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

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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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