Ocular pathology of GM₂ gangliosidosis – Type 2 (Sandhoff's disease)

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The introduction in recent years of more refined techniques for the isolation and characterization of biological lipids has led to the detection of a number of disorders which share with Tay-Sachs disease a disturbance of ganglioside metabolism. Gangliosides are sphingosine-containing glycolipids distinguished by the inclusion of neuraminic acid, and the various gangliosidoses are attributable to defects in the enzyme systems required for their degradation. Of the three disorders involving accumulation of the so-called GM₂ ganglioside, Tay-Sachs disease (infantile amaurotic idiocy) is much the most common. Recent studies, however, have shown that GM₂ ganglioside breakdown is dependent on hexosaminidase, a lysosomal enzyme which has two components referred to as A and B (Robinson and Stirling, 1968), and that, whereas in Tay-Sachs disease the A component alone is deficient (Okada and O'Brien, 1969), the entire enzyme is absent (Sandhoff, 1969) in a related disorder first described by Sandhoff, Andreae, and Jatzkewitz (1968). This results in the accumulation, not only of GM₂ ganglioside as in Tay-Sachs disease, but also of its neuraminic acid-free derivative (O'Brien, Okada, Ho, Fillerup, Veath, and Adams, 1971). The viscera in Sandhoff's disease accumulate a ceramide-based glycolipid, globoside, which is similarly dependent on hexosaminidase for its breakdown (O'Brien and others, 1971).

The clinical features and pathology of Sandhoff's and Tay-Sachs disease are virtually indistinguishable (Pilz, Sandhoff, and Jatzkewitz, 1966; O'Brien and others, 1971; Bain, Tateson, Anderson, and Cumings, 1972), and it is possible that a proportion of alleged Tay-Sachs cases, particularly in non-Jews, may in reality be examples of Sandhoff's disease.

Reliable differentiation in life can be made only on the basis of serum and tissue hexosaminidase assay (Okada and O'Brien, 1969; Okada, Veath, Leroy, and O'Brien, 1971; Bain and others, 1972).

A full account of the clinical, pathological, and biochemical feature, excluding the ocular pathology, of Sandhoff's disease occurring in a Scottish family is given by Bain and others (1972). The present report concerns the ocular findings in one of their cases.

Case report

A baby boy aged 2 yrs had made good initial progress and there had been no signs of cerebral or retinal disturbance at birth. Visual impairment was first noted at the age of 6 months, when it was observed that he did not follow objects with his eyes. Ophthalmoscopy revealed bilateral disc pallor and a cherry-red spot appearance at the macula. By 13 months visual disturbance was obvious, in that he made no effort to explore his surroundings or to reach out for objects, and at the

age of 17 months he appeared to be totally blind. Neurological deterioration involving mental and motor activity developed at the same time and he eventually succumbed to persistent respiratory infection, dying at the age of 25 months from bronchopneumonia.

Ocular pathology

CROSS EXAMINATION

Neither eye showed any external abnormality but both retinæ presented a milky-white appearance involving all but the macula, which was contrastingly dark.

LIGHT MICROSCOPY

Detectable abnormality was limited to the retina and optic nerve. Within the retina the cytoplasm of a substantial number of cells in the ganglion cell layer and occasional cells in the inner nuclear layer was distended, and presented a foamy or slightly granular appearance in haematoxylin and eosin stained sections (Fig. 1).

FIG. 1 Section of retina, showing a distended ganglion cell, the nucleus of which is pushed to one side by accumulated foamy and slightly granular material in the cytoplasm. The remaining retina and underlying choroid appear to be intact.

Haematoxylin and eosin. $\times 330$

The nuclei of such cells were frequently eccentric. Although histochemistry of paraffin-embedded sections gave entirely negative results, frozen sections of formalin-fixed material showed the bloated ganglion cells to contain a birefringent and intensely periodic acid-Schiff positive substance, which was resistant to diastase and hyaluronidase digestion (Fig. 2). Such material also reacted weakly with Sudan black B and osmium tetroxide-Q-naphthylamine (OTAN) stains. These are features characteristic of a glycolipid.

The retinal photoreceptors and pigment epithelium appeared healthy and intact. In the peripapillary region the inner retina showed evidence of probable glial replacement secondary to neuronal degeneration. Atrophy and glial proliferation was also prominent in the optic nerve.

ELECTRON MICROSCOPY

The cytoplasm of the abnormal ganglion cells was filled with membranous bodies which varied in size from 0.5 to 6 μ in diameter. While many showed a concentric or parallel lamellar arrangement

FIG. 2 Frozen section of retina, showing ganglion cells filled with PAS-positive material which is not present in paraffin-embedded tissue.

Periodic acid-Schiff and haematoxylin. $\times 330$

(Fig. 3), others had a less definite pattern and often appeared to represent a fusion of a number of smaller bodies (Figs 4 and 5). The majority of the membranous cytoplasmic bodies were surrounded by a distinct outer membrane. Because of possible artefact incurred by formalin fixation, comment on other intracellular structures is not warranted: there was, however, no apparent nuclear abnormality.

Discussion

The ocular pathology of Sandhoff's disease, as seen in this one case, hardly differs from that of Tay-Sachs disease. The only discrepancy lies in the character of the membranous cytoplasmic bodies within the ganglion cells of the retina. In Tay-Sachs disease, whether in the brain (Terry and Weiss, 1963) or retina (Harcourt and Dobbs, 1968), they are usually composed of concentric or spirally-wound lamellae and measure up to 2μ in diameter. In Sandhoff's disease, however, those occurring in the cerebral tissues have been described as having a greater degree of pleomorphism and a more prominent limiting membrane (Resibois, Tondeur, Mockel, and Dustin, 1970). The retinal findings in the present case concur with this description.

It is also to be noted that pleomorphic cytoplasmic inclusions similar in several respects to those seen in Sandhoff's disease have been described in juvenile GM₂ gangliosidosis (GM₂ gangliosidosis—Type 3) by Volk, Adachi, Schneck, Saifer, and Kleinberg (1969). Membranous cytoplasmic bodies are a feature of all the gangliosidoses and it is believed that they represent spontaneous aggregates of ganglioside with cholesterol and phospholipid orientated to form membranes (Samuels, Gonatas, and Weiss, 1965), while the demonstration that they are the site of intense acid phosphatase activity is thought to infer a possible derivation or contribution from lysosomes (Wallace, Volk, Schneck, and Kaplan, 1966). Thus it may be that membranous cytoplasmic bodies in the gangliosidoses

are autophagic vacuoles engaged in a largely ineffectual attempt to degrade the accumulated lipid.

FIG. 3 Electron micrograph of a retinal ganglion cell, showing multiple laminated membranous bodies in the cytoplasm. There is no obvious nuclear abnormality. Formal-saline/O₈ O₄/Araldite/uranyl acetate-lead citrate. $\times 29,000$

FIG. 4 *Electron micrograph, showing larger and more pleomorphic membranous cytoplasmic bodies than are seen in the preceding figure. Formol-saline/ O_5O_4 /Araldite/uranyl acetate-lead citrate. $\times 29,000$*

Although, as with all the gangliosidoses, there is no effective therapy for Sandhoff's disease, the introduction of techniques for hexosaminidase assay has greatly facilitated genetic counselling and made prenatal diagnosis possible. Thus, while the gangliosidoses

FIG. 5 *Electron micrograph, showing apparent fusion of multiple membranous cytoplasmic bodies within an incomplete cytosomal membrane. Formol-saline/0.8 Os/Araldite/uranyl acetate-lead citrate. $\times 29,000$*

are transmitted by an autosomal recessive gene, asymptomatic heterozygotes for the abnormal gene show a relative deficiency of the appropriate enzyme which can be detected by assay of serum and skin biopsies (Okada and O'Brien, 1969; Okada and others, 1971).

Accurate prenatal diagnosis can be made by estimation of enzyme levels in amniotic fluid and cells (Schneck, Friedland, Valenti, Adachi, Amsterdam, and Volk, 1970; Navon and Padeh, 1971).

Summary

A study of the ocular pathology in a case of Sandhoff's disease (GM₂ gangliosidosis—Type 2) revealed features closely similar to those found in Tay-Sachs disease (GM₂ gangliosidosis—Type 1). The only difference lay in the nature of the membranous cytoplasmic bodies in the ganglion cells of the retina, those in Sandhoff's disease being rather more pleomorphic than those in classical Tay-Sachs disease.

I am immensely grateful to Dr. A. D. Bain, Consultant Pathologist at the Royal Hospital for Sick Children, Edinburgh, for both providing the eyes from this case and putting at my disposal the detailed information he has collected about the condition. It is also a pleasure to acknowledge the comments of Prof. Norman Ashton, the technical contributions of Messrs. V. Elwood, A. McNeil, and D. Wood, and the secretarial assistance of Miss B. A. Streek. This study was supported in part by a grant from The Wellcome Trust.

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