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Neuronal Ceroid Lipofuscinosis (Batten's Disease)

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Gordon, N. S., Marsden, H. B., and Noronha, M. J. (1972). *Archives of Disease in Childhood*, **47**, 285. **Neuronal ceroid lipofuscinosis (Batten's disease).** Four patients are described, who on clinical, histological, and biochemical criteria are considered to be suffering from neuronal ceroid lipofuscinosis. It is suggested that this may be the commonest condition included under the term amaurotic family idiocy. A number of gangliosidoses can be classified on a biochemical basis and considerable advances have been made in identifying the enzyme deficiencies. The aetiology of neuronal ceroid lipofuscinosis is unknown, and it is possible that there is more than one cause.

Visual symptoms and signs are not always present. Though generalized convulsions occur at the start of the illness, myoclonus tends increasingly to dominate the clinical picture. An abnormal sensitivity to photic stimulation at a very slow frequency is a suggestive finding. Evidence of cerebral atrophy on air-encephalography favours this diagnosis, as the brain tends to be enlarged in the gangliosidoses. A definite diagnosis can only be made in life by examination of a cortical biopsy. Biochemical analysis will show a normal ganglioside pattern, and histological examination by light and electron microscopy will reveal characteristic changes.

An age dependent classification of amaurotic family idiocy is no longer justifiable, and if full investigations are carried out, an increasing number of these patients can be diagnosed as suffering from a specific type of disorder.

The purpose of this paper is to suggest that neuronal ceroid lipofuscinosis may be the commonest condition included until very recently in the group of 'storage diseases' of the amaurotic family idiocy type. In a recent examination of 7 cortical biopsies which initially had been considered to support a diagnosis of a cerebral lipidosis, most probably Tay-Sachs disease, only one of them proved to be an example of that condition.

Though there may be nothing pathognomonic in the clinical presentation of neuronal ceroid lipofuscinosis there are certain features which may suggest this diagnosis and several investigations which are helpful, though only a cortical biopsy will give absolute confirmation.

Case Reports

Firstly the case histories of 4 children recently admitted to the wards of the Royal Manchester Children's Hospital will be given.

Case 1. This girl, born April 1963, was considered to have had a normal gestation and birth, and she was thought to be a normal child by her parents, apart from some delay in speech development, until aged 3 years (May 1966). At that time she had her first convulsion and these became frequent and difficult to control, despite the use of various anticonvulsants. Seizures included generalized tonic-clonic attacks, minor attacks, during which she became unresponsive, limp, with her eyes deviating upwards for only a second, and also frequent myoclonic jerking of the limbs and trunk. During the initial 6 months she regressed rapidly in her mental and motor development so that she was unable to sit unaided or stand, and speech was completely lost. From the age of $5\frac{1}{2}$ years her vision deteriorated and she now lies in bed more or less completely unresponsive to visual or auditory stimuli, with no voluntary movement. The response to antiepileptic drugs has been very limited. There is no consanguinity and no family history of a similar disorder. Her brother aged $4\frac{1}{2}$ years is alive and well.

She is a thin emaciated girl, tube fed because of difficulties with swallowing and an inability to cough up sputum. She has frequent myoclonic jerks and responds only to movement or painful stimuli. There is bilateral optic atrophy with no pigmentation in the region of the macula. In the limbs bilateral corticospinal signs are present, associated with contractures of both calf muscles. Other systems are normal.

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Investigations. Blood counts and tests for metabolic disorders normal. Urinary chromatogram normal and no metachromatic granules present in the urine.

X-rays: Skull and chest normal. Virus studies: negative. CSF: normal. EEG on 23 June 1966 showed generalized slow wave abnormality; on 14 September there were brief outbursts of generalized epileptic activity which appeared to be involving subcortical structures. Serial recordings have shown similar findings.

Nearly 3 years later EEG showed severe generalized abnormalities with frequent multifocal and generalized discharges, some of which were accompanied by observable jerks. During photic stimulation repetitive myoclonic jerks accompanied by epileptic discharges occurred in direct relation to the photic stimulation, especially at slow rates, 2 to 3 per second, and increasing in frequency though diminishing in amplitude up to nearly 8 per second.

Brain biopsy, right frontal, showed the cortex to be macroscopically normal.

Light and fluorescent microscopy: The major part of the specimen was retained for chemical analysis but a thin slice including grey and white matter was used for histological examination. Sections were examined by fluorescent microscopy and cryostat and paraffin sections were stained by H and E, PAS, and Sudan IV. The neuronal cytoplasm was distended, though considerable variation was noted in the different cells, and the nucleus in many retained a central position with relatively little disortion. Refractile granules were sometimes noted and the cytoplasm showed bright fluorescence. The material was PAS and Sudan positive in both cryostat and paraffin preparations. Some gliosis was noted in the cortex with proliferations of fibrous astrocytes, and PAS-containing macrophages were seen around vessels in the white matter.

Biochemistry.

Thin-layer chromatography (Professor Cumings). Both white matter and cortex showed a normal phospholipid pattern; cerebrosides and sulphatides were normal in amount and proportions; cholesterol ester was not increased above normal. The cortex showed a normal ganglioside pattern.

Case 2. A boy, born 5 June 1965, had normal gestation and birth. Development was slow up to the age of 2½ years when he was able to walk and run; he had a vocabulary of a few words and was able to feed himself. After this he deteriorated, and gradually his parents noticed that he had lost his speech, and more recently he had not responded to them. He had also become unsteady in his gait and fell frequently and was unable to feed himself. His behaviour deteriorated so that he was difficult to manage at home. In 1969 he began having attacks of generalized twitching of his limbs lasting a few minutes, but it was difficult to assess whether there was an associated impairment of consciousness. When seen in January 1970, he was hyperactive and did not respond to questions or commands. He sat with his mouth open, drooling saliva, and did not utter any speech.

The optic fundi showed bilateral optic atrophy, but the maculae were normal. In the limbs there were bilateral corticospinal signs, mild, and mild to moderate cerebellar ataxia. There was slight truncal ataxia as well. Other systems were normal.

Investigations. Haematological and biochemical investigations normal.

Urinary chromatogram. Normal. No metachromatic deposits in the urine.

Skull and chest *x*-rays. Normal.

CSF. Traumatic tap: cells and protein normal, negative Lange curve. Virus and toxoplasma studies negative.

EEG on 2 February 1970 showed generalized slow wave abnormalities, occasionally paroxysmal, and this was considered to be compatible with a diffuse disturbance of cerebral function.

Brain biopsy. Right frontal. The cortex was macroscopically normal, though of a yellow-brown colour.

Light, fluorescent, and electron microscopy. The biopsy was treated in a similar way to the previous case, but in addition a small fragment was taken from each corner and after suitable preparation was examined with an AEI electron microscope.

Examination by light and fluorescent microscopy showed neurones with swollen cytoplasm containing fluorescent material which stained by the Ziehl-Nielson method and also by PAS and Sudan IV in both cryostat and paraffin sections. On electron microscopy there was granular material in the cytoplasm resembling lipofuscin, as well as relatively less electron dense material (Fig. 1). At a higher magnification a membranous component could be detected in the less dense material, possibly the so-called curvilinear bodies (Fig. 2). No membranous cytoplasmic bodies as encountered in G_{M2} gangliosidosis were noted. The nucleus showed scattered dense aggregations.

Biochemistry.

Thin-layer chromatography (Professor Cumings). Both white matter and cortex showed a normal phospholipid pattern, and the cerebroside : sulphatide ratio was normal. Cholesterol esters were not increased above normal. Gangliosides showed an almost normal pattern.

Case 3. A boy, born 12 September 1964, whose gestation, birth, and subsequent development were normal up to the age of 3 years when convulsive seizures developed. This was shortly followed by the occurrence of behaviour disturbances, intellectual deteriora-

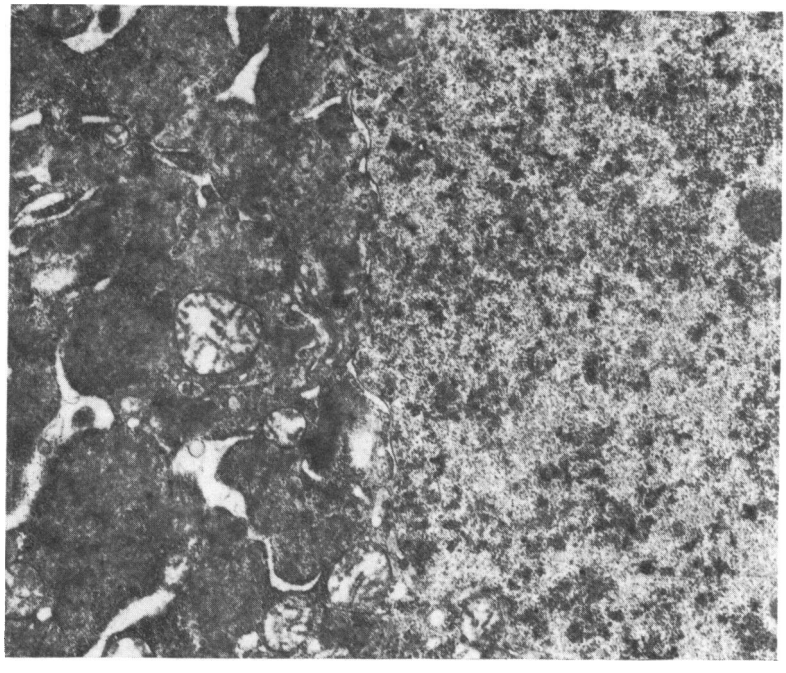

FIG. 1.—*Electron microscopy—appearance of a neurone in Case 2. The nucleus shows dense aggregation and the cytoplasm has dilated cisternae with granular electron dense material.* (× *4,800.*)

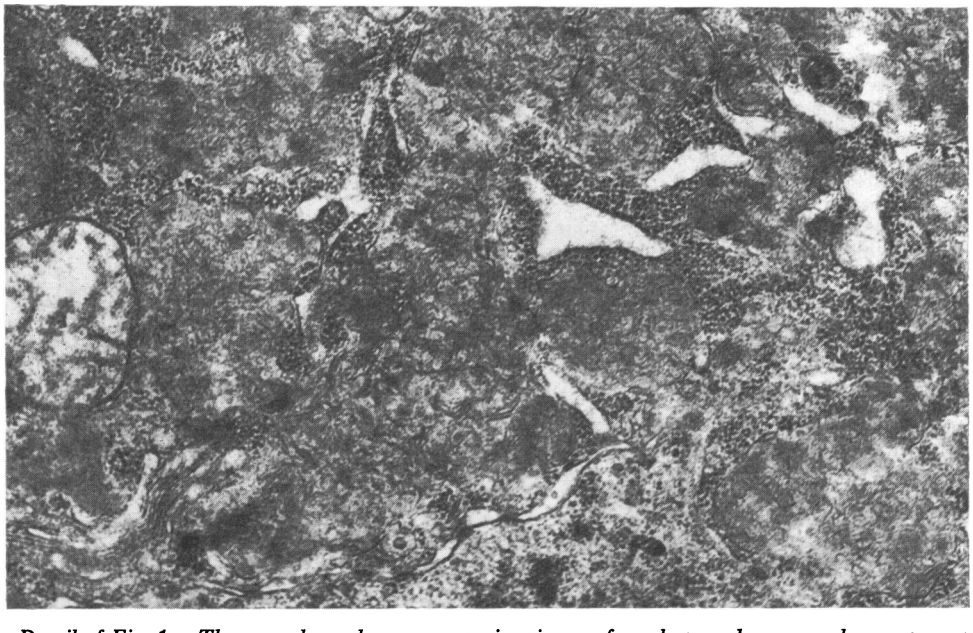

FIG. 2.—*Detail of Fig. 1. The cystoplasm shows a composite picture of an electron-dense granular component, and less dense material in which a membranous structure can be detected. Golgi apparatus in addition to a mitro chondrion are present.* (× *12,000.*)

tion, and myoclonic seizures. He was admitted to hospital at the age of 4½ years (9 April 1969), at which time he barely responded to verbal commands. He had frequent myoclonic jerks, continuous facial grimacing, and athetoid movements of the limbs and truncal musculature. Treatment with phenytoin and nitrazepam was started, but this has only partially controlled his seizures. Periods of myoclonic status lasting 2 to 3 days have occurred on 2 occasions subsequently, and they have been terminated by intravenous diazepam. There has not been much deterioration during the past 12 months though he is now completely unresponsive to verbal stimuli.

Physical examination showed abnormalities confined to the CNS consisting of corticobulbar and bilateral corticospinal signs, and extrapyramidal rigidity of the limbs; the optic fundi were normal.

Investigations. Haematological and biochemical investigations were normal. No urinary metachromatic granules observed.

CSF. Normal.

X-rays. Skull and chest normal.

EEG on 9 April 1969 showed rhythmic slow activity and also frequently occurring spike activity, which was associated with myoclonic jerking. On the next day there was a slight improvement in the record which showed less epileptic activity. The following day there was an increase of generalized slow wave activity with occasional generalized outbursts of spikes and slow waves. 4 days later there were frequently occurring brief epileptic discharges in the occipital areas which were usually symmetrical. The following month the record again showed frequent epileptic discharges. There was sensitivity to photic stimulation at a flash frequency of 2 to 5 flashes per second, but higher rates were not used.

Brain biopsy from (R) frontal cortex, showed the arachnoid membrane to be thickened, and the subarachnoid space generous with wide sulci.

Light and electron microscopy was done. The biopsy was treated in the same way as the previous case (S.M.) and the findings on light and fluorescent microscopy were similar though minor differences were noted on electron microscopy. The nuclei showed dense aggregations. There was a composite picture of an electron dense granular component and less dense material. Membranous structures were not encountered even with higher magnification.

Biochemistry (Professor Cumings). Both white matter and cortex showed a normal phospholipid pattern and there was no increased cholesterol ester. The sphingolipid pattern was normal, and cerebrosides and sulphatides were in normal proportions. Both white matter and cortex showed a normal ganglioside pattern.

Case 4. A boy born 7 February 1957, the brother of Case 3, had a normal gestation and birth history. At 5 months of age he vomited but nothing abnormal was detected. Subsequent development was slow, and at the age of 3 years he was able to walk, say a few words, feed and dress himself. At the age of 3½ years he began deteriorating in that he was unable to walk, lost his ability to speak, and was unable to feed himself. When seen in 1961 he did understand what was said to him and screamed if touched. The optic fundi were pale and bilateral corticospinal signs were present in the limbs. While in hospital he had 3 generalized tonic-clonic seizures lasting a minute and these responded to phenobarbitone orally. A cortical biopsy was considered but not carried out. He was transferred to a long-stay hospital and died in February 1963. Unfortunately necropsy was not performed.

Investigations. Haematological and biochemical investigations normal.

Urinary chromatogram was normal. *X*-rays: skull and spine normal. CSF, normal. EEG on 16 November 1960 showed medium high voltage theta activity in central and postcentral areas, with paroxysmal burst of high voltage 2–3 c/s waves sometimes associated with sharp waves, focal on one side and then the other. On 16 March 1961 the record was still very abnormal, showing diffuse dysrhythmia in addition to paroxysmal discharges which appeared to be arising from within the diencephalon. On 26 October 1961 the record showed diffuse abnormalities of an epileptic nature. The epileptic discharges did not tend to localize in any particular area.

In 3 of these patients the findings were compatible with a diagnosis of neuronal ceroid-lipofuscinosis and, in view of the family history, there can be no doubt that the fourth suffered from the same condition.

Gangliosidoses

The use of eponyms may have been necessary when conditions such as amaurotic family idiocy were first described and knowledge was confined to clinical and histological descriptions. Now that the biochemistry of these disorders is beginning to be understood, it is possible to start on a more sensible method of classification, though no entirely satisfactory terminology is yet available. It seems reasonable to abandon the old subdivision of amaurotic family idiocy. Infantile amaurotic idiocy, or Tay-Sachs disease, with its early onset and typical cherry-red spot at the macula, may be used as alternatives for G_{M2} gangliosidosis, though the multiplicity of names appears to be unnecessary. There is even less justification for using the terms 'late infantile type' of Bielschowsky-Jansky beginning between the ages of 2 and 4, and 'juvenile amaurotic idiocy' with age of onset between 6 to 8 years, which includes the Spielmeyer-Vogt type with fundal changes akin to retinitis pigmentosa, and the Batten-Mayou type with pigmentary changes at the macula. Adult family amaurotic

idiocy or Kufs's disease is an even more unsatisfactory subdivision.

Now these diseases can be divided into 2 main groups. The clinical picture and the routine histological findings may be somewhat similar, but the first group shows a grossly abnormal profile of cerebral sphingolipids on thin layer chromatography of brain extracts and the second group has a normal sphingolipid profile. The first group contains undoubted disorders of lipid metabolism such as G_{M2} gangliosidosis (Tay-Sachs disease). This may be associated with the absence of the isoenzyme, hexosaminidase (Okada and O'Brien, 1969), leading to an accumulation of G_{M2} ganglioside in the cells. It is suggested that lack of this enzyme can enable a prenatal diagnosis to be made on cells collected by amniocentesis (Schneck *et al.*, 1970). However, the defect may be related to an absence of galactosyl transferase which converts G_{M2} to G_{M1} ganglioside (Cumings, 1968). There appear to be 3 types of the condition depending on variations of the enzyme deficiency (Cumings, 1971). Type 3 is of relatively late onset.

Gangliosidoses with an onset between 2 and 4 years may show an accumulation of G_{M1} gangliosides in the neurones, related to a deficiency of β galactosidase. The patients, apart from rapidly progressive mental and physical retardation, have peculiar facies, enlargement of the liver and spleen, and the skeletal changes similar to Hurler's syndrome. They have been referred to as familial neurovisceral lipidosis, generalized gangliosidosis, and pseudo-Hurler's disease (O'Brien, 1969). In addition to the excess of G_{M1} gangliosides in the cells of the brain and viscera, there may also be an accumulation in the latter of an abnormal acid mucopolysaccharide resembling keratin sulphate. There may be another form of the disease in which only cerebral symptoms occur (Kint, Dacremont, and Vlientinck, 1969). An example of G_{M3} gangliosidosis may have been recorded (Pilz, Sandhoff, and Jatzkewitz, 1966).

Among older children, Cumings (1971) mentions two brothers aged $4\frac{1}{2}$ and 6 years who at necropsy showed raised levels of G_{M3} and G_{M4} in both brain and viscera. A case of juvenile G_{M2} gangliosidosis (Type 3) has recently been reported (Suzuki *et al.*, 1970). The patient developed personality changes and dementia about the age of 6 years, and this was followed by seizures and cerebellar, extrapyramidal, and pyramidal signs. Light microscopy examination showed features of both juvenile lipidosis and infantile G_{M2} gangliosidosis. Electron microscopy revealed neuronal inclusions, some of which were similar to the membrane cytoplasmic bodies of G_{M2} gangliosidosis, and others were less well-defined lamellar structures. Some of the latter proved to be lipofuscin bodies. The chemical abnormalities are qualitatively identical with those of Tay-Sachs disease, though quantitatively milder. The total ganglioside content in the grey matter was twice normal. It is not known whether this patient represents a new disease or merely a variant of the infantile form with the same enzymatic defect. Cumings (1971) has also reported a child who developed this condition at the age of 5 and is still alive 3 years later.

Neuronal Ceroid Lipofuscinosis

In the second group with normal sphingolipid profiles the neuronal accumulations consist of lipopigments of the ceroid lipofuscin type, and our limited experience suggests that in the area served by the Manchester Children's Hospitals it may be a more common condition than the gangliosidoses. Neuronal ceroid lipofuscinosis has an autosomal recessive mode of inheritance and the pattern within a family can be fairly constant. However, the age of onset may vary from infancy to adult life, and the course of the disease from a few months to many years. It, therefore, occurs in all the various subdivisions of amaurotic family idiocy previously described.

Clinical features

There are a number of findings on clinical examination which may suggest this diagnosis. Symptoms and signs of visual failure are by no means always present. If optic abnormalities are present, they will typically consist of optic atrophy with attenuated retinal vessels, macular degeneration of the granular type, and pigmentation in the peripheral parts of the retinae.

Epileptic seizures are an integral part of the disease, often starting as generalized convulsions to be superseded by myoclonus which becomes generalized and can develop into a myoclonic status lasting for days on end. It has been suggested (Zeman and Dyken, 1969) that the occurrence of seizures has an effect on the course of the disease, and that if they can be controlled this will be favourably affected, though the frequency of the fits and the ease with which they can be prevented may only be a manifestation of the degree of severity of the cerebral degeneration.

The dementia is not always progressive, and in some patients personality changes may predominate. Motor disturbances include dystonia, involuntary

movements, ataxia, and spastic quadriplegia. Admittedly there is nothing specific in the mental and physical findings but they tend to be less relentlessly progressive than in the gangliosidoses. In fact no change may occur in the child's condition for long periods. Occasionally remission is so prolonged that the disease process seems to have been arrested. This makes it difficult to give an exact prognosis and sometimes to plan the best way of managing this serious disease, both from the point of view of the child and the family.

Investigations

Certain tests may give positive results suggestive of neuronal ceroid lipofuscinosis; for instance the presence of vacuoles in the lymphocytes of the peripheral blood though this is a nonspecific finding (von Bagh and Hortling, 1948). Excessive azurophilic granulation of the neutrophils is in a similar category (Strouth, Zeman, and Merritt, 1966).

The EEG can show a number of interesting features. In most cases there are bursts of slow waves and irregular spike and wave complexes. At times the diffuse epileptic activity may be almost continuously present throughout the record, and some of the paroxysmal discharges will be associated with myoclonic jerks. Asymmetries in the record are not uncommon. There is normally a progressive deterioration in the EEG findings concomitant with the changes in the child's clinical state.

Pampiglione and Lehovski (1968) have reported a suggestive combination of EEG features in the late infantile type of family amaurotic idiocy. There were polyphasic spikes and irregular slow wave activity with disappearance of the alpha rhythm, and the occurrence of large spikes over the posterior half of the hemisphere in response to low rates of photic stimulation. These findings were not noted in the records of children with Tay-Sachs disease, which led these authors to speculate that the underlying deranged neurophysiological mechanisms might differ considerably in the 2 groups. Certainly in 2 of the patients reported in this paper, who were examined in this way, there was an abnormal sensitivity to photic stimulation at a flash frequency of 2 to 5 per second.

There are 2 other findings which may be useful (Green, 1971). The electroretinogram is usually abolished in neuronal ceroid lipofuscinosis but preserved in G_{M2} gangliosidoses because of the widespread degeneration of the rods and cones and pigment epithelium in the former, as opposed to the destruction of the ganglionic cell layer in the latter. Evoked potentials to both visual and peripheral nerve stimulation were found to be of particularly high voltage, and though such responses have been found in a number of other conditions it is another piece of positive evidence if the diagnosis of neuronal ceroid lipofuscinosis is being considered. With advanced retinal disease the visual evoked response is abolished.

An air-encephalogram will sometimes show evidence of cerebral atrophy with thinning of the cortex, as opposed to the larger size of the brain in G_{M2} gangliosidosis.

Pathology

When such tests have been carried out, the results of these and the clinical history may be considered sufficient to support the diagnosis, and obviously this will be the case if another child in the family has been similarly affected. There will be certain situations when it is considered justifiable to employ all possible means of reaching an exact diagnosis and only a cortical biopsy can do this.

On examination of cerebral tissue, either from a biopsy or at necropsy, there is a severe loss of neurones affecting the cerebrum, cerebellum, and in the subcortical nuclei. The remaining neurones are swollen by granules which stain with Sudan Black B and PAS both in frozen and paraffin preparations. They give positive reactions with all stains for ceroid and lipofuscin and are fluorescent. On electronmicroscopy the granules have a structure often arranged in crystal lattices and fingerprint-like patterns, in contrast to the membranous cytoplasmic bodies found in G_{M1} and G_{M2} gangliosidosis. This technique may well develop into one of the main criteria in the differential diagnosis of these conditions (Gonatas, Gambetti, and Baird, 1968).

Classification

Neuronal ceroid lipofuscinosis cannot be classified among other disorders of sphingolipid metabolism. There is no definite evidence that this disease is due to a disorder of lipid metabolism and in the present limited state of knowledge it can only be regarded as a syndrome. As Zeman and Dyken (1969) suggest, a genetically determined defect may damage the neurones, and in those that survive there may be an accumulation of lipopigments: 'ageing pigments' whose quantity is usually known to bear a relation to the age of the individual. This may be a secondary phenomenon and possibly related to an inability to get rid of waste products or to an increased rate of production. Minor differences found on electron microscopy may also indicate that the aetiology is not always the same, but the possible noxious agents remain unknown.

The biochemical analysis of brain tissue will be of obvious importance, especially of biopsy material, in order to establish if there is a normal or abnormal ganglioside pattern. Professor Cumings confirmed that in none of the three fresh biopsy specimens he reported on in this paper were there any gross changes in the phospholipids and cerebroside: sulphatide ratio. The cholesterol esters were not increased above normal and the ganglioside patterns were normal. The total neuraminic acid in the cerebral cortex was normal.

It seems that now a more rational classification of this type of degenerative disease is possible. If neuronal ceroid lipofuscinosis is not due to a primary disorder of lipid metabolism it is obviously of importance to recognize these patients so that further studies can be carried out in an effort to identify factors which may damage the neurones.

Treatment

Brady (1966) has suggested possible future therapeutic measures that might be attempted in diseases of this type, such as replacement of a missing enzyme when it has been identified, or by influencing the role of nucleic acids. Until the cause of neuronal ceroid lipofuscinosis has been found perhaps it may be worth trying to influence the accumulation of the 'ageing pigments' by large doses of vitamin E (Abrahams *et al.*, 1964) or by giving drugs such as meclofenoxate hydrochloride. This has been tried in Case 2, but so far with no detectable effect.

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