Heredopathia atactica polyneuritiformis (Refsum's disease)

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Summary. A female patient started to develop deafness and vertigo at the age of 29. In the following years she became atactic and retinitis pigmentosa was discovered. The diagnosis of Refsum's disease was reached on the grounds of the high concentration of phytanic acid in plasma. The patient died 23 years after onset of the first symptons. Liver, spleen and kidney showed lipofuscinosis and pigment-laden macrophages. The retina was atrophic and its pigment discontinuous. The meninges contained lipid-laden macrophages. The nerve cells in brain and spinal cord as well as the astrocytes and perivascular macrophages stored substances weakly PAS-positive and sudanophilic. The nerve cells accumulated lysosomes and residual bodies. In the astrocytes, the residual bodies were extremely polymorphous and contained inclusions with bilamellar ribbon-like structures. In the oligodendroglia the residual bodies displayed high electron density and finger print-like pattern. Peroxisomes were found in glial cells and microperoximes in neurons. The ultrastructural findings in the present case demonstrate that in terminal stages phytanic acid can reach the brain parenchyma passing through the BBB. Further autopsy studies will be necessary to determine whether these changes are consistent findings in Refsum's disease.

Key words: Nervous-system, Refsum's disease, Storage-disease, Peroxisomes, Blood brain barrier

Introduction

Thiebaut et al. (1939), described a congenital disease with neurologic, otic, and ophthalmologic symptoms and some years later Refsum examined several members of two unrelated Norwegian families and found them and found them suffering from the same disease which, in his opinion, had never been identified before. Some of the symptoms recurred in these patients with such regularity that Refsum —realizing their diagnostic significance— felt justified to call the syndrome «heredopathia atactica polyneuritiformis» (Refsum, 1945, 1946). The leading symptoms are: 1) polyneuritis, paresthesiae, ataxia, muscular atrophy, and elevated albumin and globulin levels in the CSF; 2) retinitis pigmentosa and partial deafness; 3) electrocardiographic abnormalities; 4) bone lesions with epiphyseal dysplasia in the joints; 5) ichthyosis.

In 1963 Klenk and Kahlke analysed post-mortem tissues from a patient with this syndrome and found large amounts of phytanic acid (3,7,11,k 15-tetramethyl hexadecanoic acid), and a 20 carbon atom branched chain fatty acid normally present in only very small amounts. The accumulated phytanic acid was primarily of exogeneous origin (Steinberg et al., 1967a) and the enzyme defect affected the first step in its metabolic degradation, i.e. its conversion to alpha-hydroxy-phytanic acid (Herndon et al., 1969; Mize et al., 1969). An infantile form of the disease has been reported (Kahlke et al., 1974; Bolthauser et al., 1982; Ogier et al., 1985), which is closely related to neonatal adrenoleukodystrophy and the Zellweger syndrome (Cervós-Navarro, 1990).

Since a dietary treatment was succesfully introduced patients dying in the terminal stage of the disease are extremely rare and to our knowledge electron micros-copy data concerning the brain have only been reported in the infantile form (Torvik et al., 1988). In the present case ultrastructural changes could be detected in the brain as well as in the peripheral nerves.

Materials and methods

The 52-year-old female patient had neither consaguinity nor a genetic disease in her family history. The first symptoms manifested themselves at the age of

29, after delivery of her first child, when she started to develop deafness. Subsequently she suffered progressive loss of visual acuity and frequent attacks of vertigo. Ophthalmological investigation at the age of 42 disclosed retinitis pigmentosa and constriction of the visual fields. Numbness of the lower extremities and generalized weakness developed during the last 10 years with short intermittent periods of amelioration. In spite of the transitory remissions, the patient could not resume her previous occupation as a janitor. A few months before death the ataxia and serious disturbances in sensation and weakness in the upper and lower extremities became more accentuated and the patient became blind and deaf, and reflexes were abolished.

The cerebrospinal fluid protein content was highly increased (albumim 336 mg%; globulin 19.2 mg%). The cell number was normal. Ichthyosis was marked and generalized. The confirmation of the diagnosis of Refsum's disease was reached on the grounds of the high plasma phytanic acid concentration (38% of all plasma lipids). Before a dietary treatment could be established the patient died of pulmonary complications 23 years after onset of the first symptoms.

In the general autopsy the body was 153.5 cm long, wasted and weighed 35 kg. There was diffuse ichthyosis of the skin. On histological examination the myocard showed striped yellow spots. Some of the myocardial fibres were hypertrophied and contained large bizarre-shaped nuclei. Some fibres contained clear cytoplasmic vacuoles, that by Sudan IV appeared as fine deposits of a brownish material. The liver showed severe diffuse lipofuscinosis and in the hepatocytes intracytoplasmic vacuoles were numerous.

The retina showed loss of the normal architecture, with severe atrophy and marked rarefaction of rods and cones. The pigment epithelium of the retina consisted of a single distontinuous layer of melanin-containing cells, and in many areas the pigment epithelium was absent (Fig. 1a).

Small blocks of brain and spinal cord were obtained 2 hours after death and fixed in 5% glutaraldehyde at pH 7.5. After washing in saccharose solution, the blocks were postfixed in 1% osmium tetroxide and embedded in Micropal. One micrometer thick sections were stained with Giemsa. The ultrathin sections were contrasted with lead citrate and studied with a ZEISS EM 10 electron microscope.

The rest of the material was fixed in 10% buffered formalin. Frozen sections as well as large slices of the brain and different segments of the spinal cord embedded in celloidin were stained with Sudan IV, hematoxylin and eosin, Nissl, Woelcke, van Gieson and periodic acid Schiff.

Results

Gross and light microscopic study

The brain weighed 1,420 g after fixation. The leptomeninges were moderately thickened. Coronal sections

Fig. 1.a. Retinal gaps in the pigment epithelium and severe atrophy of all the cellular layers. Celloidin embedding. HE. × 180. **b.** Mounted meningeal membrane. Numerous macrophages loaded with neutral fat. Sudan IV. × 250
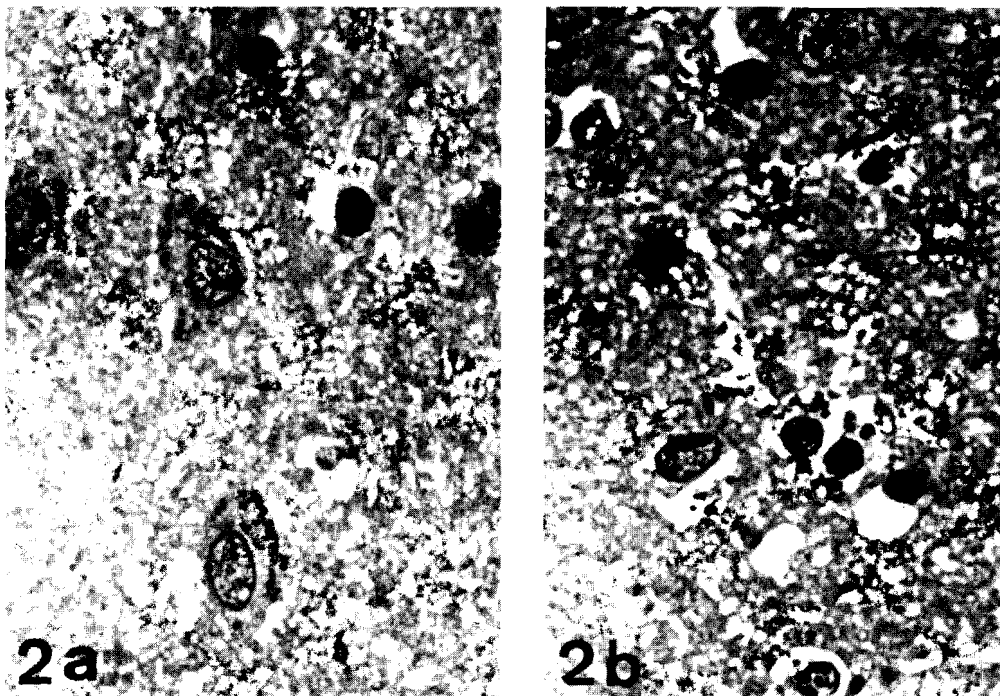
Fig. 2. Frontal cortex.
The cytoplasm of the neurons
(a) and astrocytes
(b) contains pigment granula.
One μm micropal sections
Giemsa stain. (a) × 750.
(b) × 600

showed mild cortical atrophy, especially in the frontal lobes of the cerebrum and in the vermis of the cerebellum.

The meninges contained large amounts of macrophages with neutral fat inclusions (Fig. 1b). In the basal ganglia, specially conspicuous in the globus pallidus as well as in the frontal and temporal lobes, some of the nerve cells showed a storage of dark granula (Fig. 2a) lightly stained with PAS and weakly sudanophilic. Occasionally, sudanophilic deposits were also present in the swollen dendrites. Patchy loss of nerve cells was conspicuous in the nucleus dentatus of the cerebellum and in the cytoplasm of the inferior olives.

Anterior horn neurons in the cervical and thoracic segments of the spinal cord displayed retrograde degeneration with central chromatolysis and eccentric nuclei (Fig. 3a). Scattered neuronophagias were present (Fig. 3a). Some cells were enlarged with deposits of pigment granules. Neuroaxonal dystrophic changes were found in the spinal cord (Fig. 3a) as well as in nucleus and fasciculus gracilis. The astrocytes (Fig. 2b) in the cortex and in the subependymal region, as well as some perivascular macrophages, contained dark granula of larger size than the neuronal granula. Diffuse reactive proliferation of the astroglia was observed throughout the neuraxis; moderate in the anterior horns and more pronounced in the white matter. Circumscribed areas of the ependymal layer appeared eroded with concomitant proliferation of subependymal glia (Fig. 4a). In the vicinity of an ependymal break in the posterior horn there was a circumscribed necrotic focus of 200 μm diameter with sparse mesenchymal reaction in the border (Fig. 4b).

Electron microscopy

The main ultrastructural finding in the central nervous system was the accumulation of intracellular inclusions. The cytoplasm of the nerve cells in the cortex and basal ganglia contained lysosomes with a moderate electron-dense matrix and secondary lysosomes with the appearance of lipofuscin granules (Fig. 5). Higher magnifications revealed within the lipofuscin granules densely-packed straight and curved tubular structures (Fig. 6). A few cisternae of the endoplasmic reticulum were enlarged and contained a lightly dense floccular matrix. Lipofuscin granules and low electron-dense secondary lysosomes could also be detected in the dendrites close to the perikaryon. The axons, as well as the dendrites at 1-2 μm distance from the perikaryon, contained multivesicular bodies. Residual bodies with loose membranes and lamellae were frequent in segments of axons more distant from the perikaryon.

In the cerebellum the Purkinje cells displayed closely-packed piles of neighbouring cisternae of the smooth endoplasmic reticulum and only isolated lipofuscin granules with electron-dense filamentous inclusions. The granular cells showed no lysosomal inclusions in the perikaryon.

The astrocytes of all regions studied exhibited numerous and pleomorphic residual bodies that could be detected along their processes extending to the perivascular spaces (Fig. 7a). Electron-dense needle-like structures (10 nm diameter) were conspicuous in the residual bodies as well as being free in the cytoplasm without apparent enveloping membranes (Fig. 7b). Residual bodies were occasionally in contact with round vacuoles of low electron density in a
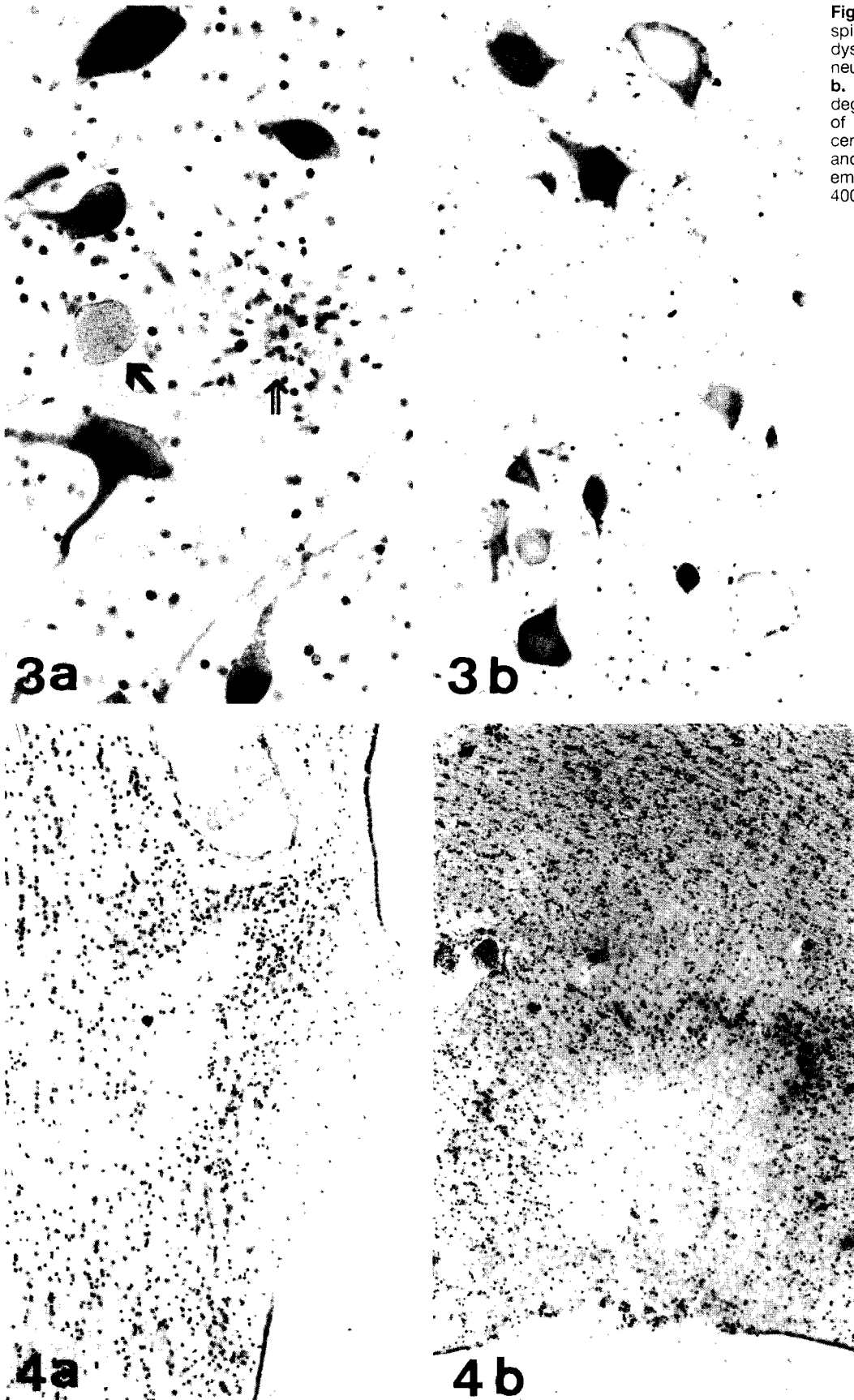
3a

3b

Fig. 3. Anterior horn of the spinal cord. **a.** Neuroaxonal dystrophy (arrow) and neuronphagia (double arrow). **b.** Round shaped, retrograde degenerated neurons with loss of Nissl substance from the central part of the perikaryon and eccentric nuclei. Celloidin embedding. Nissl stain. a × 400, b 350

4a

4b

Fig. 4.a. Circumscripted erosion of the ependymal layer. **b.** Necrotic focus with sparse mesenchymal reaction in the border. Celloidin embedding. Nissl stain. × 60

honeycomb arrangement (Fig. 7c). At higher magnifications in some of the residual bodies bilamellar structures embedded in a granular matrix, and aggregates of straight or irregularly ribbon-like structures could be observed (Fig. 8). Other inclusions contained fragments of lamellar material with spherical and oval profiles. Randomly, the cytoplasmic processes contained autophagosomes filled with remnants of membranes and vacuoles surrounded by double unit membranes giving them a ring-like appearance. The stored material in the cytoplasm of the oligodendroglial was charaterized by high electron density and laminated structures mimicking a finger print pattern (Fig. 9). In the spinal cord the cytoplasm or oligodendroglial cells occasionally showed occasionally clusters of myelin-like membranous formations arranged around a homogeneous centre and polyglucosan bodies (Fig. 10). The astrocytic processes in the spinal cord contained large amounts of thickly-packed gliofilaments (Fig. 10). Peroxisomes were found in oligodendroglial less frequently than in astrocytes (Fig. 11) while microperoxisomes were found in neurons (Fig. 12). In cerebral vessels adventitial cells displayed processes filled with lysosomal residual bodies and abundant lipid droplets.

Discussion

Clinical and laboratory findings

There is a wide variability in the clinical picture of Refsum's disease, even between members of the same family. The clinical findings, the course of the disease, and the raised plasma-phytanic-acid level in the present case were characteristics of the heredopathia atactica polyneuritiformis. The appearance of the first symptoms immediately after delivery corresponds to the often described aggravation during pregnancy (Kjellson, 1953; Fleming, 1957; Toussaint et al., 1959; Thiebaut et al., 1961; Harders and Dieckmann, 1964; Nevin et al., 1967; Fryer et al., 1971). The relapsing course of the peripheral neuritis has been recorded in many cases with and without dietary treatment (Edström et al., 1959; Pecker et al., 1963; Quinlan and Martin, 1970; Lundberg et al., 1972; Stokke and Eldjarn, 1975; Steinberg, 1978; Gibberd et al., 1979; Lenz et al., 1979).

A consistent finding in our case was the raised level of protein in the cerebrospinal fluid without an increase in cell number. There is no obvious explanation for this protein-cell dissociation; it is, with few exceptions, a
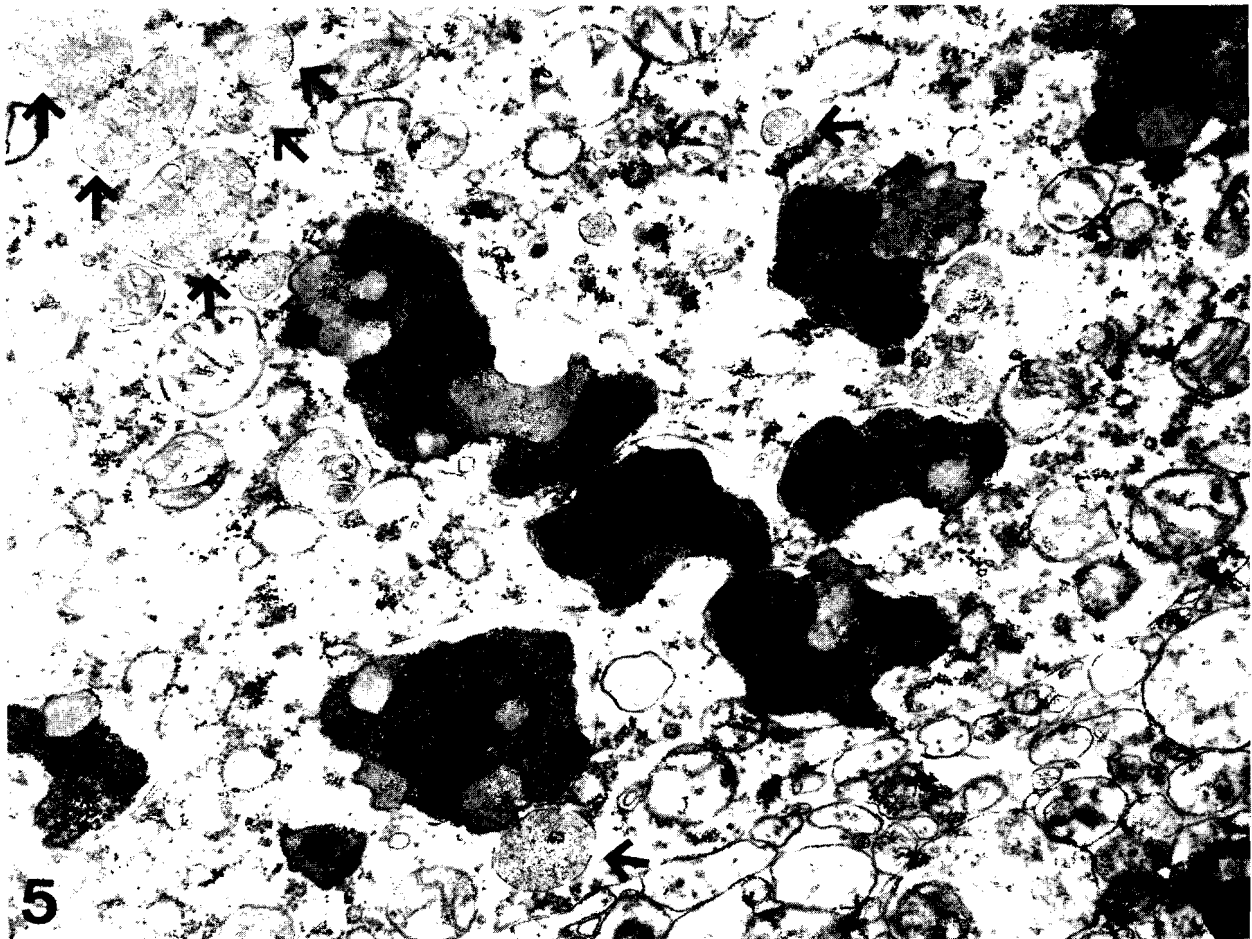

Fig. 5. Neuron of the frontal cortex. Large amounts of secondary lysosomes (arrows) and lipofuscin-like inclusions. × 20,000

constant feature in Refsum's disease and helps to differentiate the syndrome from other ataxias and from peroneal muscular atrophy, in which a protein-cell dissociation is very rare (Gordon and Hudson, 1959).

The relationship between accumulation of phytanic acid and the clinical manifestation is still not clear, but Gibberd et al. (1979) showed that when a patient is losing weight the blood-level of phytanic acid mobilised from the fat stores rises, and the patient's condition deteriorates. If the phytanic acid level has already been high, starvation could raise it to toxic amounts and precipitate arrhythmia. As a rule, patients, as it was in our case, had lost weight immediately before death. Moreover, it has been shown that in the liver, heart and kidneys the phytanic acid content, and the levels of cholesterol are markedly increased (Skrbic and Cumings, 1969). Death of patients may be associated with these cholesterol infiltrations rather than with the increase in the amount of the unusual fatty acid (Cumings, 1971).

Pathology

The morphological findings in the different organs in the present case resembled those described by others (Reese and Bareta, 1950; Edström et al., 1959; Gordon and Hudson, 1959; Thiebaut et al., 1961; Nevin et al., 1967; Fryer et al., 1971).

The fat-laden macrophages in the leptomeninges in our case correspond to findings of different authors (Cammermeyer and Haymaker, 1954; van Bogaert et al., 1967; Cammermeyer, 1975). Pathological changes in the pallidum were less obvious than in previously described cases (Cammermeyer, 1946; Kjellson, 1953; van Bogaert, 1967). The patchy atrophy of the nucleus dentatus as well as the inferior olive have been observed previously in Refsum's disease (Gordon and Hudson, 1959). It cannot be excluded that acute circulatory disturbances in the prefinal stage have contributed to this lesion. The neuronophagias in the anterior horn of the spinal cord seems to confirm the existence of acute
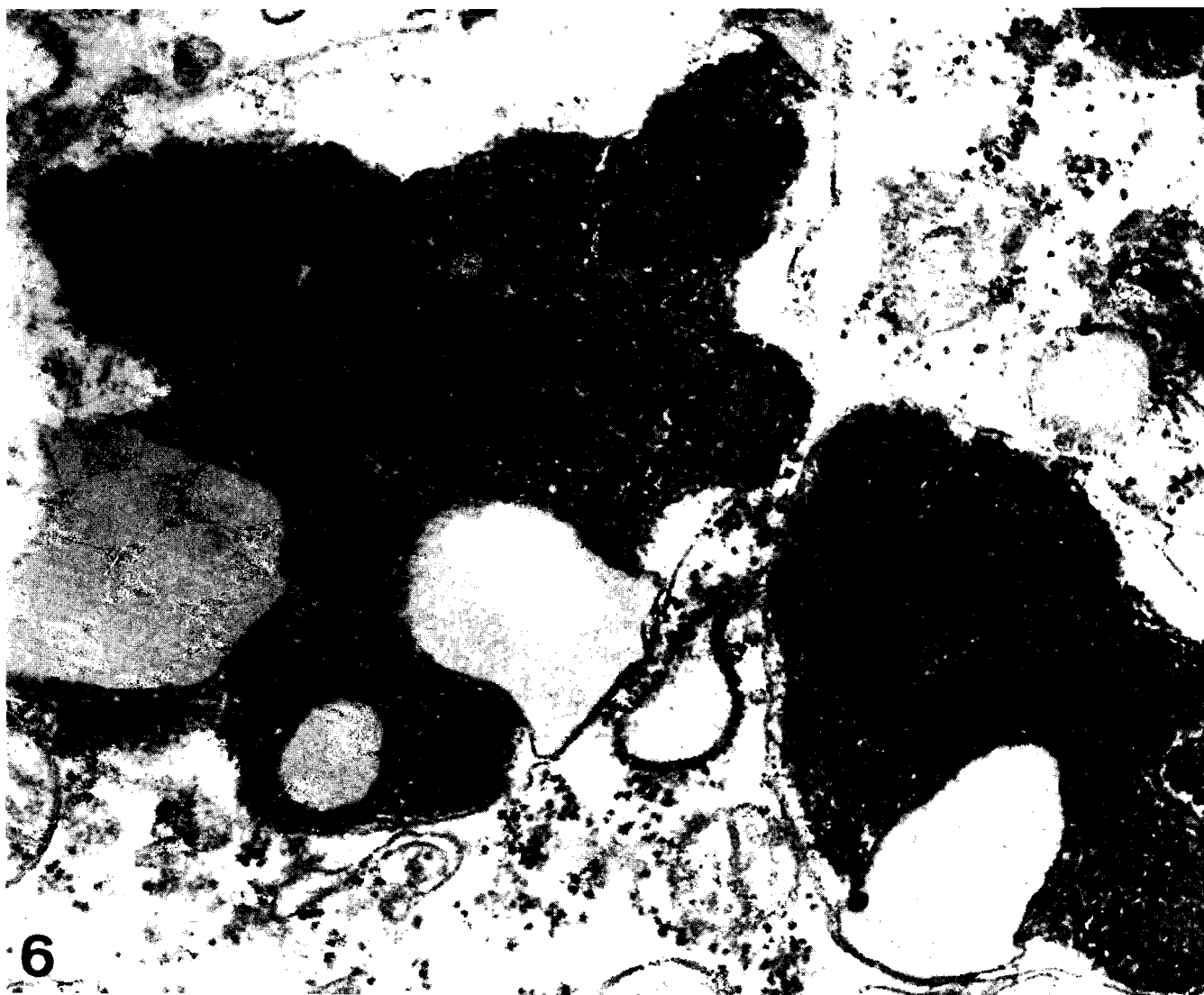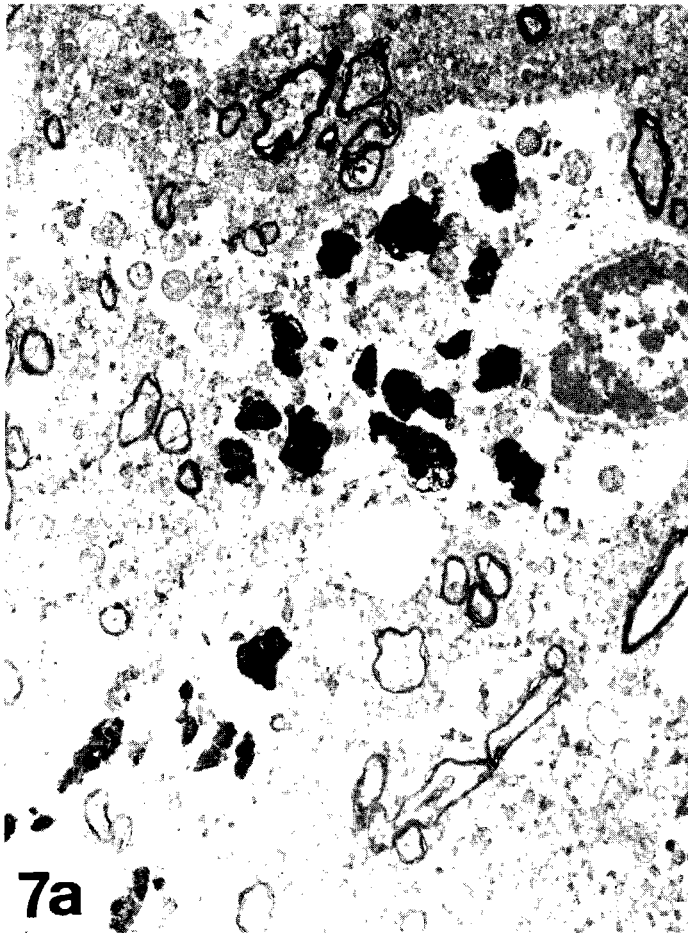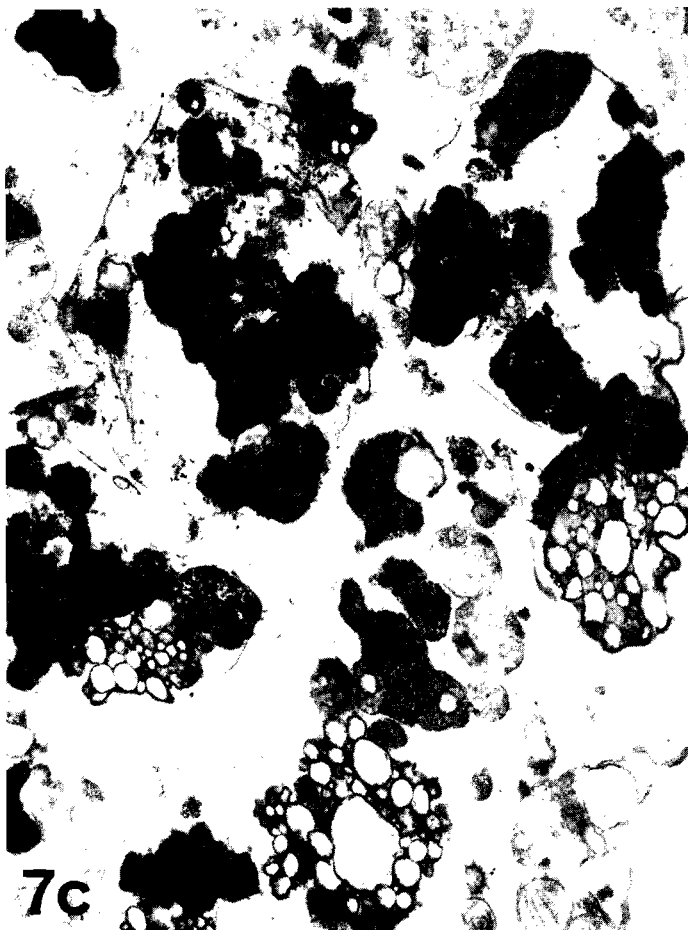

Fig. 6. Lipofuscin-like inclusion with densely-packed tubular structures. × 90,000

Fig. 7. Frontal cortex. **a.** Perivascular astrocyte containing abundant residual bodies. × 2,700. **b.** Electron-dense nedle-like structures lying partly free in the cytoplasm. × 26,000. **c.** Pleomorphic residual lysosomal bodies. × 20,000

disturbances immediately before death.

Ependymal granulation has been described as an incidental change by Steinberg et al. (1967b). In the present case there were occasional erosions. In connection with these findings the increased protein and phytanic acid content in the cerebrospinal fluid is of interest. Phytanic acid accumulation was shown to occur also in the brain of patients with Refsum's disease (McBrin and O'Brien, 1968), but to a lesser extent than in peripheral nerves. The brain contains 3-4 times smaller amounts of phytanic acid as in other organs, probably because of the relative impermeability of the blood-brain barrier to phytanic acid. The possibility of the penetration of phytanic acid into the brain through the erosions of the ependymal layer has to be kept in mind.

The most conspicuous finding in the central nervous system was the great number of lysosomal residual bodies. In the astrocytes a common feature were the characteristic needle-like structures, identical to those previously described in liver biopsies in infantile Refsum Syndrome (Scotto et al., 1982; Poulos et al., 1984) and in many cases of neonatal adrenoleucodystrophy (Kelley et al., 1986). Similar structures were very prominent in macrophages, liver cells and astrocytes in the only postmortem examined case of

Fig. 8. High magnification of a residual body with bilamellar ribbon-like structures. × 80,000

infantile Refsum's disease up to the present (Torvik et al.; 1988). Participation of phytanic acid as well as other very long chain fatty acids in the composition of these inclusions seems probable.

The frequent occurrence of free bilamellar structures in astrocytic cytoplasm might indicate that they were due to an intrinsic metabolic disturbance rather than resulting from phagocytosis of phytanic acid or its metabolites. This would correspond to observations of Adachi et al. (1971) on primary alterations in astrocytes in various lipidoses. However, the possibility of phagocytosis of inclusions ejected from damaged neurons cannot be dismissed.

The findings in the cerebellum have been surprinsingly scarce. The stacks of cisternae present in the cytoplasm of Purkinje cells are non specific and have been described in various types of cells under normal conditions (Bestetti and Rossi, 1980).

Pathogenesis

Peroxisomes have shown to participate in the beta oxidation of fatty acids (Kindl and Lazarow, 1982) and to contain an alpha-hydroxy-acid-oxidase that could conceivably take part in phytanate oxidation. In a liver biopsy from a child that was thought to suffer from an infantile form of Refsum's disease peroxisomes were not detectable (Ogier et al., 1985). In our material structures corresponding to the original description of the peroxisomes (Rhodin, 1954) were found in the astrocytes and more prominently in the oligodendrocytes. This is in accordance with the assessment of Holzmann (1982), who found the largest amounts of peroxisomes in the rat brain oligodendrocytes. Our results are also in

Fig. 9a. Oligodendrocyte process. × 7,000. **b.** At high magnification laminated structures mimicking finger prints. × 100,000

agreement with the findings of Beard et al. (1985) in fibroblasts from skin of adult patients with Refsum's disease. In the neurons there were peroxisomes of small size similar to the microperoxisomes observed in several peroxisomal diseases (Arias et al., 1985).

Because of its chemical structure phytanic acid accumulates in membranes and therefore in myelin. Two main possibilities have been envisaged (Steinberg et al., 1967b; McBrin and O'Brien, 1968; Steinberg, 1978).

1) The «thorny» surface of phytanic acid molecules is likely to disturb packing of the hydrophobic fatty acid chains. This can be expected to increase fluidity and destabilize the structure of myelin («molecular distortion hypothesis»). In our case a status spongiosus (Solcher, 1973) has not been seen, but demyelinization was present, and the changes in the peripheral nerve (Cervós-Navarro, 1990) adduced evidence in favour of the molecular distortion hypothesis. 2) In view of the

Fig. 10. Spinal cord. Astrocytic processes with densely-packed gliofilaments, and a polyglucosan body containing branching filaments. **(a).** Oligodendrocyte with myelin-like membranous formation **(b).** × 5,500. Inserts: **a** × 32,000, **b** × 18,000

structural similarity of phytanic acid to vitamin E, competitive inhibition of its function was considered likely («antimetabolite hypothesis»). The marked increase in lipid pigment granules including different inclusions and residual bodies indicate enhanced lipid peroxidation and polymerization. Also, the neuroaxonal dystrophic changes in spinal cord and in the nucleus gracilis probably testify to this situation. Thus, the «antimetabolite hypothesis», which assumes interference ith the antioxidant function of vitamin E, is also supported by the present findings. It is quite obvious that the two suggested hypotheses are not mutually exclusive.

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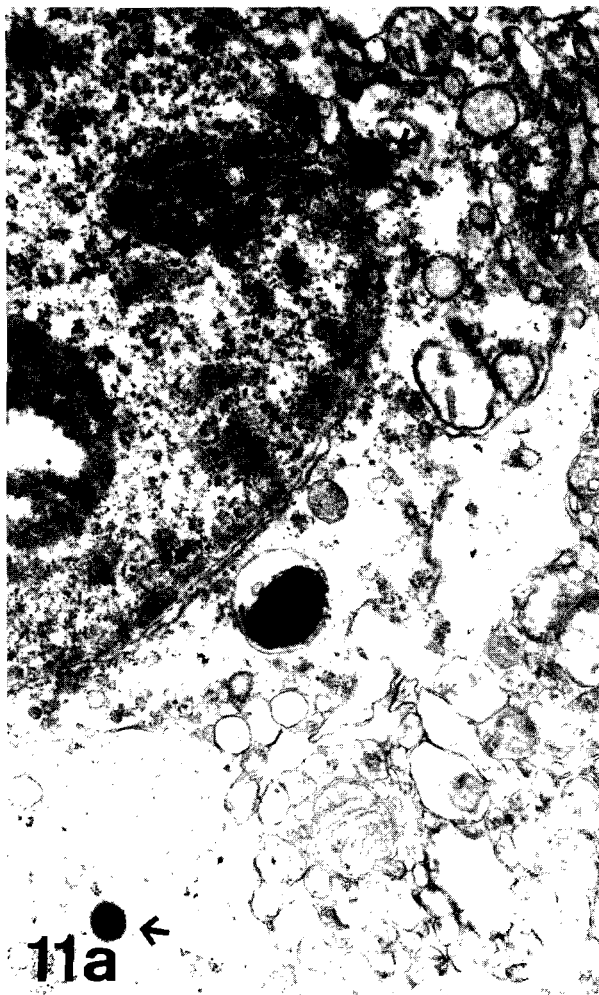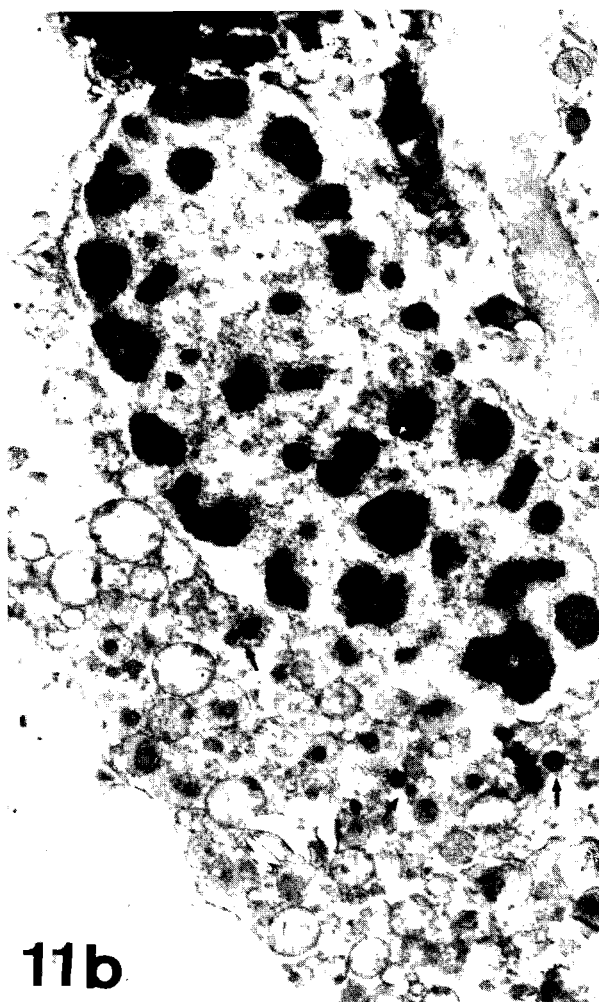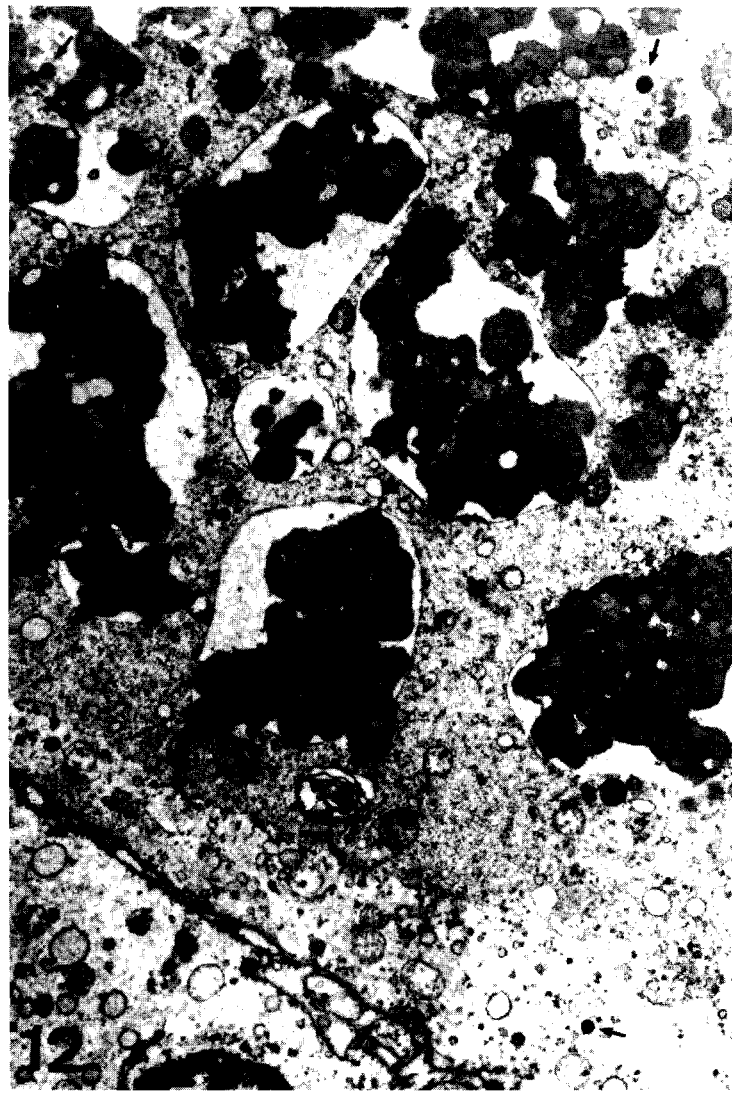
Fig. 11. Frontal cortex. Peroxisomes (arrows) in the cytoplasm of (a) astrocyte and (b) oligodendrocyte. **a** × 18,000. **b** × 12,000

Fig. 12. Frontal cortex. The cytoplasm of a neuron with large amounts of lipofuscin and scattered peroxisomes (arrows). × 12,000

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