CEREBROMACULAR DEGENERATION

WITH CLINICAL AND PATHOLOGICAL NOTES OF A CASE.*

By

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AFTER amaurotic family idiocy had been first recognized for its ocular changes in 1881 by Warren Tay, Batten, in 1903, published a description of a disease which he described as 'cerebral degeneration with symmetrical degeneration in the maculæ.' This condition he regarded as having some of the characteristics of Tay-Sachs disease but differed from the latter in that: (1) it was not limited to Jews; (2) there were not the same fundus findings; (3) the first signs began at a later age; and (4) the progress was slower. Since these original descriptions the apparent gap between the two diseases has been bridged by the recording of cases (known as the late infantile form of amaurotic family idiocy) occurring between the age-periods of Tay-Sachs disease and of cerebromacular degeneration. The bridge has been strengthened by the fact that findings which had been described as typical of one form of the disease were reported as occasionally appearing in the other. Holmes and Greenfield state that the pathological change is 'a special form of degeneration of the cell-body associated with the deposition in it of a peculiar form of lipid.' Often the axon undergoes secondary degeneration, but it may remain intact even when its cell-body is damaged.

Sachs describes the cell-degeneration as tending to pass through the following stages: (1) huge increase in size, (2) vacuolization, (3) disappearance of the nucleus, (4) distortion of the entire cell-mass, (5) swelling of dendrites. He regards this degeneration as tending to affect every ganglion-cell in the nervous system.

The precise nature of the disease-process is still in dispute. Sachs, Bielschowsky and others regarded the condition as a hereditary one associated with primary changes in mesodermal tissues. They say that there is a surprising relationship with (1) Gaucher's disease and with (2) the familial infantile disease occurring in Jews and closely resembling Gaucher's disease, called lipid cellular splenohepatomegaly or 'Niemann-Pick disease.' Both are said to be variants of general lipid degeneration, with which they group

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Tay-Sachs disease and cerebromacular degeneration. Mixed cases are said to have been observed. Lipoids from degenerating mesodermal tissue, predominantly the reticulo-endothelial system, are, on this hypothesis, presumably deposited in the ganglion-cells.

Schaffer denies this relationship and regards Tay-Sachs disease and cerebromacular degeneration as being a germ-layer disease with a primary ectodermic selectivity, i.e., a primary degeneration of the ganglion-cells of the nervous system. He finds microscopical differences in the nervous system between Tay-Sachs disease and Niemann-Pick's disease.

CLINICAL CASE.

D. I., male, aged six years at time of death. He was aged four years and four months when first admitted to hospital, on June 22, 1928. The patient was a full-term child of non-Jewish parents. There was nothing of note in family history, an elder brother being alive and well. He sat up at five months of age, walked at 17 months, and talked at 18 months. Except for being somewhat retarded in development and the gait being clumsy, the patient showed no obvious signs of illness until the age of three years, when in March, 1927, he had a convulsive seizure, with loss of consciousness for about a quarter of an hour. Similar attacks followed at about fortnightly intervals, during which it was noted that the left arm was drawn up. At three and a half years of age his gait was so clumsy that he could not walk without support. Vision was progressively impaired.

On examination (May, 1928).—The only physical sign observed was a slight degree of spasticity of the left arm and leg, and it was noticed that there was a wandering look about the eyes.

On admission (June 22, 1928).—Mentality impaired. Although up to the end of 1927 he had been able to discern pictures, he now appeared to be quite blind. The pupils were equal and reacted to light. A primary optic atrophy was present with diminished size of the vessels, and pigmentation and 'peppering' of the retina as in complete degeneration, but there was no cherry-red appearance of the maculæ. Hearing appeared normal, and the boy always smiled when a shrill whistle was blown. At first he seemed to recognise his own name, but later even loud sounds produced no reaction. Cold air blown into the right auditory meatus produced nystagmus in 30 seconds, and into the left ear in 40 seconds. Other cranial nerves were normal. Cutaneous sensation, so far as it could be explored, appeared to be normal. The patient did not speak, but occasionally made a noise.

Jerky movements were frequent, chiefly on the left side, especially of the left hand and arm. All tendon-reflexes were present and equal on the two sides. The plantar responses were at first somewhat doubtful in character, but a month later were definitely extensor.

The cerebrospinal fluid was clear, not under pressure, showed less than 1 small lymphocyte per c.mm.; total protein 0.02 per cent.; no excess of globulin; and a Lange's colloidal gold curve 0111000000, with a negative Wassermann reaction both in the fluid and in the blood.

During his stay in hospital, the patient developed measles, from which he recovered.

Three months after admission, convulsive attacks of generalized clonic spasm became more frequent, with loss of consciousness for a few seconds, the eyes

open and fixed, the arms flexed, and the legs extended and rigid, without any biting of the tongue or incontinence.

The condition continued more or less as already described throughout 1928 and 1929, and then gradually became worse, with continuous generalized myoclonic contractions. Towards the end of 1929, the attitude of complete flexion, with increasing rigidity, was adopted. The patient was discharged from hospital on December 23, 1929, but died at home of bronchopneumonia eight days later.

A post-mortem examination was carried out by Dr. Stanley G. James, to whom we are indebted for the following notes.

PATHOLOGY.

Post-mortem Examination.—The body was moderately emaciated, with considerable post-mortem discoloration of the skin, and with extensive bed-sores over the buttocks and sacrum.

Head.—The skull-cap was thick and heavy for a child of this age; anterior fontanelle closed; shape asymmetrical with bulging of left parieto-occipital and right frontal regions; dura moderately adherent to bone. The superior longitudinal sinus contained a firm dark brownish-red thrombus, extending to the torcular but not into the lateral sinuses—all the surface veins on the superior convexity of the brain being distended and firm, and giving a dark purplish appearance to the brain. The base of the skull showed no obvious abnormality.

The *spinal cord* and several of the larger nerve-trunks to the limbs were removed for examination, nothing of importance being noted in their naked-eye appearances.

No remains of the thymus were found.

The *heart* showed great dilatation of right auricle and ventricle, which were distended with agony thrombus, but there was no endocarditis. The bronchi contained much mucopurulent exudate, and the lung-tissue was congested, with some patchy bronchopneumonia at the bases, but no generalized pneumonic consolidation. Beyond some congestion and cloudy swelling combined with some fatty degeneration of the liver and kidneys, nothing of note was found in the abdominal organs, the *spleen* being recorded as showing no obvious abnormality. The immediate cause of death appeared to be the cerebral thrombosis and bronchopneumonia following upon septic absorption from bed-sores.

Further examination of the brain after fixation in 10 per cent. formal-saline.—In addition to the thrombosis of the great longitudinal sinus and its main tributaries from the surface of the hemispheres, there was also recent red thrombus in the left internal carotid and middle cerebral arteries. The whole brain was distinctly small with general diminution in the size of the convolutions, particularly those of the occipital lobes, with corresponding widening and exaggeration of the intervening sulci. The diminished size of the cerebellum was particularly noticeable, giving it a shrivelled or

'miniature' appearance, its individual folia being small and narrow (fig. 1). On horizontal section through the hemispheres, the lateral ventricles were considerably dilated, evidently owing to retraction of the atrophic brain-substance, the white matter being considerably reduced in amount, and the grey matter of the atrophic cerebral cortex being distinctly narrowed. The third and fourth ventricles and the aqueduct of Sylvius were also considerably dilated, and the small size of the cerebellum appeared to be due mainly to atrophy of cortical grey matter in rather greater degree than to atrophy of the white, though this also was much reduced in volume. The white matter of the cerebral hemispheres was distinctly greyer than normal, contrasting less markedly with the grey matter, but the change was more or less uniform and without the patchy character seen in Schilder's periaxial encephalitis, the characteristic sparing of the subcortical arcuate fibres typical of the latter disease not being here in evidence.

FIG. 1.—Naked-eye view of cerebellum (natural size) to show atrophy, especially of the cortical folia.

Histological Examination: Peripheral Nerves.—From the left arm, the median, and from the left leg the sciatic and internal and external popliteal nerves were examined, both in longitudinal and transverse section. All showed a moderate degree of fibrosis, mostly around the main funiculi, with patchy old-standing degeneration of the fibrils, advanced in some parts of the nerves, especially in the external popliteal, and, to a lesser degree, in the median. There was no recent fatty degeneration of the myelin sheaths with Marchi, but there was a considerable increase in the numbers of the neurilemma nuclei.

Spinal Cord.—The white matter throughout did not show any very obvious changes—no appreciable degree of recent fatty degeneration of myelin or older demyelination. The direct pyramidal tracts, especially in the dorsal region, appeared to be rather smaller than normal; whilst the posterior columns throughout were perhaps a little larger in proportion to the slightly reduced remainder of the cord. All the nerve-cells, but especially those of

the anterior horns, showed varying degrees of degeneration throughout the whole cord, but most markedly in the lumbar region. The margins of many of the cells were indistinct, and the cytoplasm of many showed a clear hyaline swelling. In paraffin sections stained by van Gieson's method this globose swelling stained a faint diffuse yellowish colour, while some finely granular protoplasm usually survived around the peripherally placed nucleus. In

FIG. 2.—General low power view of the rolandic cerebral cortex showing spongy appearance of the middle and deeper zones of the cortex in paraffin section. Compare figs. 3 and 4, the former a high-power view of the area in this section marked with the bracket; the latter a frozen section in which the nerve-cells are not so contracted and vacuolated. (Hæmatoxylin-eosin).

the dorsal region and in the lumbar enlargement these changes showed varying degrees of advancement up to complete disappearance of the nucleus, with only a clear, more or less shrivelled and yellowish necrotic-looking remnant of the cells surviving, and in practically all the cells the Nissl-granules had completely disappeared.

Cerebrum : Cortex.—The surface vessels were engorged, but there was no cellular infiltration around them or in the leptomeninges. In paraffin sections the grey matter of the middle and deeper zones had a general spongy appearance (fig. 2). The ganglion-cells looked small, rounded or irregular, and shrunken, with the nucleus retracted to one side but usually staining fairly well and surrounded by a zone of granular cytoplasm of varying extent. The latter was generally scanty and in some cells almost absent, the remainder of the cell-body appearing at first sight like a clear space or vacuole to one side of which lay the nucleus and the surrounding residual

FIG. 3.—High-power view of area marked with bracket in fig. 2, showing the small retracted appearance of the nerve-cells in paraffin sections, the nuclei, surrounded by a little granular protoplasm, being retracted to one side of vacuole-like spaces. (Compare with frozen section of a similar area shown in fig. 4). (Hæmatoxylin-eosin.)

protoplasm. This clear vacuole-like space, however, had usually a fairly definite border, and in frozen sections was found to be filled with somewhat granular to more or less homogeneous-looking greyish material suggestive of coagulated fluid. The granules around the nucleus stained pinkish-orange with Sudan III. For convenience of description only, the general appearance might be likened to that of a coarsely granular eosinophil myelocyte stained with Leishman (figs. 3 and 4). In the grey matter glia-cells were not increased but rather diminished in numbers, while comparatively few 'parasitic' small round cells could be seen around the ganglion-cells. The spongy appearance of much of the cortex was due to tangential sections of the swollen cytoplasm of the nerve-cells. No cellular infiltration around capillaries was seen.

FIG. 4.—High-power view of a similar area to that shown in fig. 3. The magnification is the same, but the section is a frozen one and the nerve-cells, etc., do not show the retraction seen in the paraffin section. The granules in the cytoplasm are stained pinkish-orange with Sudan III, and the vacuole-like spaces are less exaggerated and contain more or less amorphous material, perhaps fluid or semi-fluid coagulated by the formalin fixation. (Sudan III-hæmatoxylin.)

FIG. 5.—White matter of cerebral hemisphere. Compound granular corpuscles containing fat, stained with Sudan III, lying in perivascular space. Frozen section.

White Matter.—In contrast to the grey matter of the cerebral cortex, in the white matter of the cerebrum were seen numerous small glia-cells and also small lymphocyte-like cells diffusely distributed. Capillaries and small venules stood out clearly with well stained endothelial walls. These appeared unduly numerous and were mostly distended with red blood corpuscles. Dilatation of the perivascular spaces was not a very marked feature, but occurred in moderate degree, with also a varying amount of perivascular cellular infiltration, mostly minimal or absent. Only slight fatty degeneration of the capillary endothelium was demonstrated by the Marchi method, but with Sudan III in frozen sections occasional clumps and masses of fat-containing compound granular corpuscles were found in the perivascular spaces, especially at the junctions of capillaries with small veins, where also the lining endothelium sometimes contained localized collections of fat globules and granules in considerable amount (fig. 5). In Weigert-Pal preparations there was almost complete demyelination of the white fibres. Only a minimum of faintly stained narrow shrivelled fibrils and an occasional one rather thicker, with varicose swellings like the bulbs of Higginson's syringes, were stained. A somewhat similar picture was obtained with Sudan III in frozen sections, but there was no result on staining for fat by the Marchi method.

Cerebellum.—The cortex was very atrophic. The granular layer was much thinned, being in most places only two or three cells thick. The Purkinje cells were also much diminished in number and irregular in their distribution, with great diminution in their cortical arborisations, some of the primary divisions or 'antlers' of which had enormous globoid or irregular swellings upon them as described by Schob in 1912 (fig. 6), who pointed out their fatty nature. In the white matter there was marked demyelination, especially in the smaller folia, and this change, though still marked in degree, was rather less in and around the dentate nuclei (fig. 7).

Pons.—A transverse section at the level of the nuclei of the trigeminal nerve showed well-marked demyelination, especially of the pyramidal bundles; a transverse section through the medulla oblongata about the middle of the olivary region also showed demyelination of the pyramids and anterior spinocerebellar bundles, while the medial lemnisci, etc., were not similarly affected. In the pons and medulla Marchi's stain gave no evidence of any recent fatty change, only an occasional myelin sheath being stained in the least demyelinated areas. In some parts of the pons the vertical, and especially the pyramidal, and in others the horizontal fibres, were more affected. All stages of degeneration were seen from moderate to complete loss of myelin, some fibres showing varicosity, others attenuation, etc.

Optic Nerves.—Here there was no recent fatty change in the myelin sheaths demonstrable with osmic acid, though small fatty granules were

FIG. 6.—Cerebellar cortex showing extreme atrophy, diminution of the cells of the granular layer, and one of the malformed Purkinje cells with an enormous swelling upon one of its 'antlers.' (Hæmatoxylin-eosin.)

FIG. 7.—Cerebellum. Low-power section showing the atrophy of both cortex and medulla. (Hæmatoxylin-eosin.)

visible in the cytoplasm of endo- and perithelial cells of the small vessels. The myelin sheaths themselves were variable in appearance (fig. 8), some appearing varicose or beaded, others attenuated and in process of disappearing.

The condition of the axis-cylinder processes, etc.—In a series of frozen sections stained by the Bielschowsky method the neurofibrils of the dendrites and axis-cylinder processes of the nerve-cells of the cerebral cortex generally appear to be markedly reduced in number and complexity, though surviving in greater degree than might have been expected from a study of sections

FIG. 8.—High-power view of optic nerves showing beading and attenuation of myelin sheaths and partial atrophy. (Wiegert-Pal).

stained by other methods (fig. 9). Within the nerve-cells they traverse only the periphery of the cytoplasm and appear to be pushed aside by the globose swellings. In many of the cells, however, they have entirely disappeared. In the white matter the axis-cylinders also survive in much greater degree than the myelin sheaths, though they are distinctly scantier in the white matter of the cerebellum than in that of the cerebrum.

The spleen was unfortunately not kept for section, but the liver did not show any appreciable increase in the reticulo-endothelial Kupffer cells in the walls of the intercellular blood-sinusoids, and one may therefore infer that the condition was not of the Niemann-Pick splenohepatomegalic type.

SUMMARY.

A case of so-called cerebromacular degeneration is recorded in which, however, macular changes were not in evidence. The patient, a male child of non-Jewish extraction, was three years old at the onset of the disease, which lasted three years, with progressive loss of vision, hearing, and mentality. The pathological findings were those typical of this group of diseases, though perhaps more advanced and extreme than in some of the cases recorded—probably owing to the long course of the illness. All the

Pyramidal cortex of case.

Pyramidal cortex of normal control.

FIG. 9.—Thick frozen sections stained by Bielschowsky's method for neurofibrils. It was difficult to obtain these in focus in any numbers in the photographs, which are shown here to illustrate loss of shape and character of the nerve-cells, which are scarcely recognisable in the cerebromacular case.

nerve-cells throughout the brain and cord showed varying degrees of globose swelling, the presence of fatty granules in the surviving perinuclear cytoplasm, disappearance of Nissl-granules, and a gradual but progressive diminution of dendrites. Some of the latter had curious swellings upon them (e.g., on those of the Purkinje cells). Progressive and widespread demyelination of the white nerve-fibres of the cerebrum (including the optic nerves), cerebellum and brainstem was found. In the latter the pyramidal bundles were especially affected. In the spinal cord, although the nerve-cell changes were well marked, the white matter was relatively little affected,

This case falls clinically into the group described by Batten and named by him 'cerebromacular degeneration.' A thorough pathological investigation revealed no evidence in support of the theories of Sachs, Bielschowsky and others that the disease is related to Gaucher's and Niemann-Pick's disease and is a form of general lipoid degeneration. Schaffer's view that cerebromacular degeneration is a primary degeneration of the ganglion-cells seems to gain support from this case.