CEREBELLAR ATROPHY ASSOCIATED WITH ÉTAT MARBRÉ OF THE BASAL GANGLIA

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THIS paper records the occurrence in a 33-year-old idiot of bilateral état marbré of caudate nucleus, putamen, and thalamus, together with a small atrophic cerebellum, atrophied inferior olives, and sclerosis of the nuclei pontis and the transverse pontine fibres. This combination of lesions is surprising since état marbré of the corpus striatum is in the large majority of cases a phenomenon of infancy (Scholz *et alia*, 1938) and olivo-ponto-cerebellar atrophy is in general a disease of the sixth or fifth decades. A search of the literature concerning the former condition has failed to reveal its association with systematic cerebellar atrophy, although small foci of degeneration in the cerebellum may be found in cases of striatal état marbré, especially when the cerebral cortex is involved and epilepsy present. On the other hand, it is well known that symptoms referable to disease of the extrapyramidal motor system may complicate olivo-ponto-cerebellar atrophy. Among several cases may be mentioned the examples recorded by Guillain and co-workers (1926) in which Parkinsonian rigidity and tremor were observed, and the case of Van Bogaert and Bertrand (1930) in which there was tremor without rigidity. Pathological confirmation of extrapyramidal lesions of a more conclusive character than the above-mentioned observers were able to furnish was provided by Scherer (1933), who in four cases of olivo-ponto-cerebellar atrophy demonstrated well-defined lesions in the substantia nigra and putamen. État marbré was not observed. It would seem that the present case, although having affinities with these adult conditions, differs from them in several respects, notably in the early onset of the pathological process. Another peculiar feature is the absence of clinical signs suggestive either of extrapyramidal or cerebellar disease. For these reasons I have thought it worthy of record.

Case Record

The patient, a male idiot, was admitted to Stoke Park Colony when 8 years old. The records state that he began to walk at the age of 1 year 9 months and that signs of mental deficiency were first observed at the end of the first year.

Family History.—The father earned his living for about 20 years as a corporation roadsweeper. He was certified as a lunatic in 1922 owing to mental depression and

delusions of persecution. He was discharged after 2 years. In 1938 he had a stroke and died after a second attack in 1940.

The mother, aged 73, is mentally normal. The home is well cared for. The patient was the third of a family of four. The eldest sister is married; she had had a healthy illegitimate child. The next sister, who works in a corset factory, has two healthy children. She was on probation for two years for theft. The youngest sister, also married, but with no children, does daily work. This family history, though perhaps indicative of moral shortcoming, provides no evidence of inherited nervous disease.

On admission he was classified as an idiot with mental age under 3 years. Speech was limited to noises. He did not suffer from epilepsy. There was imperfect control of bladder and rectum. No abnormality in the various physical systems was discovered. In 1933, when 27 years old, his performance in the Merrill-Palmer scale of tests indicated a mental age of 2 years 3 months. Considering the idiot level of his achievement, the detailed report of these tests did not indicate a special failure in tasks requiring motor co-ordination. Thus he was able to build a tower of nine blocks, could stand on one foot and put pegs into the Wallin Peg Board B in 21 seconds (3-3½ year level). His failures could be ascribed to general intellectual defect rather than to specific physical handicap.

A physical examination made at this time showed considerable retardation in development. Head length: 175 mm., head breadth 142 mm., head height 120 mm. The calculated capacity of skull was 1,195 c.mm. (about the 7th year level). Standing stature 1,469 mm. (14-year level); sitting stature: 797 mm. (15 year level); weight 39.4 kilos (14-year level). The only abnormality noted in the nervous system was spasticity in the lower limbs. In 1935 he developed acute nephritis, making a good recovery. In 1937 he was critically ill with diphtheria and remained in hospital for four months. The spasticity in the legs increased after this illness. At no time was athetosis, tremor, Parkinsonian rigidity, or inco-ordination of cerebellar type observed. He was described by the nurses who had charge of him as a very timid boy, and he had two characteristic tricks which consisted of pointing upwards with extended index finger and licking his lips with a circular movement of a very long tongue. In 1939 at the age of 33 years he died from broncho-pneumonia.

Post Mortem Report

Lungs: purulent bronchiolitis with small patches of lobular consolidation. Microscopic examination showed a lipoid pneumonia of long standing, with a superimposed terminal hæmorrhagic broncho-pneumonia of influenzal type. **Heart:** normal save for a few subepicardial petechiæ. **Kidneys:** macroscopically and microscopically showed a moderate degree of fibrosis. **Adrenals** were healthy. **Liver:** showed fatty changes. **Spleen:** was moderately enlarged, soft, pulpy. **Skull:** was abnormally convex in the temporal regions, there being no depressions beneath the temporal muscles. The sphenoidal sinus contained a mucopurulent exudate.

Brain.—On removing the dura the cerebral convolutions were found to be somewhat flattened. The brain as a whole was small. There was a purulent meningitis in places at the base of the brain and a localized purulent exudate in the pituitary fossa.

On stripping the leptomeninges the convolutional pattern showed no gross departure from normal. The right calcarine fissure was short and indented the convex border of the hemisphere rather high up on the occipital lobe. The cerebellum (Figs. 1, 2) was grossly reduced in size, the reduction chiefly affecting the lateral lobes in symmetrical fashion, the vermis being unduly visible. Viewed from the side it was seen that the white matter was exposed owing to the poor development of the cerebellar gyri of the superior and inferior surfaces (Fig. 3). The sulci of the lateral lobes were widened, chiefly in the posterior and lateral part of the cerebellum (superior and inferior semilunar lobules) and the consistency was increased in this situation, suggesting glial sclerosis. The pons and medulla were not obviously reduced in size

(when compared with the brain as a whole). Total brain weight (stripped): 1,151 gm.; right hemisphere: 541 gm.; left hemisphere: 546 gm.; cerebellum with pons and medulla: 64 gm. Brain, length: 158 mm.; breadth: 124 mm.; height: 105 mm.

Fig. 1.—Ventral surface of cerebellum showing small size of lateral lobes the sulci of which are widened. $\frac{2}{3}$ natural size.

Fig. 2.—Dorsal surface of cerebellum. $\frac{2}{3}$ natural size.

Fig. 3.—Right lateral lobe of cerebellum viewed from side showing exposure of central white matter. Natural size.

Fig. 4.—Part of the inferior semilunar lobule showing varying degrees of atrophy. The Purkinje cells are almost absent from the better preserved folia. Cresyl violet ; $\times 5$.

Microscopical Examination of the Nervous System

Cerebellum.—Sections were prepared from representative areas of the vermis and lateral lobes (chiefly on the left side) and stained by standard methods for nerve cells, axis cylinders, glia, and myelin.

Lateral lobes: the most marked pathological changes were found in the macroscopically atrophied semilunar lobules. Both sides were equally affected. In the shrunken gyri there was an almost complete absence of Purkinje cells, the granular layer being thinned, but seldom totally atrophied (Fig. 4). The remaining Purkinje cells had a shrunken atrophic appearance. Empty basket fibres of coarse calibre were a conspicuous feature of such areas (Fig. 5). Axonal torpedoes were only rarely seen. There was considerable diminution in the number of myelinated fibres present in the granular layer, but the central core of white matter showed but little thinning even in the atrophic gyri. The molecular layer was thin in the gyri showing marked outfall of Purkinje cells. The tangential fibres were well preserved. There was a heavy fibrillary gliosis affecting the Bergmann glia of the molecular layer (Fig. 6), and also the central white matter in the atrophic gyri. Gliosis was not marked in the granular layer except in those areas where gross reduction in numbers of nerve cells was present.

These pathological changes varied considerably in different parts of the cerebellum. In the macroscopically less affected parts of the semilunar lobules (adjoining the vermis) and in the posterior quadrangular lobule the Purkinje cell loss was not so severe, and the granular layer was well preserved. Empty basket fibres were common. The size of the Purkinje cells varied, many small forms being seen. In such areas the molecular layer was of normal depth and only an occasional thickened Bergmann fibril could be demonstrated. A mild fibrillary gliosis was usually present in the granular layer. In the white matter of the folia, however, excess of fibrous glia was the rule. The myelin picture in these less atrophic regions differed little from normal. In one section taken from the less shrunken part of the right superior semilunar lobule a large cluster of heterotopic Purkinje cells with attendant basket fibres was seen in a malformed folium. In the anterior part of the quadrangular lobules no pathological changes could be found.

The left tonsil showed some reduction in Purkinje cells and coincident empty baskets. Small poorly staining Purkinje cells were common. The intensity of the atrophic changes varied considerably from folium to folium. In general the myelin picture was normal. There was a well-marked fibrillary gliosis in the white matter, but the molecular layer seemed unaffected and was of normal depth.

In the left flocculus there was some thinning and beading of the myelinated fibres in the granular layer. The nerve cell loss was insignificant. There was gliosis of the white matter.

Vermis: in the superior vermis only mild changes were present. Clusters or reduplication of Purkinje cells were occasionally seen. Rarely, gaps in the Purkinje cell layer were present, but empty basket fibres were unusual. Apart from a heavy fibrillary gliosis of the white matter, little abnormal was seen. There was no demyelination. Similar findings were recorded in the inferior vermis. The Purkinje cells varied in size both in cresyl violet and Bielschowsky preparations. In the pyramid empty basket fibres were fairly common. As elsewhere, the white matter was sclerosed without any evidence of corresponding myelin defect. No axonal torpedoes were seen in any part of the vermis.

Dentate nucleus: a few areas devoid of nerve cells were found. In general, however, the nerve cells and their processes appeared healthy. Lipochrome deposits were present to an extent equal to that found in a normal adult. The fibrous gliosis, present throughout the white matter of the cerebellum, was intensified round the cells of the dentate nucleus, especially so in the areas of nerve cell atrophy.

Cerebral Cortex.—Representative areas including the Rolandic areas and cornu Ammonis were examined from both hemispheres. Apart from minor irregularities in arrangement and size of cell commonly seen in low-grade defectives little abnormality was detected. No atrophic changes were found in the many areas examined. A mild fibrillary gliosis was seen in the white matter of the calcarine area and in the fimbria and dorsal part of dentate gyrus of the hippocampus.

Fig. 5.—Empty basket fibres in folium showing well preserved granular layer. Bielschowsky's stain; $\times 180$.

Fig. 6.—Heavy fibrillary gliosis in molecular and granular layers of cerebellum. Holzer stain; $\times 270$.

Fig. 7.—Coronal section through right corpus striatum. État marbré in caudate nucleus and putamen. Partial demyelination of globus pallidus. Anderson's modified Kulschitsky-Pal stain; $\times 2\frac{3}{4}$.

Fig. 8.—Left thalamus—coronal section. État marbré in medial nucleus. Modified Kulschitsky-Pal stain; $\times 3\frac{1}{2}$.

Basal Ganglia.—A well-marked état marbré was present in the caudate nucleus and putamen of both sides of the brain (Fig. 7). The myelinated networks were widely distributed throughout the ganglia, though densest in the lateral and dorsal part of the putamina. Except in the areas affected by hypermyelinization the large and small nerve cells were not noticeably reduced in numbers. The myelinated strands were the seat of a fibrillary gliosis and a finer proliferation of glial fibres was also visible in intermediate areas. No sign of regenerative activity was seen in the axis cylinders.

The globus pallidus of both sides showed glial sclerosis and poverty of myelinated fibres in its central portion (Fig. 7). There was marked beading of the remaining fibres in the areas poor in myelin.

The thalami were the seat of état marbré of a less pronounced character than that found in the striate bodies. It affected the medial nuclei (Fig. 8). Increase in glial fibres was present over a wide area and a close correspondence between gliosis and

Fig. 9.—Atrophy of inferior olives. Kulschitsky-Pal stain; $\times 2\frac{1}{2}$.

Fig. 10.—Sclerosis of inferior olives. Holzer stain; $\times 2\frac{1}{2}$.

hypermyelinization could not be demonstrated. Except in the areas affected by état marbré there was no obvious nerve cell reduction.

The hypothalamic nuclei appeared normal.

Substantia nigra.—No cell loss or depigmentation was found in sections taken from several levels. The cephalad extremity of the substantia nigra showed some glial sclerosis without obvious changes in the nerve cells.

Pons.—Nerve cells and myelin preparations showed no abnormality. The Holzer stain revealed a well-marked proliferation of glial fibres in the transverse fibres and in the nuclei pontis. The pyramidal tracts did not share in this change.

Medulla.—Atrophy of the inferior olives was a conspicuous feature, the total size of these structures being greatly reduced. There was almost complete disappearance of nerve cells in the lateral portions, a few shrunken cells remaining in the ventral and medial coils. A gross reduction in numbers of myelinated fibres (Fig. 9) and an extremely dense glial sclerosis (Fig. 10) were present in the atrophic areas. Sections taken at different levels showed that both olives were affected in this way throughout the greater part of their extent. There was, however, little cell loss in the most cephalad portion, though here also an increase in glial fibres was present. The pyramidal tracts were normal.

Spinal Cord.—The cervical region of the spinal cord showed no pathological change as regards myelin or glia.

Discussion

One of the most remarkable features of this case is the discrepancy between the clinical condition (one common to a host of low-grade mental defectives)

and the gross and widespread lesions in the nervous system. There is, it is true, often little parallelism between the extent of cerebellar disease and the functional disability thereby produced. Time of onset seems to be an important factor in the production of symptoms, for some congenital cerebellar defects may have no obvious clinical consequences, e.g. the Arnold-Chiari deformity (Aring, 1938) and the lesser degrees of simple hypoplasia. Although in the present case it is impossible to date with accuracy the inception of the pathological process, some of the cerebellar abnormalities present appear to have dated from early life and are possibly congenital. The exposure of the white matter along the margins of the lateral lobes owing to the small size of the cerebellar folia in this situation is more suggestive of inhibited development than the result of atrophy and shrinkage of a previously fully formed organ. Also the fact that the main part of this small cerebellum showed but little evidence of pathological change supports this view. Small cerebella, the size of which is out of proportion to the extent of the histological lesions found in them, have frequently been reported in cases of adult cerebellar ataxia, especially in the hereditary spino-cerebellar form (Wilson, 1940), and it is not clear in such cases as to what emphasis should be laid upon the factors of "hypoplasia" or "atrophy" in discussing their pathogenesis. In the present case it seems reasonable to suppose that a process of atrophy starting not later than infancy has inhibited the growth of the cerebellum. This hypothesis of an infantile onset of atrophy is supported by the coincident changes in the basal ganglia, for, as previously pointed out, *état marbré* of the striatum in the majority of cases manifests itself in very early life.

Even more remarkable than the absence of cerebellar symptoms is the lack of clinical signs pointing to involvement of the corpus striatum. Had this patient been a typical example of double choreo-athetosis few surely would have doubted that the anatomical substratum of his physical condition lay in the lesions of corpora striata and thalami. It is true that athetosis may not be shown by cases in which the cerebral cortex, in particular the motor area, is atrophied (Norman, 1938), but in this instance no pyramidal tract or cortical lesion was found.

Furthermore, "while the rigidity and exaggerated postural fixation of extra-pyramidal disease can be regarded as 'corresponding opposites' (Jackson) of cerebellar hypotonia, the diminution of certain automatic activities, as failure of the arms to swing in walking, the static tremor which may appear during the maintenance of posture, the poverty of automatic movements, the slowness of motion and the difficulty in performing alternate movements are symptoms common to disease of both the extra-pyramidal system and the cerebellum and indicate a functional relationship between these two organs" (Holmes, 1939). One would have thought, therefore, that a combination of cerebellar and striatal disease as in this case would have produced an increase and not a "cancelling out" of some of the above clinical signs. Although finer tests of co-ordination cannot be satisfactorily carried out on non-co-operative idiots, it is apparent that the clinical condition of this patient did not accord with such theoretical suppositions.

This case throws no light upon the question of ætiology either of état marbré or of cerebellar atrophy. The family history gave no indication that a genetic factor might be held responsible and the probable early onset of the pathological process hardly suggests a pre-senile degeneration in the sense implied by Scherer in his examples of adult olivo-ponto-cerebellar atrophy. With regard to état marbré, Scholz's conclusion that it is the result of "partial tissue necrosis" advances the problem of pathogenesis very little further than Vogt's original conception of "pathocclisis." Birth injury does not appear to be a factor in the present case. The demyelination of the globus pallidus has also been described in cases of état marbré by Onari (1925), Meyer and Cook (1936), and Gozzano (1934). One is left with the rather nebulous conception of an atrophic process of unknown ætiology starting in early life and affecting more or less selectively and symmetrically the basal ganglia and the neo-cerebellar system with its olivary component.

Summary

In the brain of a 33-year-old non-epileptic idiot bilateral état marbré of caudate nucleus, putamen, and, to a lesser extent, thalamus was found. There was demyelination of the central part of each globus pallidus. The cerebellum was considerably reduced in size, especially in the lateral lobes, where an atrophy of Purkinje cells was present chiefly affecting the superior and inferior semilunar lobules. The inferior olives were grossly atrophied and demyelinated save in their most cephalad parts. The nuclei pontis and transverse fibres of the pons showed mild glial sclerosis only. The cerebral cortex showed no atrophic changes. It is suggested that the element of hypoplasia shown by the cerebellum was due to the onset of atrophy prior to the full development of the organ. A peculiar feature of the case was the absence of clinical signs referable either to cerebellar or striate disorder.

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