

Ocular manifestations of familial amyloidotic polyneuropathy type I: long term follow up

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Abstract

Aims—To obtain precise information on ocular manifestations of familial amyloidotic polyneuropathy (FAP) type I, the incidence of five main ocular manifestations—abnormal conjunctival vessels (ACV), keratoconjunctivitis sicca (KCS), pupillary abnormality, vitreous opacity, and glaucoma, were compared through long term follow up.

Methods—Ocular examinations were performed in 37 FAP type I patients (Met30) from once to 12 times over a period of 1 to 12 years and 7 months.

Results—The following incidences were observed on initial examination of each patient with FAP: ACV in 75.5%, pupillary abnormalities in 43.2%, KCS in 40.5%, glaucoma in 5.4%, and vitreous opacity in 5.4%. All ocular manifestations increased with the progression of FAP, and the incidence of ACV reached 100% during follow up; this may be helpful in the diagnosis of FAP.

Conclusion—Since no precise statistical ocular study on FAP with long term follow up has been performed, this report may provide important information to help elucidate the mechanism of the amyloid distributing process in the amyloid targeted organs of FAP and to provide the natural course of ocular manifestations of FAP.

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Familial amyloidotic polyneuropathy (FAP) is a heterogeneous collection of familial diseases characterised by the systemic accumulation of amyloid fibrils in the peripheral nerves and other organs.¹⁻³ Knowledge of the biochemical nature of the amyloid fibril proteins in these hereditary syndromes is limited. Currently, the disease is subclassified according to the following clinical features and ancestry or geographic origin: type I, polyneuropathy with onset in the lower limbs and severe autonomic dysfunction (Portuguese, Japanese, Swedish, and Jewish families); type II, polyneuropathy with onset in the upper limbs and mild autonomic dysfunction (Swiss-German families); type III, polyneuropathy, renal failure and cranial neuropathy; and type IV, lattice corneal dystrophy type II (Finnish, Irish, American, and Japanese families).⁴⁻⁸

Recent studies have revealed that FAP types I⁷ and II⁸ are associated with variant of transthyretins (TTRs), and FAP type III is

related to a variant form of apolipoprotein AI (apo AI).⁶ FAP type IV is related to variants of gelsolin.⁵

Replacement of valine-30 of TTR by methionine is a prerequisite for the formation of amyloid deposits in FAP type I. It is well known that TTR is synthesised in the retina as well as the liver and choroid plexus in the brain.⁹ Thus, the precise examination of ocular tissues in patients with FAP may provide important information on the mechanism of amyloid formation in TTR related FAP.

Among the four types of FAP, FAP type I is most common, with vitreous opacity and glaucoma the well known clinical findings along with other organ failures.^{1-4 10 11} In addition to these ocular symptoms, we have recently reported that abnormal conjunctival vessels (ACV) are also common in this disease.¹² However, the incidence of these ocular symptoms and changes in the incidence during the progression of the disease have not been well documented. Moreover, comparison between ocular manifestations and systemic symptoms of amyloidosis and also comparison of ocular manifestations among the patients in different endemic areas have not been discussed.

Since FAP type I is prevalent in Arao district, Kumamoto, Japan, a long term follow up was carried out and the incidence of ocular manifestations in each clinical stage of FAP were compared.

Patients and methods

SUBJECTS

Thirty seven patients with FAP type I (aged 24-63 years, average 38.0 (SD 9.7) years, 24 males and 13 females) were examined for ocular abnormalities. Thirty five of the patients (23 males and 12 females) were early onset cases (younger than 52 years) and only two were late onset cases (one male and one female, older than 52 years). The division of these two groups was based on the report by Sequeiros *et al.*¹³ Two male and one female FAP asymptomatic carriers began to show clinical findings of FAP during the follow up. All the patients were referred to Kumamoto University School of Medicine, Arao City Hospital or Nakashima Clinic. Patients with FAP were diagnosed by protein chemistry or genetic investigation^{14 15} in addition to clinical findings. All the patients had an obvious family history. The number of the patients followed up more than 1 year was 29 (19 males and 10 females). The duration of follow up was from 1 year to 12 years and 7 months (average 3 years and 6 months). Seventeen patients were

Table 1 Incidence of ocular manifestations at the first ocular examination

Ocular symptoms	No of patients	Incidence (%)
ACV	28	75.7
KCS	15	40.5
Pupillary abnormality	16	43.2
Vitreous opacity	2	5.4
Glaucoma	2	5.4

ACV = abnormal conjunctival vessels; KCS = keratoconjunctivitis sicca.

followed for less than 5 years; 13 for 5–10 years; six for more than 10 years; and one unknown.

METHODS

To obtain precise information on ocular manifestations of FAP, five main ocular manifestations, ACV, KCS, pupillary abnormality, vitreous opacity, and glaucoma, were studied in addition to routine ocular examination.

Observation of ACV

All the patients underwent slit-lamp biomicroscopic examination to determine the presence of ACV according to the method used in a previous study.¹²

Diagnosis of KCS

The diagnostic criteria of KCS were the degree of decreased tear secretion (Schirmer test < 5 mm) or fluorescein and rose Bengal staining in the keratoconjunctiva.

Results

INCIDENCE OF OCULAR SYMPTOMS IN PATIENTS WITH FAP TYPE I (MET30)

Table 1 indicates the ocular symptoms of patients with FAP type I when the first ocular examination was performed.

KCS

KCS was seen in 15 patients with FAP (40.5%) (10 females and five males) when the first examination was performed. Another eight of the 22 patients (21.6%) began to show KCS during the follow up. No KCS was recognised in 10 patients during the follow up and, in four the corneal examination was not carried out. For treatment of KCS, most of the patients received topically instilled artificial tears or agents to protect the cornea. In five patients with severe KCS, closure of the lacrimal punctum was performed in three and tarsorrhaphy in two.

Glaucoma

Glaucoma was recognised in only two patients (5.4%) (left eye of a 34-year-old man, right eye of a 55-year-old man). Since two of the patients had drug resistant glaucoma, trabeculectomies were carried out. The 34-year-old man died 5 months after the operation because of the cardiac failure. In the 55-year-old man, intraocular pressure was well controlled without any particular treatment for 2 years after the operation, and the other eye exhibited no glaucomatous change. A 50-year-old man whose duration of the disease was 13 years began to show glaucomatous change in his left

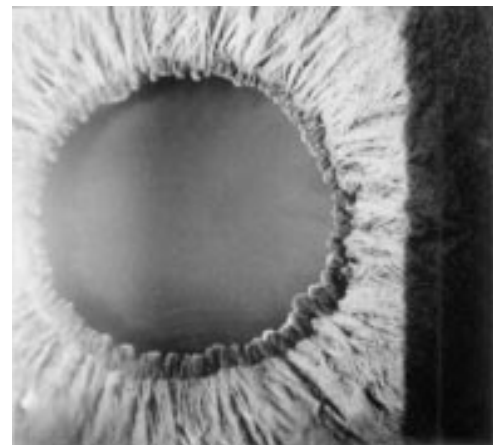


Figure 1 Slit-lamp examination. Pupillary border with irregularity and white membranous material observed in a 53-year-old man.

eye 13 months after the initial ocular examination. Topical instillation therapy was started immediately; however, control of intraocular pressure was impossible, and 1 year and 10 months after the initial examination, the patient died because of the deterioration in his general condition. Amyloid deposition was confirmed in the pupillary border and the surface of the lens capsule in these patients by slit-lamp (Fig 1) and histopathological examinations (Fig 2).

Vitreous opacity

Vitreous opacity was observed in two patients (5.4%) (left eye of a 34-year-old man, and left eye of a 42-year-old woman). During the follow up, another four patients began to show vitreous opacity. No vitrectomy was performed in these patients because five patients showed slight changes without severe visual disturbance and one patient who had to undergo the operation died with this disease before the operation.

Other ocular manifestations

Pupillary abnormality was recognised in 16 patients (43.2%) (11 males and five females): decrease in the light reflex, eight (21.6%); deformity of the pupil, eight (21.6%); amyloid deposition in the pupillary border, seven (18.9%); and decrease in the light and near reflex, one (2.7%). The number of patients without pupillary abnormality was 19 (51.4%), and unknown two (5.4%). Another 11 patients began to show pupillary disorders during the follow up: decrease in the light reflex, four (36.4%); deformity of the pupil, eight (72.7%); amyloid deposition in the pupillary border, four (36.4%). Seven patients exhibited no pupillary disorders at all during the follow up. ACV were recognised in 28 patients (75.7%) (18 males and 10 females) at the initial examination; only seven (18.9%) patients did not exhibit ACV with unknown two (5.4%). Another four patients began to show ACV during the follow up. Only one patient did not show vessel abnormality at all during the follow up. He had been an asymptomatic carrier without any clinical symptoms and started to

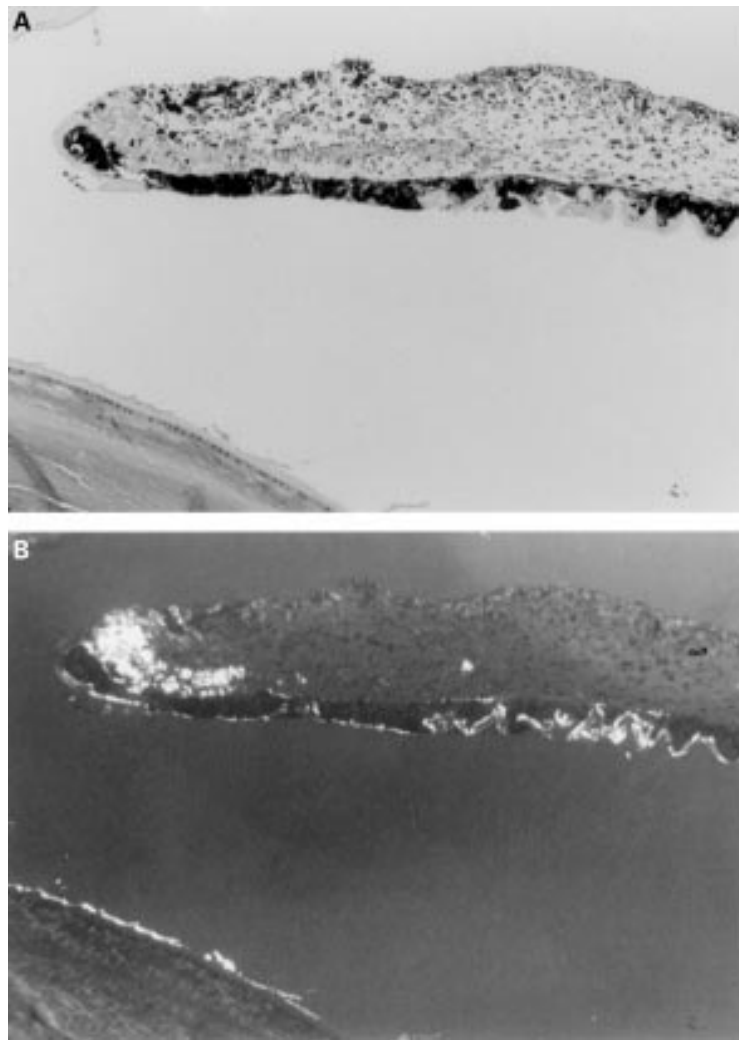


Figure 2 Histopathological findings of the iris in a patient with FAP. (A) Necropsied iris in a 53-year-old man stained with phenol Congo red with haematoxylin. Congophilic substance was deposited on the lens capsule, anterior, pupillary, and posterior surface of the iris. The same change was also recognised in the sphincter and dilator muscles of the iris (magnification $\times 100$). (B) The same area as (A) was photographed under polarised light. The substance positive for Congo red was shown as green birefringence (magnification $\times 100$).

exhibit systemic amyloidosis within 1 year after the ocular examination.

Change in the retina was seen in eight patients (21.6%) at the initial examination: small retinal haemorrhage, four; soft exudate (cotton wool patch), three; neovascularisation in the peripheral retina, one; splinter haemorrhage of the optic disc, one; and fungal endophthalmitis, one. No additional changes were observed during the follow up.

DURATION OF FAP AND INCIDENCE OF OCULAR SYMPTOMS

To evaluate the effect of the progression of FAP on changes in the ocular symptoms, the initial ocular symptoms were compared between three groups—A (less than 5 years after onset, $n = 17$), B (5–10 years after onset, $n = 13$), and C (more than 10 years after onset, $n = 6$). All ocular manifestations of FAP increased with progression of FAP (Table 2). Incidence of ACV and pupillary abnormality reached 100% in group C during the follow up.

Table 2 Duration of familial amyloidotic polyneuropathy and incidence of ocular symptoms

Ocular symptoms	Incidence (%)		
	A	B	C
ACV	76.5	75.0	100
KCS	11.8	61.5	83.3
Pupillary abnormality	11.8	46.2	100
Vitreous opacity	0	8.3	16.7
Glaucoma	0	8.3	16.7

ACV = abnormal conjunctival vessels; KCS = keratoconjunctivitis sicca.

A = <5 years after onset; B = 5–10 years after onset; C = >10 years after onset.

Table 3 Duration of familial amyloidotic polyneuropathy before the presence of main clinical symptoms

Ocular symptoms	Duration (years)
ACV	2.8
KCS	4.4
Pupillary abnormality	5.6
Vitreous opacity	9.5
Glaucoma	14.5

ACV = abnormal conjunctival vessels; KCS = keratoconjunctivitis sicca.

TIME TO APPEARANCE OF OCULAR SYMPTOMS

During the follow up, the incidence of newly acquired symptoms was evaluated. As indicated in Table 3, ACV were recognised first in most patients and then KCS, pupillary disorders, vitreous opacity, and glaucoma in that order.

Discussion

Ocular manifestations in 37 patients with FAP type I (Met30) were presented through long term follow up in Arao district, Kumamoto, Japan, which is one of the most well known endemic areas for this disease.^{4–16} Statistical analysis revealed that ACV showed the highest incidence among the ocular disorders. The incidence of KCS, pupillary abnormality, vitreous opacity, and glaucoma followed ACV. It is well documented that amyloid deposition is commonly found in the perivascular area^{2–3} so ACV may reflect the microscopic changes in the vessels.

It is believed that unmyelinated fibres, which correspond to autonomic nerve fibres, are first impaired during the course of the disease.¹⁷ In fact, many ordinary FAP patients start to develop autonomic dysfunctions before sensory dominant polyneuropathy.¹ We previously reported that ACV are possibly induced by autonomic nervous dysfunction as well as amyloid deposition around the vessels themselves because all patients we examined with pandysautonomia showed the same changes.¹² Therefore, it is also natural that the susceptibility of autonomic nerves in the early stage of FAP should reflect the high incidence of pupillary disorder and KCS. Concerning KCS, we reported histopathological changes in the lacrimal gland in FAP patients¹⁸: most of the secretory cells themselves remained almost normal, though amyloid deposition was recognised around the acini, the duct, the vessels and the nerves in the lacrimal glands in all cases. In this study, we assumed that early lacrimal deficiency in FAP patients should be

Table 4 Difference in ocular manifestations between Sweden and Japan

	Incidence (%)	
	Sandgren (Sweden)	Ando (Japan)
KCS:		
Early onset case	13/25 (52.0)	25/35 (71.4)
Late onset case	4/26 (15.4)	1/2 (50.0)
Total	17/51 (33.3)	26/37 (70.3)
Vitreous opacity:		
Early onset case	3/32 (9.4)	6/35 (17.1)
Late onset case	13/52 (25.0)	0/2 (0)
Total	16/84 (19.0)	6/37 (16.2)

KCS = keratoconjunctivitis sicca.

induced by the disturbance of the nerves innervating the lacrimal gland before the loss of secretory cells.

Interestingly, ACV were recognised in most of the patients from the early stage (less than 5 years after onset) and the incidence of this abnormality reached 100% by the end stage of FAP. This result supports the finding of ACV to be helpful in the diagnosis of FAP.¹²

Sandgren *et al*¹⁹⁻²¹ have carried out an important ocular study on FAP patients in the northern part of Sweden which is another well known endemic area, but their study was limited to KCS and vitreous opacity. Compared with our findings, the incidence of vitreous opacity was almost the same; however, that of KCS was surprisingly higher in Japanese than in Swedish patients (Table 4). The most important aspect to explain these differences may come from the difference in age of onset. The average age of onset of FAP in our Japanese patients was at 34.6 (SD 5.6) years of age while that in Swedish patients is 55.6 (6.3) years of age.²¹ In the Swedish study, the late onset cases (more than 52 years old)¹³ comprise half of the total number of patients with FAP examined (54.6%); however, in this Japanese study, they comprised only 5.4%. Sandgren *et al* pointed out that KCS was the most common finding in the early onset cases while in the late onset cases vitreous opacity was the most common. Their comment explains our incidence of KCS and vitreous opacity. Most Japanese FAP type I patients show severe autonomic dysfunctions as well as sensory dominant polyneuropathy, which might also be influenced by the onset of FAP.¹

We do not know which factor(s) control the age of onset and the progression of FAP. Although no systematic or long term study of ocular manifestations of FAP has been performed, our report may help to elucidate the mechanism of amyloid distributing process in the amyloid targeted organs of FAP as well as indicating the natural course of ocular manifestations of FAP.

Dr Eiko Ando is temporarily working as a research fellow at the Department of Ophthalmology, Umeå, University Hospital.

- Ando Y, Araki S, Shimoda O, Kano T. Role of autonomic nerve functions in patients with familial amyloidotic polyneuropathy as analyzed by laser Doppler flowmetry, capsule hydrograph, and cardiographic R-R interval. *Muscle Nerve* 1992;15:507-12.
- Araki S. Type I familial amyloidotic polyneuropathy (Japanese type). *Brain Dev* 1984;6:128-33.
- Ando Y, Yi S, Nakagawa T, Hirota M, Miyazaki A, Araki S. Disturbed metabolism of glucose and related hormones in familial amyloidotic polyneuropathy: hypersensitivities of the autonomic nervous system and therapeutic prevention. *J Auton Nerv Syst* 1991;35:63-8.
- Araki S, Ikegawa S, Yi S, Murakami T, Ando Y, Miyazaki A, *et al*. Atypical cases of familial amyloidotic polyneuropathy (FAP) in Japan. In: Costa PP, Freitas AS, Saraiva MJM, eds. *Familial amyloidotic polyneuropathy and other transthyretin disorders*. Porto:Arquívus de Medicina, 1990:267-70.
- Haltia M, Prelli F, Kjiuru S, Somer H, Palo J, Frangione B. Amyloid protein in familial amyloidosis (Finnish type) is homologous to gelsolin, an actin-binding protein. *Biochem Biophys Res Commun* 1990;167:927-31.
- William CN, Richard EG, Bryan B Jr, Merrill DM. A mutation in apolipoprotein A-I in the Iowa type of familial amyloidotic polyneuropathy. *Genomics* 1990;8:318-21.
- Tawara S, Nakazato M, Kanagawa K, Matsuo H, Araki S. Identification of amyloid prealbumin variant in familial amyloidotic polyneuropathy (Japanese type). *Biochem Biophys Res Commun* 1983;116:880-8.
- Dwulet FE, Benson MD. Characterization of transthyretin (prealbumin) variant associated with familial amyloidotic polyneuropathy type II (Indiana/Swiss). *J Clin Invest* 1986;78:880-6.
- Martone RL, Herbert J, Dwork A, Shon EA. Transthyretin is synthesized in the mammalian eye. *Biochem Biophys Res Commun* 1988;151:905-12.
- Falls HF, Jackson J, Carey JH, Rukavina JG. Ocular manifestations of hereditary primary systemic amyloidosis. *Arch Ophthalmol* 1955;54:660-4.
- Futa R, Inada K, Nakashima H, Okamura R. Familial amyloidotic polyneuropathy. Ocular manifestations with clinicopathological observations. *Jpn J Ophthalmol* 1984;28:289-98.
- Ando E, Ando Y, Maruoka S, Sakai Y, Watanabe S, Yamashita R, *et al*. Ocular microanopathy in familial amyloidotic polyneuropathy, type I. *Graefes Arch Clin Exp Ophthalmol* 1991;230:1-5.
- Sequeiros J, Sousa A, Coelho I. Sex differences and age-dependent penetrance in FAP type I. In: Natvic JB, Forre O, Husby G, Husebekk A, Skogen B, Slettern K, Westermark P, eds. *Amyloid and amyloidosis*. Dordrecht: Academic Publishers, 1991:687-700.
- Sakaki H, Sakai Y, Matsuo H, Goto I, Kuroiwa Y, Sahashi I, *et al*. Diagnosis of familial amyloidotic polyneuropathy by recombinant DNA techniques. *Biochem Biophys Res Commun* 1984;125:636-42.
- Nakazato M, Kurihara T, Kangawa K. Diagnostic radioimmunoassay for familial amyloidotic polyneuropathy (letter). *Lancet* 1984;2:1274-5.
- Ando Y, Araki S, Ando M. Transthyretin related amyloidosis. *Intern Med* 1993;32:920-2.
- Ausbery AK, Johnson PC. Pathology of peripheral nerve. In: Bennington JH, ed. *Major problems in pathology*. Philadelphia: Saunders, 1980:148.
- Maruoka S, Ando E, Inada K, Okamura R, Yamashita R, Ando Y, *et al*. Histopathological changes in the lacrimal gland in familial amyloidotic polyneuropathy- pathogenesis of lacrimal deficiency. In: Shimizu K, ed. *Current aspects in ophthalmology*. Amsterdam: Elsevier, 1992:203-6.
- Sandgren O, Holmgren G, Lundgren E. Vitreous amyloidosis associated with homozygosity for the transthyretin Met-30 gene. *Arch Ophthalmol* 1990;108:1584-6.
- Sandgren O, Ericson A. Lacrimal dysfunction in familial amyloidotic polyneuropathy (FAP), Swedish type. In: Costa PP, Freitas AS, Saraiva MJM, eds. *Familial amyloidotic polyneuropathy and other transthyretin disorders*. Porto: Arquívus de Medicina, 1990:329-33.
- Sandgren O. Vitreous opacity in familial amyloidotic polyneuropathy, Swedish type. In: Costa PP, Freitas AS, Saraiva MJM, eds. *Familial amyloidotic polyneuropathy and other transthyretin disorders*. Porto:Arquívus de Medicina, 1990:334-8.



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