Familial motor neurone disease

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Motor neurone disease is a relatively common condition with a gross prevalence rate of about 4 per 100,000 (Kurland, 1957). It is fairly uniformly distributed throughout the world, with the exception of the Chamorro population of Guam and Rota in the Mariana Islands and Chamorro emigrants in California. In this ethnic group the prevalence is about 420 per 100,000 (Kurland, 1957) and familial examples are frequent. Elsewhere, however, familial occurrence is only rarely reported, although it is probably more common than is realized. Kurland and Mulder (1955) found a positive family history recorded in the case notes of five out of 58 individuals with motor neurone disease reviewed retrospectively, and Haberlandt (1959) reported a positive family history in 13.5% of 251 patients with the disease.

Myrianthopoulos and Brown (1954) reviewed eight non-Chamorro pedigrees of familial motor neurone disease and Kurland and Mulder (1955) gave details of 21 others dating back as far as Aran's original description in 1850. Mulder (1957) reported six more pedigrees and Kurland (1957) mentioned 13 further families, although in none of these cases were details provided.

Since then 13 more reports have appeared, covering 15 further families (Boudouelle and Bouyges, 1957; Klaus, Freyberger, Kavka, and Vodička, 1959; Dierssen Gervas, 1959; Engel, Kurland, and Klatzo, 1959; Alajouanine and Nick, 1959; Campanella and Bigi, 1959; Bunina, 1960; Green, 1960; Lopez Aydillo, 1960; Magee, 1960; Weisendanger, 1961; Espinosa, Okihiro, Mulder, and Sayre, 1962; Mackay, 1963.) Thus, apart from the Chamorros and those recorded merely as showing a positive family history, at least 63 families showing characteristic features of motor neurone disease have so far been reported.

Details are now presented of three further examples of the disease in one family. Two other members of the family suffered from disseminated sclerosis. Three members of the family (II 2, 3, and 4) were seen and examined personally, two in their homes and the third in hospital. I, 1 and II, 6 were already dead but the medical records of their final illnesses were kindly loaned by Edinburgh Royal Infirmary and Dumfries and Galloway Royal Infirmary respectively.

While investigating this family, information was obtained about a second family, three of whose members also evidently suffered from motor neurone disease. Unfortunately full details were only obtainable for one of these individuals. The family is, however, included in this report in order to place it on record. Although both families lived within a small area of south-west Scotland there was no known relationship between them.

FAMILY A

CASE I, 1 Margaret T. was quite well up to the age of 53 when she first noticed weakness and stiffness of all her limbs and difficulty in speaking. Examination at that time showed a generalized increase of muscle tone, most marked in the legs, with hyperreflexia and bilateral extensor plantar responses. There was weakness, wasting and fasciculation of the arm muscles, especially distally and in the hands, but none in the legs where power was good. In spite of her complaint of dysarthria none was noted at this time and cranial nerves appeared intact. There was no nystagmus or sphincter disturbance. Sensation of all forms was normal. The cerebrospinal fluid was normal and the Wassermann reaction negative.

Bulbar involvement was first noted three months later with fasciculation of the tongue, dysphagia, and obvious dysarthria. The limb musculature became more flaccid and tendon and plantar reflexes unobtainable. Deterioration was rapid and death occurred during a chest infection one year after the onset of symptoms, when the patient was aged 54 years. The diagnosis was motor neurone disease.

CASE II, 1 Jean MacC. was quite well up to the age of 52 when she first noticed stiffness of the legs and difficulty in walking. After a few months this disappeared but returned a short time later and progressed thereafter without further remission.

Examination four years after the onset of symptoms showed weakness and spasticity in the lower limbs with slight weakness of the right arm and the small muscles of both hands. No wasting or fasciculation was observed. There was minimal loss of stereognosis and two-point discrimination in the right hand and vibration sense below both knees. Sensation was normal elsewhere. The tendon reflexes were moderately increased in all limbs, the right more so than the left; abdominal reflexes were absent. Plantar responses were extensor. Nystagmus was present to the right and there was intention tremor on finger

nose testing, more marked on the right. No visual, sphincter, or mental disturbances were found. The speech was slightly slurred but no other cranial nerve involvement was noted. The cerebrospinal fluid was normal and the Wassermann reaction negative.

Deterioration was rapid initially and she was first admitted to hospital after one year. Shortly afterwards she was discharged and remained fairly active at home for nearly four years. At length she became increasingly disabled, with spasticity and incoordination, and was re-admitted to hospital. She died quite suddenly four months later, six years after the onset, aged 58 years. Diagnosis was probably disseminated sclerosis.

CASE II, 2 Agnes J. was quite well up to the age of 50, when she first noticed stiffness of the left leg and difficulty in walking. This has become progressively worse up to the present time without any remissions.

Examination six months after the onset of symptoms showed spasticity and hyperreflexia of the legs, the left more so than the right, with bilateral extensor plantar responses. There was slight nystagmus and slight intention tremor on finger-nose testing but no other abnormality.

Examination two and a half years after the onset showed no nystagmus or ataxia but, in addition to the signs in the legs as before, there was loss of abdominal reflexes and impairment of sensation to pinprick, light touch, and vibration below both knees.

The condition has slowly progressed since then. Now, four and a half years after the onset, she can still get about with a stick. She has a return of ataxia, with nystagmus, intention tremor of the arms, and a staggering, broad-based gait. New features are bilateral temporal pallor of the optic discs and left foot-drop without, however, muscle wasting. Power, tone, reflexes, and sensation are all normal in the arms and there is no sphincter disturbance or cranial nerve involvement other than in the eyes. She is mildly euphoric. The diagnosis is probably disseminated sclerosis.

CASE II, 3 Margaret M. was quite well up to the age of 48 years. Her first symptom was that of clumsiness of the right hand and of frequently catching the right toe while walking.

Examination at that time showed hyperreflexia in all limbs, and weakness, wasting, and impairment of fine movements in the right hand and wasting of the muscles of the right foot and antero-lateral compartment of the right leg, with foot drop. There were no sensory disturbances.

Within two months the left hand and foot were similarly affected and examination then showed markedly reduced tone in the distal parts of all limbs, with gross weakness and wasting and extensive muscle fasciculation. Proximally tone was increased and power good but slight wasting and fasciculation were present even there. The biceps, triceps, and knee reflexes were increased but supinator, finger, ankle, and plantar reflexes were unobtainable. Sensation of all forms was normal and there was no ataxia.

Cranial nerves became involved 12 months after the

onset, with dysphagia, nasal regurgitation of fluids, and dysarthria. Latterly there was some weakness of the right facial muscles and fasciculation of the tongue. From the start of the illness the patient was mildly euphoric. The cerebrospinal fluid was normal and the Wassermann reaction negative. She died in the course of a chest infection two and a half years after the onset, aged 51 years. The diagnosis was motor neurone disease.

CASE II, 4 Hugh T. was not seen, but was said by his sisters to be alive and well, aged 50 years.

CASE II, 5 Helen T. was quite well up to the age of 44 years. She presented with weakness and tiredness of all limbs, the right arm having been the first involved.

Examination showed extensive muscle fasciculation in all limbs, with wasting of the small muscles of both hands. Power was markedly reduced and tone increased, except at the extreme periphery, with hyperreflexia and extensor plantar responses. Sensation was normal throughout and the cranial nerves were intact. The cerebrospinal fluid was normal and the Wassermann reaction negative.

The course was rapid and the limb musculature soon became flaccid and wasted. Superficial and deep reflexes were unobtainable. Only six months after the onset she was completely incapacitated, being unable even to feed herself. Dysphagia developed and she died in the course of a chest infection one year after the onset of symptoms, aged 45 years. The diagnosis was motor neurone disease.

FAMILY B

CASE I, 1 For Andrew W. no clinical details were available. He died aged 67 years. The diagnosis (from the death certificate) was progressive muscular atrophy.

CASE II, 1 John W. was quite well up to the age of 45, when he first noticed weakness and tiredness of both ankles and slight difficulty with his speech.

Examination at that time showed generalized muscle weakness with increased tone and hyperreflexia but without wasting or fasciculation. Plantar responses were flexor. There was slight slurred dysarthria but no other cranial nerve involvement. There was no mental, sphincter, or sensory disturbance and no ataxia.

Dysphagia was noted one year later. Re-examination then showed marked wasting and fasciculation of the distal limb musculature, with loss of supinator, ankle, and plantar reflexes. The proximal reflexes were hyperactive and the power of the proximal musculature, though reduced, was still fair. Other features were as before.

The limb musculature became progressively more flaccid and weak and all tendon reflexes were lost. Dysphagia increased, with nasal regurgitation of fluids, and he died in the course of a chest infection two years after the onset of symptoms, aged 47 years. The diagnosis was motor neurone disease.

CASE II, 2 For Hugh W. no clinical details were available. He died aged 45 years. The diagnosis (from the death certificate) was glosso-labial-laryngeal paralysis.

DISCUSSION

The aetiology of motor neurone disease is unknown and careful study among the Chamorros failed to demonstrate any external cause (Mulder and Kurland, 1954). Whatever the aetiology may be in sporadic examples, the evidence from this group strongly suggests some genetic link in familial cases, and in most pedigrees the disease (or the predisposition to it) appears to be transmitted as an irregular autosomal dominant. Indeed, Kurland (1957) argues plausibly for such an aetiology in all cases and explains the sporadic examples as the expression of a mutant gene with incomplete penetrance.

FIG. 1. The family trees of the affected families compared.

Some writers make a distinction between motor neurone disease in its sporadic and familial forms and published reports indicate one or two slight differences. For example, the female: male ratio in familial examples is approximately 3:2 as against approximately 4:1 in sporadic cases (Wilson, 1954). It has also been said (Gowers, 1899) that direct transmission occurs most often in those cases with a late onset, and in such familial examples 'the malady is nearly always myopathic and not spinal'. (If this is taken to mean a predominance of lower to upper motor neurone signs it agrees with the general picture presented by family A.) These however are small points and the weight of opinion is against the view that the two forms are essentially different.

Genetic predisposition to a disease may sometimes be responsible for the development of different varieties of the same disorder in different members of a family, depending, for example, on the sex and the age at onset. It is only a short step from this to argue that an underlying genetic abnormality might sometimes express itself as two apparently dissimilar disorders, and in support of this hypothesis are the reports of families in which two distinct disorders are transmitted separately or in combination (often as incomplete or abortive forms). Family A is an illustration. In that family there were three examples of motor neurone disease and one of disseminated

sclerosis of late onset. The fifth affected member (Agnes J.) also probably had disseminated sclerosis but showed the additional feature of left foot drop. She could, therefore, be considered to have minimal evidence of motor neurone disease as well as disseminated sclerosis.

Alternatively, one could attempt an 'overall' diagnosis for the whole family. One possibility would be hereditary spastic paraplegia. Many examples of hereditary spastic paraplegia showing muscle wasting and weakness have been reported, and there is evidence that the presence of ataxia is also quite compatible with this diagnosis (Roe, 1963). However, the rapid progress and predominant muscle flaccidity in three members makes this unlikely. On the other hand, could Jean McC. and Agnes J. be examples of spino-cerebellar degeneration? This is known to occur as a familial condition and Schut and Haymaker (1951) have shown a possible link between it and motor neurone disease. It is unfortunate that in no case was post-mortem examination performed, for without histological details it is impossible to decide the point.

There is less of a problem in family B and there seems no doubt that the diagnosis was motor neurone disease in all three affected members.

SUMMARY

A family is reported in which three out of six members in two generations suffered from motor neurone disease. All affected individuals were female.

Two others in the family presented a clinical picture similar to disseminated sclerosis.

Mention is made of a second family showing three examples of motor neurone disease in two generations, but insufficient details are available to make a complete report.

Possible alternative diagnoses are briefly mentioned.

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