A CASE OF LATE INFANTILE AMAUROTIC IDIOCY, WITH PATHOLOGICAL REPORT

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Few degenerative diseases of the nervous system have acquired a wider expansion of their original definition than amaurotic idiocy. Believed in the first place to be limited to Jewish infants (Waren Tay¹, Sachs²), it was not long before cases were discovered among Gentiles, in whom also the ocular changes and age of onset were not typical (Batten³). During the last fifty years these variations of the disease have appeared under various titles; 'late infantile form' (Jansky⁴, Bielschowsky⁵); 'juvenile form' (Vogt⁶, Spielmeyer⁷, Greenfield and Holmes⁸); and more recently 'late form' (Kufs⁹, Meyer¹⁰). Clinically there may be great differences in these various types; in fact, but for the characteristic histo-pathological changes in all of them, it would be difficult to establish a common identity. The clinical picture of Tay-Sachs' disease in infants, for instance, is quite unrecognizable in Kufs' ex-service man of 42. The marked differences in the appearance of the disease depend on variations in the intensity, extent and special localization of the cell degeneration in the brain. The rate at which the degenerative process proceeds also plays an important part, and in the juvenile and late forms the illness may be prolonged for over ten years (Schönfeld¹¹, Kufs⁹). Not uncommonly the case remains undiagnosed until a study of the morbid anatomy becomes possible.

Even the name amaurotic family idiocy may finally need modification, since sporadic cases are not uncommon at any age, and amaurosis may be absent or play a secondary part in the juvenile and late forms. Idiocy appears to be the only constant feature. The greatest changes in the clinical picture of the varieties of this disorder make their appearance somewhere between the infantile and juvenile forms. Hence the rare 'late infantile' cases become especially important as a link between the two, for already the hall-mark has become blurred. Racial preponderance is no longer obvious, macular changes are often absent and the course of the disease is more protracted.

These considerations prompt us to publish this 'late infantile' case, particularly as it is the earliest in a Gentile which has been pathologically

recorded. The degree of swellings on the axons in the cortex is probably also unique.

Case report.

Pauline M. first came under observation at the age of 1 year and 10 months. She was the first child of English parents with no history of Jewish intermarriage in the family, and there had been no previous miscarriage. The birth had been normal, with an easy confinement lasting twenty-four hours. Up to the age of 6 months the child appeared to be developing normally. She seemed intelligent, smiled and cried like an ordinary infant, and had already become well trained in the use of the chamber. At 10 months the parents first noticed something amiss when no attempt was made to sit up, and it was not until 14 months that the infant began to lift her head from the pillow. The two other most obvious signs of backwardness were an inability to take solids and very indefinite grasping at objects. Meanwhile the previous cleanliness in habits gradually gave way to incontinence, the child no longer smiled or uttered a cry, but lay still and apathetic in her cot. Short convulsions lasting about a minute commenced at the age of 15 months, two or three daily for three or four days every few weeks. At the same time the child was noticed to jump at any sudden noise.

When first seen spasticity of the arms and legs was already most obvious and the 'toes were pointed.' All the tendon reflexes were much increased, those of the upper extremity less markedly so than the knee and ankle jerks. The abdominal reflexes were absent and the Babinski plantar responses extensor. A loud noise produced a sudden straightening of all the limbs with increased spasticity as in decerebrate rigidity. Gradually the child's general condition deteriorated, the appetite diminished, wasting was rapid, and the fits, which throughout were uninfluenced by luminal and bromide, eventually gave way to complete drowsiness with periodic twitching of the face. The arms were held straight and pronated with the wrists and fingers tightly flexed, while the legs were fixed in a position of moderate talipes equino-varus. The eyes fixed on no object and appeared to be blind; the pupils were half dilated, reacted sluggishly to light, and a varying left external strabismus was present. Both discs showed primary optic atrophy, but there were no macular changes.

The Wassermann reaction of both blood and spinal fluid was negative, and an intradermal Mantoux test provoked no reaction. Further examination showed the cerebro-spinal fluid to be clear and colourless, with less than one cell per c.mm. Sugar was present, globulin absent, and the protein 30 mgm. per c.mm.

The final course of the disease was rapid and the child succumbed to broncho-pneumonia at the age of 1 year and 10 months.

Pathological examination*.

The brain, spinal cord and optic nerve with small portion of retina were removed within twelve hours of death and immediately placed in formol saline.

Dr. Ellison who performed the rest of the post-mortem examination reported patches of broncho-pneumonia. The liver and spleen were carefully examined but showed no changes such as described by Neimann and Pick. Other organs in the body showed no morbid changes of any particular interest.

Histological examination.—Frozen sections of the brain and spinal cord were stained with Scharlach R. and an acid haematoxylin counterstain to demonstrate lipoid deposits in the nerve cells; and histo-chemical tests were performed on frozen sections of the basal ganglia in order to ascertain the nature of these deposits. Anderson's Victoria blue method for neuroglia, and Da Fano's modification of Bielschowsky's method for neurofibrils were also used on frozen sections. Celloidin

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sections were made from various parts of the brain, spinal cord and optic nerve. These were stained by the Nissl method, by iron haematoxylin with van Gieson's counterstain, by Mallory's phosphotungstic acid method for neuroglia, and by the Weigert-Pal method. The fragment of retina was embedded in paraffin and subsequently cut in serial section.

The essential features of the microscopical examination are conveniently discussed under the headings of the nerve cells, the neuroglia, and the myelin.

THE NERVE CELLS.—The changes in the nerve cells in this case conformed generally to those which have been described previously in the infantile form of amaurotic family idiocy. The nerve cells of the frontal, temporal and occipital cortex, and of the basal ganglia, midbrain, pons, medulla and spinal cord, all presented the rounded, ballooned appearance characteristic of this disease. The cell bodies were swollen and distended by lipid deposits, the nature of which will be considered later. In the

FIG. 1.—Two pyramidal nerve cells from the occipital cortex with balloon-like swellings on the axons (Bielschowsky stain).

FIG. 2.—Two pyramidal nerve cells with balloon-like swelling on their axons; in one the cell body is also distended with lipid (Bielschowsky stain).

cortex cerebri many cells showed fusiform or globular swellings on the proximal part of their axon. The most bizarre forms were seen in the occipital cortex (Fig. 1 and 2). Here many of the pyramidal nerve cells appeared normal in size, whilst the swellings on their axons were larger than the cells themselves. The shape of the swellings was variable; globular, elliptical and fusiform examples were common, and occasionally in the occipital cortex curious kidney-shaped swellings were found.

Among the nerve cells of the frontal cortex there were some smaller cells with a globular, sharply outlined cell body, and a small irregular nucleus resembling that of microglial cells. With Scharlach R. these cells stained rather more brightly than the nerve cells, and with high powers could be seen to be filled with clear yellowish or pale pink globules. Darker staining fatty granules could also be seen in some of them.

The cerebellum was not greatly atrophied, nor was there much shrinkage of the foliae, although they had a more rounded contour and felt firmer than normal.

Histologically the changes here were diffuse rather than intense. The Purkinje cells were not noticeably decreased in number and were surrounded by normal basket fibres. Their cell bodies were considerably swollen with lipoid, and lipoid swellings were seen on their dendrites, usually at the points of branching (Fig. 3). The granule cell layer was considerably atrophied. At least half the granule cells had disappeared, and between those that remained were seen numerous small globular cells filled with yellowish clear pigment, similar to those found in the frontal cortex. There was also, external to the thinned zone of granules and in line with the Purkinje cells, a fairly compact layer, one or two cells thick, of clear, oval nuclei which appeared to give origin to firm neuroglial fibres (Fig. 4). Similar nuclei were seen among the granules and

FIG. 3.—Purkinje cells from cerebellar cortex, showing antler-like swellings on their dendrites. In one the axonal end of the cell is also distended with lipoid (Bielschowsky stain).

in the white centre of the foliae. No lipoid could be seen round any of these neuroglial nuclei.

Although the contour of the nerve cells throughout the central nervous system was altered by the deposition of lipoid substances within their cytoplasm, the neurofibrils were singularly unaffected. Bielschowsky preparations showed that the neurofibrils were displaced to the periphery of the body of the affected cell, but that they passed normally into the dendrites and through the swellings.

Histo-chemical investigation of the intracellular lipoid deposits gave the following results:—with Scharlach R. the lipoid gave a bright pink coloration

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distinct from that given by neutral fats. Heidenhain's haematoxylin stained the intracellular lipoid deeply. It was not dissolved out by immersing sections for twenty-four hours in absolute alcohol, acetone, chloroform or acid alcohol, but thereafter no coloration, or only a faint pink tinge, was obtained with Scharlach R. It was not doubly refractile.

A comparison between the chemical nature of the intracellular lipoid peculiar to the disease process in amaurotic family idiocy, normal myelin and the neutral fat products of degeneration resulting from disintegration of myelin, was possible by

FIG. 4.—Cerebellar cortex, stained by Mallory's neuroglia stain, and showing a great overgrowth of neuroglia throughout the cortex, especially in the subpial layer:

a study of Kultschitsky-Pal preparations through the basal ganglia. Widespread degeneration of myelinated fibres in the internal capsule had taken place, and in both the anterior and posterior limbs of the capsule were to be seen a large number of compound granular corpuscles loaded with fat granules. The effect of mordanting frozen sections for different lengths of time in Weigert's mordant and subsequently staining them with Kultschitsky's haematoxylin, as recommended by Hurst¹², was to demonstrate that the intracellular lipoid in the case under consideration occupied a position in the fatty series, according to Hurst's classification, mid-way between the composition of normal myelin and the neutral fats. After twenty-four hours in mordant normal myelin stained fairly well with haematoxylin; neither the lipoid granules nor the products of myelin degeneration stained at all. Normal myelin stained best after

forty-eight hours in mordant, at a time when the degeneration products did not stain at all, though the intracellular lipid stained well. Optimum staining of the intracellular lipid was obtained by mordanting for four days. The degeneration products of myelin also stained well when mordanted for the same length of time, whereas normal myelin gave only a faint blue coloration. The intracellular lipid was recognizable at the end of a week in mordant, when no appreciable staining of normal myelin could be obtained. The neutral fat in the compound granular corpuscles and in the degenerated fibres stained well after this period of mordanting. These results indicated that the intracellular lipid consisted of a compound of phosphatides and cerebrosides, which, in its reactions, was intermediate between normal myelin and neutral fat.

FIG. 5.—Frontal cortex stained by Weigert-Pal method. The lipid swellings stain along with the radial fibres.

NEUROGLIA.—The sub-pial neuroglia in the cerebral cortex had greatly proliferated, producing a dense gliosis of the superficial layers of the cortex. This was especially well seen in the occipital region, where there was a thick down-growth of neuroglia into the third layer of the cortex. Peri-ventricular gliosis was also striking, especially in the fourth ventricle. Other regions of the brain showed a remarkable gliosis; in the cerebellum there was considerable gliosis of the molecular layer, especially just under the surface, where a thick feltwork of neuroglial fibres was to be seen in preparations stained with Victoria blue or phosphotungstic acid haematoxylin (Fig. 4). In the thalamus, which had felt unduly firm macroscopically, a very severe gliosis was found, perhaps more intense in the medial than in the lateral part. The lenticular and caudate nuclei were relatively unaffected, though some proliferation of neuroglia had occurred in them also.

MYELIN.—The fibres in the cerebral cortex were, in general, well myelinated, though in the frontal region some of the more superficial tangential fibres stained

poorly. In the internal capsule, the fibres in the anterior two-thirds of the anterior limb of the capsule had undergone almost complete degeneration. In the genu there were many finely myelinated fibres, but in the posterior limb, with the exception of a few finely myelinated fibres in its most anterior part, all the fibres

FIG. 6 & 7.—Transverse sections of medulla and cervical cord, stained by the Weigert-Pal method to show the degeneration of the pyramidal tracts.

had degenerated. The outer parts of the crura were unaffected, but the medial and fronto-pontine fibres were degenerated. In the medulla there was almost complete destruction of the pyramids, and the pyramidal tracts were degenerated throughout the spinal cord.

OPTIC NERVE AND RETINA.—In longitudinal sections of the optic nerve many poorly myelinated fibres were seen, and in addition there were many fibres in an early stage of degeneration. There was no neuroglial reaction to this degeneration.

It was not possible to decide whether the appearance of the retina was pathological or not, owing to the conditions of its fixation. The only definite opinion that could be given on the fragment sectioned was regarding the number of ganglion cells; these were considerably fewer in number than those seen in sections of a normal retina. Those present appeared healthy.

Summary.—1. The nerve cells throughout the central nervous system presented the swollen, ballooned appearance characteristic of amaurotic family idiocy.

2. This swelling of the nerve cells was due to distension by deposition in them of a lipid substance. Histo-chemical tests showed this to be a compound of cerebroside and phosphatides, occupying an intermediate position chemically between normal myelin and neutral fat.

3. Similar swellings were found on many axons of nerve cells; in some situations, notably in the frontal and occipital cortex, these axonal swellings were larger than the cells themselves.

4. Intense gliosis was present in the superficial layers of the cerebral cortex and of the cerebellum; also in the optic thalamus and round the ventricles.

5. There was degeneration of the fronto-pontine and of the pyramidal fibres, and of some fibres of the optic nerve.

6. There was a loss of ganglion cells in the retina.

Discussion.

The view of both Pick and Bielschowsky¹³ is that all forms of familial amaurotic idiocy are due to a disturbance of lipid metabolism, and Marinesco's¹⁴ work goes a long way towards establishing this. The same primary disturbance of lipid metabolism is present in certain cases of Niemann-Pick disease, and it is now generally held that the two conditions are related by more than a chance association, and that, in fact, they are different manifestations of the same disease process. That cases of amaurotic idiocy do occur with no lipid changes in the liver and spleen, and vice versa, is no reason to doubt this.

The alteration in the cells of the liver and spleen in Niemann-Pick disease is mainly due to a deposition of phosphatid molecules. In amaurotic idiocy we have shown, as others have done, that the lipid deposit causing distension of the cells of the brain is also largely composed of phosphatid. The fundamental cause of this disturbance of lipid metabolism, however, still remains unknown.

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