A Family with Sudanophilic Leucodystrophy

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Since the appearance of the original publications of Schilder, the literature dealing with the diseases of the white matter of the cerebral hemispheres has been steadily expanding. Following a period during which these diseases were viewed principally in connection with inflammatory processes, there came a period during which the inborn errors of metabolism focussed attention on hereditary factors, whilst during the past few years the auto-immune diseases have added themselves to the group of allergic diseases.

It is customary in organising one's study of the material, to give a great deal of attention to the neuropathological forms, to the age at which the disease manifests itself, and to the histochemical aspects. Perhaps too little consideration has been given to the significance of the duration of the illness with regard to the histological and histochemical findings. In the present article, we call attention to a family, for four members of a single generation of which pathological-anatomical information was available, as well as the necropsy report and microscopical slides from a relative belonging to the preceding generation, while finally certain clinical and anamnestic data were also available. The picture of the disease as it thus emerges for us is in many respects a more differentiated one than has been found for a good many isolated cases described in the literature.

Case Reports

Case I (pedigree IV 33). Boy who died at the age of 12 years (May 24, 1963). The duration of the illness had been 5 years. The first symptoms were character-changes, and disturbances of gait, speech, hearing and vision. In October, 1958, the patient was admitted for observation to the Neurology Department of Dijkzigt Hospital.

The child showed a virtually complete lack of initiative, lay inert with generally impoverished motor activity, very little expressiveness facially or in gesture, and monotonous speech. There was an increased tonus of the muscles of the arms and legs. There were bilateral hyperactive tendon-stretch reflexes and Babinski reflexes. The visual acuity for both eyes was found to be 3/6. Dis rampant deafness was also found. EEG (Dr. M. De Vlieger): increased slow-wave activity; slight signs of diffuse cerebral disturbance. P.E.G. (Dr. P. Cezee): no abnormalities. C.S.F.: 56/3 lymphocytes; 18/3 polymorphonuclear leukocytes; albumen 38 mg-\textsuperscript{0}/\textsubscript{00}; Lange normal; Benzo\textsubscript{o} colloidal curve 000 001355530 000.

The second clinical observation took place in 1959. The patient's condition had deteriorated in all respects, with complete blindness and deafness, increased spasticity and increased
pathological reflexes. The optic discs were very pale and the pupillary light-reflex was very feeble. Examination of the blood and C.S.F. yielded no further information.

In January, 1960, the patient was admitted to the Beatrix-kliniek (a hospital for severely oligophrenic children), and during the subsequent years deteriorated further. Ultimately, he became completely confined to his bed, was incontinent, spastic, deaf and blind. On May 24th, 1963, the patient died.

Necropsy (performed by Dr. SCHEELLINGS, Central Pathological Institute of Rotterdam). The cardiovascular system showed a slight atheromatosis of the abdominal aorta, and changes in several of the vessels in the myocardium: splintering of the elastics, thickening of the intima, occlusions and myocardial infarction. The alimentary tract showed a cholesterolosis of the gallbladder, with deposits of sudanophilic substance in the submucosa. Respiratory system: acute purulent bronchitis; bronchopneumonia cellularis. Skeletal musculature: The m. triceps surae showed an increase in the number of perimysial nuclei, abnormal spread in the diameters of the fibres in cross-section, and a few lymphocytic infiltrations.

Central Nervous System. (Examination of the spinal cord was not feasible.) Weight: 1090 g. Internal hydrocephalus. In the coronal sections of the brain, the white matter of the cerebral hemispheres and cerebellum appeared greyish-brown and sclerotic.

The neuropathological picture was characterized by a diffuse loss of myelin, including the U-fibres (Fig. 1). In the demyelinated white matter, a diffuse, fibrous gliosis was visible. The oligodendroglia had largely disappeared.

Granular cells were found around the blood-vessels, and sometimes also lying free in the white matter. There were no inflammatory infiltrations. The number of axis cylinders was markedly reduced; many degenerated axis cylinders were also discernible, some of them still surrounded by a very thin layer of myelin (Fig. 2).

Histochemical Examination. In frozen sections, sudanophilic granules were found around the processes of the astroglia, and in the granular cells around the blood-vessels. The sudanophilia was undiminished after extraction (16 hours) with cold acetone. Extraction with cold acetone removes cholesterol, cholesterol esters and fatty acids (STAM, HESLINGA and DEERE-KRAUT, 1962).

Schulz' reaction for cholesterol and cholesterol esters was negative, thus confirming the extraction-test.

The sudanophilia persisted even after extraction with hot chloroform/methanol mixtures. Thus, the sudanophilic granules proved to be insoluble in fat-solvents. It was therefore not surprising that they were also found in the paraffin sections. Their insolvibility in fat-solvents made it seem likely that the sudanophilic substances would have to be bound to proteins. This proved indeed to be so. The coupled tetrazonium reaction was positive, but was negative after preliminary benzoylation. The granules stained deeply with Sudan black. Further, the sudanophilic granules proved to be PAS-positive. We are thus dealing with glycolipids which by virtue of their being bound to proteins are not soluble in fat-solvents.

With the Bial-reaction, modified according to SVENNERHOLM, the granules proved to be unstainable: hence, they contained no neuraminic acid. With the methylene-blue extinction-test, the granules around the processes of the astroglia cells disappeared below pH 4.3, whilst those in the granular cells first disappeared below pH 1.5. Thus, the granules showed a property of variable basophilia. Using the combined PAS-Hale-technique, we saw in many granular cells PAS-positive and blue granules in a varying ratio to one another. The granules around the glial cells proved to be Hale-negative. In the granular cells around the blood-vessels, thus, not only were glycolipids found, but also strongly acid lipids or lipid break down products.

With the strongly basophilic products in the granular cells proved not to stain metachromatically with toluidine-blue or cresyl violet (according to PEIFFER and HIRSCH). The granules in the granular cells stained very deeply with Nile-blue sulphate, even after washing with 1% acetic acid. With Klüver's myelinstain they were coloured a faint blue. The phosphate reaction with uranyl nitrate and potassium ferrocyanide (method of HEIDERMANNS and WURMBAECH, modified according to HESLINGA and STAM) showed the presence of phosphate groups in many of the granular cells. Using the Fontana-Masson method for melanin, many black granules were found in a number of granular cells. The bleaching reactions proved to be negative.