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# Infantile mitochondrial leucodystrophy – a case report

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**Abstract**

*We retrospectively analyzed a case of a 7-month-old infant with a delay of psychomotor development, slow pupillary light reflexes, horizontal nystagmus, spasticity and bilateral optic nerve atrophy. At the end of life there were problems with swallowing. Ventriculography showed widening of the lateral ventricles and atrophy in the frontal lobes. EEG revealed generalized changes. Clinically, leucodystrophy was diagnosed. General autopsy revealed cardiac hypertrophy. Neuropathological picture showed orthochromatic leucodystrophy with some features characteristic of neuropathology of mitochondrial disease: capillary hyperplasia and hypertrophy, spongiosis and symmetrical, bilateral damage of brain stem structures. The last one is characteristic of Leigh syndrome. Electron microscopic evaluation showed abnormal mitochondria, myelin and neurofibrils destruction. Hypertrophy of the heart may be also connected with mitochondrial disease.*

***Key words:*** *infants, mitochondrial disease, leucodystrophy, orthochromatic myelin destruction,, vascular reaction, white matter spongiosis, Leigh disease*

## Introduction

Myelin abnormalities are not particularly prominent in the mitochondrial diseases [1]. We report an infantile leucodystrophy with some neuropathological features of mitochondrial diseases.

## Case report

Clinical data: A five-month-old boy was admitted to the neurological clinic because of the delay of psychomotor development. He was born at term (1973) after uneventful pregnancy and delivery (birth weight 4250 g, length 55 cm) in good state. At the time of admission the general examination was normal. Neurologically, he was irritable, without any interest in the surrounding. There were slow pupillary light reflexes, bilateral horizontal nystagmus, spasticity with bilateral Babinski sign. Fundoscopic examination showed bilateral optic nerve atrophy. Ventriculography showed widening of the lateral ventricles and cortical atrophy of the frontal lobes. EEG revealed generalized changes with high voltage slow wave. Cerebrospinal fluid as well as urine metabolic tests were normal. At the end of life there were problems with swallowing. He died at seven months of age. Three older relatives were

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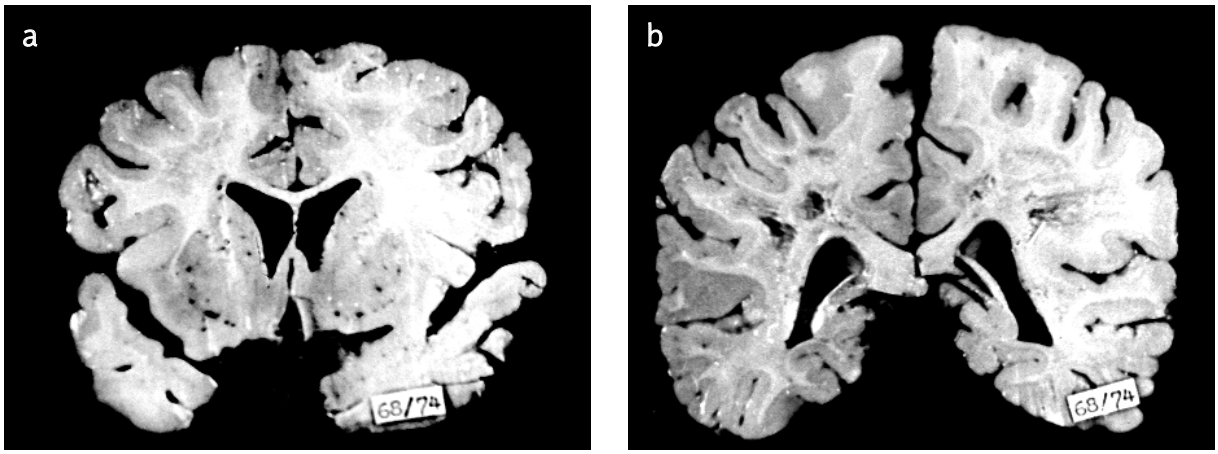


**Fig. 1.** Diffuse damage of the cerebral white matter a. Frontal lobes. b. The cavitation in occipital lobes. Macroscopic appearance

healthy, none of them had neurological problems. Clinical diagnosis was *Leucodystrophy*.

General autopsy diagnosis was: Interstitial pneumonia. Hypertrophy of the heart and fibrosis of the liver.

## Material and methods

The brain was fixed in formalin. Then, specimens from the cerebral hemispheres, brain stem and cerebellum were taken and embedded in paraffin. The sections were stained with hematoxilin-eosin (HE), Spielmeyer, Kluver-Barrera and Bielschovsky methods. On frozen specimens from the white matter, Sudan-black and red-oil reactions were made. For electron microscope evaluation small fragments of spongy degenerated white matter were taken from paraffin blocks. After deparaffinizing and washing several hours in water the material was processed routinely for ultrastructural examination.

## Neuropathology

Macroscopic evaluation showed a diffuse damage of the cerebral hemispheres white matter with cavitation in the parieto-occipital lobes (Fig. 1a, b). Similar changes in the white matter of the cerebellar hemispheres and cerebellar medium peduncles were

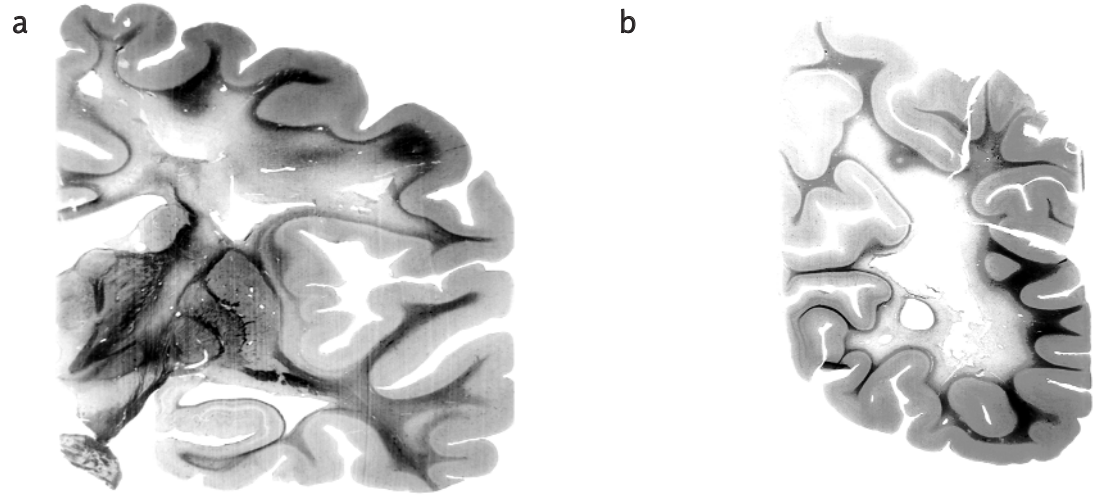


**Fig. 2. a, b.** Diffuse demyelination of the central white matter with relatively better preserved myelin in the axis of the gyri. Myelination of the temporal lobe is adequate to the age and U-fibers are not yet myelinated. Spielmeyer

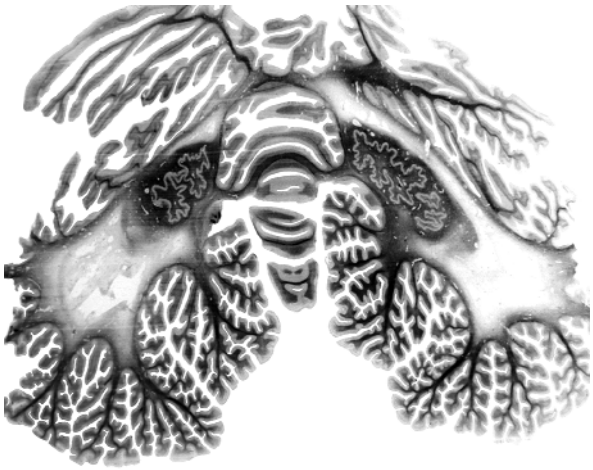

**Fig. 3.** Demyelination of the cerebellar white matter. Spielmeyer

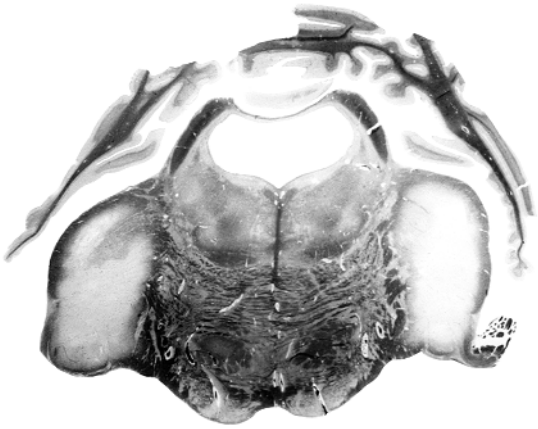

**Fig. 4.** Severe damage of the middle cerebellar peduncle. Myelination of the other pons tracts is adequate to the age. Spielmeyer

seen. There was atrophy of the anterior part of the corpus callosum with widening of the lateral ventricles. Both pyramids in the medulla oblongata were small. The microscopical evaluation showed normal for age development of the brain, cerebellum and brain stem with adequate to age myelination except of pyramids in the medulla oblongata where the lack of myelin was seen. The most prominent change was demyelination with destruction of the white matter of both cerebral hemispheres and cerebellar hemispheres (Fig. 2). The same type of lesions, symmetrical and bilateral, were seen in the brain stem in the middle cerebellar peduncle (Fig. 3, 4). There was moderate to severe glia reaction with cavity formation in the central part of lesions, macrophages were moderate in number in some areas, but absent in others (Fig. 5a, b). In the less severe damaged tissue there were proliferation and hypertrophy of capillaries (Fig. 6a, b). The most severe white matter changes were seen in the centrum semiovale of the cerebral hemispheres, in the cerebellar hemispheres and cerebellar medium peduncles. There was relatively good preservation of myelin in the axis of the cerebral gyri, basal ganglia and brain stem (with the exception of cerebellar middle peduncle), but there were extensive spongiform changes (Fig. 7). The cerebral and cerebellar cortex, basal ganglia and neuronal structures of the brain stem were without remarkable changes.

At the ultrastructural level some of the mitochondria were markedly enlarged with aberrant

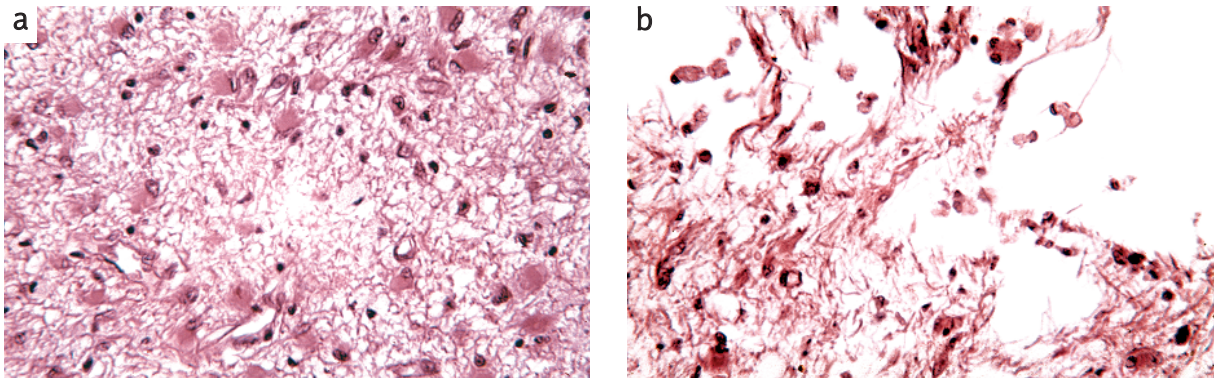


**Fig. 5.** Cerebral white matter destruction with glia reaction (a) and cyst formation (b). H-E, x 200

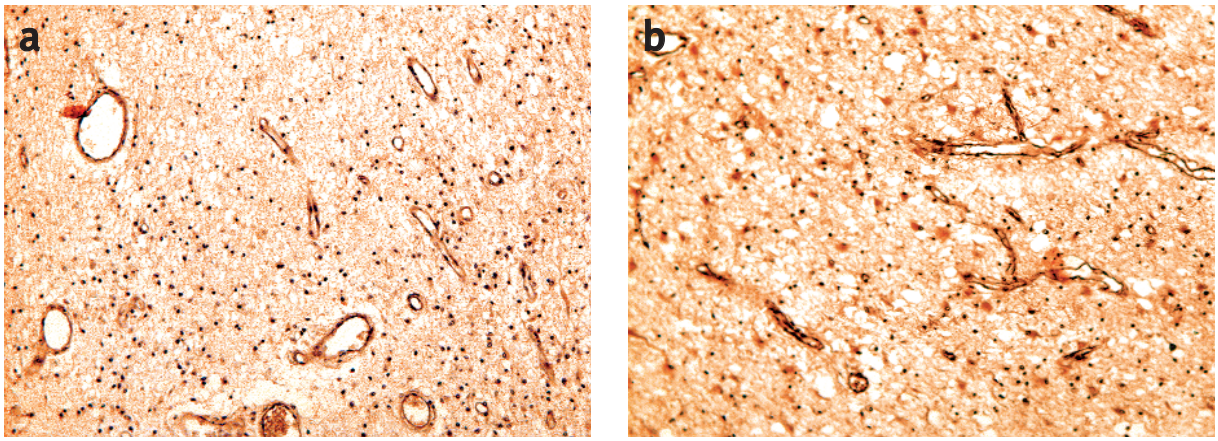


**Fig. 6. a, b.** Damage of the cerebral white matter with vascular hyperplasia and hypertrophia. H-E, x100

configurations of cristae. Sometimes, pathological mitochondria possessed only few centrally situated cristae (Fig. 8).

## Discussion

Enormous progress in molecular genetics and biochemistry that has taken place for the last twenty years caused verification of certain previously established clinico-neuropathological diagnoses.

We examine and discuss the case which was previously diagnosed in 1974 as leucodystrophy. Clinical symptoms suggested the white matter disease.

Neuropathological picture confirmed the clinical diagnosis and at that time ortochromatic leucodystrophy was recognized. The coexistent spongiotic changes, vascular proliferation and hypertrophy and focal changes in the brain stem were considered as special features of this case. A very similar case was reported in 1968 by Osetowska [6], who had discussed the cause of diffuse destruction of the brain white matter accompanied by extensive vascular proliferation and spongiotic changes with symmetric focuses of damage in the brain stem. Now we know that capillaries proliferation and hypertrophy, especially surrounding necrotic foci are a distinctive neuropathological feature of mitochondrial diseases [1]. The symmetric, bilateral damage of the brain stem structures and/or basal ganglia is characteristic of Leigh syndrome. Myelin is known to be damaged in the mitochondrial disease, but mitochondrial diseases are not typically on the list of degenerative disorders

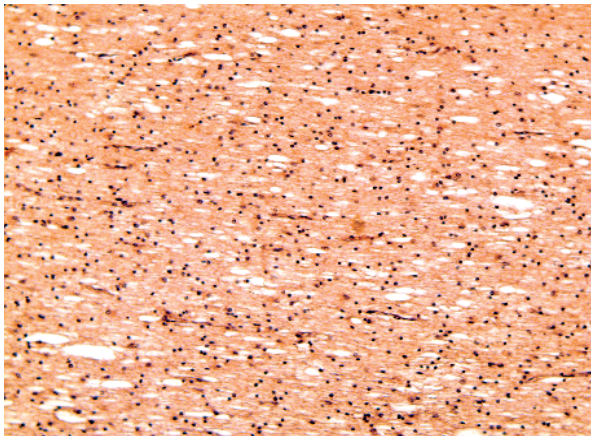

**Fig. 7.** Spongiotic changes in the cerebral white matter. H-E, x 100

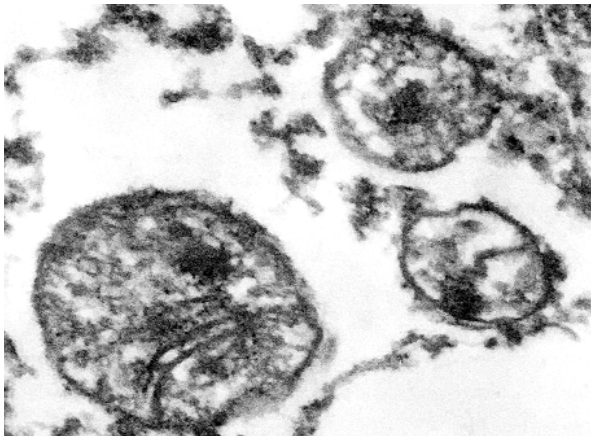

**Fig. 8.** Enlarged mitochondrium showing few concentrated cristae. Orig. magn. 20 000x

of the white matter [1]. Valanne et al. [7] report six cases with brain abnormalities with the most prominent changes in the white matter in MRI and CT. In one case there were also focal lesions in the brain stem. All of the infants were found to have mitochondrial enzyme dysfunction.

Nakai A. et al. [5] also report diffuse leucodystrophy in a patient with mitochondrial DNA (mtDNA) deletion and suggest to take this etiology for consideration in unknown diffuse leucodystrophies.

The tissue and organ involvement in mitochondrial diseases can be attributed to heteroplasmy (normal and mutated mtDNA in one cell or tissue) and the threshold effect. The proportion of mutated mtDNA determines phenotypic expression [2,3]. The topography of the lesions in the brain is not clear [3].

In the reported case it was the cerebral and cerebellar white matter and middle cerebellar peduncle damage with capillary proliferation and hypertrophy and also heart hypertrophy. The latter is the most important cardiac presentation of mitochondrial diseases. All these specific findings confirm the diagnosis of mitochondrial encephalocardiopathy. When clinical or laboratory evaluation excluded other disorders, mitochondrial disease should be considered [4].

Atypical MRI/CT findings resembling leucodystrophies with symmetrical focuses of damage in the brain stem may suggest mitochondrial etiology of disorders.

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