Severe diffuse lamellar keratitis after femtosecond lamellar keratectomy

A femtosecond laser microkeratome is becoming a popular device for performing lamellar cuts before laser ablation during laser-assisted in situ keratomileusis (LASIK) surgery, achieving good refractive outcomes and a low rate of complications.[1–5]

Inflammatory reactions at the interface after using a femtosecond laser for creating lamellar cuts have been communicated at ophthalmology meetings but not yet published in papers. We present a case of severe diffuse lamellar keratitis (DLK) after using IntraLase (IntraLase Corp, Irvine, CA) for performing LASIK surgery.

Case report

A 32-year-old Caucasian male patient attended our clinic for refractive surgery. He had nonrelevant medical or ocular history. The preoperative cicloplegic refraction was right eye, −1.25 sph, −1 cyl×80° visual acuity = 1 (decimal scale); left eye, −1.25 sph, −1.75 cyl×90° visual acuity = 1. Pachymetry and topography were adequate for excimer laser ablations. The rest of the ocular examination was unremarkable.

He underwent uneventful bilateral LASIK using IntraLase. Parameters used for cutting: 120 μm (depth of the cuts), 50° for superior hinge, 9 mm (diameters of the flap), 1.6 mJ of energy for the lamellar cut and 2.5 mJ for the side cut. An esiris excimer laser (Schwind, Frankfurt, Germany) was used for the refractive ablation. Standard postoperative treatment was prescribed: Tobradex (Alcon-Cusí, El-Masnou, Barcelona, Spain) every 6 h for 1 week and preservative-free tears (Vislube, Thea, Barcelona, Spain) every 12 h for 1 month.

Forty eight hours after surgery, the patient complained of misty vision in his right eye and had uncorrected visual acuities of 0.9 for the right eye and 1 for the left eye. Biomicroscopy showed a dense aggregate of clumped cells in the whole interface, including visual axis (fig 1) affecting the right eye and more scattered cells at the periphery of the flap in the left eye, with DLK stages III and I being diagnosed, respectively. A confocal microscopy examination (Tandem Scanning Confocal Microscope-165A; ASL, Reston, Virginia, USA) was performed (fig 2), and intensive topical corticosteroid treatment was started every hour.

Three weeks after surgery, the patient's uncorrected visual acuities were 0.5 for the right eye and 1 for the left eye, and the subjective refraction: right eye: +2 sph, −0.5 cyl×145° visual acuity = 0.7; left eye: −0.25 cyl×90°, visual acuity = 1.2. Biomicroscopy showed the appearance of stromal melting with moderate scarring and corrugated ''mud cracks'' in the right eye. The manifest refraction of the patient 3 months after LASIK was right eye: +2.5 sph, −0.5 cyl×115° visual acuity = 0.8; left eye: +0.5 sph −0.25 cyl×90°, visual acuity = 1.

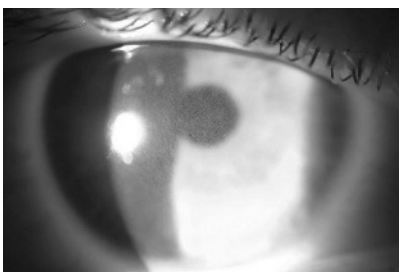

Figure 1 Biomicroscopy showing a dense aggregate of clumped cells in visual axis.

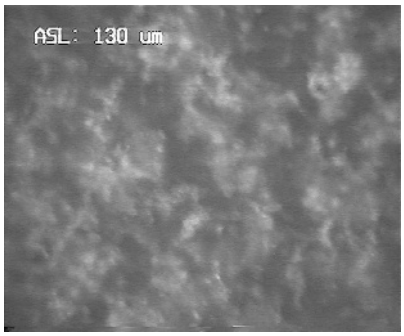

Figure 2 Confocal microscopical examination after surgery.

Discussion

DLK is a multi-aetiological syndrome characterised by an inflammatory response at the interface in patients operated on by LASIK.[6–8]

The ability of Nd-YAG photodisruption to evoke this syndrome after LASIK using IntraLase has not been published previously. The diagnosis of DLK in our case was based on the clinical features and the confocal microscopy images.[9] Before the presentation of this case, some mild inflammatory interface reactions (DLK I and II) after IntraLase cuts had been seen in our unit.[10] A posterior reduction in the levels of energy to 1.2 mJ (lamellar cut) and 1.4 mJ (side cut) was followed by the disappearance of the reaction.

A specific inflammatory-related complication after using femtosecond laser microkeratomes has been recently reported, the transient light sensitivity syndrome.[11] For this new syndrome, a positive correlation between its incidence and the energy settings has been found.

As the initial parameters of energy installed in our IntraLase unit were standard, and as the chance of evoking inflammation at the interface seems to be related to the levels of energy, these parameters should be carefully monitored at the installation and customised for each unit.

Jaime Javaloy, Alberto Artola, María T Vidal, Gonzalo Muñoz
Department of Cornea and Refractive Surgery, VISSUM, Instituto Oftalmológico de Alicante, School of Medicine, Miguel Hernández University, Alicante, Spain

Victoria de Rojas
Fundación Instituto Galego de Oftalmoloxía, Santiago de Compostela University, Santiago de Compostela, Galicia, Spain

Jorge L Alió
Department of Cornea and Refractive Surgery, VISSUM, Instituto Oftalmológico de Alicante, School of Medicine, Miguel Hernández University, Alicante, Spain

Correspondence to: Dr J Javaloy, Instituto Oftalmológico de Alicante, Avda Denia, sn Edificio VISSUM, Alicante, Spain; jjavaloy@coma.es

doi: 10.1136/bjo.2006.104075

Accepted 3 August 2006

Competing interests: None.

References

1 **Ratkay-Traub I**, Ferincz IE, Juhasz T, *et al*. First clinical results with the femtosecond neodynium-glass laser in refractive surgery. *J Refract Surg* 2003;**19**:94–103.
2 **Binder PS**. Flap dimensions created with the IntraLase FS laser. *J Cataract Refract Surg* 2004;**30**:26–32.
3 **Principe AH**, Lin DY, Small KW, *et al*. Macular hemorrhage after laser in situ keratomileusis (LASIK) with femtosecond laser flap creation. *Am J Ophthalmol* 2004;**138**:657–9.
4 **Tran DB**, Sarayba MA, Bor Z, *et al*. Randomized prospective clinical study comparing induced aberrations with IntraLase and Hansatome flap creation in fellow eyes: potential impact on wavefront-guided laser in situ keratomileusis. *J Cataract Refract Surg* 2005;**31**:97–105.
5 **Durrie DS**, Kezirian GM. Femtosecond laser versus mechanical keratome flaps in wavefront-guided laser in situ keratomileusis: prospective contralateral eye study. *J Cataract Refract Surg* 2005;**31**:120–6.
6 **Smith RJ**, Maloney RK. Diffuse lamellar keratitis: a new syndrome in lamellar refractive surgery. *Ophthalmology* 1998;**105**:1721–6.
7 **Holland SP**, Mathias RG, Mork DW, *et al*. Diffuse lamellar keratitis related to endotoxins released from sterilizer reservoir biofilms. *Ophthalmology*. 2000;107: 1227–33; discussion 1233–, 1234.
8 **Shah MN**, Misra M, Wihelmus KR, *et al*. Diffuse lamellar keratitis associated with epithelial defects after laser in situ keratomileusis. *J Cataract Refract Surg* 2000;**26**:1312–18.
9 **Tervo T**, Moilanen J. In vivo confocal microscopy for evaluation of wound healing following corneal refractive surgery. *Prog Retin Eye Res* 2003;**22**:339–58.
10 **Javaloy J**, Vidal MT, Abdelrahman A, *et al*. Femtosecond and mechanical microkeratomes: a comparative quality control study using confocal microscopy. *J Refract Surg*, 2006.In press.
11 **Stonecipher KG**, Dishler JG, Ignacio TS, *et al*. Transient light sensitivity after femtosecond laser flap creation: clinical findings and management. *J Cataract Refract Surg* 2006;**32**:91–4.

Evidence for retinal remodelling in retinitis pigmentosa caused by *PDE6B* mutation

Retinitis pigmentosa is a genetically heterogeneous group of progressive retinal degenerations.[1] Autosomal recessive retinitis pigmentosa caused by mutations in the gene encoding the β-subunit of rod photoreceptor cyclic guanosine monophosphate-phosphodiesterase (PDE6B) was one of the first forms to be identified, and there are well-studied murine and canine animal models as well as proof-of-concept success of somatic gene therapy.[1–4] Rapid rod photoreceptor degeneration in the animal models is complicated by morphological changes involving the inner retina.[5 6] It is unknown, however, whether the human form of retinitis pigmentosa is also complicated by retinal remodelling; the answer could have implications for treatment potential. We used optical coherence tomography (OCT) to study the retina of a patient with retinitis pigmentosa with a known *PDE6B* null mutation,[7] and found there was abnormal laminar architecture suggesting retinal remodelling.

Case report

A 25-year-old woman with retinitis pigmentosa was homozygous for the Cys270X mutation in *PDE6B*. There was no rod function and only severely impaired cone function.[7]

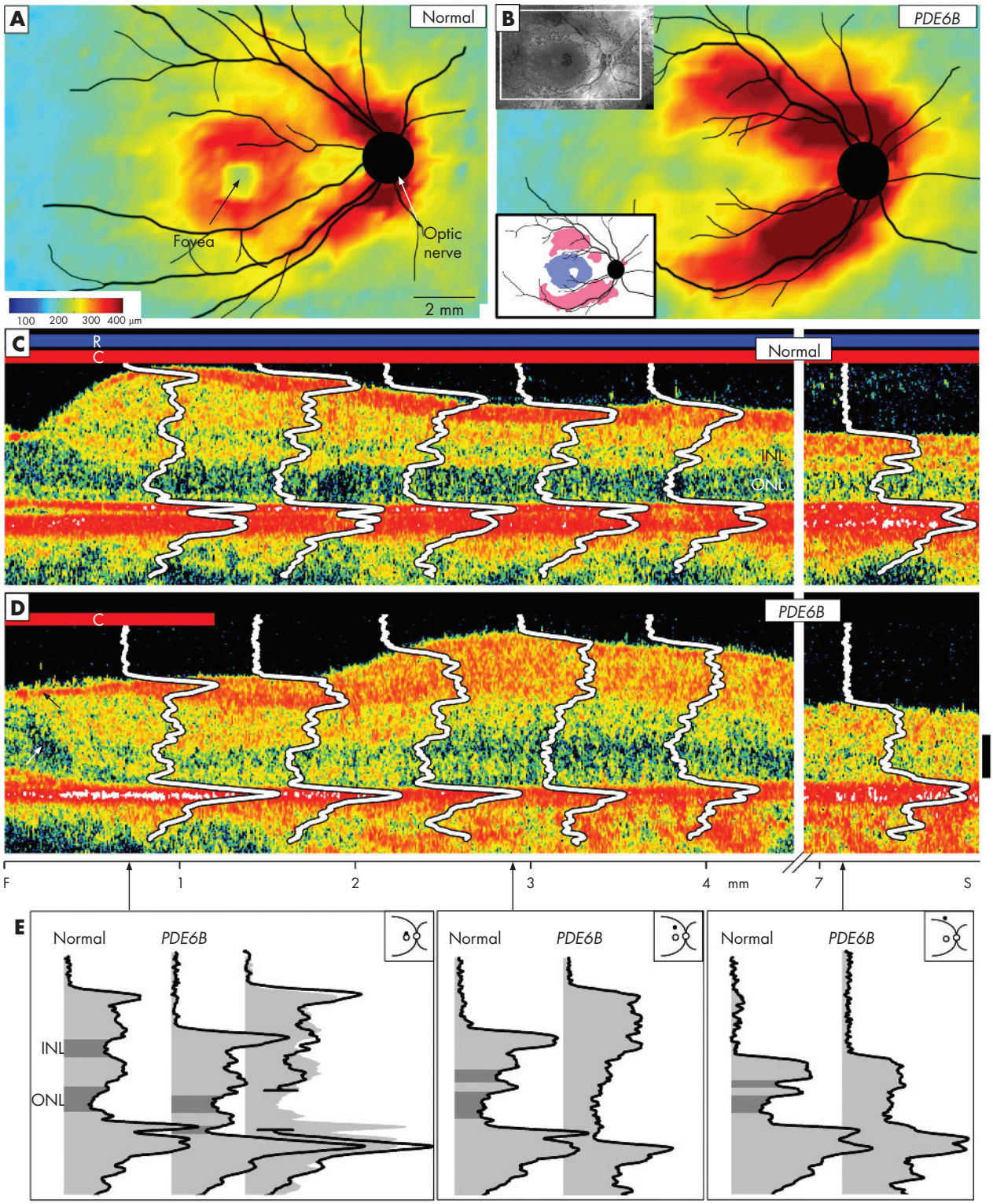

Figure 1 (A,B) Retinal topography in a normal subject (26 years of age) and in a patient with retinitis pigmentosa with *PDE6B* mutations (34 years of age). Insets in (B): upper left, fundus view and window where optical coherence tomography (OCT) mapping was performed; lower left, difference map from normal thickness (n = 5, ages 21–26 years). White represents within normal limits (±2SD); blue represents below and pink above normal limits. Fundus landmarks of the optic nerve and major retinal vessels are drawn on the maps. Cross-sectional OCT images with overlaid longitudinal reflectivity profiles (LRPs) from the fovea into the superior retina of a normal subject (C; aged 28 years) and of the patient (D; arrows points to cystoid oedema, which was also evident on ophthalmoscopy, and epiretinal membrane). Bars above the cross-sections indicate presence or absence of rod (R) and cone (C) function, measured by dark-adapted perimetry. The patient has no rod function and detectable cone function in the central field only. Calibration bar at right: 100 µm. (E) Reflectivity profiles from three loci (0.7, 2.9 and 7.5 mm superior) to illustrate the differences between the patient's laminae and those of the normal subject. At the 0.7 mm locus, the patient profile is split and the two parts overlaid on the representative normal profile (third profile at the right in this subpanel). This is to test the hypothesis that lost photoreceptor components explain the thinness of the retina. At 2.9 and 7.5 mm superior loci, the abnormal lamination in the patient profile precludes testing the hypothesis about missing components. F, fovea; INL, inner nuclear layer; ONL, outer nuclear layer; S, superior.

At 34 years of age, her best-corrected visual acuity remained 20/30, but visual fields had decreased to only a central island. OCT was performed using topographical mapping and longitudinal reflectivity profile (LRP) analyses.[8] Retinal thickness topography in the patient differed dramatically from normal (fig 1A). Especially notable was the abnormally thickened retina along the arcades (fig 1B). A difference map highlights parafoveal thinning and patches of thickened superior and inferior retina (fig 1B, inset). Laminar architecture was explored using LRPs overlaid on cross-sectional images from the fovea into the superior retina (fig 1C,D). The patient had laminated but thinned retina in the parafovea, and, with increasing eccentricity, there was a coarsely laminated and thickened region. At further superior loci, the retina had normal thickness but was delaminated. A more detailed comparison was made of LRPs at three eccentricities (fig 1E). At the parafoveal locus, thinning could be accounted for by missing retinal layers, specifically loss of photoreceptor waveform components. At the more superior loci, whether increased in thickness or not, the patient's retina had no comparable lamination with normal retinal.

Comment

The OCT results in this patient with retinitis pigmentosa and *PDE6B* mutations are complex but interpretable. Parafoveal thinning is attributable to rod (and cone) photoreceptor layer losses. The remarkable thickening and loss of normal laminar pattern at further eccentricities is probably an OCT marker for retinal disorganisation. Thickened and dysplastic-appearing retina on OCT scans has been previously reported in two early-onset retinal degenerations with a developmental component: one, a form of Leber congenital amaurosis caused by *CRB1* mutations,[8] and the other, enhanced S cone syndrome due to *NR2E3* mutations.[9] The present observations are the first in a form of retinitis pigmentosa. We propose that the results represent in vivo evidence for retinal remodelling, a process involving neuronal loss and migration, glial hypertrophy and aberrant circuitry occurring in reaction to photoreceptor death. Retinal remodelling has been demonstrated using histopathology in postmortem human retinas and in animals with retinal degeneration,[10] including those with *PDE6B* mutations.[5 6] Identifying retinal remodelling in human retinal degenerations will be valuable in future clinical trials as a structural criterion to determine the potential for therapeutic benefit.

Acknowledgements

This study was supported by the Foundation Fighting Blindness, Macula Vision Research Foundation, Macular Disease Foundation, Ruth and Milton Steinbach Fund, Alcon Research Institute, Mackall Foundation and the FM Kirby Foundation. We thank Elizabeth Windsor, Alejandro Roman and Malgorzata Swider for help with data collection and analyses.

Samuel G Jacobson, Alexander Sumaroka, Tomas S Aleman, Artur V Cideciyan
Department of Ophthalmology, Scheie Eye Institute, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Michael Danciger
Department of Biology, Loyola Marymount University, Los Angeles, California, USA

Debora B Farber
Department of Ophthalmology, Jules Stein Eye Institute, UCLA, Los Angeles, California,USA

Correspondence to: Dr S G Jacobson, Scheie Eye Institute, 51 N 39th Street, Philadelphia, PA 19104, USA; jacobsos@mail.med.upenn.edu

doi: 10.1136/bjo.2006.104463

Accepted 9 September 2006

Competing interests: None declared.

References

1 **Kalloniatis M**, Fletcher EL. Retinitis pigmentosa: understanding the clinical presentation, mechanisms and treatment options. *Clin Exp Optom* 2004;**87**:65–80.
2 **Bowes C**, Li T, Danciger M, *et al*. Retinal degeneration in the rd mouse is caused by a defect in the beta subunit of rod cGMP-phosphodiesterase. *Nature* 1990;**347**:677–80.
3 **Farber DB**, Danciger JS, Aguirre G. The beta subunit of cyclic GMP phosphodiesterase mRNA is deficient in canine rod-cone dysplasia 1. *Neuron* 1992;**9**:349–56.
4 **Pang J**, Cheng M, Stevenson D, *et al*. Adenoviral-mediated gene transfer to retinal explants during development and degeneration. *Exp Eye Res* 2004;**79**:189–201.
5 **Strettoi E**, Porciatti V, Falsini B, *et al*. Morphological and functional abnormalities in the inner retina of the rd/rd mouse. *J Neurosci* 2002;**22**:5492–504.
6 **Zeiss CJ**, Allore HG, Towle V, *et al*. CNTF induces dose-dependent alterations in retinal morphology in normal and rcd-1 canine retina. *Exp Eye Res* 2006;**82**:395–404.
7 **Danciger M**, Heilbron V, Gao YQ, *et al*. A homozygous PDE6B mutation in a family with autosomal recessive retinitis pigmentosa. *Mol Vis* 1996;**2**:10.
8 **Jacobson SG**, Cideciyan AV, Aleman TS, *et al*. Crumbs homolog 1 (CRB1) mutations result in a thick human retina with abnormal lamination. *Hum Mol Genet* 2003;**12**:1073–8.
9 **Jacobson SG**, Sumaroka A, Aleman TS, *et al*. Nuclear receptor NR2E3 gene mutations distort human retinal laminar architecture and cause an unusual retinal degeneration. *Hum Mol Genet* 2004;**13**:1893–902.
10 **Marc RE**, Jones BW, Watt CB, *et al*. Neural remodelling in retinal degeneration. *Prog Retin Eye Res* 2003;**22**:607–55.

Changes in the retinal inner limiting membrane associated with Valsalva retinopathy

Valsalva retinopathy was first described in 1972 by Thomas Duane as ''a particular form of retinopathy, pre-retinal and haemorrhagic in nature, secondary to a sudden increase in intrathoracic pressure.'' Incompetent or no valves in the venous system of head and neck allow direct transmission of intrathoracic or intra-abdominal pressure into the head and neck. Sudden elevation of venous pressure may cause a decompensation in the retinal capillary bed, with subinternal limiting membrane haemorrhages (Hg) that rarely may break through and become subhyloid or intravitreal 1. We report the histological findings of internal limiting membrane (ILM) peel in a case of Valsalva retinopathy.

Case report

A 41-year-old Caucasian male was referred to the vitreoretinal services with a spontaneous and sudden loss of vision in left eye for 3 weeks. There was no history of trauma or violent exertion but the patient had hay fever and had frequent episodes of sneezing. On examination his vision was 6/6 and hand movements in right and left eyes, respectively. Anterior segment examination was normal. Dilated fundoscopy revealed a dense vitreous haemorrhage in the left eye and normal fundus appearance in the right eye. Ultrasound echography revealed a posterior vitreous detachment, vitreous haemorrhage and a macular elevation in the left eye. Systemic examination was normal. Laboratory investigations showed normal complete blood count, prothrombin time and activated partial thromboplastin time. Blood pressure and urine analysis were normal. After discussions with the patient, a decision was made to perform a 20-gauge three-port pars plana vitrectomy. Intraoperatively, after core vitrectomy and removal of the vitreous haemorrhage, a sub-ILM haemorrhage typical of Valsalva retinopathy was noted. ILM peel was performed without the assistance of dye, and the excised tissue was processed for histopathological assessment. Postoperatively, 3 months the patient's vision had improved to 6/6 unaided, with no secondary complications.

Histological examination of the excised tissue (fig 1A) revealed that it contained convoluted ILM. The vitreous (smooth) surface of the ILM was free of cells but there was a cellular component in the specimen, and this component was on the retinal side (undulated surface) of the ILM (fig 1B). The cellular component included a prominent multilayer aggregate of cells that was immunoreactive for cytokeratin 7 (fig 1 C), which is a marker of transdifferentiated retinal pigment epithelial (RPE) cells 4. These cells were negative for glial and neural markers. Nevertheless, glial and neural elements were present elsewhere in the specimen, again on the retinal rather than the vitreous surface of the ILM (fig 1D,E). CD68pg-positive macrophages were scattered through the specimen and there was also scattered pigment that was partly intracellular and partly extracellular. Perls (Prussian blue) staining confirmed that the pigment was a mix of melanin and haemosiderin (fig 1F).

Discussion

The plane of retinal Hg in Valsalva retinopathy is sometimes difficult to determine, especially in the absence of PVD. Ocular coherence tomography (OCT) has been used to determine the exact location when the vitreous medium is clear and it is generally agreed that it is sub-ILM in location. Following core and posterior vitrectomy, we could confirm that a sub-ILM haemorrhage was present. The Hg was possibly a consequence of the patient's hay fever-related sneezing that is thought to occur from a sudden rise in the intrathoracic pressure caused by a forceful exhalation against a closed glottis.

Therapeutic options in Valsalva retinopathy include conservative management, surgery (vitrectomy) and laser membranotomy. Epiretinal membrane (ERM) formation with ILM wrinkling has been reported 10 months after ND-YAG membranotomy of Valsalva Hg.[3] Histological examination of surgically removed ILM revealed the presence of haemosiderin within macrophages on the retinal side of the ILM and a fine glial ERM, resembling glial proliferation on the vitreous surface of the ILM 3. Our case also revealed haemosiderin on the retinal surface of the ILM, again confirming the sub-ILM location of the haemorrhage, but