INFANTILE TYPE OF SO-CALLED NEURONAL CEROID-LIPOFUSCINOSIS

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Attention was recently drawn to a progressive encephalopathy with early amaurosis. The disease has its clinical onset at the age of 8-18 months with rapid psychomotor deterioration, ataxia, muscular hypotonia. In the 45 cases examined microcephaly and myoclonic jerks were other prominent features; convulsions were few or did not occur at all. In all patients the disease reached a burnt-out stage during the third year. After the age of 5 years all children had a permanent increased flexor tonus in all limbs and flexion contractures were common. The mean age of death was 7.6 years. Early extinction of ERG, typical ophthalmological findings, and EEG records rapidly approaching isoelectricity were additional features.

The disease has an autosomal recessive mode of inheritance. A total of 52 cases are known in Finland. Histologically, an almost total destruction of cerebral and cerebellar neurons was observed. The surviving neurons and glial cells contained granular material which histochemically resembled lipofuscin but ultrastructurally differed from those in earlier reported patients with neuronal ceroid-lipofuscinosis. The cases observed seem to form a clearly separable infantile type of so-called neuronal ceroid-lipofuscinosis.

INTRODUCTION

From the heterogeneous category of the amaurotic family idiocy two main groups have emerged. The first group comprises diseases with an abnormal ganglioside metabolism. The second group, showing no evidence of any primary disturbance in ganglioside metabolism, is chemically less well defined, but displays characteristic histochemical features; for this group Zeman and Dyken introduced the term neuronal ceroid lipofuscinosis (1969).

Recently Santavuori et al. (1973) and Haltia et al. (1973) drew attention to a progressive encephalopathy beginning about one year of age with mental retardation, accompanied with ataxia, loss of vision and myoclonic jerks. Studies of brain biopsies disclosed severe neuronal destruction, massive occurrence of macrophages in the cerebral cortex, and advanced astrocytic hyperplasia and hypertrophia. The remaining neurons and macrophages contained deposits with the histochemical characteristics of lipofuscin, but with a constant homogeneous, finely granular ultrastructure. Haltia et al. (1973) concluded that their cases form a clearly separable infantile type of so-called neuronal ceroid-lipofuscinosis.

CLINICAL MATERIAL

Altogether 45 children, 26 boys and 19 girls, were examined. Including 7 cases, who had died earlier, the total number of cases known in Finland is 52. In 7 of the 38 families there were more than one

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affected sibling, both boys and girls. The parents, their siblings, and grandparents, were clinically normal. This indicates an autosomal recessive mode of inheritance.

Clinical Course

In all patients the developmental milestones were within normal limits until the age of eight months. A total of 29 children learned to speak single words; 18 learned to walk alone and 19 other learned to stand up. In most children retardation of mental development was noticed at the age of 1-1.5 years. Slightly later the motor development ceased. Thereafter, generalized hypotonia together with truncal and limb ataxia appeared. In some cases hypotonia and ataxia were the initial signs. All patients had microcephaly wich became more pronounced with increasing age.

Visual disturbance in some cases was already observed at the age of 12 months. In all patients visual impairment was established at ophthalmological examination after the age of 18 months.

All patients had myoclonic jerks at about 2 years of age. Somewhat earlier, characteristic knitting movements were observed in the hands and forearms. They disappeared after some months. Many patients were hyperexcitable and difficult to manage during the second year.

About half of the children showed convulsions, usually unfrequent. In some cases it was difficult to estimate if the child had had seizures or frequent myoclonic jerks.

In all patients the disease reached a burnt-out stage during the third year. The children were completely unresponsive and without voluntary movements. The patients were hypotonic, but had episodes of opisthotonus with hypertonic flexion in the arms and extension in the legs, and in some cases also rigidity. There was no head control, except in two cases. After the age of 5 years all children had a permanently increased flexor tonus in all limbs, and flexion contractures were common. The oldest patients had an opisthotonic posture with severe flexion contractures. Nine patients of the present series died later. The mean age of death was 6.6 years.

Special Investigations

A total of 35 children were examined by the same ophthalmologist. The ophthalmological findings were uniform (cf. Raitta 1973).

None of the patients had a normal EEG. The most characteristic features were slowing of rhythmic activity and later, usually after some months, diminution in overall amplitude, which in some cases was first seen over the parietal and occipital regions. Irregular generalized bursts of slow waves and occasional sharp waves and spikes were also seen. In all patients who were followed up to over 3 years of age, serial records showed an almost, or completely, isoelectric EEG. The results of EMG and nerve conduction velocity studies were normal.

Routine blood and urinary tests were normal. No vacuolated lymphocytes were found. Many patients had neutrophilic hypergranulation. The CSF cell count as well as the protein concentration were normal. The electrophoretic pattern was also considered normal; however, an absence of tau fraction was later noticed in 6 patients.

Histological and Histochemical Studies

From 17 patients brain biopsy material and from 8 patients autopsy material was obtained for morphological and histochemical investigations.

In autopsied cases the brain was exceedingly small (the fresh brain weights were between 325 and 420 g) owing to diffuse cerebral gyral atrophy. The cerebellum was also very atrophic but the brain stem and particularly the spinal cord were less affected.

Almost all sections of the cerebral and cerebellar cortex were entirely depleted on neurons. Thin cortical rimes consisted only of a spongy network of fibrillary astroglia with scattered macrophages and blood vessels. The only notable exceptions were the giant cells of Betz in the motor cortex and the pyramidal cells of Ammon's horn. The basal ganglia and thalamus also showed an advanced degree of neuronal loss, ballooning of the remaining nerve cell bodies with granular cytoplasmic deposits, and profound machrophagic and astrocytic reactions. In contrast, the primary motor neurons of the brain stem and spinal cord were preserved, but contained large amounts of granular material. In the

brain biopsy material the cortical cytoarchitecture was severely disturbed even in the youngest patient (1.7 years of age).

The biochemical studies did not show evidence of any primary disturbance in ganglioside metabolism.

DISCUSSION AND CONCLUSIONS

The clinical picture of our patients with onset, before the age of 18 months, of rapid psychomotor deterioration combined with ataxia, frequent myoclonic jerks, visual failure with typical ophthalmological finding, and microcephaly, is very characteristic. The early extinction of the ERG and rapid flattening of the EEG are further characteristics which help to distinguish the present condition from the other progressive encephalopathies of the age group in question. Morphological findings are diagnostic and they are supported by biochemical observation, showing that our cases had some features in common with the group of neuronal ceroid-lipofuscinosis (NCL) as defined by Zeman and Dyken (1969).

The age of onset, the rapid course and the absence of vacuolated lymphocytes in the infantile type, seen as a constant phenomenon in Spielmeyer-Sjögren type NCL (Plum and Stubbe-Tegelbjaerg 1961, Rayner 1962), distinguishes the latter from present disorder. Peculiar, often polyphasic spikes during low rate of photic stimulation are typical for Jansky-Bielschowsky disease (Pampiglione and Lehovsky 1968, Pampiglione and Harden 1973). These were not seen in any of our patients. Also the ophthalmological findings and ERG in Jansky-Bielschowsky disease (Copenhaver and Goodman 1960, Zeman et al. 1970, Menkes et al. 1971), differ from the infantile type of NCL.

Thus, the uniform clinical, morphological, and biochemical findings in our series differ from the findings in previously recognized types of NCL.

The disturbed metabolism of polyunsaturated fatty acids, found in clinically identical cases (Svennerholm et al. 1974) opens new views for research and might give the answer to the pathogenesis and the prevention of this disorder.

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