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A CASE OF ALZHEIMER'S DISEASE WITH UNUSUAL NEUROLOGICAL DISTURBANCES¹

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Our knowledge of Alzheimer's disease is still so limited as regards its symptoms, clinical differentiation and the peculiar anatomical process, which has been found in the central nervous system, that further observations should be of interest.

Clinically the case we will report developed at an unusually early age and showed during its course neurological disturbances of a type and degree not yet noted in this disease. For the clinical records we are indebted to the medical officers of the Pontiac State Hospital.

The patient was a woman who was admitted to the Pontiac State Hospital at the age of 35 and died 2 years later, in 1910.

She was a married woman with no known evidences of syphilis, and no history of illness until she was 31, when following an abortion she had a curettage of the uterus. At about 33 she began to show evidences of some nervous and mental disturbance. She would wander about the house and street quite unmindful of her surroundings. As a result of this careless wandering she was often in danger of injury. But little else was known about

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her until she came into the hospital in September, 1908. She was then in poor nutrition, but there were no serious physical disturbances, except a slight albuminuria.

She was unable to stand with feet together, even with open eyes. As she sat in a chair her feet were held stiffly together and there was hyperextension of the toes of the right foot. She walked clumsily and found it difficult to maintain an upright position. There was constant coarse tremor of both legs even while lying quietly in bed. This tremor was frequently interrupted by jerking of the legs and arms, particularly of the right side and less frequently of the head. Often single muscles or parts of muscles gave coarse twitching movements. This was particularly marked in the triceps muscles. The legs were held rigidly together and could only be separated by a considerable effort.

The speech was indistinct, slow and stammering and at times explosive. As she talked there was marked tremor of the facial muscles. The ocular movements were not impaired. The pupillary reflexes were present. The elbow and wrist jerks were increased and the tendon reflexes of the legs much exaggerated. Babinski's reflex was present in the right foot but not in the left. The right arm was in a spastic condition. Hand movements were ataxic and the result of an attempt to write her name was a scrawl in no way resembling writing.

Her mental reaction was that of one greatly demented. Only in rare instances could she comprehend what was said to her. She was able to execute a few commands. She would answer no questions concerning herself. Her moods changed rapidly; at times she would laugh in a simple way, and again cry out loudly without any apparent cause. She could not be kept in bed but wandered aimlessly about her room.

About one month after her admission she had an attack in which she fell unconscious and there were convulsive movements. After this the right side was considerably less useful than the left. As she stood with support she leaned to the right and as she sat in a chair she had to be strapped to the back or she would fall out to the right. A few weeks later another convulsion occurred; she grew more unable to control any of her movements; she was totally unable to comprehend what was said to her and she never talked.

In November, 1908, a lumbar puncture showed no pathological findings in the cerebro-spinal fluid. Several convulsions occurred during December. In June, 1909, she was continuously in bed. Her arms were rigid and flexed at the elbows. Any attempt towards active movements of the arms or legs showed great ataxia. If she were supported she tried to walk, but the legs were held stiffly, she stepped on her toes and often she stumbled from the interference of her feet.

In May, 1910, she was entirely helpless; she was continuously

in bed and great care was necessary in feeding her to avoid choking. The muscles of the arms, legs and head were rigid. The pupils were not abnormal. She swallowed slowly and with difficulty. She could not talk, but uttered strident unintelligible sounds. The knee jerks were exaggerated; the Achilles jerks were present; Babinski's reflex was obtained in both feet; there was no control of the bowel and bladder. Lumbar puncture showed 2 cells per cm. and an albumen content of about 0.02 per cent.

In August, 1910, she could not protrude the tongue which was thin but not wrinkled. Often she cried out in high pitched tones. The pharyngeal reflex could not be obtained. As she lay in bed her head was pushed back strongly against the pillow and the hair was worn off from its back. The pupils were not abnormal. The arms were contracted, the right more than the left. The muscles showed extreme wasting. The tendon reflexes were exaggerated. The legs were spastic, both flexor and extensor muscles being stretched tensely. The left foot was crossed over the right; the small toes were held in a claw-like position, the great toe being even more extended than the others. The muscles of the legs showed most extreme atrophy. It was possible to entirely enclose the thigh, at its usually thickest part, in the grasp of one hand. The patellar and Achilles jerks were present; no Babinski was now obtained; when the sole of the foot was stroked the great toes were flexed and the small toes extended. She reacted as if in pain when the skin of the legs or arms was pinched; other than this no sensory tests were possible. Several examinations of the fundus oculi showed no pathology. She progressively became weaker. Decubitus developed upon the back and shoulders and death occurred October 31, 1910.

Autopsy Findings.—The autopsy was performed 2 hours after death and showed no acute pathological conditions of the body organs. The lungs were moderately edematous. The heart was small, weighing 130 grams. The kidneys showed a moderate degree of chronic diffuse nephritis.

In removing the brain there was found to be a marked increase of the cerebro-spinal fluid. The brain together with the dura mater covering its convexity weighed 880 grams.

The material available for study consisted of the brain and spinal cord, which had been preserved in 10 per cent. formaline, and portions from several regions of the cortex, fixed in alcohol.

After several weeks' fixation in formaline, the brain was examined. The smallness of its size was very striking. Portions of the dura mater which were still attached to the brain showed nothing important. The pia mater was thickened and opaque over the frontal and parietal regions, but comparatively clear over the base and occipital regions. The larger pial veins were moderately full of blood. The consistency of the brain substance

was firmer than usual even when similarly preserved. The convolutions of the entire brain showed extreme atrophy with flaring summits and much widened sulci. In places the otherwise smooth surface of the convolution was finely pitted.

FIG. 1. Longitudinal section through hemispheres showing the extreme atrophy.

The cranial nerves so far as they were preserved were not peculiar.

The cerebellum was small and atrophic in appearance. The left lobe was smaller than the right. The basal vessels were free from sclerosis.

Longitudinal sections through the middle of the thalami showed extreme atrophy of both white and gray substance in all regions (Fig. 1). There was considerable injection of the fine cortical vessels. The lateral ventricles were widened. There were no coarse focal lesions.

The histological examination included the study of preparations from all regions of the cortex, from the cerebellum, basal ganglia, peduncles, pons, medulla and cord. A variety of methods were used including the methods for the demonstration of "Abbauvorgänge" as given by Alzheimer (1).

All regions of the cortex showed numerous plaques and the peculiar neuro-fibril alterations described by Alzheimer and others as characteristic for this disease.

The plaques in numbers exceeded those in any case we have yet studied (Fig. 2). A rough estimate of their number was obtained by the method used by Simchowicz (2), in which is taken the maximum number of plaques which can be found in the field of a Leitz Obj. No. 3 and Ocular No. 3. There thus were found in one field of the right superior parietal convolution 104 plaques. In the right anterior central 63, and in the right occipital 75. The greatest number which Simchowicz found in any senile brain were: frontal region 80, cornu ammonis 28, central cortex 22.

In their distribution through the cortex they were most numerous in the upper strata; and were numerous in the first layer of the cortex. They were found in both optic thalami, corpora striata, and were abundant in the region of the claustrum. They were present in the cerebellum, although in few numbers. In one section there were seven large plaques in one field of the $\frac{1}{2}$ objective. In size the plaques varied between 28μ and 100μ . The largest were found in the cornu ammonis.

The appearance of the plaque depends upon the method of preparation, but in the sections it was possible to find all of the characteristic details which have been described in the various contributions to this subject. As in other cases we have studied, it seems as if the earliest stages of the plaque formation showed as a focal necrosis of the tissue with loosely arranged products scattered through the area. In Herxheimer's preparations these early stages showed numerous brilliant red stained fatty particles. As the area ages the products become included in phagocytes which cluster around the area. Certain products remain in the area, and these form into a homogeneous mass which persists as

the core of the plaque and becomes excapsulated through progressive reactions in the surrounding glia.

In general it seemed as if the forms with the compact homogeneous centers were more numerous than the looser organized areas.

FIG. 2. Plaques in frontal cortex. Bielschowsky stain.

As to the primary cause of the plaques, our studies can add nothing to this obscure part of the subject.

In all sections stained by Bielschowsky's method there were nerve cells showing the peculiar thickened and looped tangles of intracellular fibrils. These showed all of the characteristic forms which have commonly been found in this disease and senile dementia. Many cells were in various stages of disintegration. In the area of the plaques there were found the clubbed and flask-shaped fibrils which were described by Fischer (3).

In Nissl preparations there was evident in all regions a considerable loss in the number of nerve cells. This loss occurred in a patch-like distribution and where cells were gone, it was usually possible to demonstrate the peculiar homogeneous substances with surrounding types of pathological cells, which by other methods appear as plaque areas. The nerve cells showed many pathological forms, many were severely changed and in a process which leads to complete destruction of the cell. In general the cells of the deeper layers were less altered. Of the various types of alteration two occurred with greatest frequency. In one type the cells were shrunken, with wavy processes and darkly stained Nissl granules and nucleus. A type of alteration resembling chronic shrinkage.

In the other type the cells were pale and swollen. The processes were faintly stained. The nucleus was pale and irregular in outline. This type of alteration seemed to lead to a fragmentation of the cell body and nucleus. Both of these types of cell change were observed by Simchowicz in his senile cases. There were numerous cells well advanced towards disintegration, the earlier stages of which could not be determined.

In Herxheimer preparations many nerve cells contained excessive amounts of fatty pigments. This was especially notable in the cells of the cornu ammonis.

Among the cellular elements of non-nervous appearance were many peculiar forms. Many of these were glia cells in various stages of progression and regression. Some were phagocytic for products of the degeneration process. Excessive amounts of fatty pigments were observed in many glia cells, even away from the neighborhood of a plaque. Rod cells were common near the plaques. There were no sclerotic changes in the vessels; some had large accumulations of fat pigments in their walls but there was no infiltration.

In the cerebellum plaques were present in the molecular layer among the granule cells, in the layer of Purkinje cells and in the white substance. The glia of the white substance was increased in amount, large spider cells were common and along the blood vessels there was a dense massing of glia fibers. In one area of the cerebellum there was rarefaction or atrophy of the nervous ele-

ments of the molecular layer, and the Purkinje cells adjacent to this were shrunken and stained differently than elsewhere. The largest number of plaques which were found in the cerebellum occurred near this area. Quite generally the Purkinje cells showed excessive amounts of fatty substances. These were

FIG. 3. Showing the degenerations of the descending cortico-spinal tracts in various levels of their course. Pal-Weigert stain.

scattered through the dendrites and marked their course for long distances from the cell body. By methods which showed the relation of the medullated fibers there were found in the cortex numerous patches in which fibers were absent; these in their outline and location marked the position of plaques. The white centers of many convolutions showed a considerable diminution in the number of fibers.

In neuroglia preparations it was found that there was in places an increase in the density and thickness of the glia feltwork in the upper part of the first cortical layer. Sometimes this showed a ragged free edge which projected towards the pia.

One of the most important features of the present case is the striking degeneration which was found in the pyramidal tract. This was traceable from the peduncles into the lower sacral regions of the cord (Fig. 3).

Sections through the internal capsule on one side showed by the Weigert-Pal method a small area of slight paleness in the anterior part of the posterior limb. On the opposite side the capsule showed no certain degeneration.

In the peduncles the degeneration was about equal on the

FIG. 4. Sixth cervical segment of spinal cord; showing the degeneration of the cortico-spinal tracts and the degeneration in the ventral field of the lateral columns.

two sides and appeared as a distinct paleness of the segment in which the pyramidal fibers course.

In the pons there was considerable loss of pyramidal fibers. Both pyramidal bundles in the medulla were pale and at the level of the decussation the degeneration was particularly distinct.

The cord showed pronounced degeneration in both ventral and lateral columns and a slight paleness of Goll's column. The areas of degeneration were most striking in sections through the cervical region. In a section through C VI (Fig. 4) the degeneration was present in a broad strip bordering the ventral fissure, somewhat wider on one side than on the other.

In the lateral column the degeneration included the area of the crossed pyramidal fibers and in addition it extended ventrally through the lateral column becoming more narrow and opposite the lateral tip of the ventral horn, curved toward the margin of the cord and faded away in a paleness which bordered the ventro-lateral margin of the cord. This ventral extension took in the area occupied by Monakow's bundle and in addition involved other fibers the nature of which is not certain. The dorsal columns showed slight paleness of Goll's column.

The mid-thoracic sections showed prominent ventral column degeneration and in the lateral columns the degeneration was confined to the pyramidal tract.

The lower thoracic sections showed well-marked degeneration of the lateral columns and a strip of paleness extended along the ventral and lateral margins. The importance of this marginal degeneration and a slight paleness of Goll's column are less certain. In sections from L I, L III and S IV the degeneration was almost entirely limited to the lateral columns.

The degeneration in the ventral and lateral regions was still active and all through the area there were scattered epithelioid cells with inclusions of fatty substances. There were no demonstrable changes of the gray matter of medulla or cord. In the medulla the nucleus of the twelfth nerve contained an abundance of well stained fibers and the nerve cells showed no certain pathological changes.

In sections from a number of regions there were intraspinal parts of the ventral roots. These were in all instances well stained and showed no diminution in their number of fibers. Throughout the cord, the number of cells present in the ventral horns was within normal limits and the cells showed well preserved Nissl granules and no alteration of form. The only change that was demonstrable was a rather large amount of pigment in the cells.

The anatomical findings which we have here given in detail, offer an interesting explanation of the clinical symptoms which were present during the course of the disease. At no time during life was the diagnosis satisfactorily clear.

The combination of the mental disturbances with the striking neurological symptoms suggested general paralysis. Against this

was the unusual character of the neurological disturbances, the lack of pupillary involvement and the negative findings in the cerebro-spinal fluid. As the paralysis and spasticity progressed and the bulbar disturbance and atrophy became prominent, the clinical picture resembled amyotrophic lateral sclerosis with unusual prominence of the cerebral involvement and this diagnosis was generally held until death.

In the study of this case two particularly interesting features are present. These are the early age at which the disease occurred, and the unusual and dominating character of the neurological disturbances. Alzheimer's disease has always been described as a disease of the presenile period. The condition takes its name from Alzheimer (4) who in 1906 reported upon certain peculiar changes in the cortex of a case of mental disorder occurring in the presenile period.

In the years following his report, plaques similar to those he described and frequently the neurofibril alterations were observed in the brains of seniles, and a number of contributions appeared dealing with the relation of these changes to senile dementia. From all that has thus far been ascertained it seems that this peculiar process, at least the occurrence of the plaques, in the central nervous system bears an important relation to the pathology of senile dementia, and there is much to justify the conclusions of Simchowicz that "the cases in which these are entirely absent belong to some other form of disease."

Among the considerable number of reports upon cases in which plaques and neurofibril changes occurred, there are some which have been observed in adult years, but mostly in a period usually designated as presenile, and clinically and anatomically have corresponded to the type described by Alzheimer.

Spielmeyer (5) in his recent review of the senile diseases of the central nervous system differentiates Alzheimer's disease to include those cases which vary from the usual type of senile dementia, in that they occur before the true senium and develop a severe dementia accompanied by focal symptoms of aphasic and asymbolic type.

The ages of onset of all of the cases which have been reported as cases of Alzheimer's disease have been Alzheimer (1) 51, Perusini (6) 40, 60, 63, Barrett (7) 50, Bielschowsky (8) 58,

Alzheimer (9) 54, Schnitzler (10) 31, Sarteschi (11) 64, Lafora (12) 57, Janssens (13) 55, Fuller (14) 54. All of these have shown much that is common in the clinical symptomatology and excepting the case recently reported by Schnitzler (10) a common histopathological process. In Schnitzler's case, which occurred at the age of 31, there were no plaques but the neurofibril alterations were characteristic.

The circumstance that there seems to be no difference in the character of the plaques and neurofibril alterations between these presenile and the truly senile cases, excepting in the intensity of the process, and that there also occur in each similar changes in the neuroglia of the marginal layer, and the accumulation of lipoid substances in the nerve cells, glia cells, and blood vessels has led to the explanation, that these early cases are prematurely senile and that senility is not essentially a matter of years but of tissue aging. It has become difficult to limit disease processes by age periods, and Alzheimer comments that "anatomical investigation has taught us that progressive paralysis may occur as late as the 70th year and the pathological process of senility as early as the 40th year."

Whether or not one is justified in extending still further forward the limits of presenility to include the case we have reported as developing at 33 is questionable. This same question is raised by Schnitzler, in regard to his case which occurred at 31. He, however, attempts to get around this difficulty by the circumstance that his case showed an enlarged thyroid and the physical appearance of myxedema, and compares the similarity in appearance of the physical and mental involution which occurs from thyroid disease and senility and suggests that the thyrogenic disturbance furnishes a basis, comparable with that present in senility, for the production of the characteristic histological process.

In the present case, there was no disease of the thyroid gland and the physical appearance in no way suggested this. The outward appearance of the woman was not senile, but rather that which one sees in unusually severe organic diseases of the central nervous system.

At the present time it seems impossible to state more regarding the clinical position of this case, than that it shows as far as age

is concerned that Alzheimer's disease is not confined to presenile years.

A characteristic feature of Alzheimer's disease are the focal symptoms. In all cases reported, symptoms referable to localized lesions in the central nervous system have been observed. In most instances there have been convulsions, or aphasic and apraxic disturbances.

In no case was there marked paralysis, but in two instances, the case of Schnitzler (10) and Alzheimer (9), there was lateral column degeneration, and in Perusini's case IV (6), which was complicated with syphilis, there was both posterior and lateral column degeneration.

In no other case has there been such a degree of paralysis and bulbar disturbances and such atrophy as the case here reported.

The clinical resemblances of the symptoms to those of amyotrophic lateral sclerosis are interesting and although the anatomical studies did not show any degeneration of the gray substances of medulla or cord, the peculiar type of the fiber degeneration was that of this disease, namely, in the lateral columns of the cervical region the degeneration extended beyond the limits of the pyramidal tract.

The findings in the brain offer a satisfactory explanation of the cord degeneration and one may look upon these as secondary to the extreme degeneration of the nervous elements of the cortex which involved motor as well as all other cortical areas. The process which caused the degeneration was the characteristic one of Alzheimer's disease.

The muscular atrophy which clinically was so well marked, was probably of cerebral origin. Not infrequently an atrophy, rarely so widely distributed as in this case, has been noted in cerebral lesions; and may, as v. Monakow (15) suggests, be due to extensive loss of sensory and motor impulses to the muscles.

Cortical alterations are not uncommon in amyotrophic lateral sclerosis and in some instances the degeneration of the pyramidal tract has been traced into the motor cortex. But the nature of the process which produced the degeneration has not as yet been described. We find, however, that much the same type of descending fiber degeneration may be produced by Alzheimer's disease.

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