

X-linked recessive type of pure spastic paraplegia in a large pedigree: absence of detectable linkage with Xg

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Summary. A family with 24 males affected by an X-linked type of spastic paraplegia is reported. Twelve affected members were personally examined showing the pure form of the disease. Half of the affected males had many descendants, all normal. Linkage studies strongly suggest that this X-linked form of spastic paraplegia and Xg loci are not at a measurable distance on the X chromosome.

Seeligmüller (1876) and Strümpell (1880) were the first to describe familial cases of spastic paraplegia. Since then many pedigrees of this condition have been reported displaying either an autosomal dominant, or more frequently, an autosomal recessive pattern of inheritance. The pure form of the disease tends to be transmitted as dominant while the recessive cases frequently show additional signs. Two sex-linked pedigrees of spastic paraplegia associated with other disabilities were described by Blumel, Evans, and Eggers (1957), with 4 affected males, and by Johnston and McKusick (1961), with 16 affected males. In both kindreds the disease had early onset and progressive evolution leading to a precocious disability. In the first pedigree none of the affected males left progeny, while in the latter only one affected male patient had procreated.

More recently, Thurmon *et al* (1971) and Raggio, Thurmon, and Anderson (1973) reported two more kindreds showing spastic paraplegia, with no other associated abnormalities transmitted through an X-linked pattern of inheritance.

Patients and methods

In the present paper a large Brazilian pedigree with 24 males affected by a pure form of hereditary spastic paraplegia is presented, which shows a typical recessive X-

linked mode of inheritance. Affected males were found in five generations and half of them have had many descendants. The disease began in late childhood or adolescence and had very slow progression. The fertility and, apparently, the longevity of the affected subjects was not reduced. Among 18 male members personally examined, whose mothers were certain carriers (risk of one-half of being affected), 12 already showed clinical signs of the disease. Their ages varied from 9 to 65 years. Precise information was obtained about the rest of the family.

Creatine kinase (CK) activity determinations were estimated in 9 individuals in the family according to the method described in the Sigma Bulletin (1967). The upper limit of normal was taken as 20.0 Sigma units for males and 10.0 for females (Zatz *et al*, 1976).

Linkage studies were performed with respect to colour-blindness, G6PD, and Xg blood groups loci in an attempt to obtain informative data.

The study of G6PD was made by spectrophotometric assay and G6PD variants were identified by horizontal starch gel electrophoresis. These methods are described in detail in Saldanha, Nobrega, and Maia (1969).

Ishihara plates and the AO-HRR (American Optical Hardy-Rand Rittler) pseudoisochromatic plates were used for colour vision test.

The Xg blood groups were determined in London by Dr Ruth Sanger and the staff of the MRC Blood Group Unit.

Family report

Fig. 1 shows the complete genealogy. Information on the individuals who could not be examined was cross checked separately through several members of the family.

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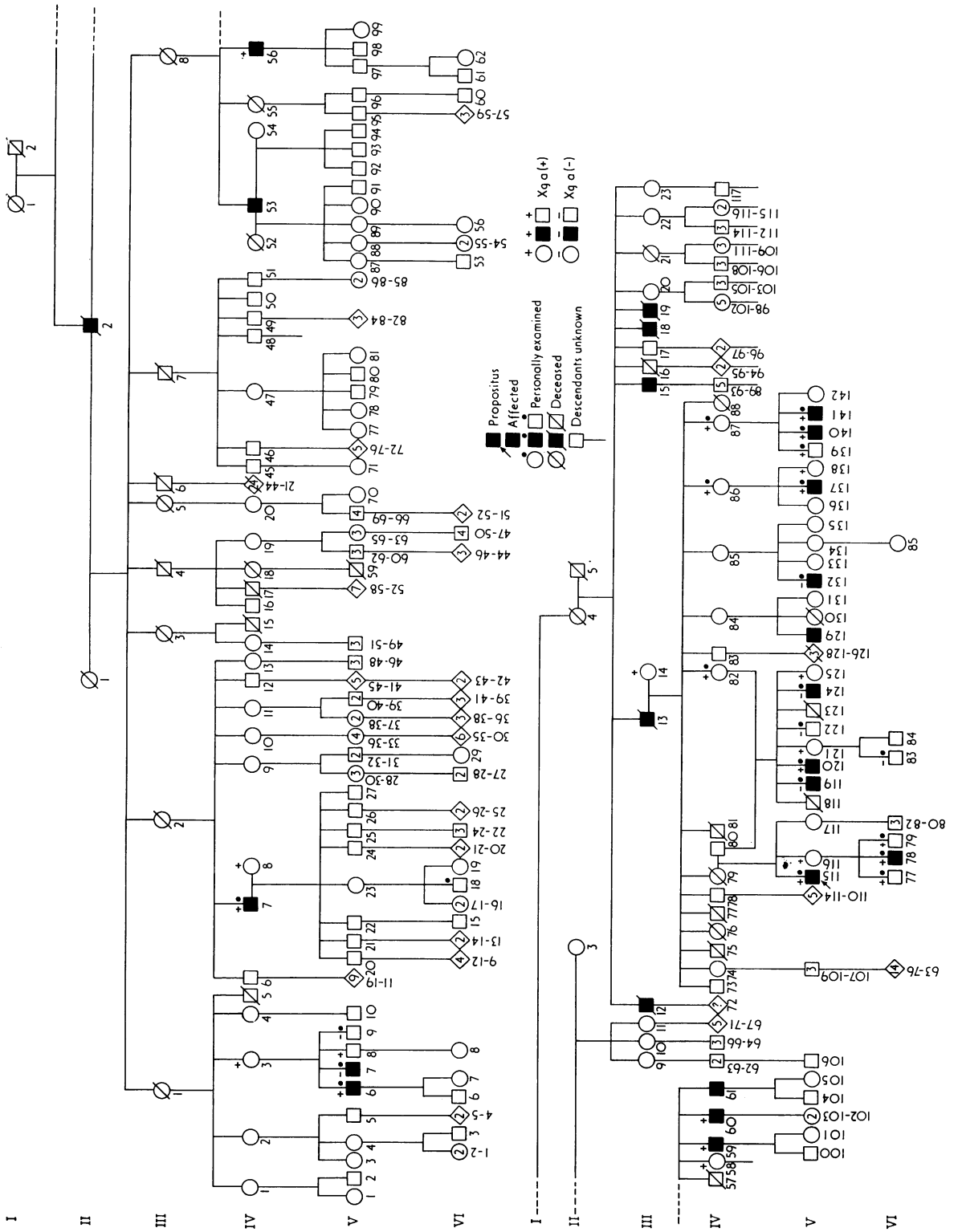


Fig. Pedigree of the family

The X-linked recessive mode of inheritance is proved by the following evidence:

(1) Only males were affected (probability of $(1/2)^{24}$ of chance occurrence if not sex-linked).

(2) There was no instance of male-to-male transmission. Among the sons of affected males, 20 who had already reached the age of manifestation of the disease were normal. The probability of this occurring by chance on the hypothesis of an autosomal dominant inheritance limited to males would be $(1/2)^{20}$ or 9.5×10^{-8} .

(3) The two oldest affected males (II.2 and III.13) had through their daughters a total of 27 grandsons, already old enough to show clinical signs of the disease if they had the gene. Among them, 15 were affected. This proportion is very close to the expected 1:1 ratio.

Case reports

Twelve affected males were personally examined. Muscular atrophy in the upper limbs was absent in all patients. Deep and superficial sensibility, sphincter functioning, co-ordination, and equilibrium were normal in all affected males, with the exception of IV.7 who had an unstable equilibrium. Table I summarizes the most important clinical findings in the series.

Male individuals V.9, V.122, V.139, VI.18, VI.77, VI.79, and VI.83 were also clinically examined; with the questionable exception of individual VI.18 (8 years old) whose neurological examination was inconclusive (he had very brisk deep reflexes in the lower limbs), all were clinically normal. Three female carriers IV.82 (CK activity: 5.0 Sigma units), IV.86 (CK activity: 3.5 Sigma units), and IV.87 were also examined and no abnormalities were found.

Linkage results

Colour-blindness and G6PD markers were not informative for linkage purposes.

Among 33 individuals who had their Xg blood groups determined 8 male members were shown to segregate informatively. They belong to two sibships (V.6 to V.9 and V.119 to V.124).

The data were analysed by the application of the lod-scores of Morton (1955) as set out in the tables of Maynard-Smith, Penrose, and Smith (1961). The sum of lod-scores of this family is shown in Table II.

Discussion

The disorder here described is a pure form of spastic paraplegia affecting only the lower limbs. The age of onset varies from 6 to 25 years old, but the clinical features are very similar in all affected members. The disease progresses very slowly until the fourth decade when it becomes non-progressive. All affected adults have a spastic gait but are able to walk without support. The difficulty in walking is more pronounced downwards than upwards. All, with one exception (individual V.7),

are psychologically well adjusted to their disease. No impairment of intelligence was observed. In no case was there an involvement of the upper extremities, cranial nerves, or cerebellar functions. The fertility and probably the longevity of affected males are not reduced. No abnormalities or sub-clinical signs of the disease were found in the certain carriers of the gene who were studied.

Normal CK values were obtained in all tested subjects, as expected, in a disease of neurogenic origin (Heyck and Laudahn, 1963; Fowler and Pearson, 1964; Hess *et al*, 1964; Zatz *et al*, 1971).

Since the first report of spastic paraplegia in 4 children of the same family (Seeligmüller, 1876), about 200 families with affected members have been described (Bayley, 1896; Rhein, 1916; Van Gehuchten, 1920; Bremer, 1922; Futer, 1929; Bell and Carmichael, 1939; Van Bogaert, 1952; Schwarz, 1952; Michaux, Teyssyre, and Fandre, 1952; Funk, 1957; Aaganaes, 1959; Hariga and Matthys, 1961; and others). A variety of associated signs has been reported in those cases. Involvement of the upper extremities, ataxias, and mental deterioration are common. However, the clinical picture is usually very similar within families, though it varies considerably from family to family. Haldane (1941) suggested that this variability could be the result of three different alleles located on a hypothetical homologous segment of the X and Y chromosomes. This hypothesis is, however, no longer tenable.

The pure form of spastic paraplegia is rare, according to Aaganaes (1959) and Becker (1968). It is characterized by spastic paraplegia of the lower extremities and exaggerated deep reflexes without other manifestations. The paralysis of the legs is non-progressive or very slightly progressive. Most of the familial cases show an autosomal dominant pattern of inheritance (Bayley, 1896; Van Gehuchten, 1920; Appel, 1949; Garland and Astley, 1950; Schwarz, 1952; Schwarz and Liu, 1956; Funk, 1957; Aaganaes, 1959). The disorder occurring in the family here described is a pure type of spastic paraplegia, but its clear X-linked mode of inheritance distinguishes it from the dominant form.

The pedigrees of X-linked spastic paraplegia reported in the literature by Blumel *et al* (1957) and Johnston and McKusick (1961) are not of the pure type.

In Blumel and co-authors' family, the two affected males personally examined were never able to walk or to stand alone; nystagmus was found in both and a diagnosis of spastic paraplegia with cerebellar involvement was made. None of the 4 affected males left progeny. Though the pedigree

TABLE I
CLINICAL AND NEUROLOGICAL FINDINGS OBSERVED IN 12 X-LINKED S

| | Individuals | | | | | | |
|--|--|---|--|--|--|--|--|
| | V.115 | IV.7 | V.6 | V.7 | V.119 | V.129 | V.124 |
| Age (yr) | 28 | 65 | 36 | 33 | 25 | 24 | 18 |
| Age at onset of first symptoms (yr) | 14 | 19 | 18 | 25 | 16 | 18 | 18 |
| Mental state | Normal | Logorrhoeic psychism | Normal | Psychic bad adjustment | Normal | Normal | Normal |
| Gait | Spastic | Atypical | Spastic | Spastic | Spastic | Spastic | Spastic |
| <i>Musc. atrophy</i> Lower limbs | Discrete | Absent | Severe | Absent | Absent | Absent | Absent |
| <i>Reflexes</i> Patellar Achilles Stylo-radial Bicipital Tricipital | Hyper. Hyper. Normal Normal Normal | Hyper. Hyper. Brisk Brisk Brisk | Brisk Brisk Normal Normal Normal | Hyper. Hyper. Normal Normal Normal | Hyper. Hyper. Normal Normal Normal | Hyper. Hyper. Normal Normal Normal | Brisk Brisk Normal Normal Normal |
| Ankle clonus Patellar clonus | Slight Slight | Marked Marked | Slight Slight | Marked Marked | Not obt. Not obt. | Slight Slight | Slight Slight |
| Babinski's sign | Absent | Absent | Absent | Absent | Absent | Absent | Absent |
| CK activity | 15.0 | — | — | — | — | 4.0 | — |

Hyper. = hyperactive; not obt. = not obtained; ap. norm. = apparently normal.
* Observed by their mothers.

is compatible with a sex-linked inheritance, the possibility of an autosomal dominant mode of transmission limited to males cannot be excluded.

In the family reported by Johnston and McKusick (1961) the disorder began as pure spastic paraplegia, but over the course of many years it gradually involved the upper extremities, brain stem, optic nerves, and cerebral cortex. Dysarthria and nystagmus were found in some affected patients and one affected member became severely demented. The onset was very early and fertility was severely reduced.

In the kindred described by Thurmon *et al* (1971) 8 affected males in two generations were found showing a typical X-linked pattern of inheritance.

Three affected males were married and two among them have had normal offspring. Five patients were personally examined. With the exception of one 40-year-old man who was in a wheelchair for most of the time, the other subjects seem to have the pure form of spastic paraplegia.

Raggio *et al* (1973) reported 9 males with hereditary spastic paraplegia in a second family following an X-linked inheritance pattern. The disorder has been found not to be associated with other abnormalities. The authors suggest the possibility that this second family might be related to the previous one.

The description of this Brazilian family with pure spastic paraplegia displaying typical X-linked inheritance confirms that there is a gene responsible for this disorder located on the X-chromosome.

Although the clinical picture of the disease in its pure form is quite different from that described in the two first reports of X-linked spastic paraplegia (Blumel *et al*, 1957; Johnston and McKusick, 1961) there is no way at present of deciding if the two disorders depend on different loci or on the same locus of the X chromosome. If the latter is the case, the differences could be ascribed to the action of different alleles. The same doubt existed with respect to the Duchenne and Becker types of progressive muscular dystrophy. However, recent linkage studies with the colour-blindness and G6PD loci

TABLE II
LOD-SCORES FOR X-LINKED SPASTIC
PARAPLEGIA AND X_g

| Present Study | Recombination Fraction (θ) | | | | |
|-------------------------------|-------------------------------------|--------|--------|--------|--------|
| | 0.05 | 0.1 | 0.2 | 0.3 | 0.4 |
| $z_1:2:2$ $e_1:2:2$ | -1.469 | -0.911 | -0.405 | -0.159 | -0.037 |
| $z_1:2:2$ $e_1:3:1$ | -1.461 | -0.899 | -0.392 | -0.152 | -0.035 |
| Sum of lod-scores | -2.930 | -1.810 | -0.797 | -0.311 | -0.072 |
| Antilog = relative likelihood | 0 | 0.01 | 0.16 | 0.49 | 0.85 |

LEGIA AFFECTED MALES

| V.132 | V.137 | V.140 | V.141 | VI.78 |
|--|--|---|--|--|
| 23 | 17 | 8 | 7 | 11 |
| 10 | 14 | 6* | 7* | 10* |
| Normal | Normal | Normal | Normal | Normal |
| Spastic | Spastic | Ap. norm | Ap. norm | Spastic |
| Absent | Absent | Absent | Absent | Absent |
| Hyper. Hyper. Normal Normal Normal | Hyper. Hyper. Normal Normal Normal | Hyper. Brisk Normal Normal Normal | Brisk Brisk Normal Normal Normal | Hyper. Hyper. Normal Normal Normal |
| Marked Not obt. | Slight Sketched | Not obt. Not obt. | Not obt. Not obt. | Not obt. Not obt. |
| Positive | Absent | Absent | Absent | Absent |
| 6.5 | 5.0 | 7.5 | 4.0 | — |

strongly support the two loci hypothesis (Emery, 1966; Emery, Smith, and Sanger, 1969; Skinner, Smith, and Emery, 1974; Zatz *et al.*, 1974).

Linkage studies were performed in Johnston and McKusick's genealogy and in the present one, but no informative data were obtained with colour-blindness or G6PD.

Xg blood group studies performed in Johnston and McKusick's family have shown one non-recombinant and one recombinant.

The sum of the lod-scores of our genealogy suggests strongly that the present form of X-linked spastic paraplegia and Xg loci are not at a measurable distance on the X-chromosome. This allows little hope that the Xg locus will help to decide this question.

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