Ocular changes in heredo-oto-ophthalmo-encephalopathy

Toke Bek

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.

(Hereto-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.
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

<table>
<thead>
<tr>
<th></th>
<th>Age at examination (years)</th>
<th>Cataract</th>
<th>Neovascularisations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV.2</td>
<td>20</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>V.2</td>
<td>45</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>V.3</td>
<td>none</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>VI.1</td>
<td>21</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>IV.4</td>
<td>unknown age of onset</td>
<td>unknown age of onset</td>
<td>unknown age of onset</td>
</tr>
<tr>
<td>IV.5</td>
<td>none*</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

*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.
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 a retinal vessel (arrows). Glial fibrillary acid protein immunoreactivity representing Müller cell processes that obliterate the lumen of retinal vessels (arrows).
The preretinal vessels consisted of von Willibrand 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. However, the role of the retinal Müller cells in the pathophysiology of retinal neovascular disease is not well understood. 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. 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 stereomicroscopy of the retina that these lesions did not represent vitreous opacities.

The key sign of HOOE in the eye was 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. The development of preretinal new vessels in ocular amyloidosis has been described earlier, 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. 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. 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. 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 ganglion cells. The reason for this selective affection of different retinal cell types remains unknown.

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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