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

Schlüsselwörter
- Retinitis pigmentosa
- Flammer-Syndrom
- Endothelin
- Augendurchblutung
- vaskuläre Dysregulation

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. The purpose of the present study was to determine, with the help of a questionnaire, whether symptoms of Flammer syndrome occur more often in patients with retinitis pigmentosa than in controls.

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

Hintergrund: Retinitis pigmentosa umfasst eine Gruppe genetisch bedingter, degenerativer Augenerkrankungen. Das Flammer-Syndrom umfasst die primäre vaskuläre Dysregulation zusammen mit weiteren vaskulären und nicht-vaskulären Symptomen und Zeichen. Das Ziel dieser Studie war es, mit Hilfe eines Fragebogens zu prüfen, ob die Symptome des Flammer-Syndroms bei Patienten mit Retinitis pigmentosa häufiger oder seltener sind, als bei Kontroll-Personen.

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 Symptomen oder Zeichen waren nicht signifikant seltener bei Patienten mit Retinitis pigmentosa.

Schlussfolgerungen: Patienten mit Retinitis pigmentosa haben Symptome und Zeichen des Flammer-Syndroms häufiger als Kontroll-Personen. Signifikant häufiger sind ein tiefer BMI, tiefer Blutdruck, schnelles Frieren, Migräne, erhöhte Empfindlichkeit auf Gerüche und Perfektionismus. Der Grund dieser Zusammenhänge ist noch unklar und potentielle Folgen sind Gegenstand zukünftiger Untersuchungen.

Bibliography
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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 retrooocular 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 retrooocular 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 retrooocular 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**.

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.

Symptoms and signs of Flammer syndrome	Reference(s)
Cold hands or/and feet	[24]
Reduced feeling of thirst	[49]
Low blood pressure	[50]
Dizziness	–
Increased response to certain drugs	[51]
Migraines	[52]
Headaches	–
Tinnitus	[53]
Low body weight	[25–27]
Feeling cold	[54]
Long sleep onset time	[55]
Good smell perception	[56]
Increased pain sensation	[57]
Reversible skin blotches (red or white)	[28]
Tendency towards perfectionism	[28]

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 without any complaints.

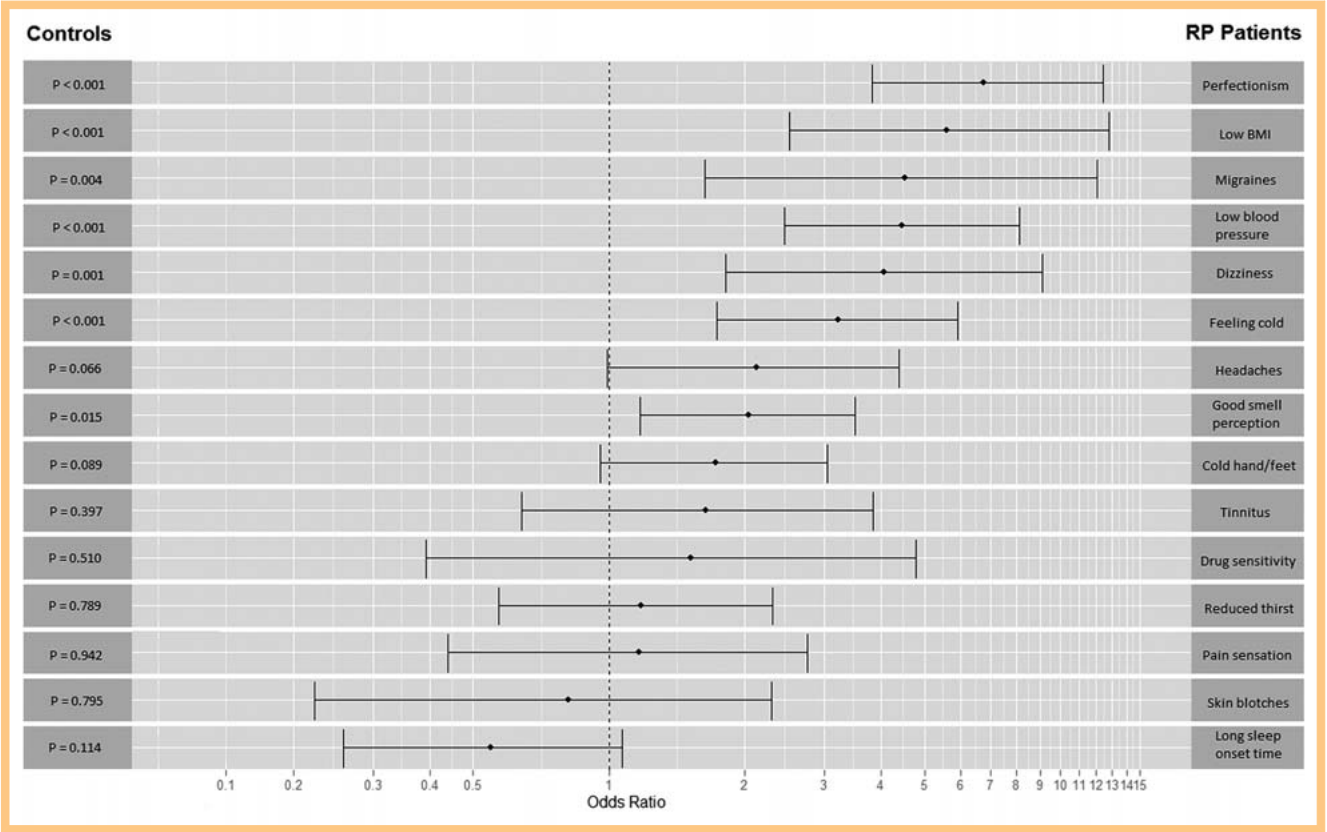

Fig. 1 Frequency of symptoms and signs of Flammer syndrome in patients with retinitis pigmentosa (RP) (n = 76) in comparison to controls (n = 274). For each of the questionnaire items listed in **Table 1**, results are presented as odds ratios (ORs) and 95% confidence intervals (CIs), with corresponding p-values. Results are sorted by differences between the two groups, beginning with the largest one. Ratios greater than 1.0 indicate that the symptom or sign occurs more often, and ratios less than 1.0 indicate that the symptom or sign occurs less often in RP patients than in controls.

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 (OR) and 95% confidence intervals (CI), with corresponding p-values. Additionally, age, gender, and a possible interaction between gender and item were included in the regression models.

A p-value < 0.05 was considered significant. This study was exploratory; therefore, p-values were not adjusted for multiple comparisons. All analyses were done using R version 2.12.0 [39].

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 (**Fig. 1**). Ratios greater than 1.0 indicate higher frequency of the symptom or sign in RP patients, and ratios less than 1.0 indicate higher frequency of the symptom or sign in controls.

Seven of 15 symptoms and signs of FS were significantly more often positive in RP patients than in controls. Six additional symptoms and signs also tended to occur more often in RP patients (not significant), whereas two symptoms and signs tended to occur less often in RP patients (not significant).

No significant interactions between gender and questionnaire items were found (p > 0.1); therefore, these interactions were removed from the regression models. Age and gender altered ORs only very slightly and not significantly. Therefore, ORs were not adjusted for age and gender.

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 blotches 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.

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Conflict of Interest

None.

References

1 *Kajiwara K, Berson EL, Dryja TP.* Digenic retinitis pigmentosa due to mutations at the unlinked peripherin/RDS and ROM1 loci. Science 1994; 264: 1604–1608
2 *Mansergh FC, Millington-Ward S, Kennan A et al.* Retinitis pigmentosa and progressive sensorineural hearing loss caused by a C12258A mutation in the mitochondrial MTTS2 gene. Am J Hum Genet 1999; 64: 971–985
3 *Ferrari S, Di Iorio E, Barbaro V et al.* Retinitis pigmentosa: genes and disease mechanisms. Curr Genomics 2011; 12: 238–249
4 *Grunwald JE, Maguire AM, Dupont J.* Retinal hemodynamics in retinitis pigmentosa. Am J Ophthalmol 1996; 122: 502–508
5 *Falsini B, Anselmi GM, Marangoni D et al.* Subfoveal choroidal blood flow and central retinal function in retinitis pigmentosa. Invest Ophthalmol Vis Sci 2011; 52: 1064–1069
6 *Cellini M, Strobbe E, Gizzi C et al.* ET-1 plasma levels and ocular blood flow in retinitis pigmentosa. Can J Physiol Pharmacol 2010; 88: 630–635
7 *Polak K, Petternel V, Luksch A et al.* Effect of endothelin and BQ123 on ocular blood flow parameters in healthy subjects. Invest Ophthalmol Vis Sci 2001; 42: 2949–2956
8 *Cellini M, Santiago L, Versura P et al.* Plasma levels of endothelin-1 in retinitis pigmentosa. Ophthalmologica 2002; 216: 265–268
9 *Vingolo EM, Lupo S, Grenga PL et al.* Endothelin-1 plasma concentrations in patients with retinitis pigmentosa. Regul Pept 2010; 160: 64–67
10 *Finzi A, Cellini M, Strobbe E et al.* ET-1 plasma levels, choroidal thickness and multifocal electroretinogram in retinitis pigmentosa. Life Sci 2014; 118: 386–390
11 *Todorova MG, Josifova T, Konieczka K.* Endothelin-1 Plasma Levels in Patients with both Retinitis Pigmentosa and Flammer Syndrome. Klin Monbl Augenheilkd 2015; 232: 514–518
12 *Ohguro H, Mashima Y, Nakazawa M.* Low levels of plasma endothelin-1 in patients with retinitis pigmentosa. Clin Ophthalmol 2010; 4: 569–573
13 *Strobbe E, Cellini M, Fresina M et al.* ET-1 Plasma Levels, Aqueous Flare, and Choroidal Thickness in Patients with Retinitis Pigmentosa. J Ophthalmol 2015; 2015: 292615
14 *Nakazawa M, Ohguro H, Takeuchi K et al.* Effect of nilvadipine on central visual field in retinitis pigmentosa: a 30-month clinical trial. Ophthalmologica 2011; 225: 120–126
15 *Liang SY, Lee LR.* Retinitis pigmentosa associated with hypomagnesaemia. Clin Experiment Ophthalmol 2010; 38: 645–647
16 *Meyer P, Lang MG, Flammer J et al.* Effects of calcium channel blockers on the response to endothelin-1, bradykinin and sodium nitroprusside in porcine ciliary arteries. Exp Eye Res 1995; 60: 505–510
17 *Dettmann ES, Luscher TF, Flammer J et al.* Modulation of endothelin-1-induced contractions by magnesium/calcium in porcine ciliary arteries. Graefes Arch Clin Exp Ophthalmol 1998; 236: 47–51
18 *Konieczka K, Flammer AJ, Todorova M et al.* Retinitis pigmentosa and ocular blood flow. EPMA J 2012; 3: 17
19 *Sorrentino FS, Bonifazzi C, Perri P.* The Role of the Endothelin System in the Vascular Dysregulation Involved in Retinitis Pigmentosa. J Ophthalmol 2015; 2015: 405234
20 *Konieczka K, Ritch R, Traverso CE et al.* Flammer syndrome. EPMA J 2014; 5: 11
21 *Flammer J, Konieczka K, Flammer AJ.* The primary vascular dysregulation syndrome: implications for eye diseases. EPMA J 2013; 4: 14
22 *Flammer J, Konieczka K, Bruno RM et al.* The eye and the heart. Eur Heart J 2013; 34: 1270–1278
23 *Saner H, Wurbel H, Mahler F et al.* Microvasculatory evaluation of vasospastic syndromes. Adv Exp Med Biol 1987; 220: 215–218
24 *Guthauser U, Flammer J, Mahler F.* The relationship between digital and ocular vasospasm. Graefes Arch Clin Exp Ophthalmol 1988; 226: 224–226
25 *Mozaffarieh M, Fontana Gasio P, Schotzau A et al.* Thermal discomfort with cold extremities in relation to age, gender, and body mass index in a random sample of a Swiss urban population. Popul Health Metr 2010; 8: 17
26 *Kavroulaki D, Gugleta K, Kochkorov A et al.* Relation of body mass index and blood pressure to subjective and objective acral temperature. Klin Monbl Augenheilkd 2009; 226: 328–331
27 *Gasser P, Stumpfig D, Schotzau A et al.* Body mass index in glaucoma. J Glaucoma 1999; 8: 8–11
28 *Flammer J.* Glaucoma. 3rd edn. Bern: Hogrefe & Huber; 2006
29 *Emre M, Orgul S, Gugleta K et al.* Ocular blood flow alteration in glaucoma is related to systemic vascular dysregulation. Br J Ophthalmol 2004; 88: 662–666
30 *Kochkorov A, Gugleta K, Zawinka C et al.* Short-term retinal vessel diameter variability in relation to the history of cold extremities. Invest Ophthalmol Vis Sci 2006; 47: 4026–4033
31 *Oettli A, Gugleta K, Kochkorov A et al.* Rigidity of retinal vessel in untreated eyes of normal tension primary open-angle glaucoma patients. J Glaucoma 2011; 20: 303–306
32 *Gugleta K, Zawinka C, Rickenbacher I et al.* Analysis of retinal vasodilation after flicker light stimulation in relation to vasospastic propensity. Invest Ophthalmol Vis Sci 2006; 47: 4034–4041
33 *Gugleta K, Kochkorov A, Waldmann N et al.* Dynamics of retinal vessel response to flicker light in glaucoma patients and ocular hypertensives. Graefes Arch Clin Exp Ophthalmol 2012; 250: 589–594

34 *Fang L, Baertschi M, Mozaffarieh M.* The effect of flammer-syndrome on retinal venous pressure. BMC Ophthalmol 2014; 14: 121
35 *Flammer J, Orgul S, Costa VP et al.* The impact of ocular blood flow in glaucoma. Prog Retin Eye Res 2002; 21: 359–393
36 *Konieczka K, Frankl S, Todorova MG et al.* Unstable oxygen supply and glaucoma. Klin Monbl Augenheilkd 2014; 231: 121–126
37 *Yeghiazaryan K, Flammer J, Orgul S et al.* Vasospastic individuals demonstrate significant similarity to glaucoma patients as revealed by gene expression profiling in circulating leukocytes. Mol Vis 2009; 15: 2339–2348
38 *Konieczka K, Choi HJ, Koch S et al.* Frequency of symptoms and signs of primary vascular dysregulation in Swiss and Korean populations. Klin Monbl Augenheilkd 2014; 231: 344–347
39 *Team RDC.* R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2012
40 *Heckenlively JR, Yoser SL, Friedman LH et al.* Clinical findings and common symptoms in retinitis pigmentosa. Am J Ophthalmol 1988; 105: 504–511
41 *Iwasaki S, Maruyama Y, Hotta Y et al.* Survey in to the prevalence of hearing loss in patients diagnosed with retinitis pigmentosa. Int Ophthalmol 2004; 25: 277–282
42 *Mozaffarieh M, Schoetzau A, Sauter M et al.* Comet assay analysis of single-stranded DNA breaks in circulating leukocytes of glaucoma patients. Mol Vis 2008; 14: 1584–1588
43 *Komeima K, Rogers BS, Lu L et al.* Antioxidants reduce cone cell death in a model of retinitis pigmentosa. Proc Natl Acad Sci U S A 2006; 103: 11300–11305
44 *Martinez-Fernandez de la Camara C, Salom D, Sequedo MD et al.* Altered antioxidant-oxidant status in the aqueous humor and peripheral blood of patients with retinitis pigmentosa. PLoS One 2013; 8: e74223
45 *Gaspar AZ, Gasser P, Flammer J.* The influence of magnesium on visual field and peripheral vasospasm in glaucoma. Ophthalmologica 1995; 209: 11–13
46 *Strenn K, Matulla B, Wolzt M et al.* Reversal of endothelin-1-induced ocular hemodynamic effects by low-dose nifedipine in humans. Clin Pharmacol Ther 1998; 63: 54–63
47 *Nyby MD, Hori MT, Ormsby B et al.* Eicosapentaenoic acid inhibits Ca2+ mobilization and PKC activity in vascular smooth muscle cells. Am J Hypertens 2003; 16: 708–714
48 *Shirao S, Fujisawa H, Kudo A et al.* Inhibitory effects of eicosapentaenoic acid on chronic cerebral vasospasm after subarachnoid hemorrhage: possible involvement of a sphingosylphosphorylcholine-rho-kinase pathway. Cerebrovasc Dis 2008; 26: 30–37
49 *Teuchner B, Orgul S, Ulmer H et al.* Reduced thirst in patients with a vasospastic syndrome. Acta Ophthalmol Scand 2004; 82: 738–740
50 *Gherghel D, Orgul S, Gugleta K et al.* Retrobulbar blood flow in glaucoma patients with nocturnal over-dipping in systemic blood pressure. Am J Ophthalmol 2001; 132: 641–647
51 *Wunderlich K, Zimmerman C, Gutmann H et al.* Vasospastic persons exhibit differential expression of ABC-transport proteins. Mol Vis 2003; 9: 756–761
52 *Gasser P, Meienberg O.* Finger microcirculation in classical migraine. A video-microscopic study of nailfold capillaries. Eur Neurol 1991; 31: 168–171
53 *Palmer KT, Griffin MJ, Syddall HE et al.* Raynaud's phenomenon, vibration induced white finger, and difficulties in hearing. Occup Environ Med 2002; 59: 640–642
54 *Krauchi K, Deboer T.* The interrelationship between sleep regulation and thermoregulation. Front Biosci 2010; 15: 604–625
55 *Pache M, Krauchi K, Cajochen C et al.* Cold feet and prolonged sleep-onset latency in vasospastic syndrome. Lancet 2001; 358: 125–126
56 *Mozaffarieh M, Hauenstein D, Schoetzau A et al.* Smell perception in normal tension glaucoma patients. Mol Vis 2010; 16: 506–510
57 *Pache M, Ochs J, Genth E et al.* Increased plasma endothelin-1 levels in fibromyalgia syndrome. Rheumatology (Oxford) 2003; 42: 493–494