Increased Prevalence of Flammer Syndrome in Patients with Retinitis Pigmentosa

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Increased Prevalence of Flammer Syndrome in Patients with Retinitis Pigmentosa

Gehäuftes Vorkommen des Flammer-Syndroms bei Patienten mit Retinitis pigmentosa

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Abstract

Background: “Retinitis pigmentosa” refers to a group of degenerative eye diseases with a genetic background. Flammer syndrome encompasses a set of symptoms and signs, mainly but not exclusively related to dysregulation of blood vessels.

Methods: 76 patients with retinitis pigmentosa (members of the Swiss patient organization for retinitis pigmentosa) and 274 control subjects answered a questionnaire (Flammer Syndrome Questionnaire) on 15 symptoms and signs of Flammer syndrome.

Results: Seven of 15 symptoms and signs of Flammer syndrome were significantly more often positive in retinitis pigmentosa patients than in controls. Six additional symptoms and signs occurred non-significantly more often and 2 non-significantly less often in patients with retinitis pigmentosa.

Conclusion: Retinitis pigmentosa patients suffer significantly more often from symptoms and signs of the Flammer syndrome than control subjects. This includes low body mass index, low blood pressure, feeling cold, migraine, increased smell perception and perfectionism. The reason for this association between retinitis pigmentosa and Flammer syndrome and the potential implications need to be determined.

Zusammenfassung


Methode: 76 Patienten mit Retinitis pigmentosa und 274 Kontroll-Personen füllten einen Multiple-Choice Fragebogen (Flammer-Syndrom Fragebogen) aus. Es wurde nach 15 Symptomen und Zeichen des Flammer-Syndroms gefragt.

Ergebnisse: 7 von 15 Symptomen oder Zeichen des Flammer-Syndroms waren signifikant und 6 weitere nicht signifikant häufiger bei Patienten mit Retinitis pigmentosa als bei Kontroll-Personen. 2 Symptome oder Zeichen waren nicht signifikant seltener bei Patienten mit Retinitis pigmentosa.


Key words
Retinitis pigmentosa
Flammer syndrome
endothelin
ocular blood flow
vascular dysregulation

Schlüsselwörter
Retinitis pigmentosa
Flammer-Syndrom
Endothelin
Augendurchblutung
vaskuläre Dysregulation

Abbreviations
CCB: calcium channel blocker
ET-1: endothelin-1
FS: Flammer syndrome

OBF: ocular blood flow
ONH: optic nerve head
PVD: primary vascular dysregulation
RP: retinitis pigmentosa
Introduction

Retinitis pigmentosa (RP) refers to a group of hereditary diseases characterized by the degeneration of rod and cone photoreceptor cells and the loss of retinal pigment epithelium function. The main symptoms are night blindness and progressive visual field loss, leading to tunnel vision and eventually blindness. The classic clinical triad of RP is bone-spicule retinal pigmentation, retinal vessel attenuation, and waxy disc pallor. In electroretinography, a- and b-waves are reduced or even absent.

RP is genetically heterogeneous. The condition can be inherited in an autosomal-dominant, autosomal-recessive, or X-linked fashion. Non-Mendelian inheritance patterns, such as digenic [1] and maternal (mitochondrial) [2] inheritance, have also been reported. For the mode of inheritance patterns, we refer to a recently published review [3]. The fact that many different types of mutations in different genes can lead to the clinical picture of RP explains the large heterogeneity of phenotype, age of onset, progression, and severity of the disease. Even though the disease clearly has a genetic background, it is possible that additional factors influence its manifestation and progression.

One potential modifying factor is ocular blood flow (OBF). Indeed, reduced OBF in RP patients has been described in both the retina [4] and the choroid [5]. Color Doppler imaging of retinal vessels has also revealed decreased peak systolic velocities [6]. Furthermore, baseline cutaneous capillary blood flow in RP patients is significantly reduced, the maximal flow reduction after cold provocation significantly slower and warm recovery time significantly longer [6].

Endothelin-1 (ET-1) is a factor reducing OBF, particularly in the choroid and the optic nerve head (ONH) [7]. ET-1 is increased in the plasma of RP patients [6, 8–11], although this has not been confirmed by all authors [12]. In addition, the reduction of retinal blood flow and the increase of ET levels in RP patients are correlated [6], and the increase of ET-1 plasma levels is negatively correlated with choroidal thickness [10, 13]. The calcium channel blocker (CCB) nilvadipine slows the progression of central visual field defects in RP patients [14]. In a patient with a clinical picture of RP without genetic history, the visual field progression was stopped after the treatment of a chronic hypomagnesemia with magnesium substitution [15]. CCBs and magnesium (a physiological CCB) have a neuroprotective effect and improve the regulation of OBF, partially by antagonizing the effect of ET [16, 17].

OBF in RP patients is reduced, obviously secondary to the degeneration of the retina. However, an additional primary component of OBF reduction is likely [18, 19] as OBF reduction precede a major degeneration [6, 10, 13], and blood flow is reduced also in the retinal vessels [6] and even in cutaneous capillaries [6] and ET in the circulating blood is increased.

What could be the cause of this primary component? In general, the most common factor leading to reduced blood flow is atherosclerosis. The fact, however, that reduction of OBF in RP patients occurs already at a relatively young age [6] indicates that it might be due to other causes. We hypothesize that one such cause could be Flammer syndrome [20–22].

The Flammer syndrome (FS) has been described recently. It is characterized by a predisposition to respond differently to a number of stimuli like coldness [23, 24] or emotional stress. The FS is relatively common [25] and occurs more often in females than in men [25], in slim than in obese subjects [25–27] and in academics than in blue-collar workers [28]. An essential component of FS is the primary vascular dysregulation (PVD) [21] explaining some of the symptoms of FS such as cold extremities. One potential sign of PVD are vasospasms, explaining why in the past, the term vasospastic syndrome was also used. However, FS encompasses a number of additional signs and symptoms, listed in Table 1.

Whilst FS influences the entire cardiovascular system [22], its impact on OBF has most extensively been studied [21]. It is accompanied by reduced autoregulation [29], increased spatial irregularities [30] increased stiffness [31] of retinal vessels, reduced vascular response to flickering light [32, 33] as well as increased retinal venous pressure [34]. FS is supposed to increases the risk for several eye diseases [21], particularly normal tension glaucoma [35, 36].

FS can be diagnosed by tests such as cold provocation [21] on nail fold capillaries or gene expression of lymphocytes [37]. A fast and quite accurate method is a targeted patient history. To standardize this history, we use our questionnaire both clinically as well as for studies [38], including the present study.

The purpose of our study was a comparison of subjective perception of symptoms and signs related to FS between RP patients and controls.

Methods

Participants

In cooperation with and by courtesy of the Swiss RP-patients Association (Zürich, Switzerland) 130 questionnaires were sent to the members of this organization. Seventy-six RP patients (42 women and 34 men) completed the questionnaire and sent them back anonymously. At the same time, 274 control subjects (159 women and 115 men) visiting shopping centers were recruited and asked to fill out the same questionnaire also anonymously. In both groups, we did not use inclusion or exclusion criteria. In other words, both the controls and the RP patients were selected identically – the only difference between these groups was presence or absence of RP. The study was designed and conducted in accordance with the tenets of Declaration of Helsinki. All subjects completed the study with any complaints.

Table 1 The items asked in the Flammer Syndrome Questionnaire. The references in the list refer to publications describing the presence of the corresponding symptom or sign in FS.

<table>
<thead>
<tr>
<th>Symptoms and signs of Flammer syndrome</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold hands or/and feet</td>
<td>[24]</td>
</tr>
<tr>
<td>Reduced feeling of thirst</td>
<td>[49]</td>
</tr>
<tr>
<td>Low blood pressure</td>
<td>[50]</td>
</tr>
<tr>
<td>Dizziness</td>
<td>–</td>
</tr>
<tr>
<td>Increased response to certain drugs</td>
<td>[51]</td>
</tr>
<tr>
<td>Migraines</td>
<td>[52]</td>
</tr>
<tr>
<td>Headaches</td>
<td>–</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>[53]</td>
</tr>
<tr>
<td>Low body weight</td>
<td>[25–27]</td>
</tr>
<tr>
<td>Feeling cold</td>
<td>[54]</td>
</tr>
<tr>
<td>Long sleep onset time</td>
<td>[55]</td>
</tr>
<tr>
<td>Good smell perception</td>
<td>[56]</td>
</tr>
<tr>
<td>Increased pain sensation</td>
<td>[57]</td>
</tr>
<tr>
<td>Reversible skin blotches (red or white)</td>
<td>[28]</td>
</tr>
<tr>
<td>Tendency towards perfectionism</td>
<td>[28]</td>
</tr>
</tbody>
</table>
Questionnaire
The questionnaire (Flammer Syndrome Questionnaire) consisted of 15 multiple-choice items with the following choices: “often”, “sometimes”, “never”, or “I do not know”. The items asked in the questionnaire are listed in Table 1. The references in the list refer to publications describing the presence of the corresponding symptom or sign in FS.

Statistical analysis
In order to study the effect of questionnaire items on RP patients compared to control subjects, logistic regression analysis was performed, with each item as a predictor. The most positive answer category was compared to the combined rest answer categories (e.g. “sometimes”, “never”, “I do not know”). Results are reported as odds ratios (ORs) and 95% confidence intervals (CIs), with corresponding p-values. Results are sorted by differences between the two groups, beginning with the largest one. Ratios greater than 1.0 indicate higher frequency of the symptom or sign in RP patients than in controls.

Results
Each questionnaire item was compared between RP patients and controls. The results are reported as odds ratios and sorted by difference between the two groups, beginning with the largest one p-values. Results are sorted by differences between the two groups, beginning with the largest one. Ratios greater than 1.0 indicate higher frequency of the symptom or sign in RP patients than in controls.

Discussion
The present study indicates that most symptoms and signs characteristic for FS occur more often in RP patients than in controls. As FS is associated with altered OBF [20,21], it is likely, although not proven, that the earlier reported alterations of OBF in RP patients are not only secondary to the retinal degeneration but partly also due to a primary component.

The items in our questionnaire are based on the present knowledge of FS. It is therefore possible that other symptoms and signs, not yet described in the literature, will also be important. In addition, the questionnaire only provides clues on subjective perceptions and may not always be related to objective differences.
Nevertheless, the fact that the RP patients declared themselves different from controls subjects is interesting. An increased frequency of headaches [40] and tinnitus [41] has already been reported. The fact that RP patients report even less often skin blanching might be related to the visual disturbances.

We can only hypothesize why FS may occur more often in RP patients. Genetic mutations leading to RP may also cause symptoms of FS or an independent occurrence of FS in subjects with a genetic predisposition to RP may increase the risk for the manifestation of the phenotype. We know that FS increases oxidative stress [42], and this, in turn, may contribute to the RP damage [43]. This assumption is supported by the observation of reduced ocular antioxidants and an imbalance of the antioxidant-oxidant status in the peripheral blood of RP patients [44].

Our findings, if confirmed by future studies, have some potential implications for RP patients in terms of lifestyle, nutrition and treatment. Although FS seems to have a certain genetic background, environmental factors such as nutrition, BMI or physical activity influence the magnitude of the symptoms which are triggered by factors such as emotional stress or coldness. The symptoms can be mitigated by treatment, such as magnesium [45], low-dose CCBs [46], omega-3 fatty acids [47,48], and others. The oxidative stress can be mitigated by an antioxidative nutrition and antioxidants such as ginkgo biloba [21].

Conclusions

We provide a first indication for an association between RP and FS. This relationship needs to be confirmed in future studies with the help of objective parameters such as cold-provocation tests. If confirmed, the cause of this relationship and its impact on manifestation and progression of RP as well as the therapeutic consequences should be established.

Acknowledgements

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Conflict of Interest

None.

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