Photoreceptor Damage in Terson Syndrome

Tomasz Szeligowski BMBCh BA[1], Dun J. Fu BMBCh PhD[1], Noa Fernandez-Ledo MD[1], Johannes Birtel MD MBA[1,2,3], Sher A. Aslam DPhil FRCOphth[1], Chetan K. Patel MSc FRCOphth[1], Kanmin Xue PhD FRCOphth[1,2,#], Peter Charbel Issa DPhil FEBO[1,2,#]

1. Oxford Eye Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom
2. Nuffield Laboratory of Ophthalmology, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom
3. Department of Ophthalmology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[#] These authors contributed equally

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[#] Corresponding authors:
Oxford Eye Hospital
John Radcliffe Hospital
Oxford OX3 9DU
United Kingdom
Telephone: +44 1865 234 737
E-mail: study-enquiry@outlook.com

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Summary Statement

In Terson syndrome, photoreceptor damage may be observed that shows poor spatial correlation with sub-internal limiting membrane haemorrhage. Photoreceptor damage may be a distinct manifestation of Terson syndrome, which is not addressed by surgical interventions.

Abstract

Purpose: To describe photoreceptor damage in patients with Terson syndrome as a potential cause for inconsistent clinical outcomes.

Methods: Clinical evaluation and retinal imaging in six patients

Results: Four patients were female and two male, with an average age of 46.8 years (SD 8.9). Four patients suffered aneurysmal subarachnoid haemorrhage, one vertebral artery dissection, and one superior sagittal sinus thrombosis. In 11 eyes, we observed a consistent pattern of outer retinal damage within the central macula affecting the ellipsoid zone and the outer nuclear layer, indicating photoreceptor damage. Areas of photoreceptor damage showed poor spatial correlation with intraocular haemorrhage, particularly sub-internal limiting membrane haemorrhage. The observed retinal abnormalities demonstrated incomplete recovery over long-term follow-up 3.5 to 8 years post-haemorrhage, irrespective of surgical or conservative treatment strategy, and had variable impact on the patients' visual function.

Conclusion: The observations suggest that photoreceptor damage in Terson syndrome likely represents a distinct manifestation of this condition, which could be caused by transient ischaemia resulting from disturbed choroidal venous outflow secondary to acute rise in intracranial pressure.

Terson syndrome (TS) is defined as intraocular haemorrhage secondary to an acute rise in intra-cranial pressure (ICP), commonly caused by subarachnoid haemorrhage (SAH) or traumatic brain injury.[1] The reported incidence of TS in SAH varies from 0.86%[2] to 16.7%.[3] This discrepancy is partly explained by underdiagnosis, as indicated by the higher frequency reported in prospective studies.[4] The occurrence of TS may result in severe visual impairment, making effective treatment of TS an important aspect of improving the care of patients with SAH.

Pars plana vitrectomy remains the mainstay treatment of TS and offers significant benefit in cases where intraocular haemorrhage does not clear over time, or where rapid resolution to the obscuration of the visual axis is needed to achieve acceptable visual function. However, previous studies have found discrepancies in final visual acuity (VA) with surgical management along with inconsistent evidence for the benefit of early surgery, which indicates that intraocular haemorrhage may not be the only pathology limiting visual function in TS. [5,6,7,8,9]

In this study, we investigate a potential structural cause for inconsistencies in treatment outcomes for patients with TS. We observed changes in the photoreceptor layer which showed poor spatial correlation with the locations of characteristic inner retinal haemorrhages and incomplete recovery over time irrespective of the treatment approach. Our observations suggest that photoreceptor damage can occur independent of intraocular haemorrhage in TS, possibly secondary to transient disruption to choroidal blood flow which may occur in the early stages of SAH as a result of acute rise in ICP.

Methods

This retrospective case series includes patients diagnosed with TS at Oxford University Hospitals in Oxford, UK. As our overall cohort of TS patients was too small to estimate the prevalence of photoreceptor damage, we only selected patients displaying outer retinal changes. The study adhered to the tenets of the Declaration of Helsinki with patient consents for publication.

All data was obtained from routine care, which is reflected in the variability of follow-up length and imaging modalities available. For all patients, spectral domain optical coherence tomography (OCT) and confocal near-infrared (NIR) reflectance imaging (Spectralis HRA-OCT, Heidelberg Engineering, Heidelberg, Germany) are provided. Ultra-widefield scanning laser ophthalmoscopy (Optos, Dunfermline, UK) was also used (Supplementary Figures only).

Results

This study includes 6 patients with TS whose basic demographic and clinical information is provided in **Table 1.** Five eyes of four patients underwent pars plana vitrectomy - 2 for clearance of vitreous haemorrhage, 1 for removal of sub- internal limiting membrane (ILM) haemorrhage, and 2 for a combination of both.

In 11 eyes of the 6 patients, OCT imaging showed a consistent pattern of photoreceptor layer abnormalities, including outer nuclear layer (ONL) thinning and disruption or reduced reflectivity of the ellipsoid zone (EZ) (**Figure 1; Supplemental Digital Content Figures S1-S5**). Affected areas could be appreciated on NIR reflectance images as well-defined areas of hypo-reflectance, mainly affecting the central macula, that varied both in size and shape.

If sub-ILM haemorrhages were present (5 eyes), they showed poor spatial correspondence with areas of outer retinal damage (**Figure 2, Supplemental Digital Content Figures S3-S4**). Although outer retinal damage was observed in areas not affected by sub-ILM haemorrhage, it was also seen overlapping with it (**Supplemental Digital Content Figures S1 and S3**). In two patients, bilateral macular outer retinal damage was observed despite unilateral sub-ILM haemorrhage (**Supplemental Digital Content Figures S1 and S5**).

Long-term observation of 3 patients revealed considerable but incomplete recovery of photoreceptor damage (**Figure 3 and Supplemental Digital Content Figures 3, 4, and 6**). This was demonstrated both by reduced visibility of hypo-reflective lesions on NIR reflectance images and improved appearance of the EZ and ONL on OCT (**Figure 3**). However, persistent thinning of the ONL and abnormal reflectivity of the EZ were seen across the follow-up periods which varied from 3.5 (**Figure 3**) to 8 years after SAH (**Supplemental Digital Content Figure S4**). In patient 3, incomplete recovery was seen to a similar extent in both eyes, despite only the left eye having undergone surgical evacuation of sub-ILM haemorrhage (**Supplemental Digital Content Figure S3**).

In 7 eyes of 4 patients, visual acuity returned to 6/6 at the most recent measurement. This could be attributed to surgical evacuation of macula-obscuring haemorrhage and relative sparing of the central foveola from photoreceptor damage. In contrast, patient 5 displayed significant visual impairment despite bilateral surgery, that can be explained by the large extent of photoreceptor damage (**Supplemental Digital Content Figure S5**).

Discussion

Here we demonstrate that TS can be associated with patchy outer retinal changes characterised by EZ disruption and ONL thinning on OCT, indicative of photoreceptor damage. If the central fovea is spared, this manifestation of TS may – despite significant visual impairment – go undetected in routine examination that is often limited to visual acuity testing as a measure of visual function. Thinning of the photoreceptor layer is also not easily visible on clinical examination, thus calling for wider use of OCT and NIR reflectance imaging in TS patients. The functional impact of these changes may be further investigated in future studies using tests that allow precise topographic mapping of retinal function, such as microperimetry or multifocal electroretinograms (mfERG).

We observed poor spatial correspondence between areas of photoreceptor damage and sub-ILM haemorrhage, indicating that direct retinal toxicity from haemosiderin is unlikely to be the cause. Alternatively, photoreceptor damage might have been caused by (rarer) sub- or intraretinal haemorrhages that have resolved by the time of initial examination. However, haemorrhages large enough to explain those changes would be unlikely to resolve before presentation, apart from patient 2 who had significantly delayed presentation. Therefore, it appears more likely that photoreceptor damage represents a distinct aspect of TS, with possible incomplete recovery despite surgical evacuation of haemorrhage.

We hypothesise that photoreceptor damage in TS may be secondary to transient ischaemia caused by disturbed choroidal perfusion in the early stages post-SAH. For instance, an acute rise in intracranial pressure, which commonly occurs in SAH,[10] may cause a temporary obstruction in the venous outflow from the choroid. As a

result, stasis may occur in the choriocapillaris leading to ischaemic damage to photoreceptors.

Surgery does not address the observed photoreceptor damage in TS. Therefore, vitrectomy and ILM peeling should be seen as a means of more rapid rehabilitation of visual function in cases where haemorrhage directly obscures the visual axis, even if final visual acuity will be limited by any underlying photoreceptor damage. Our findings highlight the importance of managing expectations and – where possible – baseline multimodal retinal imaging to guide patient counselling regarding visual potential and treatment options. Future studies should also investigate whether outer retinal damage can occur as a consequence of SAH in the absence of TS as defined by intraocular haemorrhage. If true, this would further highlight the need for retinal imaging in SAH patients.

The key limitation of this study is small sample size, precluding analysis of the prevalence of photoreceptor damage in TS patients and its overall impact on patient outcomes. This ought to be addressed by future longitudinal studies that should include standardized central visual field mapping and retinal imaging.

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Figure Legends

Figure 1. Photoreceptor layer abnormalities associated with Terson syndrome. Optical coherence tomography (OCT) images (**right**) show localized thinning of the outer nuclear layer (**White arrowhead**) and loss or reduced reflectivity of the ellipsoid zone (**black arrowhead**). No haemorrhages are present within the areas of outer retinal damage. Note that reduced reflectivity (darker areas) on near-infrared (NIR) reflectance images (**left**) is associated with outer retinal damage and hence shows the topographic extent of the lesions. White brackets indicate areas of outer retinal damage and correspond to the areas marked on NIR reflectance images with white vertical bars. (**A**) Patient 1, left eye, 3 months after SAH (**B**) patient 2, left eye, 2 months after subarachnoid haemorrhage (SAH).

Figure 2. Poor spatial correlation between sub-ILM (internal limiting membrane) haemorrhage and photoreceptor layer abnormalities in Terson syndrome.

OCT images (**right**) show outer retinal damage in areas independent from sub-ILM haemorrhages (**white arrows**). In Panel A, outer retinal damage is seen adjacent to sub-ILM haemorrhage and extending beyond it, while in Panel B their locations are independent. Likewise, areas of reduced near-infrared reflectivity on NIR reflectance images show poor correlation with sub-ILM haemorrhage (**left**). White brackets indicate areas of outer retinal damage and correspond to the areas marked on NIR reflectance images with white lines. (**A**) Patient 3, right eye, 6 weeks after SAH (**B**) Patient 4, right eye, 6 weeks after SAH.

Figure 3. Photoreceptor layer abnormalities associated with Terson syndrome show incomplete recovery over time.

Corresponding OCTs taken at different time points show that while there is considerable recovery in the integrity of outer retinal layers, both the ellipsoid zone and the outer nuclear layer remain slightly abnormal as late as 3.5 years after SAH. Recovery of outer retinal integrity is associated with normalization of NIR reflectance images. White brackets indicate areas of outer retinal damage and correspond to the areas marked on NIR reflectance images with white lines. Patient 3, left eye, at (**A**) 6 weeks and (**B**) 3.5 years after SAH.

List of Supplemental Digital Content

Supplemental Digital Content – pdf