ULTRASTRUCTURE OF THE RETINA IN TAY-SACHS'S DISEASE*†

BY

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TAY-SACHS'S disease is an hereditary disorder of lipid metabolism characterized by a biochemical abnormality which leads to the deposition of large amounts of a monosialoganglioside (acyl-sphingosine-N-triose-N-acetylneuraminic acid), which normally constitutes only a very small fraction of the total cerebral gangliosides, in ganglion cells of the central nervous system. The exact nature of the inborn error of metabolism which gives rise to this abnormal storage of lipid is unknown, but it is probably a defect in the normal catabolic pathway of the ganglioside which leads to its accumulation (Svennerholm, 1962). Ganglioside deposition causes ballooning and death of the ganglion cells, which is accompanied by Wallerian degeneration of their axons and widespread massive glial proliferation (Fredrickson and Trams, 1966). The neuro-retina, embryologically a part of the central nervous system, shares in these destructive changes, and the deposition of ganglioside in the retinal ganglion cells, where they are most numerous in the parafoveal area, gives rise to the characteristic cherry-red spot appearance on ophthalmoscopy. The light-microscopical appearances of the cerebral and retinal tissues in this disorder have long been well recognized, but the ultrastructure of cerebral biopsy specimens from cases of Tay-Sachs's disease has only recently been described (Terry and Weiss, 1963). The characteristic feature is the presence of round or oval membranous cytoplasmic bodies (MCB), principally in the cytoplasm of the cerebral ganglion cells but also in glial cells and perivascular tissue cells. These bodies appear to be unconnected with the ribosomes, mitochondria, and reticulum of the affected cell, which are normal in structure. The membranous cytoplasmic bodies, varying from 0.5 to 2.0 μ in diameter, have a unique appearance, consisting of concentric layers of electron dense material. They have been harvested by centrifugation techniques from homogenates of the brain tissue of patients who have died with Tay-Sachs's disease (Samuels, Korey, Gonatas, Terry, and Weiss, 1963) and have been found to consist mainly of gangliosides, cholesterol, and phosphatides. The gangliosides which they contain have solubility characteristics very similar to those isolated from Tay-Sachs's brain tissue (Terry and Korey, 1960). It seems likely that these structures are formed by a spontaneous aggregation of molecules of lipid, particularly of gangliosides, which have accumulated because of the metabolic defect and have become orientated to form membranes. When the ganglion cells die because of interference with their normal metabolic processes, the membranous cytoplasmic bodies are phagocytosed

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by active proliferating glial cells, where their membranous organization is lost and amorphous intracellular lipid deposits are formed, particularly in the late stages of the disease.

An electron-microscopic study of the ultrastructure of the retina in Tay-Sachs's disease has not previously been reported, and is here described.

Case Report

A male child was born of non-Jewish parents in September, 1964. One elder sibling was healthy, and there was no family history of death in infancy or of neurological disease. At the age of 9 months he was seen in the Children's Department of the London Hospital because of suspected mental retardation. Up to the age of 7 months his development had appeared to be normal except for a persistent cough and obesity. No abnormal neurological signs were found at this first hospital visit, but subsequently a progressive deterioration of his condition occurred, and at the age of 20 months, by which time he was unable to sit up, he first suffered a major convulsion. There was marked general hypotonia but with brisk reflexes 4 months later, and at this time cherry-red spots in the fundi were first noted. The head circumference was then 53 cm. and a skull *x* ray showed marked suture diastasis. The serum concentration of 1-phosphofructoaldolase was estimated at 0.43 unit/ml., a level which Prof. J. N. Cumings of the Institute of Neurology reported as not being of itself diagnostic of Tay-Sachs's disease. The child's parents were not willing for a cerebral cortical biopsy to be carried out, but the appearances of a cerebral specimen obtained by needle biopsy were suggestive of cerebral lipidosis. The child's condition continued to deteriorate and he died with terminal bronchopneumonia in February, 1967, at the age of 2 years and 5 months.

Pathology

Both Eyes

The eyes were removed 24 hours after death and opened by a coronal incision through the ora serrata. The posterior segments with the retinae exposed were fixed in a solution of glutaraldehyde 2.5 per cent. buffered with sodium cacodylate 0.09 M, at pH 7.3 for 20 hours. They were then washed in sucrose 7.5 per cent. buffer for 5 hours and post-fixed in osmium tetroxide 1 per cent. in veronal buffer for 1½ hours before being embedded in Epon/Araldite mixture (Mollenhauer, 1964). Preliminary light microscopical examination of transverse retinal sections stained with periodic acid-Schiff (PAS) showed ballooned retinal ganglion cells with foamy cytoplasm and eccentric nuclei (Fig. 1, overleaf). Electron microscopical examination revealed that the ganglion cell cytoplasm contained great numbers of membranous cytoplasmic bodies (MCB) similar in all respects to those which have been described in cerebral ganglion cells in Tay-Sachs's disease. They varied from 0.6 to 2.0 μ in diameter and were composed of closely packed electron dense double membranes arranged in a strikingly regular manner. In their centres was one or more amorphous or granular zones, and around these the laminations were arranged principally in a concentric fashion (Figs 2 and 3, overleaf, pp. 901 and 902).

Because of *post mortem* changes there were some electron dense artefacts in the cellular cytoplasm and some membranes were poorly defined, but there was no marked abnormality of the ganglion cell nuclei.

Brain

The brain was large and weighed 1526 g. In many areas the pale cerebral cortex merged imperceptibly into the underlying white matter. The ganglion cells examined throughout the central nervous system showed the typical light microscopical changes of Tay-Sachs's disease.

FIG. 1.—Photomicrograph of inner layers of retina stained with periodic acid-Schiff, showing ballooned retinal ganglion cells with foamy cytoplasm and eccentric nuclei. $\times 660$.

One cerebral hemisphere was removed for biochemical analysis by a thin-layer chromatographic technique. Prof. J. N. Cumings reported that both the white matter and the cerebral cortex showed an abnormal ganglioside pattern, with a G_{M2} band present, which is absolutely characteristic of Tay-Sachs's disease.

Conclusion

As the ganglion cells of the retina and of the cerebral cortex share a similar neuroectodermal origin and display the same pathological changes by light microscopy in Tay-Sachs's disease, it was to be expected that they would exhibit similar electron-microscopical changes in this disorder and these have now been demonstrated for the first time.

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FIG. 2.—Electron micrograph of retinal ganglion cell, showing nucleus and large numbers of membranous cytoplasmic bodies (MCB). $\times 14,000$.

FIG. 3.—Electron micrograph, showing laminated concentric structure of membranous cytoplasmic bodies under higher magnification. $\times 28,250$.