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Adrenoleukodystrophy

Preliminary Report of a Connatal Case. Light- and Electron Microscopical, Immunohistochemical and Biochemical Findings

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Summary. This is the first description of a connatal case of adrenoleukodystrophy. The clinical picture consisted of severe psychomotor retardation, convulsions and hypsarrhythmia, but no obvious signs of adrenal insufficiency. Pathologically, the adrenals were small. The entire cortex was largely replaced by large round cells. Ultrastructurally, some cells in the adrenal cortex contained inclusions with electron-lucent clefts surrounded by a membrane. The anterior pituitary lobe could be demonstrated to have produced ACTH. The central nervous system showed extensive zones of demyelination in the brainstem, the cerebellum and the right-sided capsula interna. In the demyelinated areas there was sudanophilic breakdown and an intense gliosis. Ongoing demyelination could also be demonstrated by the chemical analysis. In the gray matter there were micropolygyria of the insular cortex and swollen nerve cells in the nucleus arcuatus. Ultrastructure revealed the type of inclusions in the microglia of the same type as in the adrenals, and a different type of inclusions in unidentifiable cells, possibly neurons. These latter inclusions consisted of loosely stacked lamellar material.

The findings are interpreted as further evidence of storage taking place in this disease.

Key words: Leukodystrophy – Adrenals – Pituitary – Storage disease – Connataltype – Demyelination – Lamellar inclusions – Biochemistry.

"Adrenoleukodystrophy" (AL) is a recent name for a disease first described by Siemerling and Creutzfeldt (1923) consisting of a demyelination in the central nervous system and adrenocortical insufficiency caused by a primary atrophy of the adrenal cortex. It usually afflicts boys between the ages of 3 and 15 (Ulrich, 1971a, b; Schaumburg et al., 1972; Powell et al., 1975), but occasional adult cases have been reported (Budka et al., 1976; Pilz et al., 1973). About 100 cases of this disease have been published up to now.

Evidence is accumulating, that AL is a metabolic disease involving cholesterol- and fatty acid metabolism (Aguilar et al., 1967; Burton et al., 1974; Evitar et al., 1973; Farkas-Bargeton et al., 1967; Igarashi et al., 1976; Martin et al., 1977; Menkes et al., 1977; Powell et al., 1975; Powers and Schaumburg, 1973, 1974; Schaumburg et al., 1975; Suzuki et al., 1970). Of these authors, Powell et al. (1975) suggest explicitly that we are faced with a storage disease.

We are now going to report on the first case of connatal AL, which lends further support to the idea, that AL is a storage disease.

Case Report

M. H. male, born 26–3–1975, died 9–12–1976.

M. was the first child of healthy unrelated parents (26 and 25 years old).

In the family no heritable disorders are known. Pregnancy was uneventful. Amount and condition of amniotic fluid was normal. Delivery was at term with manual help because of breech presentation. Apgar 9/10/10. Birth weight 2850 g (P 10), 50 cm (P 50) and head circumference 37.5 cm (> P90). The placenta was normal in shape and appearance. A few hours after delivery the child seemed apathic with large open eyes, hypotonia and suckling difficulties. At 4 days the first convulsions were noted on the right arm and leg, which were followed by jerks of all extremities. Blood sugar was normal. Because of these problems the child was admitted to the Children's Hospital at St. Gallen. Upon admission the child was hypotonic with little spontaneous movements, no grasp reflex and only slight Moro reaction. Movements of the eyelids were random, the headcontrol poor and the suckling reflex weak. Multifocal epilepsy was noted in the EEG at 1 month of life, which changed into hypsarrhythmia 1 month later. Lumbar puncture revealed slightly sanguineous cerebrospinal fluid with some old erythrocytes, no infection. CSF-protein was 82 mg/100 ml. Blood gases were normal. The poor neurological condition remained during the whole 20 months of the child's life. Only the EEG-change improved for a short period under treatment with ACTH, Rivotril and phenobar-

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bital. – He died at the age of 20 months. There were no clinical signs of adrenal insufficiency.

The results of special investigations during the 5 hospitalizations were as follows:

CSF: Protein 82 mg/100 ml (neonatal period), protein 64 mg/100 ml (at $8^1/_2$ months). CSF protein electrophoresis showed a dissociation of prealbumin to albumin.

Echoencephalography, brain-scintigraphy, electromyogram and nerve conduction velocities were all within normal limits.

A nerve biopsy examined by light- and electron microscopy (Prof. A. Bischoff, Bern) showed nonspecific axonal degeneration. A re-examination of this biopsy when the postmortem diagnosis was known, did not show characteristic inclusions.

Liver biopsy (Dr. Spycher, Zürich) was not indicative of liver disease. There was, however, a proliferation of smooth endoplasmic reticulum of hepatocytes and there were slit-like cavities surrounded by a membrane in histiocytes and epithelial cells of bile ducts.

Serum-concentrations of Na, K and Cl were determined 4 times during the course of the illness. They were always normal as were the eosinophilic leukocytes.

Further investigations with normal results included serum-Fe, serum-Ca, high voltage electrophoresis of urine, lipids in the urine, bone marrow smears, lysosomal enzymes in fibroblasts and serological search for infections with toxoplasmosis, cyto-megalo-virus and rubella.

General Autopsy

A small emaciated boy with a large head. Bronchopneumonia. Very small adrenals (1 g each).

Brain

It weighed 1195 g (normal 1050 g) (Coppoletta and Wolbach, 1933, quoted by Crome and Stern). There was obvious micropolygyria on both sides involving the cortex and the insula of the temporal operculum (Fig. 2). There was demyelination visible on the cut surfaces which involved both cerebellar hemispheres, parts of the medulla oblongata, the pons and the midbrain. On the right side it extended through the cerebral peduncle into the capsula interna. It seemed to be well-delimited towards the normal white matter at the level of the basal ganglia. The ventricular system was slightly enlarged.

In the spinal cord the white matter was slightly gray.

Light Microscopy

Adrenals: Although their medulla looked normal, the cortex was very atrophic. A considerable part of it was replaced by clusters of unusually large cells (about 30 μ in diameter), clearly delimited from each other, with a homogenous or slightly granular eosinophilic cytoplasm and a nucleus moderately rich in chromatin, which was often displaced towards the cytoplasma membrane (Fig. 1 a). In spite of careful search, no striations as described by Powers and Schaumburg (1973) were seen.

Nervous System: As suspected at gross examination, there was a complete demyelination in both cerebellar hemisperes, both cerebral peduncles, the pes pontis, pyramids, the lateral pyramidal tract on both sides and the lower part of the capsula interna of the right side (Fig. 2), and a nearly complete demyelination involving all white structures in the dorsal parts of the brainstem.

Where the border of the demyelinated areas could be studied, i.e., in the right capsula interna and in the lateral parts of the pons, the delimitation was not sharp. There was a gradual transition over a zone of about 1 cm from completely demyelinated to normally myelinated parts. There was no "glial wall" between myelinated and non myelinated tissue.

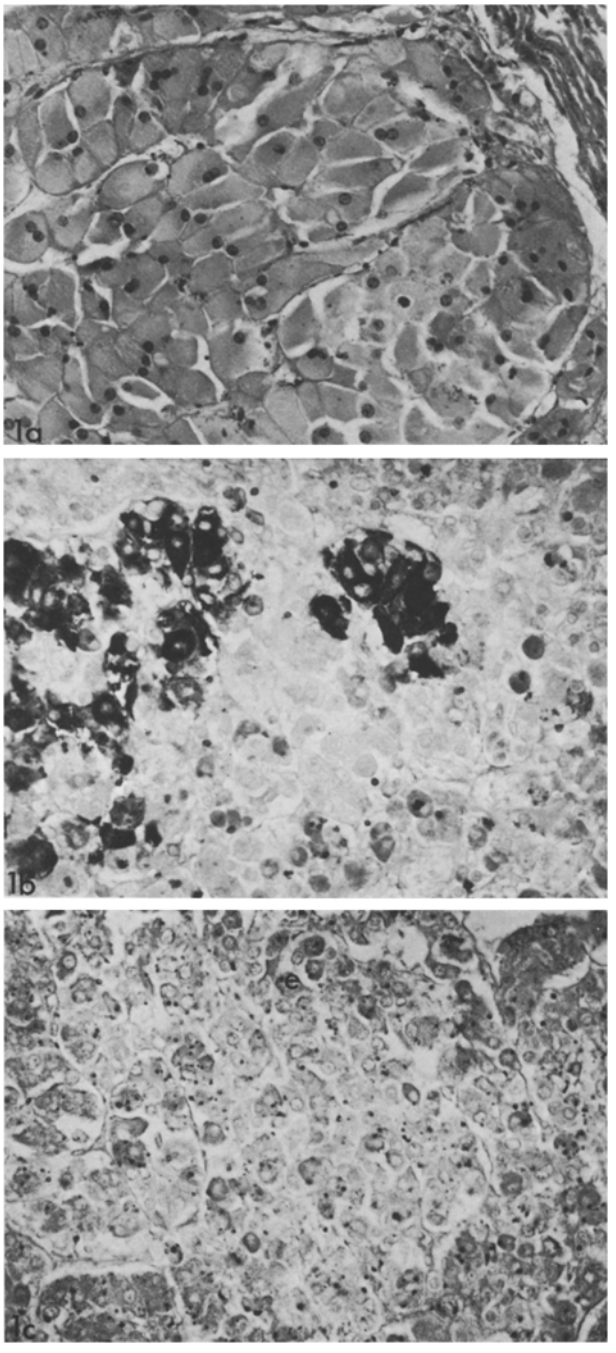

Fig. 1. Adrenal cortex. Nodule of ballooned adreno-cortical cells. (HE, ×223). **b** ACTH in anterior lobe of pituitary (technique see text). (×252). **c** Control of b with cortrophine-absorbed anti-ACTH. (×252)

The population of glial cells was about equal in number in the adjacent demyelinated and myelinated areas. However, most glial cells in the demyelinated area had a voluminous eosinophilic cytoplasm, while the cytoplasm was invisible in the myelinated part.

There were only few perivascular infiltrates with scanty lymphocytes and sometimes with a considerable number of fat granule

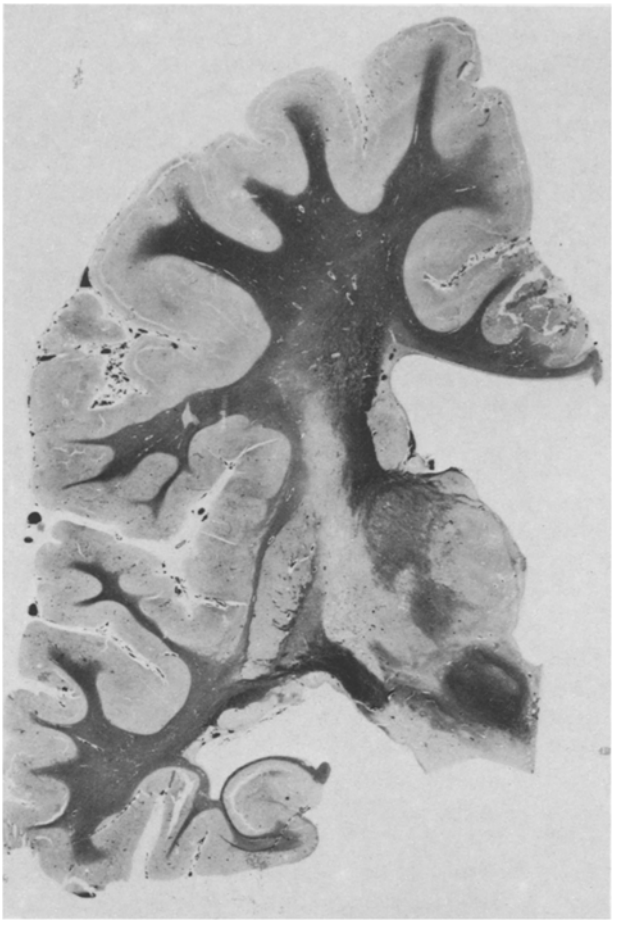

Fig. 2. Demyelination in capsula interna. Micropolygyria in insular cortex. (Woelke-stain, × 1.2)

cells. Cells with neutral fats could be seen to be distributed all over the demyelinated areas. No metachromatic deposits were present. There was a considerable glial reaction with large, often multinuclear gemistocytic astrocytes and intense formation of glial fibrils. Some of the gemistocytic astrocytes had rounded contours but no globoid and no epitheloid cells were visible.

Although the changes in the gray matter were less conspicuous than those in the white, there were also pathological findings in it: An abnormal cortical architecture within the micropolygyric regions (Fig. 2), proximal axonal swellings ("Torpedoes") in the Purkinje-cell-axons, lying in the granular layer and ballooned nerve cells in the arcuate nucleus of the medulla oblongata and possibly also in the pes pontis. These cells had a slightly granular content and a nucleus displaced towards one of the dendrites (Fig. 3a, b).

Thus, they were reminiscent of the neurons observed in Tay-Sachs disease and other lipidoses (Fig. 3a, b).

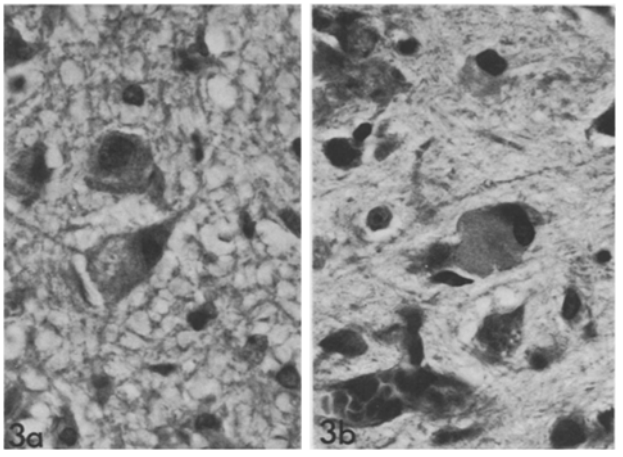

Fig. 3. a Swollen neurons in nucleus arcuatus. (HE., × 581). **b** Swollen unidentifiable cell (glia from basis pontis). (H.E., × 581)

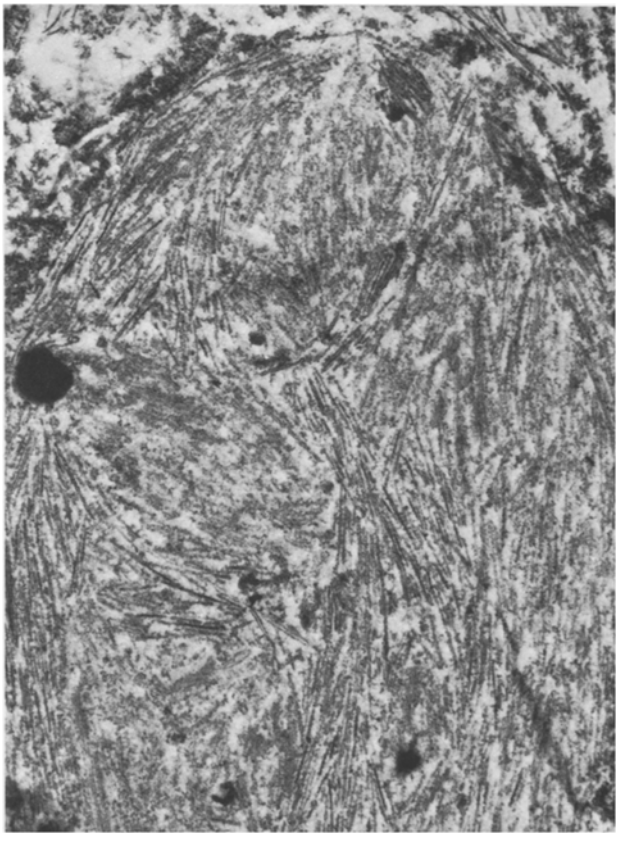

Fig. 4. A cytoplasmic inclusion from one of the adrenal cortical cells. (× 22780)

Electron Microscopy

This was performed on formalin fixed tissue refixed in osmium tetroxyde (1% pH 7.4).

Adrenals. The tissue was autolytic. The enlarged cortical cells could be identified however. Their cytoplasm could still be seen to be stuffed with mitochondria. No splinter-like material could been in these cells. Occasionally, however, cell processes close to adrenal capillaries were seen, which contained unusual ovoid-shaped cytoplasmic inclusions (Fig. 4). *Within* these inclusions there was a lamellated, nearly rectilinear splinter-like material. The individual "splinters" con-

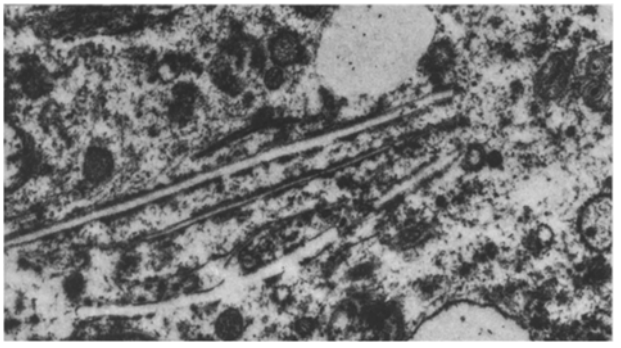

Fig. 5. Cleft-like cytoplasmic inclusion in a mesenchymal cell. (×22440)

sisted of two parallel electron dense lamellae, each 3–5 nm thick and separated by a clear space of 6–12 nm. These inclusions were well-delimited toward the cytoplasm. In some places they seemed to be delimited by a membrane.

Brain. Several blocks of the medulla oblongata (nucleus arcuatus) and the cerebellum were studied. There were severe autolytic changes and fixation artifacts.

Examination confirmed the fibrillary gliosis and demyelination. There were astrocytes, mesenchymal elements, presumably microglia, and a third type of cells, possibly neurons. These latter cells and the mesenchymal ones were rich in organelles and contained 3 types of unusual cytoplasmic inclusions:

1. Inclusions of the same type as observed in the adrenals were seen in many mesenchymal cells (Figs. 5, 6b).

2. Dark lamellar inclusions, consisting of parallel dark stripes of 16 μ. localized mainly in microglia (Fig. 6a).

3. In several cells of a different type, possibly neurons or oligodendroglia, there were inclusions surrounded by a membrane, consisting of irregular stacks of loose lamellar material. Elongated cleft-like profiles were not seen in these cells (Fig. 7a, b).

Immunohistochemical Investigations

Material and Methods

Also for these investigations, ordinary formalin-fixed tissue embedded in paraffin had to be used.

Paraffin sections (5 μ) were deparaffinized and incubated for corticotropin (CTH), growth hormone (HGH), prolactin (PRL), thyrotropin (TSH) and luteinizing hormone (LH) by the unlabeled antibody enzyme method (Sternberger, 1974). Specific rabbit antisera (dilutions: anti-ACTH and anti-GH 1/500, anti-PRL 1/750, anti-TSH and anti-LH 1/250) were used as the first layer; sheep anti-rabbit IgG (1/30) and soluble peroxidase-anti-peroxidase complexes (1/30) as second and third layers, respectively. The histochemical reaction for peroxidase was carried out using 3,3′-diaminobenzidine-tetrahydrochloride (0.5 mg/ml) and hydrogen peroxide (0.01%) in

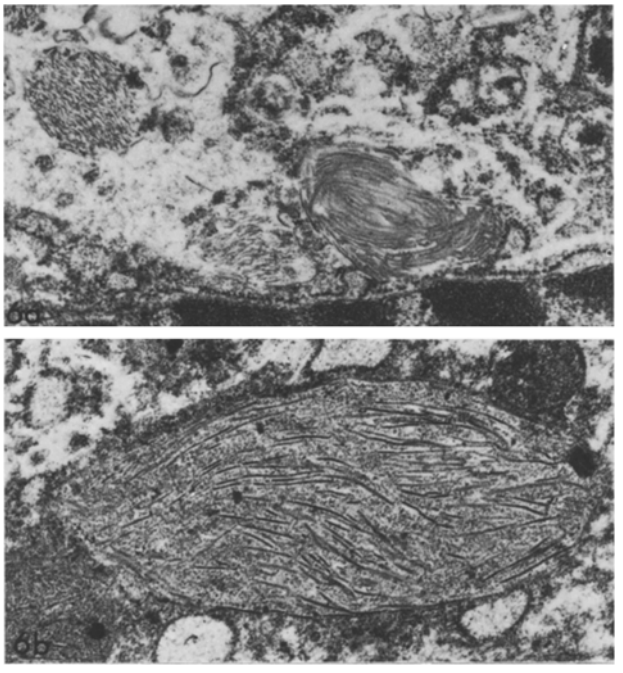

Fig. 6. a Cytoplasmic inclusion in microglial cell, probably related to myelin breakdown. **b** Inclusion in the cytoplasm of a perivascular cell in the nucleus arcuatus. **a**: ×30000; **b**: ×26000

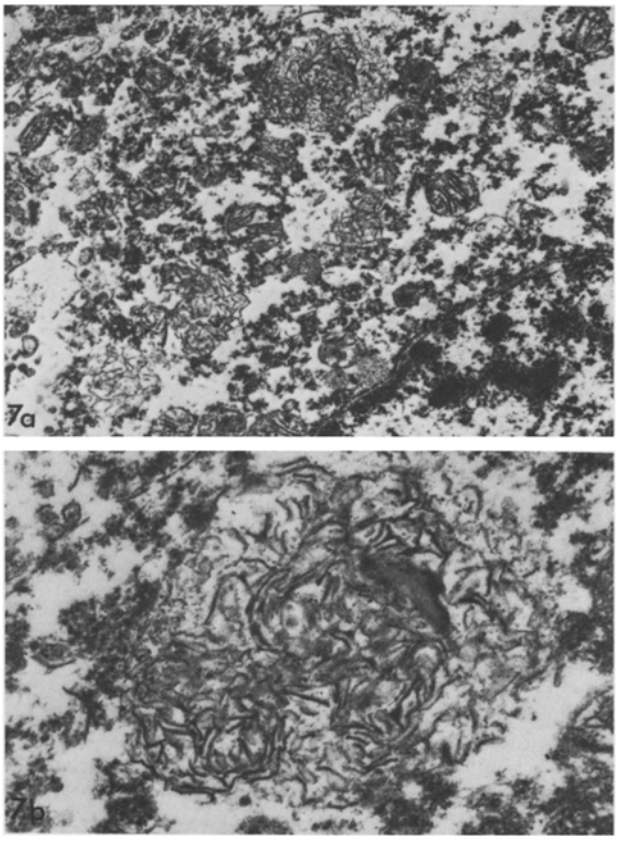

Fig. 7. a Cytoplasmic inclusions in a cell of the granular layer of the cerebellar cortex (neuron?). (×11484). **b** Detail of the same. (×37884)

Table 1. Biochemical Investigations

	Patient		Control	
	gray subst.	white subst.	gray subst.	white subst.
Water (%)	83.5	79.6	84.0	78.4
Protein (mg/g ww)	97	161	76	98
Total lipid (mg/g ww)	44.7	66	70.1	143.4
Cholesterol (mg/g ww)[a]	6.37 ± 0.3	10.43 ± 0.4	5.05 ± 0.3	16.6 ± 0.4
Cholesterol-ester (mg/g ww)[a]	0.012 ± 0.002	0.106 ± 0.003	0.03 ± 0.001	0.04 ± 0.003
Cerebrosides (mg/g ww)[a]	0.084 ± 0.002	3.98 ± 0.11	0.59	17.59 ± 0.32
Fatty acid cerebrosides		diminution of C_{24}		
Sulfatides (mg/g ww)[a]	nd	1.66 ± 0.007	0.13 ± 0.02	5.15 ± 0.74
Phospholipids (mg/g ww)[a]	21.3 ± 0.2	33.3 ± 0.2	26.9 ± 2.0	42.4 ± 0.9
Ganglioside NANA (mg/g ww)	0.675	0.635	0.747	0.290
Ganglioside pattern (GM_1, GM_2, GD_{1B}, GD_{1a}, GT)	normal	normal		

[a] Double determination, mean and extremes

0.05 M Tris-HCl buffer (pH 7.6). After fixation with osmium tetroxide (1%) in phosphate buffered saline (pH 7.2) the sections were dehydrated and mounted. Control reactions were carried out as follows:

1. Specific antisera absorbed with the antigen (anti-ACTH with Cortrophin-Z 15 IU/Ml diluted serum, anti-HGH with HGH 50 mg/ml, anti-TSH with 100 mg/ml, anti-LH with Pregnyl 500 IU/ml) as first layer.
2. Nonimmune rabbit serum as first layer.
3. Omission of 3,3′-diaminobenzidine-tetrahydrochloride or hydrogen peroxide from the incubating medium for the peroxidase reaction.

Chemical Investigations

The constituents of gray and white matter were determined by methods previously described (Herschkowitz et al., 1969). The results are given in Table 1.

Discussion

This case of a connatal neurological disease shows all signs diagnostic of adrenoleukodystrophy: There is the characteristic demyelination of the CNS white matter and the atrophy of the adrenal cortex very likely to be primary in this case, because the presence of ACTH could be demonstrated in the pituitary. Characteristic ballooned adreno-cortical cells could also be demonstrated. The localization of the demyelination was atypical, however: In cases of AL at the usual age the most involved part is not the cerebellum and brainstem, but the cerebrum (Farkas-Bargeton et al., 1967).

As expected, chemical analysis confirmed the diminution of the myelin constituents (Table 1: Total lipid, cerebrosides, sulphatides). There was also an increase in cholesterol-esters, indicating that myelin was still being destroyed actively. The pattern of fatty acids should still be explored more thoroughly. More extensive studies are also needed in order to explain the increased content in protein and neuraminic acid.

Not only the light microscopy but also the ultrastructure is similar to the cases at the typical age: splinter-like lamellar elements composed of electron-dense leaflets separated by a clear space, as have been reported recently by several authors (Powers et al., 1974a, b; Schaumburg et al., 1975; Powell et al., 1975; Budka et al., 1976) and were also observed by Bischoff and Meyer (Pers. comm., 1978).

Some morphological features, however, were different from those described in the previously published cases. We are now going to discuss these specially.

Adrenals

The degree of atrophy corresponds to the average in this disease. In the more pronounced atrophies, loss of demarcation between the zones of the adrenal cortex as was observed, is customary. Distended cells in groups, occupying all the three layers of the cortex, are typical. It is stressed in recent reports, however, that some of these cells are striated (Powers and Schaumburg. 1973) and it is stated by these authors that such striations are pathognomonic for the disease. In spite of intensive search we have not been able to observe "striations" in the distended cells. Neither could we find the linear and lamellar deposits or spicules described by electron microscopists (Powell et al., 1975; Schaumburg and Powers, 1975) to lie free in the cytoplasm of such cells. However, we saw such material aggregated in rather compact cytoplasmic inclusions sometimes surrounded by a membrane. These were always observed in comparatively small cell processes close to vessels. As preservation of the cytoplasm in the large cells was poor, it is possible that these structures were lost due to autolysis or to long storage in formalin.

ACTH-Secretion in the Pituitary

A large number of immunoreactive cells was found in all immunohistochemical reactions. Large clusters of ACTH-containing cells were particularly numerous in the central areas of the anterior pituitary.

On the basis of the histological findings in the adrenal cortex it can be assumed that the patient suffered from severe adrenocortical insufficiency. Therefore, it can be inferred that in the presence of an intact hypothalamo-pituitary-adrenocortical axis, the ACTH secretion by the pituitary was elevated, because of the lack of feed-back inhibition by cortisol. The results obtained by immunohistochemistry show the presence of hormone-producing cells in the pituitary. Thus, the hypothalamo-pituitary axis was apparently intact and synthesis of various hormones took place in the pituitary. It is, thus, probable, though not proven, that ACTH was secreted. The cells of the adrenal cortex were possibly stimulated by ACTH, assuming that cell receptors for ACTH were present and intact. This, of course, cannot be demonstrated in our material.

The interpretation of the morphological findings of the cells of the adrenal cortex is, therefore, difficult. They could be the result of: 1. an error of metabolism of the adrenocortical cells, 2. a strong stimulation of the cells by ACTH or 3. a combination of both.

Ultrastructure of Demyelinated White Matter

In mesenchymal elements as well as in Schwann cells, inclusions with lamellar parts as those described in the adrenals have been observed by several authors (Budka et al., 1976; Powers and Schaumburg, 1974). The same type of inclusions in mesenchymal elements (macrophages) is also observed in our case. Furthermore, in the macrophages and in astrocytes electron-translucent droplets of neutral fat, inclusions with irregular membranous stacks and with 16 μ thick, electron-dense aggregates were seen. These latter seem to be identical to those shown by Prineas (1975) and by Raine and Prineas (1976) in plaques of multiple sclerosis and by Hauw (1977) in progressive multifocal leukoencephalopathy. Therefore, they probably are breakdown products of myelin.

Although the same origin is possible for the irregular loose stacks (Fig. 7), their unusual aspect may be related to abnormal composition and abnormal breakdown of myelin, which is suspected to occur in these cases by some authors (Menkes et al., 1977). Another – equally unlikely – possibility is, that they are related to drug therapy, storage being observed as a sequel of various chronically applied drugs such as chloroquine. However, storage of the kind observed here, has not been seen following such treatments. Thus, it is more likely that we are faced here with a different expression of the primary storage process. Whether it is related to the swollen glial cells observed at the margin of the demyelinated area by light microscopy, cannot be decided. As judged by light microscopy, these are similar to the altered glial cells in the demyelinated areas described by Powell et al. (1975).

The fact that characteristic inclusions (Martin et al., 1977; Powers and Schaumburg, 1974) could not be observed in Schwann cells in this case, does not speak against the diagnosis of AL: Such inclusions are missing quite often in typical cases also (Bischoff, pers. comm., 1978; Cohadon et al., 1975).

Gray Matter Changes

Micropolygyria is known to occur in various inherited diseases – demyelinating and others. Similar disarrangements of cortical architecture have been observed in association with Pelizaeus-Merzbacher's disease (Seitelberger, 1954; Norman et al., 1966) and in Maple Syrup-Urine-disease (Martin and Norman, 1967).

The swollen nerve cells observed in the nucleus arcuatus and the pons are very reminiscent of those in various sphingolipidoses (Terry, 1970) and ceroid-lipofuscinoses (Zeman et al., 1970). These cells were rare, however. Although they, too, might be related to drug therapy or might represent lipofuscinosis due to the general distress, neuronal storage due to the primary disease process would seem to be more likely.

Thus, our case adrenoleukodystrophy at an unusual age gives further evidence for abnormal steroid and myelin metabolism. Some of its aspects are similar to those observed in storage diseases.

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