Autosomal dominant late onset cerebellar ataxia with myoclonus, peripheral neuropathy and sensorineural deafness: a clinicopathological report

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SUMMARY Three members of a family were affected by an autosomal dominant disorder comprising cerebellar ataxia, sensorineural deafness, myoclonus, and peripheral neuropathy. This is the second kindred with this syndrome reported to date. Necropsy of the proband showed loss of cells in the dentate nuclei, a reduced amount of cerebellar white matter, and pallor of the gracile tracts in the spinal cord.

The combination of cerebellar ataxia and myoclonus was first described by Ramsay Hunt in 1921.1 There has since been a tendency to apply the label of ‘the Ramsay Hunt syndrome’ to any patient demonstrating this combination of clinical features.2 This is confusing, as such cases are both clinically and genetically heterogeneous. Hunt’s patients clearly fell into two groups. Four were single cases who had myoclonic epilepsy before the age of 20 years and later developed progressive cerebellar ataxia. Another two, twin brothers, had a neurological syndrome resembling Friedreich’s ataxia from early childhood. Myoclonus did not occur until the third decade. Necropsy in one patient showed degeneration of the spinocerebellar tracts and posterior columns in the spinal cord, and atrophy of the dentate nucleus. Myoclonus and cerebellar ataxia occur together in a number of autosomal recessive storage disorders, including Lafora body disease, some of the lipidoses, sialidosis and ceroid lipofuscinosis.3 Other recessive cases of cerebellar ataxia and myoclonus are more difficult to classify. It is likely that many of the patients reported from Scandinavia, with Unverricht-Lundborg disease or ‘Baltic myoclonus’34 are examples of a disorder which is distinct from the majority considered to have the Ramsay Hunt syndrome.56

One striking feature of dominantly inherited late

onset cerebellar ataxia is the wealth of associated features which may be found in addition to ataxia. These include ophthalmoplegia, optic atrophy, extrapyramidal signs, pigmentary retinal degeneration, dementia and amyotrophy.7 Myoclonus occurring in combination with cerebellar ataxia of dominant inheritance is rare. Bonduelle and colleagues* described a family in which ataxia developed in the third decade and was associated with areflexia, myoclonus and ophthalmoplegia. Post-mortem examination of one patient revealed olivoponto-cerebellar atrophy with degeneration of the spinocerebellar tracts, posterior columns and anterior horn cells in the spinal cord. Gilbert et al9 reported a similar, but more slowly progressive disorder in which the age of onset was earlier and tremor more prominent. May and White10 described the association of deafness, ataxia and myoclonus which was dominantly inherited in six members of a family. The subject of this paper is a kindred similar to that of May and White, with a description of the necropsy findings in one case. The pedigree of the family is shown in fig 1.

Case reports

I.1. This man died in his seventies from an accident (type unknown) but had no neurological symptoms.

I.2. This female died at the age of 52 years from a stroke. She was said to be ‘mentally unstable’ and was known to have had difficulty in hearing.

I.3. This female, who died at the age of 74 years in 1978, was first admitted to University College Hospital in 1973. She gave a seven year history of involuntary jerky move-
ments of the face, arms and trunk, and mild hearing difficulties. The movements were nearly always provoked by bright light and had been associated with brief episodes of unconsciousness on two occasions. For five months before admission she had noticed increasing ataxia of gait. On examination there was irregularity of volume and pitch in her speech and marked ataxia of all four limbs. The gait was also ataxic. The tendon reflexes and sensation were normal. She had bilateral sensorineural deafness which was more severe on the right. There were irregular myoclonic movements of all four limbs and the face which occurred approximately six to ten times per minute. These were more severe and generalised when the patient was exposed to sudden bright lights. A resting electroencephalogram (EEG) was normal. Repetitive flash stimulation induced generalised polyspike-slow wave complexes in the EEG. Neuro-otological examination in 1973 (Dr MR Dix) revealed a moderately severe sensorineural loss bilaterally that was rather greater on the right. Recruitment was full as judged by the loudness discomfort levels.11 Vestibular function was abnormal. The caloric responses demonstrated a marked directional preponderance to the right with a superimposed canal paresis. Pursuit and saccadic movements were normal without nystagmus. Optokinetic nystagmus was deranged. There was no positional nystagmus.

In early 1974 the patient was readmitted because of increasing unsteadiness and memory loss. On examination then she was mildly demented. Her speech was scanning and explosive. There was generalised myoclonus with striking photosensitivity, and marked cerebellar ataxia in the limbs and of gait. The ankle jerks were absent but the other tendon reflexes were normal. Her somatosensory evoked responses to electrical stimulation of the digital nerves in the index and middle finger of either hand were of extremely large amplitude, showing the characteristic enhanced second surface negative wave typically found in myoclonic epilepsy. The early positivity (P32 component) measured approximately 21 μV for the left hemisphere and 32 μV for the right hemisphere, in contrast to the normal response, which has an upper limit of 8 μV in the healthy population. In spite of her photosensitivity, she tolerated repetitive flash stimulation well, although the flash-evoked response was also abnormally large. She was, however, exquisitely sensitive to the black and white checkerboard pattern reversal stimulus used to test the pattern visual evoked response, and had a partial seizure within a few seconds of the stimulus being presented. During this attack she jerked violently all over and both eyes rolled up and to the left. She was inaccessible at this time, although she became responsive within a few seconds of the stimulus being turned off. The seizure was accompanied by a continuous train of high voltage, bilateral, polyspike-slow wave complexes in the EEG. She was treated with clonazepam which led to considerable improvement of her myoclonus. Recorded again two weeks later, both somatosensory and visual evoked responses were greatly reduced in amplitude.

In December 1974 she developed intermittent drowsiness and a progressive left hemiparesis over a period of three weeks. Investigations confirmed the clinical diagnosis of a sub-dural haematoma and this was evacuated. The patient made a good recovery from this but her ataxia continued to deteriorate. She was last seen in early 1978 when she was only just able to walk. Later that year she had a series of generalised seizures which culminated in status epilepticus and the patient died. At post-mortem examination, apart from collapse of the left lung with an associated large pleural effusion, the pathological findings were confined to the nervous system. Macroscopic examination of the brain after fixation showed mild atrophy of the dentate nuclei of the cerebellum, and small areas of old softening in the left basis pontis involving the pyramidal tract. Blocks were taken from several regions of the cerebrum and cerebellar hemispheres, brain stem, spinal cord and dorsal root ganglia, and embedded in paraffin wax. Sections were stained with haematoxylin-eosin, haematoxylin-van Gieson, Gleys’ silver impregnation for axons and luxol fast-blue-cresyl violet.

In order to establish the severity of nerve cell loss in the grey matter, the relevant areas were enlarged and measured. Using a grid applied to the eye-piece, all neurons with recognisable nucleoli contained within randomly chosen fields were counted; the area of a single unit of the grid was calculated using a stage micrometer and the total number of cells in the area was estimated. The results were expressed as a percentage of the number of cells in comparable areas of an age-matched control brain.

Histological examination of the cerebral hemispheres showed circumscribed foci of laminar necrosis in the right pericallosal gyrus; most of the pyramidal cells of the Ammon horn had disappeared while the remaining ones were shrunken. In the brain stem the presence of an area of old softening with cavitation in the left basis pontis was confirmed. In the cerebellum, the folia of the vermis and cerebellar hemispheres appeared moderately shrunken; there was a mild decrease in density of Purkinje cells and the white matter was considerably reduced in volume. The ribbon of the dentate nucleus was thinner than normal and the number of nerve cells in it showed a 40% decrease in number compared with an age and sex matched control (fig.
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Fig 2. The dentate ribbon of case II.3 (A) is thinner than that in a control brain (B) and contains a few shrunken nerve cells. (Luxol Fast Blue—Nissl × 100)

Fig 3. Case II.3: Transverse section of the cervical spinal cord showing pallor of both gracile tracts. (Luxol Fast Blue—Nissl)

2 A and B). No abnormalities were found in the basal ganglia, thalamus, red and sub-thalamic nuclei, substantia nigra and medulla, including the cochlear nuclei, apart from pallor of the pyramidal tract below the site of the lesion in the pons and some gliosis of the inferior olive. In the spinal cord, the gracile tract showed moderate pallor of the myelin stain throughout its length (fig 3). The dorsal root ganglia were normal.

II.5. This female was noted to have a somewhat cyclothymic personality during the fifth decade of life; she first became unsteady and had involuntary jerking movements of the limbs at about the age of 50 years. She was diagnosed as having Huntington's chorea eight years later. On examination aged 68 there was no definite evidence of dementia. She had severe dysarthria and mild bilateral sensorineural deafness. There were prominent myoclonic jerks involving the eyes, palate, head and all four limbs. It was virtually impossible to assess cerebellar function because of the myoclonus. The tendon reflexes were normal and the plantar responses flexor. There was no sensory loss. Her somatosensory and visual evoked potentials were recorded at a time when she was showing minimal involuntary twitches of the intrinsic muscles of the left hand. Neither of the cortical potentials were abnormally enlarged at this time, nor was there any cortical wave detected by jerk-locked averaging triggered from the abnormal movements of the left abductor digiti quinti muscle. The patient died at the age of 60; no necropsy was performed.

III.8. This 40-year-old man first noticed a tendency to spill full cups of coffee in his late teens but was only aware of ataxia of gait at the age of 32. This had since been mildly progressive and he had difficulty in running and turning quickly. He had not noticed any disturbance of speech. He had been aware of mild bilateral deafness for about ten years and wore a hearing aid in the right ear. On examination he was dysarthric and had mild bilateral sensorineural deafness. The jaw-jerk was brisk. There was moderate cerebellar ataxia in all four limbs. Power was normal. The tendon reflexes in the upper limbs were normal, but the knee and ankle jerks were absent. The plantar responses were flexor. Sensation was normal. His gait was ataxic.
There were no involuntary movements.

Haematological and biochemical investigations, including serum thyroxine and glucose tolerance test, were normal. CT scan showed an area of low attenuation in the region of the left sylvian fissure which was thought to be an arachnoid cyst. EEG with photic stimulation was normal. Electromyography of the right abductor pollicis brevis muscle was normal. Motor nerve conduction velocity, (MNCV) in the right median nerve was normal at 52 ms⁻¹ but that in the peroneal nerve was slightly reduced at 44 ms⁻¹. Median, ulnar, and sural sensory action potentials (SAP) were reduced in amplitude (3.3 and 5 μV) and had latencies to peak of 4.4, 4.2 and 5.3 ms respectively.

On neuro-otological examination there was a moderately severe bilateral sensorineural hearing loss, symmetrical below 1 kHz (30 dB, 35 dB and 50 dB at 250, 500 and 1 kHz respectively) and greater in the right ear above this (50 dB, 40 dB, 40 dB in the left ear and 60 dB, 60 dB and 70 dB in the right ear at 2, 4 and 8 kHz respectively). Recruitment was full, there was no significant tone decay at any frequency and the speech audiogram was not worse than anticipated from the pure tone thresholds. The stapedius reflex thresholds were normal at all frequencies without significant decay. Brainstem auditory evoked potentials (BAEP) to a 95 dB click (peak sound pressure level) were not consistently recorded from the left ear, but a small component V (0.2 μV) was obtained to right ear stimulation at slightly increased latency (6-6 ms, upper limit of normal 6-5 ms). Vestibular function was deranged. There was no response either in the light or the dark in conventional Fitzgerald and Hallpike caloric testing. Pursuit was a little irregular, optokinetic nystagmus deranged (small drum) and saccadic movements normal. There was no nystagmus in the present of fixation or in the dark. Microsaccadic oscillations were present both in the light and in all positions of gaze. There was no positional nystagmus.

Discussion

The clinical and genetic features of this family are very similar to those of the kindred described by May and White and it is highly likely that affected individuals from both families suffered from the effects of the same rare mutant gene. May and White described three patients in detail and there was a history of similar symptoms in three relatives who were dead. The proband was a 32-year-old man who was noted to be deaf at the age of four years and developed generalised myoclonus, dysarthria and ataxia when he was 14. He had six generalised major seizures one year later. All his symptoms were slowly progressive apart from the major seizures which did not recur. His mother was clumsy during adolescence and later became progressively ataxic and dysarthric. She had no myoclonus but had one major seizure during the third decade of life. Deafness developed in early adult life. Her brother had an almost identical clinical picture. He had no myoclonic jerks and had never had any seizures.

The pedigree shown in fig 1 indicates that the disorder here is dominantly inherited, as it was in May and White's family despite the presence of consanguineous marriages in two generations. It is probable, from the details available, that case I.2 in our family was affected, but died before fully manifesting the disease.

In both families perceptive deafness and cerebellar ataxia occurred in all the affected individuals whereas the presence of myoclonus was variable. Deafness preceded other symptoms by a number of years in some instances. In two of our cases a formal assessment of this was made (case III.8 and II.3) and it appears that the deafness was probably of cochlear origin rather than due to a more central disturbance. The presence of full recruitment, some asymmetry of the thresholds between the ears, normal stapedius reflex, absence of significant tone decay and relatively normal speech audiometry all favour such an origin as does the preserved BAEP in the presence of moderately severe deafness at 1–2 kHz. At necropsy there was no evidence of involvement of the central auditory pathways in the one case examined but unfortunately the temporal bones were not obtained.

May and White did not examine the vestibular system in their cases but in the present patients it appears that the semicircular canal system was involved. It is not possible to say whether the sensory epithelium, eighth nerve, or vestibular nuclei were the site of the abnormality. The extra-ocular movement abnormalities are compatible with the presence of a cerebellar disorder, with deranged pursuit and small drum optokinetic nystagmus, but the exact site of the disturbance, that is brainstem pathways or cerebellum itself, is unclear.

One additional clinical feature in case III.8, which may also have been present in his mother, was that of a sensory peripheral neuropathy. The patient had no symptoms resulting from this although the knee and ankle jerks were absent and his sensory nerve action potentials were reduced in amplitude. Case II.3 had absent ankle jerks, but she was aged 70 years at the time of examination so this may not have been significant. None of the patients described by May and White had any clinical features attributable to a peripheral neuropathy; neurophysiological investigations were not performed. It would seem reasonable to suggest that the neuropathy found in case III.8 was part of his inherited disease; no other cause for this was found and he was not diabetic.

The pathologcal findings in the necropsied case reported here were confined to loss of neurons in the dentate nuclei, gliosis of the inferior olives, mild loss of Purkinje cells in the cerebellum, loss of cerebellar...
white matter and reduced myelin staining of the fasciculus gracilis in the spinal cord. As in many hereditary ataxic disorders, clinicopathological correlation in cases of cerebellar ataxia and myoclonus is not high. The pathological findings in previously reported cases have varied considerably. Nevertheless, the dentate nucleus is nearly always abnormal, with severe neuronal loss and gliosis\(^1\)\(^{12-15}\) although exceptions have occurred.\(^{16}\) Involvement of the inferior olives and posterior columns of the spinal cord, as were seen in our case, is almost as frequent. It is of interest that the abnormalities in the brain of case II.3 were relatively mild, and cell counting was necessary to establish neuronal loss in the dentate nucleus. The circumscribed areas of laminar necrosis seen in the cerebral hemispheres, together with the lesion in the pons, were considered to be ischaemic, or possibly traumatic due to repeated falls, in origin, rather than degenerative as suggested by Bird and Shaw.\(^5\)

It should be stressed that the disorder present in members of the family reported here, and that of May and White, is genetically and clinically distinct from that described in most cases of cerebellar ataxia and myoclonus and also from the other autosomal dominant late onset cerebellar ataxias. The existence of this disease illustrates the heterogeneity of the hereditary ataxias generally, and particularly of what has been called the Ramsay Hunt syndrome.

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References