CASE REPORT

Bilateral optic neuropathy in a patient with familial amyloidotic polyneuropathy

Steffen Hamann,¹ Peter Koch Jensen,² Hans Callø Fledelius²

¹Department of Ophthalmology, Glostrup Hospital, University of Copenhagen, Glostrup, Denmark

²Eye Clinic, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Correspondence to
Dr Steffen Hamann,
steffen.hamann@regionh.dk

SUMMARY

Amyloidogenic transthyretin (ATTR)-related familial amyloidotic polyneuropathy (FAP) is an autosomal-dominant hereditary disease characterised by slowly progressive peripheral sensorimotor and autonomic neuropathy and tissue involvement of the heart, kidneys and central nervous system. Secondary glaucoma has been reported following intraocular surgery, but optic nerve involvement unrelated to glaucoma has not previously been described. We reported a male patient in his late 40s when deceased, who previously had a liver transplant in order to reduce the abnormal protein synthesis underlying his FAP ATTR Val30Met mutation. After 11 years of ophthalmic follow-up best-corrected visual acuity was 20/100 in his seeing eye, which further had visual field findings suggestive of optic neuropathy. This was also the diagnosis underlying the preceding insidious full loss of vision in the fellow eye, with colour Doppler imaging to support an ischaemic aetiology. To our knowledge, this is the first report of ischaemic optic neuropathy in this familial amyloid disorder.

BACKGROUND

Familial amyloidotic polyneuropathy (FAP) is the most common form of hereditary systemic amyloidosis. It is due to point mutations in various genes, most of which lead to production of amyloidogenic transthyretin (ATTR), a plasma transport protein for thyroxine and retinol-binding protein/vitamin A.¹ Transthyretin (TTR) is synthesised primarily in the liver, but also in the choroid plexus of the brain and the retinal pigment epithelium of the eye. The site of synthesis reflects where TTR amyloid is mainly deposited. More than 100 TTR mutations are known.² Among them the Val30Met mutation is common and in particular found in Portuguese, Swedish and Japanese families. FAP ATTR Val30Met in people of Portuguese ancestry is a progressive disease with a mean onset age of about 35 years and often lethal within a decade. The dominant phenotype is a slowly progressive sensorimotor and autonomic neuropathy. Some patients acquire heart disease, nephropathy and ocular involvement, the latter usually in the form of pupillary abnormalities, subtle retinal lesions and vitreous opacities.³ Secondary glaucoma was reported in patients with FAP ATTR Val30Met after intraocular surgery.^{4 5} However, optic nerve involvement unrelated to glaucoma has not previously been reported. We reported a case of a Danish resident of Portuguese ancestry with FAP ATTR Val30Met who suffered from permanent

bilateral visual loss considered due to insidious ischaemia of the optic nerves.

CASE PRESENTATION

A male patient of a Portuguese family, with a biopsy-verified autosomal-dominant FAP ATTR Val30Met and ascending acro-polyneuropathy as his main problem, was followed over a decade. An episode of transient diplopia in his late 30s first led him to the neuro-ophthalmology clinic. Visual acuity was recorded 20/20, both eyes, and optic discs and retinas appeared normal. One year later, the patient had a therapeutic liver transplant in order to reduce the abnormal protein synthesis underlying his ATTR-related FAP. Another year later, the patient experienced unilateral visual loss associated to retinal haemorrhages considered ischaemic (figure 1A), but visual acuity spontaneously recovered as 20/30. Since then, no similar episodes of fundus bleedings have been observed. A scalloped pupillary margin (figure 1B), probably associated to autonomic nerve damage, was noted at subsequent examinations. Three years after his first neuro-ophthalmic examination a slightly increased intraocular pressure (28 and 18 mm Hg) was observed on a single occasion. A topical pressure-lowering prostaglandin analogue secured a lower intra-ocular pressure (IOP) since then.

Despite regular control in private practice and normal IOP values, insidious loss of all vision of the right eye occurred over the following 5 years. Eight years after his first neuro-ophthalmic examination, when re-referred to us, visual acuities were no light perception, right eye, and 20/30, left eye. Optic discs did not present localised tissue loss or atrophy and glaucoma was refuted by the glaucoma experts of our team. Contrast sensitivity (Pelli Robson) and colour perception (Ishihara plates) in the viewing eye appeared slightly impaired, whereas pattern visual-evoked potentials were close to normal. A vitreous blur because of opacities in the right eye presumably expressed amyloid formation in the retinal pigment epithelium (figures 1C and 2B), but could not explain the total loss of vision, and B scan ultrasound revealed a condensed, partly detached posterior hyaloid membrane and a few axial vitreous opacities. Contrast-enhanced MRI of the brain showed thin optic nerves with no amyloid deposits and no gadolinium enhancement. Repeated Goldmann kinetic perimetry had shown an upper altitudinal visual field defect of the left eye (figure 2A), eventually to indicate an underlying vascular cause. Colour Doppler imaging performed on the retrobulbar vessels showed severely reduced flow

To cite: Hamann S, Jensen PK, Fledelius HC. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-200445

Figure 1 (A) Fundus photograph (2 years after first examination) revealing intraretinal and subretinal haemorrhages in the right eye. The haemorrhages completely resolved after 3 months. (B) Scalloped pupil deformity. This sign, which disappears with dilation of the pupil, is essentially pathognomonic for familial amyloidotic polyneuropathy. (C) Fundus photograph (9 years after first examination) of the right eye showing vitreous opacities with a 'glass wool-like' appearance slightly clouding the fundus.

velocities in the central retinal vessels of the intraorbital optic nerves, particularly in the blind right eye (figure 2B). Peak systolic velocities of the central retinal arteries were 47% and 63% of the

normal,⁶ right and left eye, respectively, whereas the corresponding peaks for central retinal veins were too low for quantification. Flow velocities in the ophthalmic and short posterior ciliary arteries were normal.

INVESTIGATIONS

Laboratory tests taken regularly during the last 5 years revealed normal liver and kidney function, ANA, antineutrophil cytoplasmic antibody, and ACE were all negative, and ESR and C reactive protein values were normal. HIV, Venereal Disease Research Laboratory, hepatitis B surface antigen and anti-hepatitis C virus serology were negative. Testing for Leber's hereditary optic neuropathy mutations was negative.

TREATMENT

Orthotopic liver transplantation has been widely employed as the only potential cure for ATTR-related FAP patients, since TTR that circulates in serum is synthesised mainly by the liver. Our patient had an apparently successful liver transplant in 2002; however, unable to stop the relentless progression of disease which led to his death after 10 years.

OUTCOME AND FOLLOW-UP

Prior to his death 11 years, after his first neuro-ophthalmic examination, a visual acuity of 20/100 in the left eye was recorded and dark vision was poor. A full electrophysiological status including electroretinography and visual-evoked potentials was scheduled, but not feasible, with reference to his general debilitation in the extended terminal phase. During the extended 11-year follow-up period, despite the uneventful liver transplantation, the patient developed progressive difficulty in walking, progressive anorexia, muscular weakness, orthostatic hypotension and autonomic dysfunction in form of persistent nausea, vomiting, diarrhoea, constipation, incontinence and sweating abnormalities, he lost weight and vitality and finally expired due to cardiac insufficiency.

DISCUSSION

More than 100 mutation types in FAP patients have been described, and FAP ATTR Val30Met is considered the most common type that causes the classical phenotype of FAP characterised by the early onset sensory disturbances, motor weakness and wasting, marked autonomic dysfunction and steady disease progression.² The dominant phenotype may also show ophthalmological findings³ and our patient exhibited several such features: unilateral retinal haemorrhages, though only a single episode observed over 11 years (figure 1A), unilateral long-standing vitreous opacities (figure 1C) and the highly characteristic scalloped pupillary margin (figure 1B), seen bilaterally in our patient. The latter probably reflects autonomic nerve dysfunction related to TTR amyloid deposits in the iris sphincter muscle.

Retinal changes considered ischaemic are seen in about 20% of patients with ATTR-related FAP, usually in the form of asymptomatic haemorrhages or cotton wool spots,³ but literature has no reports of insidious and slowly progressing total visual loss as in our patient. Vitreous veils typically occur in FAP patients as 'glass wool' opacifications and usually cause only marginal visual impairment. The vitreous veils probably represent transthyretin deposits synthesised by the retinal pigment epithelium and visual acuity usually returns to normal when clear imaging conditions are restored by vitrectomy.⁷ In our patient, the unilateral vitreous opacities (figure 1C), could not explain the complete loss of light perception, and vitrectomy was not performed.

Figure 2 (A) Kinetic Goldmann perimetry with largest and brightest target (V, 4 e) performed 7 (top panel) and 10 years (lower panel) after first examination. There is no registration from the blind right eye. The left eye eventually showing a vascular-type upper altitudinal defect, leaving only a small lower field 10 years after initial examination. (B) Triplex Doppler ultrasound scan of the right eye central retinal vessels showing reduced flow velocity (cf text). A condensed vitreous membrane is further shown.

In general, vision loss is not profound in patients with FAP. Our patient insidiously lost all vision in the right eye, and the left eye eventually acquired a state of legal blindness, with episodes of obscurations or transient visual loss. A bilateral retrobulbar optic neuropathy most likely had caused the insidious visual loss, though with remarkably different time axes in the two eyes. It has been described, that glaucoma can appear suddenly in FAP patients with a significant increase in intraocular pressure causing severe visual loss,⁸ and combined medications and/or multiple surgeries may be required.⁹ In our patient, a slight rise in intraocular pressure of one eye was measured, but only once. It however, led to the topical administration of a pressure-lowering prostaglandin analogue and the intraocular pressure remained normal. Furthermore, repetitive optic disc and visual field evaluations by various glaucoma specialists gave no support to glaucoma as underlying the visual loss. MRI of the intraorbital optic nerves effectively ruled out bilateral compressive, infiltrative or inflammatory optic neuropathies; nor could the slow and asymmetric progression of the visual field deficits lend support to toxic or nutritional optic neuropathy. Optic nerve ischaemia as the likely aetiology of the visual loss, the perimetry of the seeing eye showed a vascular-type upper visual field defect (figure 2A).

In the context, we further considered the dual blood supply of the retina. The choriocapillaris has an anatomic relation to the retinal pigment epithelium which harbours the metabolic dysfunction under study. The colour Doppler imaging, however, indicated severely reduced blood flow velocities in the central retinal vessels (figure 2B) and the upper visual field defects further appear to relate to the vertical bifurcation of the central retinal artery, shortly behind the lamina cribrosa. Compared with the normal flow in the ophthalmic and the short posterior ciliary arteries, a 'backward' affection of the central retinal artery from intraocular metabolic amyloid deposits may be hypothesised.¹⁰ A selective decrease in blood flow of central retinal vessels, but not ophthalmic or short posterior ciliary arteries, is also seen in patients with optic nerve head drusen, probably caused by vessel compression by the drusen.^{11 12} MRI did not indicate deposits of relevance to the optic pathways,

only thinner optic nerves, and the literature on the leptomeningeal varieties of ATTR-related FAP seen in TTR mutations other than Val30Met, mentions amyloid deposits only in feeder vessels and connective tissue structures,^{13 14} not in the central nervous system parenchyma.

In summary, we have found no reports of optic neuropathy similar to what appeared in our patient, who further had a clean FAP ATTR Val30Met expression and no suspicion of the leptomeningeal form. We regard his visual loss as due to bilateral optic neuropathy, probably caused by a combination of ischaemia, possibly due to small vessel amyloid deposits and impaired autonomic autoregulation. Although ocular manifestations in FAP are well known, this is the first report of this unusual clinical association, here leading to blindness.

Learning points

- ▶ Blindness due to optic nerve involvement can occur as a rare complication of familial amyloidotic polyneuropathy (FAP), the most common form of hereditary systemic amyloidosis.
- ▶ FAP can be a rapidly progressive disease with amyloid deposits in multiple organs, including the eyes, despite successful liver transplantation in order to arrest this deposition.
- ▶ Optic nerve involvement in FAP is not always due to glaucoma.
- ▶ Ischaemic optic neuropathy is not always sudden, it can be insidious.
- ▶ In any case of unexplained progressive visual loss, with no obvious ocular explanation, in a patient with a serious underlying systemic amyloidosis, consider the possibility of affected optic nerve blood flow.

Contributors All the authors were involved in the conception and design, acquisition of data and analysis and interpretation of data. Drafting the article and revising it critically for important intellectual content. Final approval of the version published.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Ando Y, Nakamura M, Araki S. Transthyretin-related familial amyloidotic polyneuropathy. *Arch Neurol* 2005;62:1057–62.
- Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. *Muscle Nerve* 2007;36:411–23.
- Ando E, Ando Y, Okamura R, *et al*. Ocular manifestations of familial amyloidotic polyneuropathy type I: long term follow up. *Br J Ophthalmol* 1997;81:295–8.
- Dunlop AA, Graham SL. Familial amyloidotic polyneuropathy presenting with rubeotic glaucoma. *Clin Exp Ophthalmol* 2002;30:300–2.
- Beirão NM, Matos ME, Meneres MJ, *et al*. Vitreous surgery impact in glaucoma development in liver transplanted familial amyloidosis ATTR V30M Portuguese patients. *Amyloid* 2012;19:146–51.
- Guthoff RF, Berger RW, Winkler P, *et al*. Doppler ultrasonography of the ophthalmic and central retinal vessels. *Arch Ophthalmol* 1991;109:532–6.
- Sandgren O, Stenkula S, Dedorsson I. Vitreous surgery in patients with primary neuropathic amyloidosis. *Acta Ophthalmol* 1985;63:383–8.
- Doft BH, Machemer R, Skinner M, *et al*. Pars plana vitrectomy for vitreous amyloidosis. *Ophthalmology* 1987;94:607–11.
- Kawaji T, Ando Y, Hara R, *et al*. Novel therapy for transthyretin-related ocular amyloidosis: a pilot study of retinal laser photocoagulation. *Ophthalmology* 2010;117:552–5.
- Dimitrova G, Kato S. Color Doppler imaging of retinal diseases. *Surv Ophthalmol* 2010;55:193–213.
- Chern S, Magargal LE, Annesley WH. Central retinal vein occlusion associated with Drusen of the optic disc. *Ann Ophthalmol* 1991;23:66–9.
- Newsom RSB, Trew DR, Leonard TJK. Bilateral buried optic nerve Drusen presenting with central retinal artery occlusions at high altitude. *Eye* 1995;9:806–8.
- Blevins G, Macaulay R, Harder S, *et al*. Oculoleptomeningeal amyloidosis in a large kindred with a new transthyretin variant Tyr69His. *Neurology* 2003; 60:1625–30.
- Goren H, Steinberg MC, Farboody GH. Familial oculoleptomeningeal amyloidosis. *Brain* 1980;103:473–95.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow