BMC Ophthalmology

RESEARCH

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Long-term follow-up of retinal amyloid angiopathy in a large Chinese family with hereditary amyloid transthyretin

Jiangning Xu[1,6†], Nan Shu[1,6†], Xi Liu[5], Peng Gu[5], Yi Wang[4*] and Shiying Li[2,3*]

Abstract

Background Retinal amyloid angiopathy (RAA) is an ocular manifestation of hereditary amyloid transthyretin (hATTR). We aimed to investigate the characteristics of disease progression of RAA in patients with ATTR Gly83Arg amyloidosis and evaluate the effect of RAA on vision.

Methods We observed the clinical records of 131 individuals from a seven-generation Chinese family. In this family, 18 symptomatic patients were our followers. And the follow-up was 61.6 ± 47.5 months (range, 1-164; median, 48 months). RAA was diagnosed after vitrectomies based on fundus fluorescein angiography (FFA). Best-corrected visual acuity (BCVA), intraocular pressure, fundus examination outcomes, and FFA outcomes at each follow-up visit were the indicators we focused on.

Results The prevalence of RAA was 88.9% (32/36 eyes). Of 32 eyes diagnosed with RAA, neovascular glaucoma, choroidal hemorrhage, and tractional retinal detachment as complications associated with RAA were detected in 13 (40.6%). Of the 36 eyes evaluated, 14 (39%) had a final BCVA below 20/70. RAA and these complications associated with RAA were main causes of low vision.

Conclusions Complications associated with RAA become the most serious ocular manifestations in the patients with ATTR Gly83Arg amyloidosis. Vitrectomy is not sufficient to guarantee hATTR patients good visual function. Based on FFA results, RAA in ATTR Gly83Arg amyloidosis can be divided into three stages. Early screening and treatment for RAA is imperative before clinical stage.

Keywords Retinal amyloid angiopathy, Hereditary amyloid transthyretin, Gly83Arg, TTR gene

†Jiangning Xu and Nan Shu contributed equally to this work, thus should be considered as co-first authors.

*Correspondence:
Yi Wang
wangyieye@aliyun.com
Shiying Li
Shiying_li@126.com
[1]Chongqing Medical and Pharmaceutical College, Chongqing, China
[2]Department of Ophthalmology and Optometry, Fujian Medical University, Fuzhou, China
[3]Department of ophthalmology, School of Medicine, the First Affiliated Hospital of Xiamen University, Xiamen University, Xiamen, China
[4]Department of Ophthalmology, Chongqing Aier Eye Hospital, Chongqing, China
[5]Southwest Hospital/Southwest Eye Hospital, Third Military Medical University (Army Medical University), Chongqing, China
[6]Chongqing Key Laboratory of Occupational Disease Prevention and Poisoning Treatment, Chongqing, China

Introduction

Hereditary amyloid transthyretin (hATTR) is a progressive autosomal dominant disease caused by genetic variants of transthyretin (TTR) [1–3]. Different manifestations are caused by mutant TTR which is deposited in different tissues and organs, including the eyes [4, 5]. Amyloid deposits in the vitreous humor, leading to vitreous opacities (VO). Almost complete recovery of visual acuity can be achieved with pars plana vitrectomy (PPV) in those patients with VO originated from amyloid deposits [6]. The other ocular manifestations of hATTR include abnormal conjunctival vessels, keratoconjunctivitis sicca, and glaucoma [4]. Amyloid protein is also deposited in the retinal vascular leading to endothelial cell damage, causing amyloid angiopathy. Retinal amyloid angiopathy (RAA) manifests as tortuous retinal vessels, microaneurysms, retinal hemorrhages, sheathing of retinal vessels and neovascularization [7, 8].

To date, over 140 different hATTR mutant types have been recorded. ATTR Gly83Arg amyloidosis is reported in Chinese population and mainly involves the eye. This mutation type is characterized by vitreous amyloidosis, which leads to VO. Patients with ATTR Gly83Arg amyloidosis usually require vitrectomy [9]. We found that patients with the Gly83Arg mutation had a high incidence of RAA. However, hATTR is a rare disease, it is difficult to conduct a long-term follow-up study and characterized the RAA disease progression.

The clinical data were collected from a large Chinese family of 131 individuals; 18 were diagnosed with ATTR Gly83Arg amyloidosis and 16 were diagnosed with RAA, with up to 13 years of follow-up. The causes of irreversible low vision (best-corrected visual acuity, BCVA ≤ 20/70) in these patients was RAA and the manifestations associated with RAA included neovascular glaucoma, choroidal hemorrhage, and tractional retinal detachment. We divided the course of RAA into three stages according to the degree of damage to the retina to help ophthalmologist conduct prompt therapy. Patients with ATTR Gly83Arg amyloidosis require long-term fundus follow-up and prompt retinal laser photocoagulation and anti-vascular endothelial growth factor (VEGF) therapy when RAA occurred. We summarized the RAA characteristics of this mutation for the first time, evaluated the long-term impact of RAA on vision, and proposed an effective RAA diagnosis and treatment plan.

Methods

This study was approved by the Ethics Committee of Southwest Hospital, Third Military Medical University (approval code: 2011-24) and adhered to the Declaration of Helsinki. The clinical records of 131 people in a same Chinese family with a family history of ATTR Gly83Arg amyloidosis were observed. The Detailed data regarding the symptoms were collected from the members of a seven-generation Chinese family using questionnaires. Fifty-two individuals from this family underwent ophthalmic examination, including measurement of BCVA and intraocular pressure (IOP), slit-lamp examination, dilated fundoscopy, and ocular ultrasonography. And it is because that most hATTR patients with other variants can present with polyneuropathy with pandysautonomia affecting sympathetic, parasympathetic, and enteric functions [1, 10], the individuals underwent nerve conduction study and sympathetic skin response (sympathetic skin response reflects sweat gland activation in response to arousal). TTR coding exon sequencing was conducted and the DNA sequencing method and primer information were described previously [11]. The ATTR Gly83Arg amyloidosis diagnosis was made by the same senior ophthalmologist based on gene sequencing result, detailed medical history inquiry, and systemic and ophthalmic examinations.

Eighteen symptomatic patients were clinically evaluated, diagnosed, and treated at The Southwest Hospital of Third Military Medical University and Chongqing Aier Eye Hospital between January 2008 and March 2022. The average duration of follow-up was 61.6 ± 47.5 months (range, 1–164; median, 48 months). All patients underwent general examination and received a thorough evaluation of their medical history after admission to hospital. Comprehensive ophthalmologic examinations, including the measurement of BCVA and IOP, slit-lamp examination, fundoscopy, ocular ultrasonography, Ultrasound Biomicroscope (UBM), optical coherence tomography (OCT), fundus fluorescein angiography (FFA), fundus photography, ocular electrophysiological studies and the measurement of visual fields were conducted before or after surgeries. The diagnosis of RAA was based on the angiographic findings through FFA [12, 13].

Incomplete pars plana vitrectomy (PPV) was conducted in 16 patients with VO [14]. Glaucoma surgery, retinal photocoagulation or intravitreal anti-VEGF therapy were conducted when neovascular glaucoma or RAA was diagnosed. BCVA, IOP, fundus examinations and FFA were monitored at each postoperative follow-up visit.

Results

Participants

In this family, 25 individuals experienced "progressive loss of vision" (18 living, 7 deceased); 26 individuals had a pathogenic mutation in the TTR gene from glycine (GGC) to arginine (CGC) at codon 83 in exon 3. Of those who carried the pathogenic mutation, 18 came to the clinic a few years later with "significant vision loss" after having DNA sequence. Therefore they were considered symptomatic patients and the medical records of these 18

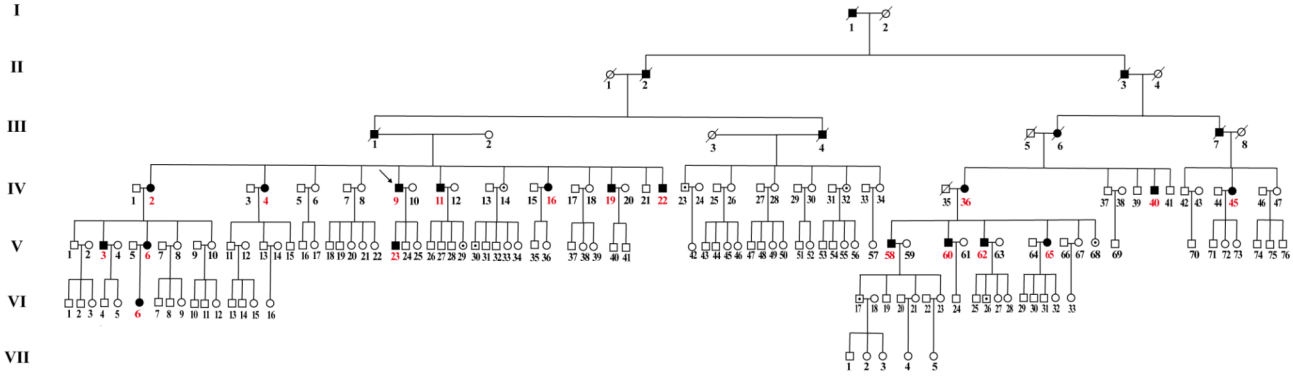

Fig. 1 The Pedigree of the family with hATTR (131 individuals). The 18 patients included in the analysis were marked red. Arrow: the proband. Filled symbols: affected symptomatic individuals. Black dot: asymptomatic individuals with the *TTR*Gly83Arg. Slashed symbols: deceased individuals. The representative case shows IV: 9 (the proband)

Table 1 Demographic of patients

	Value	Patients/Eyes
Sex	Male	10/20
	Female	8/16
Follow-up (months)	48 (1-164)	18/36
Age at diagnosis of hATTR (years)	46 (37–61)	18/36
Duration of hATTR (years)	10 (2–18)	18/36
Diagnosis of RAA (after initial symptom/years)	3 (1–15)	16/32

Data are displayed as median (min-max range)

patients were included in our assessment. The pedigree of the large family was shown in Fig. 1.

Clinical features

All patients presented with significant vision loss. At the time of presentation, most had only vision of Counting finger (CF). Routine blood workup results were within normal limits, and general examination in our hospital revealed no abnormalities in the liver, heart, nervous system, or kidneys in the patients. Fundus examination and ocular ultrasonography supported the diagnosis of vitreous opacity (VO) in all patients. To improve the vision, 16 patients (31 eyes) underwent vitrectomy; two refused surgery. The result of vitreous biopsy supported the diagnosis of hATTR based on positive Congo red staining. After vitrectomies, fundus fluorescein angiography (FFA) was conducted. The 16 patients (32 eyes, 88.9%) were diagnosed with retinal amyloid angiopathy (RAA) based on FFA findings. The demographic of the patients is described in Table 1.

Despite the presence of RAA, there was significant improvement in BCVA in 31 eyes 1 month after vitrectomy. However, various ocular manifestations appeared during long-term follow-up (Tables 2and 3). Vision loss caused by vitreous opacity was the initial symptom. Nine patients (14 eyes) were found recurrence of VO 10 ± 3.2 years (range, 4–18 years) after the initial symptom. After 12 ± 1.9 years (range, 9–15 years) of disease course, six patients (10 eyes) were found iris neovascularization, and IOP up to 30mmHg when they came the clinic again. Combined with findings of FFA (retinal neovascularization and formation of ischemic area), we diagnosed

Table 2 Manifestations of 18 patients. Age and time from onset of vitreous opacity to onset of different manifestations shown as median (min-max)

Manifestation	Prevalence	Age (years)	Onset (years)	Intervention/Observation	Patients/eyes
Vitreous opacity	100.0%	46 (37–61)	0	Observation	2/5
				Pars plana vitrectomy	16/31
Retinal amyloid angiopathy	88.9%	55 (40–65)	3 (1–15)	Observation	16/32
Recurrence of vitreous opacity	50.0%	53 (49–64)	10 (4–18)	Observation	4/7
				Pars plana vitrectomy	5/7
Neovascular glaucoma	33.3%	55 (49–65)	12 (9–15)	anti-glaucoma medication	1/2
				Trabeculectomy	1/2
				Glaucoma valve implantation	2/3
				Retinal photocoagulation	3/4
				Intravitreal injection of Anti-VEGF	2/3
Retinal detachment	11.1%	54	10/18	Observation	2/2
Intraoperative outbreak of choroidal hemorrhage	5.6%	56	10	Hematoma clearance	1/1

Table 3 Clinical characteristics of 16 patients with RAA

Patient	Gender	Laterality	Age at VO (years)	Age at PPV (years)	BCVA before surgery	BCVA after surgery	BCVA at final visit	Complications associated with RAA	Duration of hATTR (years)	Staging of RAA at final visit
IV:2	F	R	46	56	CF/40 cm	20/50	HM/40 cm	Choroidal hemorrhage	12	Clinical stage
		L	55	58	CF/40 cm	20/50	20/100	N	12	Progressive stage
IV:4	F	R	52	55	CF/40 cm	20/50	20/50	N	5	Early stage
		L	52	55	CF/40 cm	20/50	20/50	N	5	Early stage
IV:8	F	R	62	64	20/50	20/50	20/40	N	5	Early stage
		L	59	62	LP	20/50	20/50	N	5	Early stage
IV:9	M	R	46	48	CF/40 cm	20/20	HM	Neovascular glaucoma	15	Clinical stage
		L	46	48	CF/40 cm	20/25	LP	Neovascular glaucoma	15	Clinical stage
IV:11	M	R	40	43	20/250	20/50	LP	Retinal detachment	13	Clinical stage
		L	37	40	CF/40 cm	20/100	HM/40 cm	Neovascular glaucoma	13	Clinical stage
IV:16	F	R	54	56	20/50	20/32	20/32	N	2	Early stage
		L	54	56	20/50	20/32	20/32	N	2	Early stage
IV:19	M	R	41	43	CF/40 cm	20/40	20/100	Neovascular glaucoma	12	Clinical stage
		L	38	40	HM/40 cm	20/40	CF/40 cm	Neovascular glaucoma	12	Clinical stage
IV:22	M	R	52	54	CF/40 cm	20/40	20/50	Neovascular glaucoma	13	Clinical stage
		L	52	54	CF/40 cm	20/50	20/80	Neovascular glaucoma	13	Clinical stage
IV:40	M	R	61	63	CF/40 cm	20/32	20/32	N	4	Early stage
		L	63	65	20/400	20/32	20/32	N	4	Early stage
IV:45	F	R	41	44	CF/40 cm	20/50	20/70	Neovascular glaucoma	10	Clinical stage
		L	42	51	CF/40 cm	20/100	20/100	N	10	Progressive stage
V:3	M	R	42	NA	CF/40 cm	NA	CF	N	3	Early stage
		L	42	45	HM/40 cm	20/40	20/32	N	3	Early stage
V:6	F	R	40	55	HM/40 cm	20/200	NLP	Retinal detachment	18	Clinical stage
		L	40	55	HM/40 cm	20/200	20/200	N	18	Progressive stage
V:23	M	R	57	58	20/100	20/20	20/20	N	4	Early stage
		L	54	56	20/32	20/32	20/32	N	4	Early stage
V:58	M	R	41	44	CF/40 cm	20/50	20/25	Neovascular glaucoma	11	Clinical stage
		L	43	46	CF/40 cm	20/40	20/100	Neovascular glaucoma	11	Clinical stage
V:60	M	R	52	55	20/63	20/50	20/50	N	8	Progressive stage
		L	58	60	20/100	20/32	20/32	N	8	Progressive stage
V:65	F	R	39	42	CF/40 cm	20/40	20/40	N	10	Progressive stage
		L	39	42	CF/40 cm	20/25	20/32	N	10	Progressive stage

R: right; L: left; M: male; F: female. N: no complications associated with RAA were diagnosed; NA: not applicable

them as neovascular glaucoma. Therefore, five of these patients (8 eyes) had undergone surgery including trabeculectomy, glaucoma valve implantation, retinal photocoagulation and intravitreal anti-VEGF. After surgery, IOP improved but not all visual acuity improved. In the 18 patients, two of them (IV:11, V:6, 2 eyes) had retinal detachment 10/18 years after the onset of the initial symptom and they refused treatment. We excluded the surgery as a cause; the retinal detachment was diagnosed as tractional retinal detachment caused by retina neovascularization. One case of choroidal hemorrhage occurred during PPV (IV:2, one eye) 10 years after the onset of the initial symptom. During the operation, we removed the hematoma, but at the final follow-up his vision was still only hand motion. At final visit, 22 (61%) of the 36 eyes had a final BCVA of > 20/70, with a median disease duration of 2.5 years (range, 1–13). Fourteen eyes (39%) had a final BCVA of ≤ 20/70 (Table 3, IV:2 R and L, IV:9 R and L, IV:11 R and L, IV:19 R and L, IV:22 L, IV:45 R and L, V:6 R and L, V:58 L), with a median disease duration of 12 years (range, 9–18). The causes of low vision in these 14 eyes were neovascular glaucoma (8 eyes), RAA (2 eyes), retinal detachment (2 eyes), choroidal hemorrhage (1 eye), and cataract (1 eye, V:58 L). Figure 2A illustrates the Kaplan–Meier analysis of the final BCVA. The survival rates were 0.89, 0.34, and 0 at 10, 13, and 18 years of age, respectively.

During follow-up, fundus fluorescein angiography (FFA) revealed the progression of RAA in 16 patients (32 eyes). The earliest retinal vascular changes (1–5 years) included retinal vascular leakage and microaneurysms. In the progressive stage of RAA (6–9 years),

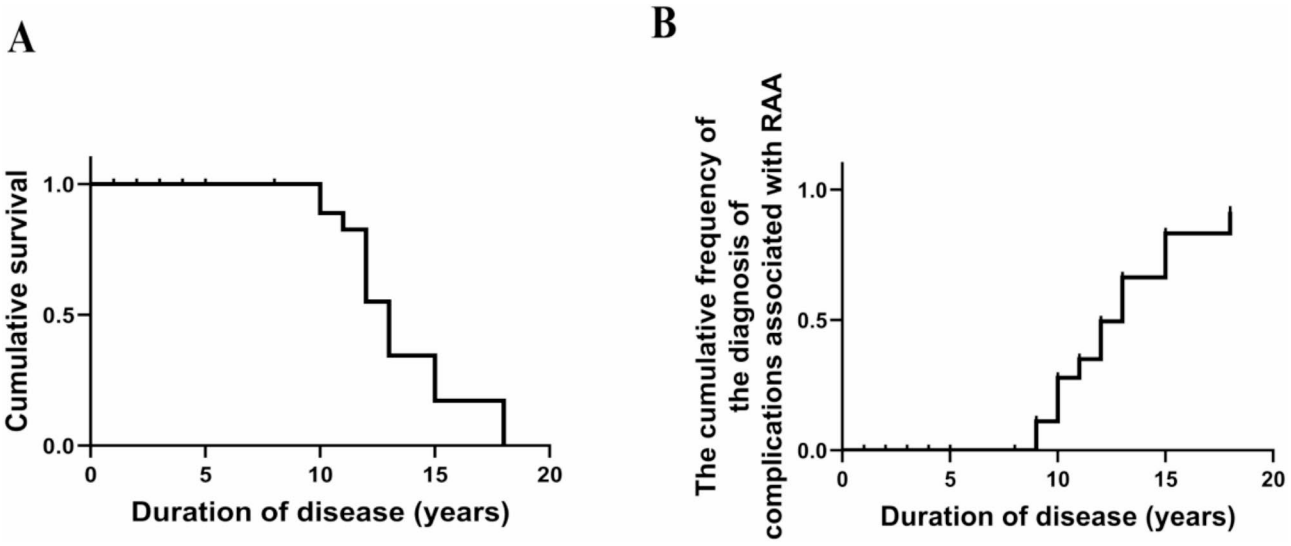

Fig. 2 Complications associated with RAA were the main causes of irreversible visual impairment. **(A)**shows Kaplan–Meier analysis of the final BCVA corresponding to each eye. Survival criteria: final BCVA, > 20/70. "Death"was defined as when the BCVA could not be improved by surgery and was ≤ 20/70 at last follow-up visit. **(B)**shows the cumulative frequency of the diagnosis of complications associated with RAA in 32 eyes. Complications associated with RAA included neovascular glaucoma, retinal detachment, and choroidal hemorrhage

retinal neovascularization and non-perfusion areas were observed. No abnormal signs were observed through ophthalmoscopy, and visual function was not affected during the early and progressive stages of RAA. However, neovasvular glaucoma, retinal detachment, and choroidal hemorrhage occurred in the clinical stage (10–18 years), leading to irreversible vision loss (final BCVA ≤ 20/70). Figure 2B depicts the cumulative diagnostic rate of complications associated with RAA during the course of disease. The complications associated with RAA were diagnosed from the ninth year of the disease course, and the cumulative diagnostic rate increased as the disease progressed, > 50% at 13 years and > 90% at 18 years. The manuscript details a representative case of the proband, patient IV:9.

Representative case

A male patient (Table 3, IV:9) was hospitalized with a diagnosis of "bilateral vitreous opacity" with the complaint of "gradual loss of vision in both eyes for two years". Systematic examination yielded no remarkable findings, and ocular examination showed visual acuity in both eyes: CF/40 cm. Slit-lamp photography showed mild cloudy lenses in both eyes. Vitreous opacity was seen after dilating the pupils, and the fundus could not be seen. B-ultrasound showed vitreous opacity in both eyes.

During hospitalization, the patient received PPV in both eyes, and the peripheral vitreous was completely removed. Intraoperatively, the vitreous was found clouded by blood, and some of the retinal vessels were found in the form of wiriness, with a small number of hemorrhagic spots and degeneration; therefore, retinal photocoagulation was performed in both eyes. The vitreous was resected for pathologic examination and the result showed positive Congo red staining. The result of TTR coding exon sequencing supported the diagnosis of ATTR G83R amyloidosis. One week after surgery, FFA was conducted; retinal vascular leakage was seen in both eyes and fundoscopy showed no abnormal signs (Fig. 3A–B). Therefore, early stage of RAA associated with hATTR was diagnosed. Postoperative visual acuity was restored with 20/20 in the right eye and 20/25 in the left eye one month after surgery.

The patient did not follow the our orders for regular visits. After 9 years, the patient came to our department for his left intraocular lens implantation found to be dislocated in the vitreous cavity. UBM suggested an open atrial angle in both eyes, and recurrence opacity of the bilateral vitreous. FFA showed capillary leakage, non-perfusion areas and neovascularization in retina bilaterally, suggesting the progression of RAA. The fundoscopy still showed no abnormal signs (Fig. 3C-D). BCVA of eyes showed 20/28 in the right eye and 20/32 in the left eye. The patient refused to undergo surgery.

Three years later, the vision decreased to Hand motion (HM)/40 cm in the right eye and Light perception (LP) in the left eye. Slit-lamp photography showed visible neovascularization in the irises (Fig. 3E), and fundoscopy showed optic nerve atrophy in both eyes. The IOP of both eyes was 38 mmHg. UBM suggested an open atrial angle and vitreous opacity in both eyes. FFA of the right eye showed increased retinal capillary dilatation and leakage in the posterior pole and peripheral retina. In the mid to late stages, the fluorescent leakage was enhanced and

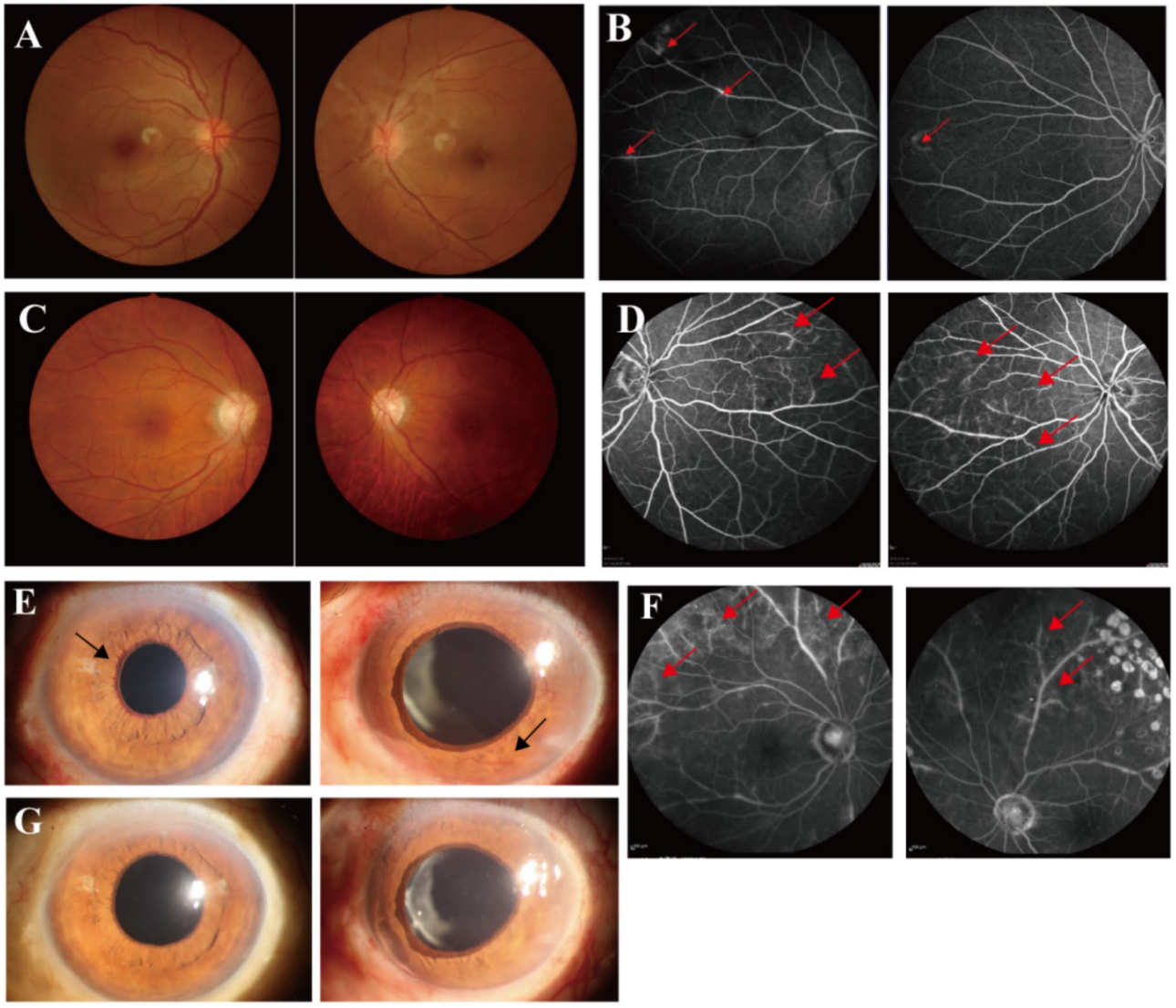

Fig. 3 Ophthalmic features of the proband. **(A)**Fundus photography showed no abnormality in the bilateral eyes after vitrectomy at first visit and **(B)**the corresponding FFA shows retinal vessel fluorescence leakage in the peripheral retinal. **(C)**Fundus photography showed no abnormality in either eye after 9 years, however **(D)**the corresponding FFA of the bilateral eyes showed peripheral retinal telangiectasia, vascular leakage, and neovascularization. **(E)**Slit-lamp photography showed iris neovascularization in the bilateral eyes 3 years after last visit and **(F)**FFA of the bilateral eyes showed a large area of non-perfusion, telangiectasia, vascular leakage, and neovascularization in the posterior pole and peripheral retina. **(G)**Slit-lamp photography showed resolution of iris neovascularization after panretinal photocoagulation and intravitreal anti-VEGF. Red arrow: abnormal capillaries in the posterior pole and peripheral retina. Black arrow: iris neovascularization

diffuse, and the veins showed focal staining. The retina showed neovascularization and large areas of non-perfusion. FFA of the left eye showed fluorescence staining in the macular area. Small patches of non-perfusion area and neovascularization occurred (Fig. 3F). Retinal photocoagulation and intravitreal anti-VEGF were therefore conducted in both eyes. One week after surgery, iris neovascularization disappeared (Fig. 3G) and IOP returned to normal (16 mmHg in the right eye and 18 mmHg in the left eye). However, visual acuity did not improve significantly (HM/40 cm in the right eye and LP in the left eye).

Discussion

This study described a large Chinese family with hereditary ocular amyloidosis in which vitreous opacity was found in 18 patients, 36 eyes. In the affected population from the large Chinese family, the prevalence of RAA was 88.9% (32/36). The result differed from the study of Kakihara et al. in which they retrospectively reviewed 102 eyes of 51 patients with ATTR Val30Met amyloidosis who underwent FFA and indocyanine green angiogramsthey. In their study, RAA was detected in 37.5% [8]. The prevalence was also higher than the study of Su et al. in which the data was also collected from patients

with ATTR Gly83Arg amyloidosis but RAA was detected in 25% [15]. There are some reasons for this discrepancy. First, in the study of Su et al., FFA was performed in only two patients. FFA might be a more sensitive test for detecting vascular changes than fundoscopy for hATTR patients, especially for detecting early vascular changes such as microaneurysms, telangiectasia and vascular closure [12]. In this study, all patients underwent FFA after vitrectomy, which greatly improved the detection rate of RAA. Second, the phenotype of hATTR may differ among different mutant types and regions. We found the age of RAA onset can be very early in ATTR Gly83Arg amyloidosis, with the earliest diagnosis being made in the first year of disease. In a cross-sectional study around patients with ATTR Val30Met amyloidosis, RAA was first diagnosed in the third year of the disease course [13]. This suggests that in ATTR Gly83Arg amyloidosis, amyloid damage to the retinal vasculature may occur very early, and may even be synchronized with pathological changes in vitreous amyloidosis. Marques et al. divided RAA into two stages, subclinical and clinical, according to the results of fundus examinations [12]. In this study, we divided RAA into three stages according to the damage to the retina: early (1–5 years after onset), progressive (6–9 years after onset), and clinical (10–18 years after onset). In the early and progressive stages of RAA, vascular abnormality was not detected by fundus photography, but FFA showed vascular damage. In the early stage, vascular occlusion, microaneurysms, telangiectasia, vascular leakage can be seen. And in the progressive stage, there is non-perfusion area and retinal neovascular. In the clinical stage of RAA, neovascular glaucoma, retinal detachment, and choroidal hemorrhage occur and there were severer retinal neovascular. In summary, RAA associated with ATTR Gly83Arg amyloidosis was characterized by early-onset and high prevalence.

Current studies report a relatively high prevalence of secondary glaucoma in several mutant types of hATTR, and IOP in the hATTR patients is difficult to control [14, 16]. Kakihara et al. [17] suggested that these findings might be due to the diffusion of amyloid fibrils into aqueous fluid, which blocked the trabecular meshwork and led to increased IOP. Beirao et al. suggested that the diffusion of amyloid fibrils into the trabecular meshwork after surgical invasion increased the risk of glaucoma after PPV [18, 19]. While in this study, neovscular glaucoma was diagnosed at a median of 12 years of disease. The prevalence of neovascular glaucoma was 33.3% (10/36). Retinal neovascularization (Fig. 3F) and iris neovascularization (Fig. 3E) were observed in patients with glaucoma. After panretinal photocoagulation and intravitreal anti-VEGF, iris neovascularization disappeared (Fig. 3G) and IOP was well controlled. We can not rule out the possibility of concomitant amyloid deposits in the anterior chamber, however, panretinal photocoagulation might be used as an anti-neovascular and anti-amyloid production treatment to control further elevation of IOP and further damage to the optic nerve [24]. More research based on the mechanisms of hATTR-associated neovascular glaucoma as well as treatment regimens is needed. Choroidal hemorrhage has also been reported as a complication of amyloid angiopathy [20]. In the progressive stage of disease, the risk of choroidal hemorrhage during surgery is very high because amyloid fiber deposition in the retina and choroidal vessels can cause vascular endothelial cell damage and increase vascular fragility. Xu et al. found that intraocular pressure fluctuation and amyloid angiopathy were trigger factors for suprachorioidal hemorrhage [20]. Shen et al. suggest conducting indocyanine green angiography (ICGA) examination before the operation to evaluate choroidal amyloid angiopathy. In this study, one patient (IV:2) underwent PPV 12 years after onset of disease and developed choroidal hemorrhage during surgery. In addition, typical clinical manifestations of ocular amyloidosis, including abnormal conjunctival vessels, pupillary changes, and keratoconjunctivitis sicca, were not observed in the patients.

Although there was a high prevalence of RAA in this family, it is not specific to the G83R mutation. RAA has been reported in other types of hATTR, such as Y114C [21], E54G [22], and A36P [23]. Involvement of ocular vessels initially presents as amyloid deposition in the muscle layer of the small arteries. Subsequently, the entire artery and arteriole walls as well as veins and capillaries in the retina and choroid are affected by amyloid protein, causing small blood vessel occlusion. Finally, retinal ischaemia and intraocular elevated VEGF lead to neovascularization [22]. As neovascularization causes severe visual impairment, retinal photocoagulation and intravitreal injection of anti-VEGF drugs must be performed before the occurrence of complications associated with RAA to prevent the irreversible impairment of visual function. In addition, retinal photocoagulation can further reduce the production and deposition of degenerative amyloid protein in the retina [24]. Given the high prevalence of RAA in ATTR Gly83Arg amyloidosis and the high risk of blindness with disease progression, the following treatment plan is recommended for patients with ATTR Gly83Arg amyloidosis: (1) asymptomatic carriers must undergo annual evaluation, including measurement of IOP, fundus examination and FFA, as the earliest retinal vascular changes can be observed using FFA; (2) patients must undergo FFA reassessment every six months after PPV and retinal photocoagulation must be conducted when non-perfusion areas are formed; (3) in the clinical stage of RAA, patients must undergo repeated ophthalmologic evaluations every three months; as it is difficult to control the progression

of ocular symptoms, multiple laser photocoagulation and intravitreal anti-VEGF are often required. Early detection and intervention will reduce the incidence of retinal function injury and complications caused by RAA and help maintain good vision.

This study has certain limitations. First, all patients included in this study were members of the same family. Second, the sample size was small. However, considering the rarity of the disease, the study cohort was relatively large. Clinical information was obtained from 131 members of this seven-generation family, and 18 patients were included in the analysis. Lastly, the characteristics of the disease progression in this study only represented TTR Gly83Arg mutation. More long-term evidence is needed on whether RAA is as destructive in other mutant phenotypes.

3. Conclusion.

This is the first long-term follow-up study of a large sample size of cases from a seven-generation family with ATTR Gly83Arg amyloidosis. This study reported the presentation and analyzed the prognosis of RAA and found that RAA and associated complications are the main causes of irreversible impairment of visual function in patients with ATTR G83R amyloidosis. The high prevalence (88.9%), early onset (1 year), and late complications associated with retinal vascular destruction are features of RAA in patients with ATTR G83R amyloidosis, which provides certain references for the study of other hATTR mutants. Early detection and intervention of RAA after vitrectomy is essential to delay permanent visual impairment. The characteristics of RAA in this study can help clinicians to make a comprehensive diagnosis of RAA in patients with hATTR, achieve timely treatment, and protect visual function when hATTR progress.

Abbreviations

RAA	Retinal amyloid angiopathy
hATTR	Hereditary amyloid transthyretin
BCVA	Best-corrected visual acuity
TTR	Transthyretin
VO	Vitreous opacity
VEGF	Vascular endothelial growth factor
IOP	Intraocular pressure
UBM	Ultrasound Biomicroscope
OCT	Optical coherence tomography
FFA	Fundus fluorescein angiography
PPV	Pars plana vitrectomy
CF	Counting finger
HM	Hand motion
LP	Light perception

Acknowledgements

The authors thank Zhenglin Yang provided infrastructure and bioinformatic expert input, and Yi Cao for expert opinion in major revision of manuscript.

Author contributions

Conceptualization, J.X. and N.S.; Methodology, J.X. and N.S.; Formal Analysis, X.L. and P.G.; Investigation, J.X., X.L. and P.G.; Data Curation, J.X. and N.S.; Writing, J.X. and N.S.; Supervision, Y.W. and S.L.; Project Administration, Y.W. and S.L.; Funding Acquisition, Y.W. and S.L. All the authors have read and agreed the published version of the manuscript.

Funding

This research was funded by [Scientific and technological projects with combination of medicine and engineering in Xiamen of China] under Grant [3502Z20224030]; [Municipal Education Commission Science and Technology Research Youth Project in Chongqing of China] under Grant [KJQN202102807]; [Key Research and Development Programs in Hunan Province] under Grant [2020SKC2003]; This work was supported by grants from the Project of Xiamen Cell Therapy Research Center, Xiamen, Fujian, China (3502Z20214001); [Nature Science Foundation of Fujian Province of China] under Grant [2022J01110650]; [Scientific and technological projects with combination of medicine and engineering in Xiamen of China] under Grant [3502Z20224030]; [Shapingba District Science and Health Joint Medical Research Program] under Grant [2023SQKWLH036]; and [Scientific research projects of Chongqing Medical and Pharmaceutical College] under Grant [ygz2024101].

Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Southwest Hospital, Third Military Medical University (China) (approval code: 2011-24). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article. Moreover, All methods in the present study were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 9 July 2024 / Accepted: 9 April 2025
Published online: 28 April 2025

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