Familial cerebral amyloidosis and spongiform encephalopathy

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SUMMARY Clinical and neuropathological investigations are presented of the “W” family in which there is a dominant inheritance of slowly progressive cerebellar ataxia and dementia. The disease is of insidious onset and its average duration more than 4 years. Pathological findings included amyloid deposition in cerebellar and cerebral tissue; vascular amyloid in one case; and spongiform encephalopathy and astrocytic hyperplasia typical of Creutzfeldt-Jakob disease. Neuritic plaques of the senile (Alzheimer) type were present to a lesser extent. This study confirms the familial association between cerebral amyloidosis and spongiform encephalopathy.

Progressive neurological disorders with dementia known to have an hereditary basis include Alzheimer’s disease particularly in its atypical forms and Creutzfeldt-Jakob disease (CJD). In an analysis of many families with CJD it was estimated that more than 15% of cases occurred within families in which two or more members were affected. Since CJD has been transmitted by intracerebral inoculation into susceptible animals the relationship between heredity and infectivity poses considerable problems.

In this paper we present the clinical histories and neuropathological findings in four members of the “W” family of which 23 members in seven generations (fig 1) were affected by a progressive neurological disease usually with dementia. The family’s origins are in Bedfordshire, England and seven generations were traced back to 1791 by Cameron and Crawford, though no details of the five earliest affected members are available. The disease has affected both males and females and has been transmitted by both males and females. The pattern of inheritance is thus consistent with transmission by an autosomal dominant gene of complete penetrance. The morphological features of the brains of these four cases include spongiform encephalopathy, amyloid and astrocytic hyperplasia—characteristics of CJD. One other member (JW) of this family had emigrated to the USA and developed CJD. Inoculation of cerebral tissue from this case into non-human primates transmitted an encephalopathy.

Clinical histories

Case 1 JM. Male, born 1912. Fifth generation, III—25 in the pedigree of Rosenthal et al. In 1972 he began to have difficulty in remembering. In 1973 examination showed little abnormality except brisk reflexes with flexor plantar responses and psychometric testing revealed generalised intellectual impairment. The EEG record was described as “poorly organised”. Examination of cerebrospinal fluid and haematological investigations gave normal results. Air encephalography showed enlarged ventricles particularly of the frontal horns. Intellectual functions deteriorated and he died in 1975. Postmortem examination showed terminal pneumonia and it was noted that the cardiovascular system was virtually free of atheroma. The brain and spinal cord were received at the National Hospital after fixation.

Case 2 JJ. Female, born 1920. Fifth generation, III—38 in the pedigree of Rosenthal et al. Until 1970 this patient was well except for a right-sided below-knee amputation for osteomyelitis at age 9. At the age of 50 yr she began to experience difficulty in walking and within 2 years was admitted to hospital unable to get out of bed or walk without assistance. She was severely depressed and withdrawn, forgetful and confused, neglectful of personal hygiene and doubly incontinent. On examination she was demented with slurring of speech, a flaccid hemiparesis and hypotonia of both arms. By 1973 she was debilitated, mute, unresponsive and totally bedridden. Pupils were
dilated and reacted sluggishly to light and left disc pallor was noted. There was no nystagmus. She died of bronchopneumonia 3 years after the onset of her illness. The post-mortem examination was done at the National Hospital (Professor Blackwood).

**Case 3** EU. Female, born 1914. Fifth generation, III—50 in the pedigree of Rosenthal et al. She was well until 1971 when she became unsteady on her feet, had numerous falls and sustained minor injuries. In 1972 she was noted to be depressed but without abnormal physical signs. Within a year her unsteadiness was worse, she had difficulty in climbing stairs, was tearful and slept poorly. Examination showed dysarthria, an immobile face with a positive jaw jerk and a left hemiparesis with a left extensor plantar response. By 1974 she was confined to a wheelchair because of progressive weakness and ataxia and her handwriting was illegible. Her final admission to hospital was in 1975 by which time she was withdrawn, confused, disoriented and doubly incontinent. There was no spontaneous speech and mixed dysphasia was noted. Marked weakness of both lower limbs was present with absent deep tendon reflexes and bilateral extensor plantar responses. Investigations which gave normal results included ESR, urea and electrolytes, liver function tests, B12, folate, chest and skull radiographs and WR. Haemoglobin was 17 g/dl, white cell count raised at 17 000/mm³ with a normal differential, a random blood glucose 100 mg/dl and fasting cholesterol 380 mg/dl. She died in January 1976, 5 years after the appearance of symptoms. Postmortem examination (Professor Blackwood) showed bronchopneumonia, pulmonary infarcts and calf vein thrombosis. The viscera were macroscopically normal but no sections were available for histological examination. The brain was divided mid-sagittally, the left half deep frozen and subsequently samples of this were inoculated intracerebrally into laboratory animals at the National Institutes of Health, Bethesda, USA. To date no inoculated animals have developed encephalopathy but they are still under observation (Gajdusek, personal communication).

**Case 4** JC. Female, born 1934. Sixth generation, IV—58 in pedigree of Rosenthal et al. Formerly a theatre sister. Her first symptoms appeared in spring 1974 and consisted of paraesthesiae in both thighs and difficulty in running. Subsequently her gait became more unsteady with occasional falls when turning round. In 1975 she developed intermittent diplopia on near vision, slurring of speech and clumsiness of fine movements involved in sewing and writing. She would also be woken at night with painful cramps in the limbs. On examination in March 1977 her higher functions were normal and there was minimal dysarthria. Her gait was broad-based and she showed truncal ataxia. The cranial nerves were intact and there was no nystagmus. In the limbs there was generalised hypotonia and mild cerebellar ataxia but muscle bulk and power were normal. The tendon reflexes were brisk in the arms but absent in the legs. The plantar responses were flexor and the abdominal reflexes absent. There was no sensory impairment. At this time she declined hospital admission for further investigations. She was seen again in September 1978 and admitted to hospital. She was now no longer able to walk unaided and her ataxia had increased. Her intellect was preserved but there was marked slurring dysarthria. Pursuit
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Eye movements were jerky and there was first degree horizontal and vertical nystagmus. Paresis of convergence and accommodation was present. Cranial nerve functions were otherwise normal. The upper limbs were hypotonic with cerebellar ataxia but with normal muscle bulk and power; the lower limbs were mildly spastic with a pyramidal distribution of weakness. Deep tendon reflexes were increased in the arms and absent in the legs. Plantar responses were extensor. There was subjective impairment to cutaneous sensation in a stocking distribution to mid-calf level. Examination of other systems was normal. The following investigations were normal: full blood count, blood film, folate, vitamin B12, urea, electrolytes, glucose, liver function tests, urinary and plasma aminoacids, serum lipids, plasma electrophoresis, specific serology, chest and skull radiographs, ECG, EEG and visual evoked responses. The ESR was 30 mm/hr and serum proteins showed a slight acute phase reaction. No lumbar puncture was performed. CT scan of the brain showed normal third and fourth ventriciles and slight symmetrical dilatation of the lateral ventriciles. Convexities and sulci appeared normal. Psychometry revealed a WAIS verbal IQ of 110 and performance IQ of 95; her memory was good. In spring of 1979 she developed impairment of recent memory, associated with a rapidly progressive deterioration in other cognitive functions. Her speech became unintelligible and she was bedridden and doubly incontinent. She developed dysphagia and drooling of saliva. On her final admission in December 1979 she showed a dementic state. She was emaciated and anarthric, making occasional grunting noises. Eye movements were random and roving with no real eye contact. There was a left upper motor neuron type facial weakness. Palatal and pharyngeal reflexes were exaggerated and there was a brisk jaw jerk. Brainstem reflexes were intact. Tone was increased in the limbs. The legs were fixed in a flexed, scissored posture. There was no purposeful movement in the arms which were maintained in abnormal postures. Primitive reflexes were present. No myoclonic jerks were observed. She deteriorated and died in January 1980, six years after the onset of her illness.

The clinical features of the other affected members of the family are briefly summarised in the Appendix and are included in tables 1-3.

Table 1 Neurological systems affected in 16 cases

<table>
<thead>
<tr>
<th>Age at onset</th>
<th>Duration (years)</th>
<th>Cerebellar</th>
<th>Pyramidal</th>
<th>Lower motoneuron</th>
<th>Sensory</th>
<th>Cranial nerves</th>
<th>Dementia</th>
</tr>
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<tr>
<td>AM</td>
<td>54</td>
<td>4</td>
<td>+</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<tr>
<td>CR</td>
<td>66</td>
<td>3</td>
<td>?</td>
<td>...</td>
<td>...</td>
<td>+</td>
<td>...</td>
</tr>
<tr>
<td>TW</td>
<td>47</td>
<td>5</td>
<td>+</td>
<td>...</td>
<td>...</td>
<td>+</td>
<td>+</td>
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<tr>
<td>DC</td>
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<td>3</td>
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<td>+</td>
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<td>7*</td>
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<td>57</td>
<td>5</td>
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<td>...</td>
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<td>...</td>
<td>+</td>
</tr>
<tr>
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<td>57</td>
<td>5</td>
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<td>+</td>
</tr>
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<td>60</td>
<td>5</td>
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<td>...</td>
<td>+</td>
</tr>
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<td>TM</td>
<td>66</td>
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<td>...</td>
<td>+</td>
</tr>
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<td>48</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
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<td>DJ</td>
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<td>5</td>
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<td>...</td>
<td>...</td>
<td>+</td>
<td>+</td>
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<tr>
<td>BD</td>
<td>38</td>
<td>7</td>
<td>+</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>+</td>
</tr>
<tr>
<td>JH</td>
<td>39</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>JC</td>
<td>40</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Accidental death.

Material and methods

The brain and spinal cord of case 1 were received from another hospital after fixation, the other necropsies being done at the National Hospital. A few blocks were taken from case 2 in 1973 and were intended to be for a preliminary study. However this brain is now no longer available and the survey of the neuropathology in this case is therefore very limited. The brains of cases 3 and 4 were divided mid-sagittally, one half being deep frozen from which samples were sent to Dr DC Gajdusek's laboratory at the National Institutes of Health, Bethesda, USA for inoculation into animals. After fixation blocks taken from many regions of cerebral and cerebellar hemispheres, brainstem and spinal cord were embedded in celloidin or in paraffin wax. Sections were stained with haematoxylin-eosin, haematoxylin-van Gieson, phosphotungstic acid haematoxylin, Holzer's method for astrocytes, Glees and Marsland's silver impregnation, luxol fast blue-cresyl violet, Congo red and periodic acid-Schiff (PAS) methods. In cases 1-3 frozen sections were cut from a frontal block and stained for fat; for microglial cells by the Weil-Davenport method and by Cajal's gold-sublimate method for astrocytes.

Neuropathology

In all cases significant pathology was confined to the nervous system. All the brains showed a slight degree of atrophy affecting gyri of frontal, parietal and cerebellar...
Table 3  Signs in order of frequency

<table>
<thead>
<tr>
<th>Sign</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsteady gait</td>
<td>12</td>
</tr>
<tr>
<td>Slurring dysarthria</td>
<td>10</td>
</tr>
<tr>
<td>Impaired memory, cognition or affect</td>
<td>11</td>
</tr>
<tr>
<td>Spastic leg weakness</td>
<td>9</td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td>7</td>
</tr>
<tr>
<td>Absent leg reflexes</td>
<td>7</td>
</tr>
<tr>
<td>Incontinence</td>
<td>7</td>
</tr>
<tr>
<td>Extensor plantar responses</td>
<td>6</td>
</tr>
<tr>
<td>Paraesthesiae</td>
<td>6</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>4</td>
</tr>
<tr>
<td>Spastic arm weakness</td>
<td>4</td>
</tr>
<tr>
<td>Sensory deficit</td>
<td>4</td>
</tr>
<tr>
<td>Scotomata or photopsia</td>
<td>4</td>
</tr>
<tr>
<td>Diplopia</td>
<td>4</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>3</td>
</tr>
<tr>
<td>Pupillary abnormalities</td>
<td>3</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>2</td>
</tr>
<tr>
<td>Paresis of convergence</td>
<td>2</td>
</tr>
<tr>
<td>Deafness</td>
<td>2</td>
</tr>
<tr>
<td>Parkinsonian features</td>
<td>2</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>1</td>
</tr>
<tr>
<td>Flaccid paralysis</td>
<td>1</td>
</tr>
<tr>
<td>Taste and smell disturbed</td>
<td>1</td>
</tr>
</tbody>
</table>

In all cases the major cerebral arteries were free of atheroma. There was a varying degree of neuronal loss in the cerebral cortex. This was severe and diffuse in cases 3 and 4 and milder and more patchy in cases 1 and 2.

Nerve cell loss in the cerebellum was a marked feature of the pathology in all four cases. Purkinje cells were absent from long stretches of cortex and empty tangles of basket cell fibres were numerous. Many of the surviving Purkinje cells showed "torpedoes". Granule cells were severely reduced in case 4 only. The cerebellar vermis showed more nerve cell loss than the hemispheres where the dorsal cortex was more severely involved than the ventral.

Status spongiosus was observed in the grey matter of all cases, varying considerably in degree and extent. In case 1 there was involvement of superior and middle frontal and superior temporal gyri, insula and parts of parietal cortex and in these areas the spongiform changes were limited to the molecular and outer nerve cell layers of the cortex. Nowhere was the full thickness of cortex affected and in many places the cortex seemed entirely spared. In case 2 a mild status spongiosus was present in the amygdaloid complex and anterior hypothalamus. Cerebral cortex and deep grey nuclei of cases 3 and 4 showed generalised status spongiosus which spared the

Fig 2  Case 4—Temporal cortex showing marked spongiform changes, neuronal loss and deposits of amyloid (arrows). H and E × 375.

Numerous degenerating terminals were present close to cells of the dentate nucleus.

Nerve cell loss in the cerebellum was a marked feature of the pathology in all four cases. Purkinje cells were absent from long stretches of cortex and empty tangles of basket cell fibres were numerous. Many of the surviving Purkinje cells showed "torpedoes". Granule cells were severely reduced in case 4 only. The cerebellar vermis showed more nerve cell loss than the hemispheres where the dorsal cortex was more severely involved than the ventral.

Fig 3  Case 3—Temporal cortex. Marked astrocytic hyperplasia and spongiform changes shown. Holzer's method for astrocytes × 400.
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Fig 4  Case 1—Occipital cortex showing several deposits of amyloid (arrows to some) in the neuropil. There is no relationship between amyloid and vessels and no spongiform changes in this region of cortex. H and E × 275.

calcarine cortex in case 4 and the cerebellum. The spongiform change (fig 2) consisted of small, rounded vacuoles, of 50-100 μm in diameter, isolated or in clusters throughout the neuropil. In places the vacuoles abutted closely together but did not seem to coalesce. Vacuoles seemed to impinge on, and distort, nerve cells and in the severely spongy areas the nerve cells were shrunken.

Astrocytic hyperplasia (fig 3) was always a concomitant of spongiform change. Numerous astrocytes were present in the molecular layer of cerebral cortex and were particularly prominent in the deep layers of cortex close to the cortex-white matter junction. Hyperplasia of Bergmann glia and fibrous gliosis were present in many places in the molecular layer. Astrocytic fibres formed a dense feltwork in the white matter of both cerebral and cerebellar hemispheres while the ventricular ependymal lining was focally deficient and replaced by tangles of glial fibres.

Amyloid deposition (figs 4-8) was a striking feature of the pathology in all cases and was found in cerebrum (fig 4), cerebellum (fig 5) and, to a lesser extent, in the brain-stem and spinal cord. The amyloid took the form of rounded bodies ranging in size from discrete droplets of less than 5 μm in diameter to large masses of more than 50 μm diameter. In places the little droplets were discrete, particularly in the granular layer of the cerebellum (fig 6) but elsewhere there were larger aggregations of amyloid spheroids of varying size particularly in the molecular layer (fig 7) of both cerebral and cerebellar cortex. Some of the deposits of amyloid had the appearance of “kuru plaques” (fig 8) with a solid central core surrounded by a halo of radiating spicules of less dense material with a reticular appearance. The staining reactions were typical of amyloid being eosinophilic and hyaline with a fairly strong positive reaction with PAS, a well-marked staining with Congo red which also conferred greenish-yellow birefringence in polarised light. The distribution of amyloid was very widespread, affecting molecular layer as well as all layers of cortex and deep grey matter. Amyloid deposits were also seen in white matter but were not numerous. They were not perivascular and were not argyrophilic.

In case 3 only, amyloid infiltration of vessel walls (congophilic angiopathy) was present (fig 9) with the typical staining characteristics. Intracerebral capillaries were not affected.

Neuritic plaques of the senile (Alzheimer) type were also identified but were few in number and present mainly in the hippocampus in case 3 and scattered in the cortex in case 4. These neuritic plaques were larger than the much more numerous amyloid deposits. Some had a

Fig 5  Case 3—Celloidin section of cerebellum. Many amyloid deposits of varying size are scattered throughout the molecular layer and the amyloid infiltration of meningeal vessels is also seen. PAS × 30.
central core of amyloid surrounded by argyrophilic bodies, astrocytes and microglial cells. In case 3 there were occasional hippocampal neurons with neurofibrillary tangles and some with granulo-vacuolar inclusions.

Venous channels were engorged with blood in case 4 (in which there had been terminal cerebral sinus thrombosis). There were also occasional perivascular cuffs of lymphocytes in the brainstem. Also in case 4 (the most extensively necropsied case) vacuolated nerve cuffs were present in the lumbar anterior horn and sensory root ganglia showed marked hyperplasia of satellite cells and numerous nodules of Nageotte. Several small, old ischaemic infarcts were noted in the cerebellar and occipital cortex of case 3 and throughout the white matter there was marked perivascular rarefaction, changes which could be ascribed to the amyloid vascular disease. Sections of skeletal muscles (case 4, sternomastoid, deltoid) showed atrophied muscle fibres with a fascicular distribution typical of neurogenic atrophy.

Discussion

The pathological findings of neuronal degeneration, particularly affecting Purkinje cells, astrocytic hyperplasia and status spongiosus are strongly indicative of CJD in the four cases reported here. The differences in severity and distribution of status spongiosus (taking the limited histological study of case 2 into account) could be ascribed to the known variation in the manifestations of CJD and we consider the changes in all these cases to be indicative of that disease. The long duration of illness and the late development of intellectual deterioration are, however, untypical of CJD in which most cases have a subacute course of less than 2 years with an earlier onset of dementia. However in cases of CJD in whom the main pathology is cerebellar dementia may develop late, or even terminally.

Amyloid plaques in CJD are closely similar to those in kuru and scrapie and are described as stellate cores. The finding of amyloid angiopathy, present in case 3, has not, to our knowledge, been described in cases of CJD but has been observed in presenile dementia particularly when there has been a familial pattern of inheritance or with a predominantly cerebellar involvement. Unlike other reported cases with cerebral amyloid angiopathy, neuritic argyrophilic plaques were an inconspicuous feature of the pathology of our cases.

Fig 6 Case 4—Cerebellar cortex. In addition to the larger rounded masses of amyloid (arrows) there are very many small deposits between the granule cells. Purkinje cell loss is also apparent. Congo red × 350.

Fig 7 Case 4—Molecular layer of temporal cortex, close to the pia. Imnumerable amyloid deposits are seen, some aggregated into rounded masses, and showing no association with cerebral blood vessels. PAS × 350.
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Fig 8 Case 1—Cerebellum. A torpedo on a degenerating Purkinje cell axon lies in the granule cell layer while there are several rounded deposits of amyloid resembling the so-called “kuru plaques” lying between Purkinje cells. Glees and Marsland silver impregnation × 350.

while status spongiosus was prominent. No mention of spongiform change appears in the published case descriptions of amyloid angiopathy although astrocytic glial hyperplasia has been described around neuritic plaques and in the molecular layer of the cerebellum where there was also cell loss and torpedoes. The familial cases reported by Gerstmann, Strausser and Scheinker and Boellaard and Schlote were very similar to the “W” family with amyloid, spongiform changes and astrocytic hyperplasia in association with progressive cerebellar ataxia and dementia. As in the “W” family inheritance was by a dominant mode of transmission. Although mental deficiency is known in association with familial ataxia or spastic paraplegia beginning in childhood, the family reported by Akelaitis was an example showing severe dementia with ataxia. However the pathology in this family is uncertain.

Families with CJD have been described in many reports. Matthews in a survey of the epidemiology of CJD in England and Wales did not describe any familial cases. We do not know whether or to what extent there was contact between the various branches of the “W” family.

We feel that the evidence presented in this paper strongly indicates that all the affected members of this family suffer from a form of CJD and a form of cerebral amyloidosis. It is not known whether the inherited disease is amyloidosis which has predisposed the CNS to superadded infection or whether the CJD virus itself has become incorporated into the genome of the host in linkage disequilibrium with the genes which predispose to amyloidosis.

We thank Mr A Beckett for the microscopic preparations and Mr JA Mills for the photographs. Some of the material was made available by Professor Blackwood and we are also grateful to Dr MFT Yealland for permission to study case 4 during her first admission.

References

2 Corsellis JAN. Ageing and the Dementias. In: Blackwood W, Corsellis JAN, eds. Greenfield's Neuropathology...
Adam, Crow, Duchen, Scaravilli, Spokes


Corsellis JAN, Brierley JB. An unusual type of presenile dementia. (Atypical Alzheimer’s disease with amyloid vascular change.) Brain 1954; 77: 571-87.


Appendix

No details are known of the illnesses in the affected members of generations I and II. The histories of GH, TM, KH, BD, and MJ have been compiled from their case notes. The others are from Rosenthal et al.

Generation III

MW (female) A daughter of this lady stated that her mother and her identical twin both died aged 55 after a similar disabling illness, the cause of death being stated as disseminated sclerosis.

Generation IV

AM (female 1883-1941) Mother of KH and grandmother of case 4. Gradual development of slurred speech, decreasing use of legs and progressive incapacitation without dementia or memory loss. Her handwriting became small.

CR (female 1891-1960) At age 66 developed pain in legs that caused difficulty in walking. Speech became incoherent and she became incontinent.

TW (male 1894-1946) The father of JW. Illness began 5 years before death, beginning with difficulties with balance. Became completely disabled within 2 years with slurred speech, difficulty with swallowing, “black balls” in his vision, numbness in extremities and impaired hearing. Family deny any evidence of dementia, memory loss or confusion until 3 weeks before death when he lapsed into coma.

DC (female 1894-1943) Developed headaches and menorrhagia at age 46 accompanied by inability to knit and difficulty with walking. During severe headaches her memory and orientation would deteriorate. Became bedridden.

ES (female 1903-1959) Died as a result of a fall down stairs which was attributed to weakness of her legs similar to that of other affected members of the family.

Generation V

EU (female 1914-1976) Case 3 of this paper.

GH (female 1909-1968) Illness began at age 57 with difficulty in use of legs, tingling sensation in the face and a black spot in the left visual field. Neurological examination May 1965 showed an inexpressive face, cogwheel rigidity of both arms, weakness of hip flexion and bilateral extensor plantar responses. By February 1967 there was marked unsteadiness, nystagmus on lateral gaze, gross dysarthria and truncal weakness. Gait was slow and shuffling with difficulty in turning round, marked weakness of hip and knee movements and ataxia of legs. Tendon reflexes brisk, in upper limbs but absent in lower limb with bilateral extensor plantars. She was well orientated and able to concentrate on questions but
was severely depressed and apathetic. By 1968 she was able to walk only with support and in that year was admitted to a mental hospital where she died some months later.

**JW (male 1930-1973)** This case was reported by Rosenthal et al. He was well until early 1972 when he developed visual disturbances, disturbances of balance, delusions and confusion. By October 1972, he was generally unresponsive, with no voluntary eye movements, frequent jerking of all limbs and bilateral extensor plantar responses. EMG and muscle biopsy showed evidence of lower motor neuron disease. Treatment with amantadine hydrochloride (200-600 mg daily) for six weeks was not beneficial and he died 13 months after the onset of his illness. Postmortem examination showed the characteristic cerebral spongiform changes of CJD and inoculation of cerebral tissue into nonhuman primates has transmitted an encephalopathy.

**Generation VI**

**JH (male 1931-1973)** Brother of case 4. Developed unsteadiness of gait in 1970, progressive dysarthria from 1971 and dysphagia from 1972. Paraesthesiae of hands and feet and distortion of his handwriting then developed. Examination in 1973 showed no intellectual impairment, speech was dysarthric and gait broad-based. Ocular movements were full and pupillary responses normal but there was nystagmus in all directions of gaze. Vibration and position sense were impaired in feet and there was weakness of knee and hip flexors. All limbs showed ataxia, tendon reflexes were present but plantar responses were extensor bilaterally. He died after a 5 year illness without dementia (no necropsy).

**JC (female 1934-1980)** Case 4 of this paper.

**MJ (female, born 1952, daughter of JH)** She did not walk until 3 years old, had many attacks of loss of consciousness. There was evidence of marked mental retardation and there have been many admissions to a mental hospital for multiple overdoses, hysterical fits and outbursts of aggression. She is considered to have a behavioural disorder in association with epilepsy and subnormality.
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