A GENETIC STUDY OF CHRONIC SPINAL MUSCULAR ATROPHY

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The identity of an autosomal recessive form of chronic spinal muscular atrophy with clinical features intermediate between acute Werdnig-Hoffmann disease and Kugelberg-Welander disease is confirmed. This form accounts for the majority of patients with spinal muscular atrophy surviving into adult life. Spinal muscular atrophy with onset after 2 years of age is a heterogeneous group and both autosomal recessive and autosomal dominant forms occur.

This study was planned with the aim of distinguishing genetic entities among the forms of spinal muscular atrophy where survival into adult life occurred. It was hoped to obtain information on which to base genetic counselling to adult patients regarding their risks for having affected children. It was expected that most patients seen as adults with spinal muscular atrophy would have had either childhood onset (that is, Kugelberg-Welander disease) or onset in adult life. However to our surprise, as will be shown, most of these surviving patients in our study had onset in the first 2 years of life.

There were 41 index patients and they came mainly from three neurological centers: the New York Neurological Institute; the Hospital of the University of Pennsylvania; and the National Institute of Health, Bethesda. Criteria for their inclusion are shown in Table 1.

The patients all had a proximal and symmetrical muscle weakness which was shown on electromyography or muscle biopsy, or both, to be neurogenic in origin; and they were aged 10 years or more. Chronic polyneuropathy was excluded by a normal sensory examination and normal nerve conduction. Amyotrophic lateral sclerosis was excluded by proximal involvement, by the lack of upper motor neurone signs, and by a duration of more than 6 years.

The present ages of the patients ranged from 10-54 years, with a mean of 26 years. Out of the 41 patients, 14 were in wheel chairs, 9 were moderately severely disabled, and 18 were relatively mildly affected, needing support for climbing stairs but able to walk alone.

Onset was in infancy or childhood in 39 patients, but 6 of these had unusual clinical features which will be described later. The distribution of ages of onset in the other 33 patients is shown in the Figure.

It can be noted that there is a group of 19 index patients who had onset before the age of 2. This group has a normal or Gaussian distribution. Then there is a tail of 14 patients, forming no obvious distribution curve and with onsets ranging from 2 to 12 years. Because of the compactness of the first group it was thought appropriate to consider the patients in two groups: those with onset before the age of 2 and those with onset between 2 and 12 years. Support for such a distinction was found when it was observed that the affected sibs in these 19 families also had early onset, that is, before 27 months of age. Their ages of onset are also shown in the Figure.

Proc. 4th Int. Congr. Neurogenet. Neuroophthalmol. (1973)
Acta Genet. Med. Gemellol. (*Roma*), 23: 229-232

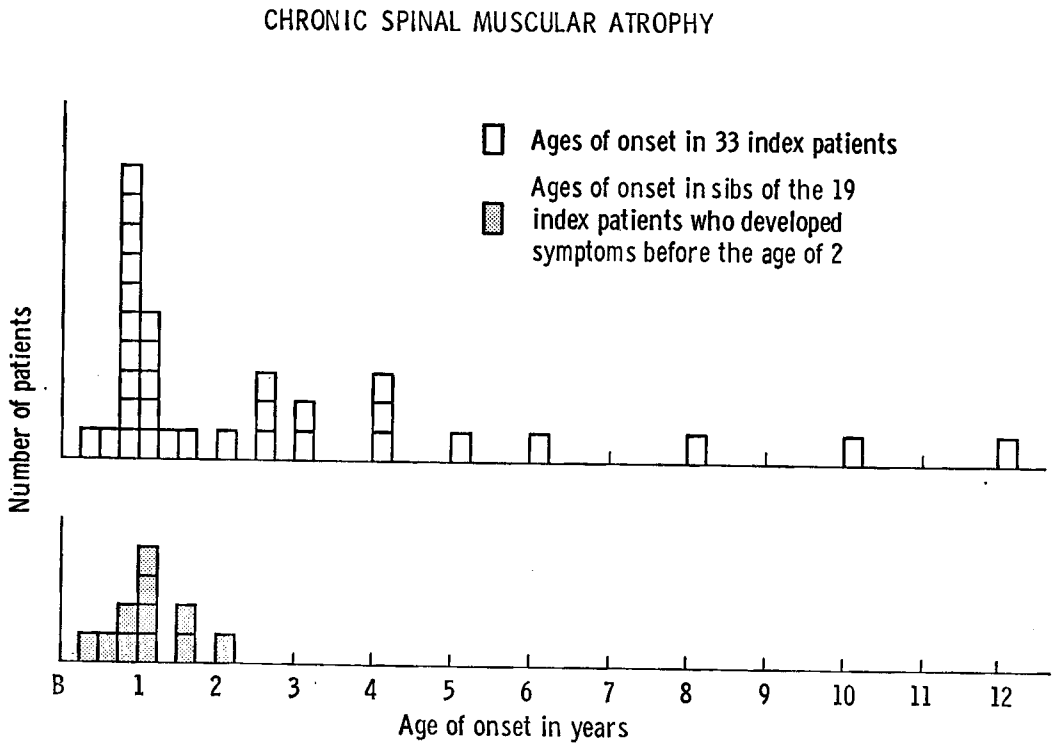
TABLE 1

CRITERIA FOR INCLUSION OF INDEX PATIENTS

1	Proximal and symmetrical muscle weakness
2	No upper motor neurone signs
3	An illness that is progressive in the early stages at least
4	An illness longer than 6 years' duration
5	Patient is aged 10 years or more
6	Evidence of denervation on electromyography
7	Normal nerve conduction times
8	Evidence of denervation on muscle biopsy

Details of the genetic findings in this group with onset under 2 years are shown in Table 2, Part A.

All but 13 of the sibs and children in these families were neurologically examined; the youngest was aged 8 and it is not thought that the disease could have been missed in any classified as normal. Sibs only were affected, in the proportion of 12 out of 57. This is less than the 1:4 proportion expected if all cases were autosomal recessive, but not significantly so. Looking at the age of onset and severity of disease in affected relatives, no intrafamilial similarity could be found sufficient to suggest more than one recessive entity. The evidence presented here supports the suggestion of Fried and Emery (1971) that there is an autosomal re-



https://doi.org/10.1017/S1120962300023829 Published online by Cambridge University Press

cessive form of spinal muscular atrophy which is clinically and genetically distinct from acute Werdnig-Hoffmann disease on the one hand, and from childhood onset spinal muscular atrophy, or Kugelberg-Welander disease, on the other hand. Dr. John Pearn at this meeting will describe the entity of acute Werdnig-Hoffmann disease. The families presented in Table 2, Part B, possibly fall into the category of Kugelberg-Welander disease.

TABLE 2

CHRONIC PROXIMAL SPINAL MUSCULAR ATROPHY: GENETIC DATA AND AGE OF ONSET

A. *Genetic data on 10 male and 9 female index patients with onset before 2 years*	B. *Genetic data on 7 male and 7 female index patients with onset 2-12 years*
* 0/38 parents affected	* 0/28 parents affected
* 12/57 sibs affected	* 2/29 sibs affected
* 0/5 half-sibs affected	* 0/7 half-sibs affected
* 0/4 children affected	* 1/8 children affected
* 1 set of consanguineous parents	* 1 double second cousin affected
	* 1 set of consanguineous parents

It can be seen at once that this group of patients is heterogeneous, for there are both sibs and children affected, suggesting at least one autosomal dominant and one autosomal recessive form. The two affected sibs of index patients had onset at 5 and 12 months, and this could mean that these two families belong to the preceding group. In one of these families a second cousin, doubly related to the index patient, was affected. However, even if these two families do belong to the earlier group, there is still evidence for an autosomal recessive childhood form as a patient with onset at 8 years had consanguineous parents.

A patient with onset at 4 years had a son with onset in infancy, and it is presumed that they have a dominant condition as there was no consanguinity.

There remain 11 families where the index patient was an isolated case, and where there was a total of 24 healthy sibs. Two adult sibs were not seen, but the remaining 22 sibs had a normal neurological examination, again making it unlikely that disease has been unrecognised. What are the possible explanations for these 11 isolated cases? Two or three are likely to be due to an autosomal recessive disorder, by chance having no affected sib. One or two are likely to be due to dominant mutations, for fitness in this condition is reduced by at least a half, and so for every familial dominant case there should be an isolated dominant mutation. A third possible explanation is that some of these isolated childhood onset cases are nongenetic.

From the point of view of genetic counselling there is a risk to sibs of an isolated case of less than 1:4, perhaps about 1:14, and a risk to children of isolated patients of about 1:8. If a sib, or parent or child, is affected, this of course indicates that the patient has either the recessive or the dominant variety.

Finally, we should mention the 8 patients not so far discussed. There were 2 patients with onset of proximal spinal muscular atrophy in adult life, one with an affected brother, and one with a possibly (but unconfirmed) affected father and paternal half-brother. There were 6 patients with unusual clinical features and these are summarised in Table 3.

There was an autosomal recessive condition of spinal muscular atrophy and opthalmo-

TABLE 3

SPINAL MUSCULAR ATROPHY WITH UNUSUAL CLINICAL FEATURES

1	Onset of muscular weakness at birth, with associated ophthalmoplegia and ptosis. 22-yr old Japanese girl, affected deceased brother, one normal brother.
2	Dysarthria from birth, onset limb girdle weakness in 20's, brisk reflexes. 30-yr old girl, affected brother, two normal brothers.
3	Weakness of scapulo-pelvic-peroneal distribution, associated with pes cavus and high CPK values. 2 unrelated patients; 0/4 affected parents; 0/6 affected sibs.
4	Onset 4-6 years, slow progression, contractures developing in childhood. Father and son affected.
5	Onset 17 years, proximal weakness, brisk UL reflexes, absent LL reflexes, extensor plantar responses. 2 affected elderly sisters, 5 normal sibs.

plegia; an autosomal recessive condition of spinal muscular atrophy with bulbar involvement, in particular dysarthria; there were 2 isolated and unrelated patients with the scapulo-peroneal syndrome; there was a dominant disorder where spinal muscular atrophy was associated with the early development of contractures; and an autosomal recessive variety where upper motor neurone signs were also present.

Acknowledgement

S. Bundey is indebted to the Muscular Dystrophy Associations of America Inc. for financial support during the duration of this study.

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