Ocular changes in heredo-oto-ophthalmo-encephalopathy

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Abstract

Background — **Heredo-oto-ophthalmo-encephalopathy (HOOE) is a dominantly inherited disease characterised by gradual loss of vision from the age of 20, progressive hearing loss from the late 20s, cerebellar ataxia in the 30s, and death in dementia in the fourth or fifth decade. Currently, no detailed description has been given of the ocular changes seen in HOOE. Therefore, the ocular changes of HOOE were described on the basis of clinical and histological data from six affected family members.**

Methods—**Three members of the family affected by HOOE were subjected to a full ophthalmological re-examination, and postmortem examination was done on three eyes from two affected family members.**

Results—**Visual loss in HOOE was caused by posterior subcapsular cataract and retinal neovascularisations leading to vitreous haemorrhages and neovascular glaucoma. In the retina there was extensive accumulation of an amyloid material, both diffusely and in the walls of the retinal vessels. The retinal glial cells showed extensive pathological changes and retinal Müller cells were seen to occlude the lumen of retinal vessels.**

Conclusion — **Heredo-oto-ophthalmo-encephalopathy is a familial amyloidosis of the central nervous system which is different from previously reported cases of amyloidosis by including cataract and retinal neovascularisations. The disease is accompanied by extensive changes in retinal glial cells that may play a part in the pathophysiology of the ocular complications of the disease.**

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Heredo-oto-ophthalmo-encephalopathy (HOOE) is a dominantly inherited syndrome characterised by gradual loss of vision from the age of 20, progressive hearing loss from the late 20s, cerebellar ataxia in the 30s, and death in dementia in the fourth or fifth decade. This phenotypical presentation has only been described in a Danish family, and recently it has been shown that the syndrome is due to an accumulation of amyloid-like substance in the affected neural tissue.[1–3]

In previous studies the neurological, psychiatric, neuropathological, and genetic characteristics of the syndrome have been described.[1–4] However, at present no detailed description has been given of the ocular changes seen in HOOE.

Here, the ocular changes of HOOE are described on the basis of clinical data from six affected family members and postmortem histopathological examination of three eyes from two affected people.

Subjects and methods

PEDIGREE

A family history could be obtained for six generations, and the disease showed a dominant pattern of inheritance (Fig 1). All affected members had developed central hearing loss during the late 20s, cerebellar ataxia during the 30s, and had died in organic dementia during the fourth or fifth decade.

OPHTHALMOLOGICAL EXAMINATION

Members V.2, V.3, and VI.1 were subjected to a routine ophthalmological examination including testing of best corrected visual acuity, slit lamp examination, applanation tonometry, ophthalmoscopy, and visual acuity testing. Furthermore, fundus photography, fluorescein angiography, electroretinography, and visual evoked potentials were performed. Members IV.2, IV.4, and V.5 had previously been followed at the Department of Ophthalmology, Århus University Hospital, since the onset of ocular symptoms, and clinical data were obtained from their hospital records.

HISTOPATHOLOGICAL EXAMINATIONS

One eye from III.6 and two eyes from IV.4 had been embedded in paraffin at necropsy, and were available from the Department of Neuropathology, Århus University Hospital. Twenty four sections traversing the macular area from periphery to periphery were studied from each eye.

Histological staining

In each eye six sections were stained with, respectively, periodic acid Schiff pretreated with α amylase, Alcian blue at pH 2.6, Congo red, methyl violet, and thioflavin.

Immunohistochemistry

Immunohistochemistry was performed using the procedure described earlier.[5–7]

Antibodies (from Dako, Glostrup, Denmark)— Polyclonal rabbit anti-human von Willebrand factor (vWf) and fibronectin, rabbit anti-cow glial fibrially acid protein (GFAP), and S-100 primary antibodies, used with swine anti-rabbit secondary antibody and rabbit peroxidase-antiperoxidase complex. Monoclonal mouse anti-human type IV collagen (clone CIV22) and actin (clone 1A4) with peroxidase conjugated rabbit anti-mouse secondary antibody, and peroxidase conjugated swine anti-rabbit tertiary antibody.

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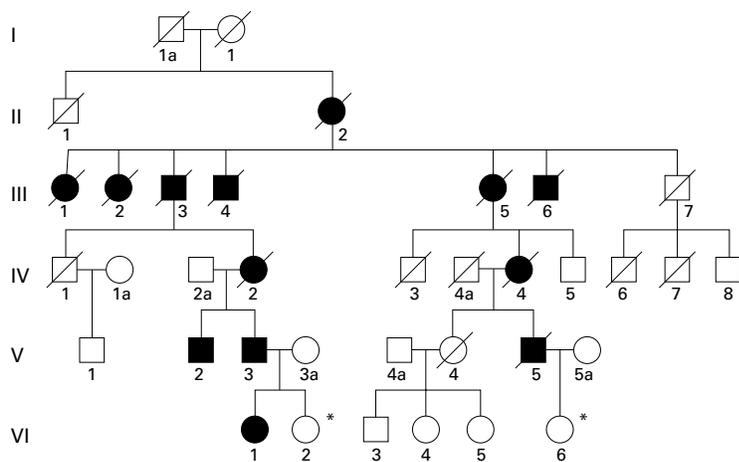T Bek

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Figure 1   Pedigree of the studied family with HOOE. Asterisks indicate family members who have not reached the age where ocular symptoms may develop.

Figure 2   The fundus of the right eye of VI.1. A cotton wool spot is seen at the lower temporal vascular arcade (arrow).

Figure 3   The temporal part of the macular area in the left fundus of V.2. The fovea is indicated with a black dot. The retina shows pronounced pathology with haemorrhages, exudates, and calibre changes of the retinal venules. The pale spots temporally in the macular area represent laser scars.

Procedure—For each immunoreaction primary antibody concentrations were defined from preliminary titration experiments—that is, vWf (1:50, 1:100, 1:200), GFAP (1:750, 1:1500, 1:3000), S-100 (1:800, 1:1600, 1:3200), type IV collagen (1:750, 1:1500, 1:3000), actin (1:4000, 1:8000, 1:12000), and fibronectin (1:500, 1:1000, 1:1500). Secondary and tertiary antibodies were used in a concentration of (1:100).

Controls—The control procedures was as described earlier.[4–6] The photoreceptors served as negative control for all immunoreactions. The following were used as positive controls: radial Müller cells for GFAP, Schwann cells around ciliary nerves penetrating the sclera for S-100 protein, smooth muscle cells in ciliary vessels for actin, and basement membranes in these vessels for type IV collagen and fibronectin. Furthermore, sections were included where the secondary antibody and the tertiary antibody/peroxidase anti-peroxidase complex, respectively, had been omitted. None of the employed antibody reactions showed any false positive or false negative staining reactions.

Results

CLINICAL DATA

The occurrence of cataract and complications from neovascularisations are shown in Table 1.

The family members who experienced visual impairment around the age of 20 had a posterior subcapsular cataract. The available patient records showed the following improvement of visual acuity after cataract surgery: IV.2 right eye: 0.1–1.0, IV.2 left eye: 0.17–0.67, V.2 right
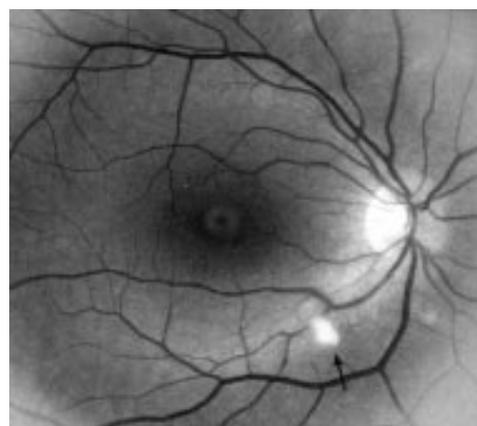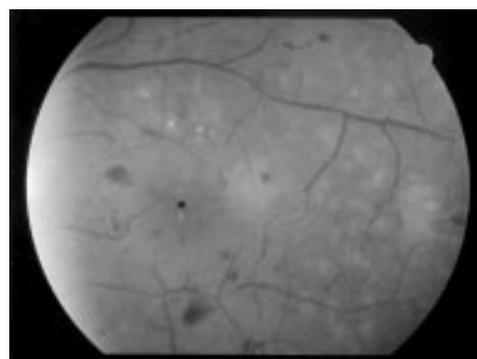
eye: unknown–1.25, V.2 left eye: 0.1–0.67, VI.1 right eye: 0.3–1.0. In VI.1 a cataract was observed on the left eye located subcortically in the posterior lens pole, but otherwise did not show any special morphological characteristics.

Cotton wool spots in the 20s in two patients were the earliest observed retinal change (Fig 2). In those family members who had experienced repeated vitreous haemorrhages both eyes were affected, and the haemorrhages had been observed to originate from preretinal neovascularisations. The affected eyes of these patients had received repeated vitrectomies and panretinal laser photocoagulation but, apart from the left eye of V.2, all became blind due to neovascular glaucoma. At the time of examination visual acuity in this eye was 0.5 with aphakia correction of +12.0. The pupil was small and immobile, but there was no rubeosis. The vitreous body and the view to the fundus was clear. The optic disc was slightly atrophic. Numerous almost confluent photocoagulation scars were seen in the retinal periphery. The macular area appeared slightly yellowish. There were calibre changes of the larger retinal venules, intraretinal microvascular abnormalities, and dispersed intraretinal haemorrhages and hard exudates (Fig 3). Fluorescein angiography of the macular area showed no leakage or non-perfusion, and the

Table 1   The age at examination and the age of onset of ocular symptoms in the studied family members

	Age at examination (years)	Age at onset of ocular symptoms (years)	
		Cataract	*Neovascularisations*
IV.2		20	none
V.2	45	20	31
V.3	42	none	none
VI.1	21	20	none!
IV.4		unknown age of onset	unknown age of onset
IV.5		none*	24

*Cataract had developed on both eyes at the age of 40 as complication to repeated vitrectomies.
!Had not reached the age where neovascularisation could be expected. Had died before the time of examination.

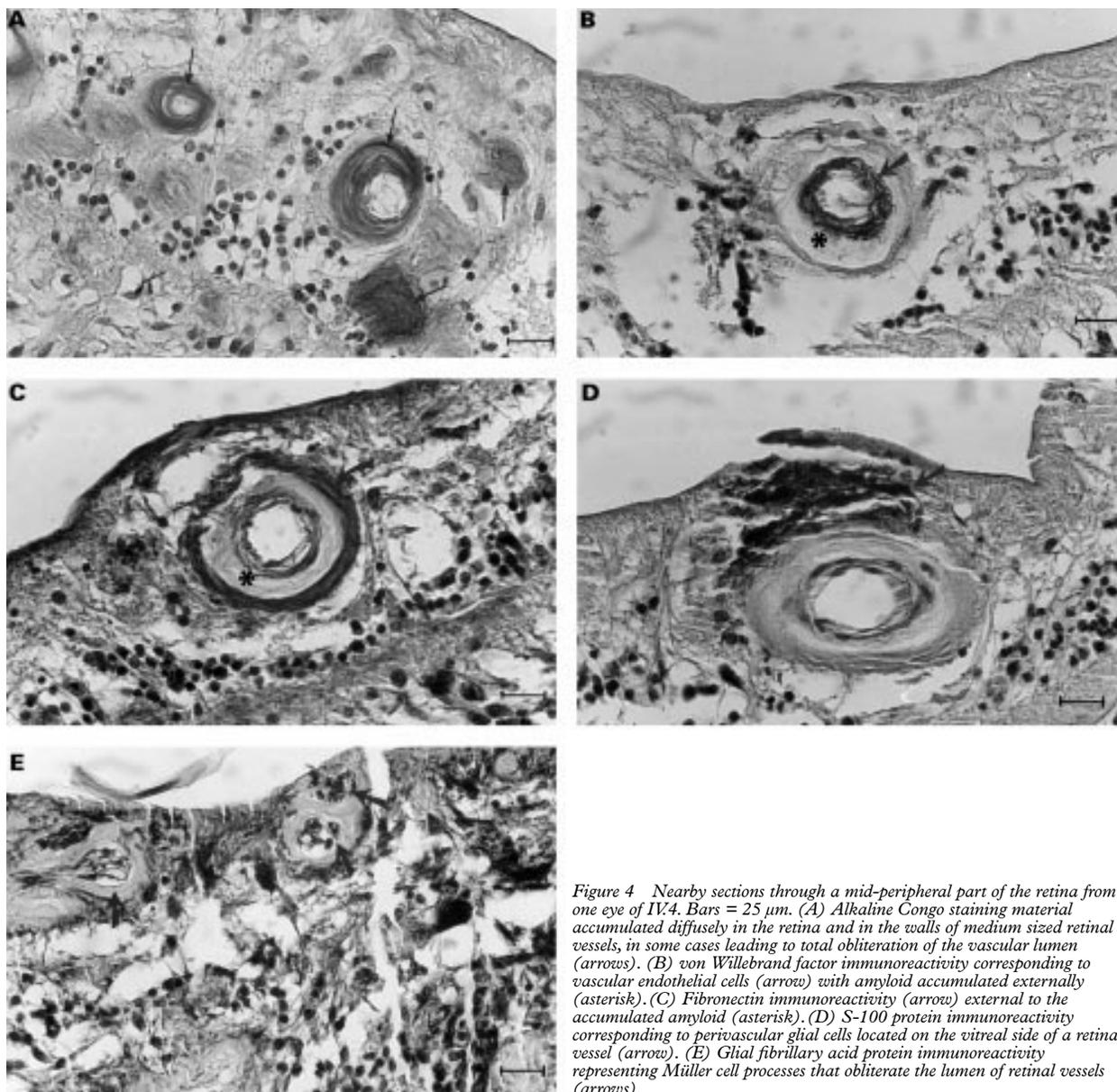*Figure 4   Nearby sections through a mid-peripheral part of the retina from one eye of IV.4. Bars = 25 μm. (A) Alkaline Congo staining material accumulated diffusely in the retina and in the walls of medium sized retinal vessels, in some cases leading to total obliteration of the vascular lumen (arrows). (B) von Willebrand factor immunoreactivity corresponding to vascular endothelial cells (arrow) with amyloid accumulated externally (asterisk). (C) Fibronectin immunoreactivity (arrow) external to the accumulated amyloid (asterisk). (D) S-100 protein immunoreactivity corresponding to perivascular glial cells located on the vitreal side of a retinal vessel (arrow). (E) Glial fibrillary acid protein immunoreactivity representing Müller cell processes that obliterate the lumen of retinal vessels (arrows).*

most noticeable characteristic was the retinal laser burns that could be seen more clearly than when inspecting the retinal background directly.

In V.2 and V.3 electroretinography showed decreased amplitude of the rod and cone responses and extinguished oscillatory potential. The latencies and implicit times, however, were normal.

The visual field was concentrically shrunk in V.1 and V.2, but was normal in VI.1.

HISTOPATHOLOGY AND IMMUNOHISTOCHEMISTRY

In all eyes studied histologically the cornea, ciliary body, choroid, and sclera appeared normal. In the retina there was extensive accumulation of an amyloid material positive to staining with methyl violet and thioflavin, Congo red, and displaying birefringence with this dye. The material did not stain with periodic acid Schiff, Alcian blue, and did not show immunoreactivity to von Willebrand factor, type IV

collagen, actin, fibronectin, S-100 protein, and glial fibrillary acid protein. The amyloid material was diffusely accumulated in the retina with a consequent loss of retinal glial cells, but was especially accumulated in the walls of the retinal vessels. Small capillaries were seen to be totally obliterated, whereas in the larger retinal vessels the amyloid was located in the middle layer of the vascular walls between a luminal zone of endothelial cells, basement membrane type IV collagen and actin containing pericytes, and an external zone consisting of fibronectin and the perivascular glial cells (Fig 4A–E). A S-100 positive subtype of perivascular glial cells predominated on the vitreal side of the larger vessels. In many of the occluded retinal vessels of medium size retinal glial cell processes were seen to extend inside the vascular lumen to occlude it. These glial cell processes could be shown to be part of the radial Müller cells spanning the retina from the inner to the outer limiting membrane.

The preretinal vessels consisted of von Willebrand factor positive endothelial cells embedded in a connective tissue matrix displaying immunoreactivity to fibronectin, but containing no amyloid staining material.

Discussion

Familial amyloidoses can be generalised or localised to specific organs such as the nervous system, including the eye.[8–10] In the eye one of the most frequently reported complication of amyloidosis is deposition in the vitreous of amyloid which is supposed to be released from retinal vessels.[11–14] However, ocular amyloidosis may also be associated with cataract formation, and may show retinal involvement as shown by the occurrence of retinal cotton wool spots.[10]

The histological examination of ocular tissue from members of the studied family confirms the diagnosis of CNS amyloidosis, since a material was found accumulated in the retina that showed positive staining with methyl violet, thioflavin, and Congo red, and showed birefringence with this dye.

In the studied family the expressivity of individual clinical features varied as is commonly seen in dominantly inherited syndromes. However, the pattern of clinical features involved was distinctly different from what has previously been reported in familial amyloidoses. Thus, in none of the affected family members were there any signs of amyloid deposition in the vitreous. There was evidence of cotton wool spots occurring early in the disease, and in one case it was confirmed by fluorescein angiography and stereobiomicroscopy of the retina that these lesions did not represent vitreous opacities.[15 16]

The key sign of HOOE in the eye were cataract and retinal neovascularisations. The finding of cataract may not be directly related to the CNS amyloidosis, but may be parallel to the development of cataract in other inheritable disorders of the retina and the vitreous perhaps as a result of a metabolic effect on the lens from the diseased part of the eye.[17–20] The development of preretinal new vessels in ocular amyloidosis has been described earlier,[14] but cases showing progression to a stage with vitreous haemorrhage and neovascular glaucoma are hitherto unreported. Generally, retinal neovascularisation is assumed to develop secondary to retinal ischaemia because the normal retinal capillaries become occluded, a phenomenon which is observed in other retinal diseases such as proliferative diabetic retinopathy, and complications of retinal vein occlusion.[6 7 19–21] In these diseases the occluded retinal vessels can be seen to be invaded by Müller cells that fill out the vascular lumen, and in patent vessels the vitreously located perivascular glial cells are activated to increasingly express S-100 protein.[19 20] The same type of retinal glial cell changes were seen in the presently studied type of amyloidosis with neovascularisation. This adds to evidence suggesting that changes in retinal glial cells are a central phenomenon in the pathophysiology of retinal neovascular disease.[21] However, the role of the retinal Müller cells especially in the pathophysiology of HOOE may be more complex. Thus, both the clinical and the histological findings of patients with HOOE disclosed that the extensive accumulation of amyloid in the retina was associated with atrophy and functional loss of retinal tissue, especially the retinal glial cells. However, the retinal neurons that remained appeared morphologically normal. This fits in with the electroretinographical findings showing generally reduced amplitudes but normal implicit times. The reduction in amplitude was pronounced in a-wave generated by the retinal photoreceptors and the b-wave generated in the middle retinal layers, but there was a total loss of the oscillatory potential which is assumed to be generated in the retinal Müller cells. The reason for this selective affection of different retinal cell types remains unknown. However, since the Müller cells play a central part in retinal metabolism, it could be hypothesised that the amyloid accumulating in the retina had induced much more damage to the Müller cells than to other retinal cell types.

in conclusion, clinical and histopathological findings in the eye are described in heredo-oto-ophthalmo-encephalopathy (HOOE). This disease is a familial amyloidosis of the central nervous system that is different from previously reported cases of familial amyloidosis by including cataract and retinal neovascularisations, eventually resulting in vitreous haemorrhage and neovascular glaucoma.

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