*Develop. Med. Child Neurol.* 1974, **16**, 644–653

# Infantile Type of So-called Neuronal Ceroid-lipofuscinosis

***Pirkko Santavuori Matti Haltia Juhani Rapola***

## Introduction

The term 'neuronal ceroid-lipofuscinosis' (NCL) was introduced by Zeman and Dyken (1969) as a synonym for Batten's syndrome, including the early-onset (Jansky-Bielschowsky) and late-onset (Spielmeyer-Sjögren) types.

We have recently reported a new type of progressive encephalopathy which begins at about one year of age with mental retardation, accompanied by ataxia, loss of vision and myoclonic jerks, and which progresses rapidly to a quiescent stage (Haltia *et al.* 1973*a*, *b*; Santavuori *et al.* 1973). Studies of brain biopsies and autopsy material disclosed severe neuronal destruction and pronounced macrophagic and astrocytic reaction. The remaining neurones and macrophages contained deposits with the histochemical characteristics of lipofuscin, but with a consistent fine granular ultrastructure. Haltia *et al.* (1973*a*) concluded that these cases form a clearly separate 'infantile type of so-called neuronal ceroid-lipofuscinosis'. Cases which were clinically and morphologically identical have also been reported from Sweden (Hagberg *et al.* 1968, 1974). In both the Finnish and Swedish patients, Svennerholm *et al.* (1974) have observed profound disturbances in the pattern of polyunsaturated fatty acids in brain tissue.

In the present paper, the clinical characteristics of this new disease are outlined in the light of 46 cases personally examined during the past few years. Special investigations of value for diagnosis and the differentiation from other types of amaurotic idiocy are briefly discussed.

## Clinical Material

Our clinical material consists of 46 patients (27 boys, 19 girls) examined at the Children's Hospital, University of Helsinki, during the period from 1st January 1959 to 1st October 1973. 34 cases were able to be followed-up for periods of between six months and eight years. Including four affected siblings and two first cousins of patients (not seen at the Children's Hospital), the total number of known cases in Finland is 52.

The patients derived from 38 families, in seven of which several children were affected. In our 46 patients the diagnosis was based on autopsy findings in nine cases; in a further 18 cases the clinical diagnosis was confirmed by brain biopsy and appendiceal biopsy; and in the remaining 19 cases the diagnosis rested on clinical criteria only.

## Clinical Course

The pre- and peri-natal histories of our

Children's Hospital and 2nd Department of Pathology, University of Helsinki, Helsinki, Finland.

TABLE I

**Age at which children with INCL reached some of the developmental milestones.**

| *Age* | *Standing up* | *Walking without support* | *Speaking words* |
|---|---|---|---|
| (*Months*) | (*No.*) | (*No.*) | (*No.*) |
| 7 | 2 | — | — |
| 8 | 1 | — | — |
| 9 | 3 | — | 1 |
| 10 | 4 | — | 1 |
| 11 | 6 | 2 | 3 |
| 12 | 13 | 5 | 20 |
| 13 | 2 | 3 | 1 |
| 14 | 2 | 3 | 1 |
| 15 | 1 | 2 | 7 |
| 16 | 1 | 1 | — |
| 17 | — | — | 1 |
| | 35 (76%) | 16 (35%) | 29 (63%) |

TABLE II

**Age of patients at the onset of main symptoms and signs of INCL***

| Age (months) | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mental retardation | 1 | 2 | 1 | 7 | | 7 | 4 | 6 | 6 | 8 | 2 | | | | | |
| Ataxia | | 1 | | 3 | | 3 | 3 | 2 | 4 | 9 | 3 | 2 | 3 | 2 | | |
| Visual failure | | | | 1 | | 1 | 1 | 3 | 2 | 4 | 7 | 4 | 3 | 6 | 3 | 4 |
| Hyperkinesia | | | | | | | | | 1 | 6 | 3 | 2 | 5 | 2 | 6 | 2 |
| Myoclonic jerks | | | | | | 1 | | 2 | 3 | 5 | 2 | 1 | 5 | 4 | 3 | 6 |

* Only those patients are included in whom the onset of a particular sympton or sign could be defined exactly.

patients did not deviate from the average Finnish material (Hartikainen 1973). In all patients the developmental milestones were within normal limits until the age of eight months. In four children a slight delay in motor development was noticed after six months, but none of them was mentally retarded at that age. 29 children learned to speak single words and 17 learned to walk alone. 19 others learned to stand up (Table I).

In most of the children retardation of mental development was noticed between the ages of 12 and 18 months, and in some even earlier. Motor development ceased slightly later, after which generalised muscular hypotonia appeared, together with truncal and limb ataxia (Table II). In some cases hypotonia and ataxia were the initial signs. In many patients the ataxia was very severe and led rapidly to motor disability. All patients were microcephalic (Fig. 1); in some cases this first became apparent after the age of two years. Visual disturbances were observed as early as 12 months of age in some cases, and all patients were virtually blind at the age of two years.

In all but one case myoclonic jerks were first noticed between the ages of 16 and 24 months, usually occurring in one or more limbs but occasionally generalised. At about the same time, characteristic 'knitting' patterns were observed in the hands and forearms, but these disappeared again after a few months. Many patients were hyperexcitable and difficult to manage during their second year.

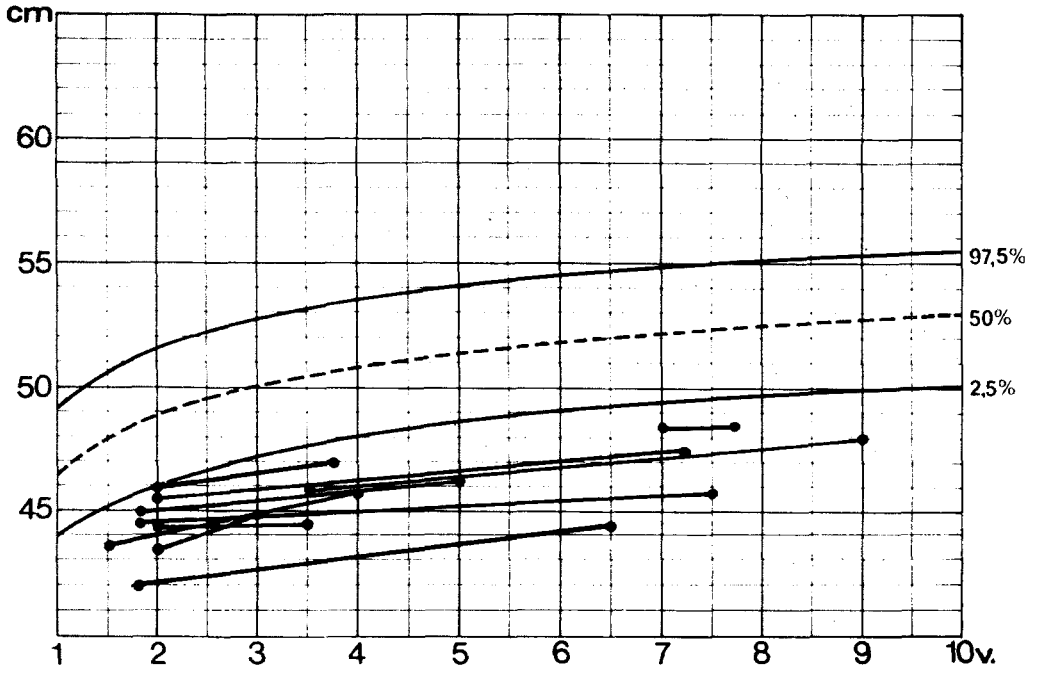


**Fig. 1.** The head circumferences of ten girls with INCL (serial measurements). In spite of the severe progressive brain atrophy, the skull may grow slightly.

Fits occurred in nine patients before the age of two years, and in 11 others after that age. In six cases it was difficult to know whether the child really had had seizures or if these were merely frequent myoclonic jerks. Usually the fits were infrequent, and 20 children had none. 16 children had generalised convulsions, often beginning with focal features. At the onset of the disease, drop attacks were noticed in five children for a short period. In two cases only occasional febrile convulsions occurred.

TABLE III

**Symptoms and signs appearing between the ages of 12 and 24 months in 46 INCL patients**

| | |
|---|---|
| Mental retardation | 46/46 |
| Visual failure | 46/46 |
| Myoclonic jerks | 45/46 |
| Microcephaly | 42/46 |
| Ataxia | 39/46 |
| Muscular hypotonia | 28/46 |
| 'Knitting' hyperkinesia | 28/46 |
| Squint | 17/46 |
| Convulsion | 9/46 |
| Rigidity | 6/46 |

In all patients the disease reached a quiescent stage during the third year. The children were grossly mentally retarded and without voluntary movements. They were hypotonic but had episodes of opisthotonus with hypertonic flexion in the arms and extension in the legs, and in some cases there was also rigidity. There was no head control, except in two cases. Many of the children were hyperexcitable and any kind of stimulation increased the myoclonic jerks, which by now also occurred in the face and trunk. After some years the hyperexcitability ceased, however, and in most cases the myoclonic jerks became less frequent. After the age of five years all children had permanently increased flexor tonus, and flexion contractures were common. The patients showed generalised hirsutism, and acne was a frequent feature. Four girls had signs of precocious puberty by the age of seven years. Some cases had a violent symmetric tonic neck reflex. The oldest patients had an opisthotonic posture

with severe flexion contractures. The mean age at death was 6½ years (range 3 years 8 months to 10 years 3 months).

**Special Investigations**

*Ophthalmological Findings*

36 children were examined by the same ophthalmologist, and the findings were uniform. Except for four cases, all patients showed signs of severe visual deterioration at the first examination. In only four cases were the fundus and pupillary reaction considered normal at the first examination. Pupillary reaction was slow or absent in every patient after the age of two years. The typical ophthalmoscopic findings consisted of progressive hypopigmentation of the fundus, dystrophy and brownish discoloration of the macula, and optic atrophy. The retina had an increased lustre and retinal vessels were attenuated. The chorioidal vessels were clearly visible. Electroretinograms were recorded in 33 patients, using a contact electrode, and was extinguished in all cases, also in the four patients with normal fundus. Fluorescein angiography was performed in 20 patients and was pathological in all cases (Raitta and Santavuori 1973).

*Neurophysiological Findings*

No normal electroencephalogram (EEG) was seen in the whole material of 107 EEGs. By the age of one to two years the EEGs showed loss of the usual rhythmic components and an increase in slow waves, which often occurred in runs. Only three children between the ages of 12 and 15 months had usual rhythmic background activity; in all other cases a slow delta-theta activity dominated in the occipital regions. However, some rhythmic activity was seen in the central and temporal regions. A rapid diminution in amplitude was a characteristic feature; in 25 EEGs this was already obvious before the age of two years (in 17 cases the amplitude did not reach 50$\mu$V, and in eight cases it did not reach 70$\mu$V). In several records the diminution in amplitude was first seen in the occipital regions. By the age of three years all children had a completely or near-completely isoelectric EEG (Fig. 2). Before the age of two years irregular generalised discharges were common, but were not seen later. Spikes and sharp waves without constant localisation were observed in 24 children (more often in sleep).

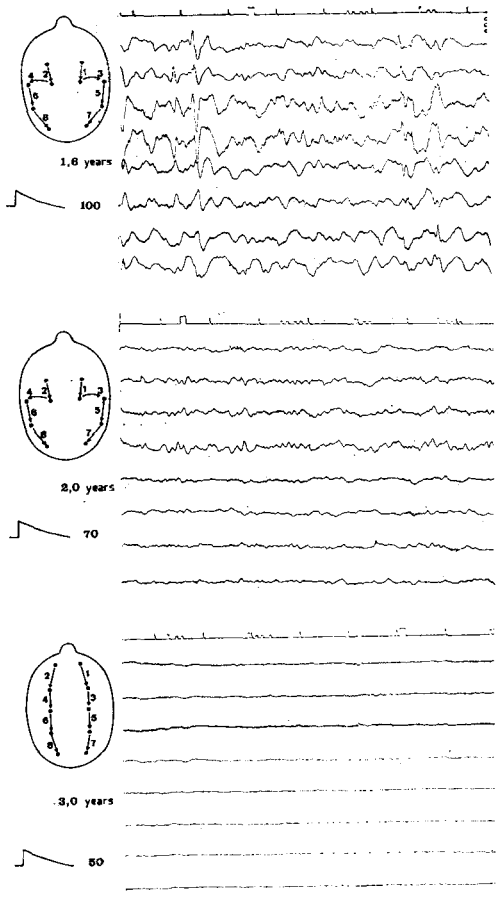


**Fig. 2a, b, c** (top to bottom). Serial EEGs of a child with INCL showing the slowing of the activity and the rapid diminution in amplitude leading to isoelectricity (eyes shut).

A response to photic stimulation was recognisable in only six records before the age of two years.

The EMG (11 children) and motor nerve conduction velocity (17 children) were within normal limits.

*Other Findings*

Certain other special investigations were of value for diagnosis.

*X-ray studies.* The skull was microcephalic in every case and in most cases the skull bones showed an increased thickness. Spinal column and long bones were normal in the seven cases examined.

*Pneumoencephalography.* 27 children showed diffuse supra- and infra-tentorial atrophy, increasing with age.

*Laboratory investigations.* Routine blood and urinary tests were normal, including the activity of arylsulphatase A. No vacuolated lymphocytes were found. Neutrophilic hypergranulation (Merrit 1968, Zeman and Strouth 1968) was found in 13 of 31 children. The CSF cell-count and protein concentration were normal in 43 children. Three children showed a slightly elevated protein concentration (40 to 55mg/100ml) between the ages of four and six years. Absence of the tau-fraction was noticed in six patients whose CSF proteins were analysed by cellulose-acetate electrophoresis.

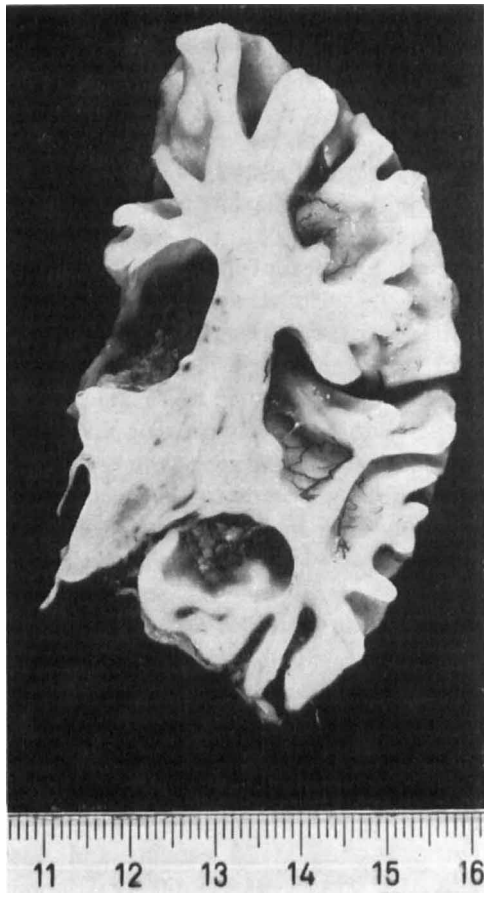


**Fig. 3.** Coronal section of the left cerebral hemisphere of a patient with INCL (boy aged 9 years). Note the extreme generalized brain atrophy. The atrophic cortex and basal ganglia can hardly be differentiated from the shrunken white matter. Scale in centimeters.

**Pathology**

The morphological findings were distinctive at the macroscopic, histological and ultrastructural levels (for more detailed neuropathological description, see Haltia *et al.* 1973*a*, *b*).

In autopsied cases the brain was exceedingly small (the fresh brain-weights varied between 325 and 420g) because of grave diffuse cerebral gyral atrophy (Fig. 3). In the youngest cases there was a conspicuous relative sparing of the hippocampal region. The cerebellum was also very atrophic, but the brain-stem—and particularly the spinal cord—were less affected. There was pronounced thickening of the skull bones and a thick layer of gelatinous tissue on the inner aspect of the dura.

The histological picture in brain biopsy and autopsy material varied according to the duration of the disease and, particularly in the cerebral cortex, three successive stages could be delineated.

In stage I (up to about 2½ years of age) there was slight to moderate cortical neuronal loss (Fig. 4a). The scanty cytoplasm of the remaining nerve cells was distended by granular, auto-fluorescent, PAS-positive, and sudanophil deposits which were acid-fast and resistant to lipid

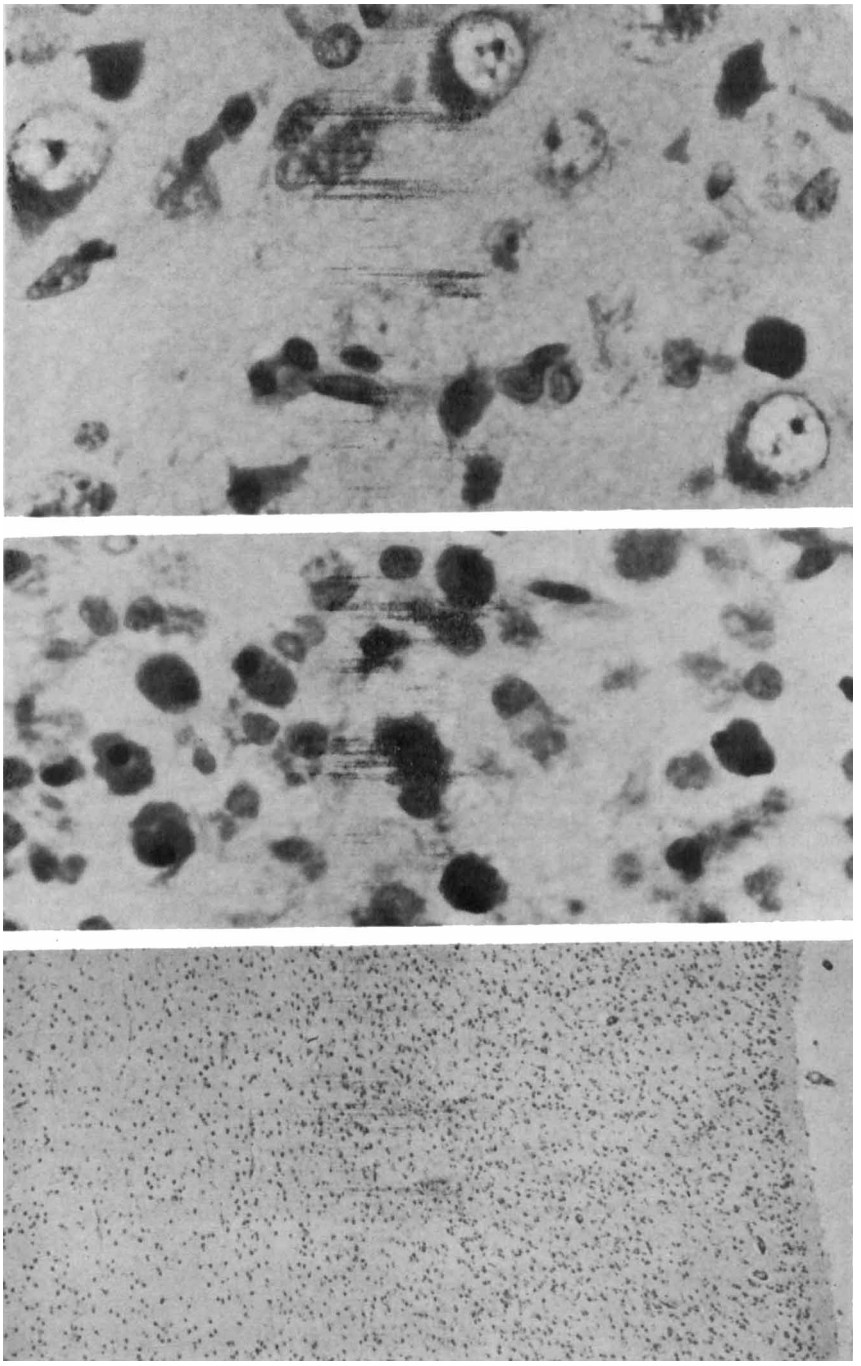

**Fig. 4a, b, c** (top to bottom). Cerebral cortex at three successive stages of INCL (PAS stain according to McManus, paraffin sections). *a.* The cytoplasm of cortical neurones is slightly distended by granular PAS-positive deposits. Between the nerve-cell bodies a few intensely PAS-positive macrophages are seen (stage I, boy aged 1 year 8 months). *b.* Severe neuronal loss. PAS-positive phagocytes dominate the picture (stage II, boy aged 4 years). *c.* Total loss of nerve cells. The atrophic cortex consists of a network of fibrillary astrocytes and blood vessels with a few scattered macrophages. The white matter (to the left) is devoid of myelin (stage III, boy aged 9 years). (a and b ×790; c ×180.)

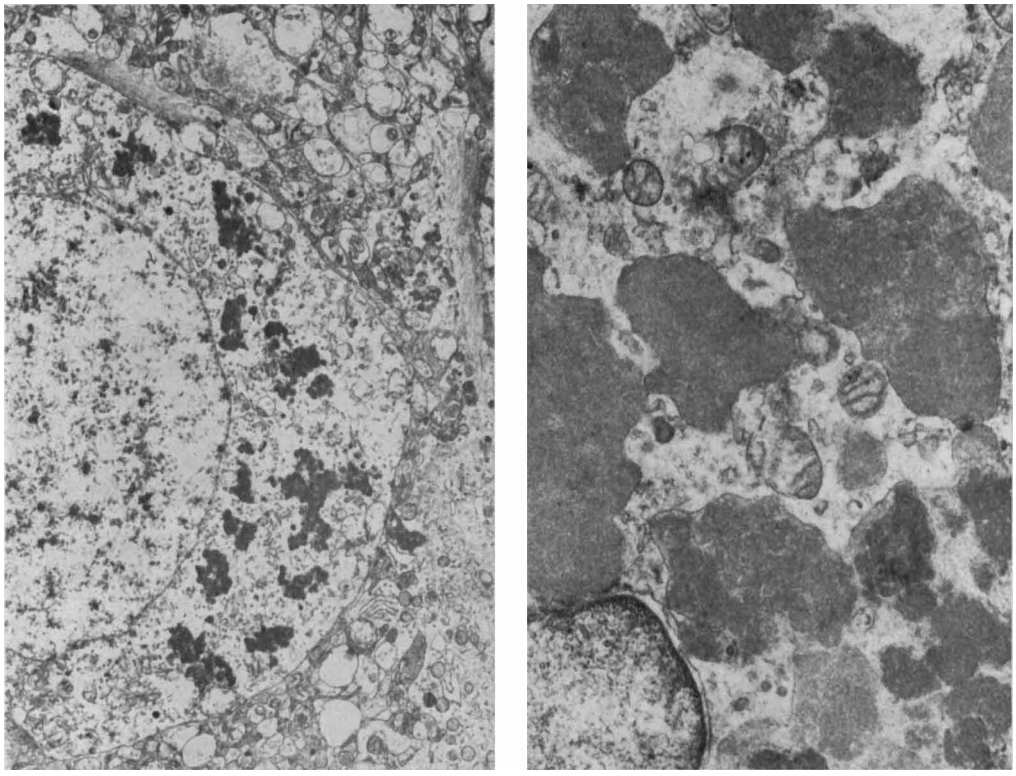

**Fig. 5a** (left). Electron-dense inclusions in the cytoplasm of a cortical neuron. The globular substructure of the storage inclusions is evident (×18,000). **b** (right). Higher magnification of the storage cytosomes in a bone-marrow macrophage. The cytosomes are bounded by a single unit membrane. The globular substructure of some cytosomes is barely visible. The material is finely granular and homogenous. (×60,000.)

solvents. A moderate number of macrophages with similar contents were seen between the neuronal perikarya, and there was intense fibrillary astrocytosis in the cerebral cortex. The white matter showed only slight changes.

Stage II (about 2½ to four years of age) was characterized by severe or almost total loss of cortical nerve cells, massive cortical macrophagocytosis and astrocytosis (Fig. 4b). The white matter showed moderate to severe loss of myelinated nerve fibres.

In stage III (over four years of age) the atrophic cortex was entirely depleted of nerve cells and consisted of a spongy network of fibrillary astrocytes and capillaries, with a slight to moderate number of macrophages (Fig. 4c). The white matter showed total loss of myelin. At this stage, even the cerebellar cortex showed total atrophy, and most subcortical centres displayed florid neuronal destruction, macrophagocytosis and astrocytosis. However, the giant cells of Betz, certain pyramidal cells of Ammon's horn, and the primary sensory and motor nuclei of the brain-stem and spinal cord were remarkably resistant.

The ultrastructure of the stored material remained constant through all these stages, in spite of the great variation in the histological picture. This stored material was in membrane-bound conglomerations of spherical globules, 0·2 to 0·5μm in diameter, with a homogenous finely granular internal structure (Figs. 5a, b). Such material occurred not only in the cytoplasm of nerve cells and macrophages, but also in other neuroectodermal cells

and many extraneural organs and tissues (Fig. 5b) (Haltia *et al.* 1973*b*, Rapola and Haltia 1973).

**Discussion**

The incidence of infantile neuronal ceroid-lipofuscinosis (INCL)—7·85 per 100,000—is far greater than the incidence of any other progressive encephalopathy in Finland. Even generally speaking, the spectrum of inherited diseases shows an unusual pattern in this country. Some of these diseases are relatively common, whereas others are extremely rare in comparison with other parts of the world. This is explained by the population structure of Finland, with consequent enrichment or lack of rare genes (Norio *et al.* 1973). In this context it is of interest to note that the incidence of other types of NCL is also comparatively very high in Finland.

The clinical separation of INCL and the classical juvenile (Spielmeyer-Sjögren) type of NCL is not difficult. More important is the differential diagnosis of INCL and some progressive encephalopathies of late infantile onset. Peculiar, often polyphasic, spikes during low rates of photic stimulation are typical for the Janský-Bielschowsky type of NCL (Pampiglione and Lehovsky 1968, Pampiglione and Harden 1973). These were not seen in any of our patients (Santavuori 1973). Also, the ophthalmological findings (Zeman *et al.* 1970, Menkes *et al.* 1971) and visual evoked response (VER) (Harden *et al.* 1973) in the Janský-Bielschowsky type differ from those in INCL.

The differential diagnosis to late infantile metachromatic leukodystrophy (MLD) is easily made. Myoclonic jerks characteristic of INCL are not seen in MLD. Visual failure is a late manifestation in MLD and the ophthalmological findings differ from those seen in INCL. The CSF protein concentration usually is elevated in MLD and is normal in INCL. The arylsulphatase A activity, low in MLD, was normal in our patients. Motor nerve conduction velocity is decreased in MLD but normal in INCL. The EEG features of MLD (Mastropaola *et al.* 1971) are strikingly different from those in INCL.

Certain cases of $G_{M1}$ or $G_{M2}$ gangliosidosis may also have their onset between one and two years of age, with symptoms of mental retardation, ataxia, pyramidal signs and fits (Derry *et al.* 1968, Suzuki *et al.* 1970, Brett 1973, Brett *et al.* 1973). However, myoclonic jerks are usually not seen in the gangliosidoses and the well-known ophthalmological findings (fundoscopy, pupillary reaction, ERG) (Derry *et al.* 1968, Suzuki *et al.* 1970, Brett *et al.* 1973) are entirely different from those seen in the present series. Vacuolated lymphocytes which may be found in cases of gangliosidosis were not found in our patients. Skeletal abnormalities seen in $G_{M1}$ gangliosidosis (Brett 1973) were not observed in our series.

It may thus be said that a combination of rapid psychomotor deterioration between eight and 18 months of age and a tapeto-retinal degeneration, reflected by extinction of the ERG before the appearance of clinical signs (Raitta and Santavuori 1973), is typical for INCL and is not seen in other diseases of the age group in question. The constant evolution of the EEG towards final isoelectricity seen in our patients is unique (Santavuori 1973, Pampiglione and Harden 1974) and facilitates the differential diagnosis in older patients.

Although the clinical picture is highly characteristic, it may be necessary to establish the diagnosis by biopsy in some cases. As far as brain biopsies are concerned, it must be stressed that the histological picture varies greatly, depending on the age of the patient and the duration of the disease (Haltia *et al.* 1973*a*). However, the finding of abundant deposits of autofluorescent granules in neurons and other neuroectodermal cells is a persistent

feature. These granules show a characteristic ultrastructure and consist of membrane-bound conglomerations of spherical globules with a finely granular internal structure. The absence of any definite lamellar structures (cytosomes with curvilinear or fingerprint profiles or membraneous cytoplasmic bodies), except for occasional zebra-like bodies, differentiates INCL from other types of amaurotic idiocy. The presence of characteristic deposits in many other organs, including the autonomic nerve cells of the gut-wall (Haltia *et al.* 1973*b*), makes possible the use of other types of biopsies. We have found appendiceal biopsy most useful (Rapola and Haltia 1973).

So far, biochemical studies have not given any specific aids for diagnosis. However, the observation of a severely altered fatty acid composition in brain and serum lipids (Hagberg *et al.* 1974, Svennerholm *et al.* 1974) may lead to a better understanding of the pathogenesis of INCL, as well as new diagnostic possibilities, including carrier detection.

*Acknowledgement:* This study was supported by the Rinnekoti Research Foundation.

SUMMARY

A series of 46 patients with rapidly progressive encephalopathy is presented. The disease was characterised by psychomotor retardation, beginning between the ages of eight and 18 months and accompanied by ataxia, muscular hypotonia, visual degeneration, myoclonic jerks and microcephaly. Death occurred at a mean age of 6½ years.

The disorder leads to an extraordinary degree of brain atrophy, caused by loss of neurons. The surviving neurons, other neuroectodermal cells and a number of extraneural cells contained excessive amounts of lipofuscin-like material with a homogenous, finely granulated internal structure.

Characteristic clinical, ophthalmological, neurophysiological and neuropathological features differentiate this condition from other progressive encephalopathies.

RÉSUMÉ

*Ceroide lipofuscinose neuronale infantile*

L'article rapporte une série de 46 cas d'encéphalopathie rapidement évolutive. La maladie est caractérisée par un retard psycho-moteur, débutant entre les âges de 8 et 18 mois, accompagné d'ataxie, hypotonie musculaire, de dégénération visuelle, de secousses myocloniques et de microcéphalie. La mort survient à un âge moyen de 6½ ans.

Le trouble a conduit à un extraordinaire degré d'atrophie cérébrale causée par la perte neuronale. Les neurones survivant, les autres cellules neuroectodermales et un certain nombre de cellules extra-neurales contenaient une quantité excessive d'un produit semblable à la lipofuscine avec une structure interne homogène, finement granulée.

Les caractéristiques cliniques, ophthalmologiques, neuropathologiques et les aspects ultrastructuraux différencient ce syndrome des autres encéphalopathies progressives.

ZUSAMMENFASSUNG

*Infantile neuronale Ceroid-Lipofuscinose*

Es wird eine Gruppe von 46 Patienten mit rasch progredienter Enzephalopathie vorgestellt. Die Charakteristika der Erkrankung waren psychomotorische Retardierung, die zwischen 8 und 18 Monaten begann und mit Ataxie einherging, Muskelhypotonie, Sehverschlechterung, myoklonischen Anfällen und Mikrocephalie. Die Kinder starben durchschnittlich mit 6½ Jahren. Die Erkrankung führt zu einer hochgradigen Hirnatrophie,

bedingt durch Verminderung der Neurone. Die erhaltenen Neurone andere neuroektodermale Zellen und eine Anzahl von extraneuralen Zellen hatten große Mengen von lipofuscinähnlichem Material von homogener, fein granulierter interner Struktur gespeichert.

Das charakteristische klinische, ophthalmologische, neurophysiologische und neuropathologische Erscheinungsbild unterscheidet diese Form von anderen progredienten Enzephalopathien.

## REFERENCES


Brett, E. M. (1973) 'Gangliosidosis of late onset.' Paper read at the Meeting of the European Study Group on Child Neurology, Kungälv, Sweden.

— Ellis, R. B., Haas, L., Ikonne, J. U., Lake, B. D., Patrick, A. D. Stephens, R. (1973) 'Late onset $GM_2$-gangliosidosis. Clinical, pathological and biochemical studies on eight patients.' *Archives of Disease in Childhood*, **48,** 775.

Derry, D. M., Fawcett, J. S., Andermann, F., Wolfe, L. S. (1968) 'Late infantile systemic lipidosis. Major monosialogangliosidosis. Delineation of two types.' *Neurology*, **18,** 340.

Hagberg, B., Sourander, P., Svennerholm, L. (1968) 'Late infantile progressive encephalopathy with disturbed polyunsaturated fat metabolism.' *Acta Paediatrica Scandinavica*, **57,** 495.

— Haltia, M., Sourander, P., Svennerholm, L., Eeg-Olofsson, O. (1974) 'Polyunsaturated fatty acid lipidosis—infantile form of so-called neuronal ceroid-lipofuscinosis. I. Clinical and morphological aspects.' *Acta Paediatrica Scandinavica*, **63,** 753.

Haltia, M., Rapola, J., Santavuori, P., Keränen, A. (1973*a*) 'Infantile type of so-called neuronal ceroid-lipofuscinosis. Part 2. Morphological and biochemical studies.' *Journal of the Neurological Sciences*, **18,** 269.

— — — (1973*b*) 'Infantile type of so-called neuronal ceroid-lipofuscinosis. Histological and electron-microscopic studies.' *Acta Neuropathologica*, **26,** 157.

Harden, A., Pampiglione, G., Picton-Robinson, N. (1973) 'Electroretinogram and visual evoked response in a form of "neuronal lipidosis" with diagnostic EEG features.' *Journal of Neurology, Neurosurgery and Psychiatry*, **36,** 61.

Hartikainen, A.-L. (1973) *Tutkimus Pohjois-Suomen synnyttäjistä.* M. D. Thesis, Oulu.

Mastropaolo, C., Pampiglione, G., Stephens, R. (1971) 'EEG studies in 22 children with sulphatide lipidosis (metachromatic leucodystrophy).' *Developmental Medicine and Child Neurology*, **13,** 20.

Menkes, J. H., Andrews, J. M., Cancilla, P. A. (1971) 'The cerebro-retinal degenerations.' *Journal of Pediatrics*, **79,** 183.

Merritt, A. D., Smith, S. A., Strouth, J. C., Zeman, W. (1968) 'Detection of heterozygotes in Batten's disease.' *Annals of New York Academy of Sciences*, **155,** 860.

Norio, R., Nevanlinna, H., Perheentupa, J. (1973) 'Hereditary diseases in Finland; rare flora in rare soil.' *Annals of Clinical Research*, **5,** 109.

Pampiglione, G., Lehovskỳ, M. (1968) 'The evolution of EEG features in Tay-Sachs disease and amaurotic family idiocy in 24 children.' *In* Kellaway, P., Petersen, J. (Eds.) *Clinical Electroencephalography of Children.* Stockholm: Almquist and Wicksell. p. 287.

— Harden, A. (1973) 'Neurophysiological identification of a late infantile form of 'neuronal lipidosis".' *Journal of Neurology, Neurosurgery and Psychiatry*, **36,** 68.

— — (1974) 'An infantile form of neuronal storage disease with characteristic evolution of neurophysiological features.' *Brain* (in the press).

Raitta, Ch., Santavuori, P. (1973) 'Ophthalmological findings in so-called neuronal ceroid-lipofuscinosis.' *Acta Ophthalmologica*, **51,** 755.

Rapola, J., Haltia, M. (1973) 'Cytoplasmic inclusions in the appendix vermiformis and skeletal muscle in two types of so-called neuronal ceroid-lipofuscinosis.' *Brain*, **96,** 833.

Santavuori, P. (1973) 'EEG findings in the so-called neuronal ceroid-lipofuscinosis.' *Neuropädiatrie*, **4,** 375.

— Haltia, M., Rapola, J., Raitta, Ch. (1973) 'Infantile type of so-called neuronal ceroid-lipofuscinosis. Part 1. A clinical study of 15 patients.' *Journal of the Neurological Sciences*, **18,** 257.

Suzuki, K., Suzuki, K., Rapin, I., Suzuki, Y., Ishii, N. (1970) 'Juvenile $GM_2$-gangliosidosis.' *Neurology*, **20,** 190.

Svennerholm, L., Haltia, M., Hagberg, B., Sourander, P., Vanier, M. (1974) 'Polyunsaturated fatty acid lipidosis—infantile form of so-called neuronal ceroid lipo-fuscinosis.' *Acta Paediatrica Scandinavica* (in the press).

Zeman, W., Strouth, J. C. (1968) 'Leukocytic hypergranulation versus lymphocytic vacuolization as markers for hetero- and homozygotes with Batten-Spielmeyer-Vogt disease.' *In* Aronson, S. M., Volk, B. W. (Eds.) *Inborn Disorders of Sphingolipid Metabolism.* Oxford: Pergamon. p. 475.

— Dyken, P. (1969) 'Neuronal ceroid-lipofuscinosis (Batten's disease). Relationship to amaurotic familial idiocy?' *Pediatrics*, **44,** 570.

— Donahue, S., Dyken, P., Green, J. (1970) 'The neuronal ceroid-lipofuscinoses (Batten-Vogt syndrome).' *In* Vinken, P. J., Bruyn, G. W. (Eds.) *Handbook of Clinical Neurology Vol. 10.* Amsterdam: North Holland p. 588.