Fabry’s Disease in Children
An Electron Microscopic Study

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Die Fabry-Krankheit im Kindesalter
Eine elektronenmikroskopische Studie


Sie enthalten:
1. Osmiophile Substanzen, welche eine lamellenartige Struktur mit Perioden von 60—73 Å besitzen und wahrscheinlich gespeicherten Ceramid-Trihexosiden entsprechen.

Summary. Fragments of renal, liver and splenic biopsies from a boy with Fabry’s disease, and of the kidneys from two siblings with a latent form of the affection, were submitted to an electron microscopical study.

Storage of an heterogenous material was seen in the cells of all the investigated tissues. The epithelial cells of the glomeruli and those of the distal convoluted tubes are the most severely affected. The cytoplasm is full of pleiomorphic inclusions limited generally by a unit membrane.

They contain:
1. Osmiophilic formations organized following a lamellar pattern with a 60 to 73 Å periodicity and which are probably the stored ceramide-trihexosides.
2. A matrix, less abundant, transparent to the electrons after the usual techniques but well contrasted with aqueous PTA at pH 1.5, which may be of mucopolysaccharidic nature.

Fabry’s disease was first described as a dermatologic disease separately by ANDERSON and by FABRY (1898) who named it “Angiokeratoma Corporis Diffusum”. Anderson suspected that alterations similar to those of the skin vessels could also be present in the kidney because of the proteinuria of his patient.

In 1947, POMPEI et al. observed vacuoles in the arterial media of all the organs of their autopsied case and suspected that it could be a generalized disease.
Scriba (1950) demonstrated that the intracellular stored material was a lipid and claimed that it could be a glycolipid; the metabolic character of the affection was thus recognized.

Since then, more accurate informations have been acquired about the morphology of the lesions. The first ultrastructural descriptions were given simultaneously in 1963 by Henry and Rally and by Hartley et al. The first authors observed a stored osmiophilic lamellar material within the epithelial cells of the glomeruli and the distal convoluted tubuli. The same inclusions were also present in the cells of the endothelium and media of the skin vessels. Hartley et al. described similar kidney and dermic alterations. They described also myelinic figures in the Kupffer cells of the liver. The hepatocytes were normal.

According to Tanaka et al. (1965) the inclusions of the bone marrow macrophages and those of the skin vessel cells show three different aspects: they are lamellar, mosaic-like or pleiomorphic. The differences are due to variations in the arrangement of a basic lamellar pattern with a 40 Å periodicity.

However, more recently, Rae et al. (1967) described lamellar inclusions in the kidney cells with a periodicity of 51 to 98 Å.

All these studies deal with juvenile or adult cases, because of the rarity of the diagnosis in children. We had the opportunity to study three infantile cases in the same family and to examine kidney, liver and spleen biopsies. It seems of interest to report the first ultrastructural observations of these cases.

Brief Clinical Reports\(^1\)

Case 1. Mohammed A. was healthy until the age of 12. He began then to lose weight and to present high fever and pains in the hands, feet and abdomen. His skin was ichthyosic with facial telangiectases. A kidney biopsy disclosed the nature of the affection which was confirmed by the finding of trihexose ceramide in the urine.

Cases 2 and 3. Mustapha and Najat, brother and sister of the propositus, respectively 6 and 3 years old, are apparently in good health. However they present the corneal alterations characteristic of the disease.

Material and Methods

Kidney (cases 1, 2, 3), liver (case 1) and spleen (case 1) biopsies were fixed at 3°C in 4.2% glutaraldehyde buffered at pH 7.4 with Millonig’s buffer 0.1 M (Miller, 1962). The fragments were then rinsed overnight in 0.1 M buffer with 0.54 g-% glucose in order to avoid artefacts due to hypotonicity. After post-osmication with 2% osmium tetroxide (Millonig’s buffer pH 7.4), the fragments were either dehydrated in acetone and embedded in Vestopal or dehydrated in alcohol and embedded in Epon.

The sections were stained by lead hydroxide (Karnovsky, 1961) or uranyl acetate followed by lead citrate according to Reynolds (1963). Floating sections from blocks embedded in Vestopal after glutaraldehyde fixation without post-osmication were stained by 10% aqueous phosphotungstic acid at pH 1.5.

The sections, taken up on naked grids, were coated with a carbon film and examined with a Siemens Elmiskop I at 80 kV at a direct magnification of 8,000 to 80,000.

For light microscopic examination, the kidney biopsies were fixed in Bouin’s solution and embedded in paraffin. Sections were stained with PAS and Masson’s trichrome method.

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1. The detailed clinical studies and biochemical findings in these cases have been reported elsewhere (Loeb et al. 1968).