Retinal abnormalities in ophthalmoplegic lipidosis

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SUMMARY Of 2 sibs with ophthalmoplegic lipidosis the younger had a perifoveal opacification of the retina. The older child's retina was transparent but atrophic. Ultrastructural studies showed lamellated bodies in the retinal ganglion cells and electron-dense inclusions in Müller's fibres.

Ophthalmoplegic lipidosis is a recently recognised neurovisceral storage disease which is also described as 'a neurovisceral disease with vertical supranuclear ophthalmoplegia'1 or as 'juvenile dystonic lipidosis'.23

The clinical presentation varies, but there appear to be 3 groups of patients: firstly, those who present in infancy with failure to thrive, jaundice, and hepatosplenomegaly; secondly, those presenting in childhood with dementia and ataxia; thirdly, those who present as unexplained hepatosplenomegaly between the ages of 5 and 9 years. In the infantile group splenomegaly is moderate and death may be rapid—even before the neurological involvement is apparent. The older children may present with ataxia and dementia and may have minimal visceral involvement, though there is frequently a history of neonatal jaundice. The hepatosplenomegaly varies not only between patients but also in time in individual patients, even regression having been described.4 Vertical supranuclear ophthalmoplegia is a common later finding and may be the key to the clinical diagnosis.1 Usually predominantly affecting downwards saccades, the disease may also be associated with a selective disorder of vertical pursuit eye movements and defects of horizontal eye movement, and supranuclear convergence defects have been described.1

Diagnosis at the clinical level depends on the recognition of intellectual impairment, paressis of vertical gaze, ataxia, dysphagia, and dysarthria. Hepatosplenomegaly is variable, and fits may become prominent later. Bone marrow examination shows large foamy macrophages with a coarse vacuolated cytoplasm containing several darkly staining inclusions and occasional erythrocytes. Rarely, cells containing small grey-blue granules may be seen similar to those found in other neurovisceral storage diseases and in particular in the adult form of Niemann-Pick disease, but less intensively staining. Neurons, whether from brain, appendix, or rectal mucosa are vacuolated and contain a substance which histochemical analysis shows to be a water-soluble carbohydrate containing sialic acid. It has not been biochemically characterised. Electron microscopy shows characteristic involvement of liver, spleen, marrow, and neurons by numerous membrane-bound pleomorphic lamellae.154 Similar inclusions also occur in a feline neuronal storage disorder.7 Sphingomyelin was found to be increased in the spleen in some cases,179 which explained the confusion with Niemann-Pick disease, but, since sphingomyelinase levels are normal and sphingomyelin is never increased in liver or brain, this condition, which was formerly called Niemann-Pick type C or D, should now be recognised as a separate entity.10 Although retinal abnormalities are not normally present, we have recently seen 2 sibs with a rapidly progressive disease in whom membrane-bound vacuoles in the retinal ganglion cells were associated with a milky appearance of the retina, particularly around the posterior pole in one patient.

Case reports

Case 1

Patient A was a 4-year-old boy admitted to the Hospital for Sick Children, Great Ormond Street, with his brother, patient B. The product of a non-consanguineous marriage and a full-term pregnancy, he had been well until 2 years of age, but he had never stood without support, although by 18 months he had a few words and had learnt to crawl. At 3 months of age hepatosplenomegaly was noted; at 1 year a squint was diagnosed, but no action was taken.
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From 2 years of age there had been a gradual deterioration with delay and loss of developmental milestones. For the year before admission he had been bedridden and had become progressively demented, unresponsive, and incontinent.

On examination he was unresponsive to any visual or other stimulus; he was wasted and showed 2 cm of liver enlargement and 3 cm of splenomegaly. The pupils reacted very slowly to a bright light, but there was no relative afferent pupillary defect. Both fundi showed a symmetrical opalescence of the perifoveal retina with minimal loss of retinal nerve fibres (Fig. 1). The opalescence affected the whole of the posterior pole of the eyes but was much more pronounced in the perifoveal region. The optic disc and peripheral retina were normal. The electroretinogram was normal, but there was only a poorly defined flash visually evoked cortical response.

Leucocyte and serum lysosomal enzyme assays were normal. Bone marrow aspirate showed numerous foamy storage cells. A peripheral blood smear showed a few vacuolated lymphocytes. A rectal biopsy showed neurons with foamy cytoplasm and strong acid phosphatase activity. There was no staining with Luxol fast blue and only weak staining with Sudan black. The periodic acid Schiff reaction was positive, and the cytoplasm showed metachromasia with Feyrerter's thionin.

His general condition deteriorated, and he died from bronchopneumonia.

At necropsy the child weighed 9 kg and was externally normal. The spleen weighed 97 g and the liver 541 g. The brain weighed 923 g and showed atrophy of the frontal lobes but with a normal pattern of gyri. The cranial nerves and vessels were normal. Although the lateral ventricles were slightly enlarged and the thalamus showed slight shrinkage, the brain was otherwise normal. The lungs showed a nodular bronchopneumonia.

Case 2
Patient B, a 6-year-old boy, was admitted to the Hospital for Sick Children with his brother, patient A. He was normal until the age of 2 years, when hepatosplenomegaly was noted. He gradually regressed in intellectual and motor functions, so that by admission he was found to be decerebrate and was having a few convulsions each day. On examination he was wasted, had 3 cm of spleen enlargement, but no clinical hepatomegaly. He was extremely hypertonic, showed exaggerated tendon reflexes with clonus and extensor plantar responses, and was unresponsive to any stimuli. The pupils reacted slowly to light. Caloric stimuli failed to elicit any eye movement, but the eye elevated during seizure activity. Both fundi showed marked optic atrophy.

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Fig. 1 The left fundus of patient A. The focus is unclear owing to corneal drying from slight exposure secondary to the comatose state. The perifoveal retina is somewhat opaque, and gives rise to a form of cherry-red spot at the fovea. An extensive perimacular light reflex is also seen. The preservation of the retinal ganglion cell and nerve fibre layer is indicated by the relative lack of protrusion of the superior temporal artery and vein above the inner limiting membrane, shown by the reflections of light around the vessels.

Fig. 2 The left fundus of patient B. The optic disc is extremely pale and the lack of the retinal ganglion cell and nerve fibre layer can be seen by the way in which the vessels stand out against the internal limiting membrane.
Fig. 3 Light micrograph of retina from the foveal region of patient A. Above: Edge of the fovea showing massive post-mortem swelling of the inner connecting fibres of the foveal cones as they traverse the fibre layer of Henle (H). The numbers of ganglion cell nuclei (arrowed) are fewer than in a normal retina. The bar marker is 200 μm. Below: Higher power view of the inner nuclear layers showing the reduced ganglion cell (G) population. The bar marker is 50 μm.

and gross loss of retinal nerve fibres (Fig. 2). There was no evidence of the perifoveal greying of the retina seen in his sib.

The electroretinogram was normal but flash visually evoked cortical responses were absent. The electroencephalogram showed a severe abnormality with gross poverty of rhythmic activity. The peripheral blood film showed a few vacuolated lymphocytes, and spine x-rays were normal. White cell and plasma enzyme studies similar to those of the sib were normal, and a rectal biopsy showed identical changes to those of his brother. Death occurred from bronchopneumonia. At necropsy he weighed 14 kg, the spleen weighed 171 g, and the liver 850 g. The brain weighed 759 g and showed cerebral atrophy with a normal pattern of convolutions and good definition of cortex from white matter. The ventricles, the basal ganglia, the cerebellum and the cranial nerves were normal.

**OCULAR PATHOLOGY**
The eyes of patient A were removed 4 hours after death and after a transcorneal incision were immersed in 100 ml of 2-5% glutaraldehyde buffered in 0-1 M sodium cacodylate containing 10 mg/ml calcium chloride and with a final pH of 7-4. The eyes were progressively dissected in this solution, and after 1 hour specimens were briefly washed in sucrose buffer before being postfixed for a further hour in 2% osmium tetroxide buffered in 0-1 M sodium cacodylate. Samples were dehydrated through a graded series of concentrations of ethanol in water and embedded in Epon via epoxypropane. For details of microscopic preparations see Marshall et al.11
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Despite 4 hours having elapsed between death and fixation the preservation of retinal architecture at the light microscopic level was good and the relatively few post-mortem changes could be easily identified. These were: a general retinal detachment, perinuclear vacuolation of the inner nuclear layer, the ganglion cell layer, and to a lesser extent the outer nuclear layer, nonspecific vacuolation of the 2 plexiform layers, and a gross swelling of the inner connecting fibres of the photoreceptor cells in the fibre layer of Henle in the macula (Fig. 3).

The only significant finding at this level of magnification was a reduced number of ganglion cell nuclei, and this was particularly apparent in the macula, where they rarely exceeded 2 layers (Fig. 3b).

During electron microscopic analysis the normality of the outer retinal layers was confirmed, with retinal pigment epithelium, photoreceptor cells, and intermediary neurones showing no changes other than those induced by post-mortem delay.

In the innermost retinal layers 2 specific morphological anomalies were observed, one in neurones and the other in glia. The former was found in the cytoplasm of a high proportion of retinal ganglion cells and consisted of polymorphous electron-dense membranous lamellated bodies (Fig. 4a) of a similar size
and morphology to those previously described in appendiceal neurones of previous cases. These inclinations were most concentrated in the perinuclear portion of the ganglion cells and few were seen in the nerve fibre layer. In all affected cells the endoplasmic reticulum seemed reduced, but the mitochondria appeared normal.

The glial inclinations were seen in the innermost expansions of Müller’s fibres adjacent to the inner limiting membrane. These bodies were extremely electron-dense, ovoid in shape, and had a size similar to mitochondria (Fig. 4b). Microscopically they appeared similar to the lipofuscin inclinations found in the retinal pigment epithelium of the elderly.

Discussion

These cases are interesting since they broaden the clinician’s ability to diagnose a disorder which is becoming increasingly frequently recognised. Ophthalmoplegic lipidosis is, second only to Batten’s disease, the most commonly diagnosed neurolipidoses seen at the Hospital for Sick Children, Great Ormond Street. The appearance of a ‘milky’ retina in the younger sibling was associated with the presence of numerous multilaminated bodies in the retinal ganglion cells and with electron-dense inclinations in Müller’s fibres. The older sibling did not have a similar retinal appearance, since there was gross retinal atrophy with loss of the ganglion cells that were opacified by the stored material in the younger sibling.

Although the appearances in case 1 were those of opacification of the inner layers of the retina, the condition could not be confused with the cherry-red spot seen in clinical Tay-Sachs disease, acute neuroopathic Niemann-Pick disease, Gml type 1 gangliosidosis, and the cherry-red-spot-myoclonus syndrome (sialidosis), or more rarely, in infantile Gaucher’s disease and metachromatic leucodystrophy. The changes seen were more diffuse, being present for 2 or 3 disc diameters away from the macular area, although the opacification was densest at the posterior pole, except the foveal area, which lacks the ganglion cells in which most of the abnormal material was found.

The normality of both the photoreceptor cells and the retinal pigment epithelium in patient A is perhaps a surprising finding given the high metabolic demand of the outer retina and the enormous requirements inherent in the continuous membranogenesis in the photoreceptor outer segments. In many metabolic diseases there are mild perturbations in a variety of different types of chemical systems involved in the homeostatic relationship between the photoreceptor cells and the retinal pigment epithelium lead to photoreceptor abnormalities or loss. In lipid disorders it is particularly apparent. For example, the visual cell degeneration of the Bassen-Kornzweig syndrome is thought to ensue from a derangement in the renewal of lipids in disc membranes; and the build up of lipid deposits in the pigment epithelium in Refsum’s syndrome may be due either to a failure in the transepithelial transport of fatty acids or to an inability completely to degrade phagosomal particles of rod outer segments with abnormal lipid components.

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