The pathogenesis of optic disc splinter haemorrhages: a new hypothesis

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ABSTRACT.
Purpose: **To describe a hypothesized relationship between optic disc haemorrhages (ODHs) and primary vascular dysregulation (PVD).**
Methods: **Observational case report of a patient with classical PVD and five bilateral recurrent ODHs**
Results: **The ODHs were superotemporal in the right eye and inferotemporal in the left; the eyes were otherwise normal. Intraocular pressure (IOP) never exceeded 17 mmHg. Visual fields were normal. Increased blood flow resistivity, a reduced blood flow of the extraocular vessels, a low systemic blood pressure, a cold-induced flow stop of the nailfold capillaries, and elevated endothelin-1 plasma levels were found, all confirming the diagnosis of vascular dysregulation.**
Conclusions: **Optic disc haemorrhages may be due to a disturbed blood–retina barrier rather than to a mechanical rupture of the vessel. This barrier dysfunction may occur in the context of PVD.**

Key words: blood–retinal barrier – endothelin – glaucoma – matrix metalloproteinase – optic disc haemorrhage – vascular dysregulation

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Introduction

Optic disc splinter haemorrhages (ODHs) have been known for over 100 years (Bjerrum 1889). Typically, they are of small size and appear at the border of the optic disc. While the prevalence is low in healthy subjects, they occur quite frequently in glaucoma, particularly in normal-tension glaucoma (NTG) (Healey et al. 1998). The majority of ODHs tend to recur in the same region of the disc within 2 years (Drance & Begg 1970; Bengtsson et al. 1981; Kitazawa et al. 1986), and are often correlated with focal visual field progression (Ishida et al. 2000).

The pathogenesis of the ODH, however, is not yet fully understood. Various hypotheses of an underlying haemodynamic disturbance have been postulated. These include pulsatile pressure variations inside the rigid sclera, as well as turbulence due to abrupt pressure changes (Bito 1996). Presumed imbalance of intraocular pressure (IOP), venous pressure, flow velocity and unstable closing pressure with a risk of collapse of the smallest vessels in the optic disc have also been proposed as causative factors (Sonnsjo et al. 2002). Nevertheless, the abovementioned hypotheses do not explain which vessels ODHs originate from (arteriole, venule or capillary), nor why they are located at the border of the optic disc with a predilection for the superotemporal and inferotemporal regions. Why are ODHs more common in patients with NTG than in those with high-tension glaucoma (HTG) (Kitazawa et al. 1986; Siegner & Netland 1996; Healey et al. 1998), and what are the triggers for recurrences?

We present here a new hypothesis of the pathogenesis of ODHs. We do this by describing recurrent bilateral ODH in a subject with well documented primary vascular dysregulation (PVD). Primary vascular dysregulation is characterized by both inappropriate arteriolar constriction (vasospasm) and inadequate venous dilation when triggered by a challenge (e.g. coldness, physical or emotional stress) (Flammer et al. 2001). It occurs in many organs and in vessels of different sizes, with a predilection for the microcirculation. Although the pathophysiology of PVD is not fully known, there is evidence for both autonomic nerve dysfunction (Gherghel et al. 2004) and vascular endothelial cell dysfunction (Buckley et al. 2002). Subjects with the diathesis for PVD often have cold hands, low blood pressure, decreased sensation of thirst (Teuchner et al. 2004) and an elevated level of plasma endothelin-1 (ET-1) (Flammer et al. 2001). The syndrome occurs more frequently in females than in males (Prünte-Glowazki & Flammer 1991). Our observation of ODH in a patient

with PVD (Gasser & Flammer 1991) is of interest as both ODH and PVD have been associated with an increased risk for glaucomatous optic neuropathy, in particular for NTG.

Materials and Methods

A 49-year-old woman was referred to us with a history of five bilateral recurrent ODHs, photographically documented over a period of 2 years (Figs 1 and 2). She had no other ocular diseases and IOP was always within the normal range. She had, however, clear symptoms indicating vascular dysregulation: cold hands and feet; prolonged sleep-onset latency; migraine; low systemic blood pressure, and a reduced feeling of thirst. During her stay in the hospital, her IOP was measured during the day and night for 2 consecutive days. We used a Goldmann applanation tonometer during the day (from 06.00 hours to 22.00 hours), and a Perkins tonometer for the measurements at night when the patient was in supine position (from 22.00 hours to 06.00 hours). For systemic blood pressure measurements, a 24-hour blood pressure monitor (Mobil-O-Graph; IEM GmbH, Stolberg, Germany) was used. During the daytime (from 08.00 hours to 22.00 hours) and at night (from 22.00 hours to 08.00 hours) the measurement intervals were 30 mins. The patient underwent a nailfold capillaroscopy, as described previously (Mahler et al. 1989; Gasser & Flammer 1991). Briefly, a light microscope is linked to a television monitor that is in turn linked to a video recorder, allowing the observed blood flow to be videotaped for later analysis. During capillaroscopy, the nailfold area is cooled for 60 seconds by rapidly decompressing carbon dioxide at $-15\,^{\circ}$. The examination is performed in a room at a steady temperature of about $23\,^{\circ}$. During cooling, the blood in the capillaries is slowed down and sometimes stops. Digital vasospasm is defined when blood flow in one or more visible capillaries stops for longer than 12 seconds. Furthermore, the blood flow velocity of the subject's ophthalmic artery (OA) and central retinal artery (CRA) was measured by means of a colour Doppler imaging (CDI) device (Siemens, Zürich, Switzerland) as described previously (Kaiser et al. 1996). During the examination, the patient remained in the supine position, with the upper body tilted upwards at an angle of about 30 degrees. Peak systolic velocity (PSV), defined as the highest velocity of blood flow during the systolic phase of the cardiac cycle, and end diastolic velocity (EDV), defined as the velocity of blood flow at the end of the diastolic phase of the cardiac cycle, were measured in each vessel in both eyes. Choroidal blood flow assessment was performed by means of choroidal laser Doppler flowmetry (LDF). The principle of this method has been described in detail elsewhere (Geiser et al. 1999; Gugleta et al. 2003).

Results

Best corrected visual acuity (VA) was 20/20 and anterior chamber angles were open. The optic disc was physiologically excavated with a cup : disc ratio of 0.4. The ODHs were superotemporal in the right eye and inferotemporal in the left eye and recurred in the same location (Figs 1 and 2). In the stereometric analysis of the optic disc by Heidelberg retina tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany), all parameters measured were within normal limits according to the Moorfields regression classification (Wollstein et al. 1998). The macula and retinal periphery in both eyes were without any pathologies.

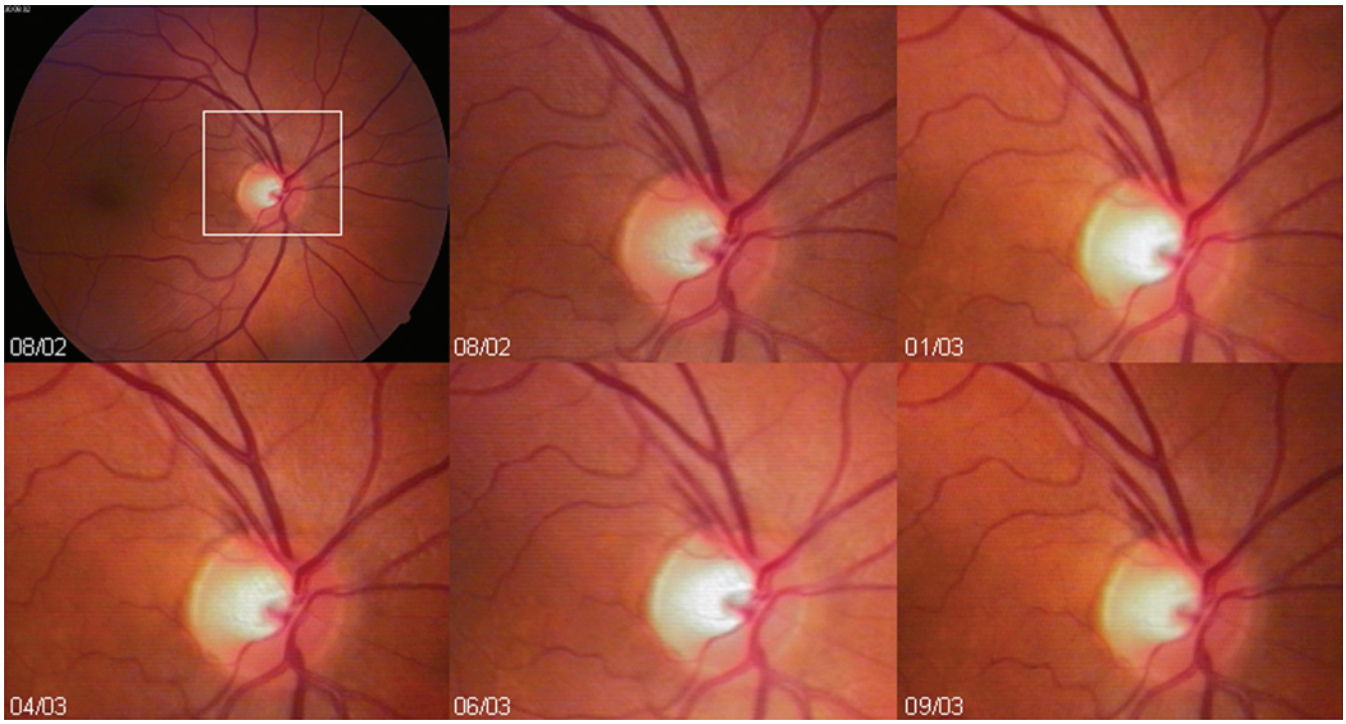

Fig. 1. Colour fundus photography of the right eye showing recurrent haemorrhages at the optic disc margin in the superotemporal quadrant in chronological sequence (from top left to bottom right).

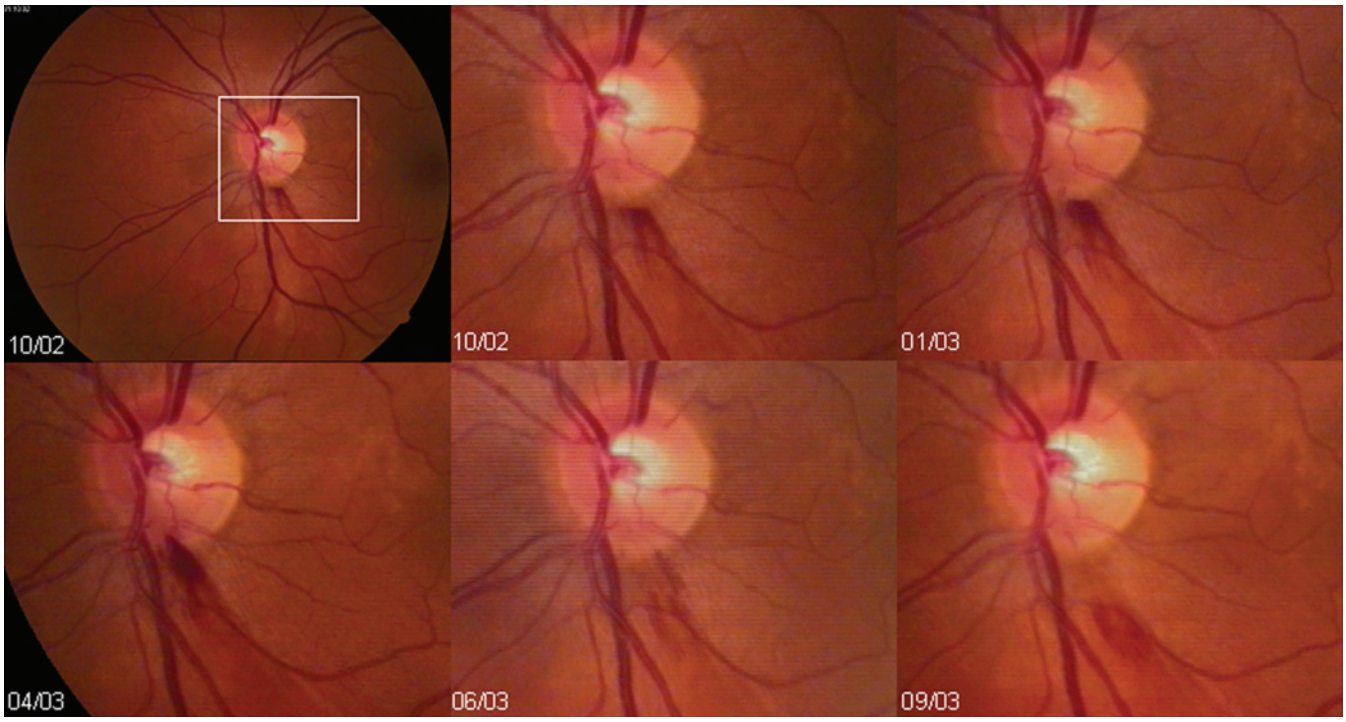

Fig. 2. Colour fundus photography of the left eye showing recurrent optic disc haemorrhages in the inferotemporal quadrant in chronological sequence (from top left to bottom right).

The IOP measurements, including several diurnal and nocturnal curves, never exceeded 17 mmHg (Fig. 3). The central corneal thickness was 520 µm in the right and 530 µm in the left eye. The 24-hour blood pressure monitoring showed a mild systemic hypotension, with the lowest measurements at night being 87 mmHg systolic and 51 mmHg diastolic. The nailfold capillaroscopy with local cold exposure test showed a cold-induced flow stop in four out of five measured capillaries for a mean duration of 92 seconds, a typical finding of vascular dysregulation (normal reference: <12 seconds in one capillary at the most). While healthy, non-vasospastic controls show an increase in blood flow during isometric exercise in choroidal laser Doppler flowmetry, an inverse response was found here (Table 1). In addition, this test revealed a significant elevation of resistance in the choriocapillaris of 20% during the isometric hand-grip test, indicating choroidal vascular dysregulation. Peak systolic and diastolic velocities of the ophthalmic arteries and the lateral and medial ciliary arteries, measured with colour Doppler imaging, were significantly reduced (Table 2). The corresponding calculated resistivity indices were increased. Visual fields, measured with the Octopus program G2, were normal. Endothelin-1 (ET-1) plasma levels, however, were slightly elevated (2.28 pg/ml; age- and gender-matched normal controls: 1.52 ± 0.24 pg/ml SD), supporting the diagnosis of vascular dysregulation. Otherwise, the serum and blood analyses were normal (Tables 3 and 4).

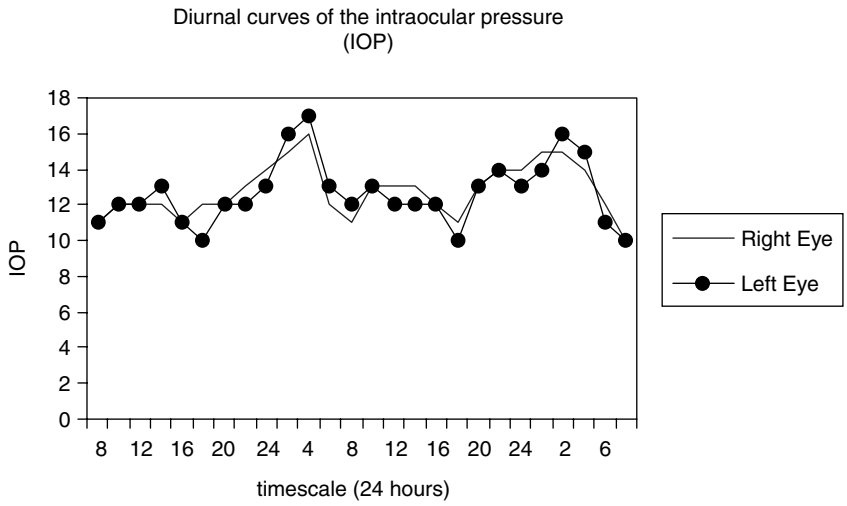

Fig. 3. Diurnal curves of intraocular pressure.

Discussion

Optic disc haemorrhages occur rarely in normal eyes, but are often found in glaucomatous eyes. At present, the pathogenesis of ODH is not known. We postulate that ODH may also be caused by PVD. To illustrate this, we reported recurrent bilateral ODH in a relatively young subject with PVD. Interestingly, ODH in this patient recurred at a stage where glaucomatous damage was not or not yet detectable and IOP not increased. The clinical characteristics of subjects with PVD has been described extensively elsewhere (Flammer et al. 2001). Briefly, it is an inappropriate response to stimuli such as stress or coldness. It

Table 1. Systemic haemodynamic and choroidal parameters.

	Vasospastic subject	Non-vasospastic* subject
At baseline		
SBP	97	123.30 ± 15.25
DBP	68	78.30 ± 8.69
MABP	77.66	93.30 ± 9.93
Flux (AU)	17.2	12.52 ± 8.26
After isometric exercise		
SBP	108	146.28 ± 16.29
DBP	71	88.33 ± 11.90
MABP	83.33	107.64 ± 11.47
Flux (AU)	15.4	13.70 ± 9.44
After 3 minutes of recovery		
SBP	86	136.42 ± 14.47
DBP	66	82.82 ± 7.99
MABP	72.66	100.69 ± 8.8
Flux (AU)	15.9	11.88 ± 7.12

SBP = systolic blood pressure; DBP = diastolic blood pressure; MABP = mean arterial blood pressure; AU = arbitrary units.
MABP = 2/3 × DBP + 1/3 × SBP.
* Normative data from Gugleta et al. (2003).

occurs more frequently in females than in males, and in Japanese than in white European patients (Beltrame et al. 1999) and apparently in intellectual people and people with low body mass index or of type A personality. Interestingly, ODH and PVD alike are linked to glaucoma and occur more often in patients with NTG than with HTG (Gasser & Flammer 1991; Healey et al. 1998).

To date, different causes for ODH have been described, but much is yet to be learned about its pathomechanism. Optic disc haemorrhage is often considered to be a consequence of microinfarction. The fact, however, that ODHs are not associated with cotton-wool spots (Jonas et al. 1999) and the corresponding visual field defects are either absent or follow weeks later (Heijl 1986; Bengtsson 1990), makes such an explanation rather unlikely. Increased IOP has also been claimed as a causal factor. This assumption does not explain the fact that ODH occurs up to four times more frequently in NTG than in HTG (Kitazawa et al. 1986; Siegner & Netland 1996; Healey et al. 1998). However, low IOP cannot be a risk factor either, as IOP-reducing therapy does not increase the frequency of ODH (Sonnsjo et al. 1991). The excavation of the optic disc was also affirmed to induce ODH mechanically.

Table 2. Blood flow velocities (cm/second) in the extraocular vessels.

	Right eye	Left eye	Normal range*
Ophthalmic artery			
PSV	30.0	29.7	32.7–49.1
EDV	4.3	4.6	5.4–13.0
RI	0.92	0.94	0.79–0.85
Central retinal artery			
PSV	9.0	8.7	9.0–14.1
EDV	3.4	2.6	2.1–4.7
RI	0.80	0.82	0.63–0.78
Short lateral posterior ciliary artery			
PSV	8.4	7.9	9.2–14.4
EDV	3.2	2.2	2.2–5.3
RI	0.84	0.81	0.60–0.77
Short medial posterior ciliary artery			
PSV	8.9	8.7	9.2–14.4
EDV	2.6	2.4	2.2–5.3
RI	0.85	0.82	0.60–0.77

PSV = peak systolic velocity; EDV = end diastolic velocity; RI = resistive index.
* From Kaiser et al. 1996

However, the fact that ODH occurs more frequently in early than in late stages of glaucoma (Airaksinen & Heijl 1983) and in NTG with predominantly shallow optic disc cupping than in HTG, also undermines this explanation. In addition, the limited and relatively small size of the ODH makes a mechanical rupture of an arteriolar blood vessel rather unlikely. Why would the bleeding always stop so quickly? Similarly, a venous congestion is unlikely to be causative in the above-described patient, because the retinal veins were neither dilated and nor was any systemic hypertension present.

How do we explain the postulated relationship between PVD and ODH? Increased levels of circulating ET-1 and matrix metalloproteinases-9 (MMP-9) may play a crucial role in the pathogenesis of both PVD and ODH. The level of ET-1, a tissue hormone with vasoactive properties, is increased in the circulating blood of both patients with PVD (Flammer et al. 2001) and patients with glaucoma (Kaiser et al. 1995; Emre et al. 2004). It is not yet totally clear why ET-1 is increased. However, it is known that an increased level of ET-1 can result from ischaemia/reperfusion (I/R) injuries (Vago et al. 2004; Kurata et al. 2005), which may occur in these patients in different organs, not only in the eye, thereby increasing ET-1 (e.g. silent myocardial ischaemia) (Waldmann et al. 1996; Flammer 2001; Bohm et al. 2004). Likewise, I/R injuries also lead to increased levels of MMP-9 (Lalu et al. 2005), which, like other MMPs, are involved in tissue remodelling (Chesler et al. 1999; Galis & Khatri 2002; Pages et al. 2003). In addition, MMP-9 has a particular effect on the basal membrane. Although MMP-9 was not evaluated here, we assume that it is increased, as it has been shown recently in NTG patients with PVD (Golubnitschaja et al. 2004). Most probably these two peptides (ET-1 and MMP-9) are, among others, involved in the pathogenesis of ODH.

But why does ODH occur at the border of the optic disc? Blood vessels of the retina form a barrier that is similar to the blood–brain barrier, consisting mainly of two components: the tight-junctions of the endothelial cells and the basal membrane. White blood cells are able to actively penetrate the wall of venules and blood

Table 3. Serum analysis.

	Patient	Reference	Units
S-Sodium	142	131–142	mmol/l
S-Potassium	3.9	3.5–5.0	mmol/l
S-Chloride	102	97–110	mmol/l
S-Creatinine	59	45–93	mmol/l
S-Urea	4.5	3.0–7.8	mmol/l
S-Bilirubin	12	5–18	μmol/l
S-AST	16	11–36	IU/l
S-ALT	21	10–37	IU/l
S-GGT	15	8–49	IU/l
S-ALP	81	31–108	IU/l
S-Calcium	2.35	2.10–2.65	mmol/l
S-Phosphate	1.19	0.80–1.50	mmol/l
S-Uric acid	214	173–359	μmol/l
S-Triglyceride	0.72	0.50–2.30	mmol/l
S-Cholesterol	5.09	3.00–5.20	mmol/l
S-HDL cholesterol	1.79	0.90–2.20	mmol/l
S-Chol/HDL cholesterol ratio	2.84	<5	–
S-LDL cholesterol	2.97	1.60–3.40	mmol/l
S-Total protein	69	62–80	g/l
S-Albumin	37	35–52	g/l
S-Globulin	32	18–34	g/l
CRP	1.0	<10.0	mg/l
S-Creatinkinase	75	38–157	IU/l
S-Amylase	31	13–53	IU/l

AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma glutamyl transferase; ALP = alkaline phosphatase; HDL = high density lipoproteins; LDL = low density lipoproteins; CRP = C-reactive protein.

Table 4. Blood analysis.

	Patient	Reference	Units
White blood cells	4.300	3.50–10.00	× 10e 9/l
Red blood cell count	4.29	4.20–5.40	× 10e 12/l
Haemoglobin	136	120–160	g/l
Haematocrit	0.39	0.36–0.46	l/l
MCV	90.8	79.0–95.0	fl
MCH	30.2	27.0–31.0	pg
MCHC	348	320–360	g/l
Platelets	353	150–450	× 10e 9/l
Lymphocytes	2.220	0.900–3.300	× 10e 9/l
Monocytes	0.180	0.120–0.620	× 10e 9/l
Neutrophils	1.550	1.300–6.700	× 10e 9/l
Eosinophils	0.190	0–0.300	× 10e 9/l
Basophils	0.040	0–0.090	× 10e 9/l
Apolipoprotein A1	1.5	1.2–2.1	g/l
Apolipoprotein B	0.9	0.5–1.2	g/l
Factor VII	71	60–150	%
APC resistance (V)	2.2	>2.1	Ratio
Antithrombin III	1.12	0.80–1.20	IU/ml
Protein C	>120	70–120	%
Total protein S	71	60–150	%
Free protein S	0.70	0.60–1.30	IU/ml
Protein S activity	73	50–120	%
Prothrombin genotype	Normal		
International normalized ratio	0.89	1.20	
Prothrombin time	32	20–45	Seconds
Quick	100	70–100	

MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration; APC = activated protein C.

plasma percolates the vessel when tight-junctions are partly opened. Red blood cells, however, can only pass the barrier on condition that both the tight-junctions of the endothelial cells and the basal membrane are weakened (Hamann et al. 1996). In tissues with an intact blood–brain barrier or blood–retinal barrier, circulating ET-1 has access only to the endothelial cell layer. However, if the barrier is incomplete, ET-1 diffuses into surrounding tissue and has direct access to small muscle cells or pericytes. In addition, ET-1 in the tissue leads to a local up-regulation of prostaglandin-E2 (Shimada et al. 2000; Miceli et al. 2001), which in turn reduces the barrier function at the level of the endothelial tight-junctions (Bhattacherjee et al. 2002; Derevjanik et al. 2002). MMP-9, on the other hand, is able to degrade the basal membrane of the vascular wall (Pages et al. 2003). The reduced function of tight-junctions and weakness of the basal membrane may, in extreme situations, grant access for erythrocytes to extravascular tissue. Indeed, MMP-9 is associated with blood–brain barrier opening after I/R injury (Rosenberg et al. 1998). According to current physiological knowledge, the microvessels in the prelaminar region of the optic disc lack classical blood–brain barrier properties and display non-specific permeability (Hofman et al. 2001). In addition, ET-1 and MMP-9 may diffuse from the fenestrated capillaries of the choroid into the neighbouring retinal tissue, reaching the peri- and epipapillary vessels from the abluminal side. Such diffusion may be enhanced in the presence of a chorioretinal atrophy and may explain the close association of peripapillary atrophy and ODH (Ahn et al. 2004). It is our hypothesis that the basal membrane must be weakened by an up-regulation of MMP-9 and the endothelial barrier must be disturbed by elevated ET-1 via prostaglandin-E2 at the same time in order to cause an optic disc haemorrhage. Patients with PVD do not have permanently high levels of ET-1, and both MMP-9 and ET-1 levels also fluctuate. In addition, the diffusion rate in the surrounding tissue of the optic disc may vary as well. Thus, the probability that both peptides reach sufficiently high levels at the same time and the same location

might be relatively low, explaining the frequency of ODH.

In conclusion, we hypothesize that a simultaneous increase of ET-1 and MMP-9 in the surrounding tissue of retinal vessels may lead to an impairment of the blood–retinal barrier at the border of the optic disc. A leakage in the area of the optic disc has indeed been demonstrated in fluorescein angiography (Arend et al. 2005). Under extreme circumstances, the impairment of the blood–retinal barrier might be so pronounced that even red blood cells escape the vessels. Extravascular blood may then induce secondary damage to the tissue, including the retinal nerve fibres, and this tissue damage may in turn become a further risk factor for recurrent haemorrhages (Borel et al. 2003). Our hypothesis that ODH might be a manifestation of PVD may explain the higher frequency of ODH in NTG than in HTG, in females than in males, in early rather than in late glaucoma or even before manifest glaucoma. In addition, it may explain its predilection for the border of the optic disc, its frequent association with chorioretinal atrophy, as well as the recurrence of ODH. Finally, it may explain the fact that an increased level of ET-1 (Emre et al. 2005) and likewise the presence of ODH (Ishida et al. 2000; Ahn & Park 2002) are both risk indicators for progression of glaucoma.

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