Short report

Familial spastic paraplegia with Kallmann's syndrome

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SUMMARY A sibship is reported in which two males have spastic paraparesis and Kallmann's syndrome (hypogonadotrophic hypogonadism and anosmia). One of the brothers also is colour-blind. The association of familial spastic paraplegia and Kallmann's syndrome has not been described previously.

Hypogonadism which is secondary to inadequate gonadotrophin release by the anterior pituitary in the presence of otherwise normal hypothalamic-pituitary function has been reported in patients with a variety of neurological disorders, some of which may be familial. These include cerebellar ataxia,1-7 the syndrome of 'ophthalmoplegia plus,'8 Moebius' syndrome with peripheral neuropathy,9-11 dystrophia myotonica,12 hereditary binomial synkinesia,13,14 Rud's syndrome,15 Laurence-Moon-Biedl syndrome,16 colour-blindness,17 nerve deafness18 and anosmia.13,17,18 The combination of hypogonadotrophic hypogonadism and anosmia is known as Kallmann's syndrome.13 Here we describe a family in which two sons are affected with both spastic paraparesis and Kallmann's syndrome.

Cases reports

A pedigree chart of the family is shown in the figure. III-4: Mr EK, 26 yr, was noted to be hypogonadal at age 14 yr. After excision of the left undescended testis and biopsy of the right, he received injections of human chorionic gonadotrophin (HCG) and then testosterone. In 1975 he had high plantar arches, mild distal arm and leg weakness and normal reflexes. His plasma testosterone was 0-45 nmol/l (normal range 10-42), follicle stimulating hormone (FSH) 0-42 IU/l (normal range 0:33-5:0) and luteinizing hormone (LH) 2-5 IU/l (normal range 3:2-23). No Barr bodies were seen in a buccal smear. Radiographs of the pituitary fossa were normal. He received methyl testosterone, 25 mg/day. By October of 1979 he was unable to walk. Three myelograms were performed over the following two years and were normal. In February 1982, he complained of increasing upper limb weakness and urgency of both micturition and defaecation. On examination, he was tall (190 cm) and obese and had relatively sparse facial, axillary and pubic hair. There was no gynecomastia; the penis was normal, the left testis absent and the right small and soft. Neurological examination revealed anosmia, red-green colour-blindness, and inability to elevate the left eye. The cranial nerves were otherwise normal. There was mild weakness of the shoulder girdle muscles and biceps brachii on the right and of the forearm and intrinsic hand muscles bilaterally. There was severe weakness of the abdominal muscles and all muscle groups in the lower limbs. Reflexes were normal in the arms but symmetrically increased in the legs. Babinski signs were present bilaterally and there was moderate spasticity at the knees. Coordination was normal. Appreciation of light touch and pinprick, and two point discrimination were impaired distally in the arms. All modalities of sensation were impaired in the distal legs. Bilateral pes cavus was present.

Investigations

The following investigations were normal: complete blood count, red cell morphology, sedimentation rate, plasma glucose, very long chain fatty acids, (by courtesy of Dr Hugo W Moser, Baltimore) serum electrolytes, creatinine, cholesterol, protein electrophoresis, antinuclear antibody, total and free thyroxine, adrenocorticotropic hormone (ACTH), cortisol, prolactin, bilirubin, alkaline

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The neurological findings in the two affected males in this family closely resemble those of familial spastic paraplegia\(^{18}\) although sensory loss in the extremities is not typical of the pure form.\(^{20}\) Another atypical feature is the presence of partial monococular external ophthalmoplegia. Extra-ocular movements are usually normal in familial spastic paraplegia although Alajouanine and Nick\(^{21}\) described two brothers who had spastic paraparesis, a supranuclear paralysis of upward gaze, weakness of facial and bulbar muscles and cerebellar signs.

The medial plantar nerve sensory action potential was absent in the index case. McLeod et al.\(^ {22}\) and Harding\(^ {20}\) reported that nerve conduction studies were normal in pure familial spastic paraplegia although Dyck\(^ {23}\) states that abnormalities of sensory conduction and quantitative histological abnormalities are present in the sural nerves of patients with familial spastic paraplegia.

Most families with familial spastic paraplegia demonstrate autosomal dominant inheritance although an autosomal recessive form exists.\(^ {19,20}\) A number of kindreds with apparent X-linked inheritance have also been reported.\(^ {24-28}\) In the present family, the mode of inheritance of familial spastic paraplegia is uncertain. The mild neurological abnormalities in III-3 and absent medial plantar and sural nerve action potentials in II-1 are possibly of no significance but would be consistent with both...
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X-linked recessive inheritance with partial expression in hemizygotes and male-limited autosomal dominant inheritance. Harding demonstrated that expression of dominantly inherited familial spastic paraplegia may be very mild in some females so the possibility of dominant inheritance cannot be excluded. Autosomal recessive familial spastic paraplegia is also possible in this family.

It is now known that hypogonadism in Kallmann's syndrome is secondary to failure of the anterior pituitary to release adequate quantities of gonadotrophins while the release of other trophic hormones is normal. Males and co-workers have suggested that the disorder is due to abnormal hypothalamic regulation of releasing factors although the mechanism is unknown. Unfortunately, very little information is available concerning the neuropathology of Kallmann's syndrome.

The pattern of inheritance of Kallmann's syndrome is uncertain. X-linked recessive, X-linked dominant, and autosomal dominant modes have all been suggested. Father to son transmission has been documented in one family in which the father was treated with gonadotrophins which suggests autosomal dominant inheritance. The fact that females may be affected in some families also favours autosomal rather than X-linked inheritance although certain X-linked disorders may be manifest in the hemizygous female. Some relatives of patients with Kallmann's syndrome may have either anosmia or hypogonadism, but not both traits, suggesting that two linked genes may be responsible for Kallmann's syndrome. In the present family the mode of inheritance of Kallmann's syndrome cannot be stated with certainty. That the mother's paternal uncle is hypogonadal suggests that the mother is a carrier but whether the gene is X-linked or male-limited autosomal dominant cannot be determined.

The presence of both familial spastic paraplegia and Kallmann's syndrome in these two brothers might be due to inheritance of two abnormal genes. This could be a result of either chance concurrence or genetic linkage. It is unlikely that both familial spastic paraplegia and Kallmann's syndrome are due to a single abnormal gene because the mother's maternal uncle, who is known to be hypogonadal, is believed to have no neurological abnormalty.

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References


