Non-specific familial presenile dementia¹

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The familial incidence of some forms of presenile dementia is well established. In addition to the clearly defined role of heredity in Huntington's chorea there have been familial studies of Pick's disease (Grunthal, 1930), Alzheimer's disease (Wheelan, 1959), Wilson's disease (Bearn, 1960), Jakob-Creutzfeldt disease (Davison and Rabiner, 1940), and the amyotrophic lateral sclerosis/Parkinson-dementia complex of Guam (Plato, Reed, Elizan, and Kurland, 1968).

We have studied a patient with presenile dementia whose brain at biopsy and necropsy resembled those described in Kraepelin's disease, a familial presenile dementia with non-specific changes in the central nervous system. On examination of the family, it was found that there were five other involved members, four of them in one generation.

This paper is a report of our case—and the family; and a critical review of the pathological entity, Kraepelin's disease.

CASE REPORTS

CASE 1 S.M., a 31-year-old, white male, was in good health until three years ago when his wife noticed that he seemed very slow in understanding new tasks. He would occasionally lose his way on simple errands and began having difficulty in calculations. One year before admission he refused to drive the car, and six months before admission he became moody and withdrawn. Psychiatric consultation provided a diagnosis of schizophrenia, but a two-week course of chlorpromazine produced no change. He was referred to the Bronx Municipal Hospital for electroconvulsive therapy. There were no hallucinations, delusions, or seizures in the present illness. The past history was unremarkable and he had no previous hospitalizations. The family tree is shown in Figure 1. General physical examination revealed a blood pressure of 120/85 and no other abnormal physical signs apart from the neurological findings. The patient was alert, cooperative, and oriented to time, place, and person. His recent memory was markedly impaired, and simple calculations were done poorly. There was striking right-left disorientation and

and constructional apraxia. The cranial nerves and motor system were normal. His coordination was good. The tendon reflexes were equal and active, and the plantar responses were flexor.

Urine analysis, haemogram, and a serological test for syphilis were normal. The cerebrospinal fluid had no cells and a protein level of 22 mg/100 ml. An EEG showed a low voltage record with a dominant frequency of 7 c/s, with some 3-5 c/s activity in the left temporal leads. A pneumoencephalogram showed moderate symmetrical dilatation of the lateral ventricles with associated widening of the cortical sulci.

In the ensuing year the patient's dementia progressed while under observation on the ward. His gait was slow and unsteady. However, motor examination showed no weakness or deficit attributable to cerebellar disease.

On 10 October 1962 the patient underwent a right frontal craniotomy with removal of 300 mg of the middle frontal lobe for biopsy. The patient recovered uneventfully from the operation, and appeared to have no neurological sequelae. In the ensuing year his mental state continued to deteriorate steadily. He remained ambulatory but had to be led about the ward by a nurse. He was transferred to a mental hospital on 18 March 1963.

After two months at the mental hospital he became uncommunicative and refused to walk. He required chlorpromazine 150 mg t.i.d. for intermittent agitation. On 24 July 1964 he was transferred back to the Bronx

FIG 1. Genetic chart.

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Municipal Hospital. On readmission he was mute, would visually follow objects, and had to be constantly restrained from putting things in his mouth. During the remaining 20 months of his hospital stay he remained neurologically unchanged. He required suprapubic cystostomy following urinary tract infections, and tracheostomy following bronchopneumonia. He died on 3 March 1966 at the age of 36. Post-mortem examination was performed.

FIG. 2. Biopsy specimen of the right frontal cortex. Note depopulation of cortical neurones, which is more severe in the deeper layers. Nissl stain, $\times 40$.

FIG. 3. Shrunken degenerative neurones in the sixth layer of the right frontal cortex. Nissl stain, $\times 400$.

TISSUE LABORATORY DATA *Biopsy chemical studies* The microsomal fraction was separated from a portion of the biopsy and incubated with C^{14} labelled lysine to study the rate of protein synthesis (Suzuki, Korey, and Terry, 1964). There was no observable difference in the activity of the patient's tissues when compared with normal specimens and with a specimen from a patient with Alzheimer's disease.

Biopsy microscopic findings The Nissl and haematoxylin and eosin preparations confirmed the presence of cortical atrophy. The total thickness of cortex was about one-third of normal, and the neuronal population was markedly decreased. All six layers were involved, but the sixth layer was most severely affected (Fig. 2). Many neurones were of normal size and shape, but occasionally shrunken or vacuolated neurones were seen (Fig. 3). The PAS stain showed large quantities of intraneuronal lipofuscin as well as moderately small deposits along vessels. A Bodian preparation showed normal axons throughout. A single neurone showed a moderate increase in the number and coarseness of neurofibrils, but they were not tangled. Senile plaques were not found. Moderate gliosis was seen in the molecular layer and in the subcortical white matter.

Biopsy electron microscopic findings For electron microscopic study, small pieces of tissue were fixed in Palade's veronal-buffered osmium with sucrose, dehydrated in alcohol, and embedded in Methacrylate, Epon, and Araldite. Thin sections were stained with lead hydroxide and uranyl acetate. The electron micrographs were taken with a Siemens Elmiskop 1.

In the cortex as well as the white matter, many degenerated cell processes were seen. Many axons and dendrites were enlarged and contained numbers of round and ovoid, dense bodies. Some of these bodies had electron-dense homogeneous central cores surrounded by thin membrane layers, and others were made up only of many concentric lamellae. Their size varied from $0.3-0.7\mu$ in diameter (Fig. 4). Interspaced among them were many small vesicles of $0.1-0.3\mu$ in diameter, neurofilaments, and mitochondria. These dense bodies were more commonly seen in unmyelinated processes than myelinated axons. Also noted in the unmyelinated processes were many single membrane-bound irregular clear spaces (Fig. 5), loosely formed myelin figures, and fragments of thin irregular membranous structures. Some of the myelin sheaths were distended and surrounded a large, clear vacuole in which remnants of degenerated axon were occasionally seen. Degeneration of myelin sheaths with or without associated axonal degeneration was also frequently encountered. The neuropil was generally compact and well formed. Gliosis appeared very slight in degree.

Neuronal perikarya contained large numbers of lipofuscin bodies. The endoplasmic reticulum and outer nuclear membranes were occasionally dilated, and were studded with ribosomes which were found free or forming small clusters in the neuronal perikarya. Irregularly shaped, small, cystic structures were sometimes encountered in the neuronal perikarya (Fig. 6), but the majority of the neurones were unremarkable.

The astrocytic cytoplasm was electron lucent, and

contained many lipid bodies composed of two parts: highly electron dense homogeneous parts, and moderately electron dense pale parts containing many vesicles. Glial fibres were prominent in the cytoplasm. Phagocytized myelin was occasionally seen. Some of the oligodendroglia contained dense homogeneous lipid bodies.

NECROPSY FINDINGS Significant findings in the general necropsy included; cachexia (body weight of 80 lb.), brown atrophy of the heart (150 g), chronic pyelonephritis, and patchy bronchopneumonia.

The brain weighed 1,000 g. The cerebral dura and superior longitudinal sinus were unremarkable. The leptomeninges were slightly thickened and opaque over

the convexity. On the lateral aspect of the right frontal lobe there was a 2×2 cm defect resulting from the biopsy. There was no adhesion between this defect and the overlying dura. The left hemisphere was frozen for chemical studies. The right hemisphere showed marked atrophy of the frontal and anterior parietal lobes, which was most striking on the medial aspect of the brain. The temporal and occipital lobes appeared grossly normal. The cerebellum, on sagittal section of the vermis, showed obvious gyral atrophy. The spinal cord and its meningeal coverings appeared normal. Coronal section of the brain revealed a cortical ribbon which was severely shrunken in all lobes, including the occipital (Fig. 7). The white matter was firm and somewhat reduced in size. The lateral ventricle was greatly dilated.

FIG. 4. A degenerative neuronal process containing many dense bodies, $\times 14,000$.

FIG. 5. Electron micrographs of a portion of the cortical neurone containing lipofuscin bodies and irregular loose membranous structures, $\times 7,000$.

FIG. 6. A degenerative neuronal process in which an irregular cystic space is evident, $\times 16,000$.

FIG. 7. Coronal sections of the right cerebral hemisphere. Note marked thinning of the cortex. The head of the caudate nucleus is flattened. Arrow indicates the site of previous biopsy.

The basal ganglia were flattened, especially the head of the caudate. The thalamus was smaller than normal, but the substantia nigra was well pigmented. The cerebral peduncles and both pyramids appeared smaller than usual. The atrophy of the cerebellar vermis was confirmed and, in the hemisphere, folia occasionally appeared small and atrophied.

On microscopic examination the cerebral cortex was shrunken to a thickness of about a third to a half of normal, and there was marked distortion of cortical architecture due to loss of neurones and an increased number of microglial cells (Fig. 8). A majority of the remaining cortical neurones showed degenerating changes. Some were shrunken with finely vacuolated cytoplasm, and small, pyknotic nuclei. Others showed chromatolytic changes with swollen, watery-clear cytoplasm, and pyknotic or clear nuclei in which clumping of nuclear chromatin was prominent. The Nissl substance was inconspicuous in these neurones, even in the large pyramidal neurones (Fig. 9). There was an excessive accumulation of lipofuscin pigments in the neuronal cytoplasm for the patient's age (Fig. 10). Only a few of the neurones had any demonstrable neurofibrils in Bodian preparations. Coarse intraneuronal neurofibrils were only rarely seen. Some neuronal satellitosis was seen in the deep layers of the cortex, but neuronophagia was not found. In spite of the severe loss of neuronal elements, astrocytic reaction was minimal in the cerebral cortex. Senile plaques, neurofibrillary tangles, and Pick bodies were not present anywhere in the sections examined.

There was a moderate degree of diffuse demyelination noted in the centrum semiovale, particularly in the frontal region. Here axons were less compact and mildly fragmented. Many oligodendroglia appeared to have clear, swollen cytoplasm, and often lined up along the blood vessels. Occasionally, brown, coarse, pigment granules were noted around the vessels in the white matter. Some of them were in the macrophages but others appeared to be in the pericytes. Sudan IV revealed no demonstrable neutral fat in the white matter except for a small amount around the vessels. Similar neuronal degenerative changes were also noted in Ammon's horn but far less in degree. The neurones of the fasciculus dentatus, on the contrary, showed marked chromatolytic changes. Their cytoplasm was swollen and watery-clear, but the nuclear changes were not conspicuous (Fig. 11). Severe degenerating neuronal changes, either shrinkage or lysis, were seen in the subthalamic nucleus and both medial and lateral thalamic nuclei. Abundant neuronal lipofuscin pigment was seen in the neurones of the basal ganglia also.

Examination of the cerebellum showed moderate thinning of the molecular layer of the superior vermis. Degenerative changes were also observed in Purkinje cells. The neurones of dentate nuclei showed only minimal degenerative changes. The neurones of the substantia nigra and locus ceruleus were unremarkable. Vacuolation of neuronal cytoplasm, shrinkage, and central chromatolysis were seen in many neurones of the brain stem. This was prominent in the nucleus gracilis and to a lesser degree in the nucleus cuneatus, ambiguus,

FIG. 8. Necropsy specimen of the right frontal cortex. Cortical architecture is markedly disorganized due to depopulation of neurones. Nissl stain, $\times 40$.

FIG. 9. Shrunken cortical neurones with inconspicuous degenerating nucleus. Nissl stain, $\times 400$.

and the anterior and lateral horn cells of the spinal cord.

The peripheral nerve taken from the left lumbar plexus revealed a minimal degree of irregular axonal degeneration and demyelination. The sections of iliopsoas muscle showed severe atrophy of muscle fibres, consistent with disuse and mild neurogenic atrophy.

CASE 2 The patient, S.F., was born in Russia and came to the United States at the age of 20. His parents both died accidentally and there was no known history of mental disease in the family. He was of above average intelligence and owned his own grocery store. There was no history of alcoholism or syphilis.

FIG. 10. Excessive accumulation of lipofuscin pigment in the cortical neurones. PAS stain, $\times 400$.

FIG. 11. Swollen neurones of the fascicula dentata. H. and E., $\times 120$.

When he was 44 he started to forget his friends' names and had difficulty in recalling details of business. In the following two years his dementia slowly progressed. On admission to the hospital the general physical examination was unremarkable. On neurological examination he was found to be dull, apathetic, and disoriented for time and place. His recent memory was very poor and remote memory was only slightly better. He was unable to do simple calculations. There were no delusions, hallucinations, or suicidal ideas. The remainder of the neurological examination was unremarkable. Examination of the cerebrospinal fluid showed no cells and a normal protein content. During his hospitalization he showed no further mental deterioration, and after one year became mute and confined to bed. Neurological examination at that time showed no focal findings or pathological reflexes. He became progressively weaker, and died on 22 April 1932, at the age of 47. No necropsy was performed. The clinical diagnosis was organic psychosis of unknown cause.

CASE 3 The patient, B.L., was born in the U.S. She had a normal adolescence and graduated from high school and business college. She assisted her mother in the grocery store until her marriage at the age of 20. She was described as a pleasant, extroverted person who had many suitors. In the first nine years of her marriage she had two uneventful pregnancies. At the age of 30 she became intermittently confused and apathetic. In the ensuing year her husband noticed a progressive memory loss and a lack of concern over her personal appearance. One year later she became pregnant. She was seen in a prenatal clinic and was thought to be mentally deficient. After the delivery of a full-term, normal infant the patient became agitated and confused. She was admitted to Bellevue Hospital on 19 August 1944. The general physical examination was within normal limits. Neurological examination revealed disorientation for time and place and severe impairment of recent memory. She was unable to do simple calculations. There were no hallucinations, delusions, or bizarre thoughts. The remainder of the neurological examination was unremarkable. A diagnosis of catatonic schizophrenia was made and she was transferred to a mental hospital. Shortly after admission she became mute and confined to bed. She died one year later aged 33, following a febrile illness. Necropsy was not performed.

CASE 4 The patient, A.F., was born in the U.S. He attended high school and after graduation worked as a salesman in a department store. He married twice, but both marriages ended in divorce. At the time of his second divorce, at the age of 44, it was noted that he seemed not to remember many of the details of the previous year. He lost his job after the divorce because he was unable to remember items from the catalogue. In the following year his memory deficit progressed. He appeared confused and agitated most of the time and was admitted to Bellevue Hospital. On admission the results of his general physical examination were normal. On neurological examination he showed confusion, disorientation for time and place, and was

euphoric during the examination. His affect was inappropriate and he had impaired memory and inability to calculate. The remainder of the neurological examination was unremarkable. Cerebrospinal fluid showed no cells and a normal protein content. A brain biopsy showed decrease in the neuronal population with moderate proliferation of astrocytes. No senile plaques or neurofibrillary tangles were seen. Following the brain biopsy the patient was unchanged. He survived for two years in a mental hospital, becoming progressively withdrawn and immobile. He died in April 1952 at the age of 48. A necropsy was performed.

Necropsy findings The general pathological examination showed chronic pyelonephritis and bronchial pneumonia. The brain was small and showed diffuse atrophy, most prominent in the fronto-temporal areas. There was also moderate cerebellar atrophy. The blood vessels and meninges were intact. Sections of the cortical tissue were examined by the authors, and moderate diffuse neuronal loss was seen in all layers. A slight increase in astrocytes was seen in the cortex. Minimal diffuse demyelination was seen in the subcortical white matter. Bodian stains failed to reveal neurofibrillary tangles or senile plaques.

CASE 5 The patient, J.F., was born in the U.S. and had an uneventful early life. He graduated from high school and worked as a salesman. He married in 1930 and had one child. In 1939, at the age of 31, he began to show unusual behaviour, was forgetful, and had to stop working. After two years he was no longer able to leave the house unattended. He was admitted to Brooklyn Jewish Hospital. Results of the general physical examination were normal. On neurological examination he showed dyslexia and agraphia. There was a profound recent memory loss and a mild receptive aphasia. The remainder of the neurological examination was unremarkable. The cerebrospinal fluid had no cells and a normal protein. A pneumoencephalogram showed moderate, generalized ventricular dilatation with increased air over the sulci. There was striking atrophy in the area of the left angular gyrus. He was transferred to a mental hospital where he survived for four more years. During that time he continued to deteriorate. He died on 20 March 1944, aged 36. A necropsy was performed.

Necropsy findings At necropsy there were patchy areas of pneumonitis, in both lungs. On gross examination the brain showed diffuse atrophy, most striking in the frontal and parietal lobes. No microscopic sections were taken.

CASE 6 The patient, Sa.M., was born in the U.S. and had an eventful early life. Shortly after graduation from high school she married a clerk. They had two children. The first (S.M.) was born two years after the marriage, the second was born in the fourth year. At the age of 29 the patient was observed to be unable to perform complex tasks and her housework became slovenly. In the ensuing year she developed a progressive memory loss and got lost in her own neighbourhood. On admission to Bellevue Hospital results of the general physical examination were normal. Neurological examination

showed memory loss, disorientation for place and time, and a short attention span. The remainder of the neurological examination was unremarkable. She was transferred to a mental hospital where she was noted to become progressively withdrawn and mute. A diagnosis of catatonic schizophrenia was made, although the psychologist felt she also had an organic mental syndrome. There were no hallucinations, delusions, or bizarre ideation. She died on 28 December 1941 of septicaemia, at the age of 33. Necropsy was not carried out.

DISCUSSION

We have described a family in which six members have died with presenile dementia. None had focal neurological findings, seizures, or a history of alcoholism. The onset of the illness in four of the cases was at a very early age—28, 31, 33, and 34.

There is nothing in the history of any case to suggest arteriosclerotic involvement of the nervous system. A review of the histories of the individual members discloses the clinical picture that is associated with presenile dementia. In none of the cases was it known that there was any family history of dementia. These individuals all died at different times and in different state institutions. There was virtually no communication between individual family members. This is an important consideration in evaluating isolated cases of presenile dementia in the literature who are said to have negative family histories.

The gross pathology in the cases of S.M., A.F. and J.F. was similar. There was atrophy of the lobes of the brain, especially pronounced over frontal, temporal, and parietal areas. Microscopic examination revealed a loss of neurones in all layers of the cortex (S.M., A.F.) with many remaining neurones showing pyknotic nuclei and loss of Nissl substance. There was very slight glial proliferation. The white matter showed diffuse demyelination. In the case of S.M. these changes were also seen in the basal ganglia, cerebellum, brain stem nuclei, and spinal cord grey matter. On careful search no infarcts, neurofibrillary tangles, senile plaques, Pick's cells or any other inclusion bodies were seen. The blood vessels had only minimal arteriosclerotic changes.

Electron microscopic findings of the biopsy sections of S.M. were those of severe degeneration of the axons and dendrites with myelin degeneration, probably secondary to the degeneration of the cortical neurones. Neuronal changes were not as striking but there was an accumulation of lipofuscin bodies in the perikarya. These results may be due to the limited material available for examination. Such degenerative changes have been seen in Alzheimer's disease (Terry, Gonatas, and Weiss,

1964), and Jakob-Creutzfeldt disease (Gonatas, Terry and Weiss, 1965) in addition to the characteristic findings, and also have been seen in the brain of the mice infected with scrapie virus (Field and Raine, 1964). Therefore, these changes are non-specific. Considering the four-year duration of the dementia in both cases, the diffuseness of the pathology, and lack of plaques, gliosis, or neurofibrillary tangles, Alzheimer's disease or Pick's disease seem unlikely. The absence of extrapyramidal disorders and seizures, the chronicity of the disease, and the lack of glial hyperplasia eliminate Jakob-Creutzfeldt disease. Therefore, a diagnosis of non-specific cortical degeneration was made. Representative sections were examined by Dr. R. D. Terry and Dr. N. Malamud who both felt it probably represented an unclassified dementia.

Isolated cases of unclassified dementias have been reported, but in most instances they have had pathologies that were strikingly different from our cases and were not familial. A recent case reported by Torack (1966) showed neuronal loss with no plaques or tangles, and on light microscopy, was similar to our case. On electron micrographs he found, in the neuronal cytoplasm, saccules filled with a homogeneous material of low density. These saccules communicated directly with the cisternae of the endoplasmic reticulum. The material frequently appeared to be incorporated into lipofuscin bodies. He felt that the accumulation of the lipid material was secondary to abnormal protein synthesis. A careful search of the electron micrographs of S.M. failed to reveal such a low electron dense lipid material in connection with endoplasmic reticulum, although, lipofuscin bodies having both granular and low electron dense components were abundant in the neuronal cytoplasm. Moreover, the protein metabolism studies in S.M. were unremarkable.

Kraepelin's disease, a hereditary presenile dementia, is pathologically similar to that in our family. There have been 17 cases in the world literature. It was first described as a form of presenile dementia characterized by anxiety, confusion, memory loss, and catatonia (Grunthal, 1930). The pathology of the original three cases was a loss of neurones with severe destruction of the Nissl substance, usually distributed in a patchy fashion over the cortex. The father of one of the patients was known to be insane. Twelve more cases were reported by Grunthal and Kuhn (1959). The common feature of all their cases was the pathological picture of the disease, which they considered distinctive. This included an involvement of the cortical neurones with pyknosis and shrinkage of the cells of the outer three layers and pallor of the neurones of the lower three layers. In all layers

there was some evidence of Nissl-type cell breakdown. There was no atrophy of the cortex in any case, and the glial proliferation was minimal. Occasionally the cells of the striatum and cerebellum were involved. Neurofibrillary tangles and senile plaques were not seen. Although Grunthal and Kuhn (1959) considered the pathological picture to be distinct, it seems to us to be non-specific. Many of these changes are seen following anoxic states of various aetiologies, and other non-specific metabolic illnesses with neurological manifestations (alcoholism, epilepsy, hypoglycaemia, etc.).

In five of the cases the patients were retarded from the first year of life. Three of the cases with adult onset underwent electroconvulsive and sleep therapy. One of these had a well-documented anoxic episode due to aspiration of vomitus. Another case was a congenital deaf mute whose intelligence was never assessed, and the final case was an alcoholic who entered with an acute delirious illness that persisted for five months. One case with myoclonic seizures and dementia was strongly suggestive of Jakob-Creutzfeldt's disease both clinically and pathologically.

In summary, there are objections to 11 of the 12 cases cited as typical of Kraepelin's disease. In each of the 11 cases there is plausible cause for the pathological changes cited. The only case which seems free of other contaminating features is Case 2, that of the 47-year-old woman who developed a manic illness followed by dementia. At necropsy, no evidence of glial proliferation was found. In addition, there was a strong family history of mental illness, two sisters were withdrawn, two brothers were schizophrenic, and another brother committed suicide as did an aunt. This case closely resembles the present family both pathologically and clinically.

It is difficult to categorize all the cases collected by Grunthal as a specific disease entity, after a close scrutiny of the clinical material in which so many factors are at work. McMenemy (1963) has stated 'the infrequency with which the disease has been reported, its variable duration and the fact that the nerve cell changes, genuine although they may appear to be, are unassociated with any significant changes in the glia renders this condition as a pathological entity still *sub judice*'. We agree with this statement, and feel further that there seems inadequate justification for assigning it an eponym.

SUMMARY

We have described a family with presenile dementia. The pathology was that of a non-specific cortical degeneration with no atypical features present

either on light or electron microscopy. Studies of protein metabolism were normal in the case investigated.

A review of the literature failed to find a disease identical with our cases, although the pathology of Kraepelin's disease is very similar. However, an evaluation of the available case reports fail to justify the existence of Kraepelin's disease as a distinct entity.

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