Acta Paediatrica Hungarica 31 (4), pp 433-442 (1991)

ULTRASTRUCTURAL INVESTIGATIONS IN LATE INFANTILE TYPE OF CEROID LIPOFUSCINOSIS (JANSKY-BIELSCHOWSKY)

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Received 2 July 1990

Ultrastructural findings of biopsy materials of four gipsy first cousin infants suffering from late infantile type of ceroid lipofuscinosis (Jansky-Bielschowsky) were investigated.

The diagnostic significance of the conjunctival biopsy is emphasized. The pericytes and the vascular smooth muscle cells of the arterioles proved to be the main inclusion storing cells.

INTRODUCTION

The term ceroid-lipofuscinosis (CL) designates a group of inherited disorders which result in motor-sensory deterioration, mental retardation, visual impairment and early death. The disease is characterized by the accumulation of tertiary lysosomes containing an electron-dense autofluorescent storage material. Four different forms have been differentiated on the basis of age of onset, clinical course, inheritance and the ultrastructural appearance of the storage bodies, Santavuori-Haltia, Jansky-Bielschowsky, Spielmeyer-Sjögren and Kufs disease. Until recently it was generally accepted that the autofluorescent pigment probably results from non-specific peroxidation of polyunsaturated fatty acids /14/.

Diagnostic criteria are: onset of visual loss at around 5 years age, dementia occurring a few years later, extinguished electroretinograms between ages 5-12 years and typical electron microscopic findings in tissues.

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Kohlschütter /10/ analyzed the clinical variability of juvenile neuronal ceroid lipofuscinosis (JNCL) using disease specific scoring system including the patient's vision, intellect, language, motor functions and epilepsy.

The results of several authors /7, 9, 13/ suggest that ceroid-lipofuscinoses might involve a defect in the metabolism of dolichol-oligosaccharides.

In this study ultrastructural findings of 4 children suffering from late infantile type of CL (Jansky-Bielschowsky) will be presented.

PATIENTS AND METHODS

Case reports: 4 gipsy first cousin infants or children were investigated suspected for heredodegenerative disorder (Fig. 1). In the investigated family, parents are II. cousins. There are autosomal recessively transmitted genes. The affected family members who died in childhood (II/1, 2, 3 and 5) have not been investigated.

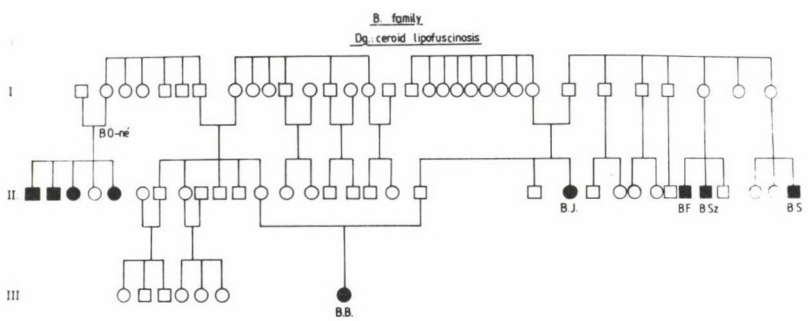

Fig. 1. Pedigree of B. family. Dg.: ceroid lipofuscinosis

Tapetoretineal degeneration, or/and optic atrophy, epilepsy (GM, or petit mal), dementia process were the main clinical symptoms. Later data are summarized in Table I.

Lysosomal hydrolases (N-acetyl-hexosaminidase-A and beta-galactosidase, arylsulfatase-A were determined by Griffith's /6/ method from the peripheral leukocytes. GM_1, GM_2 type of gangliosidosis and metachromatic leukodystrophy (MLD) had been excluded (Table II).

Light and electron microscopic examination of n. suralis, skin, conjunctival or/and liver biopsy material were carried out.

TABLE II

Lysosomal hydrolase activities of leukocyte homogenate

Name	N-acetyl-hexosaminidase total nmol/mg protein/h	N-acetyl-hexosaminidase A% nmol/mg protein/h	Beta-galactosidase nmol/mg protein/h
Szabolcs B.	745	92	81.8
Judit B.	894	80	70.4
Simon B.	609	67	85.2

	Arylsulfatase- A U/l
Szabolcs B.	76
Judit B.	51
Simon B.	48

RESULTS

Electron microscopic examination of the biopsy materials revealed inclusion bodies only in the conjunctival biopsies. The characteristic curvilinear bodies (Fig. 2) were found mainly in the pericytes or in the smooth muscle cells of small arterioles (Fig. 3) but some endothelial cells also contained such inclusions (Fig. 4). We could not demonstrate any inclusions in other cell types or organ. In the arterioles not all cells stored the specific inclusions and not all arterioles

TABLE I

Clinical and morphological findings

Case, name born	Sex	Ophthalmological visus	VEP	ERG	EEG	Onset of epilepsy	Therapy	Biopsy material EM
1. Sz.B. 5.Apr.1981 6 y. at. dg.	M	optic atrophy	extinguished		GM	18 m	Sertan B_6	skin: negative conj. +
2. J.B. 21.Nov.1982 5 y. at. dg.	F	optic atrophy	extinguished diminished amplitudes, stretched latency (l.d.) no responses (l.s.)		GM	2,5 y	Sertan B_6	skin: negative conj: +
3. S.B. 22.July 1983 5 y. at. dg.	M	optic atrophy	extinguished		PM	3 y	Sertan B_6	skin: negative conj: +
4. B.B. 12.July 1985 4 y. at. dg.	F	subnormal hardly detectable optic and retineal function	intact P_1 component	positive P_2 component subnormal nearly extinguished	slow electric activities, BNS irritative like signs	15 m	Sertan Lipoic acid B_1, B_6	liver: negative skin: negative conj.: +

M = male

F = female

P_1 = early VEP component

P_2 = late VEP component

conj. + = curvilinear bodies in endothel cells and in the pericytes of vessels.

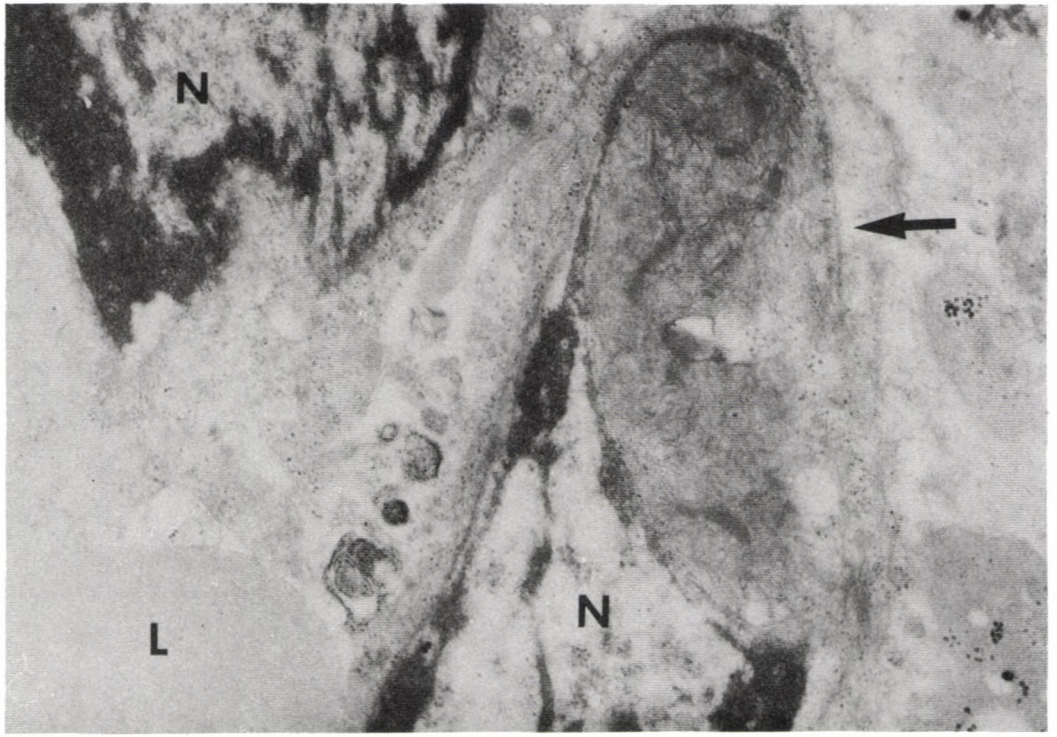

Fig. 2. Conjunctival biopsy (1461/89 K.Sz. 14.000 x EM) Intracytoplasmatic characteristic curvilinear body (arrow) in an endothelial cell compressing the nucleus (N)

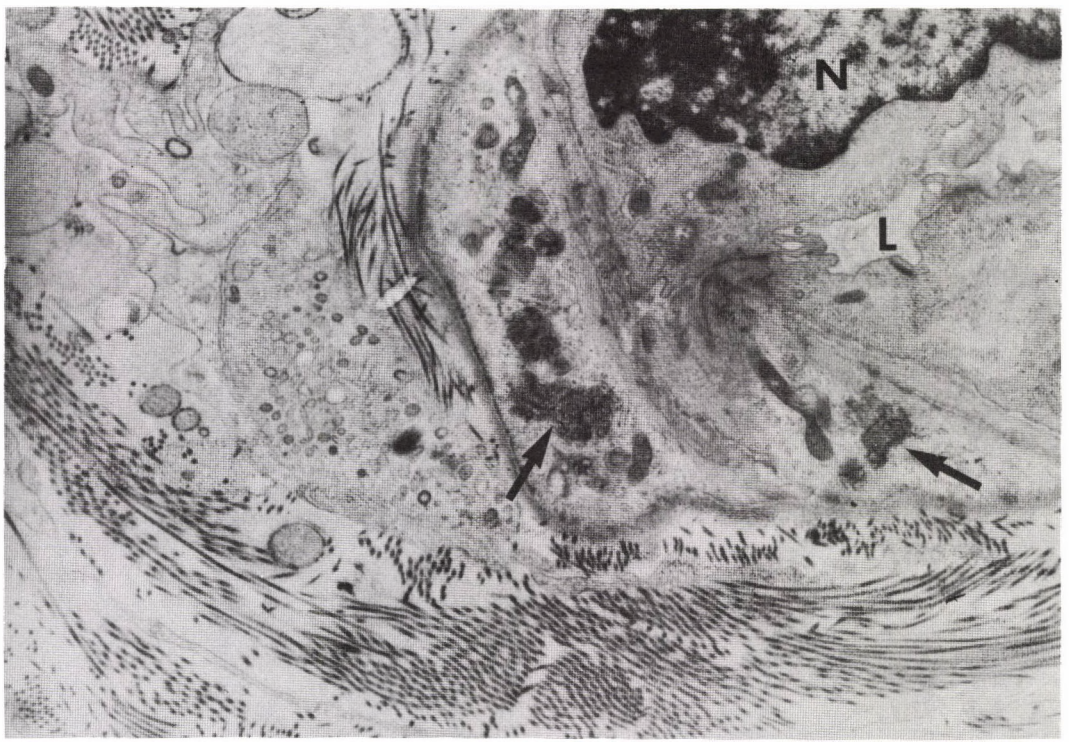

Fig. 3. Conjunctival biopsy (291/88 K.Sz. 6.000 x EM) curvilinear bodies (arrow) in the smooth muscle cells or in pericytes of arteriole (L=lumen of the arteriole)

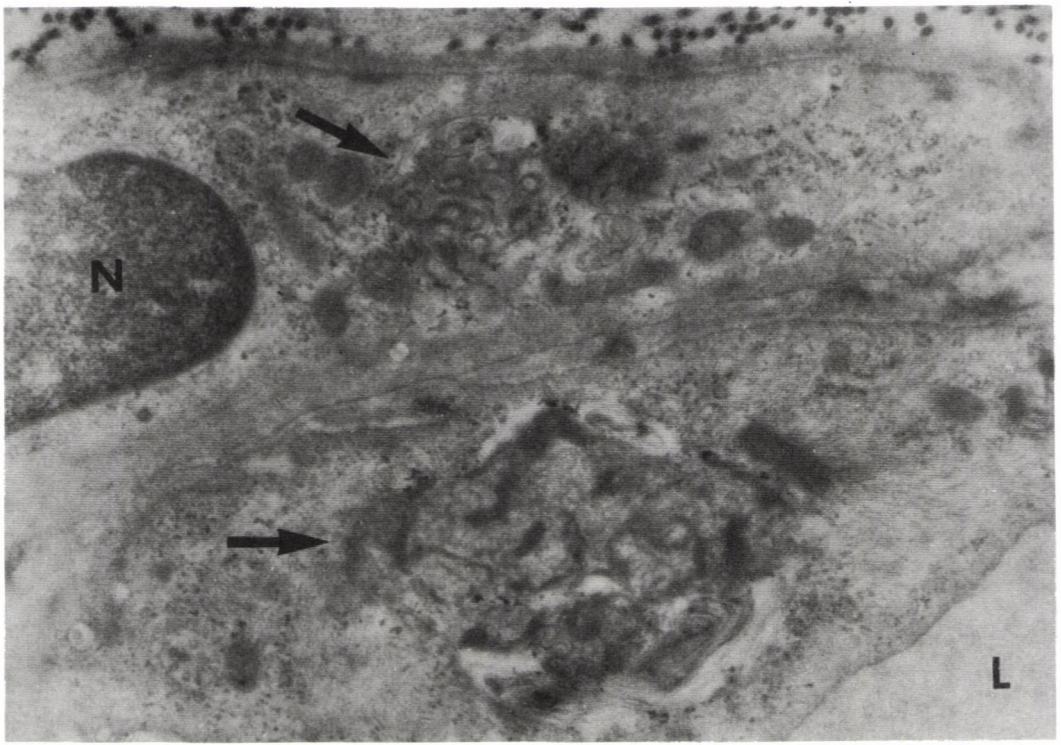

Fig. 4. Conjunctival biopsy (2722/88 K.SZ. 14.000 x EM) curvilinear bodies in an endothelial cell and a smooth muscle cell of an arteriole

contained much storing cells. The rare endothelial inclusions could be detected only after careful examination.

DISCUSSION

Kohlschütter /10/ detected typical inclusions in the rectal biopsy material of juvenile neuronal CL patients. The above-mentioned authors's score system allows definition of relatively mild and severe courses representing the variability of JBCL. Our patients must be regarded as the severe form of the disease, they are not juvenile but late infantile type.

Goebel /4/ proposed muscle biopsy examination in neural CL and also ultrastructural analysis of the peripheral nerve biopsy tissues /5/. Haynes /8/ considered electron microscopic analysis of a skin biopsy sample and of the lymphocytes to be informative in the above disease. Fingerprint-like ultrastructural formations of the lymphocytes were reported /2/ to be pathognostic in juvenile NCL. Investigating the chronic neurological diseases of childhood in conjunctival and skin biopsies the CL-s were the largest group in the patient material of Arsenio-Nunes /1/b/. In the latter material three conventional cytosome types were demonstrated with a predominance of granular inclusions in the early infantile form, of curvilinear bodies in the late infantile form and of fingerprint bodies in the juvenile form /1/a, 3, 12/. Electron microscopic study of skin and conjunctival biopsy specimens is an important diagnostic tool in chronic progressive encephalopathies /11/. Ultrastructural abnormalities are not entirely specific, as the finding of multilamellar bodies may be seen in a variety of different conditions. The biochemical techniques are available for the diagnosis of many chronic neurological diseases and these are more specific than morphological techniques, but the electron microscopic investigation may confirm and document diagnoses already suspected on the basis of the history, clinical examination and

other laboratory tests, even in the absence of a specific or available biochemical methods. According to our results the conjunctival biopsy seems to be not only a suitable but sufficient biopsy sampling. The main inclusion storing cells in the late infantile type of the CL are the pericytes, the vascular smooth muscle cells and the endothelial cells. During the ultrastructural investigation a more careful examination should be taken of the arterioles.

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