INFANTILE NEUROAXONAL DYSTROPHY*

BY

L. CROME* and S. D. V. WELLER

From the Queen Mary's Hospital for Children, Carshalton, Surrey, and the Children's Hospital, Sydenham, London

(RECEIVED FOR PUBLICATION DECEMBER 11, 1964)

One of the imperfectly understood neuropathological changes is formation of so-called 'spheroids' or 'spheroid bodies' ('Schollen'—in the German literature). These structures are usually roundish homogeneous or faintly granular bodies measuring up to a 100 μ in diameter. They are believed to be focal distensions of axis cylinders, dendrites, or parts of cell bodies, though their direct continuity with neuroplasm is often not demonstrable. They are more frequent in formations of grey matter than of white matter. The presence of occasional spheroids is not unusual in a variety of diverse conditions, such as encephalitis, diabetes, heart failure, carbon monoxide poisoning, and cerebral arteriosclerosis. However, in a few recorded cases spheroids were sufficiently numerous to dominate the morphological picture. Some of these patients were infants or children showing a somewhat uniform clinical picture and pattern of encephalopathy, so that they could have been cases of the same disease or syndrome. This condition has been designated infantile neuroaxonal dystrophy by Cowen and Olmstead (1963) who have reviewed the previous reports and fully described 2 new cases.

The total of recorded cases is only 9. The onset of the disease occurred between 2 and 3 years, and the age at death ranged from 3 to 13 years. There were 8 girls among the patients. 2 were identical twins and another 2 pairs were sibs. Cowen and Olmstead distinguished an infantile from a 'late infantile' form of the condition, the latter being of later onset, having a more prolonged course, and being, perhaps, a variant of Hallervorden-Spatz disease.

The condition was first described by Seitelberger (1952), and later reports include those by Seitelberger (1954), Rabinowicz and Wildi (1957), Gross, Kaltenbäck, and Uiberrack (1957), Seitelberger and Gross (1957), and, as stated already, Cowen and Olmstead. The pathological findings have been described in only 3 cases. Another case of late

infantile Hallervorden-Spatz disease has been recently described by Seitelberger, Gootz, and Gross (1963).

The emerging clinical picture is of apparently normal early development followed by a somewhat abrupt onset of slowly progressive motor and mental disability. However, early development may not be really normal and some of the children are stated to have been definitely mentally backward before the onset of other signs. The children then cease to stand or walk, become hypotonic, and may show strabismus and dysphagia. Blindness, and possibly deafness, develops in most cases. Some of the older children may show spasticity, involuntary movement, flexion deformity, and extensor spasms. Epilepsy was present in two instances. Microcephaly was specifically noted in 2 cases but cannot be excluded in most of the others. The signs and symptoms are of progressive dementia and paralysis. No specific laboratory findings have been reported, and it is hence unlikely that the condition could be diagnosed with any certainty unless previously established in an affected sib.

Histologically, spheroids are found in all parts of the central nervous system, being particularly numerous in the tegmentum of the brain-stem and posterior horns of the spinal cord. Their shape, tinctorial properties, and histochemical features have been studied very fully. It has been established that they contain protein in combination with complex lipids, some of which may be glycolipids. A small amount of polysaccharides may also be present. As a rule, the spheroids do not provoke any cellular reaction, but many show such evidence of regression and dissolution as uneven density, fissuring, and vacuolation of the cytoplasm. Some disappear entirely leaving empty spaces. Another feature of the condition is the occurrence of a somewhat characteristic pattern of associated pathological changes, the chief of which are cerebellar atrophy and sclerosis, accumulation of lipid and gliosis in the striatum, and degeneration of the optic pathway and of some of the long tracts in the brain-stem and spinal

* Part of the histological work was paid for by a grant, made by the National Society for Mentally Handicapped Children.

cord, i.e. the pyramidal, spinocerebellar, spinothalamic, and the gracile and cuneate fasciculi. Cowen and Olmstead have also observed accumulation of somewhat similar adventitious material to that contained in the spheroids in enlarged cells of the germ centres of the spleen and lymph glands and in some of the Kupffer cells in the liver. In 2 of the older cases (Gross *et al.*, 1957; Seitelberger *et al.*, 1963) there was deposition of pigment, as in Hallervorden-Spatz disease, in the globus pallidus and red zone of the substantia nigra.

The pathogenesis of the above-mentioned changes is obscure but the available data suggest the operation of some congenital enzymopathy with, perhaps, an autosomal recessive pattern of inheritance.

Spheroids are known to occur fairly constantly in Hallervorden-Spatz disease, and Seitelberger has, therefore, suggested that infantile neuroaxonal dystrophy is an early non-pigment forming variant of that disease. This concept is not fully accepted by Cowen and Olmstead.

We record below two further familial cases, apparently the first to be recognized in the United Kingdom.

Case Reports

Case 1. This girl, born October 28, 1951, was admitted to hospital at 10 months with feeding difficulties. She was mentally backward and had had several *grand mal* seizures. In hospital she continued having *petit mal* attacks for which she was given troxidone ('tridione'). Shortly after admission she developed pertussis from which she never fully recovered. The leucocyte counts ranged from 10,000 to 54,000 with, in general, an equal proportion of lymphocytes and neutrophil polymorphs. A radiograph showed pulmonary atelectasis of the right lower lobe. One specimen of urine, among many, showed a reduction to Benedict's solution, but a glucose tolerance test was normal. The serum calcium was 10.6 mg./100 ml. The stool trypsin was on the low side of normal. A urine chromatogram on June 18, 1952, was reported upon by Professor C. E. Dent as follows: 'A pretty normal glycine pattern of amino-acid excretion; there was a slight excess of cystine and lysine, which could suggest that the child was a heterozygote for cystinuria but it would otherwise be of no particular significance.'

Her skin was dry and, in view of the neurological peculiarities, vitamin B deficiency was suspected. She was, therefore, given a large dose of vitamin B complex without any noticeable change in her condition. She died aged 1 year from bronchopneumonia, which was confirmed at necropsy. It is recorded that other somatic organs showed no significant change, and that the brain was normal. However, the brain was not examined by a neuropathologist and no neural material was kept for subsequent re-examination or histological study.

The following sections stained with haematoxylin

and eosin have been preserved and were kindly made available for the present study: one each of the lung, lymph node, liver, and 2 of the kidney. The section of the lung showed a combination of bronchopneumonia, collapse, and inhalation pneumonia. The lymph node showed sinus catarrh. The cells of the germ centres were not enlarged and contained no adventitious material of the kind described by Cowen and Olmstead. One of the renal sections showed normal structure; the other presented a necrotic area surrounded by granulation tissue within a compressed rim of the renal cortex.

Case 2. This child was born on September 24, 1961, 10 years after his sister (Case 1 above). The family have had no other children. He was admitted to hospital at 6 months, having become rather 'jerky' during the previous fortnight; he would catch his breath and the head and arms would then jerk forward. The frequency of these episodes had increased, and at the time of admission they were recurring in thrice daily series. When he was younger it was noticed that following a feed he would become quite blue and stiff with both arms held forward, the legs shaking and the eyes staring. This would last about 10 minutes. He would then bring up some wind after which he would appear to recover.

On admission his Hb was 74% (Haldane); WBC, 13,000/c.mm. The urine was normal. The CSF contained 5 white cells per c.mm., chiefly lymphocytes, and 200 RBC's. The chlorides were 785 mg.; sugar, 60 mg.; and protein, 50 mg./100 ml. The electroencephalogram showed 'multiple discharging areas'.

He was put on phenobarbitone, gr. $\frac{1}{4}$ t.d.s., and was given a course of prednisone. This made little difference to the severity and frequency of the fits and involuntary movements, and the steroid was therefore stopped. He was discharged from hospital after three weeks. At home, the jerks became continuous. He had several severe chest infections, the last of which led to his death at 18 months.

The post-mortem examination (Dr. C. Hunter-Craig) revealed an acute respiratory infection. The liver showed slight mottling of its surface. Histologically, the lungs presented a mixed pattern of bronchopneumonia, collapse, and catarrhal pneumonia, and the liver showed a pattern of cellular vacuolation and oedema. No other somatic tissues have been preserved for histological examination.

The brain weighed 810 g. (average normal for the age, 1,026 g.). The cerebellum together with the brain-stem weighed 50 g. The brain was symmetrical and the pattern of the gyri was normal. The cerebellum was small and indurated. The vermis was particularly small not reaching the level of the inferior part of the cerebellar tonsils. The degree of myelination appeared to be consistent with the age of the child. The cut surface of the cerebellum showed absence of the normal demarcation between the cortex and white matter in the folia and generalized sclerosis (Fig. 1) of the white matter. Pallor and some blurring of the structural pattern was present at all levels of the basal parts of the brain-stem.

Blocks of the frontal, parietal, temporal, and occipital

FIG. 1.—The cut surface of the cerebellum.

lobes, the midbrain, pons, medulla, and cerebellum were embedded in celloidin and sections subsequently stained with HVG, PTAH, cresyl violet, by the Heidenhain method for myelin and the Holzer method for fibrous glia. Blocks of the optic nerves, basal ganglia, medulla, upper part of the cervical spinal cord and cerebellum were

FIG. 2.—'Spheroids' in the dorso-lateral part of the medullary segmentum. (HVG $\times 380$.)

used for frozen sections which were stained for fat, with PAS, by the Kulschitsky-Pal method for myelin and by silver impregnation methods. Blocks of the occipital and frontal lobes, cerebellum, pons, and the lowermost available portion of the medulla were also embedded in paraffin and sections stained with luxol fast blue for myelin, by the Holzer method, and the Bodian method for axis cylinders. The paraffin sections were also stained with H and E, HVG, PAS, and luxol fast blue.

The most obvious histological changes were observed in the medulla and the cerebellum.

The dorso-lateral parts of the medullary tegmentum showed areas containing numerous spheroids (Fig. 2). These varied in diameter from about 10 to 80 μ . Some were contiguous, imparting a somewhat honeycombed appearance to the affected area. Others were separated from each other by neural tissue. A few had coalesced to form larger structures (Fig. 3), while the presence of many empty spaces in the affected areas indicated corresponding disappearance of spheroids. With most of the stains the spheroids presented a nearly homogeneous or faintly granular appearance. Many showed regressive changes, being pale, fissured, vacuolated, or fragmented. Only the central portions were demonstrable in the case of some spheroids. In general, then, the staining properties were those of hyalinized, degenerating, or 'dissolving' protein. Some of the spheroids were partly or wholly

FIG. 3.—Coalescence and regressive changes of the spheroids. (HVG $\times 380$.)

argyrophil by the Bielschowsky method. Only a very occasional spheroid stained faintly with PAS, and none was sudanophil with the fat stains. The tissue around the spheroids showed no marked cellular reaction, though occasional glial cells could be seen flattened against the margins of some of them, and a few microglial clusters were also present in areas affected by spheroid formation. Some of the smaller spheroids were very inconspicuous and many were not identifiable with certainty. It is, therefore, probable that isolated spheroids, particularly in formations other than the medulla, were not recognized. In fact, only few spheroids were observed outside the medulla. These were situated in the tegmentum of the pons, the midbrain, the caudate nucleus, and the thalamus.

Besides the spheroids, and perhaps not specially related to them, there were a number of reactive microglial clusters grouped around particles of degenerating neural material both in the white and grey matter. Most of these glial clusters were seen in the medulla, but some were present in the tegmentum and the basal areas at other levels of the brain-stem. Fine fibrillary gliosis was also widespread throughout the brain-stem, particularly its basal portions. This gliosis was accentuated around the ventricles, the aqueduct, and the periphery of the brain-stem. The nuclear formations in the brain-stem had lost some neurones, especially in areas containing the spheroids, but the most marked neuronal loss with corresponding astrocytic overgrowth was present in the inferior olives, particularly their dorsal folds. The dorsal accessory olives were entirely devoid of neurones. Sections of the most caudal part of the medulla stained by the Holzer method showed generalized fibrous gliosis in all but their central portions (Fig. 4).

The cerebellum displayed generalized atrophy and sclerosis affecting all its layers (Fig. 5). Although this change was severe everywhere, some parts showed greater

FIG. 4.—Lowermost part of the medulla. (Holzer. $\times 7$.)

involvement than others. The relatively best preserved parts were the cerebellar tonsils. The molecular layer of the cerebellum was shrunken and gliotic. Both the Purkinje and granular cell layers were severely depleted and there was proliferation of Bergmann glia. The axis cylinders of a few of the surviving Purkinje cells showed cigar-shaped or torpedo-like dilatations, and it is noteworthy that their staining resembled closely that of the spheroids. The cerebellar white matter showed pallor of myelin staining and heavy fibrous gliosis. Some neuronal loss was present in the dentate nuclei, though these formations were in a better state of preservation than other parts of the cerebellum.

FIG. 5.—Cerebellum showing atrophy of all layers. (H and E $\times 170$.)

TABLE
NEUROCHEMICAL FINDINGS (PROFESSOR J. N. CUMINGS)

	Frontal Lobe and Cerebellum (g./100 g. tissue)							
	Cerebral White Matter		Normal for Age	Cerebral Cortex		Normal for Age	Cerebellum	
	Wet	Dry		Wet	Dry		Wet	Dry
Total phospholipid ..	4.50	18.00	20	2.60	14.4	18	1.80	12.50
Total cholesterol ..	3.00	12.00	13	0.95	5.70	6	0.93	5.80
Esterified cholesterol ..	0	0	0	0	0	0	0	0
Total cerebroside ..	2.10	8.40	14	0.28	1.60	5	—	—
Total hexosamine ..	—	0.41	0.4	—	0.61	0.7	—	0.39
Neuraminic acid ..	—	—	—	—	0.21	0.35	—	—
Water (%) ..	75.0		76	82.1		85	84.1	

Thin layer chromatography: White matter shows a loss of cerebroside but a normal phospholipid pattern.
Cortex: ganglioside pattern normal.

Marked focal astrocytic gliosis with neuronal loss was also present in the basal ganglia, particularly the ventrolateral thalamic nuclei. A few microglial clusters were seen in the globus pallidus. No iron deposit or pigment was demonstrable in any part of the basal ganglia and the substantia nigra contained only the expected minimal quantity of pigment. Only a small quantity of sudanophil material was present around a few of the blood vessels in the striatum.

The meninges were normal. The cerebral cortex showed terminal oedema and unevenness of neuronal staining. Some nerve cells had faded almost entirely, appearing as 'ghost cells'. Definite neuronal loss was ascertainable at the troughs of some of the cerebral sulci. The white matter of the centrum semi-ovale presented widespread fine fibrillary gliosis. The staining of myelin throughout the central nervous system was somewhat pale but the pattern of myelination was probably consistent with the age of the patient. Fat staining showed only slight accumulation of brightly sudanophil granules, and attempts to demonstrate an excess of PAS positive material in the neuronal cytoplasm were unsuccessful. Some of the larger neurones did contain a small quantity of PAS positive material, but this was probably well within normal limits.

The optic nerves and tracts showed a seemingly normal state of myelination and no ascertainable loss of axis cylinders. Only a doubtful overgrowth of fibrous astrocytes was demonstrable at the periphery of the optic nerve.

The spinal cord was not available for examination. The neurochemical findings are given in the Table.

Comment

The over-all similarity of the present case to those previously described as infantile neuroaxonal dystrophy is impressive and it is probable that the elder child had the same condition. The present cases are the youngest on record, and it seems likely that the disease had commenced at, or soon after, birth. This early onset and rapid course explain, perhaps, some of the unusual features. Blindness had apparently not developed and the optic pathway

showed only minor anatomical abnormality. The deposition of spheroids was restricted almost entirely to the medulla. The striatum showed only minimal changes while the thalamus was much more extensively involved. No excess of pigment was present in any examined part of the brain, but this should, perhaps, not be expected in a child of 18 months, even if the condition were related to Hallervorden-Spatz disease. The present data thus add little to the problem of the relation of infantile neuroaxonal dystrophy to that disease, an issue fully considered by Cowen and Olmstead.

The neurochemical findings were non-specific. The loss of cerebroside in the white matter with a normal phospholipid pattern could possibly be explained by the presence of fine fibrous gliotic tissue and a relative deficiency of myelin in the sampled material.

It has been suggested by Seitelberger that the condition is a form of lipidosis. There is nothing to support this view in the present cases.

In a recent communication, Sung (1964) reported the presence of spheroids within the gracile and cuneate nuclei, and within the nucleus of the descending tract of the trigeminal nerve in each of the 6 cases of mucoviscidosis examined by him. Citing experimental work, he suggested that the change might be due to vitamin E deficiency. Sung's description and illustrations leave, perhaps, some doubt as to the exact similarity of the lesions, particularly in number and distribution, to those presented above. Moreover, the associated cerebellar changes, as in infantile neuroaxonal dystrophy, are not mentioned by him. Nevertheless, since it is known that some spheroids can occur in a variety of conditions, there is no reason to assume that infantile neuroaxonal dystrophy is always identical in origin.

Summary

A sister and her brother died at 12 and 18 months, respectively, with mental retardation, paralysis, and

epilepsy. The brain of the second child was examined neuropathologically. Allowing for certain divergences, the changes were those of infantile neuroaxonal dystrophy. The condition was almost certainly congenital in the present patients who died at an earlier age than any of the previously recorded ones. The sister was probably suffering from the same disorder.

We are greatly indebted to Professor J. N. Cumings for the neurochemical analysis of the material, and to Professor C. E. Dent for permission to quote his findings. Dr. John Keall has kindly placed the brain of Case 2 and the remaining histological preparations at our disposal.

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