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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1984–1987	Head Physician at the Department of Ophthalmology, University of Berne
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)
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2002	Poster Award, SOG (Swiss Ophthalmological Society), Lucerne (Switzerland)
2003	Invited Professor, University of Varna (Bulgaria)
2003	Honorary Member of the Czech Glaucoma Society, Prague (Czechoslovakia)
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