·Case Report·

Transthyretin Arg -83 mutation in vitreous amyloidosis

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Abstract

• Both of the patients in the report had floaters and progressive vision loss for years. Two cases of familial vitreous amyloidosis occurred in three generations with typical white fibrilar opacities in the vitreous body. Pars plana vitrectomy was performed in the two patients. The vitreous specimens were subjected to histopathological examination. The specimens showed typical microscopic features of amyloidosis with Congo red stain and non-branching fibrils were seen randomly distributed with 5-10nm in diameter on a transmission electron microscope. All of the exons of the transthyretin gene were amplified with DNA isolated from the peripheral blood cells. Bi-directional sequencing of the transthyretin gene revealed a single base-pair substitution, which results in an amino acid substitution at position83, glycine to arginine (transthyretin Arg-83).

• KEYWORDS: vitreous; amyloidosis; transthyretin

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INTRODUCTION

Vitreous amyloidosis is a rare condition that mainly occurs in familial amyloidotic polyneuropathy (FAP). It is characterized by progressive loss of vision from amyloid accumulation of deposits on the retina and in the vitreous. In some cases, it may be the only symptom without systemic disorders[1]. Here we reported two cases of familial vitreous amyloidosis.

CASE REPORT

Case 1 A 44-year-old man had a 3-year history of floaters and visual disturbance in both eyes. His mother, maternal aunts, uncle and grandmother had all developed vitreous amyloidosis. No history of neurologic disease was found among family members. The family history is plotted in Figure 1A. Visual acuities were right FC/10cm and left 20/63. The anterior segments were unremarkable with normal intraocular pressures. Dilated fundoscopy revealed white, wispy deposits in vitreous cavity in both eyes. Some of the deposits attached to the posterior lens capsule like footplates (Figure 2A). The fundus of the right eye could not be visualized, and only partially visualized of the left. No significant finding in routine systemic studies was detected. Pars plana vitrectomy and histopathological examination of the vitreous specimens were performed. Retinal breaks occurred during operation in the left eye due to the close connection between vitreous deposits and retina. Endolaser and 10% C3F8 injection were performed, and good visual acuity with normal intraocular pressure was achieved postoperatively. On the 7th day after operation, the cornea of the right eye became edema with 29mmHg intraocular pressure when the pupil was dilated. The intraocular pressure was controlled with a topical beta-blocker. Visual acuities were improved to 20/16 in both eyes at the 1-year follow-up.

The vitreous specimens showed typical microscopic features of amyloidosis with Congo red stain (Figure 2B). All of the four exons of the transthyretin gene were amplified with DNA isolated from the peripheral blood cells. Bi-directional sequencing of exon 3 showed a single base-pair substitution, which results in an amino acid substitution at position83, glycine to arginine (transthyretin Arg-83) (Figure 3).

Case 2 A 48-year-old man presented a 5-year history of visual loss in his right eye and floaters in his left eye. Nine family members of three generations developed vitreous amyloidosis without FAP related systemic disorders. The family history is plotted in Figure 1B. The visual acuities

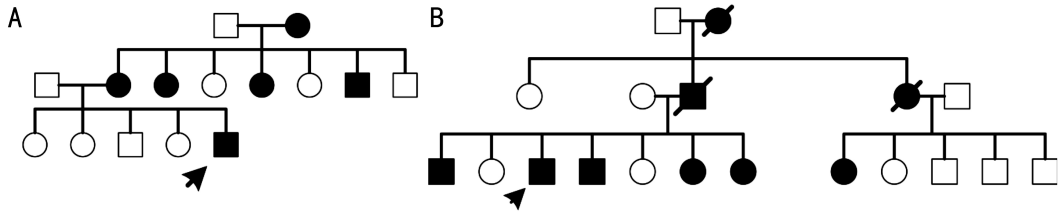

Figure 1 Gene sketch of the family A: Gene sketch of Case 1; B: Gene sketch of Case 2

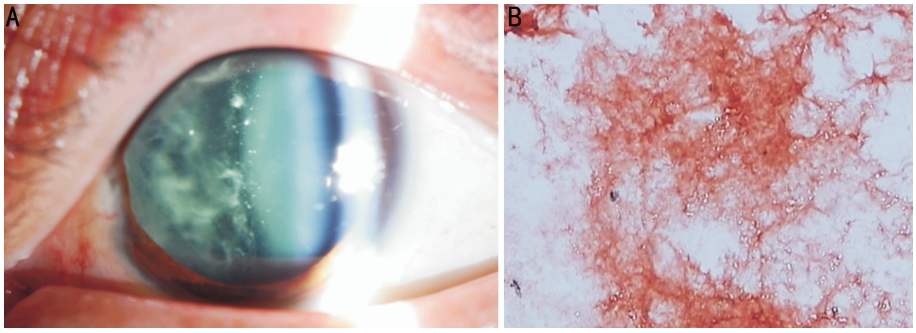

Figure 2 The characteristic white deposits and histological stain A: Slit-lamp photograph of the left eye shows white deposits on the posterior capsule and vitreous opacity; B: Vitreous specimen analysis by phenol Congo red

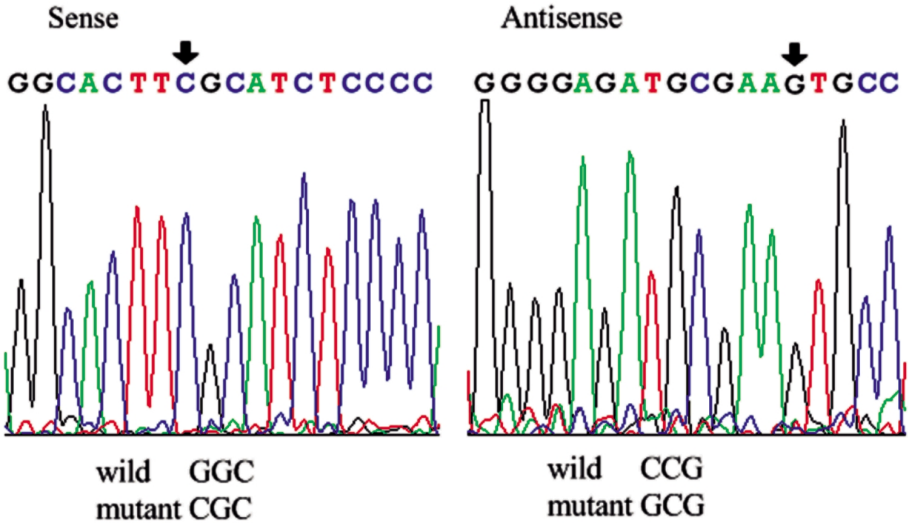

Figure 3 Direct sequencing of PCR products corresponding to transthyretin exon. The arrowheads denote the position of the point mutation

were FC/30cm and 20/32 in the right and left eye respectively. The anterior segment was normal with 13mmHg intraocular pressure in both eyes. The vitreous body was cloudy with white fibrilar opacities more prominent in the right eye. Tuftlike preretinal deposits was visualized laying over retinal vessels in the left eye (Figure 4A). There is no significant finding in routine systemic studies including cardiac and neurologic examinations.

Pars plana vitrectomy was performed in the right eye on the patients' demands. Endolaser was carried out since microvascular occlusion was detected in the temporal peripheral retina. There were no complications during and after the surgery. The visual acuity was 20/16 at the 4-month follow up. The vitreous specimens showed typical features of amyloidosis with Congo red stain. The same mutation as that of in case 1, arg-83 of transthyretin gene, was found by bi-directional sequencing. When the vitreous specimens was examined on a transmission electron microscope, non-branching fibrils were seen randomly distributed with 5-10nm in diameter, which was characteristics of amyloidosis (Figure 4B).

DISCUSSION

Vitreous amyloidosis is often the early symptom of familial amyloidotic polyneuropathy, and it may occur without systemic abnormalities [2]. Until now, there have been more than 80 mutations in the transthyretin gene reported but they are not all pathogenic [3]. The most frequent mutation is TTR-met30, which has been identified in different kindreds [4]. Arg83 mutation in our two cases is a new one that has never been reported out of China as far as we know. We are

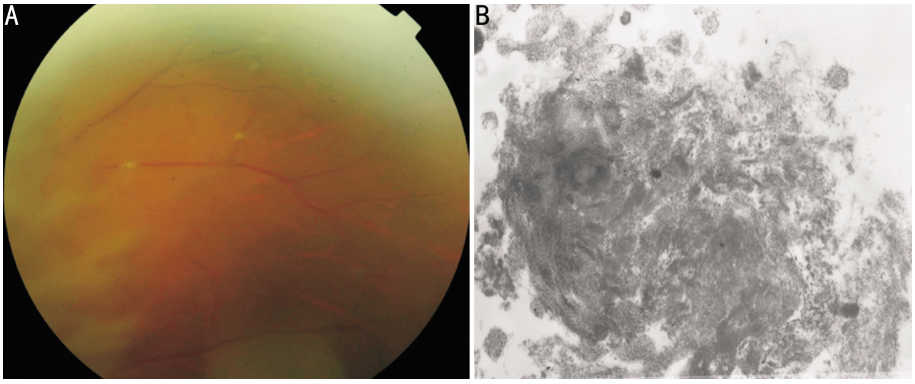

Figure 4 Fundus photograph and examination by transmission electron microscope A: Fundus periphery demonstrates vitreous opacity and perivascular white deposits; B: Non-branching fibrils were seen randomly distributed with 5-10nm in diameter by transmission electron microscope

working on collecting more DNA samples from other affected family members to ensure the pathogenic possibility of arg-83 mutation.

Retinal breaks occurred during PPV in the left eye in case 1 due to the close connection between vitreous deposits and retina. However, it is necessary to clear the deposits completely as possible. In the study reported by Doft *et al*[5] three eyes of vitreous amyloidosis required glaucoma filtering surgery after PPV. Haraoka *et al* [6] discovered amyloid deposition on the pupil and anterior surface of the lens in the eyes of secondary glaucoma in patients with familial amyloidotic polyneuropathy. The high intraocular pressure of the right eye after dilation in case 1 may be related to the residue of deposits at the trabecular meshwork. So, intensive care of intraocular pressure is important for the management of the operation complications in vitreous amyloidosis[7].

Results of vitrectomy have in general been satisfactory, but a progressive reopacification has been found with the increase of follow-up time [8]. Local environment may contribute a part to the recurrence. TTR was detected not only synthesized by the liver and the choroidal plexus, but also by the retinal cells. Amyloid in the retinal vessels has been shown to be continuous with overlying vitreous deposition[9]. It need long time observation on the changes of tuftlike deposits along retinal vessels and microvascular occlusion in our cases. We have presented tow cases of familial vitreous amyloidosis. The underlying transthyretin mutation (TTR-arg 83) has not been reported in any other kindreds. The details of other affected family members should be in the further studied.

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