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NONPENETRATING DEEP SCLERECTOMY AS AN EFFECTIVE TREATMENT OF GLAUCOMA RELATED TO FAMILIAL TRANSTHYRETIN AMYLOIDOSIS

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★ INTRODUCTION ★

Transthyretin-related familial amyloid polyneuropathy (FAP) is a systemic disease characterized by abnormal production and extracellular deposition of transthyretin (TTR). TTR is a carrier protein of thyroxin in plasma and, in association with the retinol-binding protein, transports vitamin A in the retina. More than 90% of TTR is produced in the liver, but there is evidence of TTR synthesis in the retinal pigment epithelium and the ciliary pigment epithelium [1].

A mutation of the TTR gene located on the 18th chromosome (18q12.1) is responsible for the development of the disease, and is inherited in an autosomal dominant pattern [2]. The mutation results in a structural alteration causing misfolding or aggregation of the TTR and its precipitation in tissues. There are over one hundred different types of mutations of the TTR gene described. The most common is the Val30Met substitution, frequently observed in patients of Portuguese and Swedish origins, and the Val122Ile typical for West African and African-American populations [2]. The onset, clinical features, and severity of symptoms may vary depending on the mutation.

FAP usually initiates with a sensorimotor peripheral polyneuropathy, and subsequently affects the autonomic nervous system (gastrointestinal dysfunction), cardiovascular system (cardiomyopathy, arrhythmia), central nervous system (seizures, psychosis, dementia), kidneys and eye tissues.

The disease untreated is fatal, and the clinical manifestations are most severe in patients with early onset. The treatment involves liver transplantation (LT), which replaces the main source of the faulty protein, thus preventing further systemic deterioration. The surgery however, does not cease the production of TTR in the ocular tissues and does not eliminate the risk of severe visual impairment of patients with FAP.

Ocular involvement is a common feature of FAP. The risk increases with the duration of the disease and time after liver transplantation^[1,3]. The increased life expectancy of the transplanted patients allows the amyloid protein to deposit in the ocular tissues with all its consequences, which were not as frequently observed as in the pre-transplant era. Sandgren et al. state that probably all patients will develop a severe ocular disease within 20 years of the onset of the neuropathy^[1].

The most common ocular feature observed are vitreous opacities (reported in 12.5% to 80% of patients^[1,3]) which often decrease visual acuity sufficiently to require a vitrectomy. Pathology exam of the extracted vitreous usually confirms the presence of the amyloid protein. TTR precipitates can be detected by slit-lamp biomicroscopy on the surface of the lens (33% of patients^[1]), and on the border of the pupillary margin which may be scalloped or irregular (21%^[1]). The amyloid may precipitate in the trabecular meshwork (TM^[4]), seen as pigmented deposits. Secondary glaucoma is relatively common and the prevalence which varies between 8% and 50%^[1,3,5,6] increases with the duration of the disease and time after LT. The pathogenesis of glaucoma in FAP remains unclear, but most authors suggest the trabecular mechanism in which the trabecular meshwork is infiltrated and clogged by amyloid fibrils, similar as in pseudoexfoliative glaucoma in which the pseudoexfoliative material

deposits obstruct the trabeculum^[1,7,8]. The course of glaucoma in FAP patients is usually accelerated and often requires surgical treatment, of which the trabeculectomy is performed most frequently^[5,9]. There is only one report published (Kimura et al^[5]) of a nonpenetrating filtration surgery in FAP-related glaucoma. The patient had an unsatisfactory outcome and poor control of intraocular pressure (IOP), but we have no details on the surgery and other possible risk factors.

Other less frequent ocular features possibly related to FAP include dry eye symptoms and vascular retinopathies (central retinal vein occlusion), but no direct association has been indicated^[1].

★ CASE REPORT ★

Case 1

The first patient is a 41-year-old male diagnosed with FAP with peripheral sensorimotor polyneuropathy and renal involvement. He underwent LT 14 years ago. Almost 13 years later his left eye was vitrectomized because of vitreous opacities. Pathology exam confirmed the presence of amyloid (positive Congo red staining) in the extracted vitreous humor. Other ocular findings included iris amyloid deposits with scalloped pupils, and a highly pigmented TM in both eyes. Eleven months after vitrectomy he developed open-angle glaucoma with very high IOP of up to 62mmHg, which did not respond to maximum topical and oral medical treatment. NPDS with Esnoper[®] implant and local mitomycin was performed with a good result. Three months later the patient had a rhegmatogenous retinal detachment in the affected eye, which was treated with vitrectomy, endophotocoagulation and 20% sulfur hexafluoride gas, and presented posteriorly transient IOP elevation. At 6 months after the glaucoma surgery, the patient maintains a good filtering bleb and a normal IOP, currently at 20 mmHg, and does not require additional medical treatment.

The fellow eye contains typical for FAP mild vitreous opacities, but the patient still maintains satisfactory vision and currently does not require antihypertensive therapy.

Case 2

The second patient is a 57-year-old male with FAP with predominantly neurological manifestations (sensorimotor polyneuropathy, sensorineural hearing loss), autonomic dysfunction (gastrointestinal symptoms), infiltrative cardiomyopathy, and arrhythmia. He had a LT five years ago. Just 1 year after LT the left eye required a combined vitrectomy and cataract surgery because of lens and vitreous opacities. Histological staining of the vitreous was positive for amyloid. Within 19 months the patient developed open-angle glaucoma resistant to medical treatment. NPDS with T-Flux[®] implant and local mitomycin C was successfully performed.

The fellow eye followed a similar clinical course. Three years after LT the patient had a combined vitrectomy and cataract surgery in the right eye, and after 17 months debuted with glaucoma. We opted for a similar treatment as in the left eye and performed a NPDS with Esnoper[®] implant and local mitomycin C.

Currently, 4 months after NPDS in the right eye and 22 months after surgery in the left eye, the patient has functioning filtering blebs in both eyes, maintains low IOP of 7 and 11 mmHg respectively, without signs of progression of the glaucomatous visual field defects.



Fig. 1. Patient 1. Filtering bleb (1st postoperative week)

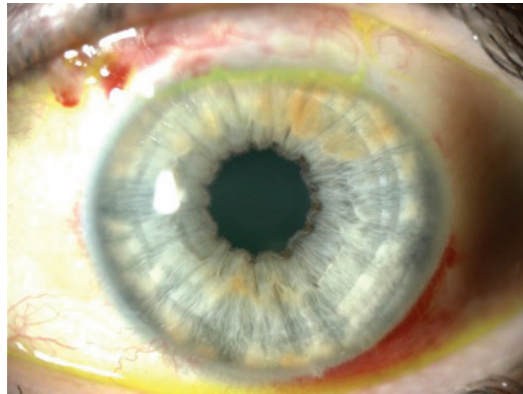


Fig. 2. Patient 1. Scalloped pupil

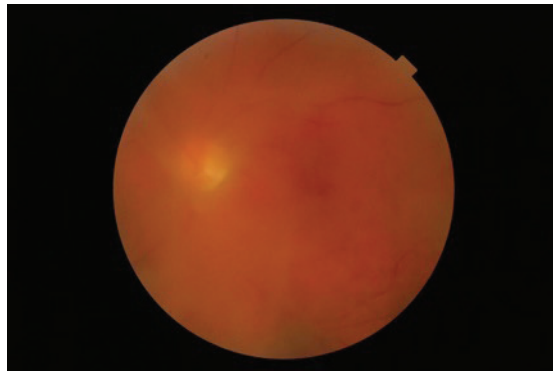


Fig. 3. Patient 2. Vitreous opacities in the left eye.

★ DISCUSSION ★

Patients with FAP are at a high risk of developing sight-threatening glaucoma, which increases with the duration of the disease^[1,3,9].

We observed a certain pattern in the evolution of ocular disease in our patients: the three operated eyes were primarily affected with significant vitreous opacities and were subsequently vitrectomized. High IOP was detected within 11 to 19 months of the surgery. The untreated eye of the first patient has only mild vitreous opacities, it has not been vitrectomized, and still maintains normal IOP. It seems reasonable to suggest that there is an apparent relation between the severity of the primary FAP ocular feature (vitreous opacities) and the development of glaucoma. Beirao et al^[9] postulates in a recent report that glaucoma is more common in vitrectomized eyes, with statistical significance, however the mechanism of the relation of the vitrectomy itself with the debut of glaucoma seems unclear, and certainly requires more studies.

There are only a few reports in literature on the types of glaucoma procedures in FAP patients. The most frequently mentioned is the trabeculectomy. Kimura et al reported 15 eyes which required surgery : 11 eyes underwent trabeculectomy, 2 sinusotomy, 1 a cyclodestructive procedure and only 1 a nonpenetrating trabeculectomy. The IOP in the patient with the nonpenetrating trabeculectomy was poorly controlled. However we do not have details on the course of the surgery such as the intraoperative use of antimetabolites and placement of an implant, which could influence the result of the operation.

The progression of glaucoma in our patients was highly accelerated, thus the need of selecting a proper filtration procedure to prevent severe glaucomatous damage. NPDS with implant is a filtration technique successfully performed for more than 20 years. The main advantage of the procedure is that it prevents the sudden hypotony which occurs in the classically performed trabeculectomy, by allowing progressive filtration of the aqueous humour through the trabeculo-Descemet membrane without perforating the eye. Its disadvantage is a longer learning curve, although when performed by an experienced surgeon, it is considered to be just as effective as trabeculectomy in managing primary open-angle glaucoma as well as some forms of secondary glaucoma of trabecular etiology, such as pseudoexfoliative glaucoma. The suggested trabecular mechanism of glaucoma in FAP made our patients good candidates for the procedure, and judging by the results, NPDS was an excellent choice in these cases.

★ CONCLUSION ★

As observed in our patients, FAP-related glaucoma is a rapidly progressive disease, which requires prompt and aggressive treatment. The surgical procedure we elected, NPDS, proved to be effective in controlling IOP in all three cases, and seems to be a good option in this type of secondary glaucoma. Therefore it is the first known report of effectiveness of NPDS in amyloidosis-related glaucoma. We are aware that a study on a larger group of patients would be more conclusive. However the results of the three surgeries, considering the advantages of NPDS, are encouraging in controlling the sight-threatening glaucoma and improving quality of life of FAP patients, and may serve as an inspiration of larger and comparative studies.

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