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ALZHEIMER'S DISEASE WITH PREDOMINATING CROSSED CEREBRO-CEREBELLAR HEMIATROPHY

BY

R. E. HEMPHILL and E. STENGEL

From the Bristol City and County Mental Hospital

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IN spite of the great number of contributions on the subject of Alzheimer's disease and its position amongst the presenile cerebral degenerations the character of the disorder is still obscure. We have investigated a case with uncommon features which we believe throws fresh light on old problems and in itself suggests new lines of investigation.

Annie O., was admitted to the Bristol Mental Hospital on 21st September, 1934, at the age of 53. Her history was as follows. No history of insanity or of specific physical illness in the family. Parents and grand-parents exceptionally long-lived. The patient herself was an intelligent child who did very well at school. She showed no noticeable mental or physical abnormality until after the birth of her only child when she was 41. The confinement was normal, but some time after the patient found difficulty in looking after the house and child. During the next eight years her intellectual powers appear to have deteriorated slowly so that she became unable to attend to her shopping or to be trusted alone in her house. She used to wander from her house and forget where she lived and did not know the date or the value of money. At the time of the menopause at 49 her mental symptoms appeared to have become more pronounced; four years later, on 21st September, 1934, she entered the mental hospital.

On admission she presented a picture of depression. She said that she felt miserable and was unable to do her work. She stated that she felt queer at times and that she was afraid of falling. The patient was quiet and well behaved and had sufficient comprehension of her mental disability to seek treatment of her own accord. There seemed to be no error of perception. Her memory was very poor and she could not even remember how many children she had. Actually she had only one.

She did not know the date and had no knowledge at all of recent events. It was noted that she would forget the position of her bed in the ward.

Physical State.—The patient was rather thin but apart from a slight trace of albumen in the urine there was no sign of physical illness. The hair was grey, the complexion sallow, and there was a commencing arcus senilis. No sign of disorder of the C.N.S. Wassermann reaction in blood negative.

Course of Illness.—During the first year of hospitalization the patient's mental condition underwent a slow deterioration. Her memory became if anything worse and while at first she could do simple tasks, such as elementary sewing, by the end of 12 months she was unable to dress and wash herself unaided. She had, however, ceased to be depressed, she looked cheerful, and always expressed the belief that she was getting better. During the next four years the deterioration continued and the case history suggests that by that time she showed aphasic phenomena. She paid little attention to what was said to her and when asked questions she merely repeated her own name. It was difficult to examine her as she was very unco-operative. She sat continually in dark corners with head bent wringing her hands. She was considerably wasted. Within a year before her death she became greatly emaciated; she was feeble and incontinent requiring constant nursing attention. She had no fits in the course of the illness. She died on 11th February, 1940, of broncho-pneumonia.

Case Summary.—This is a case of a patient in whom intellectual deterioration made its appearance at the age of 41. This deterioration was slowly progressive until the death of the patient at 59. The symptoms were those of an organic dementia, failure of memory being the earliest and most prominent symptom. Towards the end the patient was unable to look after herself. In the late stages of the illness the function of speech was disturbed and the case history suggests that this disturbance was chiefly of the executive ability. Death was due to pneumonia. During the whole course of the illness there was no evidence of delusions, hallucinations or fits, nor were there signs of paralysis. There were neither signs nor history of chronic alcoholism nor any evidence of severe cardiovascular or renal disorder.

Post-mortem Examination.—Apart from brain, the only significant findings were : Generalized wasting of body. Arteries soft. Slight atheroma of ascending aorta. Heart small and firm, no valvular nor endocardial abnormality. Lungs : Typical picture, confirmed microscopically, of a confluent broncho-pneumonia. Kidneys : Early fibrosis. No noteworthy abnormalities in other organs.

Brain.—Macroscopical Findings : Dura normal, pia-arachnoid moderately thickened and opaque, freely separable from the brain surface. Cerebro-spinal fluid present in marked quantity in the subarachnoid space. Weight without dura 870 gm. There was gross generalized asymmetrical atrophy involving both hemispheres of the brain and of the cerebellum. The right cerebral hemisphere was noticeably much more wasted than the left, the contralateral left cerebellar hemisphere being more wasted than the other. The difference in the degree of atrophy between the cerebral hemispheres was proportionately the same as between those of the cerebellum. The degree of atrophy was not uniform throughout all regions of the cerebral cortex of each side. The order of maximum wasting was the same on each side, namely, frontal, occipital, temporal, parietal lobes. The anterior and posterior central gyri were less affected. The degree of atrophy of the various lobes of the cerebellum was uniform, apart from the asymmetry. The great disparity in the amount of the atrophic process is shown in the photograph taken from above (Fig. 1). The marked pro-

section of the right cerebellar hemisphere behind the right occipital pole is strikingly demonstrated, in contrast to the normal relationship of occipital lobe and cerebellum when viewed from above. There was diffuse gross atrophy of both cerebellar hemispheres but, as mentioned before, that of the left side was the more extreme. This is illustrated in Fig. 2 which shows from the postero-caudal aspect the asymmetry of the two cerebellar hemispheres and the abnormal relationship between the left occipital pole and the left cerebellar hemisphere. The individual cerebellar folia of the left side appeared more atrophic so that there was a considerable difference in the size of the corresponding parts of the cerebellar hemisphere of each side.

Serial sections in the frontal plane revealed a diffuse hydrocephalus affecting all ventricles, those of the right cerebral hemisphere being more extensively enlarged.

The pituitary showed no significant macroscopic features.

Microscopical Findings.—Diffuse increase of fibrous tissue in the leptomeninges without signs of inflammation.

Cerebral Cortex.—Nissl staining revealed generalized reduction in the number of cells according to the degree of gross atrophy of the area concerned. The loss of cells was most pronounced in the 3rd and 5th layer of the cortex. There was an increased accumulation of lipofuscin, especially in the pyramidal elements many of which cells were disorientated. There were many small areas of "dropping out" of ganglion cells. All these abnormalities, corresponding to what is generally described as senile changes of ganglion cells, were most pronounced in the frontal and occipital lobes and in the cornu Ammonis of both sides, but more especially of the right. There were similar degenerative changes in the basal ganglia and in the inferior olives.

Fig. 1.—Brain viewed from above, showing predominately wasted right cerebral hemisphere and the projecting right cerebellar hemisphere.

Fig. 2.—Brain viewed from the postero-caudal aspect showing increased relative wasting of the left cerebellum (right in the photograph) and right cerebrum.

v. Braunmühl's silver stain revealed an enormous number of senile plaques of all known sizes and types (Figs. 3, 4, 5). There were large coarse plaques with a central clear space with or without nucleus, plaques with a darkly stained nucleus and a loosely arranged outer zone, irregular patches of argentophile substance without formation of nuclei, some of them surrounding blood vessels. The plaques were seen in all layers of the cortex, being most numerous in the 3rd and 5th layer, of sparsest distribution and of the smallest calibre in the 1st. Their number was relatively greater in the right hemisphere and in the frontal and occipital lobes and in

Fig. 3.—Right frontal cortex showing numerous argentophile plaques of various types and pyramidal cells with neurofibrillary change. Some of the cells are disorientated. v. Braunmühl's silver impregnation.

Fig. 4.—Right frontal cortex showing numerous pyramidal cells with advanced neurofibrillary change and plaques. v. Braunmühl's silver impregnation.

Fig. 5.—Right frontal cortex showing numerous excrescences on the axis cylinders ("knotted canes"). v. Braunmühl's silver impregnation.

the cornua Ammonis. Numerous smaller plaques were found in the striate body and in the pallidum. There were single elliptic plaques in the white matter adjoining the cortex. The degree of cell changes described above as well as the number of the plaques was least in the cortex of the anterior and posterior central gyri.

Alzheimer's neurofibrillary change of the ganglion cells was encountered all over the cortex, most pronounced in degree and distribution in the frontal and occipital areas and in the cornua Ammonis where it was seen in nearly all pyramidal cells, least in the gyri centrales. Fig. 4 demonstrates these changes affecting mainly the pyramidal cells. The large cells of Betz in the 5th layer of the anterior central gyrus were affected to a relatively slight extent.

There were marked and unusual changes of the axis cylinders; many were swollen, the argentophile substance showing signs of granular disintegration. Most impressive, however, was the presence of numerous excrescences of the shape of knots and buds which gave the axis cylinder in longitudinal aspect the appearance of a knotted cane or walking stick (Fig. 5). Higher magnification revealed that these excrescences consisted of a homogeneous argentophile substance. The distribution of these changes corresponded with that of the plaques. They were found in small numbers in the basal ganglia and in the cerebellar cortex.

Myelin staining showed typical degenerative changes in all cortical layers and in the basal ganglia. The myelin sheaths were swollen, there were myelin balls in many places. A certain amount of diffuse demyelination appeared to have taken place in the most atrophic areas of the cortex.

The changes of the neuroglial elements were typical, according to what has been described in similar cases. There was intense gliosis, especially around the senile plaques and affecting each of the glial elements which were enormously hypertrophied and increased in number. In many places the cerebral histiocytes and microglial cells extended into the plaques.

Cerebellum.—The atrophy was diffuse and affected all tissue elements, being more pronounced in the left hemisphere and the left part of the vermis than in the corresponding parts of the opposite side. There was, however, no distinct line of demarcation corresponding to the median plane. The pathological changes consisted in a marked reduction in the number of Purkinje cells, especially at the bottom of the gyri, where, in places, they were totally absent (Fig. 6). Most of the surviving

Fig. 6.—Left cerebellar cortex showing loss of Purkinje cells at bottom of cerebellar sulci. Nissl stain.

Purkinje cells showed tigrolysis and shrinking. Silverstain revealed fusiform swelling of the dendrites and axis cylinders of many Purkinje cells. In a number of places where the Nissl stain had shown a lack of Purkinje cells empty baskets were found

Fig. 7.—Left cerebellar cortex showing “empty baskets” of Purkinje cells. v. Braunmühl's silver impregnation.

(Fig. 7). In other places the fibres of the baskets were reduced and the Purkinje cells were present.

There was a small number of argentophile plaques in the cerebellar cortex. The plaques were either of the small solid or the diffuse granular types. The glial elements, especially the astrocytes and the Hortega cells showed diffuse proliferation, more intense in the left hemisphere.

There were no marked changes in the cerebellar nuclei but there was a general cell reduction and marked lipiodosis of the remaining elements. All changes were more pronounced on the left. There was a very obvious reduction of the myelin tissue as a whole and the myelin sheaths showed changes similar to those observed in the cerebral cortex.

Medulla.—No significant changes apart from a lipiodosis of ganglion cells. There was marked diffuse gliosis and cell reduction in the inferior olives, without noticeable asymmetry.

Blood Vessels.—No gross pathological changes. Arteriosclerotic degeneration in some medium arteries; otherwise the walls of the blood vessels all over the brain were rather thinner than normal. In the cerebral and cerebellar cortex there appeared to be an increase of small vessels and capillaries, an impression obviously due to atrophy of the surrounding tissue.

There was an advanced sclerosis of the choroid plexus in all ventricles, well in accordance with the general atrophy.

Summary of the pathological findings

A remarkably small brain of 870 grm. showing diffuse cerebral and cerebellar atrophy of an unusual degree. The atrophy was of a distinctly asymmetrical character affecting the right cerebral and left cerebellar hemispheres more than the contralateral numbers. The histological examination revealed degenerative changes, i.e. diffuse and local reduction in cortical and subcortical ganglion cells, an enormous number of argentophile plaques with the proliferation of glial elements which usually accompanies the appearance of argentophile

plaques. An uncommonly high proportion of ganglion cells of the cerebral cortex showed Alzheimer's neurofibrillary change which was not found in the cerebellum. There were very marked changes of the axis cylinders in the cerebral cortex with numerous excrescences at right angles to the course of the fibres.

There were degenerative changes in the cerebellum affecting all elements but most distinctly the Purkinje cells. The number of them was considerably reduced especially at the bottom of the gyri where many "empty baskets" were demonstrated. The axis cylinders as well as the dendrites of these cells showed fusiform swelling. All changes were more marked in the left cerebellar hemisphere.

The pathological diagnosis is that of an atypical case of Alzheimer's disease, the most impressive unusual feature being an asymmetrical atrophy of crossed cerebro-cerebellar distribution.

Discussion

The clinical symptoms of the case were rather typical. The post mortem findings confirmed the assumption that the frontal lobes were strongly affected. It is difficult to decide whether the mental deterioration commencing after the birth of a first child born at the late age of 41 is a coincidence without significance, or whether child birth in this case was one of the promoting factors of the disease. However, in view of the lack of present knowledge about such factors this coincidence deserves to be noted. McMenemey (1940) recently discussed this problem.

The kind of the tissue changes, their diffuse but locally more pronounced character and the appearance of the symptoms in middle age are typical for Alzheimer's disease. The degree of the pathological changes in our case was unusual. It is, therefore, of interest that in this case a feature which has attracted less attention, obviously because it is usually little pronounced, was extremely marked, i.e. the particular condition of the axis cylinders in the cortex. It is true that buds and knots on the axis cylinders in Alzheimer's disease were variously described, but they have been usually found on axis cylinders inside and in the immediate neighbourhood of plaques. In our case, most of the axis cylinders of the cortex, both near and at some distance from plaques, showed this abnormality which was absent in areas where there were few or no plaques. The morphological character and the distribution of these changes argue against them being artefacts, i.e. possibly precipitates through the silver impregnation. They probably are the result of a pathological process affecting the argentophile nervous elements and, at the same time, responsible for the formation of the plaque. It is rather tempting to assume that the buds and knots on the axis cylinders consist of the same material as the plaques themselves. Without entering into a discussion on the ætiology of the argentophile plaques—which has been reviewed by Critchley (1929), Wilson (1940) and many others, most recently by McMenemey (1940)—we wish to point out that our case seems to support theories which postulate some process, affecting primarily

the argentophile nervous tissue, as responsible for or essential to plaque formation. Bouman (1934) spoke of a hyperdifferentiation of the argentophile nervous elements. The glial proliferation seemed in our case as in others to be of a secondary character. Our findings do not suggest an intimate relationship between plaques and vascular distribution.

The outstanding feature in the gross pathological findings was the association of an asymmetrical cerebral atrophy with a similarly asymmetrical contralateral cerebellar wasting. The selective nature of the atrophy appeared to be the result of the different degree of the degenerative processes. In our knowledge a predominating crossed cerebro-cerebellar hemiatrophy in Alzheimer's disease has not been described hitherto. Considering the well-known anatomical and functional relationship between each cerebral and the contralateral cerebellar hemisphere the distribution of the atrophy in our case must be regarded as an expression of this correlation.

We do not suppose, however, that the left cerebellar hemiatrophy was entirely secondary to the right cerebral. There certainly was evidence of cerebellar degeneration not dependent on but accompanying the cerebral atrophy. Although in most diffuse degenerative processes affecting the cerebral cortex a certain amount of co-ordinated degeneration takes place in other parts of the brain, e.g. the basal ganglia and the cerebellum, the great difference in the amount of the atrophy of the left and right cerebellar hemispheres in our case must be regarded as resulting from its functional and anatomical relationship to the right cerebral hemisphere. It seems likely that, where a diffuse and circumscribed cerebral atrophy develops slowly a certain amount of cerebellar atrophy usually ensues especially when the cerebral atrophy affects parts of the cortex intimately connected with the cerebellum. But if the cerebral atrophy is less pronounced than in our case and not markedly asymmetrical the cerebellar atrophy is symmetrical and so little obvious that it may escape notice.

As to the aetiology of the asymmetrical character of the atrophy neither the clinical history of our case nor the pathological investigations provides a clue. The following hypotheses may be considered:—

(a) The higher degree of degeneration of the right cerebral hemisphere may be the result of a longer duration of the process in that half of the brain. This process may have begun in the right hemisphere some time before it started in the left. An atrophy of the right cerebral hemisphere in a right-handed person may develop slowly for years without causing gross symptoms. Alzheimer's disease commencing in the early fourth or third decade of life or even earlier (Malamud and Loewenberg, 1929) would not be unprecedented. In our case the enormous number of plaques and of cells showing advanced neurofibrillary changes suggest that the process was of extremely long duration, possibly longer than the eighteen years covered by the clinical history. The assumption that the process began early in the right cerebral hemisphere would make the ensuing contralateral cerebellar affection understandable, a result which is more likely to follow in young individuals.

Although an atrophy of asymmetrical distribution is quite uncommon in Alzheimer's disease, it has been encountered in Pick's degeneration. Its

occurrence in our case raises the question whether Alzheimer's and Pick's disease are fundamentally as distinct from each other as they are generally assumed to be.

(b) A certain amount of crossed cerebro-cerebellar hemiatrophy may have been in existence before the process of Alzheimer's disease set in. In some cases of infantile hemiplegia resulting in cerebral hemiatrophy slowly ensuing contralateral cerebellar hemiatrophy has been found. (Wertham (1934), Wilson (1940).) That such a process took place in early childhood or even before birth without causing noticeable symptoms or scars in the brain tissue, cannot be entirely excluded.

(c) Some process acting more recently than the onset of the dementia and unconnected with Alzheimer's disease may have been responsible for the predilection of one hemisphere. Grünthal (quoted by Wertham) has reported a case in which a trauma had affected one hemisphere long before death and where post-mortem investigation revealed a greater amount of argentophile plaques in the affected side than in the other.

It is not impossible that some cerebral complication of the pregnancy and childbirth preceding the manifestation of the clinical symptoms in our case had made one cerebral hemisphere a punctum minoris resistentiae and that the rapid and extreme atrophy of this hemisphere may have been followed or been accompanied by wasting of the associated contralateral cerebellar half.

Summary

A case of Alzheimer's disease with various uncommon features has been described. The first symptoms appeared after a late pregnancy eighteen years before death. There was an extreme degree of atrophy, the weight of the brain being 870 grm. The atrophy was diffuse but asymmetrical, affecting the right cerebral and the left cerebellar hemispheres much more than the corresponding contralateral halves. There was an extreme degree of the pathological changes characteristic of Alzheimer's disease, the argentophile nervous tissue being most severely affected. The great majority of the pyramidal cells of the cerebral cortex showed Alzheimer's neurofibrillary change. The axis cylinders in the cortex had numerous excrescences. The predominance of the affection of the argentophile nervous elements in an unusually advanced case of Alzheimer's disease seems to argue in favour of the theory that the development of the argentophile plaque is due to a process affecting primarily the argentophile tissue.

The crossed cerebro-cerebellar hemiatrophy is to be regarded as partly the expression of the anatomical and functional correlation of those parts of the brain. The ætiology of the asymmetrical character of the affection has been discussed.

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