A Sex-Linked Recessive Form of Spastic Paraplegia

ALAN W. JOHNSTON[1] AND VICTOR A. McKUSICK

Division of Medical Genetics, Department of Medicine, Johns Hopkins University School of Medicine Baltimore, Maryland

IN THEIR REVIEW of spastic paraplegia, Bell and Carmichael (1939) found 74 pedigrees, not including those with what they termed "spastic ataxia." In 25 the inheritance was apparently autosomal dominant and in the remaining 49 the inheritance was "probably recessive." They found no instance of sex-linked recessive inheritance. The last is the type demonstrated in the kindred described below. The same kindred was referred to by Ford (1937) and the sex-linked recessive inheritance was pointed out. However, the report was not noted by Bell and Carmichael. Reviews of the clinical and genetic features published more recently (Landau and Gitt, 1951; Van Bogaert, 1952; Refsum and Skillicorn, 1954; Funk, 1957; Hohmann, 1957; Bruins and Simons, 1957) have also failed to mention any families displaying sex-linked inheritance of the trait. Van Bogaert (1961) and Refsum (1961) state that they are not acquainted with any other family in which spastic paraplegia displayed sex-linked recessive inheritance.

In the kindred described below it has been possible to trace the character back seven generations to a couple born about 1780. Sixteen affected males in five generations have been identified. Eight living affected members of the family are known. We have examined seven of these, with ages varying from 4 to 61 years, and have reliable and detailed recent medical information on the eighth.

THE PEDIGREE

The full pedigree is presented in Fig. 1. Information on deceased members was derived from primary sources (census records, vital records, family Bibles, hospital records and others) in addition to members of the family.

There can be no question about the state of affection and of non-affection of the males as indicated in the pedigree, with the possible exception of individual V-30. This male, born in 1895, died at 3½ years of age. He had not yet learned to walk, and the mother—who was familiar with the disease in her brothers, uncles and sons—believed him to have been affected.

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[1]Present address: University College Hospital, London, England.

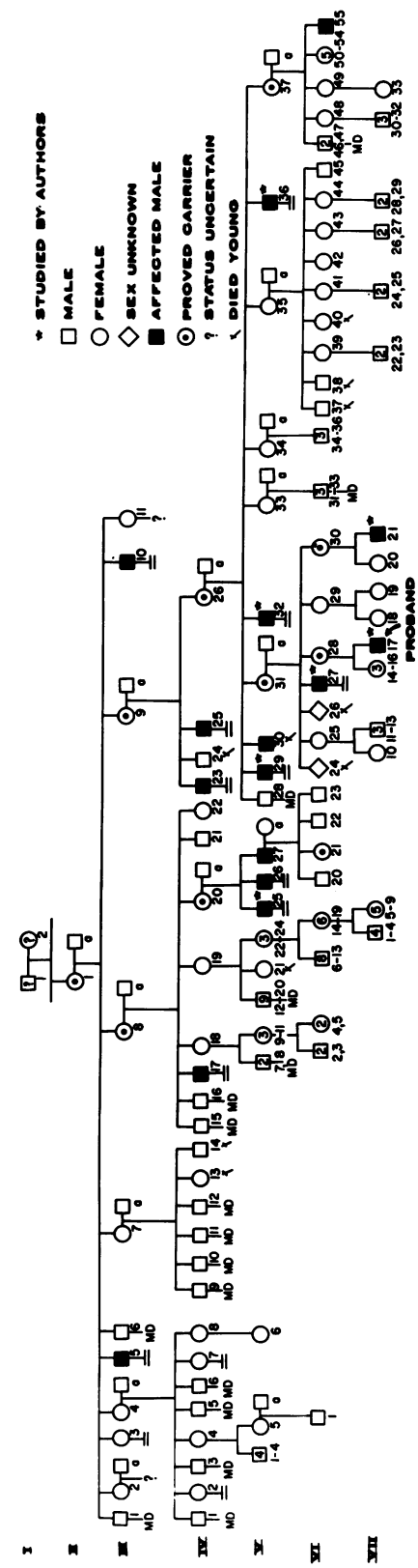

FIG. 1. Pedigree of the family described. See text for information on specific individuals as indicated by the numbers. MD = many descendants all free of spastic paraplegia; double horizontal lines under a symbol indicate no progeny.

V 30 was the oldest member of his sibship. The birth order of the others is as indicated. VI 24 and 26 were female offspring who died in the first two weeks of life. VII 11-13 are three females, not three males. Females VI 29 and VII 10, both potential carriers, have had sons born since preparation of the chart. Examination at 6 months and 3 months, respectively, showed no detectable abnormality. Except for the V 30, the males indicated as dying young of accidental causes or tuberculosis after the age of 10 years and can be considered unaffected with reasonable confidence.

BRIEF CASE REPORTS

(Information on neurologic status at the time of this study is provided in table 1.)

Case 1. W. M. (VII-21), born in 1956, tends to walk on his toes (Fig. 2) and to stumble over small objects. His balance is only fair. He pulls himself upstairs by the banister rail, but comes downstairs sitting. He can feed himself, but is able to dress himself only partly. His development has otherwise been normal. Bladder control was attained by the usual age.

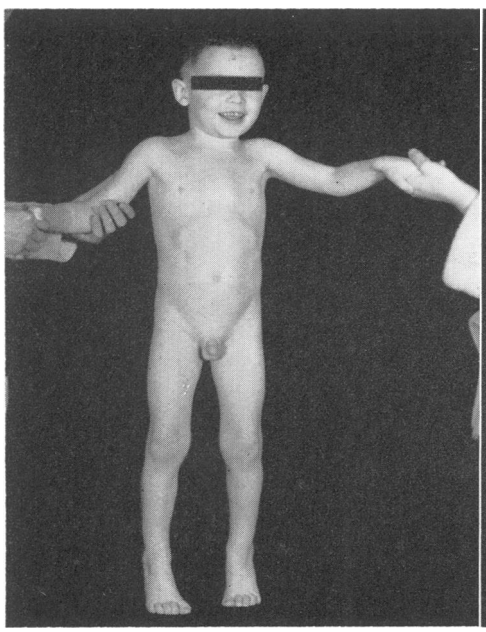

FIG. 2. The tip-toe stance is demonstrated in W. M. (VII-21). He requires support. (In J. R., VII-17, Achilles tenoplasty has been performed.)

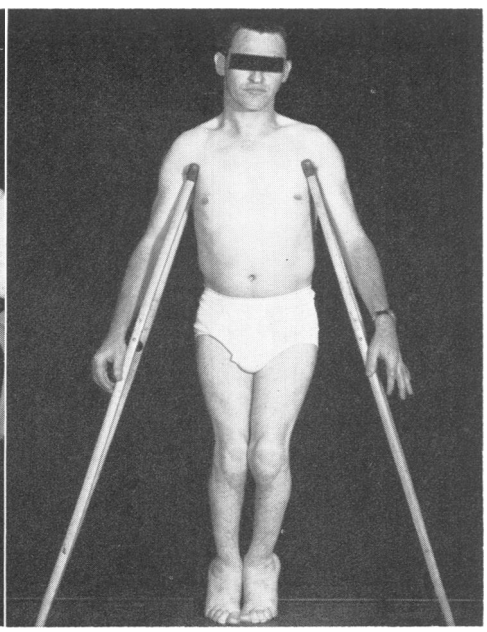

FIG. 3. The tip-toe stance, wasting of the legs and tight adduction of the legs is demonstrated in C. O. (VI-27).

Case 2. J. R. (VII-17), born in 1955, sat up and talked at the normal age, but he has not been able to walk normally. He was toilet-trained at 27 months. He uses his hands normally and speaks fairly well. He tends to walk on tiptoe with a scissors gait.

Case 3. R. G. (VI-55) was apparently well until 13 or 14 months of age when he developed an ear infection. He was febrile and lethargic for about 10 days. At that time the mother first noted paralysis of the legs which has been constant since then. The mother feels this boy has not been as fast in his mental development as were her other children. He was not walking at the time of his illness and has not learned to walk. A diagnosis of post-meningeal syndrome has been made. In September 1959 his I. Q. had been tested at 69. His "I.Q. potential" was considered "borderline normal" in the 79-85 range. His physician reports (1961) that during the last three years some involvement of the arms has become evident.

Examination on March 2, 1961 (see table 1 for details) left no doubt that the boy has the same disorder as do fourteen of his male relatives. Walking was impossible without the use of full-length leg braces and support of hands on a "rollator." In moving about he held the handles tightly and used chest, back and arm muscles to pull

TABLE 1.

	I* W.M. (VII-21)	II J.R. (VII-17)	III R.G. (VI-55)	IV C.O. (VI-27)	V G.H. (V-36)	VI J.H. (V-32)	VII C.H. (V-29)	VIII G.W. (V-25)
Age at Study	4	5	6	34	47	56	59	61
CNS								
mentality	N	N	borderline normal	prob. N	slightly impaired	slightly impaired	impaired	paranoid
vision	N	N	N	? R.O.A.	R.O.A.	impaired	O.A.	impaired
nystagmus	N	N	slight	slight	gross	ophthalmoscopic	++	none
speech	N	N	N	slurred	N	slurred	slurred	N
Arms								
power	N	N	N	N	weak interossei	weak interossei	N	N
reflexes	N	N	N	I	I	I	I	N
tone			N	I	slightly increased	I	I	
Hoffmann	none	none	+ (right)	+	+	+	+	+
dysdiadochokinesis	N	N	±	+	+	+	+	none
coordination	N		N	D		D	N	N
Legs								
wasting	N	N	++	++	+++	+++	++	+
position of feet	plantar flexion	plantar flexion	plantar flexion	plantar flexion	plantar flexion	subluxation	subluxation	talipes equinovarus
power	impaired	slightly impaired	greatly impaired	virtually none	none	none	none	greatly impaired
tone	slightly increased		increased					
reflexes	v. brisk	v. brisk	v. brisk	v. brisk	v. brisk	v. brisk	v. brisk	v. brisk
clonus	bilateral		left ankle	both ankles	both ankles	both ankles	both ankles	
plantar r.	↑	↑	↑	↑	↑	↑	none	↑
vibration sense	N	N	not tested	absent	absent	absent	absent	absent
position sense	N	N	probably absent	absent	absent	absent	absent	
circulation	N	N	N	poor	poor	poor	poor	N
elephantiasis	none	none	none	none	none	extreme	moderate	none
Sphincter control	N	N	N	N	grossly affected	N	N	N
Skeleton								
pectus excavatum	none	none	none	none	moderate	very marked	none	moderate
scoliosis	+	none	none	none	+	+	+	+

D = decreased. N = normal (or negative). I = increased. OA = optic atrophy.

*Cases are numbered according to age of patient at time of examination.

himself along, dragging his feet and "lunging" one foot in front of the other with a twisting motion of the trunk. There was no evidence of distractibility or short attention span as seen with organic brain damage and no "temper tantrums" as described in another report.

Both feet were in equinovarus position with marked pes cavus. The legs were held in scissors position even when the child was recumbent.

Case 4. C. O. (VI-27), born in 1925, has had to use crutches all his life. However, he attended school to the seventh grade, receiving home teaching for another two years. He carries on carpentry and basketry at home, and uses power tools. He thinks his hands are normal. Reading fine print, particularly with his left eye, is difficult. He has had no bladder or bowel disturbance.

The thighs are well developed though the calves are thin. The legs are tightly adducted and the feet plantar-flexed (Fig. 3). Walking and standing increases the degree of extension, adduction, and plantar flexion, giving a "scissors" posture.

Chromosome analysis using a blood culture technique as outlined in other studies (Johnston *et al.*, 1961) revealed no abnormality.

Case 5. C. H. (V-36), born in 1912, has never walked except with the aid of crutches and for about 20 years he has been confined to a wheelchair. He regards his hands as normal. His principal complaint is of retention of urine with frequency and incontinence. The symptoms began abruptly in 1936 with acute retention. Several urological operations have been performed, as well as orthopedic procedures for correction of the deformity of the feet. His bowels are, like his bladder, "unpredictable." For about 15 years his near vision has been failing, though he still does some basketry. His speech is normal.

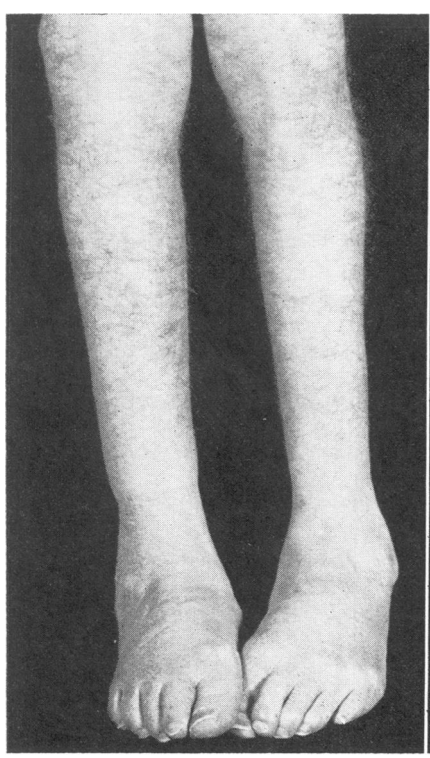

FIG. 4. Several surgical operations for straightening of the feet have been performed on G. H. (V-36).

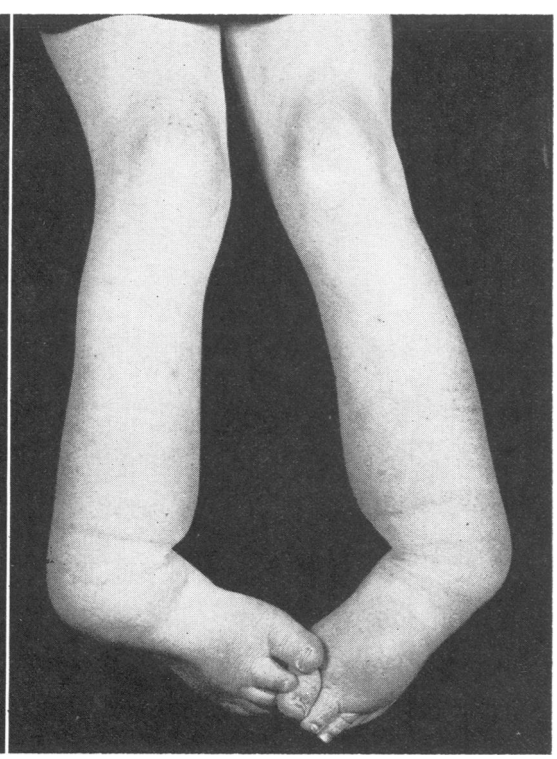

Fig. 5. The deformity of the feet, edema and trophic changes in the skin are well demonstrated by J. H. (V-32).

In the legs the calves and thighs are markedly wasted and voluntary movement is completely lacking. The legs are spastic with the right foot plantar flexed and the left both plantar-flexed and inverted. The skin of the feet is poorly nourished (Fig. 4).

As in case 4, chromosome analysis revealed no evident abnormality.

Case 6. J. H. (V-32), born in 1903, was able to walk, although with difficulty, until the age of 16. He has had to use a wheelchair for about 20 years. He thinks that his hands are normal, and he is able to work with cane and reeds. His eyesight has gradually deteriorated. His sphincters are normal.

Severe wasting of the calves is partially masked by elephantiasis from the mid calf peripherally. The skin is malnourished and the peripheral pulses cannot be felt. Both feet are plantar-flexed and so markedly inverted that the ankle joints appear subluxated (Fig. 5). There is no voluntary movement but only marked spasticity and adduction with flexor spasms.

Case 7. C. H. (V-29), born in 1901, has never been able to walk unaided and for the last 20 years has needed a wheelchair. He considers his hands and speech normal. His eyesight has been poor for about 20 years, the right eye being worse than the left. He still does a little work repairing chairs. Sphincter control is normal. He is unable to do simple arithmetic and his memory is poor for all events.

His legs are very spastic and tightly adducted (Fig. 6). The thighs show moderate wasting. Marked wasting of the calves is partially obscured by a moderate degree of elephantiasis. The right foot shows marked inversion and plantar flexion and the left is similarly, though less severely, affected. The skin is poorly nourished over the distal part of the foot.

Case 8. G. W. (V-25), born in 1899, was never able to walk without assistance or

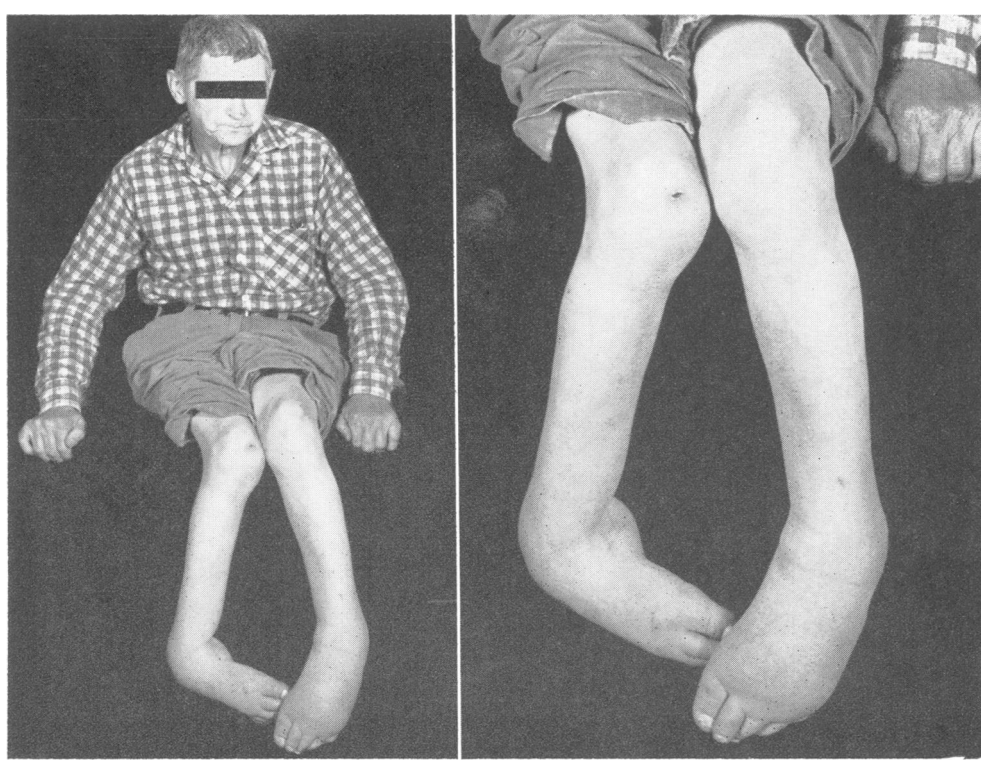

FIG. 6. The changes in the legs of C. H. (V-29) are strikingly similar to those shown in Fig. 5.

crutches. He became confined to a wheelchair at the age of 14 years. Enuresis continued into his teens and he has never had complete control of his bowels. Although he learned to read and write, his eyesight was never good and has gradually deteriorated. In his twenties he ran a flourishing bicycle repair business. In 1946 he developed marked paranoid symptoms which led to his admission to a mental hospital. He has remained at this hospital in a severely demented state for about 15 years.

On examination he is uninhibited and frankly paranoid. There are opacities in the right eye from an old iridocyclitis, while the left fundus is obscured by a cataract. The legs are spastic with inversion and plantar-flexion of the feet.

DISCUSSION

The neurology. The neurologic disorder in this family begins as pure spastic paraplegia but over the course of many years it gradually spreads to involve the upper extremities, brain stem, optic nerves and cerebral cortex. Sensory loss is confined to the posterior columns. The arms are almost always affected, but the extent and degree of involvement of the brain varies. Of the five adults, three have dysarthria (VI-27, V-29, V-32), one of three brothers, who was also the oldest patient, being spared. Similarly, the severity of the nystagmus varies from purely ophthalmoscopic (V-32) to gross (V-29, 36). Nor is there any parallelism between the dysarthria and the nystagmus. Again, of these three brothers, one has had severe visual impairment for twenty years, while his two brothers, though also having optic atrophy, are much less handicapped. Variation is probably also true of the mental state in that two out of three other affected brothers were evidently intelligent and sane (V-26,27), while the third (V-25) has become severely demented.

The genetically determined spinocerebellar degenerations are a confused group with much overlap in manifestations (Greenfield, 1954). For example, optic atrophy and mental aberration occur in somes cases (Ferguson and Critchley, 1929; Van Leeuwen and Van Bogaert, 1949). In some families (Schut, 1954; Landau and Gitt, 1951) pyramidal signs and ataxia occur together, with varying relative severity in the individual cases. These are the pedigrees classified as spastic ataxia by Bell and Carmichael (1939). However, spastic paraplegia tends to be a rather clearly defined entity in many pedigrees (e.g., in 74 of those collected by Bell and Carmichael). The clinical picture is usually highly similar within families, although it varies considerably from family to family. For example, Haldane (1941) suggested that there may be at least three groups as far as age of onset is concerned. Early onset is characteristic of the disorder in this family.

When the patients are seen in the late stages of their disease the diagnosis has evidently been uncertain. On one hospital admission for orthopedic procedures the diagnosis of Friedreich's ataxia was made (in V-36). On another hospital admission for generalized dermatitis the diagnosis was simply multiple contractures (in IV-25) with no specific neurologic label being assigned. A mistaken diagnosis may also be made in youthful cases seen without benefit of knowledge of the family history. For example, in individual VI-55 the leg manifestations were first noted by the family after an infection which probably was otitis media, and the physicians have interpreted the neurologic disorder as the residuum of meningitis.

Some practical importance attends distinguishing the disorder in the family reported here from hereditary infantile spastic diplegia (Hohmann, 1957; Bruins and Simons, 1957). The latter disorder, inherited as a dominant trait, is nonprogressive and does not involve the arms. Good rehabilitation is achieved with orthopedic treatment.

The genetics. The pattern of inheritance in the family described here is that of a sex-linked recessive trait. The sex-linked recessive hypothesis was tested (Steinberg, 1959) by determining the proportion of affected males among the grandsons of proven carriers through their daughters. The expected proportion is 0.25 (Fig. 7) and as shown in table 2 the agreement of observed with expected is excellent.

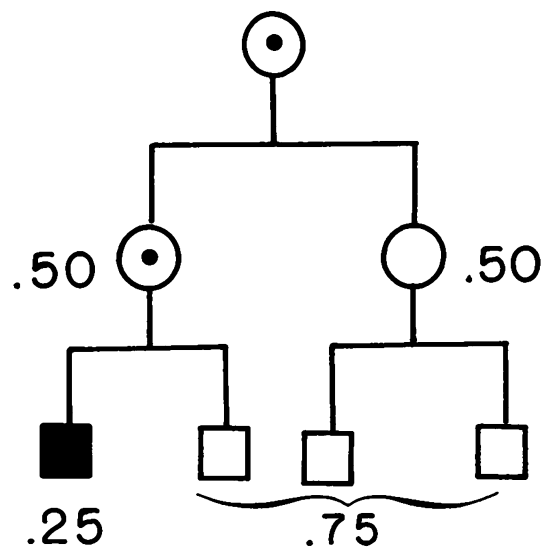

FIG. 7. The probability of affected males among the grandsons of a proven carrier (through her daughters).

TABLE 2. GRANDSONS OF IDENTIFIED CARRIERS THROUGH THEIR DAUGHTERS

Carriers	Grandsons through Daughters		
	Total	Affected	Unaffected
II 1	16	3	13
III 8	14	3	11
III 9	5	4	1
IV 20	—	—	—
IV 26	13	2	11
V 31	2	2	0
V 37	3	0	3
Observed	53	14	39
Expected		14.25	38.75

However, an autosomal dominant trait which for some reason is limited to the male sex and interferes with procreation can result in a pedigree pattern

identical to that of a sex-linked. An example is the syndrome of testicular feminization (Stewart, 1959; Grumbach and Barr, 1958). If the affected males in a pedigree do have children and if a son is affected ("male-to male transmission"), sex-linked inheritance is excluded. In the kindred discussed here one affected male (V-27) had three sons. All these were normal, a result consistent with sex-linked recessive inheritance. However, it is also consistent with male-limited autosomal dominant inheritance. According to the latter hypothesis, the probability of an affected son is one-half and the likelihood that all three sons would be normal is $(\frac{1}{2})^3$, or 1 in 8. If linkage with color-blindness can be demonstrated (Stewart, 1959) then sex-linked inheritance is established. If no linkage is demonstrated, then the two loci may be rather far apart on the X chromosome or the gene under consideration may be on an autosomal chromosome. Since color blindness was not present in the family reported here and since the family is of non-Mediterranean Caucasian origin and therefore not likely to have the glucose-6-phosphate dehydrogenase defect, no sex-linked marker is available. Thus, it is not possible on the evidence at hand to distinguish between sex-linked recessive and male-limited autosomal dominant inheritance for the spastic paraplegia in this family. However, the latter possibility is less plausible because there is no obvious mechanism by which the neurologic manifestation of a postulated autosomal gene could be limited to males.

Haldane (1941-a) suggested that in many or most of the apparently recessive cases of spastic paraplegia the disorder is in fact transmitted as a partial sex-linked recessive trait, that is, it behaves as though determined by a gene on presumed homologous parts of the X and Y chromosome. Since the existence in man of homologous parts between which crossing-over occurs is in doubt and since the genetic evidence for partial sex-linkage is dubious (Morton 1957), Haldane's proposal requires no further comment at this time.

How a chromosomal aberration could account for sex-linked recessive inheritance in this pedigree is not clear. On the basis of studies of patients 4 and 5 it can be stated that within the limitations of our present techniques no chromosomal abnormality was detected.

Although no other families displaying sex-linked recessive inheritance of spastic paraplegia have, to our knowledge, been reported, there are a number of reported pedigrees (see Fig. 8 for an example) in which persons in only one sibship were affected and in which the affected persons were all male (Bell and Carmichael 1939). That there was an excess of such sibships is not certain. Bell and Carmichael (1939) found among the apparently recessive pedigrees 75 affected males and 68 affected females, a sex ratio of 52.4 ± 4.2. The situation is similar to that found by Chung, Robison, and Morton (1959), who in connection with congenital deafness stated that "the hypothesis that the (nonsignificant) excess of affected boys is due to sex-linkage can neither be proven nor excluded." Certainly an X-borne gene can be responsible for the disorder in only a small proportion of families.

Haldane (1941-b) pointed out that there is close intrafamilial similarity in the age of onset of spastic paraplegia but considerable interfamilial variation. He suggested that genetic modifiers are not a likely explanation and that more

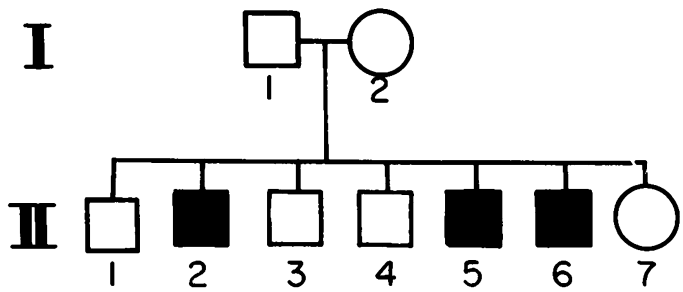

FIG. 8. Example of reported pedigree which is consistent with sex-linked recessive inheritance and which relates to a form of spastic paraplegia phenotypically identical with that in the family described here. The pedigree is, however, equally consistent with autosomal recessive inheritance. (From Krafft-Ebing, 1900).

1. Died of diphtheria at 16 months. Was walking normally.
2. Abnormality of legs noted at 5 months. Walked but clumsy at age 2. At 12 normal mentality, eyes and speech. Legs markedly weak with adductor spasm, much exaggerated knee jerks and pes equinus. Could stand alone only briefly.
3. Healthy age 10.
4. Died at 2 years of pneumonia. Was walking normally.
5. Said to have been normal until age 2 when difficulty walking noted after diphtheria. At age 8 mentally backward, speech clumsy. Strabismus, pes equinovarus, hyperextension of great toes noted. Markedly weak legs, adductor spasm, exaggerated kneejerks. Could not stand alone.
6. Disorder already evident at 2 when started walking. Speech slurred from beginning. At age 4, intelligent. Strabismus, pes equinovarus with dorsal flexion of great toe, exaggerated knee jerks. Could not stand alone.
7. Normal, age 18 months.

Sensibility normal in affected brothers. Upper extremities normal except for some increase in deep reflexes.

likely multiple alleles exist, each responsible for a somewhat different clinical picture especially as regards age of onset.

Onset was early in affected members of this family. Longevity is little reduced. From the fact that one affected person (V-27) fathered four children, it is clear that the disease does not produce complete infertility. However, for social as well as medical reasons, average effective fertility is severely reduced.

A sister (VI-49) of an affected male has idiopathic scoliosis. No scoliosis or other abnormality (such as pes cavus, exaggerated reflexes or Babinski sign) interpretable as a *forme fruste* of the neurologic disorder is present in the proved carriers who are now living. No scoliosis in carriers now deceased is recalled.

Only one of the living carriers has had a recognized miscarriage. H.H.O. (V-31) had two early miscarriages. The same person had two female offspring who died in the first two weeks of life (VI-24,26). None of the other living proved carriers has had a stillborn child or child dying in early infancy.

Although this is probably the first reported family with sex-linked recessive spastic paraplegia (Van Bogaert 1952), occasional pedigrees of Friedreich's ataxia (Turner and Roberts, 1938) and of Charcot-Marie-Tooth pero-

neal muscular atrophy (Allan, 1939) have shown this pattern of inheritance rather than an autosomal pattern. We have currently under study a pedigree in which Parkinsonism shows sex-linked recessive inheritance. Merzbacher-Pelizaeus disease, a central nervous system leukodystrophy, can be stated to be transmitted as a sex-linked recessive with the reservation that since it is a lethal disorder sex-limited autosomal dominant inheritance cannot be completely excluded.

Recently our attention has been directed to a report of sex-linked recessive inheritance of what was termed hereditary cerebral palsy. The clinical features were similar to those reported here. The kindred, Mexican, contained at least four affected males in three sibships in two generations. BLUMEL, J., EVANS, E. G., AND EGGERS, G. W. N. 1957. Hereditary cerebral palsy. A preliminary report. *J. Pediatrics* 50: 454.

SUMMARY

A possibly unique family in which spastic paraplegia is transmitted as a sex-linked recessive trait is described. The spastic paraplegia is of early onset and slow progression. Relatively late in the course the upper extremities, brain stem, optic nerves and cerebral cortex are involved.

ACKNOWLEDGMENTS

Dr. Margery W. Shaw, Department of Human Genetics, University of Michigan Medical School, examined one affected family member (VI-55) and made useful criticism of the manuscript. Mrs. Norris Harris assisted in the genealogic research, Dr. Berwind N. Kaufmann did the chromosome studies in patients 4 and 5.

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