Short report

Manifesting heterozygosity in sex-linked spastic paraplegia?

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SUMMARY An unusual form of hereditary spastic paraplegia is described. Affected females have a late-onset slowly progressive spastic paraparesis. Affected males show oligophrenia with a rapidly progressive spastic quadriplegia. The mode of inheritance is consistent with sex-linkage, with partial manifestation in female carriers.

Hereditary spastic paraplegia is both clinically and genetically heterogeneous, a point which was recognised over 40 years ago,¹ and which has been the subject of a recent comprehensive review.² Occasionally a family is encountered which poses a difficult nosological problem for both neurologist and geneticist. Such a family is now reported.

Case histories

The family pedigree is shown in the figure. There is no known consanguinity in the kindred.

(A) Affected males

Case 1 (IV 1) The four-year-old proband was born at term following an uneventful pregnancy. All developmental milestones were delayed: at 25 months he scored at the 15 month level on the Bayley Mental Scale. Recent examination revealed marked generalised hyperreflexia, extensor plantar responses, very stiff lower limbs and an alternating convergent strabismus. Investigations giving normal results included: routine haematology and biochemistry, liver function tests, uric acid, creatine kinase, thyroid function, serum aminoacids, banded karyotype, synacthen test, skull and spine radiography, cerebral CT scan and audiology. No vacuolated lymphocytes were seen.

Case 2 (III 5) Hypertonia and developmental delay were first noted in this 18-year-old boy at six months. He crawled at three years and was briefly able to walk a few steps with support at seven years. Bladder control was achieved at four years and lost at 12 years. Intelligence assessments at eight, 11 and 13 years each yielded an IQ of approximately 50 with no evidence of intellectual deterioration.

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ration. Vision was normal. On examination he showed severe spastic quadriplegia with clonus and contractures in all limbs, slurred speech, a divergent strabismus with unequal pupils which react to light, and bilateral pale optic discs with no nystagmus. Chromosomes, synacthen test, skull and spine radiography and brain scan are normal.

Case 3 (III 3) This 17-year-old boy lives in the USA. He was diagnosed as having "mild cerebral palsy" at 10 months. At 6 years he could walk with assistance and was toilet trained; these skills were lost by 13 years. At present he requires total care. Photographs suggest a spastic quadriplegia.

(B) Affected females

Case 4 (I 2) This lady tended to trip easily in her late teens, but could walk unassisted until aged thirty-five years when examination showed bilateral optic atrophy, slurred speech, spastic paraparesis and bilateral pes cavus. She became wheelchair bound at 45 years when urinary diversion was performed because of incontinence. Vision, hearing, speech, intellect and manual dexterity were normal up to the time of death, due to pneumonia, at age 49 years; no necropsy was performed.

Case 5 (II 1) This 43-year-old lady walked on her toes in childhood. At 21 years slowly progressive stiffness was treated by bilateral Achilles tendon release operations. At present she can walk only with a stick and has urgency of micturition with occasional incontinence. Vision, hearing and intellect are normal. Examination shows a gross spastic paraparesis with adductor spasm in the lower limbs, marked wasting below the knees and bilateral pes cavus with clawed toes. Sensation is intact. There is slight temporal pallor of the optic discs. Normal investigations include full blood count, routine biochemistry, serum B12 and folate, WR and visually evoked responses. Nerve conduction studies show slowing of motor conduction in the arm and leg with prolonged F-wave latencies in the arm. Sensory conduction is also slow in the arm with low amplitude sensory nerve action potentials: the sural nerve action potential is absent.

Fig The family pedigree.

Case 6 (III 1) Apart from occasional aching in her left leg this 25-year-old lady is asymptomatic. Examination reveals mildly increased tone in both lower limbs with very brisk tendon reflexes. Sensation and cranial nerve examination are normal.

Individuals I 1, II 4, II 5, II 6 and III 6 have been examined and found to be normal, although II 4 has a long history of severe depressive illness. Correspondence with II 3, who is aged 40 years and lives in the USA indicates that she is asymptomatic. II 2 died at age 9 months of pneumonia.

Linkage studies for colour vision and the Xg^a blood group were not informative.

Discussion

The presence of progressive spasticity in affected members offers a useful starting point in attempting to explain the remarkable constellation of neurological disease within this family. Hereditary spastic paraplegia can be divided arbitrarily into "pure"

and "complicated". In the pure forms clinical abnormalities are limited to spasticity and hyperreflexia. Autosomal dominant,³ autosomal recessive⁴ and sex-linked recessive inheritance⁵ have been described.

In the family now reported, the oligophrenia in affected boys and the electrophysiological results in case 5 indicate that the disease process is not limited to the cortico-spinal tracts and that their disorder cannot be classified as "pure". The "complicated" forms of hereditary spastic paraplegia include the association of spasticity and hyperreflexia with retinitis pigmentosa,⁶ optic atrophy and dementia,⁷ mental retardation⁸ and muscle wasting.⁹⁻¹² Spastic paraparesis may also occur in adrenoleukodystrophy¹³ and adrenoleukomyeloneuropathy,¹⁴ in both of which there is an abnormality of long chain fatty acid metabolism. On the basis of clinical and investigative findings the condition in this family cannot be readily assigned to any of these forms of hereditary spastic paraplegia.

The pattern of familial involvement in this kindred is also unusual. Autosomal dominant inheritance with variable expressivity and reduced penetrance, both of which are well documented in hereditary spastic paraplegia,^{15 16} is possible but unproven in the absence of male to male transmission. Equally possible is sex-linkage with manifesting heterozygosity, although review of published reports of sex-linked hereditary spastic paraplegia, as summarised in the table, fails to reveal any family with an identical condition. In order to prove sex-linkage it is necessary to establish linkage with a known X chromosome marker, such as colour vision or the Xg^a blood group, or alternatively demonstrate mosaicism for the basic defect in carrier females. The former has proved unhelpful in this family and the latter is impossible since the basic defect is unknown.

It is concluded that this family harbours an

Table Published reports of sex-linked paraplegia

Reference	Age of onset	Progression	IQ	Other features
Blumel <i>et al</i> 1957 (17)	Infancy	?	? Normal	Nystagmus
Johnston and McKusick 1962 (18)	Early childhood	Slow	↓	Nystagmus
Thurmon and Walker 1971 (19)				Optic atrophy
Ginter <i>et al</i> 1974 (20)				Spinocerebellar degeneration
Baar and Gabriel 1966 (21)	Congenital	Rapid	↓↓	Athetosis
				Cerebellar signs
Thurmon and Walker 1971 (kindred 2) (19)	Childhood or adolescence	Slow	Normal	—
Raggio <i>et al</i> * 1973 (22)	Childhood	Very slow ? static	Normal	—
Zatz <i>et al</i> 1976 (5)	Adolescence	Very slow	Normal	—
Galassi <i>et al</i> 1977 (23)	Childhood	Slow	↓	Nystagmus and optic atrophy

*Inheritance was reported as sex-linked but the family pedigree shows one instance of male to male transmission which if correct excludes sex-linkage.

unusual, if not unique, form of "complicated" hereditary spastic paraplegia with pronounced differences in expression between the sexes and a mode of inheritance consistent with either sex-limited autosomal dominance or sex-linkage with manifesting heterozygosity.

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