or magnetic resonance imaging (MRI). These cases are referred to as n*on-organic* or *functional* vision loss [39]. Except for purposeful feigning or exaggeration of symptoms, many of these non-organic visual disorders are called somatoform or conversion disorders [40]. In addition, vision loss has been associated with psychosocial problems. For example, Lim [41] reported that 36% of 140 adults and children with vision impairment reported concomitant psychosocial problems such as psychological trauma in adulthood or problems with their social interactions in childhood.

6.2 Glaucoma

Odberg [91, 92] examined the psychological impact of glaucoma in 589 patients and found that 80% reported negative emotional reactions after knowing that they had glaucoma and one third were afraid of going blind. Higher levels of anxiety [93, 94] and depression [95, 96] have been reported in patients with primary angle closure glaucoma (PACG) than in those with open angle glaucoma (POAG) [97]. Younger age was found to be a risk factor for anxiety, while an older age and increased glaucoma severity were risk factors for depression [98]. Diniz-Fiho [44] reported that faster progression of visual field loss in glaucoma was associated with the occurrence of depressive symptoms.

Table 1 Search results and their analysis of SCI publications related to the topic of stress and vision loss

Ref.	First Author	Year	Study topic				Methods used		Analysis	cause or consequence	Result
			Paper Type	Factor 1 (Vision)	Factor 2 (Psychology)	Sample	Vision	Psychology			
[166]	Zhang	2013	MC	1.VAL 2.VL	Depression	10,480	VF	Depression	SA	0	+
[167]	Burmedi	2003	RM	ALV	1. Emotion 2. Behavior 3. SF 4. Cognitive	267 studies	0	0	MA	0	+
[168]	Brennan	2002	MC	VL	Life stress	195	0	SF	SA	0	0
[169]	Rovner	2002	MC	ARMD	Depression	51	1. VA 2. VF	Depression	SA	0	+
[170]	Wulsin	1991	Ob	DR	Psycho	31	VL	SF	CO	0	+
[171]	Wahl	2006	Exp	ARMD	0	67	0	1. Depression 2. Adaptation	SA	0	0
[172]	Packwood	1999	MC	Amblyopia	Psycho	25	0	Symptom	SA	0	+
[173]	Rees	2010	MC	VA	Depression	143	0	Depression	SA	0	0
[174]	Huurre	1998	MC	VL	1. Depression 2. Distress	54	0	Depression	SA	0	0
[152]	Bittner	2010	Exp	RP	Stress	8	0	0	CO	0	0
[109]	Brennan	2000	RM	Age-related VL	Cognitive	498	VF	1. AVL 2. Depression	MA	0	0
[175]	Yochim	2012	MC	Glaucoma	1. Cognitive 2. Depression 3. Anxiety	41	0	1. Depression 2. Verbal function	SA	0	+

(continued)

Table 1 (continued)

Ref.	First Author	Year	Study topic				Methods used		Analysis	cause or consequence	Result
			Paper Type	Factor 1 (Vision)	Factor 2 (Psychology)	Sample	Vision	Psychology			
[97]	Kong	2015	MC	Glaucoma	1. Anxiety 2. Depression	150	0	1. Anxiety 2. Depression 3. Personality	SA	0	+
[176]	Erb	1999	MC	NTG	Psychology	48	0	1. Personality 2. Depression	SA	0	+
[177]	Zhou	2013	MC	Glaucoma	1. Anxiety 2. Depression	506	1. VA 2. IOP 3. Vf	1. Anxiety 2. Depression	SA	0	+
[178]	Jampel	2007	MC	Glaucoma	Depression	607	VA	Depression	SA	0	+
[179]	Piers	1948	MC	ACAG	Emotion	30	0	0	0	0	+
[180]	Pappa	2006	MC	POAG	Depression	42	0	1. Distress 2. Depression	SA	0	+
[181]	Eramudugolla	2013	MC	ARED	1. Anxiety 2. Depression	662	1. VA 2. Vf	1. Depression 2. Bipolar disorder	SA	0	+
[182]	Wang	2001	Ob	1. VL 2. Cataract	Mortality	3654	0	0	0	0	+
[183]	Scott	2003	RM	NOVL	0	133	0	0	0	0	0
[184]	Hallemani	2012	MC	VL	Stress	80	0	0	SA	0	+
[185]	Lee	2007	RM	Glaucoma	0	151	0	0	0	0	+
[186]	Rivera	2008	RM	POAG	0	0	0	0	0	0	0
[187]	Recupero	2003	MC	POAG	0	62	IOP	0	SA	0	0
[188]	Lee	2004	MC	Myopia	0	636	1. IOP 2. AL	0	0	0	0
[189]	Sauerborn	1992	Exp	Myopia	Stress	38	Vf	HR	SA	0	0

[86]	Flammer	2001	RM	Glaucoma	0	0	0	0	0	0	0
[190]	Grom	1981	MC	Glaucoma	Personality	99	0	Color test	0	0	0
[111]	Pace	2009	RM	0	Meditation	61	0	1. Stress 2. BS	SA	0	+
[191]	Amihai	2015	RM	Autonomic	Meditation	0	0	0	0	0	+
[128]	Rosenkranz	2016	MC	Imflammatory	Meditation	68	0	1. Stress 2. BS	SA	0	+
[192]	Erb	1998	RM	Glaucoma	Psycho	0	0	0	0	0	0
[39]	Shindler	2004	RM	NOVL	0	0	0	0	0	0	0
[193]	Kemeny	2003	RM	0	Stress	0	0	0	0	0	0
[194]	Kloet	1992	RM	0	Stress	0	0	0	0	0	0
[195]	Ritvanen	2006	MC	Autonomic	Stress	28	0	Pain	SA	0	0
[196]	Gherezghiher	1990	Exp	IOP	0	Cat	IOP	0	0	0	0
[197]	Emmerich	2010	RM	OAG	Psycho	0	0	0	0	0	0
[198]	Warrian	2009	MC	Glaucoma	Personality	189	VF	1. Personality 2. Depression	SA	0	0
[40]	Bruce	2010	RM	NOVL	0	0	0	0	0	0	0
[199]	Beatty	1999	RM	NOVL	0	0	0	0	0	0	0
[200]	Werring	2004	Exp	NOVL	FMRI	0	0	0	0	0	0
[201]	Burggraaff	2012	Exp	VL	0	122	0	1. Quality of life 2. AVL 3. Depression	SA	0	0
[202]	Kasten	1998	Exp	VL	0	38	HRP	0	SA	0	+
[53]	Schinazi	2007	RM	VL	Psycho	0	0	0	0	0	0
[43]	Na	2010	Exp	NTG	Autonomic	107	0	BP, ECG, HR	SA	0	+
[42]	Riccadonna	2003	Exp	NTG	Autonomic	47	0	BP, HR	SA	0	+
[110]	Tang	2015	RM	0	Meditation	0	0	0	0	0	0

(continued)

Table 1 (continued)

Ref.	First Author	Year	Study topic				Methods used		Analysis	cause or consequence	Result
			Paper Type	Factor 1 (Vision)	Factor 2 (Psychology)	Sample	Vision	Psychology			
[136]	Wu	2008	Exp	0	Meditation	20	0	HR, RR	SA	0	+
[137]	Grossman	2004	RM	0	Mindfulness	0	0	0	MA	0	+
[203]	Galvin	2006	Exp	0	Relaxation	15	0	1. Cognitive	SA	0	+
								2. Depression			
								3. Anxiety			
[204]	Vøllestad	2011	Exp	0	1. Anxiety	76	0	1. Anxiety	SA	0	+
					2. Depression			2. Depression			
					3. Mindfulness			3. Mindfulness			
[205]	Chrousos	2009	RM	0	Stress	0	0	0	0	0	0
[206]	Matousek	2010	RM	Cortisol	Stress	0	0	0	0	0	0
[52]	Mabuchi	2005	MC	POAG	Personality	419	0	Personality	SA	0	0
[207]	Sehgal	2011	RM	0	Yoga	0	0	0	0	0	0
[112]	Taneja	2014	RM	0	Yoga	0	0	0	0	0	+
[208]	Haymes	1996	MC	RP	Psycho	18	1. VA	1. Personality	SA	0	0
							2. Vf	2. Behavior			
[209]	McEwen	1999	RM	HP	Stress	0	0	0	0	0	0
[210]	Gupta	2012	MC	Glaucoma	Life quality	178	0	Life quality	SA	0	0
[50]	Çakmak	2015	MC	Glaucoma	Personality	234	0	TCI	SA	0	+
[4]	Bali	2011	Exp	Glaucoma	Depression	312	0	Depression	SA	0	+
[211]	Denollet	2005	MC	0	Personality	3813	0	Personality	SA	0	0
[115]	Flaten	2006	Exp	Pain	1. Stress	84	0	1.BS	SA	0	0
					2. Emotion			2.Stress			
								3.Pain			
[49]	Freeman	2016	MC	POAG	Cognitive	180	0	Cognitive	SA	0	0

[122]	Jin	2014	Exp	Arcuate nucleus	0	54	IOP	0	SA	0	0
[123]	Sudsuang	1991	Exp	0	Meditation	82	0	BS, BP, PR	SA	0	+
[87]	Toda	2011	RM	0	Stress	0	0	0	0	0	0
[212]	Weitzman	1975	RM	Glaucoma	0	11	IOP	BS	SA	0	0
[213]	Dampney	2015	RM	0	Stress	0	0	0	0	0	0
[214]	Nordmann	2003	MC	1. POAG 2. OHT	Life quality	13,352	VF	Life quality	SA	0	+
[215]	Keyworth	2014	Exp	1. DM 2. CHD	Meditation	40	0	1. Worry 2. Chronic thought suppression	SA	0	+
[216]	Manchanda	2014	RM	CVD	Meditation	0	0	0	0	0	+
[132]	Newberg	2010	Exp	Memory	Meditation	14	0	0	SA	0	+
[217]	Hayman	2007	MC	VAI	Depression	391	1. VF 2. VA	1. Depression 2. Anxiety 3. SF	SA	Both	+
[8]	Nyman	2012	RM	VL	Emotion	0	0	0	0	Both	+
[218]	Méndez-Ulrich	2017	RM	Glaucoma	Psycho	66 studies	0	0	0	Both	+
[219]	Niklewski	1982	RM	VF	Psycho	0	0	Personality	0	Both	+
[57]	Tolman	2005	MC	ARMD	Depression	144	AVL	1. Cognitive 2. Depression	SA	Cause	+
[220]	Grant	2011	Exp	ARMD	Depression	18	1. VA 2. AVL	Depression	SA	Cause	+
[221]	Barris	1992	Exp	NOVL	0	79	1. VF 2. VA	0	CO	Cause	+
[46]	Hahm	2008	MC	RP	Depression	144	VF	Depression	SA	Cause	+

(continued)

Table 1 (continued)

Ref.	First Author	Year	Study topic				Methods used		Analysis	cause or consequence	Result
			Paper Type	Factor 1 (Vision)	Factor 2 (Psychology)	Sample	Vision	Psychology			
[103]	Bittner	2011	MC	RP	Psycho	27	1. VF	1. Depression	SA	Cause	+
							2. VA	2. Affect			
							3. CS				
[51]	Bubella	2014	MC	OAG	Personality	50	Staging	1. Anxiety	SA	Cause	+
								2. Personality			
[222]	Khan	2006	SC	NOVL	0	1	0	0	CO	Cause	+
[223]	Taich	2004	MC	NOVL	0	71	0	Attention	SA	Cause	+
[224]	Toldo	2010	Ob	NOVL	0	58	1. VA	Psychology	CO	Cause	+
							2. Vf				
							3. CV				
[3]	Shily	1987	RM	ACAG	Stress	0	0	0	0	Cause	+
[225]	Cohen	1972	SC	ACAG	0	1	0	0	0	Cause	+
[226]	Inman	1929	SC	AG	Emotion	1	0	0	0	Cause	+
[227]	Ripley	1950	MC	OAG	Emotion	18	IOP	0	0	Cause	+
[228]	Grignolo	1977	MC	IOP	Stress	0	IOP	0	0	Cause	+
[229]	Weinstein	1975	MC	Glaucoma	1. Anxiety	0	0	0	0	Cause	+
					2. Stress						
[151]	Kaluza	1996	MC	OAG	Mental stressor	23	IOP	1. Psycho strain	SA	Cause	+
								2. HR			
[150]	Kaluza	1995	Exp	OAG	Relaxation	23	IOP	0	SA	Cause	+
[108]	Schultz-Zehden	1977	Ob	Glaucoma	Psycho	52	Vf	0	CO	Cause	+
[230]	Dane	2006	MC	IOP	Fitness	49	IOP	0	SA	Cause	+

[160]	Reinhardt	1996	MC	CVL	SS	343	VF	1. SS 2. AVL	SA	Cause	+
[231]	Moschos	2014	RM	VL	Depression	0	0	0	0	Cause	+
[153]	Ben-Zur	2005	MC	VL	1. SF 2. Personality	90	0	0	SA	Cause	+
[232]	Beining	1951	RM	Glaucoma	Psycho	0	0	0	0	Cause	+
[233]	Berger	1960	RM	Glaucoma	Emotion	0	0	0	0	Cause	+
[234]	Böhringer	1953	RM	POAG	Psychiatry	0	0	0	0	Cause	+
[235]	Flammer	1999	RM	Eye disease	Psycho	0	0	0	0	Cause	+
[236]	Schultz-Zehden	1975	RM	Glaucoma	Psycho	0	0	0	0	Cause	+
[229]	Weinstein	1975	RM	Eye disease	Psycho	0	0	0	0	Cause	+
[228]	Grignolo	1977	MC	IOP	Stress	90	IOP	0	SA	Cause	+
[90]	Iwata	2016	Exp	BS	Stress	Animals	0	0	SA	Cause	+
[237]	Abateneh	2013	MC	VL	Distress	230	0	Distress	SA	Conseq.	+
[238]	Thurston	2010	MC	VL	1. Mood 2. Cognitive 3. SF	18	VF	SF and MH	SA	Conseq.	+
[239]	Stevelink	2016	Ob	VF	Psycho	9	0	1.Depression 2.Anxiety 3.PTSD	CO	Conseq.	+
[99]	Williams	1998	MC	ARMD	Life quality	86	VA	Life quality	SA	Conseq.	+
[106]	Li	2011	MC	DES	1. Anxiety 2. Depression	162	OSDI	1. Anxiety 2. Depression	SA	Conseq.	+
[104]	Angi	1993	Ob	Myopia	1. Personality 2. Stress	57	1. PD 2. VA	1. BS 2. Anxiety 3. Stress	CO	Conseq.	0

(continued)

Table 1 (continued)

Ref.	First Author	Year	Study topic				Methods used		Analysis	cause or consequence	Result
			Paper Type	Factor 1 (Vision)	Factor 2 (Psychology)	Sample	Vision	Psychology			
[7]	De Leo	1999	RM	VL	Suicide	19 cases	0	Mental illness	CO	Conseq.	+
[6]	Kempen	2012	RM	VL	1. Depression	148	0	1. Activity	MA	Conseq.	+
					2. Anxiety			2. Depression			
					3. ADL, SS			3. SS			
[240]	Lim	2007	MC	OAG	Personality	108	0	Personality	SA	Conseq.	+
[157]	Stelmack	2001	RM	VL	Depression	0	0	0	MA	Conseq.	+
[96]	Skalicky	2008	MC	Glaucoma	Depression	165	Vf	Depression	SA	Conseq.	+
[98]	Mabuchi	2012	MC	Glaucoma	1. Anxiety	408	0	1. Anxiety	SA	Conseq.	+
					2. Depression			2. Depression			
[83]	Marc	2013	MC	POAG	Stress	151	1. IOP	Stress	SA	Conseq.	+
							2. Vf				
[241]	Casten	2004	RM	ARMD	Depression	0	0	0	0	Conseq.	+
[242]	Nyman	2010	RM	VL	Psycho	0	0	1. Depression	MA	Conseq.	+
								2. Anxiety			
								3. SS			
[243]	Carrieri	1991	MC	CSG	Mood	45	Vf	1. Depression	SA	Conseq.	+
								2. Anxiety			
[244]	Bambara	2009	MC	VL	Caregiver SP	96	0	1. SP solving	SA	Conseq.	+
								2. Depression			
								3. Satisfaction			
								4. Burden			
[245]	Altangerel	2003	RM	Glaucoma	Psycho	0	0	0	0	Conseq.	+
[246]	Teoli	2016	Exp	VF	Behavior	182	1. VA	1. Cognitive	SA	Conseq.	+
							2. Vf	2. Personality			

[247]	Vu	2005	MC	VL	Life quality	2530	0	Daily function	SA	Conseq.	+
[248]	Keeffe	2005	RM	VL	Psycho	0	0	0	0	Conseq.	+
[154]	Dreer	2005	MC	Low vision	SP	54	VF	1. SF 2. Depression	SA	Conseq.	+
[249]	Teitelman	2005	MC	Low vision	Psycho	15	0	0	SA	Conseq.	+
[250]	Heine	2002	RM	Sensory loss	Psycho	0	0	0	0	Conseq.	+
[251]	Datta	2014	RM	VL	Self concept	46 studies	0	0	0	Conseq.	+
[252]	Seybold	2005	RM	VL	Psycho	0	0	0	0	Conseq.	+
[253]	Scott	1999	MC	Low vision	Life quality	156	VF	Health	SA	Conseq.	+
[254]	Langelaan	2007	MC	VL	Life quality	128	0	Health	SA	Conseq.	+

Abbreviations are as follows: +, $P < 0.05$; 0, $P > 0.05$ or no mention; *ACAG* acute closed-angle glaucoma, *ADL* activities of daily living, *AG* acute glaucoma, *AL* axial length, *ALV* age-related low vision, *ARED* age-related eye diseases, *AVL* adaptation to vision loss, *BP* blood pressure, *BS* body substance, *CHD* coronary heart disease, *CO* clinic observation, *CS* contrast sensitivity, *CSG* chronic simple glaucoma, *CV* color vision, *CVD* cardiovascular disease, *CVL* chronic vision loss, *DES* dry eye syndrome, *DM* diabetes mellitus, *DR* diabetes retinopathy, *Exp* experiment, *HP* hippocampal plasticity, *HR* hart rate, *IOP* intraocular pressure, *MA* meta analysis, *MC* multiple case analysis, *MH* mental health, *NOVL* non-organic vision loss, *NTG* normal-tension glaucoma, *NV* normal vision, *OAG* open-angle glaucoma, *Ob* observation, *OHT* ocular hypertension, *OSDI* ocular surface disease index, *POAG* primary open-angle glaucoma, *RM* review or meta-analysis, *RP* retinitis pigmentosa, *RR* respiration rate, *SA* statistical analysis, *SC* single case report, *SF* social function, *SP* social problem, *SS* social support, *TCI* Turkish temperament and character inventory, *VA* vision acuity, *VAI* vision acuity impairment, *VF* visual function, *Vf* visual field, *VFI* vision function impairment, *VL* vision loss

6.3 AMD

There is little literature on the psychological impact of AMD. Casten [45] studied 114 elderly AMD patients and found high rates of depression which exacerbates physical disability. Similarly, others [99] tested 86 elderly adults with AMD and found them to suffer significant emotional distress with profoundly reduced QOL and impairments in their daily activities. Psychological control strategies were studied in 90 AMD patients by Wahl et al. [100]. Shortly after the initial diagnosis the patients used compensatory primary control strategies which was related to functional loss in instrumental daily activities. But within 1 year there was an increase in compensatory secondary control strategies which were associated with functional loss in instrumental daily activities. Thus, the strategies of control play a role in coping with anticipated or real functional loss.

6.4 Retinitis Pigmentosa (RP)

Retinitis pigmentosa is a set of hereditary retinal diseases characterized by degeneration of rod and cone photoreceptors [101]. A group of RP patients (n = 970) also showed significant anxiety and intense phobic pathology [102]. Greater visual field (VF) variability was found to be associated with reduced visual fields, less physical activity, or increased negative psychosocial states [103]. Hahm [46] found that patients with depression have worse vision than those without depression.

6.5 Myopia

Myopia, a condition where light focuses in front of rather than on the retina, is mainly caused by anomalies in shape of eyeball and imprecise refraction by the optical system of the eye (cornea, lens). While myopia can be fixed by glasses or contact lenses, myopia is not merely a physical problem. Rather, contrary to generally held belief, it also depends on the psychological state. Until now, it is not clear if stress could have a causal role in myopia. While Angi [104] found that the personality profile and psychophysical stress did not play a role in the pathophysiology of myopia, Avetisov [105] concluded that acute psychogenic stress could lead to myopia. After the 1988 earthquake in Armenia they examined 762 residents who had never complained of their vision before, but 30% developed pseudo-myopia. Pseudo-myopia is caused by a spasm in ciliary muscles, which thickens the lens and shortens the focal length by a shift of the focal point away from the retina rather than towards it. In fact, pseudo-myopia is thought to be caused (at least in part) by an imbalanced autonomic nervous system function, here: parasympathetic activation [55].

It is conceivable that vision acuity loss is affected by mental stress (and/or fatigue) because stress might lead to tension of the tissues and muscles around the eyes, changing the shape of the eye ball. Or vision acuity could be modulated by problems with eye muscle tone, eye movements (microsaccades), vascular changes in the eye or brain, or by brain mechanisms of visual signal resolution.

6.6 Other Ocular Diseases

There are reports of other eye conditions with psychosomatic involvement as well. This includes dry eye syndrome (DES) which is caused, among other reasons, by low tear production. Psychological stress is well known to result in a sympathetic predominance of the ANS which reduces the activity of bodily glands, such as saliva and tear production. When Li et al. [106] compared 89 DES patients with 73 control subjects, DES patients scored high on anxiety and depression on the Zung Self Rating Anxiety Scales (SAS) and Zung Self Rating Depression Scales (SDS) which correlated significantly with the DES scores of the Ocular Surface Disease Index (OSDI).

Scrutiny, analysis and interpretation of all the available evidence of associations between psychosomatic indicators and vision loss is beyond the scope of this paper. Table 1 however, lists the available references. Many papers are silent with regard to the issue of whether stress is cause or consequence; to this effect, those that are explicit about it, half argue in favour of stress as a *consequence* of vision loss and the other half as a *cause*.

7 Psychological Treatments to Reduce Stress in Vision Loss

Considering the discussion above relaxation, psychotherapy, or other stress reduction programs should be helpful in reducing the impact of low vision. There are several such reports in the literature. For example, relaxation and visual imagery techniques can reduce IOP [107], psychotherapy can be beneficial for glaucoma patients during surgical or drug therapy [108], and meditation, yoga, breathing exercises and coping strategies can help people reduce stress [109–112].

In fact, relaxation techniques and psychotherapy are the most promising methodologies with a potential to reduce the progression of vision loss or even improve vision recovery. Relaxation to counteract stress has always been part of human societies, ranging from hallucinogenic drugs (such as legal use of marijuana) to music and sports, and it is practiced in different schools of thought, religions, wellness programs and psychology institutions. Furthermore, relaxation is part of traditional (alternative) medicine and healing traditions and has recently become the focus of modern evidence-based medicine.

There are many every-day activities that can help people to relax and enhance their well-being such as sports, reading, sleeping, mind-wandering, prayer, or listening to music. But if the level of stress and tension is too high or consistently persistent for long periods, these everyday methods may be insufficient and more systematic and powerful relaxation techniques are needed to calm down the body and mind. Such techniques include meditation (transcendental and mindfulness meditation), yoga, autogenic training, progressive muscle relaxation, fantasy journeys or slow/deep breathing exercises ("pranayama"). What they all have in common is that they counteract stress and tension by rebalancing the autonomic system by reducing sympathetic and activating parasympathetic nervous system activity. Such relaxation techniques have a positive impact on all levels of the psycho-neuro-endocrine axis.

For example, meditation counteracts symptoms of the stress response by slowing the breathing rate, relaxing muscles, and normalizing blood pressure [113, 114]. On the biochemical level of analysis, relaxation increases levels of plasma endorphins, endogenous opioid neuropeptides which, in turn, inhibits pain signaling and triggers the feeling of euphoria [115]. Meditation also influence a plethora of molecular processes including oxidative metabolism, epigenetics, gene repair, aging, blood pressure, organ system maintenance, and neuroendocrine health [59, 116] and it can improve cardiovascular functions [117] and counteract brain aging associated changes [118].

Despite this long tradition, relaxation techniques are somehow novel for the treatment of visual disorders. In fact, even a single session of relaxation can acutely reduce IOP [119].

Several biological mechanisms are influenced by relaxation exercises, which ameliorate POAG. Endorphins, by way of modulation of the brain's arcuate nucleus [120] can be beneficial through its ability to reduce IOP in rabbits [121, 122], appease depression symptoms and cortisol levels [123] with concomitant decrease in blood pressure [124]. Relaxation techniques were shown to be able to reduce IOP [125], improve neuroendocrine regulation [111] of ciliary body production of aqueous humor and normalize IOP [126]. Furthermore, relaxation brings down inflammation and decreases glial activation [127, 128]. It also elevates brain and aqueous nitric oxide [129], improves outflow pathways and normalizes IOP [130]. Other observations related to relaxation are improved glutamate metabolism and decreased glutamate mediated toxicity [131], modulation of extracellular matrix and the integrity of the trabecular meshwork to maintain aqueous outflow, improved perfusion of cerebral tissue [132], and parallel gene expression changes through epigenetic modulation [133].

Though relaxation techniques may be viewed with some scepticism because of their traditional use in esoteric or religious contexts, different relaxation techniques are, nevertheless, systematic and powerful modulators of nervous system function with a widespread impact on both mental and bodily health. Moreover, in modern medicine, everything is subject to validation. Relaxation based techniques and their efficacy can be –and have been – validated through well designed clinical trials with methodological rigor and empirical reasoning.

7.1 Meditation

Meditation encompasses a family of complex practices that include mindfulness meditation, mantra meditation, yoga, tai chi, and chi gong [134, 135]. Meditation was shown to increase parasympathetic activity to reinstate sympathovagal balance [136] and help patients to cope with their clinical and non-clinical problems [137]. In a classical study of short-term yoga based meditation, Netam et al. [138] found reduced IL6 levels in patients with chronic inflammatory conditions, and mind-body therapies reduced inflammation markers [139]. In a recent randomized trial [59], a 3-week meditation based stress reduction program significantly normalized IOP, and reduced stress biomarkers and changed gene expression in such a way so as to help neuronal restoration.

7.2 Music Therapy

Music has been used since ancient times to enhance wellbeing and reduce pain and suffering [140]. Steady rhythms entrain regular respiratory patterns, and listening to classical music increases heart rate variability (a measure of cardiac autonomic balance), whereas listening to noise or rock music decreases heart rate variability [141, 142]. A meta-analysis [143] indicates that music alone and music assisted relaxation techniques significantly decreases arousal due to stress. In the Knight study [144], 89 undergraduate students were exposed to a cognitive stressor task. This significantly increased their anxiety, heart rate and systolic blood pressure, but when they were exposed to music therapy, there was a significant reduction of anxiety by 28%, in systolic blood pressure by 26% and in heart rate by 36%.

7.3 Biofeedback

Biofeedback is a method of gaining greater awareness of the body's physiological state using instruments that provide information on the activity of different bodily parameters such as brain wave activity, muscle tone, heart rate, or skin temperature. The goal is to learn to manipulate these functions at will to achieve a state of relaxation [145]. Though biofeedback has been used to improve visual fields in patients [146], it has so far only been used as a means to induce relaxation in normally seeing subjects. Amore et al. [146] reported that biofeedback-relaxation can increase finger temperature and cardiac output, decrease systemic vascular resistance and respiratory rate. Likewise, Moser et al. [147] employed biofeedback-assisted relaxation which increased fingertip temperatures. Also, Bernat and coworkers [148] and Del Pozo et al. [149] used it to increase heart rate variability in patients with

coronary artery disease. Besides des Amore study, the application of biofeedback to improve the condition of low vision patients (here: AMD) has not been studied at all.

7.4 Autogenic Training

Autogenic training is a relaxation technique introduced by the German psychologist Schultz early last century (1932). It was used for the treatment of ophthalmological diseases by Strempel and her colleagues who reported it to be beneficial for IOP normalization in open-angle glaucoma patients. Each patient's IOP could be reduced by an average of 3 mmHg, and it benefited their psychological state. At the end of the experiment 43% of her patients reduced or even stopped taking eye drops. The other 57% of the patients continue to take their medicine or changed their medicine with associated IOP reduction to levels well below their lowest values before [107, 150, 151].

7.5 Coping Strategies

There are different strategies for better coping with medical problems. They include cognitive restructuring such as optimism (looking not only at the rear mirror but looking forward), looking at the situation in relative terms such as "there are so many worse things" to keep vision loss in perspective [152]. Other methods are focusing on what one can still do and not dwelling in the past, positive social comparisons [153], and a positive prognosis that there are different means to improve vision or ways to compensate for the loss. There are also more general methods to help with emotional anger including psychotherapy or even simply "kicking and screaming" [152]. Considering that a negative problem orientation significantly predicted depression and emotional distress, while rational problem-solving skills predicted life satisfaction [154], Garnefski concluded that both cognitive and goal-related coping could be an important intervention for patients with vision loss [155].

Another interesting intervention to improve coping in patients with vision loss was described by Bryan and Lu [156]. They studied patients with Stargardt's disease, a rare condition of macular degeneration who received an expressive writing intervention for 3–6 weeks. This had a positive impact on their psychological health outcomes at 3-week follow-up and self-reported physical health at 6-week follow-up. The authors suggest that expressive writing is an effective, practical, and low-cost psychological intervention to improve QOL.

7.6 Social Support

Decreased visual acuity, visual field loss, or blurred ("foggy") vision are also associated with decreased QOL [157]. Family members can play an important role in the adaptation of patients, providing encouragement for the initiation and completion of rehabilitative services [158, 159]. In Reinhardt's [160] study, scores for support by family members were higher than those for friend. As compared to friends, family members are relied upon more often for both instrumental (practical) and emotional support [161].

8 Worldwide Research Activities on Stress Related to Ophthalmology

The above discussion demonstrates that stress can lead to a dramatic, psychosomatic reaction in the visual system while reduction in stress and enhanced blood flow can notably improve the condition. There are, however, many similar stories of vision recovery and most clinicians are aware of visual field fluctuations. Rozanski et al. [162] proposed that VF performance is not only a function of the actual vision loss itself but is highly variable due to anxiety and functional losses of vision. They presented a conceptual framework for the development of coping strategies and mindfulness-based interventions to reduce stress associated with negative thoughts and worries [162]. Though there are unexplained cases of vision loss and cases of unexpected recovery [163] yet the literature is surprisingly silent as to how the mosaic of stress, vision loss, vision recovery, and restoration are connected. It should not escape our notice that the term "unexplained" could have two meanings: no pathology found or pathological changes existed, but they could not explain the visual field.

Unfortunately, our scientific understanding is disconcertingly poor when it comes to the role of stress and the brain in ophthalmological diseases. The question nevertheless arises as to how much science exists about the role of stress in vision loss. We therefore counted on PubMed the number of scientific reports in the field of psychology/ psychosomatics of vision loss (www.pubmed.org; Oct 2017). We reasoned this might reveal some clues of how comprehensively this field is being studied worldwide (Table 2).

We first searched for general terms in the fields of *Vision* and *Psychology* and recorded the total number of hits separately for "eye" (565.167), "vision loss"(58.052) and low vision" (16.338) as well as "stress" (756.926), "psychosomatic" (19.145) or "psychological stress" (137.084). But when combining the two fields, much fewer hits were recorded: "psychology vision loss" (4.020), "stress low vision" (228), "mental stress vision loss" (146), "psychosomatic eye" (154), "psychosomatic ophthalmology" (95) or "mental stress low vision" (52); this means

that of all studies of eye/vision loss (640.000), only 4.700 (=0.7%) addressed the topic of mental stress. Such a low value of <1% was a surprise vis-à-vis the impact vision loss has on psychological well-being.

One might argue sensory functions are purely "physiological", i.e. not influenced by the patients' state of mind. To check if this "somato-centric" interpretation of vision is unique to ophthalmology, we carried out the same analysis for the sense of hearing for "ear" (172.353) or "hearing loss" (78.780). While the scientific output was only about one third of that related to "eye" and "vision", the number of publications of the combined term "mental stress hearing loss", was 1.2% (306), i.e. almost double that of vision. In other words, somato-centric thinking not only dominates vision research, but it creates also a negative bias against a role of mental-stress in vision loss.

This low number of scientific records addressing the interface of stress and vision loss dovetails what patients are also complaining about: that there is minimal interest (if any), or even a negative bias against, psychological concerns in the ophthalmology clinical and research community. Yet, there is a rich repertoire of literature on psychological treatments such as stress reduction, relaxation techniques such as yoga and meditation, cognitive therapies, psychotherapy. They might be valuable adjuvant methods for a more holistic approach in ophthalmology for treating the "person behind the eye".

One could argue that ophthalmology shows less interest in psychobiological mechanisms of visual diseases because the patients and the public at large find psychological issue is to be irrelevant for the understanding (or treatment) of vision loss. Because our clinical experience suggests otherwise, we next estimated general public interest in these topics by conducting a Google search. Table 2 shows the number of hits in *Google* as a metric of public interest and in *Google-scholar* as a metric of academic interest. This could teach us how well (concordance vs. discordance) scientific activity (PubMed hits) and public interest (google hits) match. The results are astonishing: for every scientific publication identified by the two PubMed search terms "eye/vision" and "psychosomatics" separately, there are 4.000/1.200 google items, respectively. That means the ratio of scientific activity and general public interest is in the order 1:1.000–4.000. However, when combining vision and psychological terms, this number is 1:100.000. In other words, for every science publication there are 100.000 google hits; a tremendous mismatch between general public interest and scientific activity! This confirms that many people are actively searching information about the role of mental stress in low vision. If one would ask how much scientific activity would have to increase to match public interest, the answer would be: by a factor of 25!

The rather disappointing conclusion of our google analysis is as follows: though mental stress is of major subjective concern for low vision patients and the public at large, the topic is essentially ignored by the scientific community. This is surprising if one considers that stress is a well-known factor which is known to influence mental and bodily health; it is widely recognized particularly in psychosomatic medicine. Yet, there is a rather small body of evidence for the role of stress in vision loss which will now be reviewed.

8.1 The Science-Public Disconnection

Our search revealed 139 papers, some published before the 1960s, but the majority after the year 2000 (n = 97) (Table 2). The publications discuss different eye diseases and different psychosomatic conditions. The most frequently studied disease is glaucoma (open angle or angle closure) (n = 46), followed by age-related low vision such as macular degeneration or cataract (n = 10), non-organic vision loss or functional vision loss (NOVL) (n = 9), retinitis pigmentosa (RP, n = 4), myopia (n = 3) and one paper each for dry eye syndrome (DES), diabetic retinopathy and amblyopia. Methodologies used in such studies included measurement of visual fields (VF), visual acuity (VA), contrast sensitivity (CS) the Adaptation to Age-Related Vision Loss Scale (AVL), and intraocular pressure (IOP). The study of psychosomatic consequences (or causes) varied as well, ranging from depression, anxiety, life stress, coping strategies, personality, self-concepts and the study of the effects of various relaxing methods. The psycho-diagnostic tools to assess the mental state included the following: the NEI-VFQ-25 (National Eye Institute 25-Point Visual Functioning Questionnaire) and other tests such as the Patient Health Questionnaire -9 (PHQ-9), 36-Item Short Form Survey (SF-36), Generalized

Table 2 Scientific and public interest in vision and stress research

Search term	Medline (M)	Google (G)	ratio G:M	Googlescholar (Gs)	ratio Gs:M
General vision					
Eye	565.167	2.080.000.000	3.680	4.340.000	7,68
Vision loss	58.052	3.110.000	53	147.000	2,53
Low vision	16.338	4.400.000	269	66.100	4,05
Sum	**639.557**	**2.087.510.000**	**4.002**	**4.553.100**	**14,26**
General stress					
Stress	756.926	719.000.000	950	6.050.000	7,99
Psychosomatic	19.145	4.580.000	239	591.000	30,87
Psychological stress	137.084	1.550.000	11	673.000	4,91
Sum	**913.155**	**725.130.000**	**1.200**	**7.314.000**	**43,77**
Combined vision/stress					
psychology vision loss	4.020	908	0,2	2	<0,01
Stress low vision	228	2.780	12	1	<0,01
Mental stress vision loss	146	7.160.000	49.041	1	0,01
Psychosomatic eye	154	542	3,5	37	0,24
Psychosomatic ophthalmology	95	256	2,7	4	0,04
Mental stress low vision	52	2.620.000	50.384	0	<0,01
Sum	**4.695**	**9.784.486**	**99.444**	**45**	**0,32**

This table shows the number of hits when searching medline, google, and google scholar with the respective search terms. It shows the disconnection between public interest (google hits) and scientific activity (number of medline-listed publications) in the field of stress and low vision

Anxiety Disorder 7-item (GAD-7), the Symptom Checklist-90-Revised (SCL-90), Beck-Depressions-Inventory (BDI), the Zung Self Rating Anxiety (SAS) and Depression Scales (SDS), to name but a few.

Whereas 32 papers indicate that psychosomatic factors are the *consequence* of eye diseases, another 32 seem to favor the opinion that psychosomatic influences are the *cause* of eye diseases. Yet others are ambiguous about it. Although the currently available literature is evenly divided on this, the cause-effect relationship may not be an "either/or" issue: as we demonstrated above, stress is rather both, the cause *and* result of the vision loss.

9 Conclusions and Expert Recommendations

On one hand, vision loss reduces subjective QOL, due to anxiety, fear and depression, i.e. stress being the consequence of vision impairment. On the other hand, as argued above mental stress is also a *cause* of different visual diseases, perhaps even the main cause of some of them. Both – the cause and consequence result in a vicious circle: stress leads to vision loss which causes stress, that in turn worsens the vision loss and increases stress (Fig. 2). It is important for doctors, researchers, caregivers, and patients to know about this downward spiral and to look for inhibiting the reaction chain. Due to extensive interactions between the eye, brain and vascular system, ophthalmologic diseases are not only a matter of physics and biology, but also an issue for psychology [164]. Better understanding of that would allow for advanced knowledge towards precise biological mechanisms and more effective intervention strategies directly targeting these mechanisms.

This new psychosomatic perspective has several implications for clinical practice. (i) Stress reduction and relaxation techniques should be recommended not only as complementary to traditional treatments of vision loss but possibly as preventive measures, to reduce progression of vision loss. (ii) Doctors should try their best to inculcate positivity and optimism providing information the patients are entitled to, especially regarding the relevance of stress reduction and relaxation. Statements of a grim future such as "you will go blind" should be avoided as counterproductive ones. This induces unnecessary anxiety and fear, possibly accelerating vision loss progression (Fig. 3). (iii) Medical treatments might aim at reducing the biochemical effects of stress hormones on the blood vasculature, and (iv) various psychological interventions, well established in clinical psychology, such as coping strategies, relaxation techniques and psychotherapy, should become adjuvant methods of the standard ophthalmologic care. In this spirit, the overall management of the interplay between stress and vision loss should follow the concepts of predictive, preventive, and personalised medicine outlined by Golubnitschaja et al. [165]. To this end, the element of individualised prediction plays a crucial role, because the level of mental stress could help predicting vision loss progression on the one hand, and creating therapy algorithms tailored to the person and prognosing the outcomes on the other hand. Targeted measures preventing stress could reduce the progression of

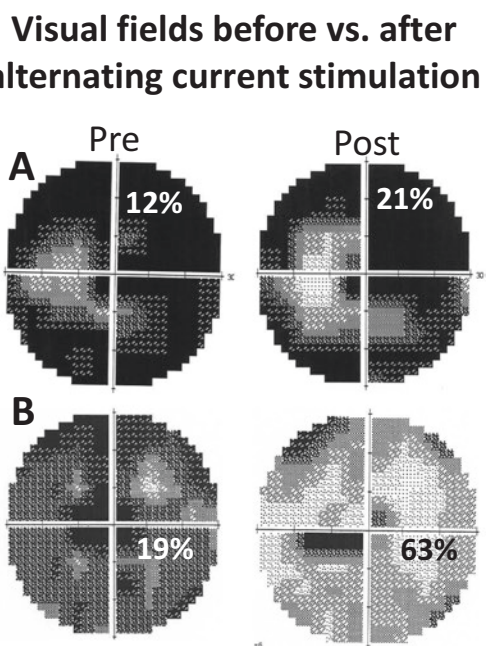

Fig. 3 Humphrey visual fields of a 78 years old woman (upper panel) with stress-induced vision loss OD before vs. after a 10-day treatment. Treatment included alternating current stimulation plus relaxation exercises and psychological consulting. In both tests the patient had neither any fixation loss nor any false positive responses. Visual field improved from 12 to 21% (pre/post mean deviation: −25.97/−22.44 dB). Subjectively, the patient reported improvement from "grey" to "white" vision with noticeably better acuity. The patient did not notice any changes in the central visual field but could better recognize faces and street signs, and was able again to see her hair in the mirror with her upper visual field. The second case is a woman who was successfully treated, due to glaucoma, with current stimulation and various anti-stress methods such as psychological consulting and relaxation

impairment and prevent the development of vision loss. All the measures should be adapted to the personal needs making the treatments truly personalised.

In conclusion, the FS provides good arguments for the acknowledgement that psychosocial factors play a crucial role in ophthalmological diseases. By linking the concept of biological stress, vascular dysregulation, and vision loss, Josef Flammer has provided new insight into the tight interplay between biological and psychological factors in glaucoma pathology. In that sense, the discovery of the Flammer Syndrome offers ophthalmology a holistic approach to consider vision loss as a multi-factorial disease including human mind as an essential component. This will help also to follow the need of many patients to be heard by treating doctors in terms of their subjective experiences and feelings regarding vision problems that should not be ignored. Considering the role of psychosomatic risk factors in development and progression of eye pathologies, further offers new leads for interventions to enrich existing concepts of treating vision loss by means that go beyond currently

used eye drops and surgery. In that sense, the Flammer Syndrome is a starting point for the dawn of psychosomatic ophthalmology. Such a new path will help addressing the central issue, namely the complex person behind the eye.

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Multiomic Signature of Glaucoma Predisposition in Flammer Syndrome Affected Individuals – Innovative Predictive, Preventive and Personalised Strategies in Disease Management

Olga Golubnitschaja, Kristina Yeghiazaryan, and Josef Flammer

Abstract The second leading cause of blindness in humans – glaucoma is a multifactorial disease; risk factors known are highly complex. A genetic component plays a role in the glaucoma pathology as well as internal and external stress factors suggesting epi/genetic patho mechanisms of the disease. Liquid biopsy analyses have been demonstrated as relevant for detecting a specific glaucoma signature in Flammer Syndrome phenotype. Multiomic approach has been proven as being of great utility for predictive diagnosis of glaucoma and patient stratification, further, providing information for potential multi-target treatments tailored to the person. The chapter highlights the omic-technologies and comprehensive molecular biological output for innovative PPPM strategies in glaucoma research with a potential to improve medical services in the area.

Keywords Flammer syndrome · Glaucoma · Primary vascular dysregulation · Patient stratification · Omics · Liquid biopsy · Biomarker panel · Molecular signature · Predictive diagnostics · Targeted prevention · Personalised medicine · Innovative strategy

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1 Primary Vascular Dysregulation (PVD) as the Basic Characteristic of the Flammer Syndrome

PVD is defined as an inappropriate vasoconstriction or insufficient dilatation in the microcirculation (see Fig. 1). PVD is the basic symptom of the Flammer Syndrome (FS) [1]. PVD is prevalent particularly in younger subpopulations which may be generally healthy but, due to vascular dysregulation, predisposed to several disorders representing, therefore, the group at risk in suboptimal health condition. Due to strong socio-economic impacts expected, PVD is a highly attractive target for innovative medical services by predictive diagnostics and primary preventive measures to protect affected individuals against "downstream" related pathologies, if tailored to the person [2–5].

Besides specialised FS-questionnaires, a valuable diagnostic tool for ascertaining vasospastic diathesis is the nail-fold capillary microscopy (see Fig. 1). The best acknowledged risk factor is an increased plasma level of endothelin-1 [6].

2 PVD Impacts on Ocular Ischemia: Glaucoma as One of the "Down-Stream" Pathologies – Precise Patient Stratification Is Needed

A wealth of literature emphasises the role of haemodynamic component in glaucoma pathology with particular impacts by PVD [1, 6, 7]. Ocular ischemia resulting from blood-flow deficits may play a major role in the initiation of glaucoma: hypoxia, followed by high secretion of excitatory amino acids and elevated levels of intracellular calcium results in the process of retinal ganglion cell death [8–10]. In our previous studies, we have demonstrated stable alterations in gene expression of circulating leucocytes isolated from glaucoma patients compared to healthy controls [11–14]. Further, similar expression profiles of circulating leucocytes between vasospastic individuals (PVD) and glaucoma patients have been published [15].

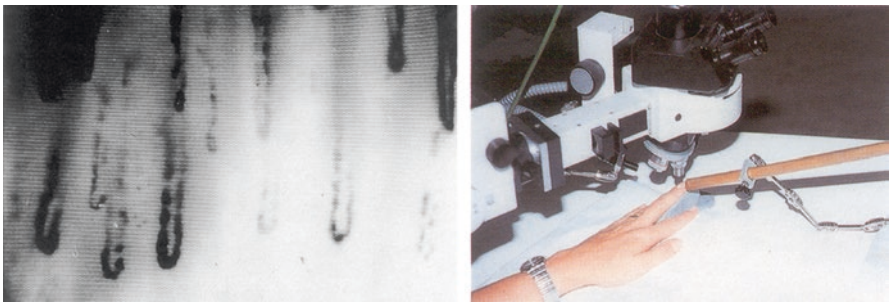

Fig. 1 Nail-fold capillary microscopy (right) enables the monitoring of microcirculation and of cold provocation of vasospasm in fingers (left) [6]

However, also significant dissimilarities of molecular patterns as compared to both glaucoma patients and healthy controls have been reported [16]. Consequently, a development of other pathologies different from glaucomatous optic nerve degeneration but related to PVD should obligatory be taken into consideration for vasospastic individuals [17, 5, 18–21] that requests precise patient stratification and specific biomarker panels to identify individual predispositions.

3 Heterogeneity of Glaucoma Patient Cohort

Intraocular pressure (IOP) is considered the most important and only modifiable risk factor in glaucoma. Although elevated IOP has been shown to be the major risk factor, there is a cohort of patients even at younger ages with normal IOP developing normal-tension glaucoma (NTG) (Fig. 2).

The frequency and incidence of different glaucoma forms vary from country to country, depending on race, sex and age [22–24].

3.1 Risk Factors of Glaucoma

The aetiology of glaucoma is not completely understood yet. It is a multi-factorial disease and risk factors known are highly complex: increased intra-ocular pressure, race diversity, female gender, genetic predisposition, myopia, corneal thickness, optic disc haemorrhages, and haemodynamics, amongst others [25, 26].

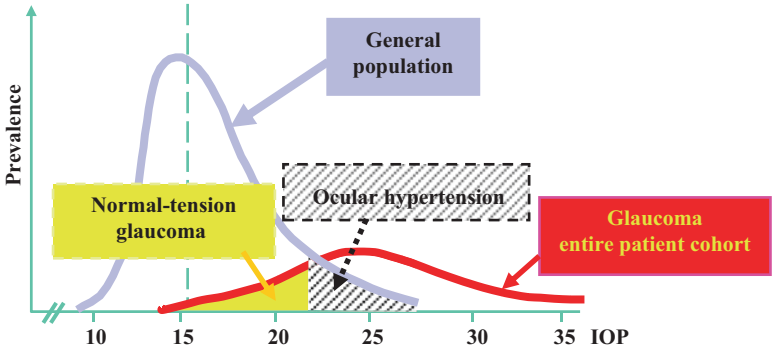

Fig. 2 Although an increased intra-ocular pressure (IOP) is a well-known risk factor, the IOP values of normal-tension glaucoma patients are within the statistical normality

4 A Genetic Component in the Glaucoma Pathology

A family history of the disease is common among glaucoma patients, suggesting impacts of a genetic element for this disorder. The existence of a genetic linkage associated with particular forms of glaucoma is well documented in the literature [24, 27–33]. The growing body of evidence suggests the idea that genetic-based approaches in early diagnosis of glaucoma and targeted treatment might yield better results than medical, surgical and rehabilitation interventions alone [33]. Although mutation research in glaucoma detected some attractive potential targets, the mutated genes found – like *TIGR* – play a limited role in the pathogenesis of glaucoma and do not explain the usual clinical picture [23, 34–38]. Therefore, genomic and pharmacogenetic approaches alone may provide only minor success in the prediction of the pathology, its targeted prevention and treatments.

5 How Relevant Is Liquid Biopsy for Glaucoma Diagnostics?

Since blood samples are relatively easily accessible, molecular blood analysis is of great clinical utility for individualised patient profiling and population screening to identify persons at risk. However, may gene expression profiles in blood be relevant for detecting eye pathology/predisposition? The answer is certainly yes – here we provide the strong argumentation supporting the approach:

1. Glaucoma patients frequently exhibit abnormal T-cell subsets and increased titres of serum antibodies to retina and optic nerve proteins; these alterations in the cellular subset indicate that the immune system plays an important role in the initiation and/or progression of glaucomatous optic neuropathy [39]. Therefore, serum antibodies to retina and optic nerve proteins might be considered as potential indicators for glaucoma pathology [40].
2. It has been demonstrated that gene expression patterns of both trabecular meshwork and Schlemm's canal are similar to those of circulating leucocytes (CL) [41].
3. Blood serum is the biggest reservoir of signalling molecules in human beings: many metabolites are simultaneously secreted from different types of cells in blood that represents a universal way of communication between cells. Although this communication is extremely complex, one of the known natural sensors affected by the tremendous number of metabolites present in blood serum is CL. The spectrum of the molecules affecting expression patterns in CL is very broad; their regulation is extremely complex and not yet completely understood. However, it is known that the resulting regulation of CL is triggered by altered gene expression patterns on the levels of transcription and translation. The resulting shift in gene expression patterns referred to a corresponding physiologic/pathologic condition can be measured at both levels.

4. Since both vascular and immune components play an important role in the pathomechanisms of glaucoma [42], the pathology-specific molecular patterns in blood are highly relevant for early and predictive diagnosis of glaucoma.

6 Innovative Strategies for the Patient Stratification, Early Diagnosis and Prediction of Glaucoma in Healthy Vasospastic Individuals

6.1 Context of Neurodegenerative Pathologies

Worldwide, about 70 million patients are affected by the neurodegenerative eye disease glaucoma. Glaucomatous optic neuropathy (GON) is the second leading cause of permanent vision loss. GON is a chronic degenerative process the onset of which is not possible to monitor by currently existing diagnostic tools. Early treatment has been reported to be highly beneficial for well-timed treatment measures to slow-down the disease progression [43]. As reviewed by the authors, molecular pathomechanisms of glaucoma demonstrate both a considerable overlap and remarkable particularities to some other neurodegenerative disorders such as Alzheimer's and Parkinson's diseases [17]. Indeed, compared to healthy controls, the neuronal thread protein (NTP) demonstrates enhanced expression levels in glaucoma, patients with Down Syndrome, Alzheimer's and some other neurodegenerative diseases indicating the axonal lesions. On the other hand, whereas the accumulation of *TAU*-protein is characteristic for Alzheimer's disease and other *tauopathies*, glaucoma patients do not demonstrate increased *TAU*-protein patterns [43, 44]. Consequently, the differentiation by *TAU*-protein patterns might be the first step in the patient stratification in the context of neurodegenerative pathologies. The follow-up procedure requires innovative predictive diagnostic strategies to cover following aspects:

– identification of possible similarities as well as dissimilarities in molecular pathways between healthy vasospastic individuals and PVD-related pathologies developed later on in life (e.g. neuro-degenerative *versus* oncologic diseases)
– multi-level diagnostics by multiomics is essential to get the most comprehensive picture of the pathology
– validation of predictive biomarker panels specific for glaucoma pathology against positive control groups of patients diseases on other neuro/degenerative pathologies
– creating final biomarker panels the preference is given to the non-invasive diagnostic approaches utilising liquid biopsy (blood, saliva, tear fluid)
– in the most optimal way, the diagnostic approach is based on the multi-target panel, further, utilised for the cost-effective preventive treatments tailored to the PVD-individual stratified as predisposed to a clearly defined pathology such as glaucoma.

6.2 Multiomic Approach

DNA Level: Sub-Cellular Imaging by *Comet Assay* Analysis

Comet Assay (*CA*) is a powerful diagnostic tool used for quantification of DNA damage (e.g. under stress condition such as systemic hypoxia) and DNA fragmentation by apoptosis – both well distinguishable in circulating leucocytes (CL) isolated from blood samples. Comparative *CA* analysis performed using blood samples collected from healthy non-vasospastic, healthy vasospastic individuals and glaucoma patients demonstrated significantly enhanced DNA damage in both – PVD individuals and glaucoma patients compared to healthy non-vasospastic controls [45]. Further, comet patterns were found to be health condition/disease-typical for all groups investigated clearly distinguishing between

– healthy non-vasospastic and healthy vasospastic individuals
– healthy vasospastic individuals and glaucoma
– normal-tension and high-tension glaucoma

as shown in Fig. 3.

Although DNA damage in the vasospastic non-glaucomatous group is not found to be significantly increased *versus* healthy non-vasospastic individuals, DNA of vasospastic individuals showed highly group-specific comet-patterns with the degree of damage intermediate between healthy controls and glaucoma patients. These findings indicate *Comet Assay* profiling of DNA-damage in CL as a powerful tool for non-invasive early and even predictive diagnostics applied to vasospastic individuals to detect individual predisposition to "downstream" pathologies [44]. Furthermore, unrepaired DNA-damage in vasospastic individuals can lead to several pathologies including but not restricted to the glaucomatous optic nerve degeneration. This predisposition should be further stratified with pathology specific biomarker panels distinguishing between several degenerative (e.g. glaucoma *versus* Alzheimer's disease [47] as well as non-degenerative (e.g. oncologic) diseases [48–52]. *Comet Assay* analysis revealed enhanced DNA damage in both high- and normal-tension glaucoma [45]. Whether the level of DNA-damage may correlate

Fig. 3 (continued) distinguishable patterns are represented by classes II and III distinguishable by the ratio R = T/r, where T represents the comet's tail length and r is the radius of the comet's head. The characteristic value of R for class I is 1 and for class IV is infinite, due to the r = 0. Comets with R values ranging between 1 < R > 3 represent class II. Abbreviations: "D" and "r" are the diameter and radius of the comet's "head", respectively; T = tail of the comet. Individual migration patterns are demonstrated in groups corresponding to the images **a**–**d** by the evaluation of comet's classes as described earlier [46]. Figure **e** shows mean values calculated for relative DNA damage in following groups as compared to the control group (100%): PVD – healthy vasospastic individuals (102 ± 7%), NTG – normal-tension glaucoma patients (160 ± 13%), and HTG – high-tension glaucoma patients (128 ± 10%); noteworthy, the highest level of the DNA damage is demonstrated in the NTG group marked in red colour

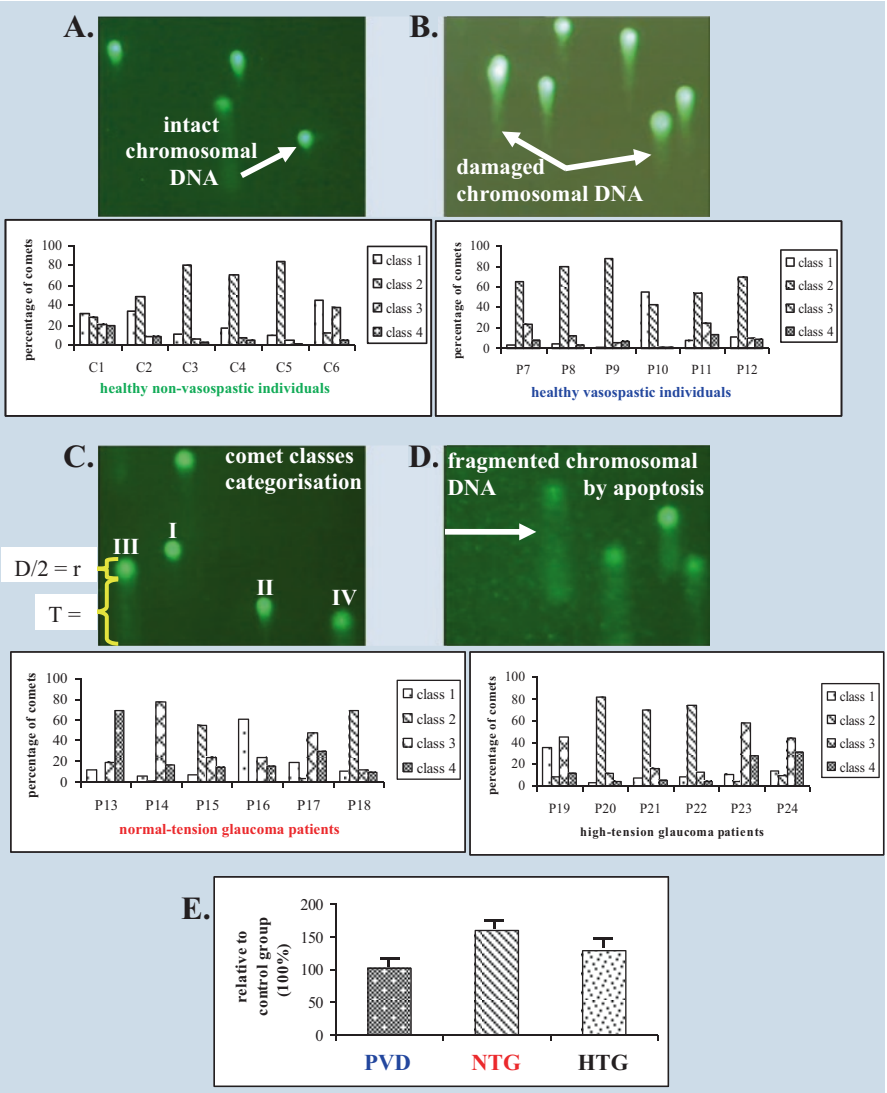

Fig. 3 *Ex vivo Comet Assay* analyses evaluated DNA damage and apoptotic fragmentation in circulating leucocytes isolated from blood of individuals stratified according to the PVD and glaucoma manifestation; data have been adapted from [45]. Figures (**a**–**d**) give examples of images typical for (**a**) healthy non-vasospastic individuals – control group, (**b**) group of healthy vasospastic individuals, (**c**) group of normal-tension glaucoma patients, and (**d**) group of high-tension glaucoma patients. Comet patterns typical for healthy controls (**A**) demonstrate mainly intact DNA. In contrast, images **b**, **c**, and **d** demonstrate partially damaged DNA (visible comet-tails and diffuse comet-heads) as well as apoptotic patterns. Evaluation of the shape of a comet allows for assessment of DNA damage. Categorisation of the comet shape: class I indicates intact DNA with a bright head and no tail, while class IV demonstrates an apoptotic DNA fragmentation characterised by no visible head and a long diffuse tail. Comets with intermediate characteristics but clearly

with a disease severity, remains to be further explored. Finally, whether a significant increase in DNA damage of leucocytes of glaucoma patients is caused by disease-specific stressors (ischemic/reperfusion events) and/or decreased efficacy of the DNA-repair machinery, remains to elucidate. The evidence for both eventualities is discussed below including simultaneous up-regulation of *p53* (stress regulated gene) and down-regulation of *XPGC* (essential member of DNA-repair machinery) demonstrated *ex vivo* in CL of glaucoma patients [53].

"Blind" *Gene hunting* Approach: Comprehensive Search for Expression Differences in Transcriptome

The basic principle of *gene hunting* by the "subtractive hybridisation" technology is schematically presented in Fig. 4. Each mRNA-pool consists of individual gene transcripts undergoing a comparative analysis by hybridisation of identical parts (marked in blue colour) which get removed by complementary hybridisation. The molecular biological "subtraction" results in identifying transcripts marked in red colour differentially expressed in the pools of comparison. The technology enables to perform both – a qualitative (present or absent) and quantitative (amount of copies per unit weight of mRNA in a corresponding pool) analysis of differences between two transcriptomes. Subtracted transcripts underwent their identification by sequencing. Consequent visualisation and quantification of the target transcripts by the "Dot-blot"-analysis (Fig. 4b, the blue marked part) has finalised the entire approach indicating the shifted expression and function of the target transcripts. The interpretation of the results is provided in the red marked column (Fig. 4b) as following: increased stress, apoptosis, protein damage and axonal damage as well as insufficient DNA-repair and altered drug-sensitivity in patients with glaucoma compared to the control group.

Guided Transcriptomics: *Expression array* in Comparative Analysis of Patterns in Stratified Glaucoma Patients, PVD and Healthy Non-vasospastic Individuals

The image of hybridised "AtlasTM Human Cardiovascular Array" discovered both –similarities and diversity in patterns specific for NTG, HTG, and healthy PVD *versus* healthy non-vasospastic individuals as summarised in Table 1.

The achieved results emphasise PVD as an intermediate health condition between healthy non-vasospastic individuals and glaucoma patients: despite significant similarities of the patterns between vasospastic individuals and glaucoma patients, still PVD individuals demonstrate the major overlap (528 gene transcripts) of their patterns and lowest diversity (60 gene transcripts) with healthy controls. This is an evidence-based and very strong argument for considering PVD as a reversible suboptimal health condition and attractive target for population screening, predictive diagnosis for persons at risk followed by cost-effective preventive measures protecting vasospastic individuals against glaucoma and other major

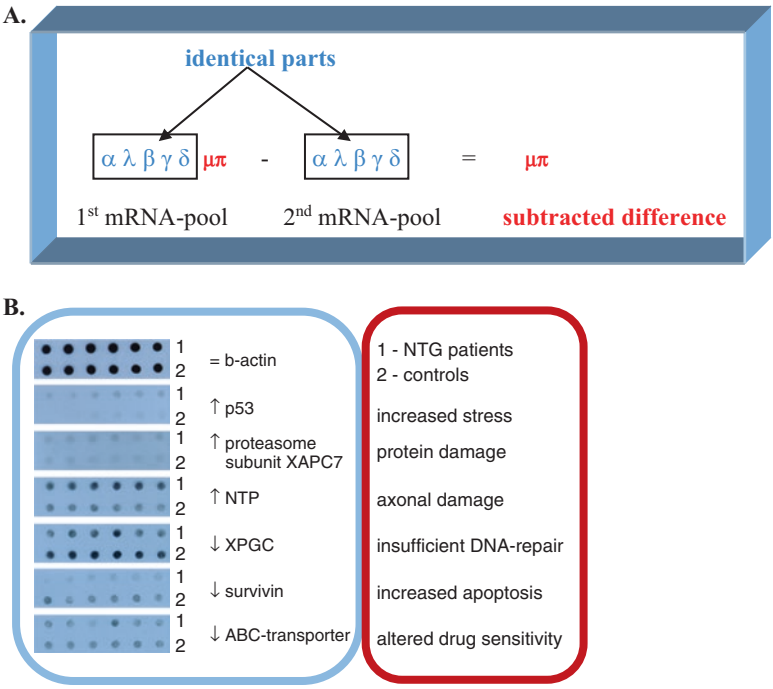

Fig. 4 *Ex vivo* differential transcriptomics utilising liquid biopsy (circulating leucocytes) for comparative analysis of transcripts in blood of NTG patients *versus* healthy controls; "blind" *gene hunting* by the "Subtractive Hybridisation" technology followed by visualisation and quantification via mRNA "Dot-blot"-analysis. (Data adapted from Ref. [54]). (**a)** Principle of *gene hunting* by the "subtractive hybridisation" technology; (**b)** Consequent visualisation and quantification of the target transcripts by "Dot-blot"-analysis (the blue marked part) with the results interpretation (the red marked column)

Table 1 Numbers of genes an expression of which is either differential or equal between the groups tested as shown by the *Expression array* analysis

Differential to controls	PVD equal to	PVD differential to
NTG → 146	Controls → 528	NTG → 109
HTG → 68	NTG → 48	Controls → 60
PVD → 60	HTG → 43	HTG → 43
NTG = HTG → 53	NTG = HTG → 34	NTG = HTG → 21

Thereby, 108 genes were found to be differentially expressed between NTG and HTG groups. 34 genes demonstrated similar alteration for PVD and both glaucoma-patient groups when compared to healthy non-vasospastic individuals (controls) (see these genes listed in Table 2)

pathologies linked to the primary vascular dysregulation (**see dedicated chapters in the book**).

Thirty four genes demonstrated similar expressional alterations in NTG, HTG, and PVD *versus* healthy non-vasospastic individuals (control group) as summarised in Table 2. As the differentially expressed overlap PVD/NTG/HTG was compared with the control group, following most significant differences were detected:

Table 2 *Expression Array* analysis: differentially expressed thirty four genes demonstrate pattern similarity in PVD, NTG and HTG *versus* healthy non-vasospastic individuals (controls); the biomarker panel is proposed for risk assessment in subpopulations of vasospastic individuals for early diagnosis and prevention of glaucoma Ref. [44]

Double-spot position in the *Array* image: expression *vs.* controls	Name of gene as given in "Atlas™ human cardiovascular array"	GenBank accession	SwissProt accession	Gene/Protein classification
Block A				
A7d increased	P2Y purinoceptor 7 (P2Y7); leukotriene B4 receptor; Chemoattractant receptor-like1 (CMKRL1)	U41070	Q15722	Other receptors (by Ligands)
			Q13305	G protein-coupled receptors
			Q92641	
A7e increased	Retinoic acid (vitamin-A1-acid) receptor gamma 1 (RAR-gamma 1; RARG)	M24857	P13631	Transcription activator & repressors
		M38258		Hormone receptors
		M57707		Nuclear receptors
		M32074		
Block B				
B1n increased	Androgen receptor coactivator 70-kDa subunit (ARA70)	L49399	Q13772	Transcription activator & repressors
B4c increased	G protein-activated inward potassium channel 4 (GIRK4); heart K+/ATP channel (KATP1); cardiac inward rectifier (CIR); KIR3.4	U39195	P48544	Voltage-gated ion channels
			Q92807	
B4d increased	Sodium/calcium exchanger 1 precursor; Na+/Ca2 + − exchange protein 1	M91368	P32418	Symporters & antiporters
B4e increased	Multidrug resistance protein 3 (MDR3); P-Glycoprotein 3 (PGY3)	M23234	P21439	Drug-resistance proteins
				Xenobic transporters
				ABC transporters
B5f increased	Endothelial nitric oxide synthase (EC-NOS)	M93718	P29474	Other metabolism enzymes
				Other intracellular transducers, effectors & modulators
B6d increased	Intercellular adhesion molecule 1 precursor (ICAM1); major group rhinovirus receptor; CD54 antigen	J03132	P05362	Matrix adhesion receptors
B7g increased	Calcium & integrin-binding protein (CIB)	U85611	Q99828	Calcium-binding proteins

(continued)

Table 2 (continued)

Double-spot position in the *Array* image: expression *vs.* controls	Name of gene as given in "Atlas™ human cardiovascular array"	GenBank accession	SwissProt accession	Gene/Protein classification
Block C				
C1g increased	Cadherin 7 (CDH7)	AF047826	O60574	Cell surface antigens
				Cell-cell adhesion receptors
C1h increased	Intestinal peptide-associated transporter 1 (HPT1)	U07969	Q12864	Other cell adhesion proteins
				Other cell adhesion proteins
				Other facilitated diffusion proteins
C2i increased	GAP junction alpha-5 protein	L34954	P36382	Cell-cell adhesion receptors
				Other membrane channels & transporters
C3m increased	Integrin beta 2 (ITGB2); cell surface adhesion glycoproteins LFA-1/CR3/ p150, 95 beta subunit precursor; CD18 antigen; Complement receptor C3 beta subunit	M15395	P05107	Cell-cell adhesion receptors
			Q16418	
Block D				
D1m increased	Cardiac LIM domain protein; muscle LIM protein; cystein-rich protein 3 (CRP3); LIM-only protein 4	U49837	P50461	Basic transcription factors
				Other transcription proteins
				DNA synthesis, recombination & repair proteins
D1n increased	Cardiotrophin-1 (CT1)	U43030	Q16619	Growth factors, cytokines & chemokines
D2n increased	Matrix metalloproteinase 16 (MMP-16)	D83646	P51512	Chromatin proteins
				Metalloproteinases
D4a increased	TIMP-3	U14394	P35625	Extracellular matrix proteins
				Proteinase inhibitor
D4b increased	TIMP-4	U76456	Q99727	Extracellular matrix proteins
				Proteinase inhibitor

(continued)

Table 2 (continued)

Double-spot position in the *Array* image: expression *vs.* controls	Name of gene as given in "Atlas™ human cardiovascular array"	GenBank accession	SwissProt accession	Gene/Protein classification
D4d increased	Sterol regulatory element-binding transcription factor 1	U00968	P36956	Basic transcription factors
				Other apoptosis-associated proteins
D4e increased	Sterol regulatory element-binding transcription factor 2	U02031	Q12772	Basic transcription factors
				Other apoptosis-associated proteins
D5h increased	Rab geranylgeranyl transferase beta subunit	Y08201	P53611	Trafficking & targeting proteins
			Q92697	Protein modification enzymes
				GTP/GDP exchangers & GTPase activity modulators
D6m decreased	Muscle-specific DNase I-like precursor (DNase 1 L1; DNL 1 L); DNase X	X90392	P49184	DNA synthesis, recombination & repair proteins
		L40817		Apoptosis-associated proteins
		U06846		
Block E				
E1b increased	Lanosterol synthase (LSS); oxidosqualene lanosterol cyclase (OSC)	D63807	P48449	Complex lipid metabolism
E3n increased	NADPH-cytochrome p450 reductase	S90469	Q16455	Xenobic metabolism
			P16435	
E4g increased	Steroid 5 alpha reductase 1 (SRD5A1); 3-oxo-5-alpha steroid 4 dehydrogenase 1	M32313	P18405	Complex lipid metabolism
		M68886		
E4h increased	Steroid 5-alpha reductase 2 (SRD5A2); 3-oxo-5-alpha steroid 4 dehydrogenase 2	M74047	P31213	Complex lipid metabolism
Block F				
F2d increased	Pregnane X receptor (PXR)	AF061056	O75469	Hormone receptors
				Nuclear receptors
F2e increased	Estrogen-related receptor gamma	AF058291	O75454	Hormone receptors
				Nuclear receptors

(continued)

Table 2 (continued)

Double-spot position in the *Array* image: expression *vs.* controls	Name of gene as given in "Atlas™ human cardiovascular array"	GenBank accession	SwissProt accession	Gene/Protein classification
F2f increased	Nuclear receptor subfamily 4 group A member 2 (NR4A2); nuclear receptor-related protein 1 (NURR1); transcriptionally inducible nuclear receptor (TINUR); NOT	X75918	P43354	Hormone receptors
				Nuclear receptors
				Transcription activators & repressors
F2i increased	Orphan nuclear receptor TR4; nuclear receptor subfamily 2 group c member 2 (NR2C2); TAK1	U10990	P55092	Orphan receptors
			P49116	Nuclear receptors
				Transcription activators & repressors
F3a increased	RAR-related orphan receptor C	U16997	P51449	Orphan receptors
				Nuclear receptors
				Transcription activators & repressors
F3e increased	LX receptor alpha (LXR alpha)	U22662	Q13133	Orphan receptors
F3i increased	Platelet-activating factor acetylhydrolase IB alpha subunit	L13387	P43034	Other metabolism enzymes
F7c increased	Myocyte-specific enhancer factor 2A (MEF2A); serum response factor-like protein 1	X68505	Q02078	Basic transcription factors
			Q14223	
			Q14224	

This biomarker panel is discussed below and has been proposed for predictive tools and risk assessment amongst applied to vasospastic individuals at risk for early diagnosis and prevention of glaucoma [15].

Differential Proteomics: Positive and Negative Risk Assessment

Whereas positive prediction for patients at high risk is important to recognise the pathology before its clinical manifestation and/or at early stages of the development for the most effective treatment and preventive measures, the negative prediction for individuals at low risk helps to avoid ineffective costly treatments and health adverse effect of untargeted medication. Individual patient profiling is the recommended tool for the risk assessment. Contextually, *differential proteomics* is a promising tool for an accurate non-invasive positive *versus* negative prediction utilising liquid biopsy such as blood samples, amongst others.

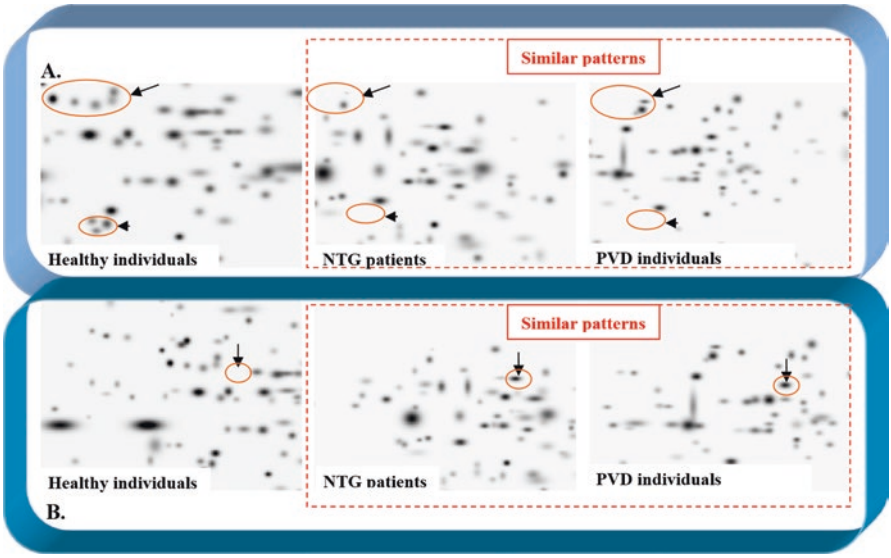

Fig. 5 *Differential proteomic* imaging of protein expression patterns in circulating leucocytes compared for healthy non-vasospastic individuals, healthy vasospastic individuals (PVD) and patients diagnosed with normal-tension glaucoma (NTG) (**a**) The protein clusters demonstrate similar patterns with suppressed expression for both – NTG and PVD. (**b**) The marked protein is highly up-regulated in both NTG and vasospasm; this protein normally is not expressed by circulating leucocytes of controls – healthy individuals without vasospasm [53]

2D-PAGE: "Blind" Evaluation of Similarity and Diversity of Expression Patterns in Protein Clusters

Protein clusters *ex vivo* analysed in circulating leucocytes demonstrate similar expression patterns in PVD individuals and normal-tension glaucoma patients *versus* non-vasospastic healthy controls as shown in Fig. 5.

Figure 6 summarises results achieved by 2D-PAGE analyses of differential proteomics images.

6.3 Interpretation of Differential Multiomic Profiles: Key Pathways and Their Relevance for Glaucoma Pathology

The comprehensive analysis reviewed above revealed the image of overall similarities and diversities between healthy non-vasospastic individuals – on the one hand and on the other hand – healthy vasospastic individuals (PVD), normal-tension glaucoma and high-tension glaucoma patients (see Fig. 7). The achieved results

SSP number	Control group	Glaucoma group	NCBI / Acc. No	Protein identified	Peptide Number Measured/ Matched	Sequence coverage (%)	Potential function
2304	*=1*	***1.6***↑	HSP70_HUMAN AAB06397	*HSP70*	47/18	35	Stress protein
3302	*=1*	***1.6***↓	-	-	-	-	-
4401	*=1*	***2.0***↑	AP-2 beta CAA64990	*AP-2β*	22/19	55	Basic transcription regulator
4502	=1	1	K1C10_HUMAN P13645	*Cytokeratin 10*	31/21	69	Cytoskeletal protein
4703	*=1*	***1.6***↓	-	-	-	-	-
4803	*=1*	***3.4***↓	ATPB_HUMAN P06576	*ATP synthase beta chain, mitochondrial precursor*	55/14	27	Energy metabolism
5503	=1	1	ACTB_HUMAN P60709	*Beta-actin*	34/19	59	Cytoskeletal protein
5703	*=1*	***1.3***↓	-	-	-	-	-
6404	*=1*	***1.4***↓	-	-	-	-	-
6406	*=1*	***2.7***↑	GSTP1-HUMAN P09211	*Glutathione S-transferase P*	11/8	46	Red-ox control
6601	*=1*	***1.6***↑	PDIA1_HUMAN P07237	*Protein disulfide-isomerase precursor*	18/6	21	Stress-response protein
6603	*=1*	***1.8***↓	-	-	-	-	-
6704	*=1*	***2.4***↓	-	-	-	-	-
6705	=1	1	PROF1_HUMAN P07737	*Profilin 1*	13/5	24	Cytoskeletal protein
6706	*=1*	***2.0***↓	-	-	-	-	-
7601	=1	1	-	-	-	-	-
7803	=1	1	ACTG_HUMAN P63261	*Gamma-actin*	31/16	38	Cytoskeletal protein

Fig. 6 Evaluation of 2D-PAGE images: *ex vivo* comparative analyses of protein expression patterns in circulating leucocytes of glaucoma patients *versus* controls; data have been adapted from Ref. [53]. Amongst 75 and 52 conserved protein spots in the control and patient groups, respectively, 17 overlapping protein spots were found to be conserved for members of the same group. Corresponding expression levels in the control group are taken as standard (=1). Glaucoma characteristic shifts in the expression levels of 12 proteins are marked with bold italics; "-" means non-identified protein spots, since the overall protein sequence coverage was lower than 15%

emphasise PVD as an intermediate health condition between healthy individuals and glaucoma affected patients. This achievement encourages considering PVD as a reversible suboptimal health condition and an attractive target for population screening, predictive diagnosis and cost-effective preventive measures protecting vasospastic individuals against glaucoma and other major pathologies linked to the primary vascular dysregulation (**see dedicated chapters in the book**).

Which molecular profiles are relevant for innovative screening tools? Table 3 summarises multiomic alterations detected by molecular profiling of glaucoma patients. Below paragraphs provide extended information about the key molecules and relevant pathways proposed for the diagnostic biomarker panel.

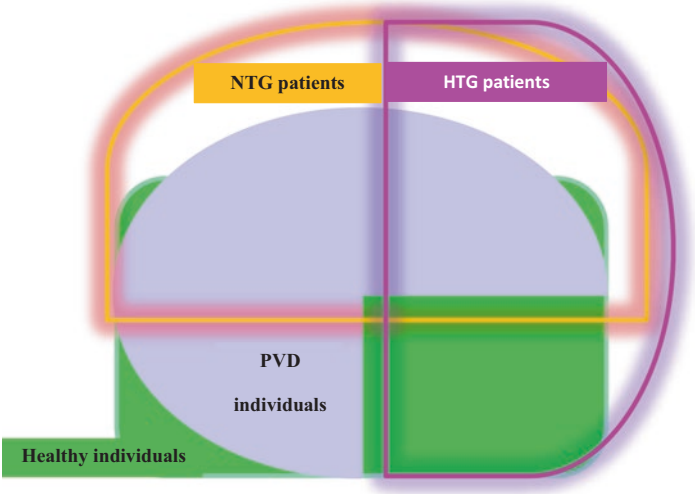

Fig. 7 Schematic image of multiomic similarities and diversities between healthy non-vasospastic individuals (green), healthy vasospastic individuals (PVD, grey), normal-tension glaucoma (NTG, yellow), and high-tension glaucoma patients (HTG, pink). (The image adapted from Ref. [49])

P2Y Purinoreceptor Is Upregulated in Vasospastic Individuals and Glaucoma Patients

The movement of leucocytes from blood into tissue is regulated by the local production of chemo-attractants – diverse molecules, the chemotactic signal of which is transmitted by G-protein-coupled purinoceptor family P2Y. These receptors respond to chemo-tactic signals of traumatic, infectious, post-ischemic, autoimmune, and various toxic injuries. Extracellular nucleotides released from the activated platelets and other damaged cell types exacerbate the inflammatory response by cell specific leukotrene generation [55]. Consequently, neutrophils generate leukotrienes B4 (LTB4) which are involved in the genesis of inflammation and oedema because of their effect on vascular permeability, plasma extravasation, diapedesis of white blood cells, and their important role in adaptive immune responses (as reviewed by Di Gennaro et al. [56]). Specifically, a highly enhanced concentration of leukotrienes B4 and C4 has been observed in CSF of patients with multiple sclerosis [57]. The member of leukotrienes receptors family – LTB4 receptor or P2Y purinoceptor 7 – has been isolated for the first time from the human erythroleukemia cell cDNA library [58]. The stimulation of monocytes, neutrophils and endothelial cells was suggested to be a physiological role for the LTB4 receptor [59]. There is a growing body of evidence indicating an important role of LTB4 receptors in the regulation of pathologic inflammation. Particularly using animal inflammatory models, a reduced disease severity has been shown when LTB4 receptor antagonists have been applied; the same effect has been observed in mice with target deletion of BLT1 – a high-affinity LTB4 receptor primarily expressed in leucocytes [60]. Furthermore, some

Table 3 Types of glaucoma-specific molecular alterations that can be potentially used for development of advanced tools for early and predictive diagnosis Ref. [43]

Type of molecule	Type of alteration	Detection technology
chromosomal DNA	1. (Oxidative) damage[a]	Comet assay
mitochondrial DNA	2. Mutations[a]	Clinical genomics
	3. Polymorphism[a]	PCR, Restriction analysis, etc.
	4. Methylation status of CpG islands[b]	Methylation-specific PCR
mRNA	1. Multiple alterations in expression patterns[a]	Differential transcriptomics:
		Subtractive hybridisation,
		Expression array,
		Reverse-transcriptase-PCR,
		Real-time-PCR, etc.
	2. Reduced mRNA editing	Reverse-Transcriptase-PCR
Proteins	1. Multiple alterations in expression patterns[a]	Differential Proteomics: 2D-PAGE, MALDI-TOF, Western-blot, etc.
	2. Posttranslational modification[a]	Western-blot, Activity tests (e.g. Zymography for gelatinase activity: MMP2, MMP9)
	3. Phosphorylation status[a]	Activity tests
	4. Protein misfolding[a]	Activity tests
Metabolites Signalling molecules Amino acids Plasma hormones amongst others	Altered profiles[a]	Disease Metabolomics: Comparative blood plasma metabolites profiling, HPLC, activity tests, amongst others

[a]Types of molecular alterations reported for glaucoma pathology
[b]Unpublished data collected in our laboratory, Radiologic clinic, UKB, University of Bonn, Germany (first author, OG)

studies support a potential role of P2Y receptors in controlling intraocular pressure although additional investigations of the issue are necessary [61].

ICAM-1 Is Upregulated in Vasospastic Individuals and Glaucoma Patients

Neutrophil-endothelium interactions are implicated in pathological alterations of blood vessel function, potentially leading to circulatory disturbances [62]. Interactions between blood cells and the vessel wall result in endothelial dysfunction and injury leading to increased blood-brain barrier permeability and even oedema formation [63]. Penetration of leucocytes into inflamed areas involves a complex interaction of leucocytes with the endothelium through a regulated expression of surface adhesion molecules. Found in this work to be highly expressed in PVD, NTG and HTG groups ICAM-1 molecule is believed to be largely responsible for the adhesion and trans-endothelial migration of the leucocytes [64]. This is well

in agreement with earlier developed strategies aimed at the inhibition of endothelial interactions with leucocytes via the use of adhesion molecule monoclonal antibodies, which successfully reduce cerebral ischemia/reperfusion injury, infarct size, and demonstrate a neuroprotective effect generally [65–67]. In our study, highly expressed ICAM-1 was found in leucocytes of glaucoma patients; in contrast, at most, only traces of the target expression were detected in the leucocytes of healthy non-vasospastic controls.

Sodium Calcium Exchanger (NCE) Is Upregulated in Vasospastic Individuals and Glaucoma Patients

Many studies examined the levels of cytosolic Ca^{2+} ($[Ca^{2+}]_c$) and Na^+ ($[Na^+]_c$) in human blood cells, whereby leucocytes have been the main target of studying the relationship between blood pressure and intracellular content of both ions (as reviewed by Horiguchi et al. [68]). As it has been shown by Horiguchi et al., the resting $[Ca^{2+}]_c$ correlates well with NCE expression so indicating NCE expression regulation to be an adaptive mechanism for Ca^{2+} extrusion mediation. The same study also observed a gender effect on $[Ca^{2+}]_c$ / $[Na^+]_c$ regulation in circulating leucocytes being in relationship with blood pressure. Further, the role of the endothelial intracellular Ca^{2+} concentration in molecular mechanisms of vasoconstriction/vasodilatation has been intensively studied and the functional association between P2Y purinoceptors, endothelial NO synthesis and calcium transport in terms of vascular regulation is well documented in the literature [69, 70]. Our findings here clearly demonstrate the up-regulation of both – P2Y purinoceptor and Na^+/Ca^{2+} exchanger in circulating leucocytes of glaucoma patients as well as vasospastic individuals *versus* healthy non-vasospastic controls.

Tissue Remodelling Metalloproteinases Are Upregulated in Vasospastic Individuals and Glaucoma Patients

Significantly increased protein expression rates of both latent and active forms of metalloproteinases *MMP-9* and *MT1-MMP* in circulating leucocytes correlate well with the enhanced levels of transcription and with glaucoma diagnosis [12]. Once activated, both hydrolases necessarily contribute to remodelling or even degeneration of the tissue whereto they are secreted by circulating leucocytes. This up-regulation might be a consequence of repeated mild ischemia/reperfusion postulated for both vasospastic individuals and glaucoma patients [44]. Further, hyperactivation of tissue-remodelling enzymes correlates well with the clinical picture of the tissue degeneration characteristic for GON [71]. However, the question remains open, whether there might be a correlation between an increased *MMPs* activity and glaucoma severity.

Finally, the increased synthesis of tissue remodelling hydrolases detected in the blood of healthy vasospastic individuals can potentially lead to the development of

further pathologies that have not yet been considered as related to vasospasm. To the potential list of them belong impaired wound healing, some types of tissue degeneration and increased metastases activity [3, 4, 12, 51, 72]. It is essential that large-scale studies are performed in order to validate proposed impacts of vasospasm for the above listed pathophysiologic processes / manifested pathologies. This allows a targeted prevention at the stage of pre-lesions, upstream disease manifestation.

Stress Response, Apoptosis and DNA-Repair

An increased oxidative stress is well documented for both – PVD and glaucoma [1, 73]. Several proteins modified by oxidative stress have been demonstrated in retinal protein lysates isolated from ocular hypertensive eyes of a rat-model of glaucoma [74]. Consequently, altered gene expression patterns, particularly for stress response factors, can be expected. Indeed, the alteration of *heat shock 27 kDa protein 1* expression was stable in retinas of rat hypertensive eyes [75]. *Gene hunting* technology by "Subtractive Hybridisation" followed by visualisation and quantification of target transcripts (see Fig. 4) revealed an up-regulation of both the pro-apoptotic factor *p53* and proteolytic enzyme *20S proteasome subunit XAPC7* in NTG patients [6], the activity of which is usually increased during reperfusion [14]. In agreement with this, both an apoptotic inhibitor *survivin* and DNA-repair *Xeroderma pigmentosum gene C* have been found to be down-regulated in NTG [13]. Contextually, *ex vivo* sub-cellular imaging by *Comet Assay* analysis demonstrated significantly increased (un-repaired) DNA-damage in PVD, NTG and HTG [44, 45].

Adhesion, Blood-Brain-Barrier (BBB)-Breakdown and Tissue Remodelling

Gene expression profiles characteristic for an activated adherent function have been identified in transcriptome of NTG: up-regulated transcripts of *lymphocyte-IgE-receptor* (*Fc-epsilon-RII/CD23*), *T cell-specific tyrosine kinase* (*ITK*), *thromboxan-A2-receptor*, and *alkaline-phosphatase* have been detected by "Subtractive Hybridisation" [11]. Adherent circulating leucocytes (CL) could be an important contributor to BBB-breakdown observed in glaucoma pathology [76]. The subtraction of metalloproteinase *MMP-9* and *MT1-MMP* transcripts highly increased in CL of glaucoma patients provides further evidence for this functional link and indicates pathways involved in the extensive tissue remodelling observed in glaucoma [12] as discussed above.

Transcription Regulation

Dramatically altered transcription patterns in glaucoma were reported by several research groups [13, 12, 53, 75]. A reason for this extensive shift in transcription regulation was unclear for a very long time till a significant up-regulation of the

basic transcriptional regulator *AP-2ß* was attributed to glaucoma pathology: *AP-2ß* has been identified in CL using the smart technology of disease proteomics [53]. Protein mapping and differential proteomic analysis including *AP-2* patterns are demonstrated in Figs. 5, 6. *AP-2* proteins play a decisive role, particularly in eye morphogenesis. While the activation of *AP-1* leads to an increased stromelysin (metalloproteinase-3) production in the trabecular meshwork *in vitro* [77, 78], the expression and activity of *AP-2* controls the activity of the *gelatinase B* (*MMP-9*) [79]. In consensus, *MMP-9* was demonstrated to be significantly up-regulated in leucocytes of glaucoma patients and to play an important role in tissue remodelling as a part of glaucomatous degeneration [12]. Therefore, the concerted up-regulation of *AP-2ß* and *MMP-9* in leucocytes of glaucoma patients has been proposed to be an important part of the molecular mechanisms in glaucoma pathology and a reliable biomarker for early diagnosis.

Multi-Drug Resistance

An extensive deregulation of *ABC-transporters* has been demonstrated in glaucoma pathology [13, 80, 81]. *ABC-transporters* (*ATP-binding cassette transporter*) usually translocate a wide variety of structurally unrelated lipophilic compounds being responsible for drug efflux, and therefore, for multi-drug resistance. *ABC 1* has been shown to be stably up-regulated in CL of glaucoma patients [81]. Joyce et al. demonstrated a crucial role for *ABC 1* in protection against atherosclerosis [82]. An activity of *ABC 1* has been shown to have a regulating effect on endothelial function and stimulate nitric oxide bio-activity in arterial walls [83]. The up-regulation of *ABC1* in CL of glaucoma patients might indicate the involvement of this gene in chronic vascular dysregulation and has been suggested as a potential marker for early diagnosis of glaucoma [81].

Energy Metabolism

"Gene hunting" in CL of glaucoma patients revealed down-regulated transcripts of *Na^+/K^+-ATPase* [11]. An identification of the subtracted transcripts is demonstrated in Fig. 4. Further, abnormal sodium handling has been proposed to be associated with ocular hypertension and to contribute to a progression of optic nerve damage in both normal-tension and high-tension glaucoma [84, 85]. *Na^+/K^+-ATPase* is known to be down-regulated in lymphocytes of patients with acute myocardial infarction [86], and may be one of the reasons for ventricular arrhythmias and coronary artery spasms. A decrease in intracellular potassium concentration and an increase in intracellular calcium concentration may play a major role in the pathomechanism of coronary artery spasms. Inhibition of *Na^+/K^+-ATPase* is one of functional consequences of oxidative membrane damage caused by an increased oxidative stress [87], which is triggered e.g. under ischemia/reperfusion. This

affects central thermogenic mechanisms, since *Na^+/K^+-ATPase* has been shown to play a key role in cellular energy balance and thermogenesis [88, 89]. A decreased activity of *Na^+/K^+-ATPase* triggers vasospasm [90]. Being an important co-factor of cellular *ATPases*, magnesium can reverse delayed vasospasm and reduce the extent of acute ischemic lesions [91]. Magnesium therapy demonstrates beneficial effects in vasospastic syndrome and glaucoma [23].

7 Concluding Remarks

Detected similarities in multiomic signature between glaucoma patients and PVD individuals against healthy non-vasospastic controls indicate, on the one hand, a predisposition of PVD individuals to glaucomatous damage, and, on the other hand, an important role of a vascular component in glaucoma pathology.

Detected dissimilarities in multiomic signature between PVD and glaucoma patients indicate glaucoma-specific pathomechanisms that are not involved in the PVD signature. Further PVD signature demonstrates the major overlap of molecular patterns with healthy controls. Both actualities create a very strong argument for considering PVD as a reversible suboptimal health condition and attractive target for population screening, predictive diagnosis for persons at risk followed by cost-effective preventive measures protecting vasospastic individuals against glaucoma and other major pathologies linked to the primary vascular dysregulation. Both similarities and dissimilarities might be useful in ascertaining the predictive diagnosis of glaucoma.

Glaucoma-specific multiomic signature includes following pathways: apoptosis induction, stress response, DNA-repair, energy production, transcription regulation, drug resistance, tissue remodelling and degeneration.

Development of other "downstream" pathologies different from glaucoma but related to primary vascular dysregulation should be obligatory considered for PVD individuals by thoroughly performed stratification regarding the personal predisposition utilising the pathology-specific multiomic signature.

Pathology-specific multiomic signature may create a robust platform for the development of specific biomarker panels based on a minimally invasive approach liquid biopsy utilising blood, saliva and tear fluid samples for early/predictive diagnosis of glaucoma and other "downstream" pathologies [19, 92].

Based on precise predictive diagnosis multi-target treatments tailored to the personal profiles are recommended for the cost-effective preventive measures [93, 94]. Indeed, traditional, complementary and alternative medical approaches demonstrate a potential to provide effective prevention for persons in suboptimal health condition and specifically PVD and Flammer syndrome as reviewed in the recent literature [95, 96]. Thereby, modifiable (means preventable) risk factors have been reported to play a very important role. Consequent recommendations are provided by recently published articles [97] and in the dedicated chapter of this book.

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Interrelation Between Dry Mouth and Flammer Syndromes: Neglected Risks in Youth and New Concepts of Personalised Prevention

International Multi-centre Study

Analtolij Kunin, Jiri Polivka Jr, Natalia Moiseeva, and Olga Golubnitschaja

Abstract "Dry mouth" syndrome (chronic hyposalivation) can be caused by a number of pathophysiological conditions such as acute and chronic stress exposure, abnormal body weight (both – too high and too low), eating disorders (such as *Anorexia nervosa*), metabolic syndrome(s), Sjögren's and Sicca syndromes, drugs and head/neck radiotherapy application. In turn, the chronic hyposalivation as a suboptimal health condition significantly reduces quality of life, may indicate a systemic dehydration, provoke and contribute to a number of pathologies such as a strongly compromised protection of the oral cavity, chronic infections and inflammatory processes, periodontitis, voice and digestive disorders, amongst others. Consequently, "dry mouth" syndrome might be extremely useful as an indicator for an in-depth diagnostics of both – co-existing and snowballing health-threating conditions. However, predictive diagnostics, targeted prevention and personalisation of

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treatments are evidently underdeveloped for individuals at high risk suffering from the “dry mouth” syndrome.

In our presented study, for both – the target group (hyposalivation) and positive control (periodontitis), FS-phenotype was demonstrated to be more specific compared to the disease-free (negative control) group. Moreover, self-reports provided by interviewed young individuals of the target group frequently recorded remarkable discomfort related to “dry mouth” syndrome, acute and chronic otorhinolaryngological infections, and even delayed wound healing. Further, interviewed individuals do worry about these symptoms which might be indicative for potential diseases; they are also amazed that too little attention is currently paid to the issue by caregivers.

Epi/genetic regulations involved into pathophysiologic mechanisms of hyposalivation in FS-affected individuals should be thoroughly investigated at molecular level. Identified biomarker-panels might be of great clinical utility for predictive diagnostics and patient stratification that would sufficiently improve personalised care to the affected individuals.

Keywords Predictive preventive personalised medicine · Hyposalivation · Xerostomia · Sicca syndrome · Periodontitis · Voice disorder · Digestive disorder · Flammer syndrome · Phenotype · Dehydration · Impaired healing · Patient stratification · Risks · Dentistry · Otorhinolaryngology · Dry mouth · Innovative concepts · Predictive preventive personalised medicine

1 Introduction

Saliva is a life-important body fluid essential for an effective immune defence, antibacterial and antifungal function, buffering, remineralisation and lubrication of the oral cavity, tasting, swallowing and speaking, amongst others [1, 2]. Saliva consists of up to 99% of water molecules and about 1% of both organic and inorganic compounds; salivary molecular patterns analysed by saliva-multiomic technologies is a valuable source of information for early and predictive diagnostics [3] Salivary secretion is individually ranging between half of litter and litter of the fluid per day [4]. Hyposalivation – a reduced salivary flow also known as the “dry mouth” syndrome and the most common aetiologic factor in xerostomia [5] – can be caused by a number of patho/physiological conditions such as acute and chronic stress exposure, abnormal body weight (both – high and low), eating disorders (such as *Anorexia nervosa*), metabolic syndrome(s), Sjögren’s and Sicca syndromes, drugs and head/neck radiotherapy application, amongst others [2, 4, 6–10]. Saliva secretion disorder may be manifested at any age. Hence, a strong correlation between disadvantageous and handicapped psychological health conditions (such as stress and anxiety) and development of abnormal saliva flow and its composition can be observed early in life as it has been demonstrated for bullied children [11]. In turn, the chronic

hyposalivation as a suboptimal health condition reduces quality of life, may indicate a systemic dehydration, provokes and contributes to a number of pathologies such as a strongly compromised protection of the oral cavity, chronic infections and inflammatory processes, periodontitis, voice and digestive disorders, amongst others [2, 4, 10]. Consequently, early detection of chronic hyposalivation might be extremely useful as an indicator for an in-depth diagnostics of both – co-existing and snowballing health-threating conditions. An example: as recently published, "dry eyes" and/or "dry mouth" syndrome is even more indicative for diagnostics of depression than Sjögren's syndrome itself [12]. In contrast, the factor of hyposalivation is rather neglected in currently applied screening programmes, though recently published articles clearly demonstrate that some phenotypes are strongly predisposed to a systemic dehydration with consequent snowballing health-threating effects such as an increased risk of compromised detoxification and breast cancer predisposition specifically in young subpopulations [13, 14]. Contextually, Flammer syndrome (FS) individuals demonstrate strongly reduced feeling of thirst that, if daily liquid intake is not permanently controlled by mind, might be potentially linked to a systemic dehydration [15]. Further, a strongly pronounced FS-phenotype has been demonstrated for premenopausal breast cancer patients with particularly aggressive metastatic disease [16].

All the above noted actualities have motivated this study estimating potential relationship between the FS-phenotype and evidence-based hyposalivation – the "dry mouth" syndrome.

2 Working Hypothesis

The degree to which an individual is effected by hyposalivation or xerostomia (chronic hyposalivation, defined as the subjective sensation of the oral dryness) is ubiquitously determined by the Bother xerostomia Index (BI) utilising a questionnaire of 10 issue-specific items [17].

An extent to which individuals included in the study are the carriers of the FS-phenotype is estimated by a questionnaire of 15 items [4, 7].

We have hypothesised that individuals demonstrating FS-phenotype may suffer from the "dry mouth" syndrome, due to restricted feeling of thirst and consequently limited daily liquid intake potentially resulting in the systemic dehydration with individually pronounced level of severity. To verify the hypothesis, healthy controls (negative control) versus individuals with evident hyposalivation as well as patients with periodontitis (positive control) observed and treated at the dental clinic (authors AK and NM) have been interviewed according to the FS-questionnaire. Statistically evaluated results are summarised and discussed below.

3 Study Design

All the patients and individuals involved in the study were informed about the purposes of the study and consequently have signed their *consent of the patient*. All procedures involving human participants were performed with the permission of the Ethical Committee of the Voronezh N.N. Burdenko State Medical University, Voronezh, Russia which are in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

3.1 Hyposalivation Proof

Hyposalivation or xerostomia (chronic hyposalivation) was determined by the Bother xerostomia Index (BI) utilising a questionnaire of 10 issue-specific items [17] and monitoring of a matt roof of the mouth in dental practice (see Fig. 1).

3.2 Flammer Syndrome: 15-Item Questionnaire

The Flammer Syndrome (FS) phenotype has been characterised earlier [15]. The FS questionnaire applied to the actual study has been developed at the University Hospital Basel, Switzerland [18]. The actual version of the FS-questionnaire has been effectively applied to study the FS symptomatic in different populations [19]

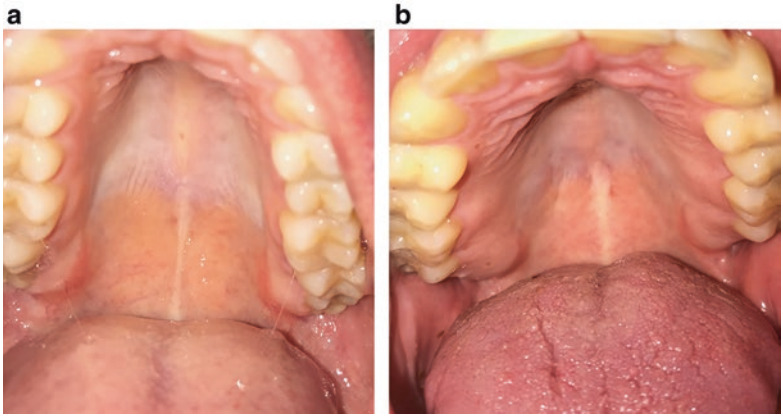

Fig. 1 Visual estimation of the diagnosed xerostomia in dental practice; (**a**) normally salivated roof of the mouth versus (**b**) strongly hyposalivated (matt) roof of the mouth; this methodology has been used additionally to the Bother xerostomia Index (BI) utilising a questionnaire of 10 issue-specific items described in the "Methods"

as well as in a spectrum of potentially relevant pathologies such as eye diseases, individual breast cancer subtypes [14, 20] and aggressive metastatic disease [21, 22], amongst others [23].

3.3 Recruitement of Patients and Disease-Free Individuals

Altogether 60 individuals recruited at the specialised medical centre (Department of Hospital Dentistry, Voronezh N.N. Burdenko State Medical University, Voronezh, Russia) were involved in this international study and equally distributed between three groups of comparison, namely the disease-free group (20 individuals), the target group with hyposalivation (20 individuals) and the group of patients diseased on periodontitis (20 patients). Gender and menopausal status in female individuals were not considered as stratification criteria in the design of the presented study; however, corresponding statistical evaluations have been performed (see Table 2).

Disease–Free Individuals

The control group comprised staff members of the medical centre who regularly undergo full check-up of their health condition and who voluntarily have participated in the study. Individuals with no history of major pathologies have been included into the (negative) control group.

Selection of Individuals with Hyposalivation

The target group comprised staff members and students of the Voronezh N.N. Burdenko State Medical University who voluntarily have participated in the presented study. Based on the Fox's criteria, individuals who positively responded to at least one question numbered 1,2,3 and 4 (see Table 1) have been classified as a person with hyposalivation [4] and considered for the target group of the study. The scoring according to the Bother xerostomia Index (BI) has been performed [17]. Finally, individual monitoring of a matt roof of the mouth in the treating dental practice has been documented (see Fig. 1).

Excluding criteria: Individuals with history of major pathologies such as oncologic diseases, neurodegenerative disorders, diabetes mellitus, acute and chronic infectious diseases, rheumatic and autoimmune diseases, as well as pregnant women and persons with alcohol and/or drug abuse.

Table 1 10-item questionnaire to estimate hyposalivation (xerostomia); based on the Fox's criteria, individuals have been classified as suffering from hyposalivation, if they have positively responded at least to one of the italicised questions [4]

1. *Do you have a feeling of dry mouth when you eat?*
2. *Do you have difficulty swallowing food?*
3. *Do you need to drink when eating?*
4. *Do you have a feeling of hyposalivation most of the time?*
5. Do you have a feeling of dry mouth at night or when you get up?
6. Do you have a feeling of dry mouth at other time during the day?
7. Do you use chewing gum or candy to improve your sense of dry mouth?
8. Do you wake up at night for drinking water?
9. Do you have problems of food tasting?
10. Do you have a feeling of burning tongue from time to time?

Periodontitis Patients

Since periodontitis is considered as one of the pathologies resulting from chronic and severe hyposalivation (xerostomia) [4, 9, 10], patients observed and treated due to periodontitis at the Department of Hospital Dentistry, Voronezh N.N. Burdenko State Medical University in Voronezh have been recruited to create the positive control group for the presented study.

3.4 Statistical Analysis

For analytical and statistical evaluations, the data have been transferred to Microsoft Excel. SPSS Statistics v20.0.0 software (IBM, Armonk, New York, USA) has been applied. The prevalence of individual symptoms in groups of comparison has been evaluated and expressed in percentages. Pearson's chi-square test of associations has been applied. p values below 0.05 have been considered as statistically significant.

4 Achievements of the Study

4.1 Statistics for the Age, Gender and Menopausal Status in Groups of Comparison

Table 2 presents statistics provided for the disease-free (negative control) group, target group of individuals who suffer from hyposalivation and patients with periodontitis (positive control group) with 20 participants per each group of comparison. The disease-free group created the youngest group, the age mean (33.3 y.o.) of which, is, however, close to this of the target group (37.2 y.o.). Substantially older group was created by patients diagnosed with periodontitis (46.9 y.o). Although the difference was found statistically non-significant, the absolute majority of participants were pre-menopausal women in each group of comparison.

4.2 Evaluation of the FS Prevalence in the Groups of Comparison

Figure 2 summarises the prevalence of individual "Flammer Syndrome" symptoms utilising the 15-item questionnaire in three groups of comparison. Complementary to that, Table 3 specifies the portion of individual group members who responded with "no" versus "yes"/"frequently" and/or "sometimes"/"rather" as well as the level of specificity of individual symptoms for individual groups providing corresponding level of significance for the group specific differences. Noteworthy, all 15 items demonstrated highly significant differences between the groups of comparison (see Table 3).

For the target group, (hyposalivation), FS-phenotype was demonstrated to be more specific compared to the disease-free (negative control) group with the exception of two items, namely 11- slightly less and 13- equal to the negative controls. Further, the most significant prevalence of the FS symptoms has been demonstrated for altogether 10 items: 1, 2, 3, 4, 5, 6, 7, 8, 12 and 15.

Table 2 Age and gender related statistics for the groups of comparison: the age mean of the target group with otherwise healthy individuals who suffer from the "dry mouth" syndrome is close to this of the negative control group (youngest one); the oldest one is the group of periodontitis patients

Characteristics	Patient subgroup			P value
	Periodontitis	Hyposalivation	Disease-free	
Female	13	12	13	0.931
Male	7	8	7	
Pre-menopausal	10	12	10	0.193
Post-menopausal	3	0	3	
Patients age mean (min-max) [years]	46.9 (33–60)	37.2 (24–54)	33.3 (19–67)	<0.001

For the periodontitis patients (positive control) similarly to the target group, FS-phenotype was demonstrated to be more specific compared to the disease-free group with the exception of only one item, namely 12 (average body weight of the majority). Further, the most significant prevalence of the FS symptoms has been demonstrated for altogether 12 items: 2, 3, 4, 6, 7, 8, 9, 10, 11, 13, 14 and 15.

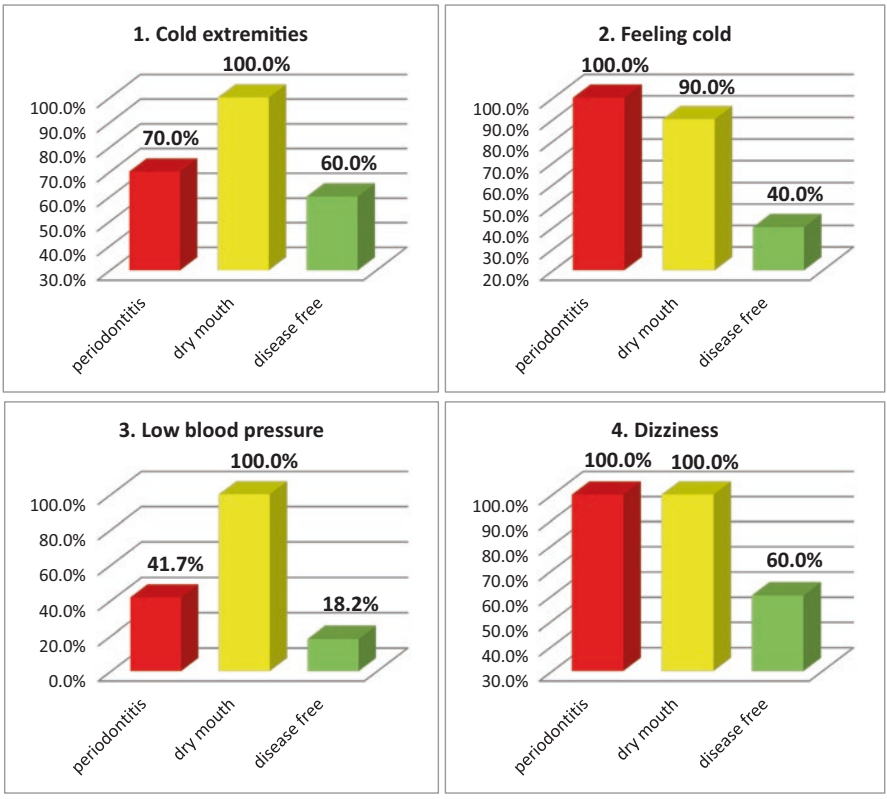

Fig. 2 Evaluation of the prevalence of individual symptoms (1–15) of the Flammer Syndrome phenotype in the groups of comparison: "dry mouth" syndrome versus "disease- free" reference (negative control) group versus positive control group with periodontitis patients. The prevalence in each individual group is presented by percentage of individuals who have responded to the corresponding question with "frequently" and "sometimes" pooled together. Responders answering with "I do not know" have been excluded from the overall numbers/calculations; Question 6 answered as "I do not feel thirsty and control my liquid intake by mind" is presented; Question 12 – answers "very slim" and "slim" are pooled together and presented in %; Question 13 – answers "yes" and "rather" are pooled together and presented in %

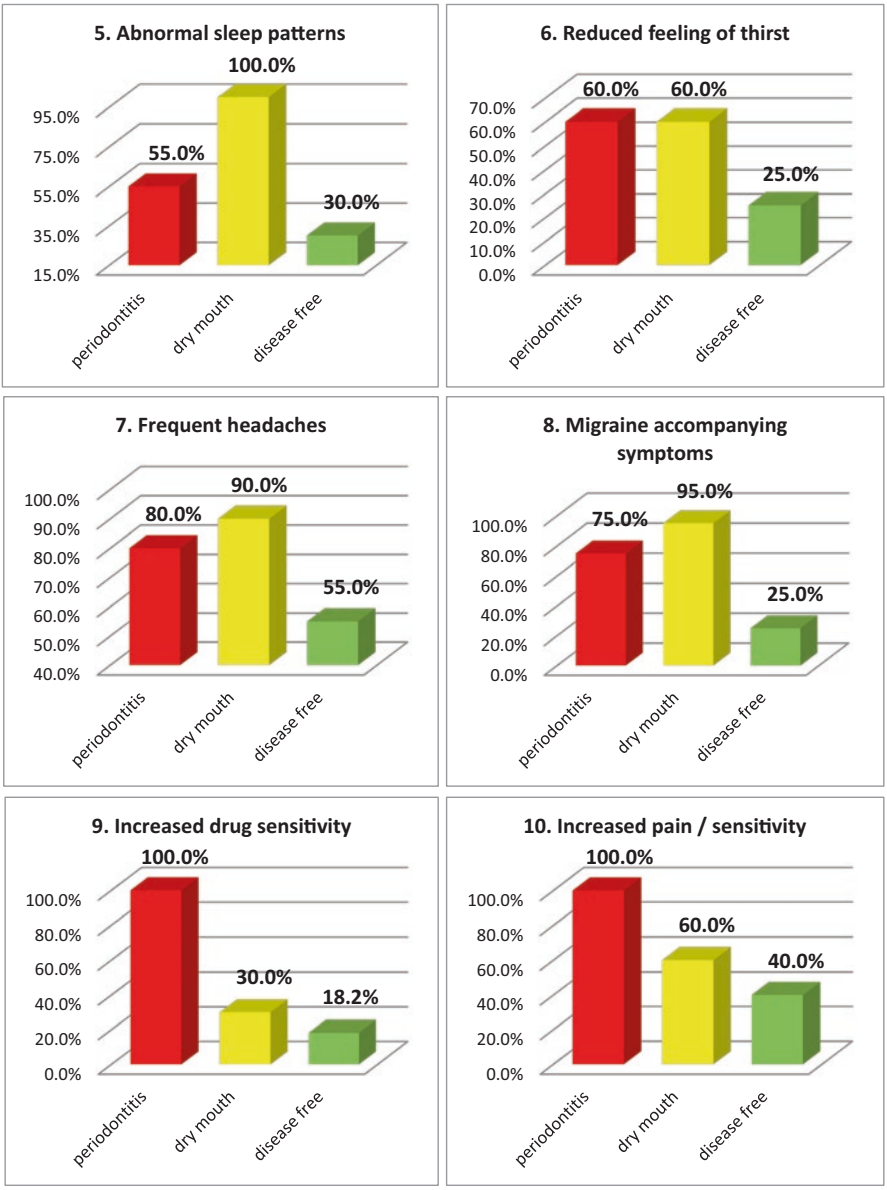

Fig. 2 (continued)

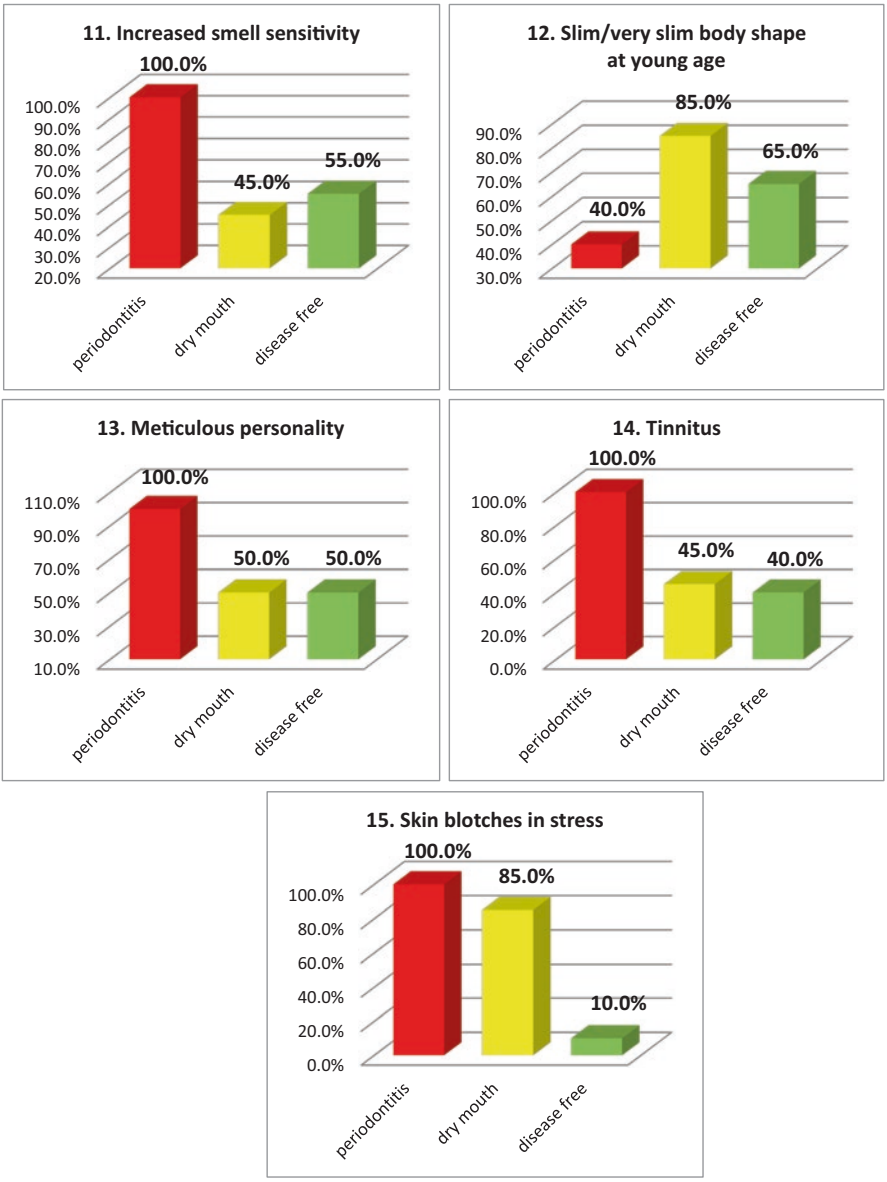

Fig. 2 (continued)

Table 3 Statistics summarised for the specialised 15-item FS-questionnaire; the most representative answer (highest percentage) for each group of comparison is noted

Number of item (specialised FS-questionnaire)	Group of comparison			
	Disease-free controls (C)	Hyposalivation (H)	Periodontitis (P)	Comments
1.	NO – 40%	Frequently – 70%	Sometimes – 40%	H > P > C
	Frequently – 35%	NO – 0%	NO – 30%	$p = 0.015$
2.	NO – 60%	Sometimes – 70%	Frequently – 65%	P > H > C
	Frequently – 10%	NO – 10%	NO – 0%	$P < 0.001$
3.	NO – 82%	Yes – 65%	Rather – 42%	H > P > C
	Yes – 0%	NO – 0%	NO – 58%	$p < 0.001$
4.	Sometimes – 47%	Sometimes – 100%	Frequently – 100%	P > H > C
	NO – 40%	NO – 0%	NO – 0%	$p < 0.001$
5.	NO – 70%	Yes – 65%	If feel cold – 55%	H > P > C
	If feel cold – 20%	If feel cold – 35%		$p < 0.001$
	Yes – 10%	NO – 0%	NO – 45%	
6.	Normal 55%	Don't feel thirsty – controlled drinking 60%	Don't feel thirsty –controlled drinking 60%	H=P > C
				$p < 0.001$
		Normal – 0%	Normal – 0%	
7.	NO – 45%	Sometimes – 90%	Frequently – 55%	H > P > C
	Frequently – 15%	NO – 10%	NO – 20%	$p = 0.007$
8.	NO – 75%	Sometimes – 95%	Frequently – 40%	H > P > C
	Frequently – 0%	NO – 5%	NO – 25%	$p < 0.001$
9.	NO – 82%	NO – 70%	Sometimes – 100%	P > H > C
	Frequently – 0%	Sometimes – 30%	NO – 0%	$p < 0.001$
10.	NO – 60%	Sometimes – 40%	Sometimes – 100%	P > H > C
	Frequently – 0%	NO – 40%	NO – 0%	$p < 0.001$
11.	NO – 45%	NO – 55%	Sometimes – 60%	P > H > C
	Frequently – 25%	Sometimes – 45%	NO – 0%	$p = 0.001$
12.	Slim – 45%	Slim – 80%	Averaged – 60%	H > C > P
	Averaged – 35%	Averaged – 15%	Slim – 40%	$p = 0.007$

(continued)

Table 3 (continued)

Number of item (specialised FS-questionnaire)	Group of comparison			
	Disease-free controls (C)	Hyposalivation (H)	Periodontitis (P)	Comments
13.	NO – 50%	Rather – 50%	Rather – 70%	P > H > C
	Yes – 25%	NO – 50%	NO – 0%	$p = 0.001$
14.	NO – 60%	NO – 55%	Sometimes – 75%	P > H > C
	Frequently – 0%	Sometimes – 45%	NO – 0%	$p < 0.001$
15.	NO – 90%	Sometimes – 80%	Frequently 50%	H > P > C
	Frequently – 0%	NO – 15%	NO – 0%	$p < 0.001$

"No" answer is noted for each group as well as "frequently" for the control group, since "no" was the most frequent answer provided in this group; "Comments" demonstrate which group the corresponding sign/symptom is more *versus* less typical for, such as H > P > C means more typical for "hyposalivation" than for "periodontitis" and least typical for the control group; H=P means equally typical for "hyposalivation" and "periodontitis"; statistical significance (*p*) is noted for each item

Comparing the target group with periodontitis patients the FS symptoms of "cold extremities", "low blood pressure", "sleep patterns", "migraine with accompanying symptoms", "(very) slim body shape" were found to be more specific for the target group, while "altered sensitivity towards drugs", "pain", "strong sense of smell", "meticulous personality", "tinnitus", and "skin blotches under stress" were found to be more specific for periodontitis patients.

4.3 Hyposalivation – Interview with Selected Individuals

Case 1

19-years old female responder studying medicine, generally healthy, has been interviewed towards FS-symptoms. The interview resulted in 12 positive responses from the maximum of 15. The negative responses were given regarding the symptoms 5 (answered as "rather normal sleep onset"), 8 (absence of accompanying symptoms of migraine), 9 (rather normal reaction towards medication). Particularly noticeable responses have been given towards the following symptoms:

- Symptom 1 – frequently observed cold extremities
- Symptom 2 – feeling cold frequently
- Symptom 3 – evidently low blood pressure
- Symptom 10 – increased pain sensitivity
- Symptom 11 – strongly pronounced smell perception
- Symptom 12 – slim body shape

- Symptom 13 – strongly pronounced tendency towards perfectionism
- Symptom 14 – frequent tinnitus
- Symptom 15 – evident skin blotches in stress situations

Self-reported additional information:

- since early childhood the responder suffers from acute and chronic otorhinolaryngologic infections: chronic tonsillitis is clinically manifested
- the responder records cold extremities even during warm period of time, remarkably low blood pressure, feeling vertiginous, "dry mouth" syndrome and related discomfort, impaired wound healing
- the responder does not feel thirsty and drinks too little
- the responder is an excellent student with remarkably good notes at any educational level
- the responder worries about achievements but also about symptoms which might potentially indicate a predisposition to diseases which however, are not recognised by general practitioners.

Case 2

20-years old male responder studying medicine, generally healthy, has been interviewed towards FS-symptoms. The interview resulted in 11 positive responses from the maximum of 15. The negative responses were given regarding the symptoms 5 (answered as "rather normal sleep onset"), 8 (absence of accompanying symptoms of migraine), 9 (rather normal reaction towards medication), and 10 (rather normal pain sensitivity). Particularly noticeable responses have been given towards the following symptoms:

- Symptom 1 – frequently observed cold extremities
- Symptom 2 – feeling cold frequently
- Symptom 11 – strongly pronounced smell perception
- Symptom 12 – slim body shape
- Symptom 13 – strongly pronounced tendency towards perfectionism
- Symptom 15 – evident skin blotches in stress situations

Self-reported additional information:

- since early childhood the responder suffers from acute and chronic otorhinolaryngologic infections: chronic tonsillitis is clinically manifested
- the responder records cold extremities even during warm period of time, feeling vertiginous, "dry mouth" syndrome and related discomfort, impaired wound healing
- the responder does not feel thirsty and drinks too little
- the responder is an excellent student with remarkably good notes at any educational level

– the responder worries about achievements but also about above reported symptoms which might potentially indicate a predisposition to diseases which however, are not recognised by general practitioners. More information regarding impaired healing processes is provided in the book chapter "Flammer Syndrome in the Context of Healing Impairments – Facts and Hypotheses for Multiprofessional Consideration" by Eden Avishai and Olga Golubnitschaja.

5 Results Interpretation

In 2018 Springer has selected around 250 articles across all areas with *a potential to change the world*, which have been awarded the title "groundbreaking scientific findings that could help humanity and protect our planet" [24]. Specifically in the category "Medicine and Public Health", 60 articles have been selected [25], one of which published by the *Nature Reviews Clinical Oncology* clearly demonstrates the added value of patients' self-reports [26]. The paper emphasizes the crucial role of the patient experience as "a key measure of health-care quality". Hearing the patient voice at greater volume, indeed, should be the leading principle of personalised healthcare. Contextually, early this year, EPMA J. has published a self-report of an individual with a strongly pronounced Flammer syndrome phenotype, who provided a lot of crucial information indicating a predisposition to several pathologies as well as caregivers' mistakes, who ignored mild signs and symptoms appeared early in life of and self-reported by the patient [27]. Due to potential relevance of the FS-phenotype monitored early in life, and a number of pathological conditions recorded later on for the person introduced in the above noted paper, current project has carefully analysed signs and symptoms reported for the adolescent period of life which, if not paid attention to, may potentially lead to severe complications and clinically manifested severer pathologies. Although, if ignored, the dental component is known to play a central role in transition between precondition and clinically manifested pathologies [3], evidently mild oral and dental symptoms in FS-affected individuals have not been taken into consideration as a potential early predictor till now. In the presented study, a hypothetical link between signs and symptoms generally known for individuals with the FS-phenotype and a predisposition to the "dry mouth" syndrome with consequences got thoroughly analysed. Collected data clearly demonstrate the relevance of the FS-phenotype for both "dry mouth" syndrome and manifested periodontitis. Moreover, while altogether 10 items of the FS symptoms were prevalent in the target group with hyposalivation of otherwise healthy individuals, the patients with manifested periodontitis demonstrated the prevalence of altogether 12 items typical for FS-phenotype (see Fig. 2, Table 3).

5.1 Most Consolidated Answers

The most consolidated answers in the groups of comparison have been provided as summarised in Table 3. Seventy percent of individualised with hyposalivation frequently suffer from cold extremities and 65% of patients with periodontitis feel cold soon. One hundred percent of patients with periodontitis feel frequently vertiginous and 100% of individuals feel it at least sometimes. One hundred of individuals with hyposalivation have/had earlier low blood pressure and 100% of them noted altered sleep patterns. Ninety percent of individuals with hyposalivation suffer from headache and almost all of them receive a migrainous attack with accompanying symptoms. One hundred percent of patients with periodontitis suffer from pain and tinnitus and all of them note altered drug sensitivity and skin blotches under stress conditions; all of them are perfectionists and recognise smell very strongly.

5.2 FS Signs and Symptoms in Individuals with Delayed and Impaired Healing Process

Amongst all three groups of comparison, specifically in the target group (hyposalivation) and patients with periodontitis we have identified a significant number of persons who reported delayed or even impaired healing on themselves (see self-reports for "Case 1" and "Case 2" provided above). This question has been included additionally to the 15-item FS-questionnaire. Due to a relatively low number of the identified persons, currently we do not provide any statistical evaluation. However, our preliminary observations of individuals with self-reported delayed and impaired healing process indicate their highly pronounced FS-phenotype. The most indicative prevalence of the FS symptoms is for altogether 12 items: 2, 4, 6, 7, 8, 9, 10, 11, 13, 14 and 15. Similarly to individuals with hyposalivation, individuals of this subgroup feel cold soon and vertiginous, they suffer from increased pain sensitivity and frequent headache/migraine with accompanying symptoms. The majority of them don't feel thirty. All of them note altered drug sensitivity and very strong sense of smell. All of them estimate their attitude as being perfectionistic. Frequently they suffer from tinnitus and observe skin blotches under stress conditions.

6 Concluding Remarks and Expert Recommendations

Chronic hyposalivation – "dry mouth" syndrome (xerostomia) is a major risk factor of strongly compromised life quality and oral disorders such as dental erosion, caries and periodontal diseases, which, if neglected, may contribute or even provoke a cascade of follow-up pathologies including systemic inflammatory process and cancer. Moreover, the prevalence of xerostomia in the general population is remarkably

high comprising up to 46% of female and up to 26% of male subpopulations [28]. Therefore, it is astonishing how little attention is paid by caregivers to this health condition, particularly in young populations, where targeted prevention is highly cost-effective. Specifically predictive diagnostics is strongly underdeveloped for individuals with "dry mouth" syndrome. To our best knowledge our publications to the topic are the very first ones aiming at the precise phenotyping of the "dry mouth" syndrome individuals. Knowing the phenotype with specific symptoms and signs is crucial for creating innovative screening programmes, patient stratification, predictive diagnosis and targeted prevention. In our study we hypothesised the relevance of the Flammer syndrome phenotype for the prevalent manifestation of the "dry mouth" syndrome based on the data published earlier [23, 27]. Indeed, on the one hand, primary vascular dysregulation, altered stress reactions, perfectionism, altered sense regulation (such as reduced feeling of thirst), and evident similarities to the Sjögren's syndrome are characteristic for the Flammer syndrome individuals [23]. On the other hand, manifested Sjögren's syndrome, chronic stress (e.g. due to obsessional personality) and, eating disorders (such as perpetual dieting and anorexia nervosa), and insufficient liquid intake – individually and/or synergistically have been demonstrated to reduce salivary flow and to alter the salivary composition [9, 10, 29]. Contextually, results of the presented study clearly confirm the relevance of the FS-phenotype for the manifestation of xerostomia and – against the control group – high prevalence of the specific FS symptoms in "dry mouth" syndrome individuals and patients with periodontal disease as analysed above. Although the pilot character of the study should be mentioned as a limitation considering a small number of participants included and involvement of only one medical centre which has recruited individuals and patients for the presented study.

6.1 What Are the Next Steps Recommended?

FS-questionnaire is strongly recommended for its application by general practitioners (family doctors) to select individuals at high risk; consequently, targeted preventive measures can be triggered early in life (e.g. at teenager age). TCAM (traditional, complementary and alternative medicine) such as acupuncture (by releasing vasodilating neuropeptides and improving microcirculation, activating salivary glands, amongst others) [30, 31] and "Qigong" exercise programme – both demonstrate positive effects in individuals with hyposalivation and xerostomia [32]. For in-depth diagnostics, certainly a specific epi/genetic regulation involved into pathophysiologic mechanisms of hyposalivation in FS-affected individuals should be investigated at molecular level. Hence, an altered regulation of the hyposalivation-relevant pathways has been demonstrated for some pathologic conditions such as hypertension [33]. Further, "multi-omics" might be the first choice for constructing advanced diagnostic tools specifically utilising liquid biopsies as well justified by the most recent literature [3], and an innovative "machine learning" approach should be considered for the multi-parametric analysis, development of the

clinically relevant models and accurate patient stratification [34]. Corresponding biomarker-panels might get selected for the patient stratification, predictive diagnostics and targeted prevention. Predictive services might be then offered considering several potential diagnoses: development of disorders of the oral cavity and digestive tract, chronic inflammation such as tonsillitis mentioned in the above listed patient cases, cancer predisposition etc. An individual level of the disease severity can be adequately estimated, once specific biomarker-panels are ready for their routine application. More information regarding potential health risks by body dehydration in FS-affected individuals is provided in the book chapters "Specific Symptoms of Flammer Syndrome in Women Suffering from Vaginal Dryness: Individualised Patient Profiles, Risks and Mitigating Measures" by Vadym Goncharenko with co-authors, ""Young Stroke" Risks Potentially Linked to the Flammer Syndrome Phenotype: Facts and Hypotheses" by Jiri Polivka Jr. and co-authors, "Feeling Cold and Other Underestimated Symptoms of Flammer Syndrome in Breast Cancer Diagnostics: Is Innovative Screening on the Horizon?" by Olga Golubnitschaja with co-authors.

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Specific Symptoms of Flammer Syndrome in Women Suffering from Vaginal Dryness: Individualised Patient Profiles, Risks and Mitigating Measures

International Multi-centre Study

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Abstract Vaginal dryness (VD) affects both pre- and postmenopausal women at any age. Since the hormonal changes during the climacteric period are considered as being the main course of the VD, affected women prefer not to talk about the problem. However, the problem does exist, and unfortunately if any, relatively minor group in the population possesses the health literacy at sufficient level to understand that VD is a suboptimal health condition which carries a multi-factorial character. Thereby, some of the contributing factors are clearly preventable and, therefore, if treated properly, have a potential to milden the VD. Current chapter demonstrates specific signs and symptoms of Flammer Syndrome (FS) in women suffering from vaginal dryness, although individualised patient profiles clearly discriminate between pre- and postmenopausal women regarding the subgroup-specific symptoms. Noteworthy, about 20% of

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the VD patients involved in the study notify a delayed or even impaired wound healing self-reported over a couple of years.

Optimising modifiable risk factors accompanying FS phenotype at the level of primary prevention is strongly recommended. Individualised patient profiles provide important information for VD mitigating measures tailored to the person. Further, future projects should essentially deal with the complexity of vulvar-vaginal dryness as the part of the Sicca Syndrome in individuals with FS phenotype, in order to prevent genital female cancers which occur at any age. In contrast to the human papilloma virus as possible trigger of the disease, the role of the vulvar-vaginal dryness as an important risk factor is strongly underestimated in currently applied diagnostic and treatment approaches.

Keywords Flammer syndrome · Vaginal dryness · Vaginal dysfunction · Vasoconstriction · Dehydration · Sicca syndrome · Stress · Altered sense regulation · Blood pressure · Menopause · Hormonal regulation · Microbiome · Pain · Sexual intercourse · Headache · Psychological aspects · Life quality · Dyspareunia · Vulva cancer

1 Vaginal Dryness Is a Problem Which Women Reluctantly Speak About: What Is Behind the Issue?

Vaginal dryness (VD) affects both pre- and postmenopausal women at any age. Since the hormonal changes during the climacteric period is considered as being the main course of the VD, affected women prefer not to talk about the problem. However, the problem does exist, and unfortunately if any, relatively minor group in the population possesses the health literacy at sufficient level to understand that VD is a suboptimal health condition which carries a multi-factorial character. Furthermore, some of the contributing factors are clearly preventable, the mitigation of which therefore has a potential to milden the VD manifestation.

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2 VD Is a Widespread Problem Negatively Impacting the Life Quality

2.1 Some Statistics

According to several population studies, more than 50% of post-menopausal women aged over 51 years suffer from mild or severe VD related to specific changes in hormonal regulation linked to the decreasing level of oestrogen. On the other hand, it is also true that around 17% of premenopausal women aged 17–50 years do experience problems with a sexual intercourse, due to vaginal dryness and painful sex [1].

2.2 Diagnosis

Usual symptoms of the VD are skin irritation, burning, itching and/or simply discomfort in the area – all primarily of non-bacterial origin that should be determined by gynaecologist.

2.3 Severe Consequences

Painful intercourse strongly contributes to the lost sexual desire. Dyspareunia and anxiety towards regular sexual intercourse are severe consequences negatively impacting the life quality of the affected females and couples [2, 3]. Further, severe VD strongly influence daily life of the affected individuals by causing uncomfortable or even painful sit, stand, sport and exercise etc. [4] Finally, dry vaginal tissue in a long-term is strongly predisposed to frequent infections affecting and diminishing physiologic functioning of the urogenital tract. Therefore, normal vaginal lubrication, acidic vaginal pH and normal vaginal microbiome are the life-important physiologic conditions which effectively help defending against permanent attacks by pathologic microbial contamination. Contextually, VD is associated with significant microbiome alterations demonstrating low abundance of *Lactobacillus* which is an important component of healthy vaginal microbiome [5].

3 Known VD Triggers and Contributors

Main contributors known triggering VD and worsening the condition are summarised below. Amongst them, the best acknowledged is the hormonal down regulation of oestrogen; all other factors are strong contributors which, however, are much less investigated.

3.1 Hormonal Regulation Changes

Hormonal regulation changes by low and/or decreasing level of oestrogen usually occurs in peri- and post-menopause but also during breastfeeding – both are physiologic processes.

Menopausal symptoms including VD may result also from non-physiologic events such as intensive vaginal douching, cigarette smoking, cold medications, surgical removal of the ovaries, anti-oestrogen medication (e.g. to treat endometriosis and uterine fibroids), application of some anti-depressants (e.g. tricyclic ones) as well as irradiation and chemotherapy implemented to cancer patients.

Finally, several relevant pathologic conditions may lead to onset of VD such as immune system related disorders (allergies and Sjögren Syndrome) [6] and application of antihistamines, as well as premature ovarian insufficiency (e.g. due to accelerated ageing) [7] and diabetes, amongst others.

3.2 Dehydration

Sufficient liquid intake is essential for the proper vaginal lubrication [8]. The whole body dehydration may strongly contribute to the Sicca syndrome including VD and headache, amongst others [9]. Artificial lubrication with the vaginal moisturising gels is one of the most effective treatments against vaginal dryness.

3.3 Excessive Vasoconstriction

Some studies have demonstrated that a lack of lubrication may be caused by significantly decreased blood flow to the vaginal walls demonstrated particularly due to excessive primary vascular dysregulation, secondary vasoconstriction (e.g. due to cancer treatment), ageing, abnormal metabolism related pathologies such as diabetes, and changes in vaginal innervation also augmenting vasoconstriction and promoting vaginal dryness [10].

3.4 Psychologic Factors and Stress Overload

Psychologic factors play an important role in VD development and secondary complications [11]. For example, it is evident that not enough foreplay before sex frequently causes VD in both – pre- and post-menopausal women. Further, significant stress overload and anxiety negatively impacts both – libido and vaginal lubrication [2, 3].

4 Hypothesised Relationship Between Flammer Syndrome and VD

The above summarised facts strongly support the hypothesis that both pre- and postmenopausal women demonstrating Flammer Syndrome phenotype may be strongly predisposed to vaginal dryness. In particular,

- On the one hand, excessive vasoconstriction plays the central role in expression of the FS phenotype and, on the other hand, strongly contributes to the VD onset;
- Specific psychological aspects are characteristic for FS such as meticulous personality and tendency to perfectionism that can result in significant stress overload demonstrated as a strong contributor to the VD development;
- An altered sensation regulation is typical for the FS affected individuals such as strongly reduced feeling of thirst, amongst others; in this condition, if the sufficient liquid intake is not well controlled, it may lead to significant body dehydration and consequent Sicca syndrome including VD manifestation [6, 7, 9, 12].

5 Results of the Pilot Study

Specialised questionnaire presented in the previous chapters utilising signs and symptoms characteristic for Flammer Syndrome has been used in our recent multicentre study to investigate, whether women suffering from VD demonstrate some specific features of the FS-phenotype. Further, VD patients recruited in the study have been stratified in subgroups according to their menopausal status to answer the questions, whether the VD contributing factors are similar for or differ between pre- and postmenopausal patients. The most significant differences between the subgroups as well as between VD patients and healthy controls are summarised in Fig. 1. Noteworthy, about 20% of the VD patients involved in the study notify a delayed or even impaired wound healing self-reported over a couple of years. More information regarding impaired healing processes is provided in the book chapter "Flammer Syndrome in the Context of Healing Impairments – Facts and Hypotheses for Multi-professional Consideration" by Eden Avishai and Olga Golubnitschaja.

6 Conclusions and Expert Recommendations

The results of the pilot study strongly support the hypothesis that both pre- and postmenopausal women suffering from vaginal dryness more frequently demonstrate symptoms and signs characteristic for the FS phenotype than VD-free controls. The most significant differences are presented in Fig. 1 and concluded below.

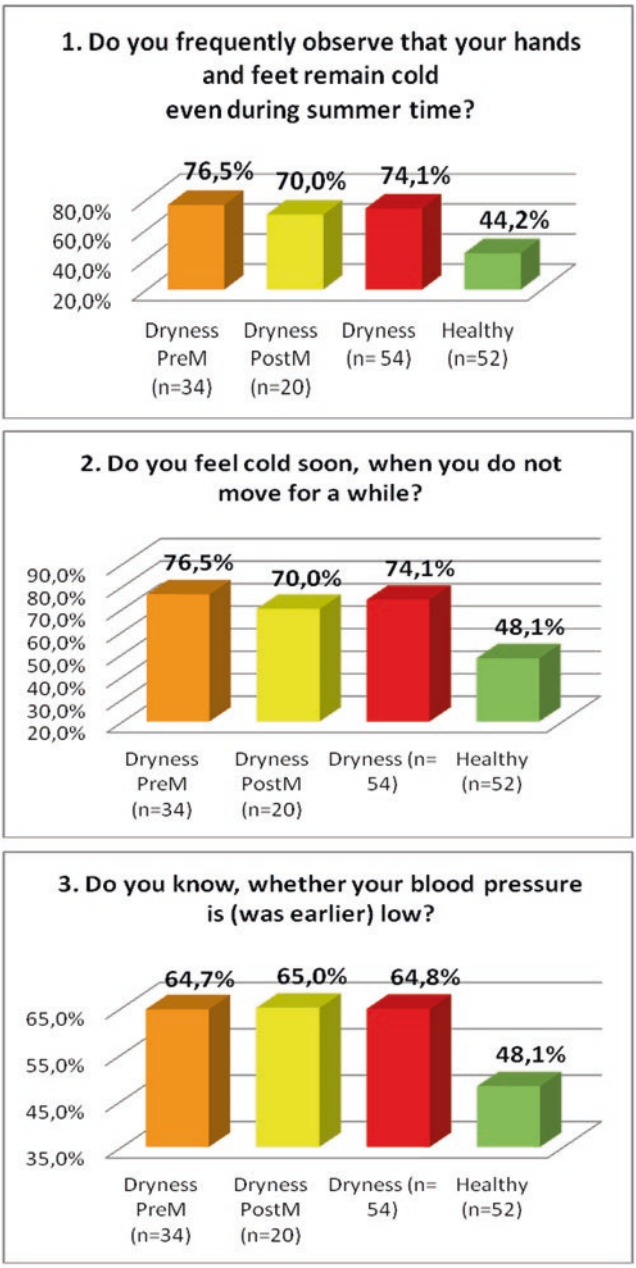

Fig. 1 Most significant differences between VD patients and healthy controls are demonstrated presenting positive answers considering individuals signs and symptoms characteristic for the FS-phenotype; "PreM" = premenopausal and "PostM" = postmenopausal VD patients; "Dryness" combines both subgroups; "Healthy" = control group; Statistical significance (P-value $\leq$0,05) has been demonstrated for symptoms 1, 2, 6, 7; Specifically to the question 6, the answer "I do not feel thirsty" is displayed

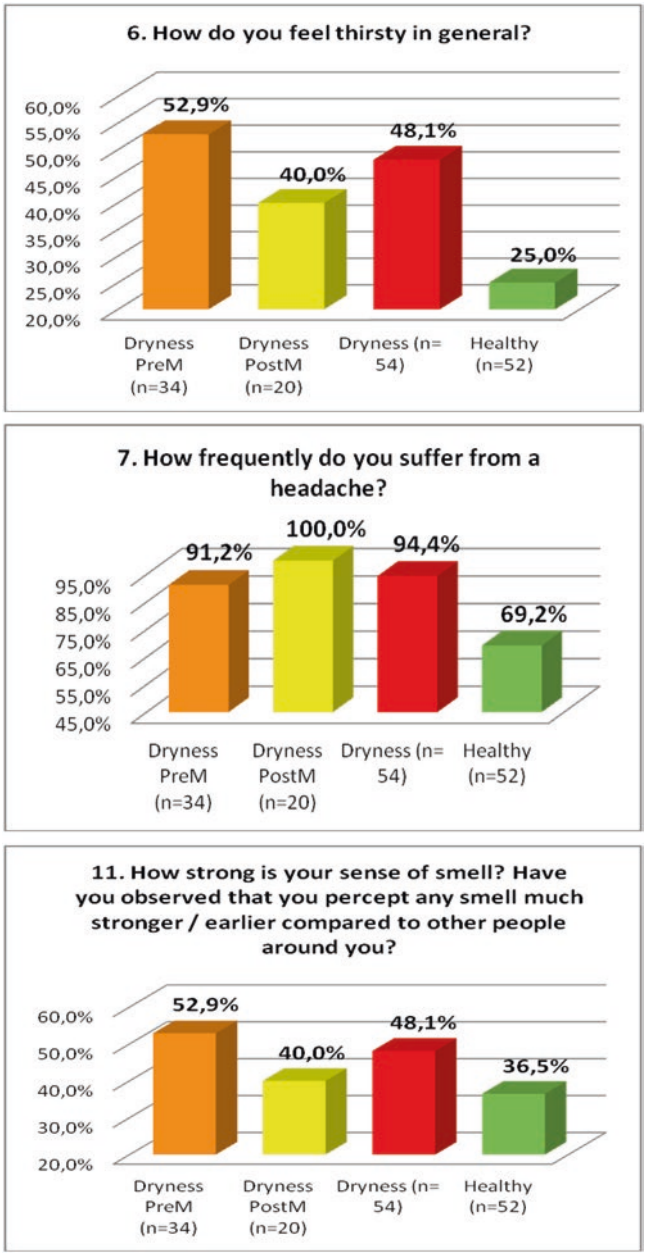

Fig. 1 (continued)

6.1 FS Symptoms and Signs with Similar Profiles for Both Pre- and Postmenopausal VD Patients

- Major role of the vascular component by excessive vasoconstriction (symptoms 1 and 2)
- Low blood pressure (symptom 3)
- Altered sense regulation such as smell perception (symptom 11); in particular, decreased perception of thirst (symptom 6) may play an important role leading to insufficient liquid intake and body dehydration that is strongly support by another FS-symptom 7, namely much more frequent headache in VD patients compared to the control group. To this end, frequent headache has been demonstrated as one of the typical symptoms of the body dehydration.
- Although being statistically non-significant, following FS-symptoms have been demonstrated as more prevalent in VD patients than in controls: dizziness, altered sleep-patters, increased drug-sensitivity, slim body shape, and tinnitus.

6.2 Menopausal Specific Difference in FS-Related Profiles

- No feeling of thirsty is more strongly pronounced in pre-menopausal VD patients
- Also smell perception is stronger in pre-menopausal VD patients
- Vasoconstriction is more pronounced in pre-menopausal VD patients
- In contrast, longer sleep onset is reported by post-menopausal VD patients who also to 100% suffer from frequent headache and more frequently report on accompanying symptoms such as an impaired vision and deafness appeared in the extremities
- Painkillers are taken more frequently by post-menopausal VD patients who also more frequently report on low BMI in early adulthood than pre-menopausal VD patients
- Tinnitus is more frequent in pre-menopausal VD patients than in postmenopausal counterpart.

6.3 Most Frequent Combination of the FS-Symptoms in Premenopausal VD Patients

- Excessive vasoconstriction
- Feeling cold soon
- Low blood pressure
- Dizziness
- Strongly reduced thirst perception
- Headache

- Strong smell perception
- Perfectionistic personality
- Tinnitus

6.4 Most Frequent Combination of the FS-Symptoms in Postmenopausal VD Patients

- Excessive vasoconstriction
- Feeling cold soon
- Low blood pressure
- Dizziness
- Prolonged sleep onset
- Headache and migraine with accompanying symptoms
- Pain
- Low BMI in early adulthood

6.5 Recommendations

Optimising modifiable risk factors at the level of VD primary prevention is strongly recommended. To this end, the above presented profiles provide a lot of information for the targeted prevention. Corresponding measures should be tailored to the individual as discussed in other chapters as well. However, general measures consider regulation of vaginal pH and microbiota depending on the hormonal status, microbial composition and the phase of menstrual cycle. Regarding the microbial composition, dietary interventions may be suggested supporting the primary colonisation by Lactobacilli to the vaginal microbiota [13].

Finally, future projects should essentially deal also with vulvar-vaginal dryness as part of the Sicca Syndrome in females with FS phenotype predisposed to lichen sclerosus of vulva (LSV). LSV demonstrates clear symptoms of the tissue dryness (skin sensitivity and irritation, burning, itching, pain etc.) and step-by-step leads to vulvar atrophy, fibrosis and dysplasia that may result in a manifestation of the vulvar carcinoma, if not effectively treated well in time. To this end, in the USA, women have a 1 in 333 chance of developing vulvar cancer at some point during their life. The American Cancer Society reports on about 6190 cancers of the vulva in the USA in 2018, and about 1200 women die of this cancer [14]. In contrast to the human papilloma virus as possible trigger of the disease, the role of the vulvar dryness as an important risk factor is strongly underestimated in currently applied diagnostics and treatment standards.

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Relevance of Flammer Syndrome to the "Sleep-Wake" Rhythm: Possible Mechanisms, Risks and Preventive Strategies

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Abstract Sleep and chronobiology have decisive effects on human health and disease status. Chronobiology is relatively recently recognised as a prominent scientific area, particularly as in 2017 three American researchers received the Nobel Prize for their discoveries on molecular mechanisms behind the internal clocks and biological rhythms that govern human lifes. Genetic make-up responsible for the self-sustaining clockwork inside the cell regulating fundamental functions such as behaviour, hormone levels, sleep, body temperature and metabolism has been discovered. Research data demonstrate that sleep is connected to cell regeneration, detoxification of the body, memory consolidation, and psychological recovery. Consequently, being in a state of sleep deficit can be dangerous; short sleep duration correlates with increased risk of cardiovascular and metabolic diseases, and untreated insomnia can lead to severe depression. Many people think that if they sleep less, they can work more. But the truth is that self-induced short sleep leads to impaired work ability.

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Car accidents, work accidents, as well as impaired concentration - all may result from the sleep deprivation. Pathomechanisms of severe neurological disorders have been demonstrated as being connected to impaired sleep patterns. Noteworthy, highly increased mortality, due to accidents generally, car accidents in particular, sleep disorders, depression and neurodegenerative impairments have been recorded specifically for individuals with low BMI (see the introductory chapter "Flammer Syndrome in the Global Context – The "U-Shape" of Health Risks").

This chapter highlights mechanisms of the sleep patterns alteration characteristic for the FS affected individuals, discusses a potential link between the long-term consequences and increased risks of exemplified pathologies and provides expert recommendation for effective PPPM strategies applied to sleep medicine.

Keywords Flammer syndrome · Phenotype · Primary vascular dysregulation · Sleep latency · Chronotype patterns · Insomnia · Circadian rhythm · Thermal regulation · Vasoconstriction · Risks · Shift work · Mechanisms · Associated pathology · Metastatic breast cancer · Preventive strategies · Predictive preventive personalised medicine · Sleep medicine

Abbreviations

PVD	primary vascular dysregulation
TDCE	thermal discomfort from cold extremities
DLMO	Dim Light Onset Melatonin
SCN	suprachiasmatic nucleus
NTG	normal tension Glaucoma
BMI	body mass index
FS	Flammer Syndrome

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1 Flammer Syndrome Individuals Demonstrate Altered Sleep Patterns – Possible Link to Manifestation of Related Pathologies?

Patients with Flammer syndrome suffer from primary vascular dysregulation (PVD), referring to irregular constriction of blood vessels, mainly in the microcirculation [1]. Flammer syndrome (FS) is relevant for thermal discomfort from cold extremities (TDCE), normal tension glaucoma, low blood pressure, variant angina, myocardial infarction without arteriosclerotic lesions, tinnitus, migraine, headaches, reduced feeling of thirst, increased sensitivity to smells and pain, altered drug sensitivity, amongst others [1–3]. Typical sleep disturbances in persons with Flammer Syndrome are prolonged sleep latency and difficulties initiating sleep. Populations with prevalent Flammer syndrome include females and Asians [1, 3]. FS symptoms in females are connected to oestrogen levels and typically change during puberty and menopause [4].

It is important to note that FS is not a disease and does not require treatment per se. However, some of its possible consequences, such as NTG or (too) low BMI, may require an intervention. This also true for the sleep compliant which is a common part of Flammer syndrome's multimodal clinical picture: prolonged sleep latency and sleep initiation (insomnia) [3]. Changes in distal vasodilatation play an important role in regulating core body temperature, which is in turn a key process in the human circadian rhythm, including sleep initiation [5]. The endogenous circadian pacemaker in the suprachiasmatic nucleus (SCN) is entrained to a 24-h cycle and activates heating mechanisms in the body in the morning hours, as well as cooling mechanisms, such as increased distal vasodilatation, in the evening [6]. Disharmonisation between the endogenous circadian rhythm and core body temperature can cause a very specific sensations such as feeling inappropriately cold that has been described in the literature as, on the one hand, frequently observed in otherwise healthy persons with Flammer Syndrome phenotype, and, one the other hand, in some specific patient cohorts such as breast cancer diagnosed patients [7]. Maintaining thermal comfort needs well-organised energy supply by concentrated mitochondrial cooperation at molecular and cellular levels: a dysfunction of the mitochondrial respiratory chain is assumed in FS-affected individuals and has been clearly demonstrated in breast cancer patients as recently reviewed [7]. Further, specifically breast cancer patients with aggressive metastatic disease demonstrate more frequently the FS phenotype and its characteristic symptoms including disturbed microcirculation (cold extremities) as well as altered and disturbed sleep patterns [8]. More information to the topic is provided in the book chapter "Feeling Cold and Other Underestimated Symptoms of Flammer Syndrome in Breast Cancer Diagnostics: Is Innovative Screening on the Horizon?" by Olga Golubnitschaja with co-authors.

This chapter highlights the mechanisms of the sleep patterns alteration in FS affected individuals, discusses a potential link between the long-term consequences and increased risks for exemplified pathologies, and provides expert recommendation for effective PPPM strategies applied to sleep medicine.

2 Prolonged Sleep Latency: What Is Behind the Issue?

Disturbed temperature regulation is strongly linked to the sleep initiation and insomnia [9]; insomnia occurs in about 10% of the general population, affecting women more often than men [10]. The main symptoms of insomnia are prolonged sleep latency, frequent awakening with difficulties to fall asleep, as well as disturbed daytime functioning [11].

Pathophysiologically, insomnia is strongly correlated with cognitive, emotional and physiological hyperarousal with enhanced activity of the sympathetic nervous system at night [12]. This is opposed to the normal circadian rhythmic with parasympathetic activity at night and sympathetic activity at the day time indicating that the circadian rhythm of the autonomic nervous system is disturbed in insomnia. Circadian variations of the sympathetic activity can be associated with increased arterial vascular tone and cause prolonged sleep latency in patients with vascular spasms [13]. Interestingly, the SCN controls not only the regulation of the core body temperature, but also parts of the autonomic nervous system [14] suggesting a deep link between the two mechanisms.

The prevalence rates of thermal discomfort from cold extremities and disturbed sleep of women and men was investigated in a random sample of 2800 Swiss men and women aged 20–40 years. Nearly every third woman exhibited thermal discomfort from cold extremities, whereas men were suffering 4.5 times less frequently [1, 9].

The discrepancy between the habitual sleep-wake cycle and the circadian rhythm was further investigated by Gompper and colleagues [15]. In this study, women with vascular dysregulation and sleep disturbance showed delayed changes in foot skin temperature compared to controls. However, the groups did not differ regarding their sleep-wake cycle measured by actometry. The authors conclude that women with vascular disturbance exhibit a phase delay of distal vasodilatation with respect to their habitual sleep-wake cycle and other circadian phase markers such as DLMO.

In accordance with these findings, the thermophysiological state of body heat conservation (i.e. cold hands and feet) seems to be significantly associated with prolonged SOL in the general population [9]. Every seventh person with TDCE may suffer from disturbed sleep. The authors recommend chronobiological interventions, such as warming up the extremities before going to sleep and phase advancing of the circadian system by morning light or phase delaying of the sleep–wake cycle.

Women with vascular disturbance exhibit reduced parasympathetic activity and increased sympathovagal balance, as derived from heart rate variation spectral analyses [16], which could be responsible for distal vasoconstriction [15].

Women with vascular regulation disturbance tend to stay in bed longer after awakening and suffer from tiredness connected with a longer duration of the distal vasoconstriction in the morning. This sleepiness usually dissipates over the course of the day and is less pronounced in the evening [17]. This finding is in accordance with studies showing a close relationship between the circadian rhythm of sleepiness and distal vasodilatation [18].

3 Sleep Initiation Mechanisms and FS Symptoms

In people with primary vascular dysregulation, at least five risk factors functionally linked to circadian rhythms play a role in the altered initiation of sleep and seem to be insufficiently synchronized: sympathetic activity, core body temperature, vasodilatation/vasospasm, melatonin secretion, and the level of motoric activity.

Pache and colleagues [1], compared subjective sleep ratings and sleep latency of 32 participants with vasospasm against 30 controls. In the vasospasm-group higher rates of subjectively impaired sleep quality were observed (55% vs. 23%); sleep onset latency was significantly prolonged, not only at the beginning of the sleep period, but also after a nocturnal awakening. While 63% of the people with vasospasm named cold feet as the reason for sleep onset difficulties, whereas no one in the control group noted this item. The authors' explanation for prolonged sleep-onset latency in persons with vasospasm was that the habitual time for going to bed is too early in relation to their endogenous circadian rhythm phase and assume disturbance of the circadian rhythm involvement.

Peripheral vasoconstriction depends not only on circadian rhythms, but also on food intake and individual stress sensitivity. Light may also play important role in the regulation of the peripheral skin temperature and the secretion of melatonin [19].

Additional studies on preventive and therapeutic interventions for vascular dysregulation and associated prolonged sleep latency and disturbed sleep-wake rhythm are needed. Possible strategies include light therapy, warm socks/clothes, and relaxation techniques.

Sleepiness in the morning and alertness in the evening indicate the tendency to the evening chronotype in Flammer syndrome phenotype. Therefore, future studies should investigate the impact of the chronotype on the circadian rhythm of the peripheral vasospasm and therapeutic interventions on the circadian sleep rhythm including light therapy.

4 PPPM Strategies in the Overall Management of Sleep Disorders

Sleep and chronobiology have decisive effects on human health and disease status. Chronobiology is relatively recently recognised as a prominent scientific area, particularly as in 2017 three American researchers received the Nobel Prize for their discoveries on molecular mechanisms behind the internal clocks and biological rhythms that govern human lifes. Genetic make-up responsible for the self-sustaining clockwork inside the cell regulating fundamental functions such as behaviour, hormone levels, sleep, body temperature and metabolism has been discovered. Research data demonstrate that sleep is connected to cell regeneration, detoxification of the body, memory consolidation, and psychological recovery. Consequently, being in a state of sleep deficit can be dangerous; short sleep duration

correlates with increased risk of cardiovascular and metabolic diseases, and untreated insomnia can lead to severe depression. Many people think that if they sleep less, they can work more. But the truth is that self-induced short sleep leads to impaired work ability. Car accidents, work accidents, as well as impaired concentration - all may result from the sleep deprivation. Moreover, the pathomechanisms of severe neurological disorders such as these of Alzheimer's disease are connected to impaired sleep patterns [20]. Noteworthy, highly increased mortality, due to accidents in generally, transport-related, not transport-related, self-harm related, mental, behavioural and neurological issues have been recorded specifically for individuals with low BMI [21] – see more information in the introductory chapter "Flammer Syndrome in the Global Context – The "U-Shape" of Health Risks".

5 Shift Work and Chronobiology

The chronobiological research shows the importance of the connection between chronotype and shift work: early chronobiological types work better in early shifts, whereas late types tolerate late and night shifts better [22]. Excessive fatigue and sleep disturbances caused by shift work can lead to reduced work performance, processing errors and accidents at work. Sleep disturbances among shift workers can cause absenteeism, reduced quality of life, whereas depression and rotating shifts can be a risk factor of different somatic and psychiatric diseases such as cardiovascular, gastro-intestinal, metabolic, reproductive and malignant diseases. To this end, the interrelations between shifted circadian rhythms, impaired healing processes, cancer predisposition, and Flammer syndrome phenotype are highlighted in the book chapter "Flammer Syndrome in the Context of Healing Impairments – Facts and Hypotheses for Multi-professional Consideration" by Eden Avishai and Olga Golubnitschaja. Sleep strategy, chronotype and genotype contribute to the adaptation of the circadian system to an environment that switches frequently and/or irregularly between different schedules of the light-dark cycle and social/workplace time. Seeing as many key shareholders in healthcare such as nurses and physicians but also other professionals such as police officers who often are shift workers, these findings could have important implications for healthcare and preventive medicine. The decision to choose a job according to chronotype is personalised and should be made at early age with the aim to prevent severe psychiatric and somatic diseases caused by misalignment between the internal clock of the body and external working and living conditions. Genetic analysis, family anamnesis for certain diseases such as breast cancer and chronotype are crucial in the decision-making process on working over the day only or as a shift worker [23]. Parents, health insurances, education institutions, and young people themselves should use knowledge available on the matter to support the decision-making process by looking for an optimal career-path to be made in a good health condition over the entire lifespan.

There are general recommendations for some coping strategies against sleep disorders associated with shift work, such as napping and exposure to bright light. Still, more evidence is needed for the personalised approach towards chronic primary and co-morbid insomnia in shift workers using cognitive-behavioural techniques. These individual and personalised coping strategies based on the sleep habits of the shift worker should be considered in workplace health promotion programmes of each work environment [24, 25].

6 Predictive, Preventive and Personalised Approaches in Insomnia

Sleep disorders are very frequent, and insomnia affects 10–15% of the general population [10, 26]. Risk groups for insomnia include women of all ages and especially people working in rotating shifts. Typical symptoms of insomnia consist of difficulties falling asleep at night, frequent waking during the night, early waking up being unable to get back to sleep, feeling insufficiently refreshed after sleeping, and fatigue during the day.

3P Model of Insomnia
Spielman [27] described three groups of factors responsible for the development of insomnia:

Predisposition factors that place specific groups at risk of sleep disorders (gender, age, other vulnerabilities),
Precipitating factors that can trigger the onset of sleep disorders (critical live events, puberty, perimenopause) and
Perpetuating factors that contribute to the vicious cycle of insomnia (bad sleep habits such as spending too much time in bed, going to bed too early, continuously checking the clock at night) [27].

This **3P** Model of insomnia can be coped with the **PPP** approach (Predictive, Preventive, Personalised):

Predictive – Predisposing: predicting risk of insomnia by considering predisposing factors
Preventive – Precipitating: prevention of insomnia by regarding possible precipitating factors
Personalized – Perpetuating: implementing individualised cognitive behavioural short therapy.

Consequently, the PPP approach can recommend:

Prediction of Insomnia
Genetics, chronotype, age, gender, sleep habits and personality characteristics.

Prevention of Insomnia
Sleep education for school children, adolescents, shift workers, nursing mothers, and entire working and elderly population.

Personalised Approach to Insomnia
Analysing and recording sleep habits and risk factors of individuals including the determination of the chronotype can lead to person-centered sleep profile of the affected individual. Recent innovations in the field of tele medicine can enable 24 h-recordings of movement, heart rate, heart rate variability, skin temperature, and skin resistance, enabling personalised profiles of the sleep-wake cycle and of the stress burden of every person.

This data can be used for a tailored approach to the improvement of sleep and stress coping strategies.

Education adapted to the PPP approach in sleep medicine should be implemented in schools, companies, hospitals, as well as retirement homes, with the aim to improve prediction, prevention and personalised treatment of sleep disorders.

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Flammer Syndrome and Autoimmune Inflammatory Conditions of the Central Nervous System: Multifactorial Interrelations

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Abstract Multiple sclerosis (MS) is the most frequent autoimmune inflammatory and neurodegenerative central nervous system disorder that affects mostly young females and manifests with transient or irreversible neurologic dysfunction caused by demyelination and subsequent axonal transection and neuronal demise. Besides genetic susceptibility, environmental risk factors play a causative role. Although the exact immunopathogenesis has not been fully clarified, the condition is – albeit incurable – amenable to treatment with immunomodulatory drugs. Structural and functional changes in the brain and retinal vasculature in MS causing cerebral hypoperfusion may be a potential pathophysiological link with Flammer Syndrome (FS). However, only one study thus far has systematically investigated the co-occurrence of MS and FS and has shown that multiple symptoms and signs considered as characteristic of FS occur more often in MS patients than in unselected controls. While there is some overlap in symptomatology and clinical findings between the 2 conditions, this does not imply causality, but this preliminary observation should trigger more research on pathophysiological commonalities and clinical course of patients who are eventually diagnosed with both disorders. Susac Syndrome (SuS) is a very rare presumably immune mediated central nervous system disease that affects microvessels in the brain, the retina and the inner ear. This may cause secondary vascular dysregulation and thus signs and symptoms of FS, while it was also proposed that FS may predispose to SuS. However, as in MS assumptions on a potential association of SuS with FS are still poorly supported by rigorous data.

Keywords Multiple sclerosis · Flammer syndrome · Neuroinflammation · Autoimmunity · Demyelination · Neurodegeneration · Vasculature · Perfusion · Vascular dysregulation · Personalized and predictive medicine

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1 Introduction

Data on the co-occurrence or association of Flammer Syndrome (FS) with autoimmune inflammatory diseases of the central nervous system is scant. However, as there may be some overlap in clinical presentation and pathophysiological commonalities between FS and inflammatory autoimmune CNS disorders, further research in this field is warranted. This chapter briefly summarizes key clinical features and pathogenetic hallmarks of multiple sclerosis (MS) and Susac Syndrome (SuS) and their potential association with FS, both from a clinical and a pathophysiological perspective.

2 Multiple Sclerosis (MS)

2.1 Epidemiology and Symptomatology

Multiple sclerosis (MS) is a chronic autoimmune inflammatory and neurodegenerative disease of the central nervous system (CNS), affecting the brain, optic nerve, and spinal cord. More than two million people worldwide suffer from this incurable condition [1], most of them (approximately 70%) young females in childbearing age [2, 3], rendering MS the most prevalent chronic inflammatory CNS disease [1]. Patients diagnosed with MS complain of burdensome and often disabling symptoms such as visual impairment, motor weakness, sensory disturbances, gait and coordination problems, bowel and bladder dysfunction, but also of depression, fatigue, cognitive dysfunction, pain and poor sleep [1, 4–11]. In most (80–90%) affected persons MS follows a relapsing or relapsing-remitting (RRMS) disease course with bouts of fully or partially reversible neurological deficits with a duration of several days to weeks [12]. Typical and frequent presentations are amongst others optic neuritis with eye pain and vision loss, oculomotor abnormalities or ataxia due to brain-stem or cerebellar affection, or transverse myelitis with limb weakness, sensory disturbances (sometimes with a sensory niveau), and bladder or bowel dysfunction. Many of these patients with an initial RRMS disease course convert to a secondary progressive disease course (SPMS) with or without superimposed relapses after a variable disease duration of approximately 10–30 years [12]. In these, impaired ambulation and cognitive dysfunction are among the most salient features. 10–15% of patients follow a primary progressive disease course (PPMS) with insidious accumulation of neurological disability from disease onset, mostly with impaired ambulation.

2.2 Etiology and Risk Factors of MS

The cause of MS is unknown. No single trigger or causative factor has been identified, while individual disease susceptibility is presumably determined by multiple genetic and environmental risk factors. More than 200 gene variants increasing the MS risk have been identified by genome wide association studies [1]. The most relevant variant is the HLA DRB1*1501 with an odds ratio of approximately 3. The risk of MS in people with an affected first-degree relative is between 2 and 4% in comparison to 0.1% in the general population. Environmental risk factors comprise infection with the Epstein-Barr-Virus (EBV) or infectious mononucleosis in postpuberal adolescents and young adults, latitude (higher risk with increasing latitude and in temperate climates), vitamin D deficiency (linked to sunlight exposure and thus the latitude gradient), diet and obesity, and tobacco exposure [1, 13–21].

2.3 Neuropathological Features

The neuropathological manifestation of MS is characterized by focal and disseminated demyelinating lesions ("plaques") predominantly in the white matter of the brain (with a predilection for the periventricular area, the corpus callosum, the inferior temporal lobe, the brainstem and the cerebellum), the optic nerve and the spinal cord. The majority of these white matter lesions is located around a small cerebral vein [22, 23] which suggests some pathogenetic association of lesion formation with the cerebral vasculature. Different pathologic patterns have been described in active MS lesions, some of which display mononuclear phagocytes and perivascular and parenchymal T cell infiltration, while others (additionally) show prominent immunoglobulin and complement deposition [1]. Another characteristic neuropathological finding is oligodendrocyte apoptosis in a subset of lesions. The fate of a newly emerging lesion subsequent to its acute stage may be manifold. The extent of axonal transection in white matter lesions and thus its destructivity may vary across subjects and in different brain regions and disease stages. The drivers of lesion evolution over time that determine whether a new myelin sheath is formed (remyelinated lesion), whether inflammation recedes but remyelination fails (chronic inactive lesion), or whether inflammation prevails accompanied by subtle progressive myelin degeneration (smoldering lesion) are incompletely understood. However, deeper insights into the molecular mechanisms that follow lesion formation are urgently needed as they are a prerequisite for devising neurorestorative and remyelinating therapies and for deploying factors that may have the potential to enhance endogenous repair mechanisms [24]. Moreover, the extent of axonal

damage resulting from an inflammatory lesion and the success of remyelination are key determinators of long-term disability. In recent years and with the advent of more sophisticated imaging techniques (for example, special magnetic resonance imaging (MRI) sequences enabling visualization of the cortical ribbon, ultrahigh field MRI at 7 T) it became clear that myelin damage and focal inflammatory lesions are not confined to the white matter. Cortical lesions and cortical demyelination occur frequently in MS, in particular in advanced disease stages, and are relevant drivers of disease progression and long-term disability including cognitive impairment [25–27]. Some of these cortical lesions are located subpially and it was suggested that they are triggered by leptomeningeal inflammatory aggregates [1, 28]. Of note, not only the cortical gray matter is affected in MS, also the deep gray matter, especially the thalamus, is frequently involved and exhibits besides lesions that are only partly visible on conventional MRI images pronounced atrophy over the course of the disease, but also from earliest disease stages [29–31]. Thalamic atrophy is a major driver of cognitive dysfunction [26, 31]. As a consequence of the multi-site and disseminated tissue damage brain atrophy is often detectable at a group level already in very early disease stages, even before MS becomes clinically apparent [30], and progressive brain volume loss over the course of the disease in untreated patients is accelerated about 1.5–2-fold in comparison to brain volume reductions in healthily ageing subjects [32, 33].

The optic nerve and the retina which are composed of CNS tissue are also frequently affected. Inflammatory lesions in the optic nerve are visible on orbital MRI in conjunction with clinically apparent optic neuritis, and retinal axons and ganglion cells may degenerate subsequently to an inflammatory attack to the optic nerve, indicated by thinning of the retinal nerve fiber layer and ganglion cell layer that is measurable with high resolution optical coherence tomography [6, 34–42]. However, thinning of the retinal nerve fiber and ganglion cell layer have been reported even independent of attacks of optic neuritis, presumably indicating sublinical affection of the optic nerve or retrograde transsynaptic degeneration [43–47]. Thinning of retinal layers is detectable from earliest disease stages on and is associated with reduced visual function, such as impaired low contrast visual acuity and altered visual quality of life [48–52]. Whether a primary retinal atrophy exists in MS, is currently a matter of debate [53–55].

The spinal cord is another predilection site of inflammatory demyelination and axonal transection. The cervical portion is more frequently affected than more caudal parts of the cord. Lesions may cause significant clinical disability, in particular impaired ambulation and bladder problems, and may result in cord atrophy [56–58]. The latter may also occur as sequelae of neuroaxonal degeneration of tracts elsewhere in the CNS and was proposed to indicate the onset of the progressive phase of the disease [59].

2.4 Immunopathogenesis of MS

The immunopathogenesis of the disease is not fully understood. It is widely accepted that MS is caused by immune dysregulation that involves both the adaptive (helper (CD4+) and cytotoxic (CD8+) T cells, B cells) and the innate immune system (macrophages, monocytes and microglia as endogenous phagocytes of the CNS) [1, 60]. According to one of the strongly favored hypotheses, the primary contact between CNS antigens and the immune system may be in the cervical lymph nodes. However, as in MS autoreactive T cells were found in the blood of healthy subjects, demonstrating that the presence of these cells is not sufficient to initiate the disease [61], and these lymph nodes drain CNS antigens also under normal circumstances. This suggests that there may be mechanisms in healthy subjects that prevent the activation of autoreactive encephalitogenic T cells, or that activation of autoreactive T cells occurs in MS patients [61]. The activation of such autoreactive cells of the adaptive immune system may be triggered by molecular mimicry or novel autoantigens [60]. By contrast, cells of the innate immune system might be activated through exposure to environmental factors such as bacteria, viruses, smoke constituents and others at mucosal surfaces. The migration of activated immune cells into the CNS is leveraged by disruption of the blood-brain-barrier causing abnormal vascular permeability which precedes inflammatory demyelination in the animal model of multiple sclerosis (experimental autoimmune encephalomayelitis (EAE)) and presumably the development of white matter lesions in human MS [1, 62–64]. The invasion of activated immune cells and their intricate interaction with glial cells (oligodendrocytes that are indispensable for an intact myelin sheath, astrocytes and microglia) and neurons including their axons are the major driver of tissue damage in multiple sclerosis.

2.5 Diagnosis of MS

A diagnosis of multiple sclerosis in the context of a first clinical event considered typical of MS (see above, termed “clinically isolated syndrome” (CIS)) is established when characteristic MRI features in the brain and spinal cord are present, often accompanied by typical findings in the cerebrospinal fluid (increased intrathecal immunoglobulin synthesis or oligoclonal bands indicating an immune reaction in the CNS) after the exclusion of alternative diagnoses. Diagnostic criteria (the so-called “McDonald criteria”) were established to facilitate MS diagnosis as early as possible with high sensitivity when a typical clinical manifestation is present, the latest version of which was released in 2017 [65]. This recent revision enables an MS diagnosis after a first clinical event, however, as in previous versions, the

relevance of so-called “red flags” (clinical or radiographic findings that are atypical of MS and may rather suggest another diagnosis) was emphasized. This is particularly important as there is no clinical, radiographic or laboratory marker pathognomonic for MS and the number of patients who have another disease but are misdiagnosed with multiple sclerosis is alarmingly high [66]. Major relevant differential diagnoses comprise vascular diseases, neuromyelitis optica spectrum disorders, rheumatologic diseases, Susac syndrome as well as hereditary and metabolic disorders affecting the white matter (for details, see [67]).

2.6 Treatment of MS

Although MS is an incurable disease, numerous so-called immunomodulatory drugs (the term “disease-modifying drugs” is used synonymously) have been approved over the past 20 years, most of them for treating RRMS [68, 69]. All of these medications have been shown to reduce the number of clinical attacks (relapses) by approximately between 30 and 70% in clinical trials with a duration of mostly one or 2 years only. Although these relative risk reduction magnitudes seem impressive, the absolute differences between the verum arm and the placebo arm (or the active comparator) in the pivotal trials that led to the approval of these medications are sometimes disappointingly low, meaning that some drugs prevent on average one relapse in 4 or 5 years more than the comparator. Some of the licensed medications have an additional often marginal benefit on disability progression. Again, these data were acquired in clinical trials with durations of rarely more than 2 or 3 years per individual participant, which means that inferences as to the long term beneficial effect of these drugs are impossible. Nonetheless, several so called post approval studies and meta-analyses as well as registry data suggest that with the advent of immunodulatory therapies the prognosis of the disease has improved for many patients and critical disability milestones such as limited walking distance or wheelchair dependency can be significantly delayed [70, 71]. Most compounds also have a profound effect on brain lesion metrics by reducing the number of new inflammatory brain lesions, and some drugs reduce progression of brain tissue loss compared to untreated patients, however, the long-term clinical benefit of the effect on radiographic measures of disease activity for the individual patient is far from clear [72–75]. None of the available drugs has proven neuroprotective or neurorestorative capacities, which underlines the unmet need for regenerative therapies for people with MS [24, 76, 77]. Several attempts to target potentially modifiable environmental factors in MS (for example diet, obesity, smoking, vitamin D supplementation etc.) have yielded inconclusive results or are still underway [78–83]. Besides efforts to target the dysregulated immune system and hereby reduce relapse rates and disability progression, therapeutic efforts to alleviate burdensome and disabling fatigue, depression, sleep disorders, cognitive dysfunction and pain are equally important, although evidence-based treatment recommendations on “symptomatic therapy” are scant [84–89].

2.7 What Could Be a Potential Pathophysiological Link Between MS and FS?

Although MS is not considered a predominantly vascular disease, the involvement of the vasculature of the brain and retina in MS is beyond doubt [90]. Although not in use in clinical practice, measurement of cerebral perfusion (defined as "volume of blood flowing through a given volume of tissue per time unit" [90]) is technically feasible and has been carried out in MS with various techniques (for example single-photon emission computed tomography (SPECT), positron emission tomography (PET), dynamic susceptibility contrast-enhanced MRI (DSC-MRI), or the non-invasive arterial spin-labeling MRI technique (ASL)) in the past 20 years. Parameters of interest in this context are the cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) [91]. Multiple groups have since reported decreased CBF in both the grey and white matter of MS patients [90]. Reduced CBF and increased MTT have also been described in the so-called "normal-appearing white matter" (NAWM) that does not show abnormal appearance on conventional MRI sequences (T1- and T2-weighted) [92, 93]. Moreover, reduced perfusion was found also in the cerebral cortex and subcortical grey matter of MS patients [90, 94]. Interestingly, in one study CBF was found to be decreased in the NAWM of patients with CIS [95], and another study reported decreased venous density in the periventricular areas of patients with short disease (CIS and early RRMS) [96]. These findings suggest that perfusion changes and venous vascular alterations are a phenomenon occurring already early during the course of the disease. The debate as to the causes of cerebral hypoperfusion in MS is ongoing and is particularly interesting in the context of a potential association of MS with FS. It was long believed that cerebral hypoperfusion is secondary to axonal and neuronal degeneration, reflected by brain volume loss (meeting a simple equation "less brain tissue = less oxygen and metabolic demand = less perfusion). However, neither the work by Varga et al. in CIS patients nor another study that investigated the normal-appearing corpus callosum of RRMS patients with diffusion-weighted and perfusion imaging support this seemingly oversimplified hypothesis [95, 97]. In CIS, brain atrophy is subtle if present at all, so it is hardly conceivable that negligible brain volume loss would cause CBF reduction. In the diffusion weighted imaging study by Saindane et al. [97], decreased perfusion was associated with decreased mean diffusivity but did not correlate with fractional anisotropy. If reduced NAWM perfusion was secondary to axonal degeneration, increased diffusivity and decreased functional anisotropy would have to be expected. However, this does not rule out that reduced or impaired axonal activity contribute to hypoperfusion in the NAWM [98]. While Flammer and colleagues suggested blood flow disturbance to trigger activation of retinal astrocytes and Müller cells [99], an alternative mechanism may be present in MS. It has been hypothesized that energy metabolism of astrocytes is dysfunctional and it was shown that astrocytes in MS lack beta-2 adrenergic receptors regulating glycogenolysis [90, 100]. Astrocytes were also found to have diminished phosphocreatine metabolism resulting from decreased cytosolic creatine kinase B

concentrations and activity [101]. Under normal conditions, astrocytes take up K+ that is released at the nodes of Ranvier during axonal discharge through inward-rectifying K+ channels (Kir). K+ is then redistributed within the astrocyte and released perivascularly at the astrocyte endfeet, which leads to arteriolar vasodilation [90, 102, 103]. The operation of the astrocytic Na+/K+ pump that is a major factor for establishing the negative membrane potential is highly energy consuming. In light of this it is conceivable that reduced astrocytic energy production in MS is responsible for lower K+ recovery in the perivascular space and thus reduced arteriolar vasodilation [90]. Interestingly, the advent of OCT angiography and retinal functional imaging has very recently stimulated research on structural and functional alteration of retinal vessels in MS. Although most data are preliminary and were acquired in small patient cohorts, first reports suggest that arteriolar and venular retinal blood flow velocities are reduced both in MS eyes with and without optic neuritis compared to healthy controls [104, 105]. Moreover, structural alterations (rarefaction of superficial and deep retinal vessels) was found in MS eyes with optic neuritis [106]. Another retinal finding, rigidity of retinal vessels, is a commonality of both MS and FS [107]. The clinical relevance of these findings for patients with MS need to be explored in more detail.

Hypoperfusion in MS might also be caused or influenced by increased concentrations of the vasoconstrictive endothelin-1 (ET-1) that were reported in MS, in one work in association with reduced extraocular blood flow velocities [108–110]. Increased plasma levels of endothelin-1 are considered a typical sign of FS [99, 111, 112].

2.8 Do MS and Flammer Syndrome Coincide?

Data on co-occurrence of MS and FS are scant. The only study on this topic was published by Konieczka et al. in 2016 [113]. The authors distributed a questionnaire covering 15 characteristic symptoms and signs of FS to 58 MS patients in a Swiss Rehabilitation Centre and 259 control subjects visiting shopping centres. Of note, MS patients had a mean age of 44.7 years (range 36–76) and a relatively high mean score of 5.58 (range 2.5–8.5) on the EDSS (Expanded Disability Status Scale), indicating significant neurological disability with impaired ambulation in many patients. Six of the 15 FS signs and symptoms were found significantly more often in MS patients than in unselected controls: dizziness, low body mass index, cold hand/feet, tendency toward perfectionism, reduced thirst, feeling cold. Other symptoms that occurred more often in MS than in controls, albeit not statistically significant, were tinnitus, headaches, increased pain sensation, long sleep-onset time, migraines, increased response to certain drugs, and low blood pressure. Some of these features have been previously described in patients with MS and can be related to MS as a CNS disease affecting multiple areas of the brain and spinal cord including tracts and nuclei involved in autonomic functions (tinnitus, headaches, migraines, dizziness, impaired thermoregulation, sleep problems, pain) while data on low BMI in

the MS group seem to contradict previous work proposing overweight and obesity as risk factors for MS [114, 115]. The study is limited by a highly selected MS cohort (inpatients with advanced disease). To further substantiate a possible association of FS and MS, newly diagnosed MS patients in the CIS or early RRMS stage will have to be investigated. Moreover, causality of the reported co-occurrence in either direction cannot be inferred. If FS increases the risk of MS through vascular dysregulation or if MS causes FS-like symptoms and signs through secondary vascular dysregulation (see above) remains to be clarified in subsequent studies.

3 Susac Syndrome (SuS)

Susac syndrome is a very rare and probably immune mediated condition with female preponderance affecting small arteries and arterioles of the brain, retina and inner ear [116–119]. Occlusions of these microvessels are thought to cause a characteristic clinical triad of visual disturbances owing to branch retinal artery occlusions, hearing deficits (hearing loss, less frequently tinnitus) and CNS dysfunction, namely encephalopathy with cognitive impairment, confusion, emotional disturbances, behavioural and personality changes [116, 120]. Neurologic abnormalities indicating CNS dysfunction such as vertigo, ataxia, gait abnormalities, upper motor neuron signs, sensory disturbances and others were reported in up to 25% of patients [116]. Diagnostic procedures comprise CSF analysis (elevated protein characteristic, oligoclonal bands not a typical feature in contrast to MS), MRI (supratentorial white matter lesions, involvement of the corpus callosum (CC) with “snowball lesions” in acute stage and pronounced atrophy of the CC in chronic stages, spinal cord lesions typically absent) [116, 121], and fluorescein angiography (FAG) in conjunction with OCT to detect retinal affection (BRAO and arterial wall hyperfluorescence on FAG, patchy thinning of the retinal nerve fiber layer, ganglion cell layer, inner plexiform layer, inner nuclear layer and outer plexiform layer on OCT suggesting a retinal vascular pathomechanism) [122–124]. Audiometry is important to assess sensorineural hearing loss which occurs more frequently bilaterally than unilaterally [116, 117]. Serology markers (autoantibodies) are not helpful in making the diagnosis, and in particular antiendothelial cell antibodies (AECA) that were proposed as serological marker for SuS have low sensitivity and specificity [117, 119]. Only several hundred cases have been published in the world literature, although the true prevalence is presumably higher as many patients are probably misdiagnosed with MS. Moreover, establishment of the correct diagnosis is frequently delayed because the classical clinical triad is incomplete in most patients at disease onset [117]. Therapeutic strategies comprise immunosuppressive therapy with high dose methylprednisolone and eventually plasmapheresis in acute stages and prednisolone, intravenous immunoglobulins, azathioprine, methotrexate, rituximab and others for maintenance immunosuppressive therapy [125], while classic MS immunomodulators such as beta-interferons and natalizumab must be avoided as they may cause disease exacerbation [125–127]. In addition, many publications

have reported the use of antiplatelet or anticoagulant therapy with the idea of reducing the risk of thrombosis in small arterioles. Flammer and colleagues reported increased ET-1 levels in SuS [128] and proposed that patients with primary vascular dysregulation/FS have an increased risk for SuS [99]. However, Flammer et al. emphasize that SuS through its involvement of microvessels may as well cause secondary vascular dysregulation [112], and rightly so call for further studies that help clarify the presumed causality of the association between SuS and vascular dysregulation and the temporal evolution of pathogenic events.

4 Concluding Remarks and Expert Recommendations

Preliminary data suggest that FS and MS may share some pathophysiologic commonalities and that MS patients show signs and symptoms of FS more often than unselected controls. However, data is not sufficient to assume an increased risk of MS in people with FS and vice versa. In order to further clarify a potential association of FS and MS, investigations on the presence of FS in patients with newly diagnosed MS are warranted. These patients need to be followed over longer periods of observation to assess a potential association of concomitant FS signs and symptoms with MS disease course. On the contrary, patients with diagnosed FS that show symptoms suggestive of MS should be investigated rigorously by a neurologist or neuroimmunologist for other findings compatible with an inflammatory autoimmune CNS condition. Pathophysiological studies should aim at unraveling in more detail the potential structural and functional changes of the cerebral and retinal vasculature in patients with MS and in those with concomitant FS signs and symptoms and associations with disease course. A deeper insight into the mutual relations between both conditions both on a clinical and a pathophysiological level will hopefully enable more precise prediction of disease course and prognosis and personalized treatment approaches for patients diagnosed with MS and FS.

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"Young Stroke" Risks Potentially Linked to the Flammer Syndrome Phenotype: Facts and Hypotheses

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Abstract Currently, the stroke is registered amongst the five leading causes of death and disability worldwide. From the European perspective approximately 1.1 million individuals become stroke diagnosed each year. The disorder demonstrates severe socioeconomic consequences: the associated total EU costs are as high as €45 billion annually.

Even if the majority of the stroke cases are diagnosed in the elderly, about 10% of all patients experience the disorder at the age below 50 years – so-called "young strokes". Moreover, the incidence as well prevalence of stroke in young adults is dramatically increasing worldwide. Further, the proportion of strokes with unknown etiology among the youngest subgroup of patients reaches up to 39.6–42% that remains largely unexplained. Therefore, specifically modifiable risk factors such as

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suboptimal heath conditions are proposed to be considered for innovative risk assessment in the “young stroke” prediction and prevention.

Due to symptoms characteristic for the Flammer syndrome (FS), we hypothesised a potential relationship between FS phenotype and increased risks for the “young stroke” predisposition. FS characteristic symptoms and signs analysed in the chapter may further synergistically contribute to the cerebrovascular events being potentially indicative for the stroke predisposition in young individuals.

If the hypothesised association become confirmed by multi-centre studies run, FS phenotype may get of great clinical utility for creating innovative strategies of predictive, preventive and personalised medicine for the stroke management utilising novel screening programmes, individualised patient profiling, specialised questionnaires and novel biomarker patterns for an effective risk assessment, targeted prevention, and therapy monitoring tailored to the person.

Keywords Young adults · Flammer Syndrome · Phenotype · Risk factors · Individualised patient profile · Aetiology · Vascular · Abnormal BMI · Blood flow · Microcirculation · Life style · Sleep patterns · Migraine · Hormonal regulation · Psychology · Stress · Screening program · Questionnaire · Risk assessment · Baroreceptor sensitivity · Cardiac · Circadian rhythm · Tinnitus · Thermoregulation · Altered sensation · Body dehydration · Predictive preventive personalised medicine

1 Introduction

Stroke belongs to the most important civilisation diseases with a high impact on the health and quality of life affecting more than 15 million new patients annually worldwide [1]. Stroke is recorded amongst the five most common causes of death and disability. It is a devastating disease with 1-month case-fatality rates ranging from 13 to 35%. From the European perspective approximately 1.1 million individuals suffer a stroke each year [2, 3]. Stroke has also important socioeconomic consequences as the EU total cost of stroke in 2015 was calculated as high as €45 billion.

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Though the majority of stroke cases are diagnosed in the elderly, there is a substantial number of individuals (approximately 10% of all cases) suffering from first-ever stroke below the age of 50 years, so-called "young strokes" [4]. Moreover, both - the incidence and prevalence of stroke in young adults is dramatically increasing for the high-income as well as middle and low-income countries representing a major present-day health problem worldwide [5].

The dramatic burden of young strokes in the recent years may be explained, at least in part, by an increasing incidence of the major vascular risk factors of stroke in youth and even in children [5, 6]. The well-known risk factors such as hypertension, hyperlipidemia, diabetes mellitus, smoking, heavy episodic alcohol consumption, low physical activity, coronary heart disease, and obesity are now commonly prevalent amongst young adults. This actuality provides an opportunity for the targeted and personalised primary prevention of stroke in adolescents and young adults with asymptomatic patient profiles.

Further, about 20–30% of stroke cases in young adults remain of the unknown aetiology [4, 5, 7, 8].

2 Definition of Young Stroke

In the majority of studies the young stroke is defined as the first-ever cerebrovascular event presenting in adults aged between 18 and 50 years [4, 9]. However, some studies dedicated to young strokes do refer to other age limits e.g. 45 [10, 11] or 55 years [7, 12] as well as go for a wider range starting by 15 years of age [13]. Because of distinct and more specific stroke aetiologies in neonates, children, and young teenagers, these patient groups are discussed separately in the vast majority of studies [14–17].

3 Classification of Young Stroke

About 80% of young strokes are ischemic, the rest are hemorrhagic. The ischemic young strokes are classified (same as the strokes in general population) into the aetiological subtypes by the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification [18]. These subtypes are (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-vessel occlusion, (4) stroke of other determined etiology, and (5) stroke of undetermined aetiology also called cryptogenic. It is well documented, that the stroke of other determined aetiology (such as cervical arterial dissection, hematologic diseases, vasculitis, malignancies, Illicit drug use, pregnancy and puerperium, thrombophilia and others) is more prevalent in the younger patients (<45 years and even more <35 years) compared to the older ones (>45 years) [4, 8, 10, 19]. The proportion of cardioembolism (due to cardiomyopathy, atrial fibrillation/flutter and others) is also higher in younger patients. In contrast, the

large-artery atherosclerosis occurs relatively rarely in very young adults but its incidence increases with the age enhancing the stroke risk.

In contrast to the elderly, a large number of strokes aged mainly between 18 and 35 years [4, 8] demonstrating unknown aetiology reaches up to 39.6–42% in some studies [13, 19]. That is extremely challenging for the healthcare sector and society at large.

4 Changing Milieu of Young Stroke Risk Factors

Originally it was observed that the profile of risk factors in young stroke differes from that in general stroke population, because of more frequent occurrence of so-called "rare" risk factors and aetiologies presented mainly in young patients (such as cervical arterial dissection, hematologic diseases, vasculitis, malignancies, Illicit drug use, pregnancy and puerperium, thrombophilia, infections, Fabry's disease, patent foramen ovale and others) [4, 20].

However the prevalence of traditional vascular risk factors originally identified mainly in old patients (hypertension, dyslipidemia, diabetes mellitus, smoking and others) is now dramatically rising also in the group of very young adults with stroke, and even in young healthy populations in general [7, 21–23]. Moreover, the combination and synergic pathogenic effects of such risk factors significantly contribute to the stroke burden in young adults. The recently published results from the large international study including 32 countries from Asia, America, Europe, Australia, the Middle East, and Africa clearly showed that the potentially modifiable risk factors represented 92.2% of population attributable risks (PARs) of stroke in patients aged under or equal to 55 year [24].

Similarly, the eight established and modifiable risk factors (namely: arterial hypertension, hyperlipidemia, diabetes mellitus, smoking, heavy episodic alcohol consumption, low physical activity, obesity and coronary heart disease) together explained 78.9% of all first-ever young strokes from 26 clinical stroke centers in patients aged 18–55 years [6]. These observations are of substantial relevance for better primary prevention of stroke in young population.

Risk factors acknowledged as clearly associated with the etiology of young stroke are overviewed in the Table 1.

Table 1 Risk factors associated with young stroke

Risk factors	Relevance to young stroke (prevalence of risk factor among patients/controls, increased risk of stroke)	Study details (number of participants, age category)	References
Vascular risk factors			
Arterial hypertension	46.6% prevalence (29.3% under 45 years)	4467 patients, age 18–55 years	[7]
	28.3% prevalence (29.3% IS vs. 19.1% HES)	724 patients, age 18–50 years	[65]
	39.3% prevalence (9% under 35 years)	990 patients, age 15–49 years	[66]
	38.3% prevalence (42.9% men vs. 24.3%, women)	149 patients, age 15–44 years	[11]
	44.4% prevalence	1395 patients, age 18–45 years	[67]
Dyslipidemia	34.9% prevalence (39.3% men vs. 28.5% women), 23.7% under 44 years	4467 patients, age 18–55 years	[7]
	26.8% prevalence (26.2% IS vs. 5.9% HES)	724 patients, age 18–50 years	[65]
	45.5% prevalence in first-ever stroke 47.9% prevalence in recurrent stroke	837 patients, age 18–54 years	[19]
	52.7% prevalence	150 patients, age under 50 years	[68]
	48.2% prevalence	2118 patients, age 18–50 years	[69]
	7.5% prevalence	134 patients, age 18–45 years	[70]
Diabetes mellitus	10.1% prevalence (vs. 4.3% in controls)	2125 patients, age 18–55 years	[6]
		8500 age-matched controls	
	18.8% prevalence in first-ever stroke	837 patients, age 18–54 years	[19]
	9.7% prevalence in recurrent stroke		
	6.7% prevalence	150 patients, age under 50 years	[68]
	13.8% prevalence	1395 patients, age 18–45 years	[67]

(continued)

Table 1 (continued)

Risk factors	Relevance to young stroke (prevalence of risk factor among patients/controls, increased risk of stroke)	Study details (number of participants, age category)	References
Obesity and overweight	Higher risk (HR 1.57, 95%CI 1.28–1.94) for BMI >30 kg/m^2	1201 patients, age of 15 and 49 years	[71]
		1154 age-matched controls	
	10.6% prevalence	990 patients, age 15–49 years	[66]
	16% prevalence	150 patients, age under 50 years	[68]
	19.5% prevalence (18 to 44 years)	4467 patients, age 18–55 years	[7]
	24.1% prevalence (45 to 55 years)		
	Higher risk with increased waist-to-hip ratio (third vs. first tertile HR 1.56, 99%CI 1.23–1.98)	4216 patients, aged ≤55 years	[24]
		4234 age-matched controls	
Abnormally low BMI – underweight	Higher risk (HR 1.44, 95%CI 1.431–1.450) for BMI <18.5 kg/m^2	491,773 participants	[72]
	Higher risk (men HR 1.29, 95%CI 1.01–1.49; women HR 1.92, 95%CI 1.49–2.47) for BMI <18.5 kg/m^2	104,928 participants	[73]
Lifestyle risk factors			
Cigarette smoking	Higher risk (HR 1.88) for current smokers vs. never smokers (HR 5.66 for more than 40 cigarettes/day)	615 patients and 530 controls	[74]
	Higher risk (HR 2.6, P < 0.0001) for current smokers vs. never smokers	466 patients, age 15–49 years	[75]
		604 age-matched controls	
	44.6% prevalence	990 patients, age 15–49 years	[66]
	41% prevalence (16 to 45 years)	624 patients, age 16–55 years	[8]
	45% prevalence (46 to 55 years)		
Excessive alcohol consumption	Higher risk (HR 2.20, 99%CI 1.49–3.23) for heavy episodic alcohol intake vs. never or former drinkers	4216 patients, aged ≤55 years	[24]
		4234 controls	
	33.0% prevalence (41.9% men vs 20.1% women)	4467 patients, age 18–55 years	[7]
	17.5% prevalence in first-ever stroke	837 patients, age 18–54 years	[19]
	13.5% prevalence in recurrent stroke		
	41.6% prevalence	1395 patients, age 18–45 years	[67]

(continued)

Table 1 (continued)

Risk factors	Relevance to young stroke (prevalence of risk factor among patients/controls, increased risk of stroke)	Study details (number of participants, age category)	References
Low physical activity	46.6% prevalence in men and 50.4% in women	4467 patients, age 18–55 years	[7]
	Higher risk (HR 5.8, 95%CI 5.1–6.7)	2125 patients, age 18–55 years	[6]
		8500 age-matched controls	
Abnormal sleep duration (either too short or too long)	Dose-response relationship (U-shaped) between sleep duration and stroke, higher risk either for shorter or longer sleep duration compared to 7 hours	218,155 participants, aged >45 years	[76]
	17.9% prevalence (less than 6 hours)	4467 patients, age 18–55 years	[7]
Illicit drug use	12% prevalence (18% under 35 years)	215 patients, age 18–45 years	[10]
	12.1% prevalence	422 patients, age 15–44 years	[77]
	Higher risk (HR 2.30, 95%CI 1.08–5.08) for cannabis users	218 patients, age 18–55 years	[78]
	Higher risk (IS HR 2.03, 95%CI 1.48–2.79; HES HR 2.33, 95%CI 1.74–3.11) for cocaine abuse	1935 patients, age 18–44 years	[79]
Other potential risk factors			
Migraine/migraine with aura	18.8% prevalence in men and 37.8% in women	4467 patients, age 18–55 years	[7]
	17% prevalence	990 patients, age 15–49 years	[66]
	5.7% prevalence (10.3% under 35 years)	150 patients, age under 50 years	[68]
Hormonal contraceptives (COC)	Higher risk of IS (pooled HR 1.7, 95%CI 1.5–1.9)	Meta-analysis including 24 independent studies, age 18–50 years	[80]
	Higher risk of IS (pooled HR 1.8, 95%CI 1.2–2.8)	Meta-analysis including 14 studies	[81]

(continued)

Table 1 (continued)

Risk factors	Relevance to young stroke (prevalence of risk factor among patients/controls, increased risk of stroke)	Study details (number of participants, age category)	References
Pregnancy, puerperium and associated complications	Higher risk (HR 11.9, 95%CI 5.5–25.6, for age 15 to 24 years) during peripartum period early postpartum (up to 6 weeks)	2,046,048 participants, age 15–49 years	[82]
	Higher risk (HR 3.51, 95%CI 1.08–11.35) for multiple (≥3) pregnancy loss	165 patients, age 18–50 years	[83]
	Higher risk (HR 2.06, 95%CI 0.81–5.23) for presence of stillbirth	743 age-matched controls	
Psychosocial factors	Higher risk HR 2.20, 95%CI 1.78–2.72	4216 patients, aged ≤55 years 4234 controls	[24]
	57.2% prevalence of psychosocial stress	110 patients, aged ≤55 years	[84]
	Higher risk (pooled HR 1.39, 95%CI 1.27–1.51)	Meta-analysis including 41 cohort studies and 5 case-control studies	[85]

Abbreviations: IS Ischemic stroke, *HES* Hemorrhagic stroke, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *COC* combined oral contraception

5 Hypothesised Relationship Between Flammer Syndrome Phenotype and" Young Stroke" Risks – Potential Utility of Specialised Questionnaires for the Risk Assessment

As discussed in the previous sections, the proportion of strokes with unknown aetiology amongst the youngest subgroup of patients reached up to 39.6–42% in some studies [13, 19]. No history of usual risk factors associated with atherosclerosis such as hypertension, dyslipidemia, diabetes mellitus, obesity or smoking is presented by these patients. Also neither cardiac disease nor classical "rare" aetiology is identified and, therefore, the aetiopathogenesis of such stroke in young adults remains largely unexplained.

Keeping in mind an urgent need in innovative screening programmes which would enable to provide young populations with an effective targeted prevention against clinical manifestation of the pathology, a risk assessment specifically for "young stroke" should be considered in the context of suboptimal health conditions demonstrating the relevant risks and predisposing the affected individuals to pathology manifestation early in life.

Due to symptoms characteristic for the Flammer syndrome (FS) [25, 26], we hypothesised a potential relationship between FS phenotype and increased risks for the" young stroke" predisposition. FS describes a phenotype characterised by the

presence of primary vascular dysregulation accompanied by a cluster of symptoms and signs, amongst others including frequently cold extremities, low blood pressure, prolonged sleep onset, shifted circadian rhythm, reduced feeling of thirst, altered drug sensitivity, an increased sensitivity towards stress and pain sensation. The FS phenotype is prevalent in several patient cohorts demonstrating hypoxic, ischemic and/or neurodegenerative features such as normal-tension glaucoma, anterior ischaemic optic neuropathy, retinal vein occlusions, Sicca and Susac syndromes, central serous chorioretinopathy [27], as well as multiple sclerosis and metastatic breast cancer [28–33]. Regarding the latter, systemic hypoxic effects have been demonstrated as being particularly relevant for the development of an aggressive metastatic disease such as brain metastasis frequently observed in young breast cancer patients [32] with FS phenotype [31].

The individuals with FS are less prone to atherosclerosis but exhibit signs of endothelial dysfunction [34]. The systemic imbalance in an increased release of endotelin-1 acting as the vasoconstrictor against the endothelial vasodilator NO is considered to be the key driver in the FS and related pathologies; due to the systemic effects, the mechanism may affect the functionality of the brain vessels [35]. Other FS characteristic symptoms and signs analyzed below may further synergistically contribute to the cerebrovascular events being potentially indicative for the stroke predisposition in young individuals.

The hypothesis is strongly supported by evidence provided in the recently (2016–2018) published articles which we refer in the below paragraphs to and becomes systematically evaluated in the currently run multi-centre studies under participation of the clinical and research groups presented by the authors of this chapter.

6 Cluster of FS Symptoms Potentially Relevant to Screening Programmes Focused on "Young Stroke"

6.1 Compromised Cerebral Blood Flow, Disturbed Microcirculation, Cold Extremities

Regulation of the cerebral circulating is very complex which relies on the interplay between cardiovascular, respiratory and neural physiology. Compromised cerebral blood flow is a well-acknowledged risk factor for stroke; consequently, cerebral circulation monitoring is suggested as critical for the stroke prediction, prognosis and management [36]. On the other hand, FS affected individuals frequently demonstrate strongly compromised and disturbed microcirculation that is evident by their cold extremities even during the summer time and/or in situations, when non-FS individuals feel comfortable with the actual temperature [25, 37].

6.2 Baroreceptor Sensitivity and Altitude Sickness

Increased baroreceptor sensitivity has been demonstrated in the context of compromised cerebral blood flow and predisposition to the ischemic stroke [36]. On the other hand, FS affected individuals demonstrate a prolong adaptation to the changing altitude and a tendency towards altitude sickness [38, 39].

6.3 Cardiac Component

Arterial blood pressure is one of the key players in the stroke pathomechanisms, and the cardiac component plays and important role in the regulating processes [36]. Further, specifically the intraoperative hypotension has been demonstrated as a risk factor for adverse outcomes in stroke patients [40]. On the other hand, low blood pressure and/or even cardiomyopathy have been reported for the FS individuals [25, 41].

6.4 Hormonal (Dys)Regulation: Oestrogen Level, Migraine with Aura and Vascular Risks

Hormonal (dys)regulation linked to changing oestrogen levels in blood and vascular risks - altogether play an important role in cerebrovascular pathologies as demonstrated for young stroke patients suffering from migraine with aura [42–45]. On the other hand, migraine with aura is frequently observed in individuals with FS phenotype [38] with higher prevalence of this phenotype in females [25].

6.5 Dizziness

Increased prevalence of stroke has been demonstrated for patients with isolated vertigo and vascular risk factors [46]. On the other hand, dizziness is a characteristic symptom of the FS phenotype [47]. Both vascular dysregulation and increased baroreceptor sensitivity play a role in the appearance of the FS characteristic symptoms.

6.6 Tinnitus

Tinnitus is highly prevalent in individuals with FS phenotype [47] and FS-affected patients diagnosed with xerostomia [33] and metastatic breast cancer [31]. On the other hand, the association between the appearance of tinnitus and increased risks

of ischemic cerebrovascular disease has been demonstrated specifically in young and middle-aged patients [48].

6.7 Altered thermoregulation and Feeling Inappropriately Cold

Although cerebral thermoregulation remains poorly understood, recent studies demonstrated detectable brain temperature disturbances and brain-systemic temperature decoupling involved in the stroke pathomechanisms [49]. Moreover, based on the evidence, an altered brain thermoregulation is proposed to serve as a neuroimaging biomarker in CNS injury. On the other hand, altered thermoregulation in FS-affected individuals has been demonstrated as potentially linked to FS-associated pathologies [37].

6.8 Reduced Thirst Perception and Body Dehydration

Robust statistical data demonstrate that nearly half of acute stroke patients are dehydrated at the time of admission [50]. The state of dehydration can play a role in CNS perfusion and lead to hemoconcentration and vascular sludging, exacerbating stroke. On the other hand, a reduced thirst perception is characteristic for the FS-affected individuals; consequently, if their daily liquid intake is not properly controlled, these deficits may cause significant body dehydration as well documented by recent publications [37]. Moreover, in young individuals demonstrating symptoms of xerostomia, FS phenotype is highly prevalent [33] as discussed in the book chapter "Interrelation Between Dry Mouth and Flammer Syndromes: Neglected Risks in Youth and New Concepts of Personalised Prevention" by Anatolij Kunin with co-authors.

Further, Sjögren syndrome has been demonstrated as associated with prevalent cerebrovascular disease [51, 52]. Finally, similarities between Sjögren and Flammer syndromes such as Sicca symptoms, amongst others, have been analysed in the literature [53] and is presented in the book chapter "Flammer and Sjögren Syndromes: What and Why Is in Common?" by Babak Baban and Olga Golubnitschaja.

6.9 Low BMI

Slim body shape is characteristic for FS-affected individuals [47]. On the other hand, the BMI < 25 has been demonstrated as a general risk factor for an increased mortality by cerebrovascular disorders [54].

6.10 Altered Circadian Rhythms and Sleep Patterns

Altered circadian rhythms and sleep patterns are characteristic for the FS-affected individuals [47, 55]. On the other hand, sleep-wake disorders have been demonstrated as the risk factor of stroke and deteriorated recovery [56]. The necessity for targeted prevention and personalised treatments has clearly been stated. More information to this end is provided in the book chapter "Relevance of Flammer Syndrome to the "Sleep-Wake" Rhythm: Possible Mechanisms, Risks and Preventive Strategies" by Kneginja Richter with co-authors.

6.11 Psychologic Factors and Stress

FS-affected individuals demonstrate obsessive personality and tendency to perfectionism frequently linked to increased psychologic stress [47] that has been extensively discussed in context of several pathologies potentially linked to the FS phenotype including both – neurodegenerative eye disorders [57] and oncologic diseases [29–31], and corresponding molecular mechanisms and targets for stress response have been clearly identified [58, 59]. Similarly, chronic stress and mood disorders have been proposed to play a significant role in the pathomechanisms of multi-factorial stroke predisposition [60, 61]. To this end, individuals with FS-phenotype may be predisposed to the manifestation of mood disorders early in life, as demonstrated in the book chapter "Flammer Syndrome-Affected Individuals May Be Predisposed to Associated Pathologies Early in Life: Psychological and Psychiatric Aspects" by Olga Golubnitschaja with co-authors.

7 Conclusions and Expert Recommendations

The majority of young adults with stroke are presented to the hospital too late for an efficient recovery with delayed diagnosis and usually outside the time window suitable for intravenous fibrinolysis [62]. This reactive approach needs innovative solutions improving individual outcomes such as timely educational measures to the primary healthcare givers and general population, first of all - young adults and children. However, in general, creation of innovative strategies of predictive, preventive and personalised medicine for the stroke management is essential utilising novel screening programmes, individualised patient profiling, specialised questionnaires and novel biomarker patterns for an effective risk assessment, targeted prevention, and therapy monitoring tailored to the person [63, 64].

The proportion of strokes with unknown aetiology amongst the youngest subgroup of patients reaches up to 39.6–42% [13, 19] that remains largely unexplained. Therefore, specifically modifiable risk factors such as suboptimal heath conditions

are proposed to be considered for innovative risk assessment in the "young stroke" prediction and prevention.

Due to symptoms characteristic for the Flammer syndrome (FS) [25, 26], we hypothesised a potential relationship between FS phenotype and increased risks for the" young stroke" predisposition. The FS phenotype is prevalent in several patient cohorts demonstrating hypoxic, ischemic and/or neurodegenerative features. FS characteristic symptoms and signs analysed in the chapter may further synergistically contribute to the cerebrovascular events being potentially indicative for the stroke predisposition in young individuals. The hypothesis is strongly supported by evidence provided in the recently published articles which we refer in the above paragraphs to and becomes systematically evaluated in the currently run multi-centre studies under participation of the clinical and research groups presented by the authors.

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Flammer and Sjögren Syndromes: What and Why Is in Common?

Babak Baban and Olga Golubnitschaja

Abstract Flammer syndrome (FS) occurs more frequently in females; its signs and symptoms are mainly linked to primary vascular dysregulation (PVD), increased sensitivity to various stimuli (stress, drugs, etc.) and altered sense regulation such as pain, smell and thirst perception. To this end, inflammation and immune disorders including autoimmunity are considered as a consequence of the abnormal vascular regulation processes. Decreased thirst feeling typical for FS-affected individuals may lead to extensive body dehydration resulting in increased risks for Sicca syndrome and breast cancer (BC), amongst others. Indeed, recent research demonstrated FS phenotype as being dominant in individuals with "dry mouth" syndrome even at very young age, vaginal dryness in both pre- and post-menopausal women, as well as BC patients with particularly pronounced FS phenotype in case of the aggressive metastatic disease. Further, FS-affected individuals to individual extent may be predisposed to a prolonged wound healing.

Sjögren syndrome (SS) is an autoimmune disease characterised by a progressive Sicca syndrome, specific immunologic complex and/or significant infiltrate at minor salivary gland biopsy. SS is relatively frequent, with a clinical diagnosis predominantly amongst women. Its physiopathology is a complex battery of both genetic and environmental risk factors. If left untreated, SS may be associated with and/or

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may result in impaired wound healing, severe arthritis and development of several cancer types. Further, breast inflammatory patterns were reported in females affected by Sjögren syndrome.

In this chapter we summarise the facts and hypotheses connecting FS and SS together and mechanisms potentially overlapping in both syndromes that might be of great clinical value. Multi-professional considerations presented here are an example for how to effectively enter the new era of preventive, predictive and personalised medicine benefiting the patients and healthcare system as the whole.

Keywords Predictive preventive personalied medicine (PPPM) · Health policy · Flammer syndrome · Sjögren syndrome · Sicca syndrome · Patient stratification · Vascular dysregulation · Inflammation · Autoimmune disease · Wound healing · Gender · Breast cancer · Genetic · Environment · Stress response · Xerophthalmia · Xerostomia · Risks · Reciprocal relationship · Common mechanisms

1 Introduction

Flammer syndrome (FS) is defined as a combination of symptoms resulting from a predisposition to a generally increased sensitivity to stimuli. Compared to the general population, FS-affected individuals react differently to environmental stimuli, such as cold and physical or emotional stress. Nearly all organs, particularly the eye, can be involved indicating the systemic effects by FS [1–3]. FS is characterised by strongly pronounced primary vascular dysregulation (PVD) along with a cluster of symptoms and signs that may occur as the suboptimal health condition in healthy individuals as well as in several patient cohorts investigated such as neurodegenerative disorders (glaucoma and multiple sclerosis), cancer and metastatic disease [4–9]. Although the syndrome has some protective effects against the development of atherosclerosis, however, FS presents an increased frequency of optic disc hemorrhages, activated retinal astrocytes, elevated retinal venous pressure, optic nerve compartmentalisation, fluctuating diffuse visual field defects, elevated oxidative stress, and systemic hypoxia impacting individual outcomes in several pathologies such as cancer and metastatic disease [1, 7–9]. Sjögren syndrome (SS) is a systemic chronic inflammatory disorder characterised by an impaired endothelium dependent vasodilation in primary SS patients [10] and lymphocytic infiltrates into exocrine organs. Most individuals with Sjögren syndrome present with sicca symptoms, such as xerophthalmia (dry eyes), xerostomia (dry mouth), and parotid gland enlargement. While, primary Sjögren syndrome (PSS) occurs in the absence of another underlying rheumatic disorder, secondary Sjögren (SSS) syndrome is associated with additional underlying rheumatic disease, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), or scleroderma. Given the overlap of Sjögren syndrome with many other disorders, it is plausible to explore the potential reciprocal relationship between SS and FS [11–13]. In addition to a number of epidemiologic common denominators, both FS and SS show cardiovascular dysfunction at different levels as they progress during the course of diseases [1, 12, 14]. In fact,

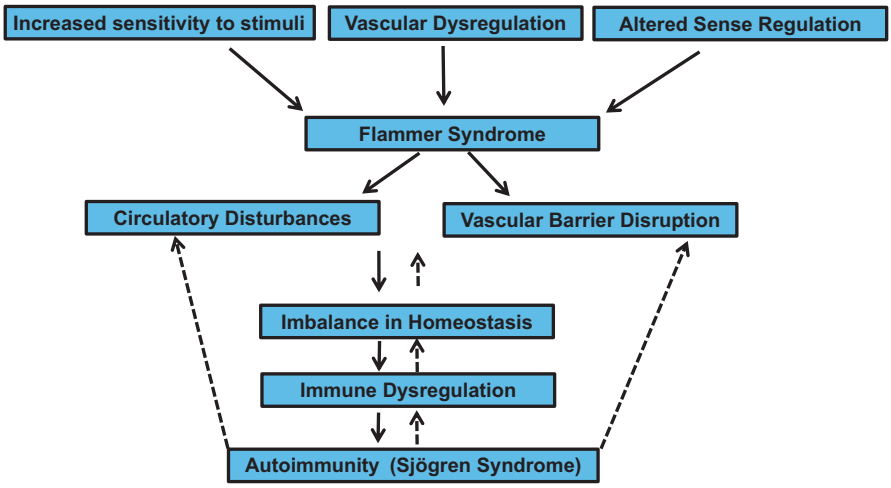

Fig. 1 The schematic potential relationship between Flammer and Sjögren syndromes

while a direct correlation between FS and retinal venous pressure (RVP) in patients with glaucoma has already been shown, it is also reported that SS patients may be more vulnerable to glaucoma. Similarly, several studies have indicated a relationship between optic neuritis and initial presentations of both FS and SS. Further, some researchers have demonstrated cardiac arrhythmias and vascular dysfunction as the initial manifestations of adult primary Sjögren syndrome [14, 15].

Here we highlight the findings that reveal some resemblances between FS and SS. These common mechanisms not only help clinicians with potential novel therapies for treating both FS and SS, but also may provide appropriate tools in the context of predictive, preventive and personalised medicine as the medicine of the future (Fig. 1).

2 Flammer Syndrome

Flammer syndrome (FS) is a relatively recently described health condition [1] linked to primary vascular dysregulation (PVD), increased sensitivity to various stimuli (stress, drugs etc.) and altered sense regulation such as pain, smell and thirst perception. It is represented by a cluster of symptoms and signs that can occur as a suboptimal health condition in healthy individuals as well as patient cohorts. The leading symptoms include cold hands and/or feet, low blood pressure, prolonged sleep onset time, shifted circadian rhythm, increased sensitivity to pain, enhanced smell perception, and reduced feeling of thirst. Although FS-affected individuals are typically less thirsty, only those who are aware of being affected by FS do drink enough controlling their water intake by head. However, FS-affected individuals who are not aware of these deficits are strongly predisposed to the whole body

dehydration that may result in several related pathologies such as dry eye and breast cancer [16]. With higher prevalence in females, FS incidence is associated with certain physical, occupational and psychological conditions. As such, FS is seen more in slender than in obese individuals and in subjects with systemic hypotension more than in subjects with hypertension. Demographically, FS is more prevalent in people with indoor jobs than in those with outdoor jobs, in academics more than in blue collar workers, and in Asians more often than in Caucasians [1]. The symptoms appear early in life with puberty and mitigate with progressing age, in women specifically after menopause. FS-affected individuals frequently indicate that one or both parents suffered from the same symptoms. Therefore, a genetic component is likely to be involved in the molecular mechanisms which underlie FS [1, 15]. Vascular dysregulation is the basic feature of FS. Importantly, it is reported that FS is associated with or predisposes to the development of diseases such as normal tension glaucoma and often contribute to low blood pressure [1, 17]. These notions were supported by the clinical findings that glaucoma patients with FS often had dilated retinal veins, suggesting the retinal venous pressure (RVP) in the subset of glaucoma patients with FS may be higher than in those glaucoma patients without FS. As a mechanism responsible for such higher RVP, it has been propounded that in FS-affected patients retinal astrocytes are more often activated, oxidative stress is increased and optic nerve compartment syndrome could more often be detected [1]. Moreover, in the patients with FS, not only the retinal vessels of the optic nerve head are less shifted to the nasal side, but also larger long-term fluctuations of the diffuse component of visual field defects are observed [1–3]. All these suggest that the vascular systems of people with FS respond differently to various stimuli (e.g. reacting with vasoconstrictions to cold or stress) [1, 18, 19]. Despite the anatomically normal appearance of their vessels, those people with FS have stiffer retinal vessels, as pulse waves in their retinal vessels propagate faster compared to those of subjects without FS [1, 20].

3 Sjögren Syndrome

Sjögren syndrome (SS) is a systemic autoimmune disease with a prevalence of 1–3%, characterised by an impaired endothelium-dependent vasodilation in primary SS patients [10], affecting more women than men (ratio of 9:1). SS is characterised by lymphocytic inflammation of lachrymal and salivary glands resulting in dryness of the mouth and ocular mucosa as well as polyclonal B lymphocyte hyperactivity with a characteristic autoantibody profile (rheumatoid factors, anti-SS-A and anti-SS-B antibodies). Clinically, in addition to the cardinal presentation of sicca symptoms of dry eyes followed by dry mouth, other common presenting manifestations of Sjögren syndrome may, therefore, include inflammatory joint and muscle pain, chronic fatigue, swollen salivary glands, demyelinating disease, neuropathies and abnormal lab values. In the pediatric population, the most common presentation of childhood SS is recurrent parotitis [12, 21, 22]. Onset of the SS

usually occurs in young women, and a benign course of the disease is often encountered [23]. The salivary gland dysfunction is of major consequence for oral health including increased susceptibility to dental caries, gingivitis, and periodontitis [12, 24–26]. SS can occur as a clinical entity alone or co-expressed with other systemic autoimmune rheumatic disorders. The serological hallmark of SS is the presence of circulating autoantibodies against soluble nuclear RNA containing antigens, Ro/SSA, and La/SSB [12, 27, 28]. The aetiology and pathogenesis of SS remain elusive. Although activation of innate immunity and infiltration of lymphocytes (B and T cells) are considered as the histopathologic hallmark of SS, however, increasing evidence suggests that immune dysfunction is not the sole mechanism underneath local and systemic complications of SS. A collection of cardiovascular irregularities including renal (e.g., glomerulonephritis), cardiac and neurologic dysfunctions may occur both prior and/or post to the onset of SS [29–33]. Thus, it is essential to unravel the contribution of the endogenous mechanisms which regulate local tissue inflammatory environment and could also contribute to the recruitment of immune and inflammatory cells with consequent further exacerbation of the disease process.

4 Common Denominators Between FS and SS: New Paradigm of Synergic Dysfunction and Potential Modality in Treating Immune-Vascular Disorders

The relationship between symptoms of FS and certain vascular dysregulation-derived and systemic hypoxic effects impacted diseases such as (but not limited to) multiple sclerosis (MS) [6], glaucoma and breast cancer with aggressive metastatic disease have been reported [1, 2, 7–9, 17].

Although a number of studies have proposed a protective role for FS against the development of atherosclerosis (ATS), however, the contribution of FS to the eye diseases such as glaucoma and retinitis pigmentosa has been shown [1, 34]. Importantly, glaucoma patients with FS have additional signs and demonstrate an unilateral nonrecurring choroidal infarction, and a chronic progressive bilateral glaucomatous optic neuropathy [1, 35]. In fact, FS is considered to be a risk factor for both occlusions of ocular vessels and glaucomatous optic neuropathy [28]. Generally, patients who develop glaucomatous damage despite a normal IOP or patients with progressing glaucomatous damage despite well-controlled IOP very often suffer from Flammer syndrome. Glaucoma patients with FS have particularly large long-term fluctuations of the diffuse component of visual field defects, which is best observed with the help of a Bebie curve [1, 22]. Noteworthy, FS-affected individuals demonstrate shifted expression patterns in circulated leukocytes that indicates an involvement of the immune system in pathogenesis of FS [4, 5]. It has been reported that patients with SS, especially those with increased positivity of autoantibodies, might be prone to developing glaucoma when exposed to other

glaucomatous risk factors, such as increased IOP or vascular dysregulation. Peripapillary retinal nerve fiber layer (pRNFL) thickness, macular ganglion cell-inner plexiform layer (mGCIPL) thickness, and optic nerve head parameters were compared between control groups and patients with SS. It was revealed that eyes of SS showed thinning of pRNFL and mGCIPL thicknesses compared to the control group [15, 36–39]. Although SS patients were not clinically regarded as having glaucomatous optic neuropathy, however, the degree of thinning correlated with increased numbers of the positive autoantibody suggesting that SS patients might be prone to develop glaucoma when exposed to other glaucomatous risk factors such as increased IOP or vascular dysregulation. These findings should be considered when diagnosing or evaluating glaucomatous structural changes in SS patients [1, 15, 38–40]. Importantly, it is known that SS often coexists with other systemic autoimmune diseases, including (not limited to) RA and SLE [40–42]. In fact, it can be at any stage of SS when patients have another well-defined major connective tissue disease, in particular, RA and systemic lupus erythematosus [40]. Interestingly, dry eye disease (DED), as one of the main complications associated with SS, is also common in RA patients [39]. To summarise, although it is still too premature to make a definite relationship between FS and SS, but it is plausible to suggest such a connection, due to a number of symptoms and signs in common. Despite the fact that the mechanisms responsible for such concordance are not yet understood, however, it is reasonable to propose that a systemic vascular dysregulation and consequent functional impairment of the wall of peripheral arteries and vasculatures may facilitate the initiation, development and progression of autoimmune diseases including SS. A combination of chronic inflammation and immunological factors may explain the dysfunction of endothelium and vascular smooth muscle cells during the course of FS and SS, supporting the potential concerted symptoms and consequences, plugging FS (e.g. genetically predisposed individuals with particularly pronounced FS phenotype) into SS. Table 1 contains some of the common clinical manifestations of FS and SS.

5 Concluding Remarks: A Paradigm Shift to Predictive, Preventive and Personalised Medicine

Vascular dysfunction is a multifactorial phenomenon known as the basis for many disorders and their consequential complications. The term Flammer syndrome (FS) was introduced to blanket a suboptimal health condition with a characteristic cluster of vascular and nonvascular signs and symptoms. FS is involved in the pathology of or even may predispose to a spectrum of diseases such as normal tension glaucoma, retinal vein occlusion in patients without classical risk factors, sudden hearing loss, dry eye, dry mouth, dry vagina, breast cancer and metastatic disease, amongst others [7–9, 15]. Sjögren syndrome (SS), a systemic autoimmune disease, shares a number of signs, causative factors and abnormalities with FS. Hence, FS-induced

Table 1 Clinical symptoms and risks shared by Flammer and Sjögren syndromes

Clinical Features	Flammer Syndrome	Sjögren Syndrome
Gender prevalence (higher in female)	**YES**	**YES**
Changes in blood supply	**YES**	Partially
Changes in blood barrier permeability	**YES**	**YES**
Modulation of immune system	**YES**	**YES**
Association with other systemic autoimmune diseases	More frequently than in general population	**YES**
Sicca symptoms	More frequently than in general population	**YES**
Inflammatory process	**YES**	**YES**
Individually pronounced predisposition to prolonged and delayed wound healing	Demonstrated to certain extend in several patient cohorts with FS phenotype	**YES**
Individually pronounced predisposition to certain cancer types and to metastatic disease	**YES** (metastatic breast cancer)	**YES**

vascular dysregulation disturbs the homeostasis of circulation which in turn may result in inflammatory responses and immunologic disorders, leading to the autoimmune diseases such as SS. Further, typical for FS decreased thirst feeling, if remaining uncontrolled, may result in the whole body dehydration with all potential consequences such as dry eyes, nose, mouth, cavities, skin as well as vaginal dryness and liver problems, amongst others – the sicca symptoms [43] which are characteristic for SS that should be reciprocally investigated in FS and SS. More information regarding sicca symptoms in FS-affected individuals is provided in the book chapters "Interrelation Between Dry Mouth and Flammer Syndromes: Neglected Risks in Youth and New Concepts of Personalised Prevention" by Anatolij Kunin with co-authors, and "Specific Symptoms of Flammer Syndrome in Women Suffering from Vaginal Dryness: Individualised Patient Profiles, Risks and Mitigating Measures" by Vadym Goncharenko with co-authors. Finally, both FS and SS demonstrate individually pronounced wound healing impairment [43–45] and cancer predisposition [7–9] as discussed in the book chapter "Flammer Syndrome in the Context of Healing Impairments – Facts and Hypotheses for Multiprofessional Consideration" by Eden Avishai and Olga Golubnitschaja. Moreover, whereas FS phenotype was clearly pronounced particularly in metastasing breast cancer [8], breast inflammatory patterns were reported specifically in females affected by Sjögren syndrome [46]. More information regarding interrelations between the FS-phenotype and breast cancer is provided in the book chapters "Feeling Cold and Other Underestimated Symptoms of Flammer Syndrome in Breast Cancer Diagnostics: Is Innovative Screening on the Horizon?" by Olga Golubnitschaja with co-authors, and "Relevance of Flammer Syndrome Phenotype to Metastatic Breast Cancer: Risks by Pre-metastatic Systemic Hypoxic Environment" by Rostyslav Bubnov with co-authors.

Consequently, better understanding of mechanisms responsible for the pathophysiology of FS and SS, targeting common features and defining interaction between them would establish more reliable platform to launch individualised preventive and predictive measures effectively [47] against further progression of both FS and SS and development of potential follow-up pathologies. Hence, further studies are needed not only to identify functional links between FS and SS but also to confirm initial findings, clarify the meaning of these associations and translate them into PPPM-guidelines [47] to foster updated health policy, higher standards of health care and life quality of affected patient cohorts.

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Flammer Syndrome in the Context of Healing Impairments – Facts and Hypotheses for Multi-professional Consideration

Eden Avishai and Olga Golubnitschaja

Abstract The chapter provides insights into risk factors, causal interrelations and consequences linked to impaired wound healing and creates the conceptual platform for multi-centre studies which explore the relationship between Flammer syndrome phenotype and the phenotype-related predisposition to impaired healing. The mission of the chapter is to motivate multi-professional considerations and to develop innovative medical and technological approaches focused on predictive, preventive and personalised management of wound healing.

Keywords Predictive preventive personalised medicine · Wound healing · Risk factors · Impairment · Vascular dysregulation · Flammer syndrome · Psychology

1 Physiologic Wound Healing as a Highly Orchestrated Process

Wound healing is a complicated orchestrated process. It is almost a daily event involved in numerous ordinary activities such as finger cut during meal preparation and also extraordinary ones such as planned surgery. It starts by tissue injury and resolved by the restoration of tissue integrity. Wound healing is composed by four well controlled phases: haemostasis, inflammation, proliferation, and remodelling [1]. In the haemostasis phase the bleeding stops and the wound is sealed by vascular

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contraction, platelet aggregation and thrombus formation. The degranulation of the activated platelet and the activation of complement components initiate the inflammatory phase. During the inflammatory phase immune cells, first neutrophils and then monocytes, infiltrate the damaged tissue. These cells seek cellular debris and bacteria and sterilise the wound. The monocyte differentiate into macrophages and together with the platelets and the local extracellular matrix (ECM) release growth factors promoting fibroblast proliferation and endothelial cell activation and by that start the proliferative phase. The now dominant fibroblast synthesise and secrete ECM proteins e.g. collagen and start rebuilding the new ECM. In parallel, endothelial cell migration and proliferation start the formation of new capillary network and keratinocyte migration and proliferation start the reepithelisation. Lastly, the new tissue needs to undergo fine tuning during the remodelling phase. During this phase, ECM changes, regulated by the balance between matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinase (TIMPs), improve wound strength. In addition, regression of some of the new capillaries occurs. This process can persists over months and even years depending on the wound characteristics and the individual health condition of the patient [1–3].

2 Non-healing Wounds: Nomenclature, Statistics, Economic Burden

Any deviation from the clearly defined individual phases will alter subsequent phases and impaired the wound healing process. Pathological impairments in the healing phases and failure in completing the entire process lead to chronic non-healing wounds and to ulceration [3, 4]. Chronic wounds fail to heal in a timely manner, exhibit excessive inflammatory phase [5] and frequently persistent infection [6].

The current nomenclature is far from agreed upon [7]. Chronic wounds are defined either as those which do not follow the physiologic and timely healing process and consequently, do not result in anatomic and functional integrity, or which indeed do proceed through the repair process, however, do not result in establishing a sustained and functional product [8, 9]. In order to be called chronic wound, the wound should show no signs of effective healing for at least 4 weeks, and by some definitions for more than 3 months [9–11].

Chronic wounds incidence has reached an epidemic dimension affecting a large portion of the world population [12]. Specifically in developed countries, 1–2% of the population experience a problematic healing during their lifetime [13] leading to disability and this disability worsens wound outcomes resulting in a vicious cycle [14].

Chronic wounds affect around 6.5 million people in the USA alone and have a negative impact on the patient life quality. They pose a heavy burden to the health care system as manifested by up to 50 billion of US dollars that are spent annually in the USA alone on the treatment of the chronic wounds [15].

3 Risk Factors Contributing to Prolonged and Impaired Healing Process

There is a great number of risk factors which individually and synergistically may predispose to impaired wound healing. Both – suboptimal health conditions and/or collateral pathologies predispose the affected individuals to a slowed/prolonged healing process and to severe follow-up pathologies such as chronic inflammation, persistent infections and cancerogenous wound transformation [3].

For simplicity, we have categorised risk factors as A. non-modifiable (unpreventable) risk factors, B. modifiable (preventable) ones and C. those which arise as frequent attributes of comorbidities known as strongly contributing to slowed and impaired healing processes. The main factors are briefly summarised below within the corresponding category as recently reviewed by Eden Avishai with co-authors [3].

(A) Non-modifiable risk factors

Inborn genetic defects with a consequent predisposition to vascular dysregulation, occlusion and vasculopathies, immune system deficits, and premature/accelerated ageing, amongst others

(B) Preventable risk factors

Unhealthy and suboptimal life style, smoking, abnormal alcohol consumption, disordered eating, abnormal body weight (both overweight and underweight), psychological stress, and imbalanced vasoconstriction, amongst others

(C) Slowed and impaired healing as a part of comorbid health conditions:

Cardiovascular pathologies, venous ulceration, autoimmune diseases, metabolic syndromes, eating disorders, mood disorders, acute and chronic infections, malignancies and anticancer therapies, amongst others.

Despite the high diversity of the origin and outcomes, A. B. and C. share specifically an imbalanced vascular regulation and/or vascular pathologies as the best acknowledged risk factors for slowed and impaired healing processes.

4 Why Flammer Syndrome Phenotype Is of Importance in the Context of Healing Impairments?

As illustrated by Olga Golubnitschaja in the introductory chapter "Flammer Syndrome in the Global Context – The "U-Shape" of Health Risks", within the entire spectrum of the general population, individuals with abnormal BMI (both overweight and underweight) are strongly predisposed to a number of pathologies which include an impaired healing. On the one hand, obesity is a well-known risk factor for diabetes mellitus type 2, chronic wounds and impaired healing process.

On the other hand, there is accumulating knowledge about the opposite extreme, namely lean people who, likewise may be strongly predisposed to healing impairment [16] and consequent pathologies [17]. Flammer syndrome (FS) is the most representative phenotype specifically in the subpopulation of young people, taking care of their body shape, therefore, physically (hyper)active demonstrating low BMI and a number of other particularities which can be clearly recognised in adolescents by applying the FS-questionnaire [18]. Contextually, prolonged and impaired wound healing has been self-reported by a number of young FS-affected individuals as presented by the book chapters "Interrelation Between Dry Mouth and Flammer Syndromes: Neglected Risks in Youth and New Concepts of Personalised Prevention" by Anatolij Kunin with co-authors, and "Specific Symptoms of Flammer Syndrome in Women Suffering from Vaginal Dryness: Individualised Patient Profiles, Risks and Mitigating Measures" by Vadym Goncharenko with co-authors. Some of the FS specific signs and symptoms which are most likely linked to healing impairments are listed below with corresponding justification.

4.1 Disturbed Microcirculation

Flammer syndrome features a strongly pronounced primary vascular dysregulation [19]. Imbalanced vasoconstriction characteristic for the FS-affected individuals provokes several reactive processes disadvantaging physiologic healing including systemic hypoxia, local ischemic lesions, nutritional and oxygen undersupply, and oxidative stress to the affected tissues with consequently restricted regenerative capacity [3, 20].

4.2 Obsessive Personality

Stress and abnormal stress reactions play an important role in both Flammer syndrome and wound healing impairments. Individuals with Flammer syndrome phenotype demonstrate a pronounced tendency towards perfectionism. They have strongly imbalanced and prolonged vasoconstriction (disturbed microcirculation) under stress conditions of different origin such as low temperature and emotion stress provocation) [19]. On the other hand, stress and abnormal stress reactions are known to slow down wound healing by interfering with the different phases of physiological healing that results in disturbed microcirculation, chronic inflammation, compromised immunity and altered gene regulation patterns which synergistically impair the physiologic healing [21–24]. Consequently, the obsessive personality and abnormally strong reaction towards stress conditions do predispose individuals with FS phenotype to impaired healing, as has been reported by recent publications [17, 25].

4.3 Low BMI and Highly Restricted Energy Resources

For individuals with FS phenotype low BMI is very characteristic. It is crucial to note here that not everybody is genetically predisposed to thinness. However, lean body shape is aggressively propagated as the symbol of beauty and healthy lifestyle by media and several industrial branches such as fashion industry, dietary products etc. Particularly young females follow the trend as discussed in the introductory chapter "Flammer Syndrome in the Global Context – The "U-Shape" of Health Risks". Obsessive personality and perfectionism, further, drive affected people to extreme success by unhealthy dieting that may result in manifested "disordered eating" or even eating disorders such as anorexia nervosa considered in the below provided paragraphs. In turn, non-physiologically low BMI is related to highly restricted energy resources that hinders the performance of repair and regenerative processes in the body. Nutritional deficits in carbohydrates, proteins and/or fatty acid result in delayed wound healing [3]. The consequences are multi-faceted including insufficient DNA repair, chronic wounds with potential transformation into pre-cancerous/cancerous lesions, and mood disorders, amongst others. On the other hand, fasting periods have been shown to deepen the FS symptoms [19].

4.4 Risks by Altered Regulation of Senses

Altered sense regulation is characteristic for the FS phenotype; the most typical is the abnormal thirst and pain regulations. Just one example: FS individuals demonstrate abnormally reduced feeling of thirst. If not consciously controlled by mind, this may lead to limited daily liquid intake potentially resulting in the systemic dehydration [19]. Systemic dehydration is a strong risk factor for headache and migraine (typical for FS-affected individuals), breast cancer predisposition (see the book chapters "Feeling Cold and Other Underestimated Symptoms of Flammer Syndrome in Breast Cancer Diagnostics: Is Innovative Screening on the Horizon?" by Olga Golubnitschaja with co-authors, "Relevance of Flammer Syndrome Phenotype to Metastatic Breast Cancer: Risks by Pre-metastatic Systemic Hypoxic Environment" by Rostyslav Bubnov with co-authors, "Triple-Negative Breast Cancer with Pronounced Flammer Syndrome Phenotype – Case Report" by Kristina Biskupska Bodova with co-authors), Sicca syndrome and hyposalivation – the most common aetiology of xerostomia [25]. Saliva is crucial for the protection of the oral cavity and digestive tract; therefore "dry mouth" frequently results in chronic infections, oral ulcers, otorhinolaryngological and dental complications, and chronic inflammatory processes which can be systemic including non-healing wounds [26]. To this end, prolonged and impaired wound healing has been self-reported by a number of young FS-affected individuals as presented by the book chapter "Interrelation Between Dry Mouth and Flammer Syndromes: Neglected Risks in Youth and New Concepts of Personalised Prevention" by Anatolij Kunin with co-authors.

4.5 Altered Circadian Rhythms

Shifted circadian rhythms (CR) are characteristic for the FS-affected individuals [19]. On the other hand, CR disorders strongly affect the quality and tempo of the wound healing process [27]. Indeed, CR allow for anticipation daily changes in the environment that corresponds with the day–night cycle and adjusts individual behaviour and physiology accordingly. From metabolic function to sleep regulation, CR have various effects at both – cellular and systemic levels. CR have been suggested to optimise cycles of cell division during wound healing, and has been shown to be crucial for proper immune system functions [28, 29]. It can affect cell migration and adhesion by modulating the cell's cytoskeleton [30]. Observational studies demonstrate that the time of injury significantly affects healing, with daytime wounds healing much faster than night-time wounds. Faster wound healing may be mediated by circadian rhythms-driven coordination of the temporal order of the essential wound healing stages: inflammation, leukocyte trafficking, tissue remodelling [31]. The interrelations between FS phenotype and sleeping patterns as well as potential consequences for the affected individuals are discussed in more details in the book chapter "Relevance of Flammer Syndrome to the "Sleep-Wake Rhythm: Possible Mechanisms, Risks and Preventive Strategies" by Kneginja Richter with co-authors. The role of the gene regulation typically altered in FS individuals is considered by the next paragraph.

4.6 Altered Gene Regulation

Systemic alterations in molecular patterns are characteristic for the FS-affected individuals [17, 32, 33]. Herewith we provide some relevant examples. Increased level of endothelin-1 (ET-1) in blood is characteristic for the FS-affected individuals [19]. ET-1 is a potent vasoconstrictor which is constitutively expressed by vascular endothelium and is important for the maintenance of vascular tone [34]. The elevated level of ET-1 links FS phenotype with the healing impairments by several mechanisms listed below.

- Hemostatic phase – ET-1 can increase platelet adhesion and aggregation [35].
- Inflammatory phase – ET-1 is known to be pro-inflammatory and can increase the expression of leukocyte adhesion molecules and regulate cytokine production [35].
- Proliferation phase – ET-1 promotes the secretion of thrombospondin [36] and alters VEGF activity [37].
- Remodelling phase – ET-1 increases the synthesis of fibronectin and by that promote fibrosis of different tissues [38, 39].

Another highly relevant abnormal gene regulation in FS phenotype considers specifically the core of tissue-remodelling proteins [33]. MMPs play a central role in the overall wound healing process [4]. Altered MMP patterns are related to

abnormal wound healing, degenerative processes, tumour promoting and metastatic activities, amongst others.

4.7 Pathologies Relevant for Both FS Phenotype and Impaired Wound Healing

Although a number of studies have proposed a protective role for Flammer syndrome against some disorders e.g. development of atherosclerosis, individuals with Flammer syndrome are predisposed to a spectrum of severe pathologies such as normal tension glaucoma, retinal vein occlusion, sudden hearing loss, aggressive breast cancer subtypes and metastatic disease, amongst others [19, 40, 41].

Anorexia Nervosa

The link between Flammer syndrome and anorexia nervosa is currently under extensive investigation. There are some indications that anorexia nervosa can be seen as an extreme case of the FS phenotype. Low BMI is characteristic for FS-affected individuals, and anorexia nervosa patients often exhibit specific FS symptoms and signs. Perfectionism in "dieting" is known for both. To this end, more information is provided by the book chapter "Flammer Syndrome-Affected Individuals May Be Predisposed to Associated Pathologies Early in Life: Psychological and Psychiatric Aspects" by Olga Golubnitschaja with co-authors. Fasting intensifies the vascular dysregulation symptoms in FS-affected individuals [42, 43]. As explained above, insufficient nutrients and oxygen supply synergistically hinders physiologic healing. Anorexia nervosa is well known as causing impaired wound healing; malnutrition, restricted energy resources, chronic inflammation, compromised immune defence, depression and hormonal dysregulation are the well-acknowledged attributes [3, 4]. To this topic more information is provided by the book chapters "Flammer Syndrome, Disordered Eating and Microbiome: Interrelations, Complexity of Risks and Individual Outcomes" by Rostyslav Bubnov and Olga Golubnitschaja, "Nutritional Approach to the Common Symptoms of Flammer Syndrome" by Niva Shapira.

Sjögren Syndrome

Sjögren syndrome and Flammer syndrome have been hypothesised as linked to each other due to a number of symptoms and signs they have in common such as epidemiological similarities, immune dysregulation, vascular barrier disruption and blood supply disturbances [44]. Compared to the general population, Sjögren syndrome patients are more prone to oral infections, inflammation and chronic wounds [45, 46] – see the book chapter "Flammer and Sjögren Syndromes: What and Why Is in Common?" by Babak Baban and Olga Golubnitschaja.

Cancer and Metastatic Disease

The systemic hypoxic environment in FS health condition is a strong contributor to aggressive metastatic disease [40]. The vascular dysregulation characteristic for the Flammer syndrome individuals may act as a risk factor for metastatic disease by creating pre-metastatic niches and a fertile microenvironment for metastases to settle in [47] as presented in the book chapter "Relevance of Flammer Syndrome Phenotype to Metastatic Breast Cancer: Risks by Pre-metastatic Systemic Hypoxic Environment" by Rostyslav Bubnov with co-authors". Specifically, in breast cancer overexpression of ET-1, characteristic for the Flammer syndrome phenotype, is linked to particularly poor prognosis [48].

The causality between wound healing and cancer has been demonstrated to be reciprocal [3, 4]. On the one hand, cancer patients frequently demonstrate delayed wound healing and are at significant risk of operative complications [49, 50]. On the other hand, the chronic inflammation of non-healing wounds may create specific microenvironment suitable for metastasis and may lead to pre-cancer lesions [51–54].

Wound healing and cancer are similar in many aspects and they share several key-cellular and molecular repertoires: epithelial movements, accelerated cell proliferation, and ECM remodelling with neovascularisation [55]. Many of the inflammatory mediators, and growth stimuli that mediates these effect are common for both wound repair and cancer onset and progression [4]. Aggressive cancer development and impaired wound healing also share abnormal activities of MMPs and abnormal growth factor profiles [4]. Above listed pathways are abnormally regulated in FS-affected individuals [17, 33].

Dysregulation of several signalling pathways critical for stem cell regulation are involved in tumour development and in impaired wound healing [4]. As described above, circadian rhythms have been suggested to strongly influence stem cell populations, cell division during wound healing, and immune progenitor differentiation and migration [28]. Due to altered circadian rhythms, FS-affected individuals may be expected to have stem cell populations which are differently regulated compared to general population.

Lastly, nutrition, which is an important aspect for the Flammer syndrome phenotype, has been found to be an issue also for many cancer patients. This increases their tendency for infections susceptibility and aggravates their wound healing impairment [3].

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Feeling Cold and Other Underestimated Symptoms of Flammer Syndrome in Breast Cancer Diagnostics: Is Innovative Screening on the Horizon?

International Multi-centre Study

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Abstract Significant deficits in breast cancer management led to the epidemic of the pathology in the early twenty-first century. Therefore, it is an emergency now to revise the persisting traditional approaches in BC management as well as to broaden our vision in many aspects regarding the BC aetiology and multi-factorial risks creating new concepts for effective screening programmes, innovative predictive, preventive and prognostic approaches tailored to the person.

Our international pilot study provides clear evidence for the relevance of the Flammer syndrome (FS) phenotype to breast cancer diagnostics and patient stratification. We conclude here that individual signs and symptoms of FS might be

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of great clinical utility for the targeted phenotyping, identification of persons at high versus low risk, predisposition to individual BC subtypes, patient stratification, and innovative screening programme applied to the general population.

What are the next steps to realise the innovation practically? Family doctors should be supplied with the FS-questionnaire to identify persons with symptoms characteristic for the FS-phenotype who may be predisposed to BC development. This patient stratification by phenotyping may be extremely useful, if becomes applied early in life, in order to mitigate modifiable risk factors and avoid the disease manifestation. For monitoring of potential disease progression, pathology-specific biomarker-panels are essential; moreover, individual BC subtypes should be carefully considered.

Keywords Paradigm change · Predictive preventive and personalised medicine · Premenopausal · Young population · Postmenopausal · Breast cancer · Epidemic · Risk factors · Aetiology · Body shape · Flammer syndrome · Questionnaire · Symptoms · Psychological factors · Obsessional personality · Diagnostics · Prevalence · Systemic hypoxia · Patient stratification · Cardiovascular · Stress · Pain sensitivity · Sense regulation · Smell · Tinnitus · Drug sensitivity · Thirst · Dehydration · Headache · Dizziness · Circadian rhythms · Sleep patterns · Endothelin · Thermoregulation · Heat production · Fever · Pro-inflammatory cytokines · Molecular targets · Individualised patient profile · Interpretation · European challenge · Innovative concepts · Screening · Phenotyping · Genotyping · Multi-centre project

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Abbreviations

BC	breast cancer
blood CA-125	cancer-specific antigen detectable in blood
BMI	body mass index
breast-MRI	magnetic resonance imaging adapted specifically to the breast diagnostics
CT	computer tomography
ER+/PR+	oestrogen-progesterone receptor positive
FIA	fibro-adenoma
FS	Flammer Syndrome
Her-2	human epidermal growth factor receptor 2
PET	positron-emission tomography
TN	triple-negative subtype of BC

1 Traditional Disease Management Resulted in the Breast Cancer Epidemic as Recognised for the Early Twenty-First Century

In 2018 Springer has selected around 250 articles across all areas with *a potential to change the world* which have been awarded the title "groundbreaking scientific findings that could help humanity and protect our planet" [1]. Specifically in the category "Medicine and Public Health", [2] the article titled "Pregnancy-associated breast cancer: the risky status and new concepts of predictive medicine" published by Jiri Polivka Jr. with co-authors in the EPMA Journal [3] has been selected as demonstrating the *potential to change the world*.

Why so much attention is dedicated to the topic of "young" breast cancer and why PPPM strategies are strongly recommended to be applied to breast cancer management that awakes particularly great hope?

Specifically in case of the "pregnancy-associated" breast cancer which is most prevalent cancer type associated with pregnancy, psychological and ethical aspects play a crucial role, due to the highest priority not to damage the foetus [4]. Therefore, it happens frequently that patients disclaim undergoing any breast cancer treatment during their pregnancy. Consequent postpartum BC treatment is more costly but less effective, due to advanced stages of the disease [5–7]. Delayed diagnosis and treatment (if any) in combination with particularly aggressive cancer type result in dramatically decreased overall survival in PABC patient cohort [8]. No any population (screening) programme, no generally accepted risk factors, no standardised diagnostic approach, and no targeted preventive measures dedicated specifically to the PABC are currently established [9]. However, the particularly bad news is that these deficits are common for the entire "young" BC patient cohort persisting over decades in breast cancer management. Perhaps this is one of major reasons why

breast cancer (BC) prevalence in all populations worldwide has reached an epidemic scale in the early twenty-first century [10]. Therefore, it is an emergency now to revise the persisting traditional approaches in BC management as well as to broaden our vision in many aspects regarding the BC aetiology and multi-factorial risks creating new concepts for effective screening programmes, innovative predictive, preventive and prognostic approaches.

2 How to Diverge from the Traditional Approach?

To diverge from the traditional approach, here we will not follow the attributes of currently persisting "stream" considering BC patients as the "carriers" of the genetic mutations (potentially) linked to the pathology. The reason for that is that the familial BC comprises less than 10% of the overall BC patient cohort. In contrast, our interest is dedicated to the absolute majority (over 90%) of the patients with so-called "sporadic" BC, who do manifest the pathology due to rather non-genetic but modifiable risk factors. That means the risks which are well preventable, if individually recognised well in time.

Some modifiable factors are well known as linked to the increased BC risks. These is an entire spectrum of endogenous and exogenous stress factors such toxic environment, smoking, inappropriate alcohol consumption, and unhealthy lifestyle including low physical activity, but also the late first full-term pregnancy without breastfeeding, obesity, imbalanced diet, and relevant pathological processes such as chronic inflammation [10]. This information is available since couple of years and even decades for educational and preventive measures applied to the general population; however, those measures seem to be less effective according to the actually recorded dramatically increasing BC prevalence.

On the other hand, there is an accumulating number of case reports in the BC-related fields which unfortunately receive too little attention by the broad scientific community being considered as "atypical" cases and/or even anecdotes which are good enough for "twitter" and patient communication-oriented websites discussing what and how individual BC patients do feel before the diagnosis, during and after the treatment. However, the question is, whether the truly mission of the "personalised medicine" and related branches (see the classification here – [11]) is not exactly about to treat each patient as an "individual" case?

Utilising this way of thinking, let us highlight a series of underestimated symptoms known as case reports and "atypical" cases which, however, seem to reach the "critical mass", in order to be considered as essential attributes of BC risks assessment and patient stratification.

3 Headache and Dizziness

In contrast to the well-recognised risk factors, such as tobacco smoke (both active and passive), uncertainty regarding its potential relevance for breast cancer begins perhaps with the headache appearance and its individual interpretation. Migraine: no relevance versus higher or lower risk for BC? These questions are relatively new and strongly disputed in the literature. Considering the matter logically, it is difficult to deny the functional link between two pathologies, due to hormonal and vascular components – both obligatory involved in BC and migraine attacks. Hence, oestrogen is one of the key molecules and regulators involved in the aetiology of both migraine and BC. However, the epidemiologic findings are controversial: on the one hand migraineurs, in general, demonstrates a reduced risk for BC [12–14]. On the other hand, an increased risk to develop particularly aggressive subtype of the triple-negative BC has been recorded amongst migraineurs without aura [15]. Those findings lead to the conclusion that better patient stratification is essential in BC in order to find clear interrelations between individual symptoms and individual BC subtypes. To this end unfortunately, early and light symptoms are frequently underestimated by conventional diagnostic procedures. However, when severe symptoms appear, it is frequently too late for curative care specifically in case of particularly aggressive metastatic BC subtypes. Just an example by corresponding case report: a young (37 years old) woman complained about persistent headache, dizziness and blurring of vision in episodes occurring up to 5-times daily. Whole-body cross-sectional CT, PET, breast-MRI, and mammography applied accompanied by investigation of blood CA-125 and axillary lymph node biopsy revealed poorly differentiated breast malignancy as the primary site followed by metastatic leptomeningeal disease. The treatment intent was palliative [16]. The major concern in this case is that the patient had experienced lighter headaches and migraines for a long time but, obviously, too little attention has been paid to this symptom by primary caregivers. First towards the appearance of severe headache and disturbances of the visual field the patient has been diagnosed and treated, when, unfortunately, only palliative approach was possible to perform.

Further, the paraneoplastic cerebellar syndrome is known for breast cancer patients diagnosed usually in the inverse sequence against the original appearance of the pathological events, namely: first the paraneoplastic cerebellar syndrome is diagnosed that finally emerged as the brain metastasis originated from the breast cancer, which however, is diagnosed secondly after the discovery of the metastasis [17]. Although, those cases are published generally by case reports, recently we have published a review article titled “Mystery of the brain metastatic disease in breast cancer patients: Improved patient stratification, disease prediction and targeted prevention on the horizon?” [18]. The article analyses important aspects of the interrelation between particularly aggressive BC subtypes and brain metastasis: on the one hand, primary brain tumours is a rare disorder responsible, however, for high mortality and morbidity; their prevalence in general population is ranging between 12.0 and 15.5 per 100,000 person-year for different countries and regions worldwide [19–22]. On the other hand, the brain is one of the predominant sites of

the metastatic spread recorded for more than 20% of breast cancer patients in several individual subgroups [23, 24]. Although being highly clinically relevant, this mystery has not been yet adequately explained. Contextually, innovative multi-level diagnostic approaches are needed to predict BC patients at high risk for the potential development of brain metastasis [18].

4 Sensitivity to Different Stimuli in BC Patients

Similarly to the above noted facts, the observations about BC patients are usually made, when BC is clinically manifested that means during BC treatment and within the survivors when plenty of additional factors (such as diagnosis-related psychological stress, post-surgical syndromes, irradiation, drug application, etc.) strongly contribute to or even modify the overall sensitivity of the treated patient towards different stimuli. Consequently, the retrospective analysis in the post-diagnosis period is not simple for reconstructing original individual phenotypes and symptoms of the disease predisposition and/or progression before the diagnosis. Nevertheless, here we intend to summarise the accumulated information about the reaction of BC patients towards individual stimuli before (if available) and after the BC diagnosis.

4.1 Pain Sensitivity

The absolute majority of the papers dedicated to the pain sensitivity in BC are focused on BC patients under treatment and in survivors. However, some recent studies demonstrated a strong correlation between preoperative and postoperative pain sensitivity specifically in breast cancer patient cohorts. Moreover, the younger ages have been identified as a risk factor for stronger pain sensitivity in this patient cohort [25]. Further studies have made a clear functional link between the increased endothelin-1 (ET-1) levels on the one hand, and spontaneous pain and temperature perception on the other hand. The ET-1 dose-dependent effects have been observed even in healthy male volunteers who underwent the ET-1 injection [26]. To this end, ET-1 is a growth factor and systemic vasoconstrictor overexpressed in breast carcinomas with particularly poor prognosis.

4.2 Thirst Feeling and Dehydration in BC

Actually a very few papers are dedicated to the thirst feeling in breast cancer and all of them are focused on the issue during BC treatment and BC patients specifically with diabetic history. On the other hand, it is well known that reduced water intake

leading to mild or severe body dehydration is a strong risk factor for several pathologies including breast malignancies [27] and headache/migraine attacks [28]. However, if any, highly restricted information is available regarding potential mechanisms of the dehydration in breast cancer predisposition and pathology. Is the thirst feeling normal or dysregulated in BC predisposed and diseased individuals? Dissatisfaction with the taste of water, imbalanced consumption of natural diuretics (e.g. caffeine and alcohol), amongst others, might be also the reasons for the reduced water intake. May one of these possible reasons be more specific for BC pathology than others? These questions remain currently non-responded in the scientific literature and medical practice.

4.3 Smell Perception

It is well known that cancer patients smell differently compared to the general population. Based on that, canine olfactory detection of human malignancy is a phenomenon well-documented in the scientific literature [29]. Specifically, a detection and identification of breast cancer volatile organic compounds biomarkers utilising highly sensitive chips technologies is described [30]. Our question is, whether the smell perception of BC patients and/or pathology predisposed individuals may be also altered against general population that can make them more or less sensitive towards the smell. This question remains currently non-responded in the scientific literature.

4.4 Sensitivity to Light Exposure, Circadian Rhythms and Sleep Patterns in BC Pathology

Sunshine/UV-light plays an essential role in BC prevention. Contextually, protecting effects by vitamin D supplements have been initially demonstrated [31]. However, recent studies suggested further mechanisms of the regular sunshine exposure strongly contributing to the BC protection, namely immunomodulation, the formation of nitric oxide, melatonin, serotonin, and the effect of (sun)light on circadian clocks [32]. Abundant epidemiological studies performed on shift work indicated circadian gene variants as candidates involved in breast cancer development [33]. Moreover, a particular role of the circadian genes is implicated specifically in the pathomechanisms of more aggressive and actively metastasing BC subtypes, such oestrogen receptor-negative BC [34, 35] that makes the issue of the circadian rhythms and, contextually, sleep patterns particularly important for our better understanding mechanisms underlying BC pathology. To this end, sleep patterns, generally, are still poorly investigated in BC patients and pathology-predisposed individuals; their role is not specified in individual BC sub-types and

development of metastatic activity. More information towards interrelations between circadian rhythms, shift work, predisposition to breast cancer, and Flammer syndrome phenotype is provided in the book chapter "Relevance of Flammer Syndrome to the "Sleep-Wake" Rhythm: Possible Mechanisms, Risks and Preventive Strategies" by Kneginija Richter with co-authors.

5 Endothelin-1 Patterns in BC

ET-1 acts as a growth factor being overexpressed in several malignancies [36]. Specifically in breast cancer, the overexpression of ET-1 is linked to particularly poor prognosis [37]. Further, ET-1 is a systemic vasoconstrictor essentially involved in vascular regulation (blood patterns). Upregulation of ET-1 levels in blood leads to local and systemic hypoxic effects [38], and hypoxia, in turn, is a strong contributor to the aggressive metastatic disease [39, 40]. Besides this general recognition, ET-1 blood patterns are poorly understood in individual BC subtypes and, currently are not utilised for a patient stratification specifically predisposed to the metastatic disease.

5.1 "Feeling Inappropriately Cold" in BC

Current literature provides sufficient evidence to conclude that breast cancer patients are frequently deficient in achieving thermal comfort: they feel excessively hot or cold even in situations, when disease-free attenders are well comfortable with ambient temperature conditions [41]. While "feeling too hot" received both scientific and clinical attention in context of menopausal symptoms (hot flashes) and related treatment approaches, "feeling inappropriately cold" was for a long time completely out of focus in the overall breast cancer management – corresponding information is still limited to the anecdotal data/case reports. If so, why do we attract a special attention to the phenomenon of the deficient thermoregulation in BC?

Well-controlled thermoregulation is crucial for the human body: all the biochemical reactions are adapted to a relatively narrow internal temperature range of 36.5–37 °C, which is rigorously kept by the body to allow for the optimal performance of all physiological processes. In general, "feeling cold" is a normal response towards changing external temperatures, in order to win back the thermal equilibrium/comfort by the well-concerted regulation mechanisms. These mechanisms trigger immediate vasoconstriction and increase the actual blood pressure and heart rates that altogether results in both – the heat production and conservation for maintaining the optimal body temperature [41]. In contrast to this immediate response leading to the normalised thermal comfort within a short time-frame, "feeling persistently cold" may indicate mainly two pathological conditions described below.

The Heat Production Is Not Effective Enough to Maintain the Physiologic Body Temperature

This condition can be reflected, for example, by persistently cold extremities. Maintaining thermal comfort is energetically costly [42] that requires well organised energy supply by concerted mitochondrial cooperation at molecular and cellular levels. To this end, dysfunction of the mitochondrial respiratory chain has been demonstrated in BC cells [43]. Further, linked to the oxidative stress mechanisms, a systemic mitochondrial dysfunction and DNA damage/misguided repair have been proposed as implemented in the BC pathology [44].

Fever or Fever-Like Conditions with Excessive Chill Attacks

For fever or fever-like conditions, excessive chill attacks are characteristic, despite normal or even increased body-temperature of the affected person. The fever condition as the response against infections demonstrates altered profiles of pro-inflammatory cytokines (IL-1, IL-6, TNF-α) regulating the immune reactions [45]. On the other hand, the same pyrogenic cytokines are frequently overexpressed by cancer patients [46] and may affect the thermoregulation function of hypothalamus by activating the cyclooxygenase 2 (COX-2) and increasing the production of prostaglandins [47].

Since BC related defects in thermoregulation might be an important diagnostic and prognostic indicator, significant efforts should be dedicated to this phenomenon investigating the underlying pathomechanisms and selecting BC specific regulatory pathways and molecular targets for diagnostic and treatment purposes.

6 Concluding Remarks Linking the Flammer Syndrome Phenotype with Breast Cancer Risks and Pathomechanisms

As already explained above, the below summarised symptoms, functional links and underlying mechanisms might be of particular interest for the overall BC management, in terms of pathology predisposition, disease development and progression as well as of patient stratification for individualised treatments, namely

- Deficient thermoregulation
- “Feeling inappropriately cold”
- Persistently cold extremities
- Altered sensitivity to different stimuli: pain, thirst, smell, light, stress provocation (including internal and external stress factors)
- Dehydration
- Altered circadian and sleep patterns
- Tendency towards headache, migraine attacks and dizziness
- Altered Endothelin-1 blood patterns
- Local and systemic hypoxic effects.

Further, as we have published recently, abnormal BMI (both underweight and overweight) is linked to BC risks [10]. While BC risk by obesity is relatively well described in the literature, abnormally low BMI is less investigated in relation to BC. To this end, very recent studies demonstrated a particular attraction of this area, since underweight women seem to be at higher risk specifically for BC with poor outcomes [48].

All the above summarised symptoms are strongly underestimated in the overall BC management. In our previous publications we have justified a highly innovative hypothesis bringing BC patient stratification in the context of the "Flammer Syndrome" (FS) phenotype [10, 49]. The main reason for that is that the above listed symptoms are characteristic for the FS phenotype extensively described in 2014 by the dedicated research group [50]. It has been demonstrated that FS-affected individuals create prominent cohorts of healthy individuals in suboptimal health condition as well as patients suffering from severe diseases [38, 51]. A particular attraction of the FS phenotype for BC research comprises the following specific features:

- onset of the FS symptoms is observed early in life (puberty)
- FS is more typical for young women
- systemic molecular events characteristic for FS are evidently involved into effective BC cancer advancement [38, 52–54]
- local and systemic hypoxic effects caused by vascular dysregulation may strongly predispose FS-individuals to the formation of "pre-metastatic niches" described as the "fertile" microenvironment for particularly aggressive BC sub-types characterised by quickly progressing metastatic disease [10] – see the book chapter "Relevance of Flammer Syndrome Phenotype to Metastatic Breast Cancer: Risks by Pre-metastatic Systemic Hypoxic Environment" by Rostyslav Bubnov with co-authors.

The multi-centre study designed by international consortium to investigate the prevalence of FS in individual subtypes of BC [49] is described below.

7 Multi-centre Study Designed by International Consortium to Investigate the Prevalence of FS in Individual Subtypes of BC

7.1 Working Hypotheses

A. FS phenotype may be more prevalent in breast cancer (BC) patients compared to the disease-free individuals as justified above
B. BC is a multi-factorial disease. Consequently, FS-related profiles of signs and symptoms may be differentially pronounced by individual BC subtypes depending on accompanying risk factors – both non-modifiable (age, genetic makeup) and modifiable (environmental risks, life-style) ones

C. If the above points are true, FS-phenotype and its individual signs and symptoms might be of great clinical utility for the targeted phenotyping, identification of persons at high versus low risk, predisposition to individual BC subtypes, patient stratification, and innovative screening programme applied to the general population.

7.2 Definition of the FS Phenotype

The FS questionnaire applied to the actual study has been developed at the University Hospital Basel, Switzerland. It is based on the knowledge currently available and collected, since the phenomenon has been described [50, 55, 56]. The actual version of the FS-questionnaire has been successfully applied to study different populations [57], FS symptomatic in retinitis pigmentosa [58] as well as in multiple sclerosis [59] and other clinically relevant patient cohorts [60, 61]. With the permanently growing knowledge about the FS phenotype, the dedicated questionnaire should be, further, adapted and improved. Actually applied questionnaire comprises 15 questions altogether describing the most relevant FS-symptoms and signs gradually as following

1. Do you suffer from cold hands and/or feet? (possible answers: “frequently”, “sometimes”, “no”)
2. Do you feel cold soon, when you are not moving? (possible answers: “frequently”, “sometimes”, “no”)
3. Do you have (or earlier had) a low blood pressure? (possible answers: “yes”, “rather”, “no”, “I do not know”)
4. Do you feel dizzy when you suddenly stand up from a resting position? (possible answers: “frequently”, “sometimes”, “no”, “I do not know”)
5. Do you need a relatively long time to fall asleep? (possible answers: “yes”, “only if feel cold”, “no”)
6. How is your feeling of thirst? (possible answers: “I do not feel thirsty and drink little”, “I feel thirsty and drink a lot”, “I do not feel thirsty but I am aware and drink a controlled amount of liquid that is much more than my feeling of thirsty desires”, “my thirsty feeling and drink attitude – both are unremarkable/normal”)
7. How frequently do you suffer from a headache/migraine? (possible answers: “frequently”, “sometimes”, “no”)
8. In case you suffer from migraine attacks, do you have accompanying symptoms (e.g. visual disturbances, transient altered sensation (e.g. cribbing) in your arms or in your legs etc.)? (possible answers: “frequently”, “sometimes”, “no”)
9. If you have to take medications (other than painkillers), do you have the feeling that you react too strongly to them and/or that you would feel better, if you would take a lower dose rate than is usually prescribed? (possible answers: “frequently”, “sometimes”, “no”, “I do not know”)
10. Do you suffer from any type of pain which you should take medication against? (possible answers: “frequently”, “sometimes”, “no”)

11. How well can you smell: Can you smell odours which other people do not smell at all or stronger than other? (possible answers: “frequently”, “sometimes”, “no”)
12. Were/are you slim at the age of 20–30 years? (possible answers: “very slim”, “slim”, “average”, “overweight”)
13. Estimating your own attitude (e.g. job performance), would you say that you have a meticulous personality tending to perfectionism? (possible answers: “yes”, “rather”, “no”)
14. Have you observed that you are/were suffering from ear noise/tinnitus? (possible answers: “frequently”, “sometimes”, “no/only after noise exposure”)
15. Have you noticed reversible blotches (white or red) on your skin when you are very excited or angry (e.g. in stress)? (possible answers: “frequently”, “sometimes”, “no”).

8 Individual BC Subtypes in Pre- and Post-menopausal Women Have Been Investigated in Slovakia

8.1 Patients’ Recruitment and Examinations

The patient data-based available at the Department of Obstetrics and Gynaecology, Jessenius Faculty of Medicine, Martin University Hospital, Martin, Slovak republic has been utilised for selecting the patients as potential responders for the above noted FS-questionnaire. Following diagnoses have been chosen as the including criterion:

– Breast cancer (BC) main types stratified as Luminal, Her2-positive and triple-negative ones
– Benign breast fibro-adenoma (FIA), free of breast cancer and any other malignancy
– Healthy individuals free of breast cancer and any other malignancy.

Altogether 155 patients have been recruited for the study divided into the following groups: 73 breast cancer free (21 FIA and 52 healthy) and 82 breast cancer diseased individuals stratified as Luminal (51), Her-2 positive (13) and triple-negative (18) BC. All participants were informed about the purpose of and their rights as participants in the study. All investigations conformed to the ethical principles outlined in the Declaration of Helsinki.

Healthy Controls

All these individuals have been clinically examined attesting an absence of gynaecological problems and interviewed personally for the study during their hospital outpatients visit. BC free condition has been confirmed either by breast sonography or mammography or both imaging approaches. The examination reports used were

not older than 6 months. Healthy controls demonstrated no history of any previously diagnosed breast pathology, no surgery performed due to breast lesions and no history of any severe gynaecologic disease including cancer other than breast malignancies or any systemic diseases such as diabetes mellitus, rheumatic diseases and neurological disorders.

Breast Cancer and Fibro-Adenoma (FiA) Patients

About 90% of these patients have been selected in the data-base and then contacted telephonically by an authorised person who have explained the meaning/rules of the study and interviewed the responders through the entire questionnaire. 10% of these patients have been personally contacted and interviewed during their stay at the clinic. Imaging technologies have been applied for the 1st choice of the entire diagnostic procedure: digital mammography Hologic system, 2D + 3D sonography – Voluson USG system E8 and E10 machine, Birads 0–6 classification scoring system with double reading of the radiologic approach. In case of positivity, the affected patients have undergone the biopsy analysis (either core needle or Mammotome's vacuum-assisted). Contextually, BC diagnosis has been confirmed by core needle biopsy prior surgery, or during surgery by frozen section in cases with non-palpable lesions, non-reachable lesions for biopsy prior surgery, small lesions not indicated to core biopsy (stereotactic, core needle or Mammotome). The preoperative diagnosis of breast cancer was a part of the surgery- and management-planning. The diagnosis has been finalised by the molecular biological classification of the breast cancer subtype. Histopathological analysis (see below) has, further, allowed for distinguishing between BC malignancy and FIA benignancy.

Histopathological Analysis

Tumour and lymph node specimens have been fixed in formalin and embedded in paraffin. Basic histological examination has been performed on 4–5 μm thin slides stained with haematoxylin and eosin. In selected cases, lymph nodes have been stained immunohistochemically to detect potentially disseminated tumour cells or local micrometastases in the tumour surrounding area. Classical morphological indicators, such as type and histological grade, have been evaluated according to WHO criteria and Nottingham grading modification [62, 63]. The disease graduation and staging (tumour size and lymph node status) have been assessed according to the criteria of the latest TNM classification [64]. BC specific biological parameters (oestrogen receptors (ER), progesterone receptors (PR) and HER-2 positive status), have been evaluated immunohistochemically; the results interpretation have been performed based on ASCO/CAP criteria released in the years 2010 and 2013 [65–67]. Tumours have been considered as being ER and PR positive, if at least 1% of neoplastic cells have stained positively. Her-2 positive tumours had to express 3+ reaction in at least 10% of neoplastic cells. Cases with 2+ reaction of Her-2 staining were considered as equivocal and have been analysed by fluorescent in situ

hybridisation (FISH) to confirm or exclude Her-2 gene amplification. Definite positivity of Her-2 status in tumours has been defined as HER-2/CEP17 ratio ≥ 2.0 or average HER-2 copy number ≥ 6.0 signals per cell [66, 67]. The molecular biological classification of breast cancer and consequent patient categorisation utilises the following system of the pathology specific parameters:

a/ER+PR+HER2-Ki67low – Luminal A
b/ER+/-PR+/-HER2-Ki67high – Luminal B
c/ER+/-PR+/-HER2+/Ki67 any – Luminal C
d/ER-PR-HER2+Ki67high – Her2-positive
e/ER-PR-HER2-Ki67high – Triple negative breast cancer.

Statistical Analysis

For analytical and statistical evaluations, the data have been transferred to Microsoft Excel. SPSS Statistics v20.0.0 software (IBM, Armonk, New York, USA) have been applied. The prevalence of individual symptoms in groups of comparison has been evaluated and expressed in percentage. Pearson's chi-square test of associations has been applied. P values equal or below 0.05 have been considered as statistically significant.

8.2 Resulting Analysis Confirmed the Working Hypotheses of the Study

Age and Menopausal Status Statistics

Table 1 presents statistics provided for individual breast cancer subgroups and the group of comparison comprising breast cancer (BC) free individuals. The latter demonstrates the parity in menopausal status. Amongst BC patients the youngest is the "triple-negative" subgroup presenting 39% of premenopausal women. In contrast the "Luminal" and "Her2-positive" subgroups – both comprise over 90% postmenopausal women.

Table 1 Age and menopausal status statistics; the data are provided for individual breast cancer subgroups ("LUMINAL", "HER2"-positive and "TN" – triple-negative) and the group comprising breast cancer free individuals

	BC – subtype			
Menopausal status	LUMINAL patient number	HER2 patient number	TN patient number	BC-free patient number
Premenopausal	5	2	7	38
Postmenopausal	46	11	11	35
Patients' age mean (min–max) years	61.84 (36–85)	61.85 (46–85)	54.11 (33–77)	50.19 (19–89)

Prevalence of Individual FS Symptoms in BC Subtypes Versus Disease-Free Individuals

In Fig. 1, results achieved are summarised demonstrating the prevalence of individual Flammer Syndrome symptoms (1–15) in two main groups of comparison – "BC total" patients versus "BC-free" individuals as well as in individual subgroups of breast cancer.

Higher prevalence in "BC total" (red) has been demonstrated for altogether 11 from 15 symptoms at the level of difference ranging between 5% and 19%. The level of significance varies correspondingly with the most significant differences demonstrated for "Pain" ($p = 0.01$), "Skin flecks" ($p = 0.06$), "Low blood pressure" ($p = 0.11$), and "Feeling cold" ($p = 0.15$).

Noteworthy, substantial differences have been recorded between individual BC subtypes, even in cases when the resulting "BC total" prevalence was non-significantly higher compared to "BC-free". Hence, in case of the symptom 2 ("feeling cold") the difference between both main groups comprises 10% ($p = 0.159$); however, the prevalence in "Luminal" BC is two-times compared with "Her-2".

"BC-free" (green) group demonstrates higher prevalence only for one symptom (8. "Accompanying symptoms") and 3 symptoms (11. "smell perception", 12. "Low body weight in early adulthood", and 13. "Perfectionism") demonstrate similar prevalence in both groups of comparison. However, in case of these four (8, 11, 12, 13) symptoms remarkable differences have been demonstrated for the prevalence, when individual BC subgroups have been compared against each other. There are two most representative examples for that, namely:

1. Although symptom 8 ("Accompanying symptoms") demonstrates slightly lower (8%) prevalence in "BC total", "Her2" BC subtypes suffers from this symptom more frequently than "BC free" and demonstrates 2-times higher prevalence compared to the "Luminal" BC subtype.
2. Symptom 12 ("Low body weight in early adulthood") is in average equal for both main groups of comparison. However, across the panel, while "Luminal" BC subtype demonstrates the lowest prevalence by 47%, obviously low body weight in early adulthood is highly prevalent in both "Her2" and "triple-negative" BC subtypes by 69% and 72%, respectively.

8.3 Four Clusters of FS Symptoms Detected as Being Differentially Relevant for BC in General and Individual Subtypes of the Disease

Table 2 shows four basic clusters of symptoms.

Cluster A (marked in green colour) represents the group of symptoms with higher prevalence in BC in general as well as all individual subgroups

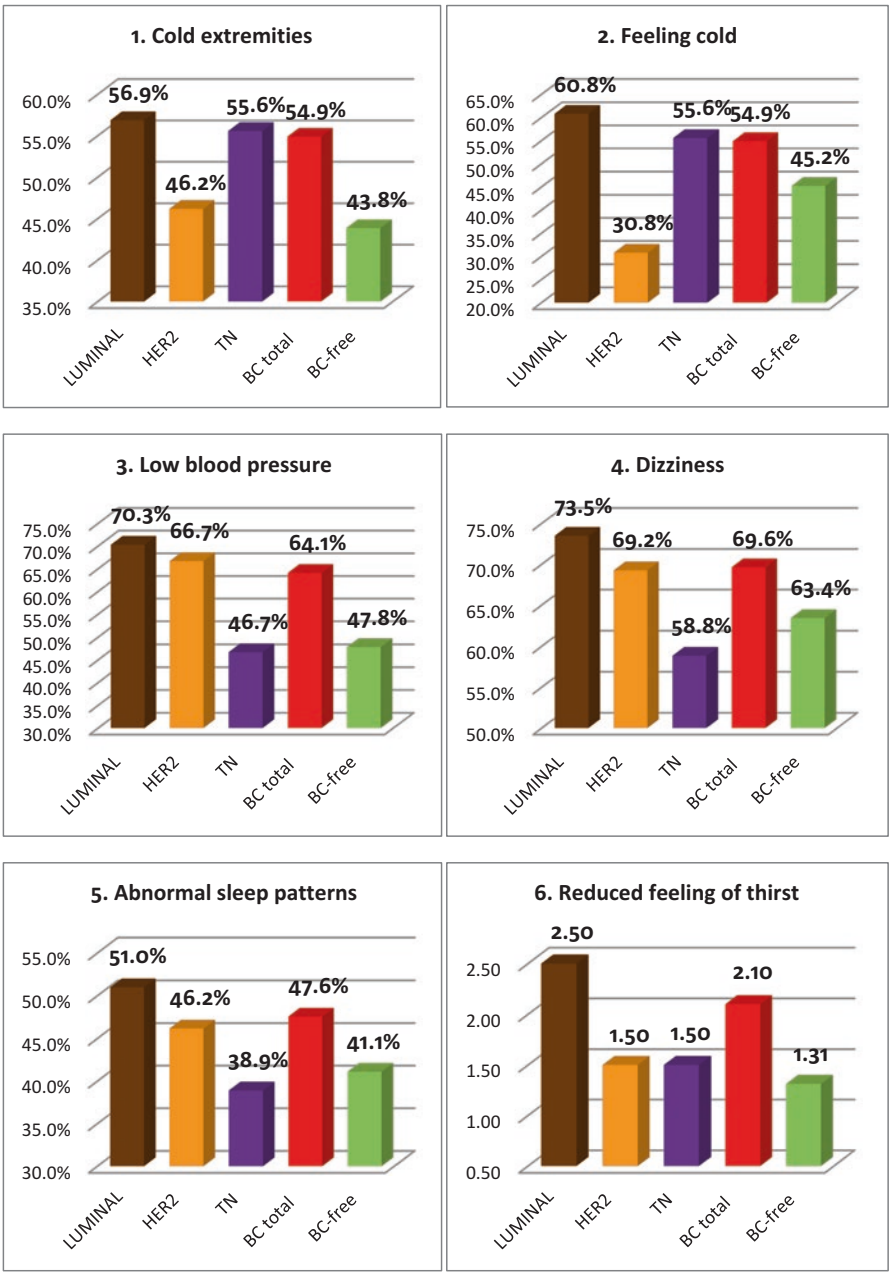

Fig. 1 Evaluation of the prevalence of individual symptoms (1–15) of the Flammer Syndrome phenotype in two groups of comparison: "Breast cancer diseased" (BC total) versus "Breast cancer free" (BC-free). Therein, the entire breast cancer patient pool ("BC total") has been additionally analysed in subgroups stratified according to the individual BC subtypes as "LUMINAL", "HER2" positive and TN (triple negative) breast cancer. For more details regarding the patient stratification – see "**Patients' recruitment and examinations**". Full description of the FS questionnaire is provided above by "**Definition of the FS phenotype"**. The prevalence in each

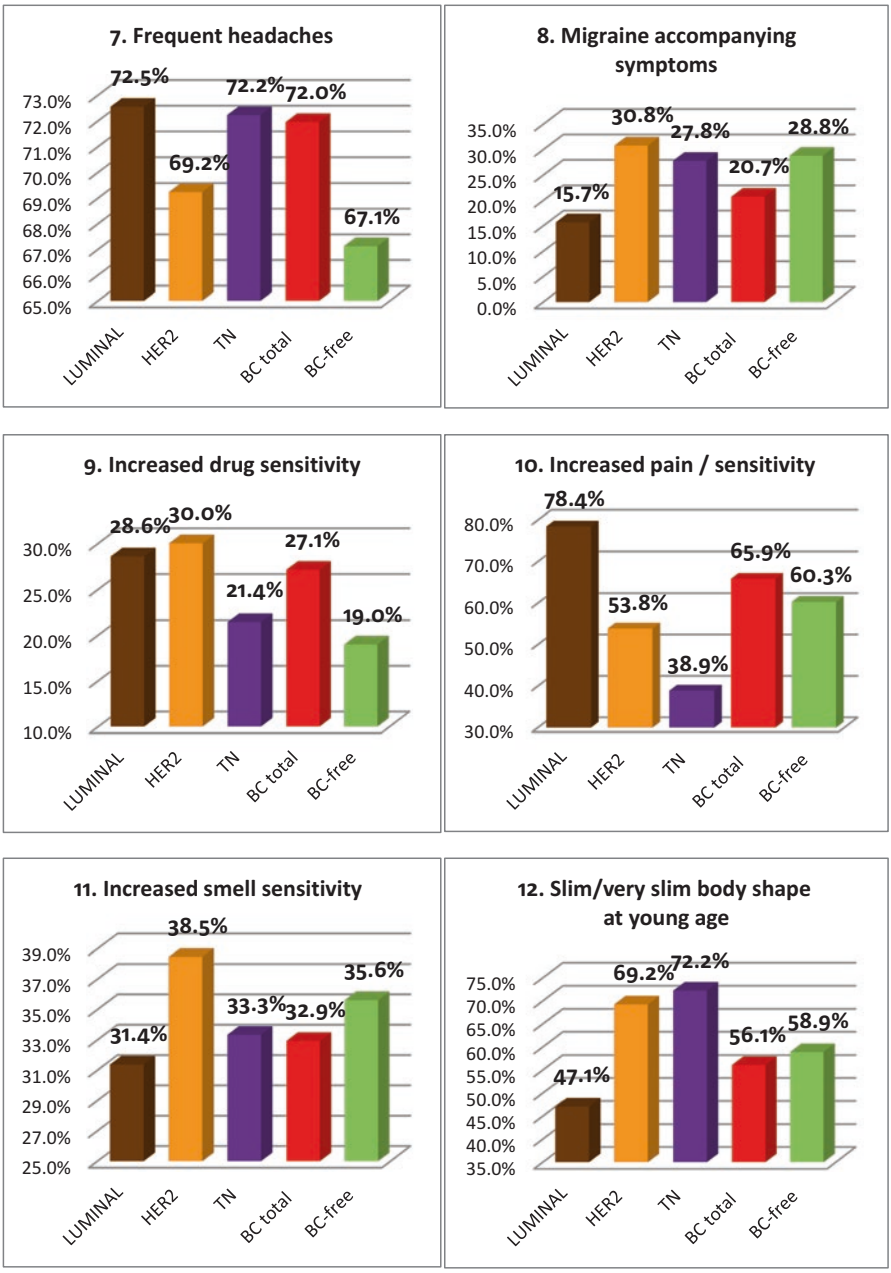

Fig. 1 (continued) individual group is presented by percentage of individuals who have responded to the corresponding question with "frequently" and "sometimes" pooled together. Responders answering with "I do not know" have been excluded from the overall numbers/calculations. Question-specific notes: Question 6 – the ratio between "I do not feel thirsty and drink little" and "I feel much thirsty and drink a lot" has been calculated and expressed in X–times; Question 12 – answers "very slim" and "slim" have been pooled together and presented in %

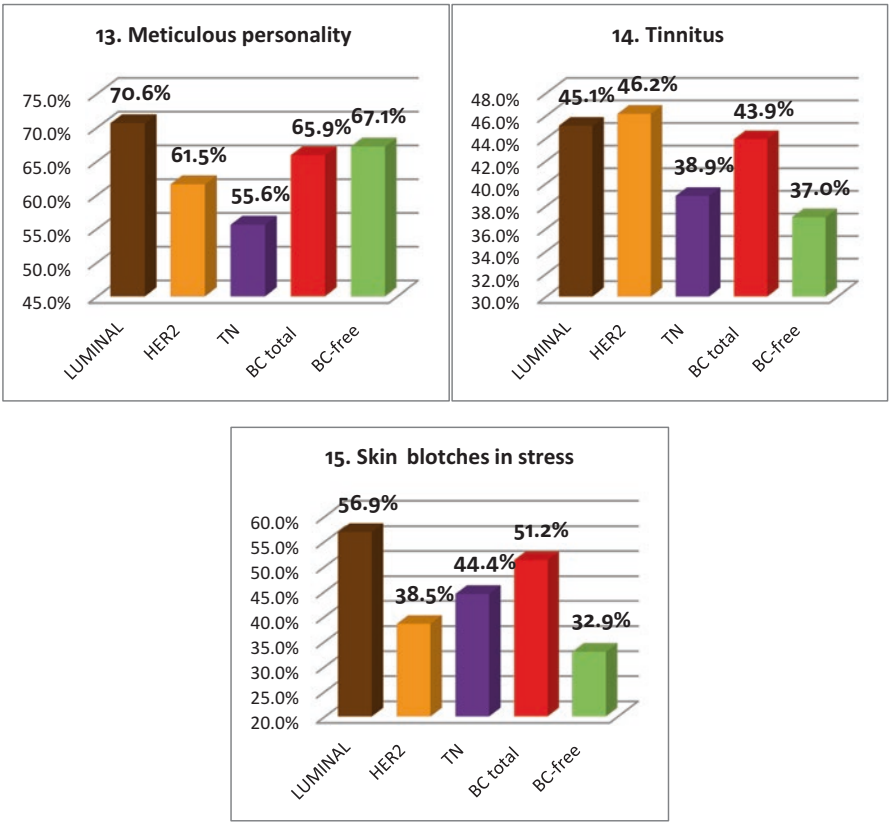

Fig. 1 (continued)

Cluster B (marked in blue colour) represents the group of symptoms with higher prevalence in BC, in general, but differential prevalence in individual BC subgroups

Cluster C (marked in yellow colour) represents the group of symptoms with the prevalence which, in general, is similar for both – BC diseased and BC-free individuals, however, variates between individual BC subgroups.

Cluster D (marked in red colour) represents a symptom with the prevalence which, in general, is lower for BC diseased patients, however, varies between individual BC subgroups.

Cluster A represents a consolidate group of symptoms relevant for all BC patients investigated in this study. In contrast, clusters B, C and D demonstrate high level of plurality regarding their prevalence in BC patients investigated.

Table 2 Symptoms of the Flammer Syndrome recorded in "Breast cancer diseased" versus "Breast cancer free" groups of comparison; the table summarises the results demonstrated in Fig. 1 by utilising the following system: with "+" the group is noted which demonstrates higher prevalence of the corresponding symptom (above the lowest average of the groups of comparison); with "-" the group is noted which demonstrates lower prevalence of the corresponding symptom (lowest average and below it); "="means both groups of comparison demonstrate similar prevalence of the corresponding symptom; "++" means the prevalence sufficiently over the highest average; "--" means the prevalence sufficiently below the highest average. Meaning of the individual clusters of symptoms marked in four different colours (green, blue, yellow, and red ones) is explained within the main text of the chapter "Results". Blue ellipses within the yellow and red clusters mark enhanced symptom's prevalence for the individual BC subgroups which appear against the main trend recorded for the BC total – equal to or even lower prevalence compared to the BC-free

Nr.	Symptoms	Breast cancer diseased				Breast cancer free
		Total	Luminal	Her2	TN	
1	Cold hands	+	+	+	+	-
6	Thirst	+	++	+	+	-
7	Headache	+	+	+	+	-
9	Drug sensitivity	+	+	+	+	-
14	Tinnitus	+	+	+	+	-
15	Skin blotches	+	++	+	++	-
2	Feeling cold	+	++	-	+	-
3	Low blood pressure	+	++	++	=	-
4	Dizziness	+	+	+	-	-
5	Sleep onset	+	+	+	=	-
10	Pain	+	+	-	--	-
11	Smell perception	=	-	+	=	=
12	Low body weight in early adulthood	=	--	++	++	=
13	Perfectionism	=	+	-	-	=
8	Accompanying symptoms	-	--	+	+	+
	∑ criteria	11+	12+ (8+ & 4++)	12+ (10+ & 2++)	9+ (7+ & 2++)	1+
		3=	2--	3-	3=	3=
		1-	1-		1--	11-
					2-	

8.4 Intermediate Concluding Remarks

A great advantage of the study design is that all participating patients and individuals have been thoroughly examined utilising conventional methodology of medical imaging and laboratory medicine and, consequently, selected for the study strictly according to the including and excluding criteria chosen, namely

- Breast cancer free health condition
- Breast cancer malignancies stratified according to the globally accepted classification
- No history of any severe gynaecologic disease including cancer other than breast malignancies
- No history of any systemic disease such as diabetes mellitus, rheumatic diseases and neurological disorders.

In this part of the study, the stratified groups reflect usual profiles of the breast cancer patient cohorts, namely: the prevalence of the "Luminal" subtype is significantly higher in "BC total" compared to both "Her2" and "triple-negative" BC; the "Luminal" subgroup is older, and about 90% of the patients in "Luminal" and "Her2-positive" subgroups are post-menopausal in contrast to the "triple-negative" BC subgroup comprising about 40% of pre-menopausal women (see Table 1). Potential influence of those unmatched parameters on FS prevalence in individual BC subtypes should be investigated additionally by the goal-dedicated projects. The results achieved here support the main hypotheses of the project clearly demonstrating the tendency of BC patients to increased prevalence of FS symptoms compared to the disease-free individuals. As summarised in the Table 2, the prevalence of 11 symptoms is higher in breast cancer patients, while only one symptom (8. "Accompanying symptoms") was demonstrated to be more prevalent in BC-free individuals. Furthermore, even in this case as well as in further 3 cases of the neutral prevalence (11. "smell perception", 12. "Low body weight in early adulthood", and 13. "Perfectionism"), remarkable differences have been demonstrated, when individual BC subgroups have been compared against each other. This actuality emphasises an extremely strong heterogeneity of the patients within the entire BC cohort. Obviously, FS prevalence does not create any exception regarding BC heterogeneity and, therefore, motivates follow-up studies investigating statistically significant correlations between single FS symptoms and specific BC patient profiles. To this end, cluster A (Table 2) as the best consolidate group of symptoms relevant for all BC patients investigated in this study, is expected to be more close to its potential application in daily medical practice by primary care units and family doctors and innovative screening programmes. In contrast, more research efforts are still needed to interpret the symptom plurality in clusters B, C, and D that might lead to novel approaches in BC patient stratification and more clear discrimination between individual BC subtypes.

9 FS Profiles in Postmenopausal Breast Cancer Patients Have Been Investigated in the Republic of North Macedonia

9.1 Postmenopausal Breast Cancer as the European Challenge

Breast cancer epidemic is worldwide recognised now as the reality of the early twenty-first century [10]. Moreover, in the Eastern- and Central-European countries amongst the four most common cancers, specifically the postmenopausal breast cancer started to approach the incidence levels earlier registered for the Northern and Western Europe, where their rates traditionally were the highest ones within the European area [68]. Increasing trends in the postmenopausal breast cancer prevalence, even for the European countries earlier demonstrating relatively stable incidence rates of the disease, are highly alarming for the healthcare-givers. This new actuality requires a substantial revision of the paradigm currently applied to the breast cancer management and creation of highly innovative concepts, first of all, for the primary prevention of breast cancer. In order to close the evident gaps in our current knowledge listed above, this part of the multi-centre study investigated the prevalence of the individual symptoms of the Flammer Syndrome (FS) specifically in the cohort of the postmenopausal breast cancer patients.

9.2 Patients' Recruitment and Examinations

For this study the patients have been recruited and interviewed by two specialised medical centres, the University Clinic of Oncology and Radiotherapy, Skopje, the Republic of North Macedonia and Department of Obstetrics and Gynaecology, Jessenius Faculty of Medicine, Martin University Hospital, Martin, Slovak Republic. Both centres were involved in the international multi-centred study working in a tight collaboration with other European partners participating in the project. The reference group comprising breast cancer free individuals ("BC-free reference" patient cohort) has been created and interviewed by the Slovakian partner-organisation. The cohort of postmenopausal breast cancer patients have been selected and interviewed in the Republic of North Macedonia. The partner-organisations of the international pilot project have elaborated both the "including" and "excluding" criteria for the study and followed the same norms of ethics in accordance with the ethical standards of the institutional and national research committees and with the international principles of the 1964 Helsinki declaration and its later amendments.

Breast Cancer-Free Reference Cohort

The patient data-base available at the Department of Obstetrics and Gynaecology, Jessenius Faculty of Medicine, Martin University Hospital, Martin, Slovak Republic has been utilised for selecting the breast cancer free individuals as potential responders (see the above part describing investigations performed in Slovakia). Altogether 73 breast cancer free individuals have been recruited for this study as reported in the original publication [69]. Following patient cohorts have been included:

- Healthy individuals free of breast cancer and any other malignancy (52 individuals of total)
- Benign breast fibro-adenoma (FIA), free of breast cancer and any other malignancy (21 patients of total).

Breast Cancer Patient Cohort

Breast cancer patients with and without metastases, treated at the University Clinic of Oncology and Radiotherapy, Skopje, the Republic of North Macedonia have been involved into the study. Patients have been selected utilising the data-base of the National eHealth System introduced in the Republic of North Macedonia on July 1st 2013. This system fulfils all requirements of the international standards and covers study-relevant information for all citizens of the Republic of Macedonia [70, 71]. Patients recruited for the current study have been identified as postmenopausal females with past history of menopause defined as 1 year after last menstrual period without bleeding, who have developed breast cancer after this time (in menopause), therefore, being postmenopausal breast cancer patients. These patients have been scheduled for visiting the University Clinic of Oncology and Radiotherapy in Skopje, the Republic of North Macedonia during the period of time between September 20th and November 20th, 2016. Diagnosis and treatment of 67 selected breast cancer patients with and without metastatic disease have been performed in accordance with the National Guidelines for Medical Care of Breast Cancer [72]. These guidelines correspond to the international standards as stated in the governmental documents cited above. The meaning of individual questions of the FS-questionnaire has been explained in extenso by the treating oncologist and/or oncologist's assistant during the communication with every interviewed patient. The questionnaire has been self-completed by the patients selected for the study.

Statistical Analysis

Statistical analysis has been performed as described in the above section "Individual BC Subtypes in Pre- and Post-menopausal Women Have Been Investigated in Slovakia".

9.3 Achieved Results

General Statistics

Postmenopausal breast cancer patients (67 of total) demonstrated the age average of 59 years against 50 years for the reference group comprising BC-free individuals (73 of total). The age difference was evaluated as statistically non-significant. Postmenopausal breast cancer group demonstrated in average the BMI = 26 (17–34). 50% of this group were overweight persons and 20% were diagnosed with diabetes type 2.

FS Prevalence Evaluated by Individual Symptoms

Figure 2 summarises the prevalence of individual "Flammer Syndrome" symptoms (1–15) in two groups of comparison – the "Postmenopausal breast cancer" patients versus the reference group of "BC-free" individuals.

Higher prevalence in the "Postmenopausal breast cancer" (red) has been demonstrated for altogether 11 symptoms. Statistically significant difference has been recorded for the symptoms 2 (feeling cold), 7 (headache), 9 (drug sensitivity), 11 (smell perception), and 12 (body weight in early adulthood); corresponding P-values are provided in the Table 1. In this study breast cancer patients demonstrated higher body weight compared to the BC-free reference group; the difference is statistically significant (P = 0.001). Although being statistically non-significant (p = 0.470), a substantially greater prevalence has been demonstrated for the symptom 6: "no feeling of thirst and drinking too little", the BC patients, in general, have demonstrated over 2-times more frequently compared to the disease-free reference group. Further, slightly higher prevalence in BC patient cohort has been demonstrated for the symptoms 1 (cold extremities), 3 (low blood pressure), 4 (dizziness), 5 (prolonged sleep onset), symptom 10 (pain), and symptom 15 (skin blotches in stress). Strong plurality has been demonstrated amongst the BC patients for the symptoms 8 (accompanying symptoms) and 10 (pain). Similar prevalence between BC patients and disease-free individuals has been demonstrated for the appearance of tinnitus (symptom 14). Slightly decreased prevalence of the symptom 13 (perfectionism) has been demonstrated for BC patients. The results are summarised in Table 3.

Breast Cancer Screening in the Republic of North Macedonia

The breast screening campaign has been started in the Republic of North Macedonia in 2007 involving 19 national mammography departments but has been criticised for only partially fulfilled requirements and standards settled for an effective breast cancer screening utilising mammographic approach [73]. Further, the field dedicated professional groups in the Republic of North Macedonia systematically work

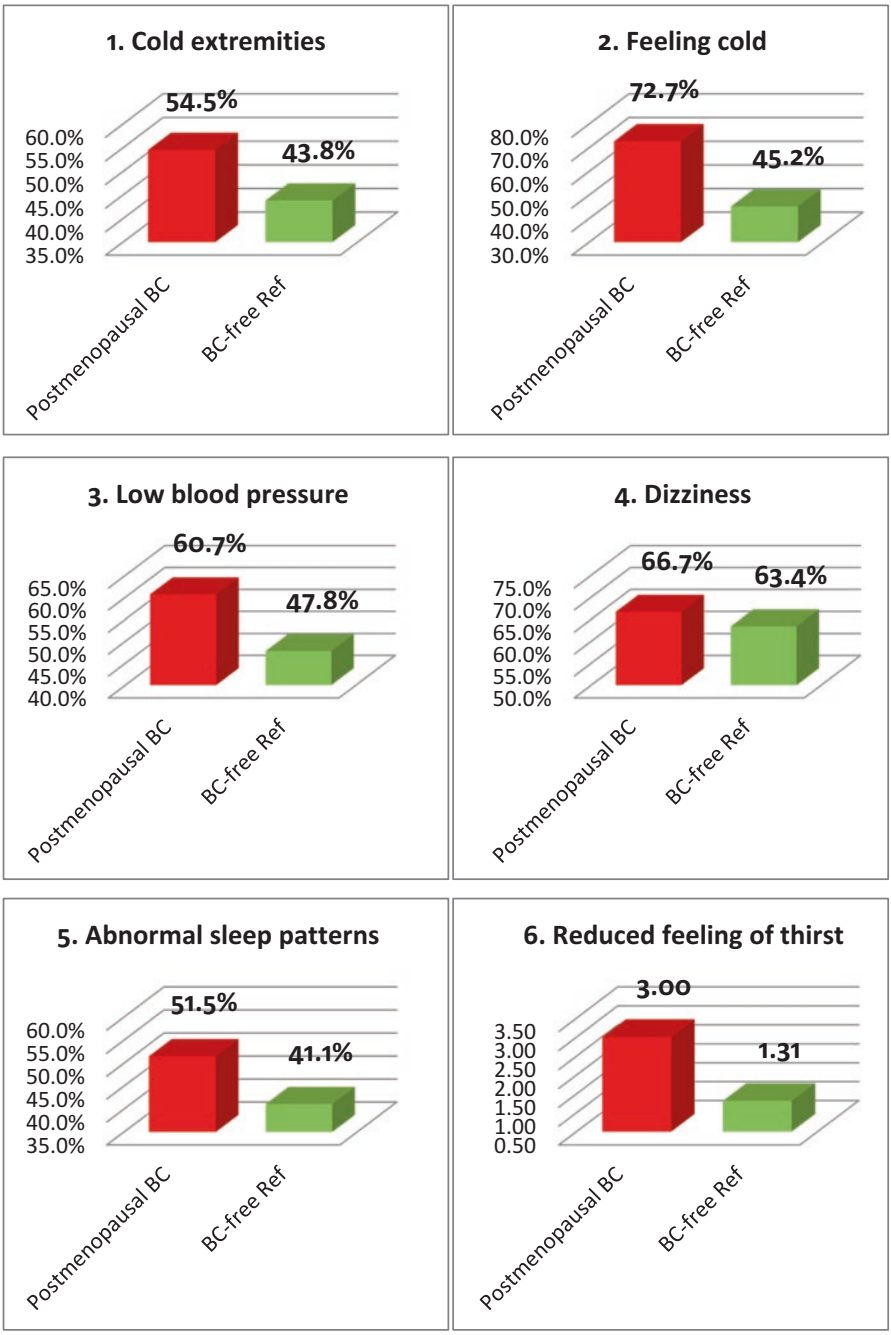

Fig. 2 Evaluation of the prevalence of individual symptoms (1–15) of the Flammer Syndrome phenotype in two groups of comparison: "Breast cancer diseased" (BC total) versus "Breast cancer free" reference pool (BC-free Ref). For more details regarding the patient stratification – see "**Patients' recruitment and examinations**". Full description of the FS questionnaire is provided above by "**Definition of the FS phenotype"**. The prevalence in each individual group is presented

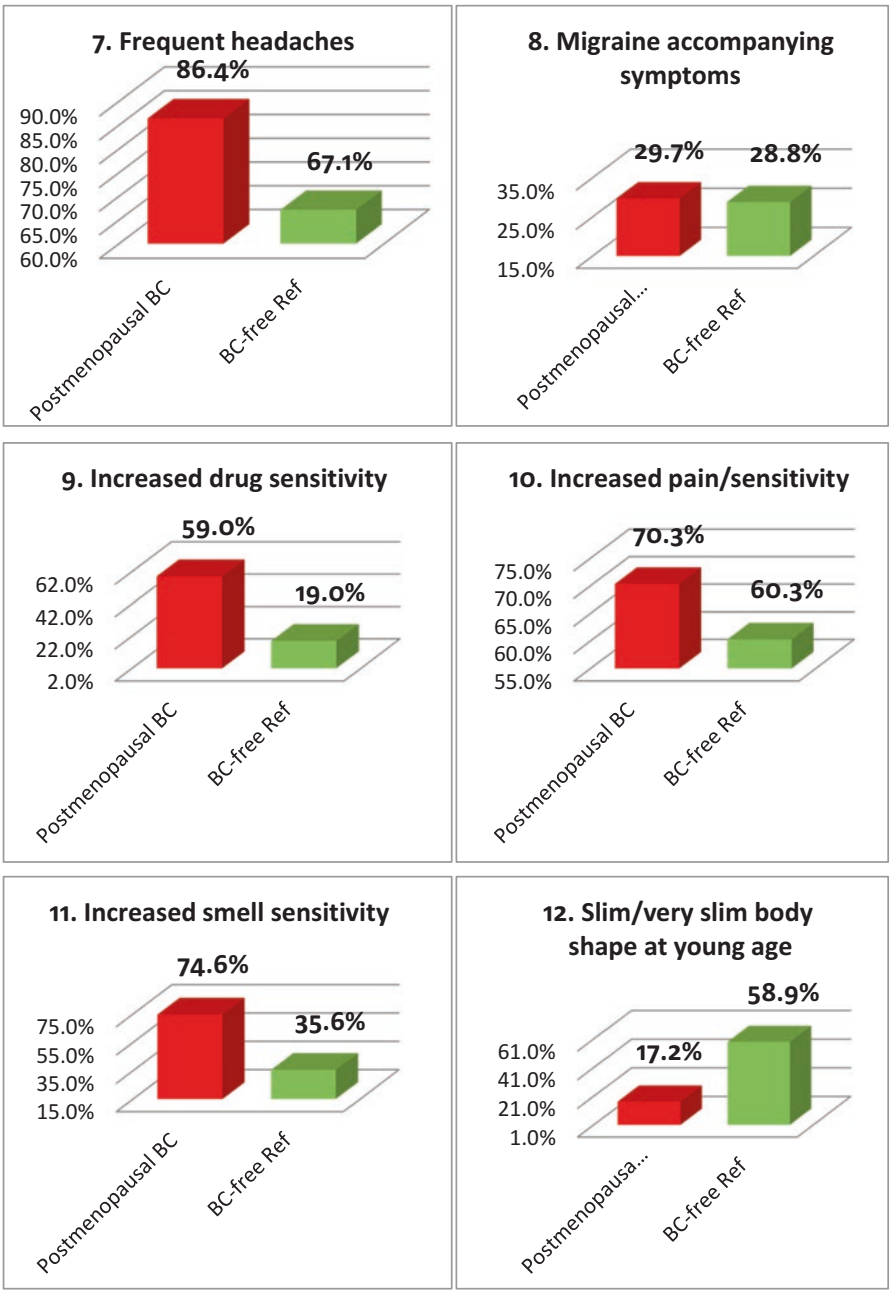

Fig. 2 (continued) by percentage of individuals who have responded to the corresponding question with "frequently" and "sometimes" pooled together. Responders answering with "I do not know" have been excluded from the overall numbers/calculations. Question-specific notes: Question 6 – the ratio between "I do not feel thirsty and drink little" and "I feel much thirsty and drink a lot" has been calculated and expressed in X–times; Question 12 – answers "very slim" and "slim" are pooled together and presented in %

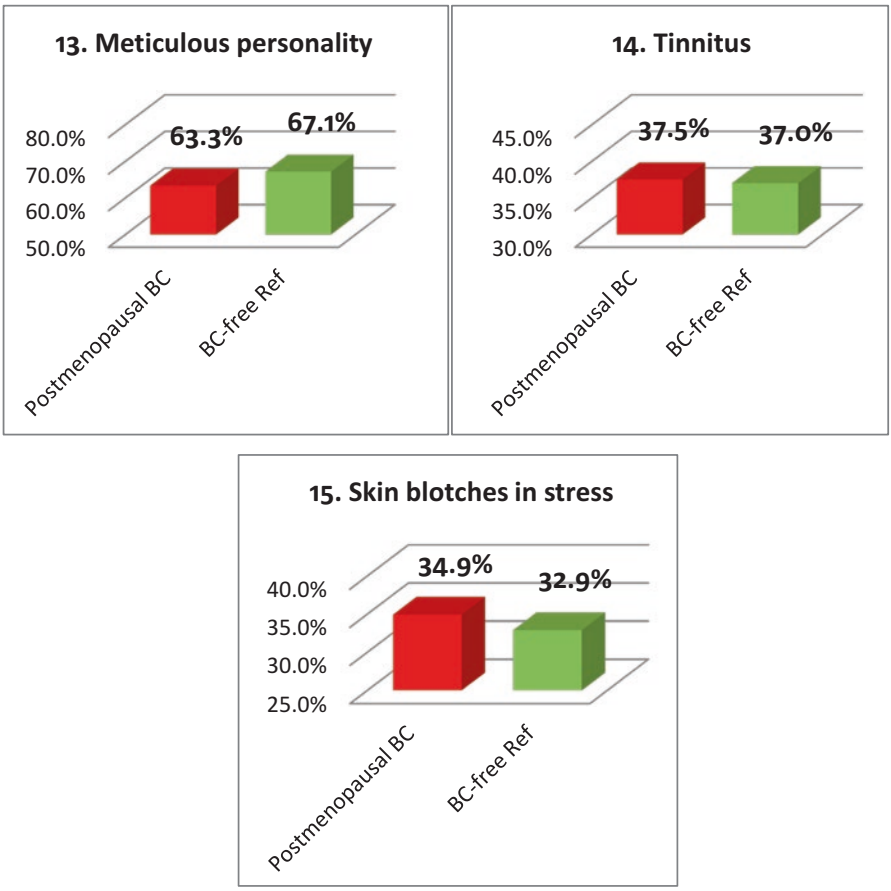

Fig. 2 (continued)

on the risk prediction models for breast cancer providing clear arguments considering currently existing approaches as unsatisfactory in general and, therefore, leading to poor results and data interpretation [74]. Contextually, Macedonian national centres have been chosen for the current multi-centre study as being highly motivated to develop innovative approaches in breast cancer screening, prediction and prevention at both – the national and European levels.

Profile of the Target Patient Group Is Typical for the Postmenopausal Breast Cancer Cohort

The purpose of the study was to investigate a potential relevance of the Flammer Syndrome for a typical postmenopausal breast cancer patient cohort. Consequently, this is to emphasise that an averaged profile of the target patient group has been

Table 3 Symptoms of the "Flammer Syndrome" recorded in "Postmenopausal breast cancer patients" versus "Breast cancer free individuals" groups of comparison; the table summarises the results demonstrated in Fig. 2; the following system is employed: "+" means higher prevalence of the corresponding symptom (above the lowest average of the groups of comparison); "-" means lower prevalence of the corresponding symptom (lowest average and below it). The level of significance is noted: P values below 0.05 are considered statistically significant and marked in red colour (symptoms 2, 7, 9, 11 and 12). 11 symptoms united within the green-marked cluster demonstrate the prevalence increased in BC. The prevalence of four symptoms united within the yellow-marked cluster is either similar or decreased in BC

Nr.	"Flammer Syndrome" questionnaire	Postmenopausal BC patients		BC-free individuals
		Prevalence	Significance P value	Prevalence
1	Cold hands	+	0.207	-
2	Feeling cold	+	0.001	-
3	Low blood pressure	+	0.144	-
4	Dizziness	+	0.695	-
5	Sleep onset	+	0.218	-
6	Thirst	+	0.470	-
7	Headache	+	0.008	-
9	Drug sensitivity	+	0.001	-
10	Pain	+	0.219	-
11	Smell perception	+	0.001	-
15	Skin blotches	+	0.802	-
8	Accompanying symptoms	=	0.906	=
12	Low body weight in adolescence	-	0.001	+
13	Perfectionism	-	0.647	+
14	Tinnitus	=	0.951	=
	∑ criteria	11+ 2= 2-	5 significant	2+ 2= 11-

created which in mini-scale reflects the demographic and physiologic parameters ubiquitously recorded for the corresponding European patient cohorts, namely

- All postmenopausal breast cancer patients treated at the national medical centre in the in the Republic of North Macedonia and involved in this study have been registered as the native Macedonian citizens
- The age of these patients ranged between 48 and 80 years old

- The low-weight persons created an absolute minority – altogether four patients with the BMI ≤20
- 50% of all postmenopausal breast cancer patients were overweight persons characterised by the BMI ranging between 26 and 34
- 20% of all postmenopausal breast cancer patients investigated in the current study have been diagnosed with diabetes type 2.
- A big portion of this patient pool has been diagnosed with the metastatic breast cancer.

10 Final Conclusions and the "Take Home"-Message of the Multi-centre Study

10.1 Breast Cancer Is a Systemic Disease

All individual parameters (1–15), the prevalence of which has been evaluated in the study, are functionally well linked to each other and altogether demonstrate systemic alterations of the affected person. Although, individual BC subtypes differ from each other in the prevalence distribution, all of them demonstrate systemic alterations compared to the disease-free individuals.

10.2 Crucial Role of the Cardio-Vascular Component in the BC Pathology

The great advantage of the FS evaluation system is that several symptoms are used as a condition-specific biomarker-panel being functionally linked to each other and, therefore, eliminate any contingency usually handicapping single biomarkers. Indeed, symptoms 1 (cold extremities), 2 (feeling cold), 3 (low blood pressure), 4 (dizziness), 8 (accompanying symptoms), and 15 (skin flecks appearing under stress conditions) create highly specific biomarker-panel demonstrating great synergies in a complex evaluation of impacts by the cardio-vascular component. All BC subgroups responded to this panel, although differing by subgroup-specific accents. For instance, whereas "Luminal" BC patients have been recorded as the strongest responders towards "feeling cold", "low blood pressure" "feeling cold", "Her-2 positive" patients responded strongly towards "low blood pressure" but mildly towards "feeling cold" (see Fig. 1). The meaning of those subgroup-specific differences should be further investigated.

10.3 Local and Systemic Hypoxic Effects in BC and Metastatic Disease

Strong impacts by the above discussed cardio-vascular biomarker panel lead to a conclusion about local and systemic hypoxic effects to be expected in BC patients responding to this panel of FS symptoms. The role of these effects in the BC pathology emerges deep investigations. The relevance of the hypoxic effects for metastatic disease is discussed in a separate book chapter "Relevance of Flammer Syndrome Phenotype to Metastatic Breast Cancer: Risks by Pre-metastatic Systemic Hypoxic Environment" by Rostyslav Bubnov with co-authors.

10.4 Interpretation of Headache, Migraine and Dizziness in BC

"Headache" and "Migraine" are frequently discussed for breast cancer patient cohort with highly controversial study outcomes and conclusions. The reason for that might be a missing context, which should obligatory include specific biomarker-panels by the FS symptoms, such as cardio-vascular component (see above), altered regulation of pain and thirst (see below).

10.5 Altered Sense Regulation in BC Aetiology?

Our study makes it obvious that BC patients may suffer from altered sense regulation and relevant receptors, due to their response to the biomarker-panel comprising the following symptoms: 6 (thirst regulation), 7 (headache), 10 (pain), and 11 (smell perception). Functional links between these symptoms make a good sense for potential interpretations. Indeed, underrepresented feeling of thirst may result in strong body dehydration and disturbed detoxification pathways, which in turn may cause significant toxic effects increasing BC risks as discussed above [75]. Body dehydration and insufficient detoxification may synergistically lead to increased frequency of headache which is a very useful indicator of impaired systemic regulations. Contextually, pain (e.g. headache) plays a crucial role indicating systemically impaired processes. To this end, symptom 10 (pain) provides very important information recording, on the one hand the highest responder rates in the "Luminal" (78.4%), and on the other hand the lowest rates in the "triple-negative" BC (38.9%). This is a very strong indication to investigate pain regulation specifically in the "triple-negative" BC patients who might be potentially pain-resistant and, therefore, inadequately reacting towards stress stimuli.

10.6 Drug Sensitivity May Be Potentially Altered in BC

Symptom 9 has recorded the highest responder rates in the "Her-2 positive" BC. This may potentially indicate altered drug sensitivity in BC patients suffering from FS. Altered drug sensitivity has been demonstrated for FS individuals and as well as glaucoma patients with FS [50, 53, 76].

10.7 Thermoregulation Symptoms in BC Pathology

The symptom 1 "cold extremities" is clearly linked to the disturbed microcirculation and consequently to the local and systemic hypoxic effects discussed above. However, as discussed above, the meaning of "feeling cold" (symptom 2) may have different interpretations. Therefore, the prevalence of both symptoms is not obligatory correlating completely in the same groups of comparison as it has been demonstrated in our study. Indeed, BC patients complain more frequently about deficits in achieving thermal comfort: they feel excessively hot or cold even in situations, when disease-free attendees are well comfortable with ambient temperature conditions [41]. "Feeling inadequately cold" may be interpreted in two ways. The first one: the heat production is not effective enough to maintain the physiologic body temperature, and the systemic mitochondrial dysfunction and DNA damage/misguided repair have been proposed as implemented in the BC pathology [43, 44]. The second interpretation is the fever or fever-like conditions with excessive chill attacks regulated by pro-inflammatory cytokines the expression profiles of which are frequently altered in cancer patients [46, 75].

10.8 Body Shape Impacts BC

Evaluation of the symptom 12 has revealed the strong subgroup specificity in BC regarding the body weight in early adulthood: while "Luminal" BC subtype demonstrates the lowest prevalence by 47%, obviously low body weight in early adulthood is highly prevalent in both "Her2-positive" and "triple-negative" BC subtypes by 69% and 72%, respectively. This actuality creates questions regarding body shape impacts in BC pathology as discussed earlier [10].

10.9 The Role of Psychological Factors in BC Pathology

Psychological factors play a role in BC predisposition, progression and individual outcomes. The biomarker panel comprising the symptoms 5 (sleep onset), 11 (smell perception), and 13 perfectionism) strongly promote this concept and motivate additional studies estimating the impacts of psychological factors and concomitantly regulated patho/physiological process in BC pathology.

10.10 Body Shape and Postmenopausal Breast Cancer Risk

In consensus with the results presented for postmenopausal BC here, it has been clearly demonstrated that both in Europe and in the USA, women aged 60 and above are more likely to be overweight or obese than any other age groups [77, 78]. Overweight, obesity and diabetes mellitus type 2 are the risk factors well described in the context of the oestrogen-receptor positive breast cancer prevalence specifically in postmenopausal women [79–82]. However, it does not explain the following facts. Firstly, far not all postmenopausal breast cancer patients are overweight, obese and or diagnosed with diabetes mellitus type 2; in the patient group investigated here the averaged BMI was 26 and exactly 50% of patients overweight. Another 50% demonstrated normal body weight by BMI $\leq$25, however being breast cancer diseased. Secondly, breast cancer is a chronic pathology developing over years or even decades of life. That means that the pre/cancer lesions were developing during premenopausal period of life, when the body weight was average. This seems to be the case in our study: about 90% of all respondents of the postmenopausal breast cancer group have noted that, although being not slim in contrast to the breast cancer-free reference group (the difference has been found significant, $P = 0.001$), their body weight was within the normal range at the young age. Indeed, some recent studies demonstrate adverse effects of long-term adult weight gain for postmenopausal breast cancer [81]. This might justify the appearance of the postmenopausal breast cancer for about 50% of our target patient cohort. However, there is no currently provided explanation for another 50% of these patients from view point of risks by overweight, obesity and diabetes mellitus type 2 in elderly.

10.11 What Is New in the Concepts Presented Here Specifically for Postmenopausal BC?

The results presented in our current stud clearly demonstrate that postmenopausal breast cancer cannot be explained by appearance of individual risk factors such as increased BMI, fluctuating body weight and/or life-time body size. It is a multifactorial systemic disease with a great number of contributing factor which should

be obligatory considered in the context of individual patient profiles for reliable prediction and prognosis. What is new in the concepts presented here? First of all, it is a systemic multi-contextual consideration of individual parameters. Just an example: since years headache is a strongly disputed symptom regarding its breast cancer relevance. So far, in general the dedicated studies have consider unilaterally the hormonal aspects of headache concluding that falling oestrogen levels which causes migraine are associated with a decreased risk of breast cancer, particularly amongst ER+/PR+ ductal and lobular carcinomas [12, 14]. In contrast, results presented here (see Fig. 2) demonstrate significantly higher prevalence ($P = 0.008$) of headache in postmenopausal breast cancer patient group versus BC-free individuals. Certainly, whether prevalent or not, headache/migraine attacks is an indicator for severe pathological events which should be deeply analysed in a multi-parametric context. This is exactly what our current study has shown: besides the prevalent headache, postmenopausal breast cancer patients investigated demonstrate a pronounced vascular dysregulation and consequently systemic hypoxic effects linked to the cardiovascular component (symptoms 1. "cold hands" and 2. "feeling cold"), altered sense regulation (symptom 11. "smell perception") and potential body dehydration (symptom 6. "do not feel thirsty and drink too little"). All of them are highly relevant for both – breast cancer progression and headache.

11 Outlook

Although limited by a relatively low number or the interviewed patients, current pilot study has confirmed the working hypotheses providing clear evidence for the relevance of the FS phenotype for breast cancer diagnostics and patient stratification. Therefore, we conclude here that individual signs and symptoms of FS might be of great clinical utility for the targeted phenotyping, identification of persons at high versus low risk, predisposition to individual BC subtypes, patient stratification, and innovative screening programme applied to the general population. What are the next steps to realise the innovation practically? Family doctors should be supplied with the FS-questionnaire to identify persons with typical phenotype who may be predisposed to BC development. This patient stratification by phenotyping may be extremely useful, if becomes applied early in life, in order to work on modifiable risk factors avoiding the disease progression. For monitoring of potential disease progression, pathology-specific biomarker-panels are essential; moreover, individual BC subtypes should be carefully considered. Contextually, recent studies report on highly-specific molecular profiles of individual BC subtypes such as the triple-negative BC with particularly poor outcomes compared to others; a comprehensive multiomic approach utilising liquid biopsy is recommended for predictive and preventive medical approach [83]. Indeed, a great number of molecular pathways are affected and represent promising diagnostic and medication targets, which include systemic expression regulation patterns, alterations in blood metabolome and molecular profiles of circulating leucocytes, multifaceted stress-response and strong

predisposition to metastatic disease [83]. Amongst others, miRNA profiles are the highly promising diagnostic target capable to predict BC development and predisposition to metastatic disease some years before the clinical manifestation [84]. The entire procedure by predictive diagnostics is highly complex that requires a "machine learning" approach which has been recently created for the multiomic-based patient stratification specifically in premenopausal breast cancer; the model demonstrate a capacity of discriminating individually between high and low BC-risk with >90% confidence [85].

Novel risk assessment approach starting with phenotyping and utilising specific molecular profiles in liquid biopsy samples has a potential to revolutionise currently existing screening programmes to meet the needs of young populations and to protect premenopausal women against a development of particularly aggressive BC subtype such as triple-negative and pregnancy-associated BC. After identification of specific profiles, persons at high risk then underwent the target prevention; several treatment algorithms are considered including the preventive chemotherapy by application of dietary phytochemicals [86].

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Relevance of Flammer Syndrome Phenotype to Metastatic Breast Cancer: Risks by Pre-metastatic Systemic Hypoxic Environment

International Multi-centre Study

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Abstract Metastatic disease is the major cause of the death in breast cancer patient (BC) cohorts. Lymph nodes, bones, lung, liver and brain are the most frequently reported sites of the metastatic disease in BC. For example, over 20% of the entire patients' cohort suffering from aggressive metastases in the liver are individuals

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with primary tumours diagnosed in the breast. Further, the brain is one of the predominant sites of the metastatic disease recorded for more than 20% of some specific BC subgroups, although in BC-free populations primary brain tumours is a rare disorder. This phenomenon has not been yet adequately explained.

The achievements of our international project have substantially extended the currently existing knowledge regarding the "Seed and Soil" theory of metastasis clearly demonstrating that a strong predisposition of individuals at risk to form the systemic hypoxic pre-metastatic niches can be established a long time before the breast malignancy is clinically manifested. The Flammer syndrome (FS) phenotype may strongly contribute to the aggressive metastatic disease. The exploitation of the acquired knowledge might be performed by creating innovative screening programmes. Contextually, we propose the FS-questionnaire to be considered by family doctors (GPs) for its practical application to the general population, in order to improve the quality of primary care by developing novel more effective approaches for the targeted prevention of the metastatic BC.

Keywords Predictive preventive and personalised medicine · Breast cancer · Metastatic disease · "Seed and Soil" theory · Liver · Flammer syndrome · Systemic hypoxia · Patient stratification

Abbreviations

BC	breast cancer
BMI	body mass index
CTC	circulating tumour cells
ECM	extra-cellular matrix
FIA	fibro-adenoma
FS	Flammer Syndrome
GPs	general practitioners (family doctors)
HER-2	human epidermal growth factor receptor 2
HIF-1	hypoxia-inducible factor 1
VEGF	vascular endothelial growth factor
TxNxMx	tumour size/number of affected lymph nodes/number of metastases

1 Introduction

Breast cancer epidemic in the twenty-first century [1] is characterised by around half-a-million deaths and 1.7 million new cases registered annually worldwide [2]. Metastatic disease is the major cause of the death in breast cancer patient (BC) cohorts. Lymph nodes, bones, lung, liver and brain are the most frequently reported

sites of the metastatic disease in BC. For example, over 20% of the entire patients' cohort suffering from aggressive metastases in the liver are individuals with primary tumours diagnosed in the breast [3]. Further, the brain is one of the predominant sites of the metastatic disease recorded for more than 20% of some specific BC subgroups [4, 5], although in BC-free populations primary brain tumours is a rare disorder. This phenomenon has not been yet adequately explained but potential solutions got well addressed in the recently published article "Mystery of the brain metastatic disease in breast cancer patients: Improved patient stratification, disease prediction and targeted prevention on the horizon?" [6]. Current statistics are much alarming from view point of the early mortality amongst BC patients with de novo metastatic disease. Hence, the issue-dedicated study recently performed in the USA has demonstrated that 15.9% and 33.2% of patients died within first four weeks and 6 months of the diagnosis, respectively, in 2000; 13.4% versus 26.3% of patients died within the same time frames in 2011 [7]. Moreover, the overall situation is even more dramatic in some specific subgroups such as the triple-negative BC with more than 50% of patients died within the first 6 months of the metastatic BC diagnosis [7]. In contrast to the lowest prevalence in LUMINAL A (2%), the highest prevalence (12%) of the local recurrence and the highest rates of distant metastases (27.4%) have been reported for the triple-negative BC followed by HER-2-positive (19.2%), LUMINAL B (12.1%) and LUMINAL A (6.4%) subtypes [8]. Contextually, triple-negative BC patients being slim (BMI < 18.5) and lymph-node-positive, demonstrate particularly poor overall survival rates [9]. Further, specifically young (≤35 years old) BC patients with metastatic disease demonstrate significantly lower 5-year disease-free survival and significantly higher prevalence of distant metastasis against elderly patients (≥65 years old) [10].

New paradigm of so-called "pre-metastatic niches" may sufficiently promote our knowledge regarding potential pathomechanisms, individual predisposition and prognosis in development and progression of the metastatic disease. The main concept is that, in order to get effectively "domesticated" and finally colonise within distant organs, circulating tumour cells (CTCs) spread by the initial cancer need a "fertile" microenvironment that means the "pre-metastatic niches". Many papers are dedicated to the cellular and molecular biological characteristics of the local microenvironment demonstrating a specific cellular makeup within the pre/metastatic sites of the hosting organ [11], essential involvement of exosomes [12] and the ECM components [13]. Specifically, the hypoxic tumour microenvironment is considered the driving force for breast cancer progression [14, 15]; consequently, the drugs inhibiting hypoxia-inducible factor have been proposed to treat triple-negative BC patients who demonstrate particularly poor outcomes as described above.

However, the crucial question remains unaddressed in the current scientific literature, whether hypoxic pre-metastatic niches in breast cancer are created by or prior to the tumour onset. So far, the interpretation of the "Seed and Soil" theory of metastasis [16, 17] proposing that the premetastatic niches (soil) may be formed by primary tumours (seeds), which "induce and guide" the process [18, 19], is uncomplete, since it does not provide satisfactory explanations towards the following facts. Firstly, there is quite a number of clinical cases with distant metastases

diagnosed prior to a detection of primary breast tumours; the latter remain undiagnosed by standard screening programmes as discussed in the article "Feeling cold and other underestimated symptoms in breast cancer: anecdotes or individual profiles for advanced patient stratification?" [20]. As described above, specifically triple-negative BC is characterised by particularly aggressive metastatic disease frequently developed in parallel to the primary tumour appearance. Secondly, considering the breast malignancy as a kind of "artificial" organ which, according to the current paradigm, "manipulates" gene expression patterns systemically, the tumour size should be essentially taken into consideration. It seems to be quite unrealistic, from the view point of physical and chemical capacity of the microscopically small tumours to be able to saturate the entire blood stream (5–7 litres) with so large quantum of gene products which are capable to change the genetic programme of incomparably larger and distant organs so that they start to create pre- and metastatic niches.

2 Working Hypothesis

We hypothesised a strong epi/genetic predisposition of individuals at risk to form the "fertile" hypoxic environment and systemic pre-metastatic niches a long time before the breast cancer is clinically manifested. According to our hypothesis, the specific phenotype of the Flammer Syndrome (FS) might be particularly stimulating for the metastatic disease by forming the systemic hypoxic environment as described earlier [20]. To this end, the specific symptoms of the FS have been described for several populations [21], pathologies [22–26] and healthy individuals [27].

The relevance of the specific FS-symptoms for BC pathology has been recently demonstrated [28]. BC-relevant symptoms of the FS, such as deficient thermoregulation, feeling inadequately cold, altered sensitivity to different stimuli, altered sleep patterns, tendency towards headache, migraine attacks and dizziness, amongst other, are assumed to be highly relevant for the metastatic disease as well. In order to verify our hypothesis, the reported here multi-centre study investigates the prevalence of FS-symptoms in patients with metastatic BC versus BC-free individuals.

3 Study Design

All procedures performed in the current study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

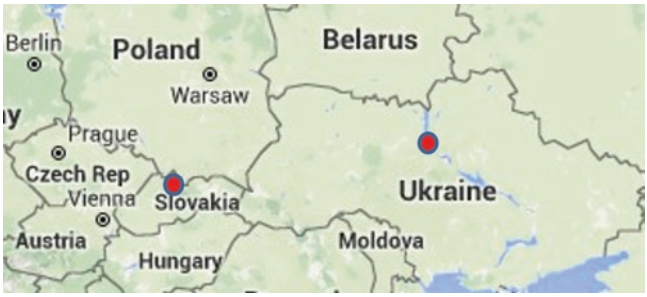

Fig. 1 The specialised medical centres in Slovakia and Ukraine (marked with red points) networked by this multi-centred project are demonstrated on the map within the European context. Slovakia and Ukraine are situated in the direct neighbourhood. Both countries border to Poland and Hungary. Populations of both countries demonstrate cultural similarities to each other

3.1 Flammer Syndrome Diagnostic Approach

The Flammer syndrome (FS) phenotype has been characterised earlier [29]. The FS questionnaire applied to the study has been developed at the University Hospital Basel, Switzerland. The actual version of the FS-questionnaire has been successfully applied to study different populations [21], FS symptomatic in retinitis pigmentosa [24] as well as in multiple sclerosis [23] and other clinically relevant patient cohorts [25, 26]. Consequently, the actual version of the FS questionnaire has been used by several oncological centres involved in our breast cancer dedicated pilot project [28].

3.2 Design of the Multi-centre Study

Patient cohorts recruited at the specialised medical centres – Clinical Hospital "Pheophania", Kyiv, Ukraine and Department of Obstetrics and Gynaecology, Jessenius Faculty of Medicine, Martin University Hospital, Martin, Slovak Republic – were involved in this multi-centre study. Thereby, the patient collective comprising breast cancer free individuals ("BC-free reference" patient cohort) has been created in Slovakia, and the cohort of patients suffering from the metastatic breast cancer have been selected and investigated in Ukraine. In Fig. 1, both centres are marked on the map within the European context. Both centres, in a tight collaboration with other partners of the international pilot project, have elaborated "including" and "excluding" criteria for the current study and followed the same norms of ethics in accordance with the ethical standards of the institutional and national research committees and with the international principles of the 1964 Helsinki declaration and its later amendments.

One part of the patients have been selected in the data-bases of the centres involved and then contacted telephonically by authorised persons who have explained the meaning/rules of the study and interviewed the responders through the entire questionnaire. The other part of the patients have been personally contacted and interviewed during their stay at the centres involved.

3.3 Breast Cancer-Free Reference Cohort

The patient data-base available at the Department of Obstetrics and Gynaecology, Jessenius Faculty of Medicine, Martin University Hospital, Martin, Slovak republic has been utilised for selecting the breast cancer free individuals patients as potential responders for the above noted FS-questionnaire. The entire methodology has been described in the original article [26]. Following diagnoses have been chosen as the including criterion:

– Healthy individuals free of breast cancer and any other malignancy
– Benign breast fibro-adenoma (FIA), free of breast cancer and any other malignancy

Altogether 73 breast cancer free (21 FIA and 52 healthy) individuals have been recruited for this study.

Healthy Controls

All these individuals have been clinically examined attesting an absence of gynaecological problems and interviewed personally for the study during their hospital outpatients visit performed in the framework of the national screening programme. BC free condition has been confirmed either by breast sonography or mammography or both imaging approaches. The examination reports used were not older than 6 months. Healthy controls demonstrated no history of any previously diagnosed breast pathology, no surgery performed due to breast lesions and no history of any severe gynaecologic disease including cancer other than breast malignancies or any systemic diseases such as diabetes mellitus, rheumatic diseases and neurological disorders.

Fibro-Adenoma (FiA) Patients

Imaging technologies have been applied for the 1st choice of the entire diagnostic procedure: digital mammography Hologic system, 2D + 3D sonography – Voluson USG system E8 and E10 machine, Birads 0–6 classification scoring system with double reading of the radiologic approach. In case of reasonable suspicion, the

affected patients have undergone the biopsy analysis (either core needle or Mammotome's vacuum-assisted). Histopathological analysis described for this multi-centred study earlier [28] has, further, allowed for distinguishing between BC malignancy and FIA benignancy. FIA-individuals have been included into the BC-free patient pool.

3.4 Metastatic Breast Cancer Patient Cohort

The patient data-base available at the clinical hospital 'Pheophania', Kyiv, Ukraine has been utilised for selecting the metastatic breast cancer patients who underwent outpatient consulting diagnosis and treatment in the time-frame from November 2015 till January 2017. *Inclusion criteria:* metastatic, locally advanced, inflammatory-edematous, recurrent breast cancer. *Exclusion criteria:* chronic infectious disease (HIV, Hepatitis, etc.), rheumatic and neurologic diseases, thyroidithis. All the selected metastatic BC patients underwent general clinical and biochemical examinations according to the standard protocols approved by the Ministry of Health in Ukraine (Governmental Directive Number 396 titled "On the approval and implementation of medical and technological documents for standardisation of medical care of breast cancer" issued on June 30th 2015) [30] which are conform to the European and international unified protocols for primary, secondary (specialised) and tertiary (highly specialised) medical care of breast cancer patients. Extensive investigations of metastatic lesions have been performed utilising the medical imaging by sonography including also thyroid, abdominal, pelvic, and musculoskeletal examinations for diagnostic purposes such as to clarify potential vascular dysregulation, hormonal and oncology-related pathologies. For diagnostic clarifications, additional examinations have been performed by magnet-resonance imaging, computer-tomography and skeletal radioscintigraphy upon individually recognised necessity.

In order to avoid any misconduct and misinterpretations, highly individualised approach was taken for the doctor-patient communication explaining the purposes of the study prior to interviewing the patients towards the FS-questionnaire. The questionnaire items have been carefully discussed during each individual interview, to avoid potential bias, and if suspicious regarding the clarity, the corresponding question was asked again for the final clarification of the correct answer, which the patient was best satisfied with, carefully choosing between "no", "yes" ("frequently" versus "sometimes") and "I do not know". IMPORTANT: The responses given towards individual questions refer to the health condition and behaviour of the patients considered in a long-term manner but not restricted to the period of time dedicated to the treatment of breast cancer and metastatic disease.

3.5 Statistical Analysis

For analytical and statistical evaluations, the data have been transferred to Microsoft Excel. SPSS Statistics v20.0.0 software (IBM, Armonk, New York, USA) have been applied. The prevalence of individual symptoms in groups of comparison has been evaluated and expressed in percentages. Pearson's chi-square test of associations has been applied. P values below 0.05 have been considered as statistically significant.

4 Achievements

4.1 Statistics for the Age and Menopausal Status in Groups of Comparison

Table 1 presents statistics provided for the group of breast cancer patients (27 of total) versus the group comprising BC-free individuals (73 of total) as well as for breast cancer subgroups subdivided according to their menopausal status. Premenopausal patients created the youngest group, the age mean (49 years old) of which, is, therefore, similar to this of the BC-free reference group (50 years old). Substantially older group was created by postmenopausal BC patients. However, a difference in the age mean values has been found statistically non-significant.

4.2 General Parameters of the Metastatic BC Patient Group Investigated

Description of the metastatic breast cancer in the patient cohort investigated by the current study is summarised in the Table 2. Noteworthy, all the premenopausal BC patients demonstrated liver metastasis; the same is true for the postmenopausal BC

Table 1 Age and menopausal status statistics for the groups of comparison: breast cancer patients (27 of total) and breast cancer-free individuals (73 of total); further, breast cancer patients have been subdivided into two subgroups, namely premenopausal (13 patients) and postmenopausal (14 patients) ones

BC menopausal status/ number of patients	Premenopausal BC	Postmenopausal BC	BC total	BC-free Ref/ number of patients
	13	14	27	73
Patients' age: mean (min−max), in years	49 (37–56)	61.38 (52–71)	56 (37–71)	50.19 (19–89)

Age mean difference is statistically non-significant

Table 2 Description of the metastatic breast cancer in the patient cohort investigated by the current study; noteworthy, all the premenopausal BC patients demonstrated liver metastasis; the same is true for the postmenopausal BC patients with one exception. The noticeable premenopausal patient marked in yellow is discussed in more detail in the main text

Menopausal status	Premenopausal BC, 13 patients	Postmenopausal BC 14 patients
T1 N1 M1	1	0
T2 N1-x M1-x	6	4
T3 N1-x M1	6	6
T4 N1-2 M1	0	4
Metastasis in liver	All patients	1 3patients
Other metastatic sites	2 patients (bone and lung)	4 patients (bone and lung)

patients with one exception. The noticeable premenopausal patient marked in yellow is discussed below as "Case 1" within the part dedicated to the "Metastatic BC – selected cases".

4.3 FS Prevalence Evaluated by Individual Symptoms

Figure 2 summarises the prevalence of individual Flammer Syndrome symptoms (1–15) in two main groups of comparison – "BC total" patients versus the reference group of "BC-free" individuals as well as in individual subgroups of BC patients subdivided according to their menopausal status. Higher prevalence in "BC total" (red) has been demonstrated for all 15 symptoms investigated in this study. Statistical significance has been recorded for the symptoms 1 (cold extremities), 2 (feeling cold), 5 (prolonged sleep onset), 7 (headache), 8 (accompanying symptoms), 9 (drug sensitivity), and 11 (smell perception); corresponding P-values are provided in the Table 3. Although being statistically non-significant ($p = 0.103$), a substantially greater prevalence has been demonstrated for the symptom 6: "no feeling of thirst and drinking too little", the BC patients, in general, have demonstrated 2-times more frequently compared to the disease-free reference group; for the postmenopausal BC this difference was even more pronounced. Also the appearance of tinnitus (symptom 14), although being statistically non-significant ($p = 0.095$), was evidently more frequent in BC, particularly in the premenopausal subgroup demonstrating about 2-times higher prevalence compared to the disease-free reference group. The symptom 3 (low blood pressure) was more specific for the premenopausal BC demonstrating 22% higher prevalence against the disease-free reference group. In contrast, the symptoms 12 (low body weight in early adulthood) was more specific for postmenopausal BC. Slightly higher prevalence was demonstrated for

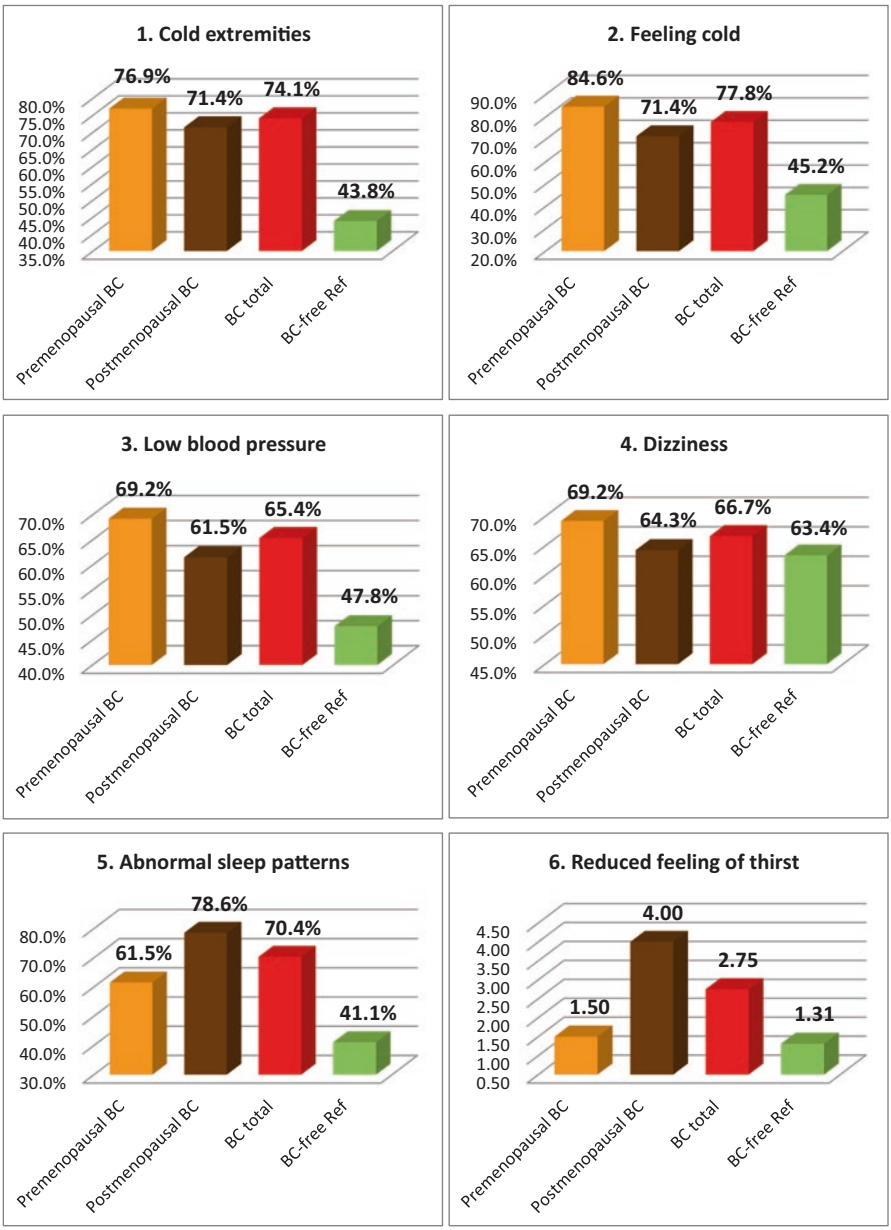

Fig. 2 Evaluation of the prevalence of individual symptoms (1–15) of the Flammer Syndrome phenotype in two groups of comparison: "Breast cancer diseased" (BC total) versus "Breast cancer free" reference patient pool (BC-free Ref). Therein, the entire breast cancer patient pool ("BC total") has been additionally analysed in subgroups stratified according to menopausal status of the patients. The prevalence in each individual group is presented by percentage of individuals who have responded to the corresponding question with "frequently" and "sometimes" pooled together.

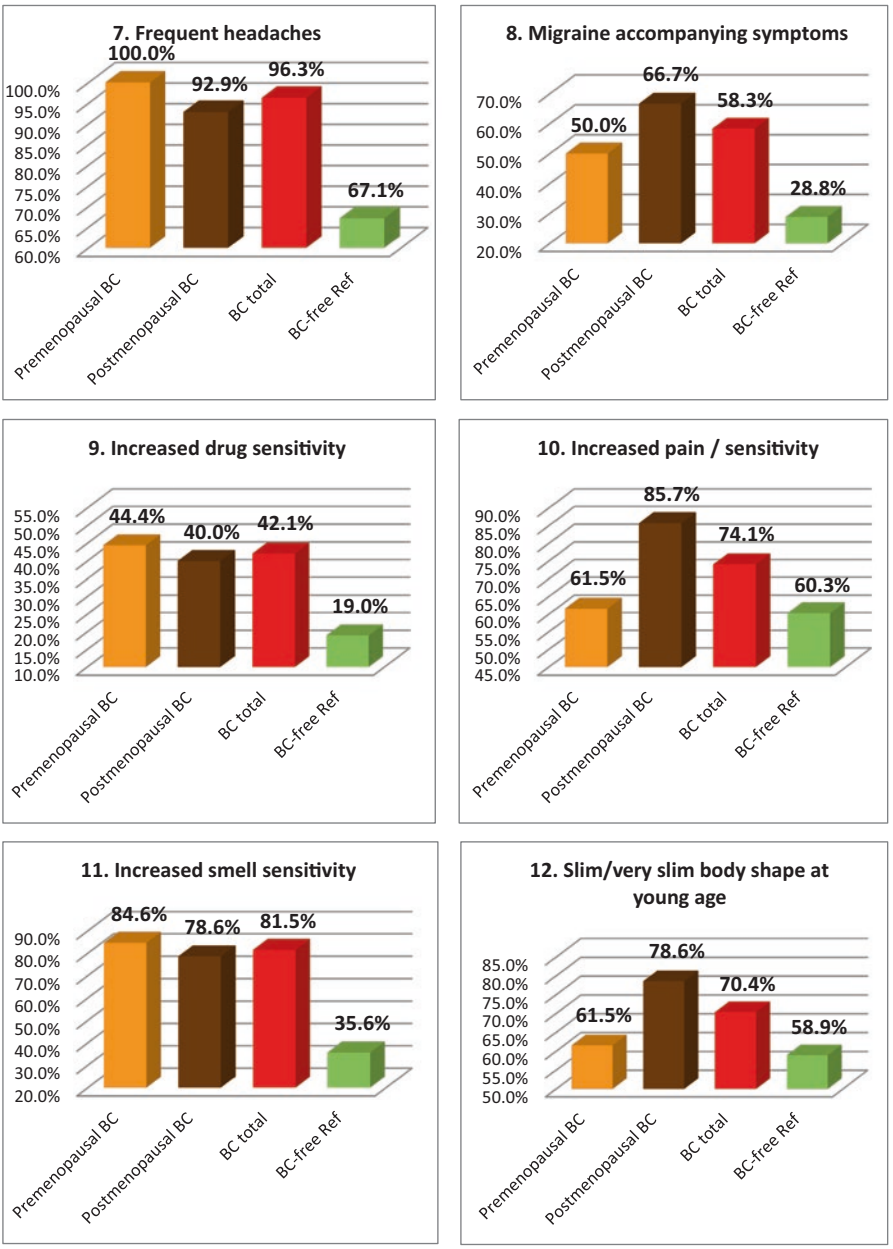

Fig. 2 (continued) Responders answering with "I do not know" have been excluded from the overall numbers/calculations. Question-specific notes: Question 6 – the ratio between "I do not feel thirsty and drink little" and "I feel much thirsty and drink a lot" has been calculated and expressed in X–times; Question 12 – answers "very slim" and "slim" are pooled together and presented in %

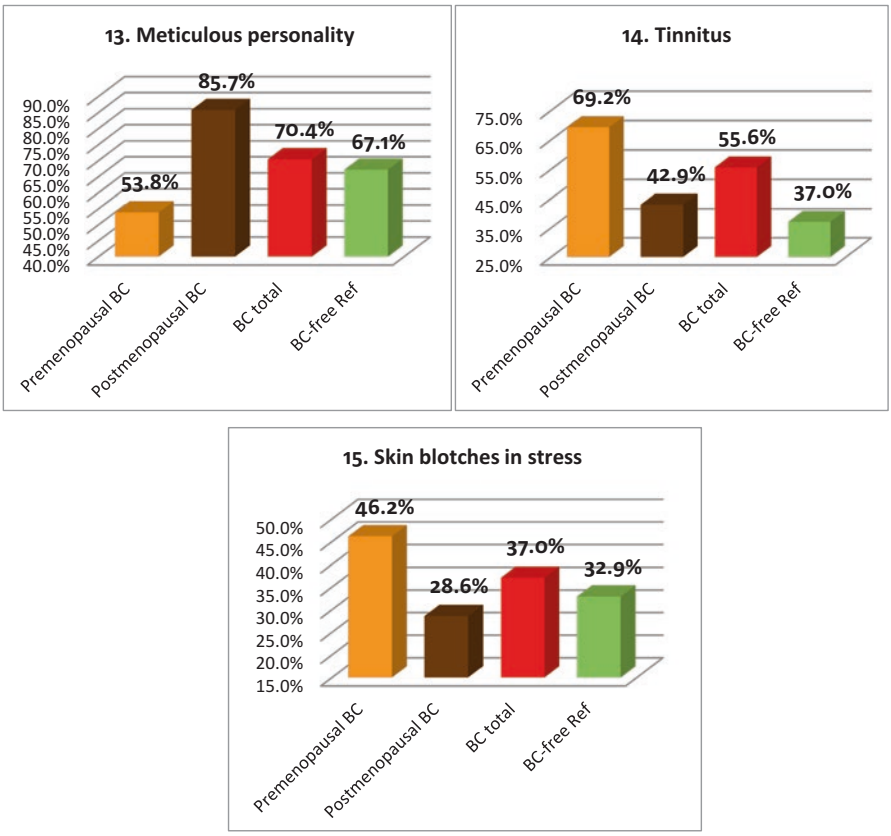

Fig. 2 (continued)

symptom 4 (dizziness) in BC. Strong plurality has been demonstrated amongst the BC subgroups for the following three symptoms: 10 (pain, more specific for the postmenopausal BC), 13 (perfectionism, more specific for the postmenopausal BC), and 15 (skin blotches in stress, more specific for the premenopausal BC) as summarised in Table 3.

4.4 Metastatic BC – Selected Cases

Case 1

This patient is marked in yellow colour within the Table 2. Corresponding medical imaging by the ultrasound examination is demonstrated in Fig. 3. Female breast cancer patient, premenopausal, aged 48 years, T1N1M1, with a small tumour (below 1 cm of size) initially detected in the breast followed by the multiple-sites secondary metastases detected in bone and liver, has been interviewed towards

Table 3 Symptoms of the Flammer Syndrome recorded in "Metastatic breast cancer patients" versus "Breast cancer free individuals" groups of comparison; the table summarises the results demonstrated in Fig. 2; the following system is employed: "+" means higher prevalence of the corresponding symptom (above the lowest average of the groups of comparison); "−" means lower prevalence of the corresponding symptom (lowest average and below it); "++" means values sufficiently over the highest average. All 15 symptoms demonstrate increased prevalence in BC total versus BC-free. The level of significance is noted: P values below 0.05 are considered statistically significant and marked in red colour (symptoms 1, 2, 5, 7, 8, 9, 11). Thirteen symptoms united within the green-marked cluster demonstrate the prevalence ultimately increased in BC total as well as BC subgroups. Although the prevalence of symptoms 13 and 15 (yellow-marked cluster) is slightly increased in "BC total" compared to the "BC-free", it varies in BC subgroups demonstrating a particularly strong plurality amongst the patients with the metastatic BC investigated in the study

Nr.	"Flammer Syndrome" symptoms	Metastatic BC patients				BC-free individuals
		Total	Pre-menopausal	Post-menopausal	Significance P value	
1	Cold hands	+	++	++	0.007	-
2	Feeling cold	+	++	++	0.004	-
3	Low blood pressure	+	++	+	0.127	-
4	Dizziness	+	+	+	0.762	-
5	Sleep onset	+	+	++	0.009	-
6	Thirst	+	+	++	0.103	-
7	Headache	+	++	++	0.003	-
8	Accompanying symptoms	+	++	++	0.009	-
9	Drug sensitivity	+	++	++	0.042	-
10	Pain	+	+	+	0.202	-
11	Smell perception	+	++	++	0.001	-
12	Low body weight in early adulthood	+	+	++	0.349	-
14	Tinnitus	+	++	+	0.095	-
13	Perfectionism	+	-	+	0.757	-
15	Skin blotches	+	+	-	0.697	-
	∑ criteria	15+	14+ 5+ and 9++	14+ 8+ and 6++	7 significant	0+
		0-	1-	1-		15-

FS-symptoms. The interview resulted in 13 positive responses from the maximum of 15. The negative response was given regarding the symptom 5 (answered as "rather normal sleep onset"); further, the patient replied as "I do not know" regarding the symptom 9 (drug sensitivity). Particularly noticeable responses have been given towards the following symptoms:

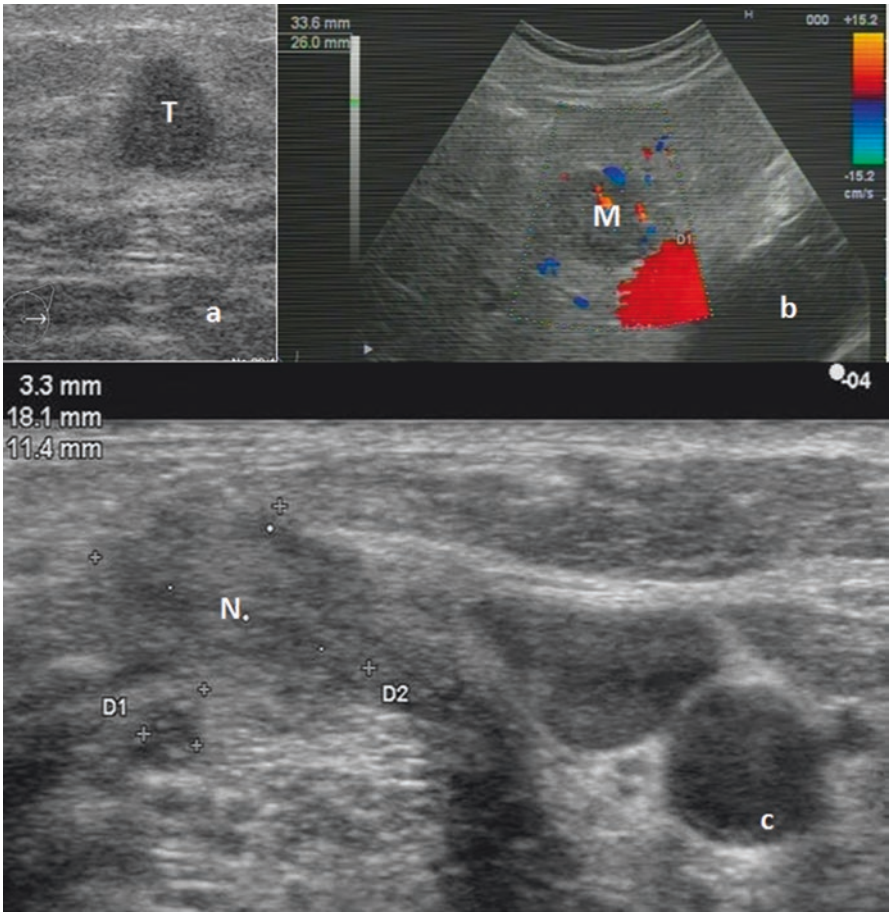

Fig. 3 Medical imaging by ultrasound illustrating the "Case 1" (within the subchapter "Metastatic BC – selected cases") of the patient diagnosed with the metastatic breast cancer T1N1M1; the exact description of this case and its relevance for the Flammer Syndrome, please see above; (**a**). small initial tumour in the breast (T); (**b**) a metastatic lesion in the liver (M); (**c**) a metastasis in the axillary lymph node (N)

- Symptom 2 – feeling cold frequently
- Symptom 8 – strong migraine attacks and frequently observed accompanying symptoms such as an impaired vision, deafness appeared in the extremities etc.
- Symptom 11 – strongly pronounced smell perception
- Symptom 12 – slim body shape in early adulthood
- Symptom 13 – strongly pronounced tendency towards perfectionism
- Symptom 15 – evident skin blotches in stress situations.

Case 2

Female patient, postmenopausal, aged 60 years, BMI = 17.9, diagnosed with left breast cancer in 2014, T4N1M1, 2016 – aggressive metastatic disease in liver, lungs

and bones, despite the chemotherapeutic treatment. The patient has been interviewed towards FS-symptoms. The interview resulted in 9 positive responses from the maximum of 15. The negative responses were given regarding the symptoms 3 (low blood pressure), 9 (drug sensitivity), 14 (tinnitus) and 15 (skin blotches). The body shape in early adulthood was rather averaged (symptom 12). No answer was provided for 8 (accompanying symptoms). Particularly noticeable responses have been given towards the following symptoms:

– Symptom 1 – frequently cold extremities
– Symptom 2 – frequently feeling cold
– Symptom 5 – evidently prolonged sleep onset
– Symptom 6 – do not feel thirsty and drink too little
– Symptom 7 – frequent headache
– Symptom 13 – strongly pronounced tendency towards perfectionism.

Case 3
Female patient, postmenopausal, aged 62 years, diagnosed with Paget's disease of the left breast (T1N0M0) in 2014, 2016 – aggressive metastatic disease in liver and bone, despite chemotherapeutic treatments. Collateral disease: angina pectoris, miocardial infarction, heart failure. The patient has been interviewed towards FS-symptoms that resulted in 12 positive responses from the maximum of 15. The negative responses were given regarding the symptoms 9 (drug sensitivity) and 14 (tinnitus). No answer was provided for 8 (accompanying symptoms). Particularly noticeable responses have been given towards the following symptoms:

– Symptom 1 – frequently cold extremities
– Symptom 2 – sometimes feeling cold
– Symptom 4 – frequent dizziness
– Symptom 5 – evidently prolonged sleep onset
– Symptom 6 – do not feel thirsty and drink too little
– Symptom 7 – frequent headache
– Symptom 10 – frequent pain
– Symptom 11 – strongly pronounced smell perception
– Symptom 12 – slim body shape in early adulthood
– Symptom 13 – strongly pronounced tendency towards perfectionism
– Symptom 15 – evident skin blotches in stress situations.

Case 4
Female patient, postmenopausal, aged 58 years, BMI = 20.8 diagnosed with metastatic breast cancer, (T3N1M1, liver metastasis), followed by aggressive metastatic disease in bone and lung, despite the chemotherapeutic treatments. Corresponding medical imaging by a complex ultrasound examination is demonstrated in Fig. 4. The patient has been interviewed towards FS-symptoms that resulted in 14 positive responses from the maximum of 15. The negative response was given against the symptoms 6, answered as "I feel thirsty and drink a lot". Particularly noticeable responses have been given towards the following symptoms:

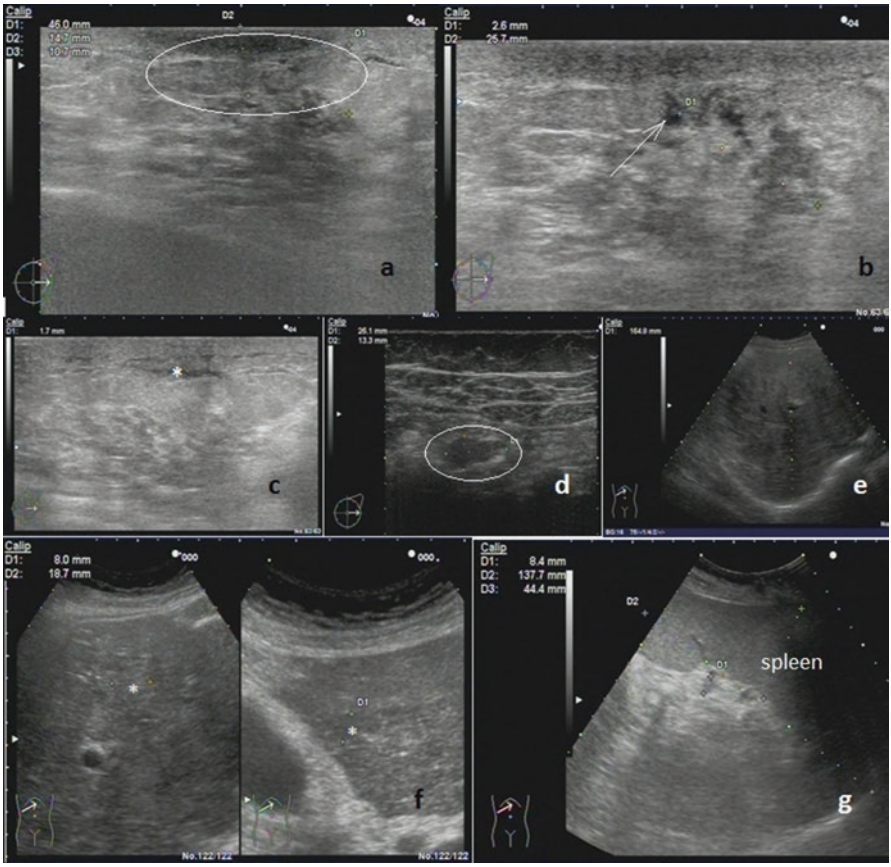

Fig. 4 Medical imaging by ultrasound illustrating the "Case 4" (within the subchapter "Metastatic BC – selected cases") of the patient diagnosed with the metastatic breast cancer. T3N1M1; the exact description of this case and its relevance for the "Flammer Syndrome", please see above; (**a**) – left breast sub-areolar lesion (ellipse); (**b**) – ductal ectasia (arrow); (**c**) – signs of lymphostasis (asterisk); (**d**) – axillar lymphatic node (ellipse); (**e**) and (**f**) – diffuse multiple metastatic liver lesions (asterisk), intrahepatic cholestasis; (**g**) – splenomegaly which as a usual sign of portal hypertension; notable – the liver parenchyma is diffusely (sub-totally, in all segments) mottled by the merging multiple iso-, hypo-, and hyperechoic lesions (arrows). Intrahepatic bile ducts are dilated up to 2–3 mm. The liver failure and cholestasis know by their synergistic effects belong to the collateral pathologies specifically leading to the poor prognosis in metastatic breast cancer outcomes

- Symptom 1 – frequently cold extremities
- Symptom 2 – frequently feeling cold
- Symptom 11 – strongly pronounced smell perception
- Symptom 12 – slim body shape in early adulthood
- Symptom 13 – strongly pronounced tendency towards perfectionism.

5 Interpretation

The particular advantage of this study is the highly personalised management of the "doctor-patient" communication for interviewing the patients involved. As described above, all the questionnaire items have been carefully discussed during each individual interview, to avoid any potential misinterpretation and to fix the answer, which the patient was best satisfied with. Consequently, the results reported are well reliable and provide a robust scientific platform for the data analysis, presented concepts and follow-up projects expanding for higher numbers of the patients involved.

Further, it was our ultimate intension, along with the general statistics collected for the entire groups of comparison, to provide a spectrum of case reports. This spectrum demonstrates on the one hand highly individual parameters of every patient, but on the other hand a great consensus for all of them regarding both – the disease severity and corresponding pattern of the FS-symptoms.

The overall results of this study clearly support the working hypothesis presented by the authors proposing that a strong epi/genetic predisposition of individuals at risk to form the systemic hypoxic pre-metastatic niches can be established a long time before the breast malignancy is clinically manifested. FS phenotype may act over couple of years or even several life-decades as a strong risk factor contributing to poor outcomes in breast cancer and aggressive metastatic disease. The FS specific attributes, which in extenso have described earlier [29], clearly argue for this conclusion, namely

- FS is prevalent in young populations
- FS is more typical for females
- FS-symptoms appear early during the teenager period of life and moderate in the post-menopause
- Dysregulation/abnormalities of the cardio-vascular component characteristic for the FS strongly predispose the effected individuals to the chronic systemic hypoxic effects
- At the molecular level, enhanced blood levels of endothelin-1 and metalloproteinases MMP-9 and MMP-2 have been described for the FS-affected individuals [3, 27, 29, 31] that at the same time is considered as a powerful prognostic biomarker-panel for particularly poor outcomes in both – breast cancer and metastatic disease [1, 3, 32].

The meaning of individual FS-symptoms specifically for BC patient cohort has been discussed in detail in the recently published article "Breast cancer and Flammer syndrome: Any symptoms in common for prediction, prevention and personalised medical approach? [28] and in the book chapter "Feeling Cold and Other Underestimated Symptoms of Flammer Syndrome in Breast Cancer Diagnostics: Is Innovative Screening on the Horizon?" by Olga Golubnitschaja with co-authors. In this current chapter a particular relevance of the FS-symptoms for the metastatic disease in BC patient cohort should be emphasised: all 15 symptoms demonstrate

the prevalence in the metastatic BC versus BC-free reference group with a statistical significance ($P \leq 0.05$) for seven symptoms as summarised in Table 3. Other symptoms, even being statistically non-significantly prevalent, can be of great importance for the BC pathology and metastatic disease. Indeed, the symptom 3 (low blood pressure, $P = 0.127$) is particularly relevant for the premenopausal subgroup and may strongly contribute to the cardio-vascular component characteristic for the FS as explained above. Another example: symptom 4 (dizziness, $P = 0.762$) has been described earlier as being permanently present and stepwise worsening in BC followed by metastasis in brain [20, 33]. Finally, the normal feeling of thirst (symptom 6, $P = 0.103$) is extremely important and if diminished (here 2-times in BC versus BC-free) pays a crucial role in the body dehydration and BC development [20].

As for the next steps promoting our knowledge and skills within this scientific area, the severity of the FS symptoms should be essentially correlated with the specific molecular profiles relevant for the metastatic BC development and progression. Contextually, individual levels of the hypoxia-inducible factor 1, HIF-1 and vascular endothelial growth factor (VEGF) – both highly relevant for the progression of the aggressive metastatic disease [14, 34] should be correlated with the FS-phenotype. This research is expected, further, to bridge the FS-phenotype with the metastatic disease in other cancer pathologies such as the prostate cancer which shares a lot of similarities with breast cancer risks [35].

A particular attention should be dedicated to the specific molecular profiles relevant for the pain sensitivity (symptom 10) in BC and metastatic disease. The reason for that is the functional link between the pain, chronic inflammation and wound healing, which, if impaired, may lead to aggressive cancer malignancies. Recently published article "Impaired wound healing: facts and hypotheses for multi-professional considerations in predictive, preventive and personalised medicine "[36] discusses potential relevance of the FS for altered wound healing and suggests mechanisms and provides innovative concepts in the field. To this end, updated information is provided in the book chapter "Flammer Syndrome in the Context of Healing Impairments – Facts and Hypotheses for Multi-professional Consideration" by Eden Avishai and Olga Golubnitschaja.

6 Concluding Remarks

The results presented here do substantially extend the currently existing knowledge regarding the "Seed and Soil" theory of metastasis clearly demonstrating that a strong predisposition of individuals at risk to form the systemic hypoxic pre-metastatic niches can be established a long time before the breast malignancy is clinically manifested. The FS phenotype may strongly contribute to the aggressive metastatic disease. The exploitation of the acquired knowledge might be performed by creating innovative screening programmes. Contextually, we propose the FS-questionnaire to be considered by family doctors (GPs) for its practical application to the general population, in order to improve the quality of primary care by

developing novel more effective approaches for the targeted prevention of the metastatic BC. For that the best appropriate 13 FS-symptoms are grouped together within the cluster marked in green colour in the summarising Table 3. The relevance of the remaining two symptoms should be investigated additionally prior to consider their practical application, due to the high level of plurality amongst the BC patients demonstrated in the study.

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Individualised Patient Profile: Risk Assessment by the Patient's Self-Report and Potential Clinical Utility of Flammer Syndrome Phenotype

Olga Golubnitschaja and Josef Flammer

Abstract Herewith we introduce a selected patient case, who evidently demonstrates Flammer syndrome signs and symptoms which might be strongly indicative for predictive diagnostic approaches and targeted preventive measures, if a correct interpretation would be made well in time. A self-report is presented.

Keywords Predictive preventive personalised medicine · Patient self-report · Low BMI · Impaired wound healing · Flammer syndrome phenotype · Diagnosis · Cancer · Pregnancy · Asthma · Voice problem · Chronic tonsillitis · Tonsillectomy · Stress · Irritable bowel disease · Dry mouth syndrome · Sicca syndrome · Risk assessment · Multi-level diagnostics · Recommendations

1 Introduction

In 2018 Springer has selected around 250 articles across all areas with *a potential to change the world* [1]. Selected articles have been awarded the title: "groundbreaking scientific findings that could help humanity and protect our planet". Thereby, 60 articles have been selected in the category "Medicine and Public Health", [2] amongst which an article published by the *Nature Reviews Clinical Oncology* was dedicated to the great value of patients' self-reports as "a key measure of health-care quality" [3]. *Hearing the patient voice at greater volume* – the proclamation made

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by the title of the paper, indeed, should be the leading principle of personalised healthcare.

Contextually, herewith we introduce a selected patient case, who evidently demonstrates Flammer Syndrome phenotype with characteristic signs and symptoms which might be strongly indicative for predictive diagnostic approaches and targeted preventive measures, if a correct interpretation would be made well in time. A self-report is presented [4].

A. **Patient's history**

- **General information**
  - female, 55 years old, BMI = 22 kg/m2
  - academician (biomedical education)
  - made a successful international scientific career
  - permanently job-occupied since 30 years; professionally active about 10 h a day
  - taking a good care of her health (regular body exercises, sport vacations, healthy nutrition, well controlled sleep patterns)
  - stress situations are frequent
  - strongly pronounced perfectionistic personality
- **Patient interview**
  - Beginning with early childhood the patient was frequently ill by acute otorhinolaryngologic infections being also allergic to some meal products and antibiotics. Her parents tried several approaches to get her health condition more stable such as cryotherapy which she experienced as horribly stressful.
  - By the family she has been expected to have the best marks at any level of the school and in any subject that very early formed her meticulous personality and pronounced tendency to perfectionism.
  - Excellent body shape and high intellectual qualities – both were equally facilitated in her family.
  - In early teenager age she was the best pupil and the tallest girl in the class. Automatically everybody expected her to demonstrate extraordinary high sport's achievements in the school – every time running very quickly as requested led her to a feeling of going to black out but no particular attention was paid to that.
  - The patient does not feel thirsty and drinks too little: first when she feels close to fainting and/or by receiving a headache attack and/or episode of tachyarrhythmia she recognises potential deficit on a liquid intake; however, forcing more intake provokes nausea.
  - Retrospectively analysing the circumstances, it is getting obvious that her pregnancy was complicated by oligohydramnios which has not been diagnosed timely and contributed to a wrong estimation of the foetus size as a very small one. In contrast to the wrong estimates, she gave birth to a son who was 59 cm long and weighed 3.750 kg. Caesarian section was planned in a wrong way for a very small foetus; as the mistake became evident during the opera-

tion, more anaesthesia and bigger section was essential to be acutely performed that led to severe complications such as enormous blood lost; the post-surgical recovery has taken several months.
- As the wound after the Caesarian section was still not completely closed after 5 months, for the first time in her life she was concerned about the delayed or even impaired wound healing which she evidently suffers from, but that has not been diagnosed so far. This observation appeared true, due to strongly prolonged period of time necessary for healing even in case of any small finger cut.
- Further observations: The patient is extraordinarily touch and pain sensitive; not always but frequently she has dry eyes, nose, mouth and skin, particularly during the winter time; slight nausea is frequent.
- Specifically in stress situations: she suffers from very cold hands and feet, dry mouth, problems with her voice, symptoms of irritable bowel syndrome, disturbed movement coordination leading to acute injury which then heals abnormally slowly; her hearing capacity is strongly reduced and she even starts slightly stuttering.
- During adulthood, her patient records remained quite thin by the treating general practitioner, who considers her health condition "unremarkable".

- **Objective findings**

  - Since teenager age, mild irritable bowel disease with symptoms particularly pronounced during cold periods of time and after 2–3 days of unusual nutritional intake
  - Appendectomy in adolescence
  - Chronic tonsillitis; partial (left side) tonsillectomy in early adulthood
  - Mild symptoms of asthma
  - Prolapse of the mitral valve
  - Sporadic cardiac arrhythmia
  - Strong menstrual bleedings related to myomatous disease
  - Ten years ago diagnosed with malignancy (carcinoma of basal cells) which has been surgically removed; 6 years later diagnosed with the relapse – surgically removed.
  - Strongly pronounced signs and symptoms of Flammer Syndrome (see the questionnaire filled in below)

- **FS signs and symptoms**

FS-related signs and symptoms [5] have been analysed utilising the syndrome-dedicated questionnaire – see Table 1.

- **Reproductive history**

  - long menarche: regular menstrual cycle (since 10 years of age till now)
  - aged 24 years gave birth to one child by caesarean section with complications
  - 13 months of breastfeeding

Table 1 Specific signs and symptoms are clearly presented in the patient emphasising her strongly pronounced FS-phenotype

Questions	Answers (yes/no)	Comments
Cold hands and/or feet	Yes	Very frequently even in summer time and particularly in stress situations
Feel cold	Yes	Very soon
Low blood pressure?	Yes	
Dizziness	Yes	
Prolong sleep onset	Yes	Particularly as long as feet are cold and by stress/unsolved problems
Do not feel thirsty	Yes	Even in hot weather
Headache / Migraine attacks	Yes	Not frequently, but once appears it is getting very strong
Accompanying symptoms (e.g. visual disturbances)	Yes	Sometimes they appear even before the headache
Altered reaction towards drugs	Yes	Strongly pronounced
Altered pain sensitivity	Yes	Extremely touch and pain sensitive
Strong smell perception	Yes	Extraordinary pronounced
Slim at 20–30 years of age	Yes	BMI = 19–20
Tendency towards perfectionism	Yes	Strongly pronounced
Tinnitus	Yes	Reduced hearing in stress
Reversible blotches (white or red) on your skin e.g. in stress situations	Yes	

- **Lab examination summary**

General clinical biochemical profile in blood is free of any pathological finding. Tumour biomarkers are within the normal range. However, a significantly increased endothelin level by 3,2 pg/ml in blood serum has been detected.

B. **Family history**

- **General information**
  - All family lines are represented by Caucasians originated from central and Eastern European areas
  - All members of the family were obligatory literate persons; some of them were speaking several European languages
  - Members of the family lines were rather asthenic taking care of their body shape and physical aesthetics
  - Number of children per family corresponded to the average in the region
  - Socio-economic situation was favourable for all family lines excepting generally difficult periods of wars
- **Disorders in the family**
  - No history of genetic diseases
  - Excepting an accidental death and death, due to acute infectious diseases, the life-duration was sufficiently above average in all the family lines

  - Grandparents had a history of CVD and migraine; one cancer case with aggressive metastatic disease

- **Mother**
  - medical doctor who made a successful professional career being job occupied till 70 years of age
  - extremely stress sensitive person
  - has not been breastfed after the birth
  - was very slim in teenager age and early adulthood
  - since teenager age mild irritable bowel disease; appendectomy in early adulthood
  - gave birth to and breastfed two children with 19 years of age difference between them
  - was taking a good care of her body shape making regular body exercises
  - suffered from severe headache during regular menstrual periods and experienced an early menstrual onset (11 years of age) and late menopause (60 years of age)
  - suffered from strong menstrual bleedings related to myomatous disease
  - had low blood pressure before 40 years of age, however, after that suffered from hypertonic events till the end of her life
  - by the age of 60 years diagnosed with diabetes mellitus type 2 followed by CVD and severe retinopathy
  - any medication needed to be individually adapted against the average
  - died at the age of 77 years from acute thrombosis

- **Father**
  - Received a complex academic education including medical expertise
  - made a successful career as administrative manager – job occupied till 75 years of age
  - extremely stress sensitive person
  - was very slim in teenager age and early adulthood
  - was taking a good care of his body shape making regular body exercises
  - had low blood pressure before 40 years of age; afterwards his blood pressure was normalised
  - felt less thirsty than average
  - tinnitus
  - myocardial infarction in the age of 45 years
  - diagnosed with the benign prostate adenoma in the age of 60 years
  - highly sensitive to viral infections
  - strong vascular dysregulation (cold hands and feet in winter and summer time)
  - suffered from sleep disorder over several decades of his life
  - even during hot summer used heating toward the feet, in order to fall asleep in the night
  - tremor and strongly reduced hearing ability at progressed age

- any medication was needed to be individually adapted against the average
- died at the age of 88 years from stroke and sudden total collapse of vascular system

C. **PPPM-relevant lessons**

- **What can we learn from the patient history presented here?**
  - The ancestors, particularly mother and father, had already signs and symptoms of FS. This is very common for such patients. There is little doubt, that we are facing an inherited predisposition, but until now we become just acquainted with the phenotype, the mode of inheritance has not yet been studied.
  - The patient is female. Although FS occurs in both – males and females, it is clearly more typical for women. This gender difference seems to be less pronounced in Asian people. We assume that the FS-specific hormonal regulation plays a crucial role. This would also explain why FS symptoms aggravate at puberty and faint after menopause and why oestrogen replacement therapy can boost the symptoms. Central serous chorioretinopathy, a FS associated condition occurring more often in males has highest incidence in young age with the highest level of testosterone and can be provoked in females by a testosterone therapy.
  - This patient is a University graduate. This is very typical for FS-affected individuals. The FS occurs clearly more often in academics than in blue collar workers. The causal relationship is still unclear. FS is also more prevalent in subjects with indoor than in subjects with outdoor jobs. We assume a role of the light, although this is not yet proven. FS subjects have often a low level of Vitamin D, but light has many additional effects. It boots e.g. the production of nitric oxide in the vascular endothelium cells. Therefore, vitamin D dietary supplements do not compensate the UV-deficits.
  - This patient made a brilliant professional carrier. It corresponds to our experience. FS subjects are very reliable, ambitious and minute in their activities. Also in this regard, the causal relationship is not yet known.
  - This patient is taking care of her health both in term of physical activity and nutrition. Again, this is very characteristic for FS subjects. They are neither lazy nor indifferent but in fact dedicated and committed. They also have good knowledge about their own health condition. Patients with a pronounce FS often do intensive bicycling or jogging.
  - She noted an excellent body shape. In general, the lower the BMI, the more pronounced are the FS symptoms. Likewise, the FS signs and symptoms aggravate during fasting periods.
  - This patient experienced a cryotherapy, with the intention to improve health condition, as horrible. This is not surprising for a number of reasons: The core sign of the FS is an increased response of the vessels to stimuli such as coldness or emotional stress. The coldness obviously induced pronounced vasoconstriction and this induces pain. Together with an increased pain sensation

of such subjects we can easily imagine that the patient enormously suffered from a very uncomfortable condition created by the cryotherapy.

– The feeling of thirst is clearly reduced in this patient and sometimes she forgets to drink. The low intake of liquid together with the tendency to the low blood pressure makes her feeling close to fainting. This is also characteristic for FS. FS subjects normally have reduced feeling of thirst, most probably because the increased level of endothelin-1 increases production of prostaglandin E-2, which in turn suppresses the feeling of thirst. The main cause of a low blood pressure is most probably a reduced sodium reuptake in the proximal tubuli of the kidneys.
– The observed delayed wound healing seems to be related to FS, but this relationship needs to be studied. It is feasible, however, that in FS subjects a reduced and unstable blood supply inducing hypoxia and increasing oxidative stress might be unfavourable for the healing. This may also facilitate the growth and metastasis of tumours [6].

• **FS Diagnosis**

The question is: who should make the diagnosis and how [7, 8]? Due to the high specialisation in currently organised medical care, an individual specialist normally doesn't get such an entire history as thoroughly analysed in our paper. Consequently, patients are often left with the feeling that the different complains represent different diseases or at least different predispositions. This is the situation, where the central role of general practitioners comes into the play. The family doctor normally has a more holistic view on the patient. It is already a huge relief for patients, when they realize that the treating physician understands their history and that these complains are not isolated but rather parts of basically one syndrome and that the syndrome is inherited and not a consequence of a misbehaviour. It is a great easement for a patient to hear that their symptoms are comprehensible but not a manifestation of a neurotic personality. The frequent question we receive is: how is it possible that I have all these signs and symptoms, whilst I live such a healthy life? Patients are then often amazed, when they hear that the question "what is healthy" is very individually to reply. Just to give some examples. People in general population learn permanently that they should reduce salt intake. However, patents with systemic hypotension should rather increase their salt intake. Likewise "being slim", indeed, is generally healthy, but "being healthy slim" means highly individual BMI usually raging between 20–25 kg/m^2, and "being too slim" is definitely not optimal at all for being healthy [9, 10]. Unfortunately the FS is not yet well known amongst physicians; however, it is happens frequently, that patients are asking, whether they may be FS-affected and internet-promoted information distribution regarding FS has significantly contributed to this general trend.

How is the FS diagnosis made? If the signs and symptoms are so clear like in the case of the patient described here, an objective evaluation might even not be necessary. If the symptoms remain doubtful, an objective evaluation is helpful. The physician has to apply accessible approaches. This can be a cold provocation of prolonged vasospasm monitored by capillary-microscopy [11] or a light stimulation

on the dynamic retinal vessel analyser monitoring [12], quantification of retinal venous pressure [13], measurements of increased endothelin-1 levels (>2 pg/ml) in blood serum [14], as well as measurements of the condition specific molecular patterns in blood [15, 16]. Unfortunately such tests are still rare and do not belong to conventionally applied medical services.

- **What is to do, if FS is diagnosed? PPPM related conclusions and recommendations**

It is important to keep in mind that FS is not a disease: the syndrome itself does not need any treatment [17]. However, on one hand, FS with its well described signs and symptoms is very helpful for caregivers for the patient's phenotyping. On the other hand, FS is a suboptimal health condition which may strongly contribute to the development of severe pathologies, which the FS-affected patients are individually predisposed to [18]. Unfortunately, our current knowledge about the FS-related pathologies is highly limited [19]. However, what is already known is an indication strong enough to be essentially applied for advancing medical services by predictive and preventive measures as well as for personalisation of treatments [20]. Hence, FS is frequently linked to severe eye diseases such as normal-tension glaucoma [21], and particularly aggressive cancer types (metastasing breast cancer) [22], amongst others. A spectrum of severe pathologies, which FS has been linked to, indicates that an individual (e.g. family) predisposition to the concrete pathology may be, further, provoked for its development and progression by the specific FS-phenotype. Contextually, it has been clearly demonstrated that the systemic hypoxia linked to FS generates a particularly "fertile" microenvironment for cancer development and progression into aggressive metastatic disease [23, 24]. Consequently, it is strongly recommended in the case of FS-affected individuals to "zoom" for an individual pathology predisposition, which FS may strongly promote such as the family predisposition for aggressive cancer subtypes [10]. For that, the family history is an essential element in the complex "individualised patient profile" aiming at early and predictive diagnostics.

Contextually, what are the potential PPPM measures to be considered in the future?

1. FS-phenotype is highly specific and develops early in life. Consequently, parents should be advised to consult children in teenager age with family doctors regarding the FS-diagnosis in the context of known family disorders and their potential relevance to FS.
2. It makes a very good sense to educate primary caregivers regarding FS, predisposition, diagnostic approach, potentially linked pathologies, and targeted preventive measures.
3. Useless and even potentially damaging measures such as cryotherapy should be avoided for the FS-affected individuals, which, in contrast to their positive effects demonstrated in general population, make the FS-affected individuals suffering and could even lead to adverse health effects.

4. Altered drug sensitivity in FS-individuals is a crucial parameter to be carefully considered by caregivers.
5. Pain management is obviously a very specific aspect in medical services provided to the FS-affected individuals that should be carefully considered by personalisation of treatments (e.g. application of anaesthetics in dentistry, surgery, (minimally) invasive diagnostic approaches, amongst others).
6. Reduced thirst feeling typical for the FS-individuals [24] and consequently diminished liquid intake may result in a long-term body dehydration and generation of slightly toxic microenvironment linked to potential complications and even severe pathologies [10]. Some of them are well-acknowledged such as slight nausea mentioned in the patient's interview (see above), headache/migraine attacks [25] and breast malignancies [26]. Others are just assumed remaining much less investigated such as benign tissue transformation (in case of the described family, this is the prostate adenoma in males and the myomatous disease in females), altered immune response and autoimmune disorders, dry eyes, nose, mouth, cavities, skin and vaginal dryness, liver disorders [27] and potential complications in pregnancy (e.g. oligohydramnious, see the patient description above), amongst others. More information to the topic is provided in the book chapters "Interrelation Between Dry Mouth and Flammer Syndromes: Neglected Risks in Youth and New Concepts of Personalised Prevention" by Anatolij Kunin with coauthors, "Specific Symptoms of Flammer Syndrome in Women Suffering from Vaginal Dryness: Individualised Patient Profiles, Risks and Mitigating Measures" by Vadym Goncharenko with co-authors.
7. FS-phenotype is highly relevant to the *Anorexia nervosa* (AN), due to the primary vascular dysregulation, low BMI and other signs and symptoms typical for both of them [21]. In turn, AN has been linked to significantly increased risks of compromised immune system, reproductive dysfunction and impaired wound healing, amongst others. The question remains currently unanswered regarding the causality, namely, whether AN might be an extreme case of FS, or FS-phenotype is synergic with other factors (which ones?) collectively promoting the clinical onset of AN. More information is provided in the book chapter "Flammer Syndrome, Disordered Eating and Microbiome: Interrelations, Complexity of Risks and Individual Outcomes" by Rostyslav Bubnov and Olga Golubnitschaja.
8. Impaired wound healing might be highly relevant for FS-phenotype with severe consequences such as significantly prolonged post-surgical recovery, chronic wounds and cancer development [6]. More information to the topic is provided in the book chapter "Flammer Syndrome in the Context of Healing Impairments – Facts and Hypotheses for Multi-professional Consideration" by Eden Avishai and Olga Golubnitschaja.

The authors strongly emphasise the great clinical relevance of the field-related research to be promoted in accordance with the above listed facts and hypotheses.

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Triple-Negative Breast Cancer with Pronounced Flammer Syndrome Phenotype – Case Report

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Abstract In this chapter we introduce a 41 years old patient diagnosed with a triple-negative breast cancer and pronounced signs and symptoms of the Flammer Syndrome (FS) phenotype also in the family history. The chapter details on the FS questionnaires with the patient and family members. An interview is provided demonstrating a high level of the health literacy of the patient. However, remarkably little attention has been paid by primary care-givers to the treatment of the FS related complications in the family. Potential links between the FS phenotype and early breast cancer onset is analysed.

Keywords Flammer syndrome · Phenotyping · Triple-negative breast cancer · Individualised patient profile · Questionnaire · Patient self-report · Interview · Modifiable risk · Vascular dysregulation · Blood pressure · Altered sense regulation · Psychologic factors · Body mass index · Sicca syndrome · Inflammation · Altered thermoregulation · Cold stress provocation · Perfectionism · Sleep patterns · System medicine · Prediction · Prevention

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1 Patient's History

- **General information**
  - Female, 41 years old, BMI 23.7 kg/m^2
  - Academic: University graduated zoologist
  - Permanently job-occupied as professional zoologist since 24 years of age with two maternity leaves, each lasting 2 years
  - Life style: long walks in natural environment; regular aerobic exercising; low calories nutrition; vitamin rich diet; working rhythms – only over the day; regular sleep patterns, spends a lot of time with outdoor- activities in rural environment.
- **Patient's interview**

She was born as a second child to a family of academics. Mother worked as computing analyst and her father worked as electro-engineer. During her childhood she overcame common infectious diseases and minor injuries with no meaningful treatments needed.

She has always been an excellent student. Her parents shared the same meticulous personality and eagerness to achieve remarkable results in every activity. Whole family showed an interest in social life in their home village, taking an active part in organising the social events.

She and her family also shared the interest in healthy life style. They spent family holidays in sea resorts, took sport vacations and supported a wide development of intellectual and physical skills. She described herself as a physically very active person across all the seasons, although suffering a lot from cold extremities. To this end, compared to other members of her family, she feels inadequately cold at the same temperatures and needs to clothe more warmly when sitting and not moving for a while.

She doesn't consider it unusual to feel vertiginous when abruptly standing up from a resting position. She has always thought it is normal and being associated with her blood pressure which is usually low. She does not feel thirsty but forces herself to drink more than her feeling of thirsty desires. By mind controlled an increased water intake helps her against frequently recognised dry skin, dry nose and dry mouth (Sicca syndrome).

Because of her high interest in sport and exercises, she has never paid an extra attention to her body shape. Since the early childhood throughout adolescence and in the adulthood, her BMI was at the lowest level within the statistically normal range.

She observes mild red flecks around the neck and her chest, when getting agitated or angry.

Being asked about her sense of smell she notices always to have an "extraordinary sensitive nose".

Even though it usually takes her longer to fall asleep, she has never been taking medication for sleep or any other systematic medication. She tolerates the pain well and usually do not use painkillers.

In contrast to her mother and sister, who are both suffering from tinnitus, her hearing ability is in a perfect condition.

- **Objective findings**
  - Mastitis of left breast in puerperium 2011
  - Allergies: Penicilin group antibiotic medication, polen grains, grass, dog, cat
  - Laparoscopic appendectomy in 2001
  - Undergoes regular annual medical checks by the general practitioner and gynaecologist
  - In July 2018, diagnosed with triple negative multifocal ductal invasive carcinoma of right breast by the ultrasound and mammography examination + core-cut biopsy
  - Underwent right side skin sparing mastectomy and first and second stage lymphadenectomy of right axillary lymph nodes
  - BRCA mutation positivity for second-degree relatives is reported.
- **FS signs and symptoms**
  FS-related signs and symptoms have been analysed utilising the syndrome-dedicated questionnaire – see Table 1.
- **Reproductive history**
  - First menstrual bleeding at the age of 11 years, with regular uncomplicated menstrual cycle 28/5
  - 2x vaginal delivery in 2009 and 2011
  - Breastfeeding 13 months approximately

Table 1 FS-phenotype specific signs and symptoms are strongly pronounced in the patient

Questions	Answers (yes/no)	Comments
Cold hands and/or feet	**Yes**	Very frequently
Feel cold	**Yes**	Very soon
Low blood pressure	**Yes**	Very frequent
Dizziness	**Yes**	Very frequent
Prolong sleep onset	**Yes**	Very frequent
Does not feel thirsty	**Yes**	Even during hot weather period of time
Headache/migraine	**No**	
Accompanying symptoms (e.g. visual disturbances)	**No**	
Altered reaction towards drugs	**Yes**	Allergic reactions – see above
Altered pain sensitivity	**No**	
Strong smell perception	**Yes**	Extraordinary pronounced
Slim at 20–30 years of age	**Yes**	Extraordinary pronounced
Tendency towards perfectionism	**Yes**	Strongly pronounced
Tinnitus	**No**	
Reversible blotches (white or red) on the skin e.g. in stress situations	**Yes**	Strongly pronounced

- Laboratory parameters
  - Anaemia HGB 107.00, HCT 0.31, RBC 3.77- for a long time

2 Family History

- General information
  - All family members are of Caucasian origin from Eastern European areas
  - Majority of family members were/are literate people with university degrees or working in leading managing positions in their companies
  - Favourable socio-economic situation in all family branches
- Oncological diseases – grandmother from father's side – breast cancer
  - aunt (father's sister) – breast cancer
  - grandmother from mother's side – uterine cancer
  - great grandmother from mother's side – 46 years old died of gynaecologic cancer
  - great grandfather from mother's side – colon cancer
  - uncle (mother's brother) – colon cancer
- Mother
  - Born in 1954
  - Worked in computing department
  - Overcame common infectious diseases in childhood
  - Underwent hemithyroidectomy because of nodous struma
  - Laparoscopic removal of ovarian cyst- corpus luteum hemoraghicum
  - Her sister had asthma
  - First menstrual bleeding at the age of 15 years, menopause as 57 years old
  - 2 spontaneous vaginal with vasoactive drugs deliveries
  - Treated with vasoactive drugs, due to bilateral tinnitus and bilateral hypacusis sensorineuralis
  - Occasional dyspeptic disorders
  - Repeatedly treated due to the pain in the lumbal area and in knees
  - Tendency to obstipation
  - BMI up to 20 kg/m^2 (165 cm, 54 kg)
  - Liver hemangioma
  - Stress urine incontinence
  - Positive family history for cardiovascular diseases
  - Frequently suffers from cold hands and feet even during the summer time
  - Tendency to hypotension and to feeling vertiginous when standing up quickly from a resting position
  - Occasional headaches with no migraines

- a long time to fall asleep
- forces herself to drink more
- no meticulous personality tending to perfectionism
- Sometimes sensitive about the smell
- Occasionally feels pain and needs to take painkillers

FS-related signs and symptoms have been analysed utilising the syndrome-dedicated questionnaire – see Table 2.

- Sister
  - Born in 1979, nulliparous
  - Frequent respiratory tract infections in childhood
  - Underwent thyroidectomy
  - Slim with BMI up to 18 throughout the life
  - Sometimes suffers from cold hands and feet, doesn't tolerate cold well
  - Her thirsty feelings and drink attitude are unremarkable
  - Rarely suffers from headaches with no need for painkillers
  - Perfectionist
  - Suffers from tinnitus
  - She observes red flecks on her chest in stress situation

FS-related signs and symptoms have been analysed utilising the syndrome-dedicated questionnaire – see Table 3.

Table 2 Analysis of the FS-phenotype specific signs and symptoms

Questions	Answers (yes/no)	Comments
Cold hands and/or feet	**Yes**	Very frequently
Feel cold	**Yes**	Very soon
Low blood pressure	**Yes**	
Dizziness	**Yes**	
Prolong sleep onset	**Yes**	
Does not feel thirsty	**Yes**	
Headache/migraine	**Yes**	
Accompanying symptoms (e.g. visual disturbances)	**No**	
Altered reaction towards drugs	**No**	
Altered pain sensitivity	**Yes**	
Strong smell perception	**Yes**	
Slim at 20–30 years of age	**Yes**	
Tendency towards perfectionism	**No**	
Tinnitus	**Yes**	Strongly pronounced
Reversible blotches (white or red) on the skin e.g. in stress situations	**Yes**	

Table 3 Analysis of the FS-phenotype specific signs and symptoms

Questions	Answers (yes/no)	Comments
Cold hands and/or feet	**Yes**	Sometimes
Feel cold	**Yes**	Sometimes
Low blood pressure	**No**	
Dizziness	**No**	
Prolong sleep onset	**No**	
Does not feel thirsty	**Normal feeling of thirst**	
Headache/migraine	**No**	
Accompanying symptoms (e.g. visual disturbances)	**No**	
Altered reaction towards drugs	**No**	
Altered pain sensitivity	**No**	
Strong smell perception	**No**	
Slim at 20–30 years of age	**Yes**	
Tendency towards perfectionism	**Yes**	Strongly pronounced
Tinnitus	**Yes**	Strongly pronounced
Reversible blotches (white or red) on the skin e.g. in stress situations	**Yes**	Strongly pronounced

- Aunt (father's sister)
  - Born in 1940
  - Secundipara, breastfeeding both children approximately 6 months each
  - Underwent hysterectomy with bilateral adnexectomy as 43 years old
  - Diagnosed with breast carcinoma at the age of 70 years: DIC pT1c, pN0, Mx G2 on Tamoxifen therapy
  - in older age treated for varices of lower extremities, COPD, vascular encephalopathy with repeating collapses

The family tree summarising FS phenotype and breast cancer diagnosis is presented in Fig. 1.

3 Concluding Remarks

- According to the family history, the reported here patient is clearly predisposed to oncologic diseases via genetic (non-modifiable) risk factors
- However, specifically postmenopausal (>60 years of age) but not a premenopausal breast cancer has been reported for the family members till now
- The reported patient presents in the family the very first case of the premenopausal breast cancer at the age of 41 years
- There is no any "traditional" factor reported for the patient in the category "modifiable" risks.

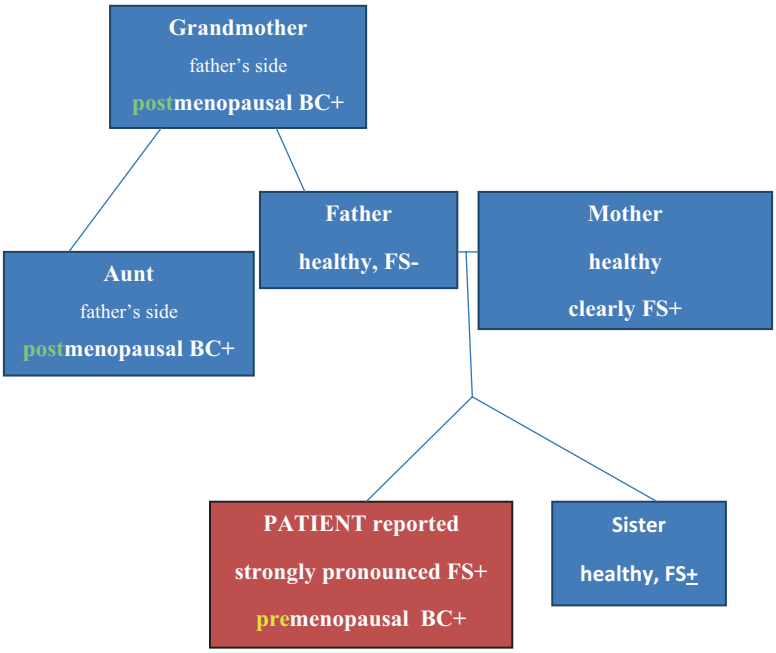

Fig. 1 Family tree analysing FS phenotype and breast cancer diagnosis

- For the first time a particular attention has been dedicated by care-givers to the specific signs and symptoms of the Flammer Syndrome (FS), when analysing the medical history of the patient and this of her family-members; the analysis revealed the most pronounced FS signs and symptoms specifically in the reported patient compared to all other members of the family, although the mother of the patient demonstrates a clear FS phenotype as well.
- The patient demonstrates clear vascular dysregulation (inappropriate vasoconstriction), dizziness, altered thermoregulation (feeling cold even when other people around are comfortable with the room temperature), altered sense regulation (strong smell perception and no feeling of thirst), low BMI, perfectionism and prolonged sleep onset – all the FS symptoms strongly relevant for breast cancer as described in the literature [1–3].
- Consequently, the life-style habits generally considered as "healthy" might be suboptimal for the patient with strongly pronounced FS-phenotype. For example, low calories nutrition (due to the low energy supply), much time spent outdoor in the low temperature environment (due to the cold stress provocation), much physical exercises (due to the excessive stress by sport), amongst others [4].
- Further persistent conditions of the patient, namely Sicca syndrome (dry skin, dry nose, dry mouth reported by the patient before the chemotherapy application; under the current chemotherapy also the vaginal dryness is an additional complication reported), and allergies (allergic rhinitis and conjuctivitis) – altogether

may strongly contribute to systemic inflammation and cancer development as described for individuals with FS phenotype [5, 6].

- For more information regarding the FS-phenotype in breast cancer context, see the book chapters "Feeling Cold and Other Underestimated Symptoms of Flammer Syndrome in Breast Cancer Diagnostics: Is Innovative Screening on the Horizon?" by Olga Golubnitschaja with co-authors, and "Relevance of Flammer Syndrome Phenotype to Metastatic Breast Cancer: Risks by Pre-metastatic Systemic Hypoxic Environment" by Rostyslav Bubnov with co-authors.

4 Recommendations

- The patient and the affected family-members should be clarified regarding their FS-phenotype and life-style habits to be adapted to their individual needs accordingly [7].
- The patient may be recommended to consider undergoing predictive diagnostics utilising currently accumulating knowledge about pathology specific miRNA-patterns and detection of the circulating tumour cells in blood [7, 8].
- After the conventional treatment is finalised, under observation of the local specialist, the patient may consider implementing a chemo-preventive therapy based on the natural plant substances [9].

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Suboptimal Health Status and Cardiovascular Deficits

Wei Wang and Xuerui Tan

Abstract Suboptimal Health Status (SHS) is the subclinical, reversible stage of pre-chronic disease. It is the physical state between health and disease, characterised by the perception of health complaints, general weakness, chronic fatigue and low energy levels. We have developed a tool to measure SHS, Suboptimal Health Status Questionnaire-25 (SHSQ-25) which assesses five components of health: (1) fatigue, (2) the cardiovascular system, (3) the digestive tract, (4) the immune system, and (5) mental status. To date, the SHSQ-25 as a self-reported survey instrument has been validated in various populations, including African, Chinese and Caucasians, therefore generating an unprecedented opportunity for the early detection of chronic health conditions, namely, cardiovascular diseases and diabetes. Our studies suggest that SHS is associated with the major components of cardiovascular health. We investigated the association between SHS and cardiovascular health metrics (defined by American Heart Association) among Chinese. Participants in the largest quartile of ideal cardiovascular health (CVH) metrics showed a lower likelihood of having on optimal SHS score compared to those in the smallest quartile after adjusting for socio-demographic factors (age, gender, marital status, alcohol consumption, income level and education). Four metrics (smoking, physical inactivity, poor dietary intake and ideal control of blood pressure) were significantly correlated with the risk of SHS. The study indicated that ideal CVH metrics were associated with a lower prevalence of SHS, and the combined evaluation of SHS and CVH metrics allows the risk classification of cardiovascular disease, consequently contributing to the prevention of cardiovascular diseases from a preventive, predicative and personalised medicine perspective (PPPM).

Keywords Suboptimal health · Questionnaire · Cardiovascular deficits · Fatigue · Digestive tract · Immune system · Mental status · Self-reported survey · Chinese population · Chronic health condition · Chinese · Socio-demographic factor · Age ·

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Gender · Marital status · Alcohol consumption · Income level · Education · Metrics · Smoking · Physical inactivity · Poor dietary intake · Blood pressure · Risks classification · Predictive preventive personalised medicine · Innovation · Strategy

1 Introduction

Suboptimal Health Status (SHS) is the physical status between health and disease, characterized by the perception of health complaints, general weakness, and low energy. SHS is regarded as a subclinical, reversible stage of chronic health condition [1, 2]. Globally, SHS has become a new public health challenge [3–10] and shares similar conditions to that of other health conditions including, unexplained medical syndrome (UMS), chronic fatigue syndrome (CFS), myalgic encephalomyelitis (ME), post-viral fatigue syndrome (PVFS) or chronic fatigue immune dysfunction syndrome (CFIDS) [1]. UMS was reported to be a cause of frequent healthcare usage and accounts for 20–50% increase in outpatient costs and 30% increase in admission rates in the United Kingdom [11]. In China, with the acceleration of paces of work and lifestyles, together with the worsening of environmental conditions and pollution, the prevalence of SHS continues to increase, and has been reported that 17.8–60.5% of people currently suffer from SHS [6–10].

The SHS encompasses five characteristics: fatigue, the cardiovascular system, the digestive tract, the immune system and mental status [1, 2] (Fig. 1).

In a cross-sectional study conducted with workers employed in urban Beijing, we demonstrated that SHS was associated with cardiovascular risk factors and contributed to the development of cardiovascular disease [9]. In a case-control study of Ghanaians, West Africa, we found that SHS questionnaire-25 (SHSQ-25) (Appendix 1) could be translated and applied as a practical tool to screen at-risk individuals of diabetes, hence, proving useful for the purpose of predictive, preventive and personalised medicine (PPPM) [3]. In a community-based cross-sectional study conducted in Russia, SHS was shown to be associated with endothelial dysfunction, indicating

Fig. 1 SHSQ-25 assesses five components of health: fatigue, cardiovascular function, digestion, immune function and mental status [1]

that the integration of SHS and endothelial dysfunction can be applied to routine screening for detecting the risks of cardiovascular diseases [5].

Moreover, in a study of Chinese students, SHS was shown to be correlated with lifestyle factors, including physical activity, health responsibility, spiritual growth, interpersonal relations and stress management [12]. Indeed, poor work-life balance and irregular breakfast eating habits were reported to be associated with increased risk for SHS in a cross-sectional study conducted in Guangdong province, southern China [13–15].

These studies suggest that SHS contributes to the occurrence of non-communicable chronic diseases (NCD), especially cardiovascular diseases. In order to investigate the causative effect of SHS in NCD, we initiated the China Suboptimal Health Cohort Study (COACS), a longitudinal study which began in 2013 [7]. The pilot results of COACS show that the risk factors for NCD, such as, socioeconomic status, marital status, education, physical activity, salt intake, systolic blood pressure (SBP), diastolic blood pressure (DBP) and total cholesterol (TG) differed significantly between subjects of SHS (SHS score ≥ 35) and those of ideal health (SHS score < 35) [8].

Taken together, these studies indicated that SHS is associated with most of the cardiovascular health metrics, defined by American Heart Association (AHA) [16]. AHA has defined seven behaviours and risk factors: (1) smoking status, (2) body mass index (BMI), (3) physical activity, (4) healthy dietary score, (5) TC, (6) blood pressure and (7) fasting plasma glucose (FPG) as health metrics and created three stages for each metric to reflect poor, intermediate, and ideal cardiovascular health status [17]. A prospective cohort study including 42,847 men in America indicated that the majority of cardiovascular events may be preventable through adherence to healthy lifestyle practices [17], while another study showed that the number of ideal cardiovascular health (CVH) metrics was a significant predictor for cardiovascular disease and mortality [18].

SHS and CVH are both associated with risk of cardiovascular disease, and therefore may be associated or interacted. In this book chapter, we present the case examples of SHS and CVH to demonstrate the potential association between SHS and cardiovascular dysregulation conducted among ethnic groups, Chinese, Ghanaians, and Russians from the perspective of preventive, predicative and personalised medicine (PPPM) [3, 5, 8].

PPPM is defined as 'an integrative concept that enables the prediction of an individual's predisposition before the onset of a disease, to provide targeted preventive measures and create personalised treatment algorithms tailored to a person [20]. Over the past few years, PPPM has made a significant impact on the prevention and treatment of diseases because it adopts a holistic approach (e.g. environmental, behavioural and traditional factors) to solving health problems [21–24].

2 Case Studies

2.1 Case One: Association Between Ideal Cardiovascular Health Metrics and Suboptimal Health Status in Chinese Population Participants

All 4313 participants (60.30% women) aged between 18 to 65 years old, were recruited from China Suboptimal Health Cohort Study (COACS) [7]. Inclusion and exclusion criteria can be obtained from our previous publication [7]. In short, all adults (from 18 to 64 years old) who participated in the baseline investigation were included and those currently suffering from diabetes, hypertension, self-reported hyperlipemia, cardiovascular or cerebrovascular conditions (including self-reported atrial fibrillation, atrial flutter, heart-failure, myocardial infarction, transient ischaemic attack, and stroke), any type of cancer and gout were excluded from the study. From 2013 to 2014, all participants underwent a standardized physical examination, including medical history, anthrophysical measures, blood hematology and biochemistry analysis, rest electrocardiography, abdominal ultrasonography, and all participants were asked to complete the SHSQ-25 under the instructions of well-trained researchers.

Determination of Suboptimal Health Status

The SHS scores were measured using the SHSQ-25, a self-reported survey tool validated in various ethnic and aged populations [1, 2], (Appendix 1). SHSQ-25 consists of 25 items of five domains of (1) fatigue, (2) the cardiovascular system, (3) the digestive tract, (4) the immune system and (5) mental status. A score ≥ 35 represents a SHS and < 35 represent an ideal health [8, 9].

Assessment of Cardiovascular Health Metrics

According to the guidelines by America Heart Association, we defined the seven CVH metrics at three levels: "ideal", "intermediate" and "poor" [16]. Data on smoking, physical activity and dietary intake were collected via an established questionnaire [7]. Smoking metrics were classified as ideal (never or quit-smoking >12 months); intermediate (former-smoking ≤12 months) or poor (current smoking). Physical activity were classified as ideal (≥150 min/week of moderate intensity or ≥75 min/week of vigorous intensity), intermediate (1–149 min/week of moderate intensity or 1–74 min/week of vigorous intensity), or poor (none). Referring to our previous literatures [25, 26], dietary intake, mainly based on salt consumption, was graded into ideal (<6 g per day), intermediate (6–10 g per day) or poor (>10 g per day). Body mass index (BMI) was classified as ideal (<25 kg/m^2), intermediate (25–29.9 kg/m^2) or poor (≥30 kg/m^2). Systolic blood (SBP) and

diastolic blood (DBP) pressures were classified as ideal (SBP <120 mmHg and DBP < 80 mmHg and untreated), intermediate (SBP 120–139 mmHg or DBP 80–89 mmHg or treated to goal), or poor (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg). Fast plasma glucose (FPG) was classified as ideal (<100 mg/dL and untreated), intermediate (100–125 mg/dL or treated to goal), or poor (≥126 mg/dL). Total cholesterol (TC) was classified as ideal (<200 mg/dL and untreated), intermediate (200 to 239 mg/dL or treated to goal), or poor (≥240 mg/dL).

Characteristics of Participants

Age, gender, education level, alcohol use, smoking, physical activity, diet, TC, SBP and DBP, FPG and BMI distribution were different among the four quartile of CVH (p for trend <0.001) (Table 1). The prevalence of SHS is statistically different in quartiles of ideal CVH metrics (p for trend = 0.012). Table 2 shows the associations between SHS with the summary score of ideal CVH metrics. Overall, participants who gave higher score of ideal CVH metrics had a lower SHS score (OR, 0.64; 95% CI, 0.49–0.85) when compared to those in the largest quartile to those in the smallest quartile of the summary score of CVH, and the association remained statistically significant when age, gender, marital status, alcohol consumption, income level, and education were adjusted (OR, 0.43; 95% CI, 0.32–0.59). In addition, stratified analyses indicated that such negative association were stronger in the male population than the female population, and in participants older than 45 years.

Results

The associations between SHS with each CVH metric are listed in Table 3. It was found that never or quit-smoking >12 months, ideal physical activity and ideal dietary intake were significantly associated with the decreased risk of SHS (OR, 0.70 (95% CI, 0.50–0.99), 0.68 (0.54–0.86) and 0.31 (0.22–0.45) for never or quit-smoking >12 months, ideal physical activity and ideal dietary intake, respectively) after adjusting for age, gender, marital status, alcohol use, income level, education level, and other 6 ideal cardiovascular metrics. However, compared to those with intermediate control of blood pressure (SBP 120–139 mmHg or DBP 80–89 mmHg or treated to goal), ideal blood pressures was shown to be associated with increased risk of SHS (OR, 1.49; 95% CI, 1.17–1.89) in the full adjusted model. The association between SHS and other CVH metrics (BMI, TC, FPG) were not statistically significant. Stratified analyses showed that the negative correlation of SHS with ideal dietary intake and positive correlation with ideal blood pressure are consistent in men and women and across different age groups (Table 3).

This case study explored the association between SHS and ideal CVH metric score. Subjects in the highest quartile of the ideal CVH metric summary score have a 57% reduced odd ratio (OR) of having SHS compared to those in the lowest quartile. We also found that never or quit-smoking >12 months, ideal physical activity

Table 1 The descriptive characteristics of the participants by quartiles of ideal cardiovascular health metrics

Characteristics	Ideal Cardiovascular Health Metrics[a]				
	Quartile1 (n = 1121)	Quartile 2 (n = 797)	Quartile 3 (n = 959)	Quartile 4 (n = 1436)	*p* for tend
Age (years)	37.48 ± 10.85	36.80 ± 10.72	36.05 ± 10.21	37.12 ± 10.31	0.016
Male (%)	869(77.52)	412(51.69)	356(37.12)	357(24.86)	<0.001
Marriage status (yes)	1008(89.92)	709(88.96)	846(88.22)	1284(89.42)	0.6411
Income, ¥/month[b]					<0.001
≤¥3000	395(35.91)	284(36.41)	288(30.51)	426(29.98)	
¥3001–5000	629(57.18)	431(55.26)	562(59.53)	887(62.42)	
≥¥5001	76(6.91)	65(8.33)	94(9.96)	108(7.60)	
Education level					<0.001
Illiteracy/primary	21(1.87)	16(2.01)	21(2.19)	14(0.97)	
Middle school	352(31.40)	227(28.48)	230(23.98)	373(25.97)	
College/University	748(66.73)	554(69.51)	708(73.83)	1049(73.06)	
Alcohol use					<0.001
Yes	51(4.55)	7(0.88)	11(1.15)	9(0.63)	
No	1070(95.45)	790(99.12)	948(98.85)	1427(99.37)	
Smoking					<0.001
Ideal (never)	436(38.89)	602(75.53)	860(89.68)	1416(98.61)	
Intermediate (former)	11(0.98)	4(0.50)	6(0.63)	2(0.14)	
Poor (current smoker)	674(60.12)	191(23.96)	83(8.65)	18(1.25)	
BMI					<0.001
deal (<25 kg/m^2)	497(44.34)	559(70.14)	754(78.62)	1318(91.78)	
Intermediate (25–29.99 kg/m^2)	520(46.39)	218(27.35)	201(20.96)	117(8.15)	
Poor (≥30 kg/m^2)	104(9.28)	20(2.51)	4(0.42)	1(0.07)	
Physical activity					<0.001
Ideal[c]	269(24.00)	264(33.12)	385(40.15)	1136(79.11)	
Intermediate[d]	120(10.70)	96(12.05)	118(12.30)	139(9.68)	

Poor (0 min/week)	732(65.30)	437(54.83)	456(47.55)	161(11.21)	
Diet					<0.001
Ideal (3–4 of components)	109(9.72)	97(12.17)	187(19.50)	615(42.83)	
Intermediate(2 of components)	517(46.12)	466(58.47)	676(70.49)	722(50.28)	
Poor (0–1 of components)	495(44.16)	234(29.36)	96(10.01)	99(6.89)	
Total cholesterol					<0.001
Ideal (<200 mg/dL)	753(67.17)	661(82.94)	846(88.22)	1335(92.97)	
Intermediate (200–239 mg/dL)	368(32.83)	136(17.06)	113(11.78)	101(7.03)	
Blood pressure					<0.001
Ideal (<120/80 mmHg)	294(26.23)	372(46.68)	576(60.06)	1083(75.42)	
Intermediate(SBP129–139 or DBP80–90 mmHg)	827(73.77)	425(53.32)	383(39.94)	353(24.58)	
Fasting plasma glucose					<0.001
Ideal (<100 mg/dL)	948(84.57)	731(91.72)	891(92.91)	1395(97.14)	
Intermediate (100–125 mg/dL)	173(15.43)	66(8.28)	68(7.09)	41(2.86)	
SHSQ-25 score ≥35	119(10.62)	80(10.04)	88(9.18)	102(7.10)	0.012

[a]Quartile 1, CVH ≤ 9; Quartile 2, CVH = 10–11; Quartile 3, CVH = 12; Quartile 4, CVH = 13–14

[b]42 subjects provided missing data in variable of income

[c]Defined as ≥150 min/week moderate intensity or ≥75 min/week vigorous intensity or ≥ 150 min/week moderate + vigorous

[d]Defined as ≥1–149 min/week moderate intensity or1–74 min/week vigorous intensity or 1–149 min/week moderate + vigorous

BMI body mass index, *SHSQ-25* SHS questionnaire 25 items, *CVH* cardiovascular health

Table 2 Associations of suboptimal health status with score of ideal CVH metrics

Metrics	Total	Gender		Age	
		Men	Women	<45 years	≥45 years
Model1					
Quartile1	1.00	1.00	1.00	1.00	1.00
Quartile2	0.94(0.70–1.27)	0.78(0.51–1.20)	0.85(0.54–1.34)	1.03(0.74–1.43)	0.61(0.29–1.27)
Quartile3	0.85(0.64–1.14)	0.39(0.22–0.70)	0.81(0.53–1.24)	0.81(0.59–1.13)	0.98(0.52–1.87)
Quartile4	0.64(0.49–0.85)	0.45(0.26–0.78)	0.50(0.33–0.76)	0.68(0.50–0.93)	0.51(0.28–0.96)
Model2					
Quartile1	1.00	1.00	1.00	1.00	1.00
Quartile2	0.77(0.56–1.05)	0.78(0.50–1.19)	0.83(0.52–1.32)	0.82(0.58–1.16)	0.53(0.25–1.11)
Quartile3	0.63(0.46–0.85)	0.39(0.22–0.70)	0.79(0.51–1.21)	0.58(0.41–0.82)	0.80(0.42–1.56)
Quartile4	0.44(0.33–0.60)	0.45(0.26–0.78)	0.49(0.32–0.74)	0.45(0.32–0.63)	0.39(0.21–0.75)
Model3					
Quartile1	1.00	1.00	1.00	1.00	1.00
Quartile2	0.75(0.55–1.03)	0.78(0.50–1.20)	0.78(0.49–1.26)	0.82(0.58–1.17)	0.51(0.24–0.60)
Quartile3	0.64(0.46–0.87)	0.39(0.22–0.70)	0.80(0.52–1.24)	0.62(0.43–0.89)	0.77(0.40–1.50)
Quartile4	0.43(0.32–0.59)	0.39(0.22–0.69)	0.50(0.33–0.76)	0.46(0.32–0.66)	0.36(0.18–0.70)

Quartile 1, CVH ≤ 9; Quartile 2, CVH = 10–11; Quartile 3, CVH = 12; Quartile 4, CVH = 13–14
Model 1: Unadjusted; Model 2: Adjusted for age and gender; Model 3: Adjusted for age, gender, marital status, education level, and income level
CVH cardiovascular health

and ideal dietary intake were independent protective factors of SHS, while ideal control of blood pressure was a risk factor of SHS.

The main findings from the present study showed that ideal CVH metric score are negatively correlated with SHS scores in a large population. This association is independent from the known confounding factors (age, gender, education level, married and alcohol drinking). This suggests that increasing ideal CVH metric scores are a new independent protective factor of SHS (besides the already existing list of factors, namely, age, gender, marital status, alcohol consumption, income level, and education), and can be applied as parameters to further address the biological characteristics of SHS. Moreover, from the present findings it can be proposed that a more effective way to prevent the onset, maintenance and severity of cardiovascular disease, from the perspective of PPPM, is an intervention that encompasses SHS while maintaining ideal CVH. Consistent with our previous research [9] and other studies in the area, reported that unhealthy lifestyle determined

Table 3 Associations of suboptimal health status with each component of cardiovascular health metrics

Metrics	Total	Sex		Age(years)	
		Male	Female	<45	≥45
Smoking					
Poor	1.00	1.00	1.00	1.00	1.00
Intermediate	1.18(0.26–5.27)	1.20(0.27–5.43)	–	0.93(0.12–7.62)	1.80(0.20–15.94)
Ideal	**0.70(0.50–0.99)**	**0.68(0.47–0.98)**	0.75(0.25–2.29)	0.73(0.50–1.06)	0.67(0.30–1.52)
BMI					
Poor	1.00	1.00	1.00	1.00	1.00
Intermediate	0.76(0.41–1.43)	1.15(0.44–3.00)	0.47(0.20–1.14)	0.72(0.36–1.43)	1.00(0.21–4.77)
Ideal	0.69(0.37–1.28)	0.88(0.34–2.30)	0.48(0.21–1.12)	0.56(0.28–1.10)	1.58(0.35–7.11)
Physical activity					
Poor	1.00	1.00	1.00	1.00	1.00
Intermediate	0.90(0.63–1.27)	0.70(0.40–1.20)	1.04(0.65–1.64)	0.94(0.65–1.37)	0.61(0.23–1.66)
Ideal	**0.68(0.54–0.86)**	**0.50(0.34–0.73)**	0.81(0.60–1.09)	**0.72(0.56–0.94)**	**0.54(0.32–0.91)**
Diet					
Poor	1.00	1.00	1.00	1.00	1.00
Intermediate	**0.65(0.51–0.84)**	0.70(0.48–1.02)	**0.62(0.44–0.87)**	**0.71(0.54–0.94)**	**0.49(0.27–0.89)**
Ideal	**0.31(0.22–0.45)**	**0.35(0.18–0.65)**	**0.29(0.19–0.45)**	**0.34(0.23–0.51)**	**0.27(0.11–0.52)**
TC					
Intermediate	1.00	1.00	1.00	1.00	1.00
Ideal	0.98(0.72–1.32)	1.03(0.65–1.63)	0.98(0.65–1.47)	1.07(0.73–1.56)	0.78(0.45–1.32)
Blood pressure					
Intermediate	1.00	1.00	1.00	1.00	1.00
Ideal	**1.49(1.17–1.89)**	**2.00(1.38–2.90)**	1.23(0.90–1.68)	**1.67(1.27–2.20)**	1.01(0.61–1.67)
FPG					
Intermediate	1.00	1.00	1.00	1.00	1.00
Ideal	0.81(0.55–1.20)	0.90(0.49–1.67)	0.76(0.45–1.28)	0.78(0.48–1.27)	0.78(0.40–1.52)

The values are presented as adjusted odds ratio (95% confidence interval). The values indicated in bold represent that the association between SHS and the CVH metrics was statistically significant The following potential confounders were adjusted for each OR: gender, age, marital status, alcohol use, income level, education level and the six cardiovascular health metrics. *BMI* body mass index, *TC* total cholesterol, *FPG* fasting plasma glucose

by the Health-Promoting Lifestyle Profile (HPLP-II), work-life balance and breakfast eating habits were also associated with SHS [13–15, 26]. Healthy diet intake is associated with a lower risk of suffering SHS, and smoking and/or physical inactivity are associated with risk of SHS. Taken together, health behaviours play an important role in contributing to the associations between SHS and the risk of cardiovascular events.

The present finding that intermediate control of blood pressure is negatively correlated with SHS score is inconsistent with our previous study, where blood pressure that was elevated in the participants with higher SHS scores. A cross-sectional study conducted in Samara, Russia showed that blood pressures are not statistically correlated with SHS score (beta = 0.069, $p = 0.199$ and beta = −0.040, $p = 0.416$ for SBP and DBP, respectively) [15]. These inconsistencies remain unexplained, but there are three possible explanations. Firstly, internal correlation among CVH and confounding factor may lead to the inconsistent association. For example, high levels of physical activity and current smoking status had negative relations to overweight or obesity [27] and it was reported that systolic blood pressure markedly declined from non-smokers to smokers [28]. Secondly, subjects who were found to have hypertension were excluded from the recruitment, which might have led to the measures of blood pressure and triglycerides being slightly lower in subjects of SHS than those of health [7]. Finally, abnormalities of blood pressure variability might be a characteristic of SHS. In concept, SHS covers confoundedly the symptoms of CFS, which is a medical condition characterized by long-term fatigue and other symptoms that limit a person's ability to carry out ordinary daily activities [29] Abnormalities of blood pressure variability occurs in CFS [30] and even lower blood pressure and abnormal diurnal blood pressure regulation occur in patients with CFS [30]. However, the inconsistent association between SHS and blood pressure remains unexplained, and further validated in large sample-sized, cross-sectional or longitudinal designed studies. In conclusion, higher ideal CVH metrics were associated with a lower prevalence of SHS. The evaluation of SHS combined with the analysis of CVH metrics allows for the risk classification of cardiovascular dysregulation.

2.2 Case Two: Incorporation of Suboptimal Health Status as a Potential Risk Assessment for Type II Diabetes Mellitus: A Case-Control Study in a Ghanaian Population, West Africa

Background

In Ghana, up to 440,000 people were documented to have T2DM in 2013, the number of those with prediabetes symptoms however, have not been recorded or identified to date [30]. Individuals can remain undiagnosed for a long period of time, some even for many decades of their life. Effective interventions for such people can only commence following the manifestation of clinical symptoms. This is a delayed response from the perspective of PPPM [1].

As with many chronic diseases, screening for prediabetes or T2DM is central in PPPM as it provides the stimulus for initiating treatment and delaying long-term complications. Most often, screening is performed in a health care facility to allow health care providers the ability to perform appropriate follow-up testing and institute quality health care [31]. However, with recent developments in public health research, there are now a number of robust screening tools that are non-invasive, inexpensive and can be applied in a health care setting, in the field, and in the general wider community. One such tool is the Suboptimal Health Status Questionnaire (SHSQ-25) [1, 2].

Participants

The study only included participants who were diagnosed as having T2DM, based on the international classification of diabetes (ICD 10) criteria. Participants on insulin medication or injections were considered to be suffering from T1DM and hence, excluded. Of the 260 T2DM participants recruited for the study [19], 19 were excluded from the analysis due to missing biochemical data. In order to screen for individuals with undiagnosed risk factors, we excluded all participants who had been previously diagnosed with diabetes and/or hypertension. In addition, individuals who were suffering from other chronic diseases related to the genitourinary, digestive, respiratory and haematological systems were also excluded. Participants were aged 18–80 years.

Characteristics of Participants

The characteristics of the 505 participants comprising of 264 controls and 241 cases are shown in (Table 4). Over 44% of all T2DM patients had hypertension, male to female ratio (98:142), were overweight (33.19%), were obese (18.26%), had tertiary education (14.52%), had moderate activity (67.21%), were employed (55.17%) and were smoking (14.10%) and had histories of alcohol intake (42.32%). The mean age for T2DM only and T2DM with hypertension was 55.89 ± 11.27 and 60.07 ± 9.93, respectively. BMI was found not to differ between T2DM and hypertensive T2DM patients ($p = 0.158$). The Weight Height Ratio (WHR) was higher among T2DM patients with hypertension (0.92 ± 0.55 vs. 0.94 ± 0.061; $p < 0.0001$) However, FPG, HbA1c, TC, TG, HDL-c, LDL-c and coronary risk were not different in T2DM and T2DM with hypertension ($p > 0.05$). T2DM patients were generally older than controls ($p < 0.0001$), had a higher WHR (0.94 ± 0.061 vs. 0.88 ± 0.08; $p < 0.0001$), higher FPG (8.96 ± 4.18 vs. 6.08 ± 1.79; $p < 0.0001$) and higher HbA1c (8.23 ± 2.09 vs. 5.45 ± 1.00; $p < 0.0001$).

However, compared with non-hypertensive T2DM patients, the controls had higher SBP (143.69 ± 25.82 vs. 122.17 ± 11.86; $p < 0.0001$), DBP (84.27 ± 15.37 vs. 89.16 ± 12.62, $p < 0.0001$) and coronary risk (5.37 ± 1.49 vs. 4.90 ± 1.52; $p < 0.011$). There were no differences in TC, TG, LDL-c and very low-density lipoprotein cholesterol (VLDL-c) between controls and non-hypertensive T2DM

Table 4 Characteristics of Ghanaian participants with or without T2DM or hypertension

Variable	Control	T2DM Only	T2DM + HPT	χ^2	*p*-value
Age groups				27.75	**0.001**
31–40 years	14(5.3)	12(9.1)	2(1.9)		
41–50 years	31(11.7)	32(24.2)*	17(15.7)		
51–60 years	74(28.0)	45(34.1)	36(33.3)		
61–70 years	87(33.0)	31(23.5)	37(34.3)		
71–80 years	58(22.0)	12(9.1)*	16(14.8)		
Gender				0.985	0.611
Male	98(37.1)	52(39.4)	46(42.6)		
Female	166(62.9)	80(60.6)	62(57.4)		
BMI				15.39	**0.017**
Underweight	13(4.9)	8(6.1)	1(0.9)		
Normal weight	107(40.5)	67(51.1)	39(36.1)		
Overweight	87(33.0)	32(24.4)	48(44.4)*		
Obese	57(21.6)	20(18.5)	24(18.3)		
Marital status				23.77	**0.003**
Married	174(65.9)	91(68.9)	72(66.7)		
Never married	29(11.0)	3(2.3)*	1(0.9)*		
Divorced	24(9.1)	12(9.1)	13(12.1)		
Widowed	37(14.0)	26(19.7)	22(20.4)		
Education				15.66	**0.048**
Tertiary	36(13.6)	17(12.9)	18(16.7)		
Senior High school	82(31.1)	38(28.8)	19(17.6)		
Junior high school	93(35.2)	38(28.8)	40(37.0)		
Lower primary	31(11.7)	26(12.1)	12(11.1)		
No formal education	22(8.3)	23(17.4)	19(17.6)		
Occupation				69.88	**0.0001**
Employed	107(40.5)	82(62.1)	51(47.2)		
Retired	23(8.7)	12(9.1)	22(20.4)		
Unemployed	32(12.2)	28(21.2)	23(21.3)		
Informal employment	102(38.6)	10(7.6)	12(11.1)		
Physical activity				11.07	0.086
Primarily sedentary	87(33.0)	35(26.5)	43(39.8)		
Moderate activity	177(67.5)	97(73.5)	65(60.1)		
Family history				54.59	**0.0001**
Yes	121(46.0)	97(73.5)	85(78.7)		
Smoking history				11.09	**0.026**
Yes	17(6.5)	17(12.9)	17(15.7)		
History of alcohol intake				9.57	**0.048**
Yes	83(31.7)	54(40.9)	48(44.4)		

All statistical analyses were performed using SPSS and tests of significance were two tailed ($p < 0.05$). *p* values indicated in bold are considered statistically significant. *T2DM* type 2 diabetes mellitus, *HPT* hypertension, *BMI* body mass index

patients. Similarly, compared to controls, hypertensive T2DM patients were older ($p < 0.0001$), had higher WHRs (0.94 ± 0.061 vs. 0.88 ± 0.08; $p < 0.0001$), higher SBP (160.48 ± 18.24 vs. 84.27 ± 15.37; $p < 0.0001$) and higher DBP (89.16 ± 12.62 vs. 84.27 ± 15.37; $p < 0.0001$) (Table 5).

The mean age of control participants was 51.67 ± 11.45 years with a male to female ratio of 98:166. A high proportion had at least a basic education (35.2%), were married (65.9%) and employed (40.5%). Women were generally obese compared to men when BMI (33.1% vs. 2.0%; $p = 0.001$) and central adiposity (68.7% vs. 5.1%; $p = 0.001$) were used, respectively, as an obesity index. A higher proportion of men, than women were smokers (15.3% vs. 1.2%; $p = 0.001$) and had a history of alcohol intake (41.8% vs. 25.6%; $p = 0.005$). There was a significantly higher DBP ($p = 0.034$), HbA1c ($p = 0.043$), TC ($p = 0.001$), HDL-c ($p = 0.011$), non-HDL-c ($p = 0.004$) and LDL-c ($p = 0.006$) among women compared to men. Levels of SBP, FPG, TG, VLDL-c, coronary risk and WHR among employment [aOR = 2.68 (1.52–4.68); $p = 0.0008$)] and primarily sedentary [aOR = 2.97 (1.38–6.39); $p = 0.034$)] were significant independent risk factors for high SHS after adjusting for age and gender. Participants with high SHS had a significantly higher mean SBP ($p = 0.004$) and DBP ($p = 0.001$) compared to those with low SHS. However, there were no significant differences between the mean lipid profile among participants with high SHS compared to low SHS ($p > 0.05$) (Table 6).

Table 5 Clinical data of Ghanaian participants with or without T2DM or hypertension

Variables	Controls	T2DM only	T2DM + HPT	*p*-value
Age (years)	51.62 ± 11.92	55.89 ± 11.27[a]	60.07 ± 9.93[bc]	**<0.0001**
BMI (kg/m^2)	25.86 ± 5.06	25.60 ± 5.38	26.80 ± 4.72	0.158
WHR	0.88 ± 0.08	0.92 ± 0.55[a]	0.94 ± 0.061[bc]	**<0.0001**
SBP (mmHg)	143.69 ± 25.82	122.17 ± 11.86[a]	160.48 ± 18.24[bc]	**<0.0001**
DBP (mmHg)	84.27 ± 15.37	75.45 ± 11.29[a]	89.16 ± 12.62[bc]	**<0.0001**
FPG (mmol/L)	6.08 ± 1.79	8.96 ± 4.18[a]	9.49 ± 4.68[b]	**<0.0001**
HbA1c (%)	5.45 ± 1.00	8.23 ± 2.09[a]	8.35 ± 2.09[b]	**<0.0001**
TC (mmol/L)	4.57 ± 1.25	4.71 ± 1.17	4.76 ± 1.39	0.342
TG (mmol/L)	1.32 ± 0.91	1.22 ± 0.57	1.33 ± 0.55	0.484
HDL-c (mmol/L)	1.23 ± 0.31	1.37 ± 0.35[a]	1.33 ± 0.29[b]	**<0.0001**
LDL-c (mmol/L)	2.77 ± 1.06	2.77 ± 1.11	2.81 ± 1.23	**<0.0001**
VLDL-c (mmol/L)	0.59 ± 0.35	0.55 ± 0.26	0.60 ± 0.25	0.928
Coronary risk	5.37 ± 1.49	4.90 ± 1.52[a]	5.05 ± 1.53	**0.011**
Creatinine (mmol/L)	91.41 ± 27.75	100.84 ± 33.37[a]	112.70 ± 49.85[bc]	**<0.0001**

Values are presented as mean ± SD. One-way ANOVA followed by Tukey Post hoc multiple comparison. *T2DM* type 2 diabetes mellitus, *HPT* hypertension, *BMI* body mass index, *WHR* waist-to-hip ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *HbA1c* glycated haemoglobin, *TC* total cholesterol, *TG* triglyceride, *HDL-c* high-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol, *VLDL-c* very low-density lipoprotein cholesterol. $p < 0.05$ was considered statistically significant

[a]*p*-value is significant (Comparison between controls and T2DM only)

[b]*p*-value is significant (Comparison between controls and T2DM + HPT)

[c]*p*-value is significant (Comparison between T2DM only and T2DM + HPT). All statistical analyses were performed using SPSS and tests of significance were two tailed ($p < 0.05$)

Table 6 Characteristics of controls stratified by gender in Ghanaian participants

Characteristics	Total	Men (n = 98)	Women (n = 166)	*p*-value
Age (years)	51.67 ± 11.45	51.09 ± 12.02	51.44 ± 11.89	0.761
Anthropometric data				
WHR	0.88 ± 0.07	0.89 ± 0.06	0.87 ± 0.08	0.148
BMI (kg/m^2)				**<0.0001**
Underweight	13(4.9)	8(8.2)	5(3.0)	
Normal weight	107(40.5)	60(61.2)	47(28.3)	
Overweight	87(33.0)	28(28.6)	59(35.5)	
Obese	57(21.6)	2(2.0)	55(33.1)	
Central obesity				**<0.0001**
Normal	145(54.9)	93(94.9)	52(31.3)	
Obese	119(45.1)	5(5.1)	114(68.7)	
Socio-economic data				
Education				**<0.0001**
Tertiary	36(13.6)	26(26.5)	10(6.0)	
Senior high school	82(31.1)	26(26.5)	56(33.7)	
Junior high school	93(35.2)	35(35.7)	58(34.9)	
Lower primary	31(11.7)	6(6.1)	25(15.1)	
No formal education	22(8.3)	5(5.1)	17(10.2)	
Marital status				**0.001**
Married	174(65.9)	75(76.5)	99(59.6)	
Never married	29(11.0)	14(14.3)	15(9.0)	
Divorced	24(9.1)	3(3.0)	21(12.6)	
Widowed	37(14.0)	6(6.1)	31(18.7)	
Occupation				**<0.001**
Employed	107(40.5)	52(53.1)	55(33.1)	
Retired	23(8.7)	13(13.3)	10(6.0)	
Unemployed	32(12.2)	1(1.0)	31(18.6)	
Informal employment	102(38.6)	32(32.7)	70(42.2)	
Biochemical data				
SBP (mmHg)	144.12 ± 26.61	145.82 ± 30.96	142.43 ± 22.25	0.305
DBP (mmHg)	83.74 ± 15.70	81.66 ± 18.02	85.81 ± 13.38	**0.034**
FPG (mmol/L)	6.08 ± 1.79	6.04 ± 1.78	6.11 ± 1.79	0.751
HbA1c (%)	5.41 ± 0.98	5.28 ± 0.91	5.54 ± 1.04	**0.043**
TC (mmol/L)	4.50 ± 1.17	4.24 ± 1.00	4.76 ± 1.33	**0.001**
TG (mmol/L)	1.29 ± 0.89	1.19 ± 0. 81	1.39 ± 0.96	0.105
HDL-c (mmol/L)	1.12 ± 0.30	1.16 ± 0.28	1.26 ± 0.32	**0.011**
Non HDL-c (mmol/L)	3.23 ± 1.09	3.07 ± 0.91	3.50 ± 1.26	**0.004**
VLDL-c (mmol/L)	0.58 ± 0.35	0.54 ± 0.36	0.61 ± 0.34	0.133
LDL-c (mmol/L)	2.73 ± 2.03	2.54 ± 0.91	2.91 ± 1.12	**0.006**
Coronary risk	5.33 ± 2.87	5.22 ± 1.28	5.45 ± 1.59	0.236
Family history and activity				
Diabetes family history (yes)	121 (46.0)	43(43.9%)	78(47.3%)	0.343

(continued)

Table 6 (continued)

Characteristics	Total	Men (n = 98)	Women (n = 166)	*p*-value
Smoking (yes)	17(6.5)	15(15.3)	2(1.2)	**<0.001**
Drinking (yes)	83(31.7)	41(41.8)	42(25.6)	**0.005**
Physical activity				**0.037**
Primarily sedentary	87(33.0)	29(29.6)	58(34.9)	
Moderate activity	135(51.1)	46(46.9)	89(53.6)	
Primarily physical activity	42(16)	23(23.4)	19(11.4)	

All statistical analysis was performed using SPSS. Data is expressed as mean ± standard deviation or (n %) and tests of significance were two tailed ($p < 0.05$). *p* values indicated in bold are considered statistically significant. *WHR* waist-to-hip ratio, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *HbA1c* glycated haemoglobin, *TC* total cholesterol, *TG* triglyceride, *HDL-c* high-density lipoprotein cholesterol, *VLDL-c* very low-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol

Results

After adjusting for age and gender, central adiposity [aOR = 1.74 (1.06–2.83); $p = 0.027$)], underweight [aOR = 5.82 (1.23–27.52); $p = 0.018$)], high SBP [aOR = 1.86 (1.14–3.05); $p = 0.012$)], high DBP [aOR = 2.39 (1.40–4.07); $p = 0.001$)] and high TG [aOR = 2.17 (1.09–4.33); $p = 0.029$)] were found to be significant independent risk factors associated with high SHS (Table 5). After controlling for age and gender, significant positive linear relationships were observed between SHS score and SBP, DBP and CR irrespective of gender ($p < 0.05$). There were inconsistent correlations between other risk factors and high SHS. SHS scores were significantly associated with LDL-c in men whilst FPG, TC and non-HDL-c were significantly associated with SHS in women ($p < 0.05$) (Table 6). There was no significant linear relationship between BMI, HbA1c, TG, HDL-c, VLDL-c and high SHS in either men or women ($p > 0.05$) (Table 6).

Discussion

T2DM is largely a consequence of accumulated metabolic damage due to increasing urbanisation, physical inactivity, unhealthy eating and sedentary lifestyle [32–35]. Early diagnosis remains the blueprint for preventing T2DM and promoting better health outcomes [36–39]. This study is premised on the hypothesis that cardiometabolic risk factors are prevalent in Kumasi, an urban city in Ghana [40]. As such, we have explored modifiable risk factors in both T2DM sufferers and healthy controls (Tables 1, 2, and 3). Among the controls, we used a simple and inexpensive tool (SHSQ-25) to reveal highly at-risk individuals.

Participants were classified into two groups based on how they rated the SHSQ-25. Here, a median score < 21 represents low SHS (good health) whereas a median score >21 represents high SHS (poor health). Ideally, filling this short questionnaire alone should encourage individuals who obtain a high SHS score to have their clinical/biochemical indicators measured. This could have a twofold effect, as those

individuals could be provided with dietary/ lifestyle modifications that will enable them to live healthier lives by health care clinicians, which in turn may delay the onset of T2DM. Alternatively, a person with a high SHS may have undiagnosed, asymptomatic T2DM, or its related co-morbidities and may need immediate intervention or therapy (Table 7).

In this study, undiagnosed hypertension was prevalent among the participants, and similar to our previous findings, high SHS is significantly associated with both DBP and SBP (Tables 4 and 6). Furthermore, this confirms the findings of another community-based study in the sub-region that showed that a high proportion of adults in sub-Saharan Africa (SSA) (44–93%) who had high blood pressure and were unaware of their condition [41, 42]. Another study in a peri-urban community in Ghana showed the prevalence of undiagnosed hypertension as 28.7% [42]. This is disturbing since high BP is by far the main risk factor for T2DM and CVD [42–44]. High BP, for example, causes 42% of all ischaemic heart diseases [45] and one third of all heart failures [46]. As such, there is an overarching need to identify individuals with these symptoms and begin treatment to avoid future adverse health outcomes. Similar to our previous findings, age was associated with high SHS (Table 4). This is not surprising since ageing is associated with less physical activity and increased sedentary lifestyles; rendering it a high-order independent risk factor for T2DM [47]. In regard to metabolism, ageing is accompanied by an imbalance in the production of reactive oxygen species (ROS) and inflammation that together lead to metabolic dysregulation. Metabolic dysregulation will lead to insulin resistance and consequently T2DM [48].

In addition, gender, education, marital status, occupation and physical activity were associated with high SHS (Table 4). Though, we could not validate the association between high SHS and higher FPG, HbA1c, TC, LDL-c and low HDL-c (Table 5). In part, this observation may be attributed to the small sample size used for this investigation. All our previous investigations involved large cohorts in China (i.e. 2799 and 4313 in 2016) [7]. Cohorts from geographically distinct populations are exposed to different stressors (e.g. variation in job types, lifestyles, socioeconomic, environmental and cultural factors). For example, whilst most of the Ghanaian participants are primarily sedentary and engage in less energy demanding jobs, the Chinese cohorts are mainly industry workers who spend long hours at work and therefore, more likely to be stressed. Subsequently, stressful conditions, particularly in the hours preceding testing, may affect biochemical assessments.

Further, it is possible that the biochemical assessments of this study are somewhat influenced by laboratory conditions or the equipment used [49]. Consequently, other highly sensitive and state-of-the-art health facilities should be available for additional validation. Similar to the finding in previous study conducted in the Kumasi region, hypertension was high among T2DM sufferers [50]. Moreover, the results from the present study show that the majority of T2DM patients had FPG and HbA1c levels higher than the recommended targets (i.e. >7 mmol/L and >7.2%, respectively), many of whom are on the path to developing complications and co-morbidities. Surprisingly, all these individuals have been using blood pressure and lipid-lowering medications long before the start of this project. On the one hand, this could be attributed to delayed interventions, ineffective treatments, untargeted medications, drug response and drug resistance [40, 50]. On the other hand, the

Table 7 Distribution of factors with or without SHS among Ghanaian participants

Variables	Total n (%)	SHS Score ≥ 21 n (%)	SHS score < 21 n (%)	*p*-value	χ^2	aOR (95%CI)	*p*-value
Gender				**0.023**	4.49		
Male	98(37.3)	42(31.1)	56(43.8)			1.0[a]	
Female	165(62.7)	93(68.9)	72(56.3)			1.7 (1.04–2.85)	**0.034**
Age (years)				**0.02**	13.34		
21–30	14(5.3)	5(3.7)	9(7.0)			1.0[a]	
31–40	30(11.4)	17(12.6)	13(10.2)			2.35(0.63–8.73)	0.332
41–50	74(28.1)	41(32.0)	33(24.4)			1.45(0.44–4.72)	0.574
51–60	87(33.1)	47(36.7)	40(29.6)			1.53(0.47–4.94)	0.569
61–70	44(16.7)	28(20.7)	16(12.5)			3.15(0.89–11.04)	0.119
71–80	14(5.3)	12(8.9)	2(1.6)			10.8(1.69–68.97)	**0.018**
Education				**0.001**	19.81		
Tertiary	36(13.7)	14(10.4)	22(17.2)			1.0[a]	
Senior high school	82(31.2)	30(22.2)	52(40.6)			0.91(0.40–2.03)	0.838
Junior high school	93(35.4)	54(40.0)	39(30.5)			2.17(0.99–4.78)	0.076
Lower primary	30(11.4)	20(14.8)	10(7.8)			3.14(1.14–8.65)	**0.029**
No education	22(8.4)	17(12.6)	5(3.9)			5.34(1.61–17.77)	**0.007**
Marital Status				**0.019**	11.76		
Married	173(68.5)	80(59.3)	93(72.7)			1.0[a]	
Never married	29(11.0)	13(9.6)	16(12.5)			0.94(0.42–2.08)	0.999
Divorced/separated	24(9.1)	16(11.8)	8(6.2)			2.32(0.94–5.72)	0.081
Widowed	37(14.1)	26(19.3)	11(8.6)			2.75(1.28–5.91)	**0.011**
Occupation				**<0.001**	27.09		
Employed	106(40.3)	36(26.7)	70(54.7)			1.0[a]	
Retired	23(8.7)	18(13.3)	5(3.9)			7.00(2.40–20.40)	**0.0001**

(continued)

Table 7 (continued)

Variables	Total n (%)	SHS Score ≥ 21 n (%)	SHS score < 21 n (%)	*p*-value	χ^2	aOR (95%CI)	*p*-value
Unemployed	32(12.2)	22(16.3)	10(7.8)			4.28(1.83–9.99)	**0.0009**
Informal employment	102(38.8)	59(43.7)	43(33.6)			2.68(1.52–4.68)	**0.0008**
Physical activity				**0.006**	12.35		
Primarily sedentary	87(33.1)	57(42.2)	30(23.4)			2.97(1.38–6.39)	**0.007**
moderate activity	135(51.3)	62(45.9)	73(57)			1.32(0.65–2.71)	0.476
Primarily physical	41(15.6)	16(11.9)	25(19.6)			1.0[a]	
Biochemical data							
SBP (mmHg)	143.69 ± 25.82	148.33 ± 24.05	139.20 ± 26.58	**0.004**			
DBP (mmHg)	84.27 ± 15.37	87.33 ± 15.35	81.24 ± 14.7	**0.001**			
FPG (mmol/L)	6.08 ± 1.78	6.15 ± 1.75	6.01 ± 1.84	0.544			
HbA1c (%)	5.45 ± 0.99	5.44 ± 0.94	5.44 ± 1.06	0.997			
TC(mmol/L)	4.57 ± 1.25	4.66 ± 1.3	4.47 ± 1.18	0.217			
TG (mmol/L)	1.32 ± 0.91	1.41 ± 1.01	1.22 ± 0.79	0.099			
HDL-c (mmol/L)	1.23 ± 0.31	1.25 ± 0.32	1.20 ± 0.3	0.177			
VLDL-c (mmol/L)	0.59 ± 0.35	0.62 ± 0.35	0.56 ± 0.36	0.155			
LDL-c (mmol/L)	2.77 ± 1.06	2.81 ± 1.09	2.73 ± 1.02	0.554			
Coronary risk	5.37 ± 1.49	5.40 ± 1.5	5.35 ± 1.47	0.805			

aOR adjusted odds ratio, *CI* confidence interval. Multivariate regression model was adjusted for age and gender

[a]Reference, $p < 0.05$. Tests of significance were two tailed ($p < 0.05$). *p* values indicated in bold are considered statistically significant. *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *HbA1c* glycated haemoglobin, *TC* total cholesterol, *TG* triglyceride, *HDL-c* high-density lipoprotein cholesterol, *VLDL-c* very low-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol

suboptimal management could be due to other factors including: (1) institutional (e.g. health care policies, facilities and resources); (2) environmental, dietary and lifestyles; (3) genetic and epigenetics and (4) individual factors (physical, mental, social and spiritual wellbeing). In sum, PPPM holds the key to revolutionising T2DM care through the promotion of adequate patient stratification, disease modelling, surveillance, optimal diagnosis and prediction of adverse drug-drug interaction. Taken together, this will lead to better health outcomes for individuals, delay the onset of complications, improve the quality of life and promote longevity.

Overall, modifiable risk factors are prevalent among T2DM sufferers, but importantly, we have shown that SHSQ-25 could be a risk stratification tool for T2DM. Compared to many survey instruments and risk prediction models [51–55], the SHSQ-25 is simple, inexpensive and can be self-completed prior to, or administered during, a consultation. The scoring system is easy to use, and data interpretation/analysis does not require special expertise to perform.

Whilst recognising this, SHSQ-25 is a subjective health measure and should be supported with advanced objective biomarkers. These days, highly sophisticated and powerful analytical tools are available for measuring, detecting and characterising important biomarkers [56–58]. This will help in the understanding of the molecular intricacies that underpin the disease' pathogenesis. For example, it is possible to determine transcriptional regulation, post-translational modifications, protein expression and interaction and altered enzyme activity [56, 57]. Our team have commenced such research where we examined N-glycosylation profiles in metabolic syndrome (MetS) [59]. We showed that nine N-glycan traits were associated with DBP, SBP, FPG and BMI and these could be potential biomarkers for MetS [59]. Moreover, another investigation of the N-glycosylation profiles in the plasma samples of participants in this present Ghana study (T2DM and controls) is ongoing [60]. As interesting as the study is, a few limitations need to be mentioned. The main limitation is the cross-sectional design as we were unable to determine the proportion of participants in the high SHS group who will develop T2DM over time. The study tried to perform age-gender matching but the recruited controls were generally younger than the cases. However, this does not invalidate the significance of the findings from this study, since potential confounding was to an extent addressed by logistic regression and multivariate analyses. The sample size of the study does not allow a generalisation to be made. Moreover, metabolic risk factors such as blood pressure, plasma glucose and lipid profiles, particularly among the controls, were limited to only one measurement and therefore the prevalence of risk factors may be either under or overestimated.

Conclusion

There is poor management of risk factors among T2DM patients in the Kumasi region of Ghana. More disturbing is the fact that the majority of people who are at risk, particularly those with hypertension, were undiagnosed. This underscores the need for novel screening tools that can identify such individuals. The SHSQ-25

represents an instrument of choice and in turn sets the platform for prediction, prevention and treatment of T2DM, which is vital, particularly for a region where laboratory-based measures are not routinely available.

2.3 *Case Three: Integration of Suboptimal Health Status and Endothelial Dysfunction as a New Aspect for Risk Evaluation of Cardiovascular Disease among Russians*

Participants

A cross-sectional study was conducted among 459 residents of the city of Samara, Russia. The study was based on random cluster sampling with district as the basic sampling unit. Participants had no history of clinical diagnosed disease and did not receive any treatment in the last 2 weeks. The investigation was carried out during the professional examinations in the clinic of Samara State Medical University and health centres in its tertiary teaching hospitals in Samara. To assure comparability of the findings, all participants were examined by the physicians who were specially trained for the study. Both the university and hospitals' research ethical committees approved this study.

All 459 participants completed the SHSQ-25 [1, 2], (Appendix 1), laboratory and instrumental measurements [5]. The mean age was 34.01 years (SD 14.10) and 58.6% were women. The participants among the group with cardiovascular risk showed higher proportions of male (51.2 vs. 35.9%, $p < 0.001$), older age (74.4 vs. 13.2%, $p < 0.001$), and labour workers (51.83 vs. 8.5%, $p < 0.001$) than those among the healthy group (Table 8).

Table 8 Characteristics of the Russian participants

Variables	Healthy group (n = 295)	Group with cardiovascular risk (n = 164)	χ^2	*p*-value
Gender				
Male	106(35.9%)	84(51.2%)	10.15	<0.01
Female	189(64.1%)	80 (48.8%)		
Age				
18–40 years	256(86.8%)	42 (25.6%)	173.19	<0.01
41–60 years	39 (13.2%)	122 (74.4%)		
Occupation				
Office workers	267(90.5%)	79 (48.17%)	101.81	<0.01
Labor workers	28 (8.5%)	85 (51.83%)		
Suboptimal health status	23 (7.8%)	14 (8.8%)	0.029	>0.05

All statistical analyses were performed using SPSS and tests of significance were two tailed ($p < 0.05$)

There were no significant differences in the proportion of individuals with SHS, between the healthy group and the group of cardiovascular risk (7.8 vs. 8.8%, $p > 0.05$). The total score of SHSQ-25 were 14.92 ± 9.14 among the healthy group and 16.42 ± 9.07 among the group of cardiovascular risk, which did not show significant difference among the two groups ($p = 0.09$). However, the SHSQ-25 questionnaire showed differences between the two groups on the three sub-scales of suboptimal status, i.e., (1) fatigue, (2) cardiovascular system, and (3) immune system ($p < 0.05$). The largest discrepancy focused on the sub-scales of the cardiovascular system and fatigue. The average scale score of the cardiovascular system among subjects with cardiovascular risk was 1.95 ± 1.81, which was significantly higher than that of the control group ($p < 0.001$), whose score was 0.90 ± 1.2. The group with risk factors for cardiovascular disease had significantly higher levels of SBP, DBP, BMI, smoking index, TC, TG, and LDL-c (Table 9).

Discussion

Changes in lipid, affect the condition of vessel wall-the endothelium. Over the last decade, there is accumulated evidence of the importance of determining the stiffness of the arterial wall as an indicator on vascular remodelling. With photopletismography arterial stiffness and endothelial dysfunction can be accessed. The higher the absolute value of stiffness index, the lower the expression of index of endothelial function (IEF) and a healthy vascular wall. Our study showed that in the group of participants with risk factors value was 7.5 ± 7.6%, which was significantly lower ($p < 0.01$) than those in healthy group, whose proportion was 18.4 ± 7.7%. The index of endothelial function was found significantly correlated with the overall performance of suboptimal health status ($r = -0.31$, $p < 0.05$), as well as with individual sub-scales of the questionnaire SHSQ-25: fatigue ($r = -0.36$, $p < 0.05$), mental ($r = -0.29$, $p < 0.05$), and the cardiovascular system ($r = -0.36$, $p < 0.05$).

Table 9 Comparison of the cardiovascular risk factors between healthy group and group with cardiovascular risk among the Russian participants

Variables	Healthy group Mean ± SD	Group with cardiovascular risk Mean ± SD	*t*	*p*-value
Index smoker	1.66 ± 10.2	7.9 ± 15.5	4.801	<0.001
BMI (kg/m^2)	22.1 ± 4.2	28.55 ± 5.0	14.12	<0.001
SBP (mmHg)	111.73 ± 12.7	129.5 ± 11.9	13.611	<0.001
DBP (mmHg)	73.86 ± 8.2	80.86 ± 8.3	8.803	<0.001
FPG (mmol/L)	4.03 ± 0.86	4.67 ± 0.96	6.403	<0.001
TC (mmol/L)	4.28 ± 0.8	5.6 ± 0.96	6.441	<0.001
TG (mmol/L)	1.11 ± 0.57	1.56 ± 0.87	2.801	0.010
HDL-c (mmol/L)	1.36 ± 0.36	1.32 ± 0.31	3.230	<0.001
LDL-c (mmol/L)	2.85 ± 0.17	3.01 ± 0.37	2.562	0.006

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *TC* total cholesterol, *TG* triglyceride, *HDL-c* high-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol

Table 10 The results of the regression analysis (dependent variable SHSQ score)

	Unstandardized coefficients		Standardized coefficients		
Variables	Beta	Std. error	Beta	*t*	*p*-value
Age	−0.132	0.053	−0.209	−2.491	0.013
Index Smoker	0.034	0.085	0.026	0.398	0.691
BMI	0.139	0.145	0.079	0.958	0.339
SBP	0.069	0.054	0.102	1.288	0.199
DBP	−0.040	0.049	0.052	−0.815	0.416
IEF	−0.248	0.068	−0.284	−3.679	0.000

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *IEF* index of endothelial function

A linear regression also revealed an association between SHS and IEF (Table 10). Given the obvious correlations between indicators of endothelial dysfunction and the values of the scales of the questionnaire SHSQ-25, we explored the integral relationship between the values of SHS indicators of endothelial dysfunction and risk factors for cardiovascular disease. In our study, a newly created instrument, SHSQ-25, was used for measurement of SHS. The SHSQ-25 is a self-rated questionnaire of perceived health complaints which is a brief and valid instrument for the assessment of SHS [1.2]. To do this, we used multivariate statistical analysis on the following parameters: the values of profiles SHS-25 subscale (1) fatigue, (2) mental status, (3) cardiovascular system, (4) digestive system, (5) immune system, and the total amount of SHS- 25, the index of the smoker, BMI, SBP, DBP and endothelial function parameters, vascular stiffness index, the index of reflection pulse wave, plasma glucose, and TC. Based on the cluster analysis on risk factors of cardiovascular system and indicators of SHS, all the subjects were classified into five clusters (Fig. 2).

The first cluster included 99 young persons, with a low value of the total index SHSQ-25, normal weight, blood pressure, lack of endothelial dysfunction, reduced levels of glucose and cholesterol. These persons were estimated as the persons with the optimal health status. The second cluster contains 121 cases. This cluster was characterized by the young age of the participants, the mean value of the total index SHSQ-25, with deviations in the mentasphere, and the immune system, normal weight, blood pressure, lack of endothelial dysfunction, reduced levels of glucose, cholesterol. This cluster was described as a cluster of SHS at low risk of disease states. The third cluster (n = 91 cases) is different from the other two by high values of the cumulative index SHSQ-25, especially on the scale of the mental sphere, digestive tract, and immune system. This cluster was described by us as a cluster of SHS with a high risk of non-cardiac pathologies profile. The fourth cluster (n = 94 cases) were aged over 35 years, with the average values of the total index SHSQ-25, but with the presence of at least 1–2 risk factors for cardiovascular disease, this was mainly being overweight or having a long smoking history. We designated it as a cardiovascular phenotype of SHS of low risk of cardiovascular disease. Finally, the fifth cluster (n = 54 cases) differs in significant variations in the total index SHSQ-

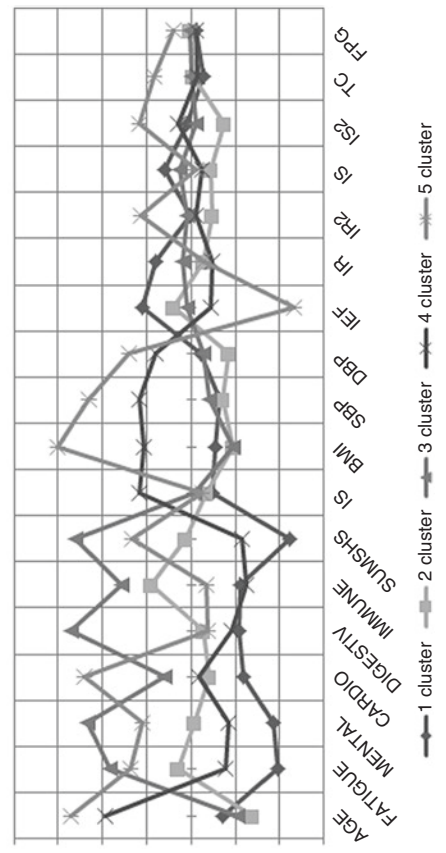

Fig. 2 Cluster analysis of integration of suboptimal health status, cardiovascular risk and endothelial dysfunction. *SUMSHS* the total amount of SHS-25, *IS* index smoker, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *IEF* index of endothelial function, *IR* index of reflection before the sample, *IR2* index of reflection after the sample, *IS* stiffness index before the sample, *IS2* stiffness index after the sample, *TC* total cholesterol, *FPG* fasting plasma glucose

25, the scale of cardiovascular disease, and the presence of risk factors for cardiovascular disease and endothelial dysfunction. These patients were referred to our cardiovascular phenotype of SHS with high risk of cardiovascular disease. Cluster analysis showed a correlation between SHS score (including total index SHSQ-25 and sub-scales of the SHSQ-25), risk factors for cardiovascular system, and indicators of endothelial dysfunction ($p < 0.001$). Among the risk factors for cardiovascular diseases, the greatest distance between the clusters 1, 2, 3 on one side and 4, 5 clusters on the other side were observed according to age, BMI, and blood pressure, indicating that the association between stiffness of vascular wall with a number of traditional determinants of cardiovascular diseases at suboptimal health stage.

The present study combined the evaluation of SHS with the analysis of the state of endothelial dysfunction, which allows us to identify the risk of developing cardiovascular disease and enables people to obtain early intervention in terms of PPPM [23, 61, 62].

Conclusions

SHS is associated with risk factors of cardiovascular disease. Effective intervention on SHS may be a cost-effective way for preventing cardiovascular disease. The evaluation of SHS, combined with the analysis of the state of endothelial dysfunction allows us to identify the risk of developing cardiovascular disease, therefore providing people a holistic picture of both subjective and objective health measures from the perspective of PPPM.

3 Summary of Cases

The current book chapter indicates that SHS is associated with majority of cardiovascular health metrics defined by American Heart Association (AHA) [16]. Higher ideal CVH metrics are associated with a lower prevalence of SHS. The evaluation of SHS combined with the analysis of CVH metrics allows the risk classification of cardiovascular disease, which may consequently contribute to the prevention of cardiovascular diseases. Currently, there are no tests that can confirm or exclude SHS as a physical state of health. Rather, it is a disease of exclusion made after common physical and mental causes of the symptoms have been excluded, and predisposing factors, triggering events and maintenance factors have been identified [1–2, 7–12]. The aetiology of SHS remains unclear, with both psychiatric/ psychological causes and physical causes such as a viral illness and metabolic disequilibrium to be considered. The newly created SHSQ-25 is an instrument that attempts to measure the

SHS qualitatively. The SHSQ-25 is short and easy to complete, and therefore an instrument suitable for use in both large-scale studies of the general population and routine health surveys.

In the initiative of PPPM, the European Association for Predictive, Preventive and Personalised Medicine (EPMA) issued a timely white paper in 2013 "*Position paper of the EPMA and EFLM: a global vision of the consolidated promotion of an integrative medical approach to advance health care*" and followed by another white position paper "*Medicine in the early twenty-first century: paradigm and anticipation - EPMA position paper 2016*" summarizing the priorities of PPPM. This book chapter addresses SHS and cardiovascular dysregulation echoing 'PPPM in cardiovascular diseases', one of the topics prioritised by EMPA [23, 61, 62].

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Appendix 1: Suboptimal Health Status Questionnaire (SHSQ-25)

The following questions ask some events about your health during the last 3 months.

Answer every question by making the appropriate box with an 'x'. You may choose from one of the following answers:

1	2	3	4	5
never or almost never	now and then	often	very often	always

How often is it, that you (your)	1	2	3	4	5
1. were exhausted without physical actives significantly increasing.	☐	☐	☐	☐	☐
2. fatigue could not be substantially alleviated by rest.	☐	☐	☐	☐	☐
3. were languid when working.	☐	☐	☐	☐	☐
4. suffered from headaches.	☐	☐	☐	☐	☐
5. suffered from dizziness.	☐	☐	☐	☐	☐
6. eyes were aching and tired.	☐	☐	☐	☐	☐
7. suffered from sore throat.	☐	☐	☐	☐	☐
8. muscles or joints felt stiff.	☐	☐	☐	☐	☐
9. have pains in shoulder/ neck / waist.	☐	☐	☐	☐	☐
10. have heavy feeling in legs when walking.	☐	☐	☐	☐	☐
11. got out of breath while sitting still.	☐	☐	☐	☐	☐
12. suffered from sore throat.	☐	☐	☐	☐	☐
13. were bothered by heart palpitation.	☐	☐	☐	☐	☐
14. got poor appetite.	☐	☐	☐	☐	☐
15. suffered from an upset stomach.	☐	☐	☐	☐	☐
16. suffered from indigestion.	☐	☐	☐	☐	☐
19. got tender fever or cold in-tolerance.	☐	☐	☐	☐	☐
20. had difficulty in falling asleep.	☐	☐	☐	☐	☐
21. had trouble with waking up during night.	☐	☐	☐	☐	☐
22. had trouble with impairment in short memory.	☐	☐	☐	☐	☐
23. could not respond quickly.	☐	☐	☐	☐	☐
24. had difficulty in concentration.	☐	☐	☐	☐	☐
25. were distracted for no reason.	☐	☐	☐	☐	☐
25. were keyed up or jittery.	☐	☐	☐	☐	☐
26. were caught with colds in the past 1 year.	☐	☐	☐	☐	☐

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Flammer Syndrome, Disordered Eating and Microbiome: Interrelations, Complexity of Risks and Individual Outcomes

Rostyslav Bubnov and Olga Golubnitschaja

Abstract Definition of abnormal body weight varies a lot depending on the population genetics, cultural specifics, gender and age. To this end, it is important to note that a "statistically normal weight" does not automatically mean "individually optimal weight". This is one of the best examples for the application of the basic principles of personalised medicine: "ONE SIZE does not FIT ALL". Contextually, "generally normal" but particularly borderline BMI values might be optimal for one person but apparently suboptimal for another one, if the genetic predisposition, geographic origin, cultural and nutritional habits as well as life-style, amongst others differ sufficiently between two persons of comparison. Slim body shape is one of the most typical signs of the Flammer Syndrome (FS) phenotype. If any, highly limited data are currently available to demonstrate functional links and potential impacts of the suboptimal body weight on predisposition to several pathologies, which, however, the FS phenotype has been demonstrated to be prevalent for as highlighted in this book. Further, FS-affected individuals are known to be physically very active and perfectionistic in anything they do including "perfect" thinness and frequent and/or rigorous dieting that may potentially lead to disordered eating and even eating disorders such as anorexia nervosa as an extreme case of long-term rigorous dieting. This chapter provides insights into mechanisms of disordered eating, eating disorders, consequently shifted metabolism, and altered microbiome – all relevant for potential onset of a cascade of severe pathologies.

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1 Definition of Normal Versus Abnormal Weight: What Is Behind the Issue?

Definition of abnormal (both overweight and underweight) BMI varies a lot depending on the population genetics, cultural specifics, gender and age. In the European area, the body-mass index in young adults (18-25 years old) ranging 19–24 kg/m^2 for females and 20–25 for males is considered as demonstrating the normal body weight. In contrast, BMI 25-30 for females and 26-30 for males corresponds to overweight or "pre-obesity" stage. The obesity levels are further graduated: BMI >30-35 (class I), BMI>35-40 (class II), BMI >40 (class III). On the other hand, the underweight levels are classified as following: grade 1 – females BMI <18.5 and males BMI < 20; grade 2 – BMI ≤17; grade 3 – BMI ≤16 [1, 2].

To this end, it is important to note that a *statistically normal weight* does not automatically mean *individually optimal weight*. This is one of the best examples for the application of the basic principles of personalised medicine: "ONE SIZE does not FIT ALL". Contextually, "generally normal" but rather borderline BMI values of 19-20 kg/m^2 might be optimal for one person but apparently suboptimal for another one, if the genetic predisposition, geographic origin, cultural and nutritional habits as well as life-style particularities, amongst others differ sufficiently between two persons of comparison.

On the other hand, even slightly deviant, both overweight and underweight are acknowledged risk factors for a shifted metabolism which, if not individually optimised and stabilised in a long-term way, may strongly contribute to the development of a number of severe pathologies as stated in the introductory book chapter "Flammer Syndrome in the Global Context – The "U-Shape" of Health Risks" by Olga Golubnitschaja.

A large number of studies is dedicated to the risks linked to the abnormally high body weight such as a strong predisposition to metabolic syndrome with consequent cardiovascular disease, neurological disorders, impaired healing processes, oncologic diseases with particularly poor outcomes, amongst others [3, 4].

Sufficiently less attention has been paid to the "down-stream" cascade of pathologies potentially linked to or even provoked in persons, who may suffer from relatively low BMI which may represent a suboptimal health condition of shifted metabolism with a spectrum of health adverse effects.

Relatively low BMI is one of the most typical signs of the Flammer Syndrome (FS) phenotype. However, if any, highly limited data are currently available to demonstrate functional links and potential impacts of the suboptimal body weight on predisposition to several pathologies, which FS phenotype has been demonstrated as being prevalent for

– specific eye pathologies such as normal-tension glaucoma [5];
– (breast) cancer [6–9];
– aggressive metastatic disease [10, 11];
– Sjögren syndrome [12];
– "dry mouth" syndrome [13];
– impaired wound healing [14, 15].

Further, FS-affected individuals are known to be physically very active and perfectionistic in anything they do including "perfectly" slim body shape and frequent and/or rigorous dieting that may potentially lead to disordered eating and even eating disorders such as anorexia nervosa as an extreme case of long-term rigorous dieting.

This chapter provides insights into mechanisms of disordered eating linked to FS phenotype, eating disorders, shifted metabolism, and altered microbiome – all relevant for potential onset of severe associated pathologies.

2 Diagnostic of Suboptimal Low BMI

As demonstrated above, BMI is not the decisive parameter for evaluation of the most optimal body weight/shape individually. Further, *statistically normal* BMI may be misleading for the optimal proportion of fat-to-mussels content that is well documented specifically for athletes [16] and elderly [17].

In this regard, more complex bio-marker panels are considered to be useful based on the anthropometric data, BMI and medical imaging [18, 19].

An example for the added value by subcutaneous (SAT) and visceral adipose tissue (VAT) measurements utilising the ultrasound imaging is demonstrated in Fig. 1.

Specific patterns by the visceral versus subcutaneous types of the fat distribution have a pivotal role for the patient stratification: the subjects with *visceral* type of the fat distribution, rather than those with the *subcutaneous* type, have been associated with impaired flow-mediated endothelium-dependent vasodilatation [20, 21].

Further, a correlation between fat distribution and gene expression patterns has been discovered [22] which is relevant for both abnormalities – overweight and underweight individuals. To this end, modest visceral fat gain causes endothelial dysfunction in healthy humans [23].

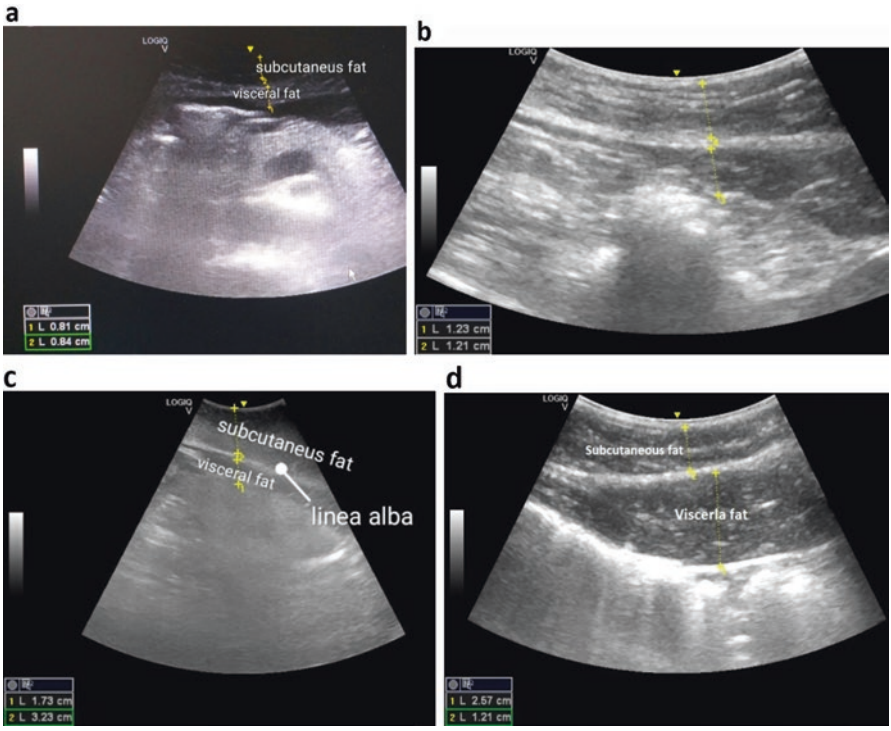

Fig. 1 Abdominal and visceral fat measurement using ultrasound clearly discriminates between abnormally slim (**a**) and obese persons (**c**) versus normal (**b**) fat distribution; SAT pattern of fat (**c**) versus visceral fat redistribution (**d**); further, gender difference is well respected by the approach demonstrating patterns specific for male (**b**, **d**) against female (**a**, **c**) types of fat distribution. The scanning was performed in the sagittal plane along the linea alba. Note: the movement during breathing can further help recognising and measuring the fat tissue in the abdominal cavity

3 Anorexia Nervosa as an Extreme Case of the Disordered Eating in Individuals with FS Phenotype

3.1 Is Anorexia Nervosa a Female Disease?

Anorexia nervosa (AN) is specifically characterised by extreme weight loss or failure to gain expected weight accompanied by fear of weight gain. AN has been traditionally described to occur in young females by 10 times more frequently than in males. Clinically manifested AN is diagnosed in about 0.4% of female USA population [24].

Although AN remains more prevalent in females, recent research demonstrates that its prevalence in males is strongly underestimated [25].

3.2 Risk Factors

The best acknowledged risk factors predisposing affected individuals to AN and associated pathologies are impaired psychosocial functioning, perfectionism, thin-ideal internalisation, negative urgency, and sensitivity to reward and punishment [26].

Recently functional magnetic resonance imaging (fMRI) studies revealed an altered set-point and/or sensitivity for sensory-interoceptive-reward processes towards food consumption that may override homeostatic needs [27]. Hardaway et al. hypothesised that eating disorder clinical phenotypes may result from stress-induced maladaptive alterations in neural circuits that regulates feeding, and that these circuits can be neurochemically isolated using animal model of eating disorders [28].

A large number of studies confirm issue-specific alterations of brain structure and tissue functionality in development of eating disorders in general and AN in particular [26, 29–31].

4 Anorexia Nervosa and Altered Microbiome

4.1 Microbiome Co-determines the Health Condition of Individuals

The gut microbiota is considered an extension of the self and, together with the genetic makeup, determines the physiology of the individual, their metabolism and digestion. Intestinal microbial population largely represented by Bacteroidetes and Firmicutes, has been proven to impact on human health and maintaining homeostasis [32–36].

The setting of the adult gut microbiota is influenced by several factors including host genetics, nutrition, dietary habits, xenobiotics (e.g. antibiotics) and other drugs intake, lifestyle, body activity (sport/exercise), and circadian rhythms, amongst others [37–45].

Malnutrition and long-term dieting have substantial and reproducible effects on the gut microbiome and the brain activity [46].

4.2 Studies on "Lean" Microbiome Are Strongly Underrepresented But Facts Available Are Impressive

The gut microbiota has been recognised as an important contributor to pathological conditions such as obesity and metabolic disorder as well to anorexia nervosa as an extreme cases of the FS phenotype. However, whereas many studies are focused on

microbiome alterations specific for individuals with abnormally high BMI, much less is known about microbiome alterations characteristic for underweight persons, AN and individuals with the FS phenotype. Consequently, the "lean" microbiome is still almost unexplored issue, presented, if any, in a very few scientific papers such as dedicated to the impaired wound healing in lean individuals [15] but also in non-scientific media [47] demonstrating clearly emphasised interest to the topic in the population which, however, remains currently unsatisfied by strongly limited issue-dedicated scientific efforts done. However, what is clear that the microbiotic difference between overweight and underweight is significant: 75% of the obesity-enriched genes originate from Actinobacteria (compared with 0% of lean-enriched genes; the other 25% are from Firmicutes), whereas 42% of the lean enriched genes originate from Bacteroidetes (compared with 0% of the obesity-enriched genes) [48].

Further, diseased eating decreases gut flora diversity and negatively impacts the microbiome by evidence of an intestinal dysbiosis in AN; also there is a reported strong association between mood, level of depression, and anxiety, on the one hand, and the enteric microbiota composition, on the other hand [49].

4.3 Gut Bacteria May Tell Us "What to Eat or Not to Eat": Lessons About AN

Phylum Bacteroidetes is known to be decreased and Phylum Firmicutes is increased in AN compared with healthy controls [50, 51]. These patterns encourage comprehensive investigation of the intestinal microbiota in both – disordered eating and eating disorders. Living in a competitive environment, certain species of intestinal bacteria may be better suited to a low-energy environment characteristic for AN and more likely to survive and dominate. The contextual question is, whether intestinal dysbioses may contribute to persistence, recovery from and/or relapse of the eating disorders [52].

Consequently, individual microbial profiling can predict metabolic changes in organism and facilitate personalised diet prescription [53].

Given that host diet is a key determinant of the gut microbial profile and eating disorders are characterised by dysregulated food intake, it is only logical to assume an association between eating disorders and an altered gut microbiota [54–63].

5 Starvation Strongly Impacts the Gut Microbiome Composition and Pathophysiology of AN

Interesting findings of the study by Smith et al. demonstrated that frozen bacterial species isolated from children with kwashiorkor (a severe form of acute malnutrition often observed in developing countries that is probably worsened by a

protein-deficient diet) as transplanted into GF mice have produced significant weight loss in these mice [64]. Starvation-induced changes in the gut microbiome were also found in an acute and chronic starvation animal model of anorexia (ABA) [65].

Alterations observed in an animal model of AN suggest that intestinal barrier dysfunction provoked by starvation may contribute to the pathophysiology of AN. After the ABA mice lost a substantial amount of weight (approximately 20%), a histological investigation of the colon revealed decreased thickness of the muscularis layer and significantly increased permeability of the colon [66].

Further, several studies demonstrated an increase in intestinal permeability during exercise, which is found in the majority of patients with AN, and represents a basic mechanism in the ABA model [67].

A disturbed gut barrier function was also found in other disorders associated with malnourishment and in volunteered fasting subjects [68].

Finally, pro-inflammatory cytokines were shown to be increased in acute AN; their levels were normalised after nutritional rehabilitation [69, 70].

6 Irritable Bowel Disease Also Called "Spastic Bowel" Is Associated with AN

Recent evidence suggests an association between irritable bowel disease (IBD) and eating disorders, amongst which AN is the most frequently reported one [71]. IBD is the most prevalent functional gastrointestinal disorder in Western societies, affecting approximately 11% of the adult population, which strongly impairs quality of life, social function, work productivity, and creates economic burden to healthcare [72, 73]. The aetiology of IBS remains poorly understood; the search for specific biomarkers is ongoing. IBD symptoms are heartburn, abdominal pain, bloating and significant changes in bowel habit. Affected patients often experience dyspepsia, chronic headache, fibromyalgia, amongst others [74].

Further, patients with functional gastrointestinal symptoms demonstrate to about 50% rate psychiatric symptoms, such as anxiety, depression or somatisation, or psychosocial stressors (e.g. unemployment, bereavement) associated with more frequent negative perceptions of the condition. [75]. In turn, excessive stress conditions can negatively influence the microbiota and mechanisms by which microbiota affects the stress response and behavioral outcomes with an emphasis on visceral pain [76].

Low density of microbiota and exhaled methane as well as a reduced prevalence of Methanobacteriales and Prevotella enterotype in microbiota were observed in subjects with severe IBS. To this end, the prevalence of Prevotella enterotype might be diminished specifically in case of severe IBD symptoms frequently accompanied by an increased prevalence of Bacteroides enterotype. Noteworthy, medications including laxatives or bulking agents, acid suppressants (mainly proton pump

inhibitors), antidiarrheals, and antidepressants drugs, do not show any significant associations with the specific microbial signature responsible for the IBS severity [77].

Individualised diet and application of probiotics are recommended as the most appropriate treatment; a holistic approach is needed to guide the clinicians towards more effective management strategy of the disease [78, 79].

7 Probiotics and Prebiotics – Outlook for Potential Treatment of Individuals with FS Phenotype

7.1 Definition of Probiotics and Prebiotics

The definition of a ***probiotic*** is *live microorganisms which when administered in adequate amounts confer a health benefit on the host* [80]; the current ISAPP panel consensus proposes the following definition of a ***prebiotic***: *a substrate that is selectively utilised by host microorganisms conferring a health benefit* [81].

7.2 Low-Energy Supply in Starving Individuals

Feeding bacteria in starving organism is one aspect amongst others regarding the re-equilibration of hypo-digestive organism; the issue-dedicated studies are required to be conducted on animal models and in clinico sets.

7.3 Individuals with Low Diversity of Microbiota

Phylum Bacteroidetes has been reported to be of low density in a gut of patients with AN [50], the phylum Firmicutes was reported to be increased in AN [52]. The microbial diversity depends very much on the conditions the individual lives in and the local traditions of lifestyle [82]. Corresponding microbiota biobanks can be further studied [36] utilising samples collected from the small intestine in the future research [51].

7.4 Individuals in Stress, Anxiety and Depression Conditions

Probiotics called *psychobiotics* might be considered to beneficially modulate patient's psyche, mood and attitude. They can be used for mitigating the FS symptoms in a pattern-specific way via the gut-brain axis. This may activate

production of specific neuromediators, which in turn may mitigate an anxiety and frustration enhancing positive feeling of taste and personal satisfaction. To this end, an individualised psychological and dietary recommendations are essential to elaborate on.

Long-term consequences provoked by early-life traumatic events and chronic stress followed by anxiety and depression can be effectively treated by psychobiotics positively modulating specific microbiome-targets and the gut-brain axis.

7.5 Individuals Suffering from IBD: The Gut Symptoms of FS?

In view of existing an extensive evidence supporting functional links between the microbiome composition and IBD [75–79] on the one hand, and on the other hand, between IBD and FS-affected individuals (to this end, see the book chapter "Individualised Patient Profile: Risk Assessment by the Patient's Self-Report and Potential Clinical Utility of Flammer Syndrome Phenotype" by Olga Golubnitschaja and Josef Flammer) IBD symptoms might be hypothesised as the *gut symptoms of the FS* phenotype. Consequently, individual severity levels might be assessed by the specific faecal microbiota-signature.

Probiotics demonstrate a potential to act via increasing production of the short-chain fatty acids (especially butyrate), in the gut microbiome that is required for optimal health activating the enteric nervous system as a part of the gut-brain axis and positively influencing major gastrointestinal physiologic functions such as motility, fluid secretion and blood flow.

7.6 Individuals Demonstrating Systemic Hypoxia

Association between the regulation mechanisms of systemic hypoxia and microbiome is a promising scientific area that could provide insights into selection of the relevant strain-candidates and probiotics-based treatments tailored to the affected person.

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Nutritional Approach to the Common Symptoms of Flammer Syndrome

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Abstract Flammer syndrome (FS) is primarily an ophthalmological phenomenon associated with central and peripheral symptoms, primarily resulting from dysregulation of systemic and local blood circulation. As nutrition is a basic factor in the body's functions, including blood flow regulation and related physiological manifestations, a dietary approach would be assumed to be most relevant to ameliorate the various disorders associated with FS, and likely support the body's response and reduce the impact of the overall syndrome.

The present chapter presents a review of the scientific literature related to the major symptoms and manifestations of FS, including low blood pressure, cold hands and feet, decreased thirst sensation, shifted circadian rhythm and prolonged sleep onset time, increased sensitivity to pain, migraines, tinnitus, and glaucoma. Considering that each of the symptoms imposes both direct and indirect risks to organ function and general health, each warrants a specific preventive approach and markers for continuous evaluation and follow-up.

The relevance of dietary intervention in FS is related to the multilevel impact of nutrition. The approach described here addresses specific symptoms, but with notable overlap and general effects due to shared physiological mechanisms expressed in the syndrome.

Keywords Flammer syndrome · Risks · Circulation · Vascular · Antioxidants · Thirst · Pain · Circadian rhythm · Sleep patterns · Glaucoma · Nutrition · Dietary recommendations · Mitigation · Symptoms · Predictive preventive personalized medicine · Blood pressure · Micronutrients · Vitamins · Omega-3 · Alcohol · Gingko biloba · Magnesium · Iron · Calcium · Caffeine · Hydration · Sodium · Fasting · Tinnitus · Milk · Folate · Homocysteine · Carbohydrates · Hypoglycemia · Arterial hypotension · Sodium · Tee · Taste · Smell · Perception · Migraine · Phytochemicals · Nitrates

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1 Introduction

1.1 History and Evolution of Flammer Syndrome

Flammer syndrome (FS) was originally identified through research on glaucoma and its interrelationships with numerous signs, symptoms, and disorders [1]. Ophthalmology holds significant potential for discovery of diseases and/or syndromes, due to the highly vascular nature of the eye and further reflection on diseases. Medical conditions such as diabetes, high blood pressure, and cholesterol imbalance are regularly diagnosed through a routine eye exam [2], and eye/vision health is a reliable indicator of these and other health problems. Correspondingly, it is possible to support protection or even correction of eye health/vision through lifestyle modifications targeting the secondary peripheral expressions. For example, a recent study linked reduced eye health in patients to a greater risk of later memory loss and poorer results of cognition testing compared to a control group with normal eye health [3].

The terminology of FS has evolved with understanding of the pattern, from vasospasm and/or vasospastic syndrome (VS) to primary vascular dysregulation (PVD) and finally to FS. Vasospasms have been known in medicine for decades, and included among the linked derangements, particularly glaucoma. However, since the clinical condition of normal-tension glaucoma (NTG) could not be explained by isolated spasms, the term PVD was suggested to be more appropriate, as 'primary' occurrence may be related to genetic predisposition rather than background disease [1].

Although the most striking impairments in PVD subjects are directly related to the dysregulation of blood pressure, FS subjects often have additional signs and symptoms that are only indirectly related or even seemingly unrelated, which are not specific to PVD, but more often occur in PVD patients, suggesting that understanding the composite may influence recommendations for prevention as well as treatment [4].

Typically, blood vessels of individuals with FS react differently to a number of stimuli, such as cold, physical, chemical or emotional stress, which serve as triggers of transient disruptions in blood perfusion, which in turn cause oxidative stress and impaired endothelial function [5].

Because nearly all organs can be involved, FS potentially contributes to increased likelihood of other diseases, far beyond the eye. Though the syndrome is generally associated with some characteristics which are perceived advantages, including low BMI and related metabolic syndrome, diabetes and/or arteriosclerosis, these apparent advantages and disadvantages are not mutually exclusive [1].

A recent review highlighted the association of the metabolic syndrome, including all its components, with various ocular conditions such as retinopathy, central retinal artery occlusion, cataracts, and raised intraocular pressure. As the prevalence

of metabolic syndrome is rapidly increasing worldwide due to the dietary and sedentary lifestyles, and its association with various ocular manifestations such as non-diabetic retinopathy, CRAO, cataract, and primary open angle glaucoma suggests that an epidemic of metabolic syndrome can have far-reaching ocular consequences as well. In contrast, amelioration of metabolic syndrome may have a therapeutic role in preventing these ocular conditions [6].

Although originally FS has been described in the context of eye pathologies, etiology has been expanded to incorporate a basic link to blood flow dysregulation and resultant hypoxia and impaired hydration/fluid balance, thermal regulation, and wound healing. FS signs and symptoms have also been suggested to be associated with a number of other pathologies, such as "dry mouth" syndrome [7], Sjögren syndrome [8], impaired healing [9, 10], and cancer [11–13], including aggressive metastatic disease [14, 15]. Some of these pathologies and their potential functional link to the FS phenotype will be discussed in individual paragraphs provided below.

1.2 Rationale of a Nutritional Approach to Flammer Syndrome

Whereas the medical approach to disease is based on one drug per symptom, the nutritional approach addresses symptoms and syndromes that are concomitantly expressed. The principle of nutritional intervention is based on the understanding that nutrient insufficiencies/deficiencies and imbalances have many manners of expression, as they are involved in many biochemical and physiological processes.

We are therefore herein evaluating the potential of nutritional intervention for managing some of the typical symptoms of FS, as well as the composite syndrome (Table 1).

Table 1 Common Flammer syndrome symptoms [1]

Glaucoma
Arterial hypotension
Cold hands and feet
Longer sleep onset
Decreased sensation of thirst
Increased sensitivity to pain, drugs and odors

2 Nutritional Aspects of Common Symptoms of Flammer Syndrome

2.1 Glaucoma

Glaucoma refers to progressive optic neuropathy that can result in irreversible vision loss and blindness [16], mostly due to intraocular pressure (IOP). Vascular dysregulation in ocular blood flow and oxidative stress are currently suggested as important risk factors for glaucomatous retinal ganglion cell loss [17]. Arterial hypertension increases the risk for ocular hypertension and thereby also the probability for high-tension glaucoma (HTG), and increases the risk for glaucomatous optic neuropathy (GON) at a given IOP, explained by ocular blood flow instability and oxidative stress [1]. Though glaucoma cannot be cured and glaucomatous damage is irreversible, if detected early, disease progression can be arrested or limited with medical and surgical treatment and potentially by nutritional intervention [1].

Nutritional Aspects

Magnesium Magnesium's support of improvement in ocular blood flow and prevention of ganglion cell loss suggest its potential benefit in glaucoma management. In *ex vivo* studies, magnesium has been shown to reduce the vasoconstrictive effect of endothelin-1 (ET-1), and potentially has a positive effect on visual fields. Magnesium has been shown to improve blood flow by modifying endothelial function via ET-1 and endothelial nitric oxide (NO) pathways [4]. Magnesium also exhibits a neuroprotective role by blocking N-methyl-D-aspartate (NMDA) receptor-related calcium influx and inhibiting the release of glutamate, thereby protecting the cell against oxidative stress and apoptosis [4]. Further studies on the effect of magnesium may open a new therapeutic era in glaucoma [18].

Calcium and Iron Calcium and iron have been suggested to play roles in glaucoma pathogenesis, through impact on trabecular meshwork and retinal ganglion cells in glaucoma patients. Supplementation of calcium and iron is associated with increased odds of glaucoma, whereas dietary intake is associated with decreased odds, thus indicating that related recommendations should be personalized, and emphasized only in patients with established deficiencies [19], with food being the primary source.

Antioxidants (Nutrients and Phytonutrients) Reduced oxidative stress has been suggested to be effective against glaucoma [17], and a preventive diet would include high amounts of antioxidants [4]. Antioxidants have been suggested to protect retinal ganglion cells, the specific cell type damaged by glaucomatous optic neuropathy [19]. Antioxidants include essential nutrients such as vitamin A, vitamin C, vitamin E, and zinc, as well as phytonutrients such as beta carotene, bioflavonoids, and

anthocyanosides from fruits and vegetables, as well as epigallocatechin gallate (EGCG) from green tea, flavanols from cacao, and curcumin from turmeric, among others, e.g. EGCG and cacao flavonols have been shown to benefit retinal cells in patients with glaucoma [20] by improving function of the endothelium, a significant component of the ocular vasculature [4]; nitric oxide, vitamin C [21], and polyphenols defend cellular integrity of blood vessels and contribute to improved blood flow to the retina; and black currant anthocyanins have been shown to meliorate abnormal levels of serum concentrations of ET-1 in patients with glaucoma [22].

Caffeine Caffeine may transiently elevate IOP, and caffeine-induced elevated IOP fluctuations in susceptible eyes may portend a pathophysiological connection for increased risk of developing glaucoma. Glaucoma patients are currently advised to limit caffeine consumption to a 'moderate' level, and avoid caffeine intake prior to visits requiring IOP evaluation [19].

Gingko biloba Ginkgo extract has been suggested to have antioxidant as well as retinal neuroprotective properties in glaucoma via blood vessel dilation [23].

2.2 Arterial Hypotension (AH)

AH is a key manifestation of autonomic dysfunction, typically observed when cardiovascular adaptive mechanisms fail to compensate for the reduction in venous return that normally occurs with sitting up and standing. It frequently affects older people and patients who have neurodegenerative disease, diabetes, or hypertension [24]. Symptoms are typically exacerbated by conditions predisposing to peripheral venous pooling and dehydration, such as heat, fever, alcohol consumption, urination, post-exercise time, and immobilization [24].

Nutritional Aspects

Recommended nutritional means of preventing hypotension [25] include adequate hydration and intake of essential vitamins and minerals, including sodium, as well as frequent small meals, stimulating/oxygenating phytonutrients, controlled carbohydrate consumption, and limited alcohol intake.

Hydration The general recommendation is to drink five to eight 8-ounce glasses of water or other liquid per day. Sports drinks that contain sodium and potassium may be recommended for occasional use, since a decrease in potassium can also lead to hypotension.

Sodium In cases of very low blood pressure, increased sodium intake may be recommended [4] to help increase blood pressure. It is important to emphasize that this

be accomplished without intake of highly processed foods. Certain vegetables and animal foods rich in salts constitute a relevant choice.

Frequent Small Meals Moderate food intake evenly spread over the day is especially protective against postprandial hypotension. By eating small amounts, less blood may be diverted to digest the food, reducing the chances of a major drop in blood pressure after meals [26].

Controlled Carbohydrate Intake Eating fast-digested foods high in carbohydrates – particularly simple types – can result in a drop in blood pressure, postprandial orthostatic hypotension related to gastric distension, release of vasodilatory peptides, and an increase in the splanchnic-mesenteric venous capacitance [25, 27].

Limited Alcohol As alcohol causes vascular dilation, which may cause a dip in blood pressure and resultant symptoms, limiting alcohol is highly recommended for cases of AH.

Vitamin B12 Even a slight deficiency in vitamin B12 can cause hypotension by leading to anemia, which can cause hypotension Supplements may help reverse hypotension in people for whom the deficiency causes the symptoms [28, 29].

Folate High-folate foods can help maintain blood pressure at a normal, functional level by lowering levels of homocysteine [30, 31].

Vitamin C Ascorbate may help blood vessels to constrict, thus normalizing blood pressure, especially in cases of shock and sepsis [32]. Ascorbate enhances the synthesis of the vasopressors norepinephrine and vasopressin by acting as a cofactor for their respective biosynthetic enzymes. Ascorbate-dependent vasopressor synthesis represents an adjuvant therapy for severe hypotension [32].

Vitamin D A research review found that vitamin D deficiency is linked to orthostatic hypotension, with particularly strong effects apparent among older women [33]. Additionally, vitamin D deficiency may result in dysfunction of the baroreflex neural arc, with inefficient short-term adaptive response to standing. Because vitamin D is involved in the proliferation of vascular smooth muscle cells, a deficiency may result in dysfunction of the arterial wall cells, vascular resistance and vascular compliance, that was improved among women who received vitamin D supplementation [34].

Nitrates Nitrates, as found naturally in beets and spinach, elevate nitric oxide in the blood vessels, which enables vasodilation and increases the flow of oxygen, thereby helping fight hypotension. Nitric oxide is the most potent vasodilating substance (endothelium-derived relaxing factor), which also participates in modulation of vascular resistance and heart function and thus in blood pressure regulation; is

involved in stress physiology and stress-related disease processes, and brief episodes may induce endothelial dysfunction, in healthy young individuals [35].

Caffeine In reasonable amounts and evenly divided over the day, caffeine can be very useful for people with low blood pressure. Caffeinated tea or coffee can cause a spike in blood pressure that may help prevent dips. However, an extreme in either direction may be deleterious, and daily management is critical [36].

Licorice Whole licorice herb can increase blood pressure. However, excessive consumption can cause potassium depletion, which can lead to dangerously low blood pressure. Accordingly, using licorice to increase blood pressure requires controlled dosing, as well as a diet moderately high in potassium [37].

2.3 Cold Extremities

A 'cold hand' sensation is defined as hands that become intolerably cold when exposed to normal temperatures in which most individuals feel no cold [38], and is caused by inadequate local blood supply. As dysfunctional endothelium may in certain persons with a predisposition lead to an inadequate organ perfusion due to vascular dysregulation, affected persons may respond pathologically to certain stimuli, e.g. emotional stress, with endothelial-mediated inadequate vascular constriction or dilatation, leading to characteristic vascular symptoms such as cold hands [5] and pale extremities, but not to white fingers or to trophic changes in the extremities [39].

Cold-hypersensitive hands and feet have also been associated with higher frequencies of the following symptoms: bad digestion, poor appetite, discomfort in the upper abdomen, motion sickness, epigastric burning, postprandial fullness, nausea, and bloating [40].

Nutritional Aspects

Colds hands and feet may indicate nutritional deficiencies, including of B-vitamins, iron, magnesium, and even quality protein, cause by either dietary insufficiency or indigestion. For example, vitamin B12 and/or iron deficiencies may cause anemia, which is associated with cold extremities, with correction of the nutrient state leading to physiological improvement. Sufficient amounts of dietary magnesium to correct an imbalance may also improve symptoms [41]; and high doses of niacin (vitamin B3) may trigger a response that causes capillaries to expand, which increases the flow of blood to the surface of the skin, and cause flashes of warmth in the extremities [42].

2.4 *Difficulties in Falling Asleep*

Sleep onset latency (SOL) – the length of time that it takes to accomplish the transition from full wakefulness to sleep – normally varies from <1 to 20 minutes [43]. Sleep is mainly controlled by hormones such as melatonin, which is derived from metabolism of the essential amino acid tryptophan to serotonin, and then to melatonin [44].

Controlled Carbohydrate Intake In several studies, SOL was significantly shorter with a high-carbohydrate diet compared to a control diet [45], as well as following a high-glycemic index (GI) meal consumed 4 h before bedtime compared to both a low-GI meal and/or the high-GI meal consumed 1 h before bedtime [46]. Several studies have also shown fruit consumption to lower SOL [44].

A high-carbohydrate diet may promote sleep through increased serotonin and melatonin production through increase in plasma tryptophan after a high-GI meal that influences both melatonin and serotonin and promoting sleep onset [44].

High-fat meals could further promote a deeper and more restful sleep, as high-carbohydrate/low-fat diet shown to significantly decrease the quality of sleep compared to an isocaloric low-carbohydrate/high-fat diet [44].

Omega-3 Fatty Acids Foods rich in omega-3 fatty acids have been shown to improve vascular regulation [4], and have been linked to a deeper, more restful sleep in children and adults [47]. Interventional research in adults linked fatty fish consumption to a positive impact on sleep in general, including reducing sleep latency, and on daily functioning [48].

L-Tryptophan Tryptophan is a precursor to the neurotransmitter serotonin and the neurosecretory hormone melatonin, both of which are linked to sleep and alertness. Tryptophan is found in various foods often consumed for purported sleep-enhancing benefits, and in supplement form has long been used as a sleep aid, with as little as 250 mg of pure pharmaceutical-grade tryptophan having been linked to improved sleep in people with related problems [49].

Vitamin B3 (Niacin) Vitamin B-3 suppresses the activity of tryptophan pyrrolase, one of the key enzymes in the conversion of tryptophan to niacin. If tryptophan is highly converted, it is not available as a precursor to serotonin in the brain. Therefore, supplementation with or sufficient dietary intake of vitamin B3 can reduce this diversion of tryptophan [49].

Melatonin and Serotonin Preformed melatonin is available as a food supplement, and both melatonin and its precursor serotonin have been detected in a considerable variety of plant species including roots, leaves, fruits, seeds, and wine. These foods may also contain tryptophan, a primary precursor of serotonin. Supplemented mela-

tonin is commonly used as a sleep aid, shown to be well-absorbed released into circulation, thus increasing plasma concentrations [49], and clinical research has demonstrated efficacy of food-based melatonin for improving sleep [50].

Vitamin D Vitamin D status is suggested to be important for seasonal changes in serotonin regulation which transformed to melatonin – the sleeping hormone, and thus can explain shorter SOL [48]. Higher serum calcifediol ([25(OH)D] a metabolic product of vitamin D3) concentrations were significantly associated with shorter SOL in the general adult population [51]. Among older men, low levels of total serum 25(OH)D are associated with poorer sleep including short sleep duration and lower sleep efficiency. These findings may suggest a potential role for vitamin D in healthy sleep [52].

Magnesium Magnesium helps activate the neurotransmitters responsible for sleep. Supplementation of magnesium has been shown to improve subjective measures of insomnia such as insomnia severity index (ISI) score, sleep efficiency, sleep time and SOL. High daily doses taken with food have been shown to improve sleep [53].

Zinc There is supportive evidence for zinc supplementation can improve sleep parameters, including shorter sleep latency [54].

Caffeine Caffeine is widely used to fight fatigue and stimulate alertness. It can be found in foods and beverages such as coffee, tea, carbonated and energy drinks, and chocolate. Unfortunately, caffeine can have unwanted effects on sleep [55–57].

Black and Green Tea Beyond caffeine/theobromide tea (*Camellia sinensis*) also contain the component L-theanine, an amino acid that induces alpha waves in the brain, suggesting tea to be a better choice than coffee for those who need to concentrate for long periods. The relaxing effect of L-theanine yields the advantage of enhanced energy and concentration without the excessively wired feeling associated with coffee [58].

Chamomile Tea Chamomile, though not scientifically supported may be taken as a 'tea' (infusion), tablets, tinctures, and inhalations or essential oils. German chamomile (*Matricaria chamomilla*) supplements are typically in doses of 90–400 mg (standardized for the active flavone apigenin) [59].

Dairy Cow's milk has traditionally been considered to have a sleep-inducing quality. Adults consuming a meal of cornflakes and milk exhibited a stronger tendency toward uninterrupted sleep, especially with melatonin-rich 'nighttime' milk, which is significantly increased if cows are milked in darkness at nighttime. Similarly, *Lactobacillus helveticus*-fermented milk enhanced sleep efficacy and reduced the number of episodes of awakening [49].

2.5 Decreased Thirst Perception

Systemic hydration status broadly affects a variety of ocular pathophysiologic pathways. For example, dehydration may be associated with development of dry eye syndrome, cataract, refractive changes and retinal vascular disease. On the other hand, excessive hydration is also associated with some ocular diseases. Recent studies implicate chronic renin-angiotensin-aldosterone system activation in the pathogenesis of diabetic retinopathy and glaucoma, suggesting it to be a useful therapeutic target [60].

Limited Alcohol Alcohol is known for causing diuresis, and excessive alcohol intake has been causally linked to dehydration [61].

2.6 Changes in Odor Perception

Taste and smell disorders can range from complete loss of function (ageusia and anosmia, respectively) to degrees of loss (hypogeusia and hyposmia); and/or inappropriate sensations for a given stimulus, termed dysgeusia (taste) and dysosmia (smell). Though chemosensory complaints identify both taste and smell loss, olfactory dysfunction is primarily responsible for most complaints [62].

Nutritional Aspects

Micronutrients Though zinc and other micronutrients (e.g. vitamin A and E, B-vitamins, copper, iodine, and iron) have been associated with chemosensory function, the overall evidence has shown supplementation to generally have limited efficacy in directly treating taste and smell disorders [62].

2.7 Increased Sensitivity to Pain

Recent findings showed a role for diet, foods, microbiome, obesity, and nutraceuticals like omega-3 fatty acids and curcumin as key elements in modulating the efficacy of analgesic treatments, including opioids. A recent Multidisciplinary Pain Research workshop (2016), concluded that patients with chronic pain should undergo nutritional assessment and counseling for including nutrition in personalizing pain medicine [63].

Nutritional Aspects

Vitamin C Recent epidemiological evidence has indicated an association between suboptimal vitamin C status and spinal pain, and that vitamin C administration can exhibit analgesic properties in some clinical conditions. The prevalence of hypovitaminosis C and vitamin C deficiency is high in various patient groups, such as surgical/trauma, infectious diseases, and cancer patients. Vitamin C administration to patients with chronic regional pain syndrome has been found to decrease their symptoms, reduce cancer-related pain, and diminish acute herpetic and post-herpetic neuralgia [64].

Fatty Acids Levels of omega-6 series polyunsaturated fatty acids were shown to be high in patients with chronic pain [65], whereas intake of omega-3 series polyunsaturated fatty acids results in a reduction in the pain associated with rheumatoid arthritis, dysmenorrhea, inflammatory bowel disease, and neuropathy. This can be explained by n-6 inflammatory eicosanoids vs. n-3 anti-inflammatory eicosanoids. An example is a reduction in pain associated with rheumatoid arthritis after intake of omega-3 fatty acids, suggesting the potential for interventions against inflammatory effects, including that associated with arthritic pain [66].

Antioxidants Antioxidants would be expected to reduce oxidation-related pain effects. Recent studies demonstrated a correlation between good plasma levels of bioflavonoids and a lower concentration of C-reactive protein (CRP), a biological measure linked with several inflammatory diseases and pain [67–69]. Tart cherries recently showed combined antioxidant and anti-inflammatory effects on prevention, treatment, and recovery of soft tissue injury and pain [70].

Zinc While a marginal serum deficiency would be unlikely to reduce muscle zinc nutriture, changes in extracellular zinc levels have been reported to influence the twitch-tension relationship in muscle, a physiologic phenomenon often directly related to pain, presumably due to a direct effect at the level of the cellular membrane [71].

Magnesium Among magnesium's many roles is blocking the brain receptors of glutamate, a neurotransmitter that may cause hypersensitivity to pain. Recent findings have demonstrated that a magnesium deficiency induces sensitization of nociceptive pathways in the spinal cord involving NMDA and non-NMDA receptors. These data are consistent with an active role of protein kinase C (PKC), NO and, to a lesser extent substance P in the intracellular mechanisms leading to hyperalgesia [72–74].

Vitamin B1 (Thiamin) A rat model of second-degree burn pain showed that local administration of thiamine provided relief from pain [75]. In humans, oral administration of thiamin 100 mg/day was shown to significantly reduced primary dysmenorrheal pain [76].

Vitamin B12 Patients with vertebral pain syndromes, degenerative neuropathies, and cancer noted excellent pain relief with doses of 5000–10,000 mcg daily, administered orally and/or by injection [71].

Vitamin D (Cholecalciferol) Vitamin D supplementation has been shown to decrease pain scores and relief pain [77, 78] suggesting a safe, simple and potentially beneficial treatment, especially in vitamin D deficiency [79].

L-Tryptophan In a study of patients with a severe level of pain, plasma free tryptophan levels were inversely related to pain severity. Tryptophan supplementation has been found to provide a mild degree of analgesia, and may be especially effective for the subset of chronic pain patients with a disorder of serotonergic transmission [71].

Phytochemical ('Herbal') Pain Relief

Some herbs have been shown to reduce pain associated with various mechanisms, including hot chili peppers (*Capsicum spp.*) yielding capsaicin, which acts by depleting substance P, responsible for conveying the sensation of pain from the peripheral to the central nervous system; ginger (*Zingiber officinale*) root, whose extracts are helpful in case of joint and muscle pains, as they may reduce inflammation; feverfew (*Tanacetum parthenium*, also known as 'bachelor buttons'), traditionally used to treat stomach and tooth aches, and currently also used against rheumatoid arthritis; turmeric (*Curcuma longa*), which has been used particularly for relieving arthritic pain and heartburn, as well as for reducing inflammation, due to its content of the anti-inflammatory compound curcumin; devil's claw (*Harpagophytum procumbens*, also known as 'grapple plant' and 'wood spider'), shown to be effective for management of arthritis and lower back pain; and sulfurous fruits, vegetables, and grains (as well as milk and fish) yielding methylsulfonylmethane (MSM), a sulfur compound that has been suggested to cause a decrease in inflammation and pain [69].

2.8 Migraine

Migraine as a disabling neurovascular disease [80] characterized by unique headaches a cluster of disorders. Migraine symptoms include pain activation, focal neurological deficits, vegetative dysfunction, and mood alteration. These symptoms can last hours to days, and can vary from one attack to the other, both in intensity and quality [81].

Nutritional Aspects

Nutrition and dietary status are very important triggers of migraines. Fasting, alcohol, chocolate, and fermented cheese are among the most commonly reported triggers. Patients with migraine may be very sensitive to one or more food components, including monosodium glutamate, nitrate, nitrite, tyramine (high in aged cheese) phenylethylamine (chocolate), octopamine (citrus fruits) and histamine (red wine and beer). Caffeine dependence and excessive coffee consumption may be also associated with throbbing headache and migraine. Elimination diets have been considered as treatment, due to the association of migraine with food allergy. A study on patients with irritable bowel syndrome and migraine evaluating the effectiveness of elimination diets reported a decrease in number and duration of attacks and symptoms [82].

Fasting and Hypoglycemia Missing a meal or fasting are common triggers of migraine in adults, and hypoglycemia has been suggested to have the potential to induce migraine [82, 83].

Alcohol Alcoholic beverages are known to trigger headache, with the specific type of beverage being important in the development of pain. The mechanism may be associated with ethanol, biogenic amines (including histamine, tyramine, and phenylethylamine), sulfides, phenolic flavonoids, serotonin release from thrombocytes, dehydration, or acetaldehyde from the principal metabolic pathway [82, 83].

Magnesium is considered to be the second-most important intracellular cation in migraine pathogenesis. Magnesium deficiency plays important roles in cortical spreading depression, platelet hyper aggregation, serotonin receptor function, and release of certain neurotransmitters. It may develop due to a genetic defect in magnesium reabsorption, magnesium loss from kidneys, emptying of magnesium stocks due to stress, low dietary intake, or other reasons [82, 84, 85].

Micronutrient Deficiencies

The deficiency of many nutrients, including vitamins B2 (riboflavin), B3 (niacin), B12 (cobalamin), and D, as well as carnitine, α-lipoic acid, and coenzyme Q10 are associated with migraines. Some researchers postulate that mitochondrial dysfunction and impaired antioxidant status can cause migraine attacks, as may an increased homocysteine level suggesting that nutraceuticals play a vital role in prevention [80].

2.9 Tinnitus

Tinnitus is described as the perception of a noise inside the otic system in the absence of auditory stimulation. The prevalence is 10–15% in the adult population, with a tendency to increase with age, in both genders. Tinnitus is generally caused by pathologies in the central nervous system, leading to abnormal neural activity that is not evoked by sound. Vascular [86] and oxidative [87] pathologies are also thought to be contributory.

Nutritional Aspects

Insufficient intake of water, protein, vitamins B2 and B3 [88], and zinc [89] may be associated with tinnitus and tinnitus-related annoyance. Dietary supplements are commonly used to treat tinnitus, including lipoflavonoids, magnesium, melatonin, vitamin B12, and zinc [87]. Zinc may affect oxidative species, and thus clinical improvement can be provided, e.g. when given for 6 months or more [89]. A combination of magnesium and B vitamins were used successfully against tinnitus [90]. Several studies found no significant improvement [91, 92], indicating that these interventions should be personalized [93, 94].

3 Summary

The present manuscript describes the various symptoms of FS and their key metabolic pathways relevant to nutrition, and related interventions based on physiological, biochemical, and biomechanical patterns.

The symptoms of FS mainly include arterial hypotension, cold extremities, difficulties in falling asleep, and increased sensitivity to pain, odors, and drugs. Each of the various aspects may potentially raise the risk of associated effects, as well as interactively lead to worsening of the combined effects. Management of the individual symptoms and prevention of their exacerbation for improvement of the current status may synergistically and cumulatively contribute to health and recovery. Considering the personalized medicine approach in viewing the cluster of symptoms as components of the syndrome may enhance the effectiveness of preventing and treating the combined aspects of the syndrome.

Most of the symptoms are responsive to nutritional imbalances and/or to corrections and functional therapy. Recommendations related to general dietary habits include small frequent meals, controlled carbohydrate intake, and avoidance or limitation of alcohol, as well as sufficient amounts of essential minerals, mainly magnesium, zinc, and iron, and vitamins such as C, D, and B-vitamins. Phytonutrients and omega-3 fatty acids should also be considered.

A nutritional approach, with emphasis on specific components as reviewed above, offers a comprehensive strategy for treating the variety of symptoms characteristic of FS, supporting increased awareness of the potential of treating individual symptoms as a gateway to treating the risk of the complete syndrome, preferably at the preventable stage for better impact on health.

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Conflicts of Interest There are no conflicts to declare.

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Positive Effects of Acupuncture Benefiting Individuals with Flammer Syndrome and Patients with Associated Pathologies

T. Blechschmidt, M. Krumsiek, and M. G. Todorova

Abstract Accupuncture has been effectively used to improve systemic blood flow and ocular blood flow. Subjects with Flammer syndrome have insufficient and unstable blood flow autoregulation. As many patients with ophthalmic diseases suffer simultaneously altered systemic and ocular blood flow, but also Flammer syndrome, accupuncture seems to be a promissing minimally invasive therapeutic approach. This review represents our acupuncture-experince on individuals suffering Flammer syndrome and associated pathologies.

Keywords Flammer syndrome · Acupuncture · Ophthalmic diseases · Sleep disturbances · Blood flow · Ocular blood flow · Prevention

1 Introduction

1.1 Acupuncture

The acupuncture treatment still accounts for a non-traditional therapeutic approach. Its positive effect has been proven in a variety of neuro-degenerative and psychosomatic diseases, following cerebral and peripheral ischemia. Acupuncture has also been applied in various diseases involving psychosomatic status: such as anxiety, depression, sleep disturbances [1]. Moreover, acupuncture has also effectively been used to improve systemic blood flow [2, 3] and ocular blood flow [4–7].

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1.2 The Eye and the Vascular Dysregulation

Even though the eye is a window of the brain, it belongs to the body. The letter explains, why alterations in the general blood flow reflect the ocular blood flow, as well. It is also known, that distribution of the blood flow to the eye, or its parts is regulated by adapting the relative local resistance. However, the autoregulation, or the intrinsic capacity to maintain constant blood flow adaptive to the needs of the respective tissue, is effective only within certain limits of perfusion pressure. In cause the regulation of blood flow is not adapted to the needs of the tissue, either due to unstable perfusion or hyper-reactivity to external and/or internal stimuli, vascular dysregulation occurs. Here, the autoregulatory capacity can be reduced in the presence of co-existing pathological condition or accompanying disease. Another specific subset of subjects with primarily reduced auto-regulatory capacity have Flammer syndrome (FS) [8, 9].

1.3 Flammer Syndrome (FS)

Flammer syndrome (FS) [9, 10], previously called primary vascular dysregulation (PVD) [8, 11, 12], refers to a predisposition to react differently to a number of stimuli, such as coldness, physical or emotional stress and systemic medication [8, 13–15]. The most prominent sign of subjects with FS is the inborn insufficient and unstable blood flow autoregulation [8, 11, 16].

1.4 Why FS Patients May Benefit from Acupuncture Treatment?

Acupuncture has already been effectively used to improve **systemic blood flow** [2, 3] and **ocular blood flow** [4–7].

Subjects with FS have **intrinsically insufficient and unstable blood flow autoregulation.** As many patients with ophthalmic diseases suffer altered systemic and ocular blood flow but also simultaneously FS [8, 11, 13, 16, 17], acupuncture seems to be a promising minimally invasive therapeutic approach. Therefore, we applied an acupuncture of the body and the ears on patients with ophthalmic diseases associated with FS (Fig. 1; Table 1).

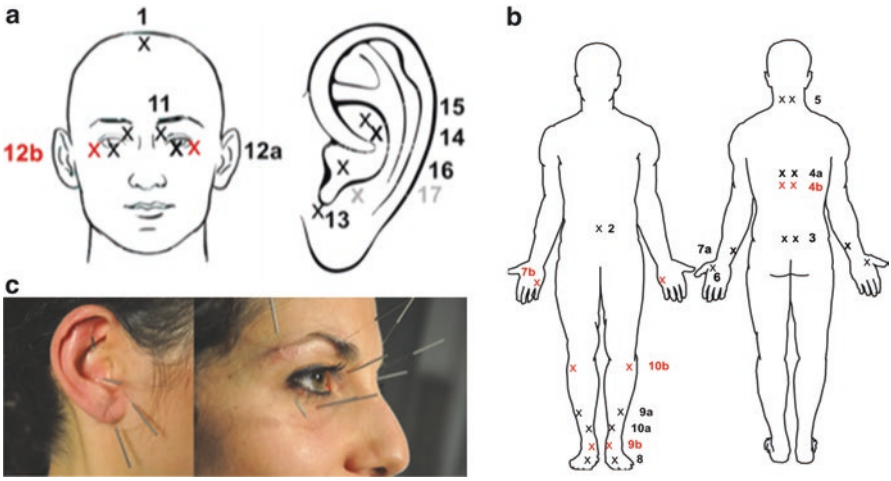

Fig. 1 Needle acupuncture of the ears (**a**) and the body (**b**) was performed following standardized protocol (Table 1). The approximate location of the needles on the face and the ears are presented on figure **a**, and on the body – on figure **b**. The needles at LI-4 (He Gu), CV-6 (Qi Hai), LV-3 (Tai Chong) and all ear needles were manually stimulated once in each session after 15 min (+/−5 min). Treatment 1 (labeled in black) alternated with treatment 2 (labeled in red). (**c**) exemplifies the points of periorbital and ears needling in a subject with FS. Reprinted and adapted with permission [18, 19]

1.5 Acupuncture Methodology Follows a Standardized Protocol

The acupuncture protocol, we applied, was developed particularly for ophthalmic diseases accompanied by vascular dysregulation as part of FS, based on the extensive clinical experience of an ophthalmologist and at once licensed and qualified well-trained acupuncturist (BT) [18, 19]. The acupuncture protocol consists of 10 sessions of 30 min duration administered twice a week over a period of 5 weeks. Before the first and after the last treatment, each patient was instructed to complete a questionnaire concerning his/her condition regarding the disease. In addition, before and following acupuncture treatment all patients completed a questionnaire assessing subjectively for presentation of sign and symptoms of FS [9] (Table 2).

The scheduling of each patient and the complete ophthalmologic examinations were performed by the same experienced ophthalmologist and acupuncturist (TB), while the orthoptic examinations were performed by the same experienced orthoptist (KM). Before the initial appointment for treatment, the acupuncturist (TB) gave the patient a brief introduction outlining the duration and the course of treatment, as

Table 1 All acupuncture points, the alternation in treatment, as well as the stimulation duration. Reprinted with permission [18]

Acupuncture study protocol			
Treatment modality	Treatment 1 (a)	Treatment 2 **(b)**	
Needle Nr:	Alternating with Treatment 2	Alternating with Treatment 1	Laterality
1	GV20 (Bai Hui)		UL
2	CV6 (Qi Hai)		UL
3	UB23 (Shen Shu)		BL
4 (a/**b**)	UB18 (Gan Shu)	**UB20 (Pi Shu)**	BL
5	GB20 (Feng Chi)		BL
6	LI4 (He Gu)		BL
7 (a/**b**)	TE5 (Wai Guan)	**SI3 (Hou Xi)**	BL
8	LV3 (Tai Chong)		BL
9 (a/**b**)	GB37 (Guang Ming)	**KI3 (Tai Xi)**	BL
10 (a/**b**)	SP6 (San Yin Jiao)	**ST36 (Zu San Li)**	BL
11	UB1 (Jing Ming)		BL
12 (a/**b**)	ST1 (Cheng Qi)	**EX-HN7 (Qiu Hou)**	BL
Additional Ear Acupuncture Points (alternately, starting with the right ear)			
13	Eye Point (24a)		UL
14	Liver Zone (97)		UL
15	Kidney Zone (95)		UL
16	Heart Zone (100)		UL
17	Thalamus Point (26a)		UL
+ one Semi-Permanent Needle (Press Tack Needle) (alternately, starting with the left ear, points in the order specified):			
14	Liver Zone (97)		UL
15	Kidney Zone (95)		UL
17	Thalamus Point (26a)		UL
Needle Stimulation (after 15 min) at following points:			
6	LI4 (He Gu)		s. above
8	LV3 (Tai Chong)		s. above
2	CV6 (Qi Hai)		s. above
13–17	Ear Points		s. above
Duration of Needle stimulation:			
30 min			

Standardized needles acupuncture protocol was applied as shown in Fig. 1. In patients suffered Flammer Syndrome acupuncture points important to be needled are positioned along the meridians Kidney Zone (95) and Liver Zone (97)

Table 2 Questionnaire items used to assess for signs and symptoms of Flammer syndrome

Signs and symptoms of Flammer syndrome
Cold hands and/or feet
Low blood pressure
Low body weight
Reduced feeling of thirst
Long sleep onset time
Increased sensitivity (increased smell and pain sensation, increased response to certain drugs)
Tendency toward perfectionism
Migraines and headaches
Tinnitus
Reversible skin blotches (red or white)

well as the possible complications. Each scheduled treatment session was only initiated after a short welcome of the patient and questions concerning his condition after the previous treatment, as well as his actual general condition. All procedures took place at the acupuncture unit at the Department of Ophthalmology of the University of Basel. The study and data accumulation were in conformity with institutional requirements, and in accordance with the statements and principles of the declaration of Helsinki, as well as all governmental regulations.

1.6 Needle Acupuncture of the Body and the Ears Applied

In patients suffering Flammer Syndrome acupuncture points important to be needled are positioned along the meridians and at the ear at Kidney Zone (95) and Liver Zone (97). In general, the procedure was performed as follows:

Sterile and disposable single-use needles of different sizes were used, namely Seirin B type needle No.3 (0.20) × 15 mm, No.5 (0.25) × 40 mm, No.8 (0.30) × 30 mm, Seirin Pyonex Press Needles P type 0.22 × 1,6 (Seirin Corporation, Shizuoka, Japan); Dong Bang needle DB106 (0.20) × 15, DB105G (0.20) × 25, Dong Bang Press Needles 0.20×2×1.0 (Dong Bang Acupuncture, Inc., Chungnam, Korea). The established protocol indicates the specific pre-selected points for all participants, needling depths and manipulation techniques. The needles were applied only by the same fully trained acupuncturist (BT). The standard points for all subjects are located around the eyes, on the head, ears, back, abdomen, arms, hands, lower legs and toes and include: GV-20 (Bai Hui), CV-6 (Qi Hai), UB-18 (Gan Shu), UB-20 (Pi Shu), UB-23 (Shen Shu), GB-20 (Feng Chi), LI-4 (He Gu), TE-5 (Wai Guan), SI-3 (Hou Xi), LV-3 (Tai Chong), GB-37 (Guang Ming), KI-3 (Tai Xi), SP-6 (San Yin Jiao), ST-36 (Zu San Li); local points: UB-1 (Jing Ming), ST-1 (Cheng Qi), ExHN-7 (Qiu Hou); ear points: Eye Point (24a), Liver Zone (97),

Kidney Zone (95), Heart Zone (100), Thalamus Point (26a). The needles were applied according to a standardized protocol (Fig. 1, Table 1). Individual choice of acupuncture points was not allowed in contrary to common Chinese Medicine (CM). Due to standardization the amount of applied needles exceeded the common practice of CM. The location of the needles was performed due to the standards of CM. It was aimed to produce the irradiating needle sensation ('de qi'), if possible. The needles at LI-4 (He Gu), CV-6 (Qi Hai), LV-3 (Tai Chong) and all ear needles were manually stimulated once in each session after 15 min (+/−5 min). Additional influencing techniques like electro stimulation, heat lamps, music during treatment etc., were not applied.

1.7 Application of Acupuncture to the FS-affected Individuals

Analogically to general vasospastic syndromes [20], one of the main systemic symptom of subjects with FS is the presence of cold extremities, particularly when exposed to cold or emotional stress [21, 22]. The FS subject reports also a reduced thirst sensation [23]. Here, increased plasma ET-1 level has been discussed as a factor in the pathogenesis of the above described signs and symptoms [20, 24]. Among other symptoms subjects suffer more often from atypical headaches and migraines [25, 26] and have increased pain sensation, since ET-1 level decreases the threshold for pain sensation [27]. On further questioning, FS subjects report to require longer time to fall asleep, especially when they are cold [22], as warm feet are generally a prerequisite for falling asleep. FS occurs more often in younger females and in thin subjects [28].

Our observation of acupuncture treatment on subjects suffering FS provided preliminary support that acupuncture helps to improve signs and symptoms of FS, as for instance: cold extremities, frequency of migraine attack, reduced low pressure dipping, and reduced hypersensitivity in general. Here, the simulation effect of acupuncture, mediated through the central nervous system, on systemic blood flow [3], seems to be of benefit for subjects, which simultaneous suffer from FS [9].

1.8 Acupuncture Benefits on Signs and Symptoms of FS in Ophthalmic Diseases

Aside from glaucoma [29], FS is described as accompanying feature in a variety of ophthalmic diseases [11, 12], such as retinal arterial and vein occlusion [30–33], anterior ischemic optic neuropathy [34], Susac syndrome [35], retinitis pigmentosa [36], multiple sclerosis [37], optic nerve compartment syndrome [38], Leber's hereditary optic neuropathy [39] and others. Therefore, we applied the acupuncture in ophthalmic diseases associated with FS, as well.

Some exemplified ophthalmic cases associated with FS which benefit from acupuncture treatment are presented below:

Patient 1: A 57 year-old female patient suffered primary open angle glaucoma. Additionally, the patient was positive for seven out of ten criteria used to screen for Flammer syndrome [9]. Following acupuncture the patient showed improvement in FS signs and symptoms, as well as significant reduction in her pericentral scotoma, of left eye (Fig. 2a). Few months later her FS symptoms as well as the pericentral scotoma occurred again (Fig. 2b). Following acupuncture a significant improvement of signs and symptoms of FS were noticed. In addition, her visual field scotoma disappeared (Fig. 2b).

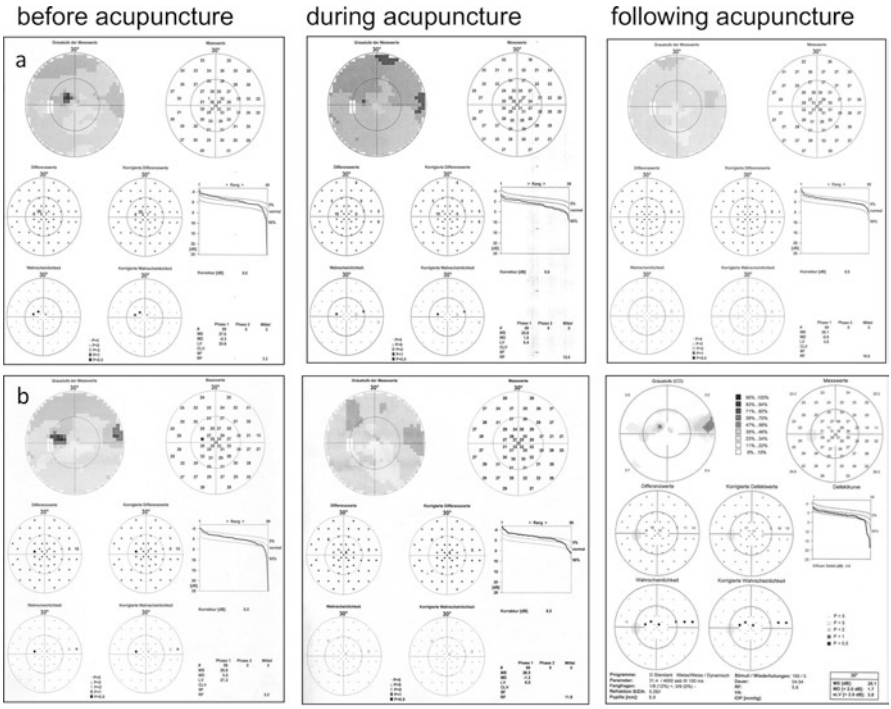

Fig. 2 Examples of ophthalmic cases associated with FS which benefit form acupuncture treatment. Figure **a** represents results of the visual filed examination before, during and following acupuncture treatment of a 57 year-old female patient suffered primary open angle glaucoma and FS. Note the reduction of the paracentral localized scotoma following acupuncture. Few months later the visual field defect appeared (Fig. b) , again following acupuncture the visual field scotoma as well as the signs of FS reduced much. Figures c and d show significant improvement of the visual field alteration in addition to the improvement of FS signs and symptoms following acupuncture in a 75 year-old male suffered FS and progressive NTG. Figures e and f represents an example of visual field alteration benefits in a 59 year-old male suffered FS and NTG

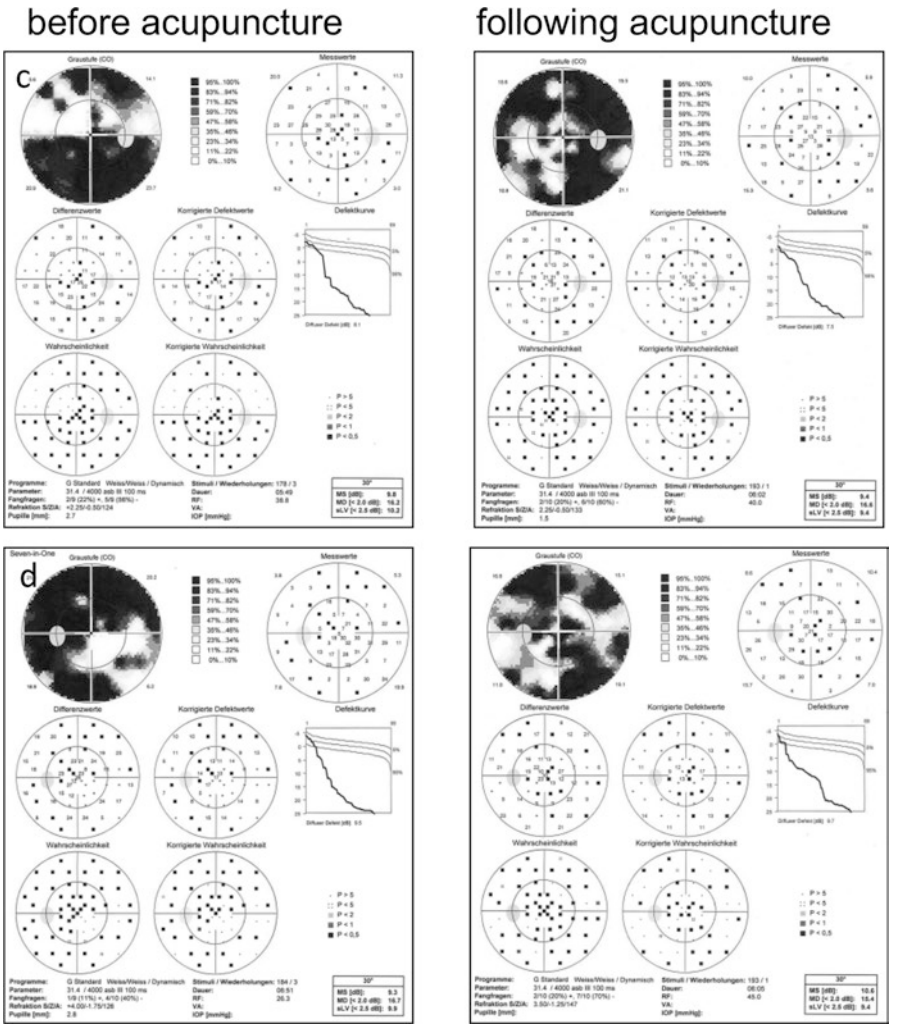

Fig. 2 (continued)

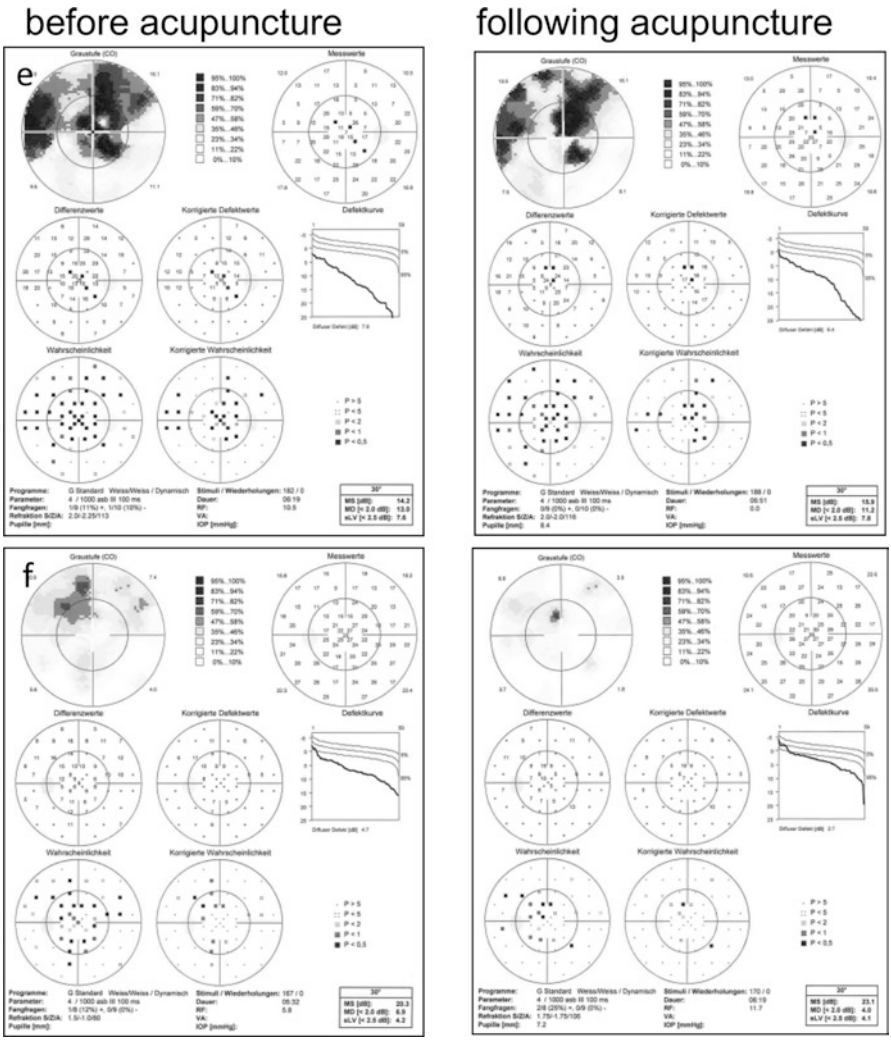

Fig. 2 (continued)

Patient 2: A 75 year-old male suffered FS and progressive NTG. Following acupuncture treatment, his visual acuity, even remaining on the right as finger-counting, improved on the left from 0.2 to 0.3. In addition, even if the mean defect of the visual field remained stable between 16.2 dB and 16.6 dB (right eye) and improved from 16.7 dB to 15.4 dB (left eye), the local defect improved significantly from 27.0 dB to 17.0 dB (right eye) (Fig. 2c) and from 25.0 dB to 17.0 dB (left eye) (Fig. 2d).

Patient 3: A 59 year-old male suffered FS and NTG. Following acupuncture a significant improvement in both, signs and symptoms of FS, as well as visual field was documented. Here by otherwise stable visual acuity 0.9 and 1.0 (right eye/left eye), the mean defect of the visual field improved from 13.0 dB to 11.2 dB (right eye) (Fig. 2e) and from 6.9 dB to 4.0 dB (left eye) (Fig. 2f)

Among signs and symptoms of FS influenced through acupuncture noted here, were again: reduction of feeling cold, frequency of migraine/headache attack, reduced low pressure dipping, and reduced hypersensitivity in general.

1.9 Application of Accupuncture to the Patients with Retinitis Pigmentosa and FS Symptoms

The quality of life in patients with inherited retinal diseases (IRDs) is supposed to be influenced from additional systemic factors, such as unstable systemic blood flow and disturbed ocular blood flow. Patients with IRDs and in particular, patients with retinitis pigmentosa (RP) have reduced and insufficient ocular blood flow [40]. Even in early stages of degeneration, RP patients have reduced blood flow in the retinal, choroidal, retroocular vessels, confirmed by laser Doppler velocity [40], colour Doppler imaging [41, 42], retinal functional imaging [43], and MRI imaging [44]. Here, insufficiency and instability in blood flow autoregulation are discussed as influencing factors for the progression of the degeneration.

Following all of the discussed above, a concept of FS in RP patients as a consequence of altered blood flow has been supposed [36] and confirmed via positive primary vascular dysregulation (PVD) questionnaire: the RP patients exhibit signs and symptoms of FS [9, 45]. The latter was supported by thermography of hands and faces, which showed a patchy-like lower temperature pattern in our RP patients (Fig. 3). Taking all of the discussed together, pointed toward systemic etiology of FS in RP patients. Thus, any attempt to stabilize ocular and systemic blood flow, seemed to be of benefit for the patient. Following that and as IRD patients suffer simultaneously from FS [9, 18, 45], the application of acupuncture promised to be a supporting alternative to the conventional treatment.

Previous reports on the application of acupuncture in patients with IRDs have shown improvement in visual function, as measured by static/ kinetic perimetry, dark adaptation, electrooculogram, contrast sensitivity [46, 47], a finding we also confirmed in our patients with IRDs treated with needle acupuncture of the body and the ears [18]. Also, application of electro-acupuncture in RP patients confirmed improvement of visual function, but also on retinal blood flow [7].

With this background in mind, we examined the effect of needle acupuncture of the body and the ears of patients with RP and of patients with other IRDs on the signs and symptoms of FS. In addition, we evaluated for which specific sign or symptom of FS the acupuncture treatment was for the IRD patient more beneficial (Table 3) [19].

In general, results of the study confirmed here a positive effect on signs and symptoms of FS in patients with IRDs [19]. More precisely, a reduction of tiredness, shorter sleep onset-time, much warmer feet and hands, and reduced frequency of migraine / headache attacks following acupuncture, were found. Surprisingly, in addition, in some RP patients and in few inherited macular dystrophy patients a significant reduction of macular edema, which persisted since years, was documented.

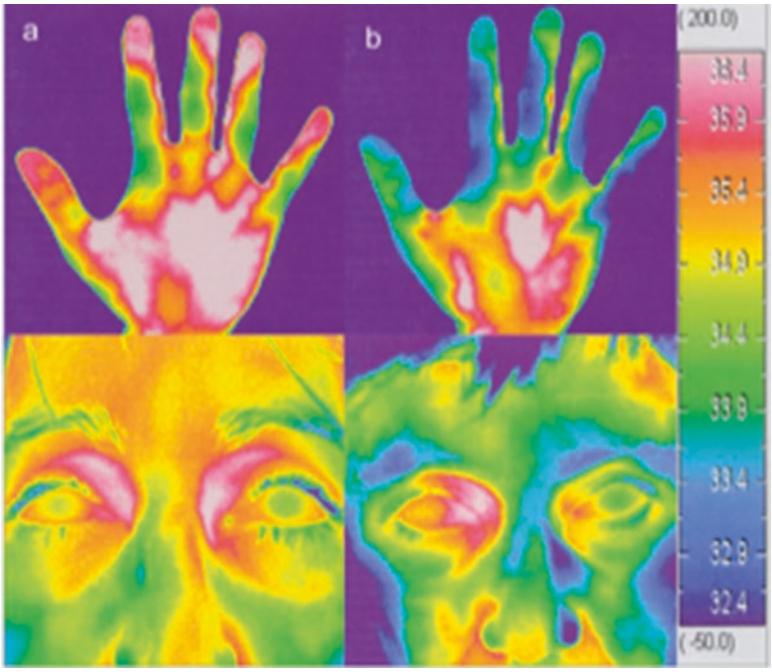

Fig. 3 Thermography of a right hand and face of a RP patient with Flammer syndrome (on the left) are presented in comparison to those of a control subject (on the right). The pictures show reduced temperature of a hand and increased heterogeneity of skin temperature of the face in RP patient with Flammer syndrome. The quantitative thermography scale is given for comparison

Table 3 The multiple-choice questionnaire consisted of 10 items with the following choices: "often", "never", or "I do not know". The mid-sided column shows how often IRD patients exhibited signs and symptoms of FS and the right-sided column represents how many IRD patients suffering simultaneously FS improved following acupuncture treatment. Printed with permission [19]

Evaluated signs and symptoms of Flammer syndrome in our IRD patients	Present before-acupuncture (Nr. patients: suffering/ total)	Reduced after acupuncture (Nr. patients: showing improvement/suffering)
Cold hands and/or feet	10/17	10/10
Low blood pressure	11/17	10/11
Low body weight	10/17	5/10
Prolonged sleep onset time	11/17	10/11
Reduced feeling of thirst	10/17	9/10
Increased sensitivity (smell and pain sensation, response to certain drugs)	9/17	7/9
Migraines and headaches	11/17	9/11
Tinnitus	10/17	8/10
Perfectionism	11/17	2/11
Reversible skin blotches (red or white)	10/17	9/10

The mid-sided column shows how often our IRD patients exhibited sign or symptom of FS. The right hand side column represents how many IRD patients suffering simultaneously the sign or symptom of FS improved following acupuncture treatment

1.10 Why Do Subjects with FS Benefit from Acupuncture?

The most prominent sign in FS is the dysregulation of ocular and extraocular vessels, which has also been discussed as accompanied feature in patients with ophthalmic related pathologies [11, 12], as for instance: in glaucoma [29], retinal vessel occlusion [30–33], anterior ischemic optic neuropathy [34], Susac syndrome [35], retinitis pigmentosa [36], multiple sclerosis [37], optic nerve compartment syndrome [38], Leber's hereditary optic neuropathy [39] and others.

1. As it is now well established, and further exemplified, patients with Flammer syndrome have **intrinsically insufficient and unstable blood flow autoregulation.**

   FS subjects often suffer from systemic hypotension [8, 48, 49] showing a completely different pattern of blood pressure variations in association with changes in distal skin blood flow than unaffected subjects [49]. Flammer syndrome subjects often suffer from systemic hypotension [8], supposedly provoked by reduced sodium reabsorption in the proximal tubule of the kidneys [50, 51]. The latter in turn is due to prostaglandin E2 release, following increased systemic or local production of endothelin-1 (ET-1).

Acupuncture has already been effectively used to improve **systemic blood flow**, an effect which is supposedly mediated in part by the central nervous system [2, 3]. For instance, studies on electro-acupuncture in rabbits with vertebro-basilar insufficiency showed improvement in their vestibulo-ocular reflex, through improvement of the basilar artery hemodynamic, inner ear blood flow and blood viscosity [2]. Moreover, the traditional acupuncture stimulation has shown its positive effect on systemic blood flow, an effect which supposedly, is in part mediated by the central nervous system [3].

A further possible explanation of the phenomena has been supposed the link between the acupuncture and the neutrophins [52]. The neutrophines, and in particular the nerve growth factor (NGF) and the brain-derived neurotrophic factor (BDNF), are proteins, responsible for the growth of neurons during development, but also for survival and regeneration of adult neurons of the ventral and peripheral nervous system [53, 54]. The relationship between acupuncture and BDNF has shown its positive effect in a rat model of stroke with loss of motor function [55]. The potentiating effect of acupuncture on NGF and BDNF has been supposed in the treatment of central and peripheral neurodegenerative diseases, as well [56, 57].

The effect of acupuncture **on ocular blood flow** has been confirmed also in healthy subjects receiving transcorneal electrical stimulation [4]. Here, an increase in the macular choroidal blood flow and in the papillo-macular area, were measured. Following needle acupuncture on visually related points on healthy subjects a significant increase in the blood flow velocities in the ophthalmic artery was confirmed [5], but also decreased vascular resistivity index in the central retinal artery and posterior ciliary arteries [6]. In RP patients, transcorneal electrical stimulation confirmed improvement of visual function, as well as of retrobulbal blood flow, particularly of the macular vessels [7].

As many patients with ophthalmic diseases suffer altered systemic- and ocular blood flow, it is not an unexpected finding that they often suffer symptoms and signs of FS. Thus, we hypothesized that a traditional acupuncture of the ears and the body would show improvement of FS signs and symptoms. In agreement, our patients with ophthalmic pathologies associated with FS could benefit from acupuncture, where a variety of signs and symptoms related to FS reduced much. It seems thus plausible, the simulation effect of acupuncture, mediated through the central nervous system, on systemic blood flow, to be the reason for the improvement [3].

Argument in favor is the fact that not only symptoms and signs of FS reduced, but also observed in several IRD patients macular edema, which persisted since several years, resolved or reduced following acupuncture simultaneously [18]. Also visual field alterations reduced significantly following the applied acupuncture protocol. However, it is also possible that the retinal structural response might be due to intraretinal microenvironment sensitivity changes to oxygen supply and oxidative stress rather than to direct effects of acupuncture stimulation. Reduced ocular blood supply, leading to unstable oxygen supply and oxidative stress [36, 58] have already been pointed in the progression of retinal degeneration [59]. Also, increase in retinal vessel oxygen saturation proportionally to retinal structural and functional alterations has been found in patients with inherited retinal dystrophies [60–62]. Furthermore, retinal blood flow has been found inversely related to oxygen tension [63]. Thus, the positive effect of acupuncture in patients with IRDs, could be a consequence of improved ocular blood perfusion, stabilized ocular blood barrier, reduced retinal oxygen tension, homeostatic balance, reduced oxidative stress, providing thus a nurturing microenvironment suitable for the rescue of apoptotic photoreceptor cells [59, 64, 65].

2. Flammer syndrome subjects **tend to react to a number of stimuli, such as cold, physical or emotional stress, and systemic medication**, like adrenaline, with marked dysregulation of vessel wall function [8, 13]. The most noteworthy problem in FS seems to be an arterial vasospasm [66]. Subjects with FS exhibit often blood pressure drop, therefore they have a **lower perfusion pressure.** The lower blood pressure is also the reason why FS subjects require longer time to fall asleep, especially when they are cold, as warm feet are generally a prerequisite for falling asleep [15, 22, 49].

Our results confirmed a clear benefit on signs and symptoms of FS in patients with ophthalmic pathologies associated with FS. More precisely, a reduction of tiredness, shorter sleep onset-time, much warmer feet and hands, and reduced frequency of migraine / headache attacks following acupuncture, were found. It is not an unexpected finding, as in depression rat model, induced by chronic stress; acupuncture has shown regulation effect on circadian rhythm of temperature and melatonin [67]. Also, acupuncture has shown its benefit in various diseases involving psychosomatic status: such as anxiety, depression, sleep disturbances [1]. Furthermore, in a mice model of Parkinson's disease, the application of electroacupuncture has proven to be effective in slowing the degeneration of dopaminergic neurons in the ventral midbrain [68]. Acupuncture has shown its positive effect in

chronic pain, here due to its inhibitory effects on the supplementary motor complex and medial prefrontal cortex [68]. Furthermore, previous studies on acupuncture in animal models supposed its indirect effect on photoreceptor survivals or function through modulation of retinal microglia, secretion of neurotrophic factors and nerve growth factors, or reduction of gene expression for proteins associated with inflammation and apoptosis [69–71].

3. High plasma **endothelin-1 level** remains a central element in the pathogenesis of the herein described signs and symptoms. Subjects with Flammer syndrome suffer from **vascular endotheliopathy** and have impaired autoregulation of their ocular blood flow.

   In inherited retinal diseases, with progression the retinal degeneration, apoptosis occurs and the retinal and choroidal blood flow undergoes neurovascular remodeling [72]. In glaucoma, unstable oxygen tension induced local oxidative stress contributes essentially to disturbed autoregulation and development of glaucomatous optic neuropathy [58]. In such altered conditions as a consequence of reduced demand for supply, blood-retinal barrier is compromised and the blood flow is reduced.

ET-1 has already been discussed to be involved in the regulation of retinal vessel size, but also to influence the blood-retina barrier [10]. In the eye, ET-1 is a confounding factor reducing ocular blood flow [73, 74], where the choroidal blood flow is generally more affected [75]. Of particular interest is the fact that, a significant increase in ET-1 plasma levels in RP patients compared to controls, has been found in a number of studies [41, 45, 73, 74, 76]. Furthermore, in a group of RP patients we found a strong association between increased ET-1 plasma levels and positive history for signs and symptoms consistent with FS [77]. However, increased ET-1 levels have been found also in other ophthalmic and systemic diseases, which surprisingly also show signs and symptoms of FS. For instance, increased production of ET-1 has already been discussed in a variety of vascular and autoimmune diseases, such as rheumatoid arthritis [78], multiple sclerosis [79], optic neuritis [34], giant cell arteritis [80], fibromyalgia syndrome [27], Sussac syndrome [35]. It is therefore to suppose, that the ET-1 plasma level alterations contribute rather to the systemic multifactorial etiology, but are merely a consequence of ocular disease.

Surprisingly, acupuncture has shown its positive effect on ET-1 plasma levels, a fact that in part may explain its positive effect on FS, as well. For instance, following acupuncture, the ET-1 plasma levels in cerebral infarction patients has been found to decrease, supposing thus improvement in the vascular elasticity and cerebral blood flow [81]. There are also previous reports on the application of electro-acupuncture in healthy subjects, where an increase in blood fluidity by decreasing platelet aggregation in the systemic vascular system has been found [82]. Furthermore, in a rat model of hypertensive aorta, electro-acupuncture has proven to be effective in reduction of ET-1 and ET-A receptor mRNA [83].

Taking all of the discussed above altogether, the positive effect of acupuncture on patients with signs and symptoms of FS seems to be more generalized and could be

a consequence multiple factors, as for instance: improved ocular blood perfusion, stabilized ocular blood barrier, reduced retinal oxygen tension, homeostatic balance, reduced oxidative stress of the respective tissue.

2 Conclusions

In conclusion, our experience on application of acupuncture on subjects suffering FS confirmed subjective and objective improvement in signs and symptoms of FS following applied acupuncture protocol and was tolerated well. Nevertheless, the objective evaluation of this complementary therapy on FS remains to be evaluated.

Acknowledgements Data Access and Responsibility: All authors have full access to all data from the study and are responsible for the data integrity and the analysis accuracy.

Declaration of Interest None of the authors has financial or proprietary interest in the presented data.

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