

MASA syndrome: new clinical features and linkage analysis using DNA probes

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Abstract

We describe a two generation family in which two males have the X linked recessive MASA syndrome (mental retardation, aphasia, shuffling gait, and adducted thumbs). A third male in this family died at the age of 15 years from congenital hydrocephalus. In the present family cerebral abnormalities are reported for the first time. Linkage analysis confirms the chromosome localisation at Xq28. A crossover between the coagulation factor VIII locus (*F8C*) and MASA syndrome, but not with *DXS52* and *DXS305*, locates the gene on the same side of *F8C* as *DXS52* and *DXS305*. The possible relationship between MASA syndrome and X linked hydrocephalus is discussed.

Hereditary spastic paraplegia is a disorder characterised by progressive spasticity of the legs. Intelligence in this pure form is normal. Inheritance is usually autosomal dominant, but X linked recessive inheritance in families has been reported.¹ In the complex form, the spasticity may be seen in combination with mental retardation, microcephaly, epilepsy, or ocular symptoms.^{2,3} The MASA syndrome is an X linked disorder first reported in 1974.⁴ Affected males show a combination of mental retardation, delayed speech (aphasia), spastic paraplegia (shuffling gait), and adducted thumbs. Since then, four families have been reported.⁵⁻⁸ In two families linkage analysis located the gene in the region of Xq28.^{7,8} In this paper we describe a family with three affected males and the clinical features in MASA syndrome are extended. The third male in this family died from congenital

hydrocephalus. Linkage analysis confirmed the localisation at Xq28, and more precisely located MASA syndrome on the same side of *F8C* as *DXS52* and *DXS305*.

Case reports

CASE 1

Case 1 (III.2, fig 1) was born in 1944 after an unremarkable pregnancy; the birth and perinatal history were normal. His psychomotor development was generally delayed. He walked at the age of 5 years and started to speak a few words at the age of about 4 years. At a young age he was treated for fits that might have been of epileptic origin. Recent evaluation at the age of 45 years showed a cooperative, moderately retarded man. He had simple speech and could not read or write. He was employed in a sheltered environment. He had a normal height, but was overweight. His OFC was 59 cm (1 cm above the 98th centile). He had a spastic gait. He stood with anteverted hips, bowed knees, and anteverted shoulders (fig 2). Apart from the macrocephaly, no facial dysmorphism was present. His left eye showed divergent strabismus. The pupils were irregularly shaped but did react to light. Fundoscopy of both eyes was normal. He held both thumbs in flexion-adduction (fig 3) and the function of the abductor pollicis longus muscle was clinically absent. The fifth fingers showed camptodactyly. Neurological examination showed a mild dysarthria and a spastic paraplegia of the legs. Chromosomes were normal male 46,XY, and fragile X screening was negative. CT scan of the brain showed asymmetry of the skull and brain and extensive widening of the lateral ventricles; the third ventricle was moderately enlarged and the fourth ventricle was normal. The lateral ventricles were irregularly shaped (fig 4).

CASE 2

Case 2 (IV.2), the nephew of case 1, was born in 1970 after a normal, term pregnancy. Birth weight and length were normal. There were no perinatal problems, but development was delayed. He started to walk at the age of 4 years, but with bowed knees. He spoke his first words at the age of 4 years. Neurological

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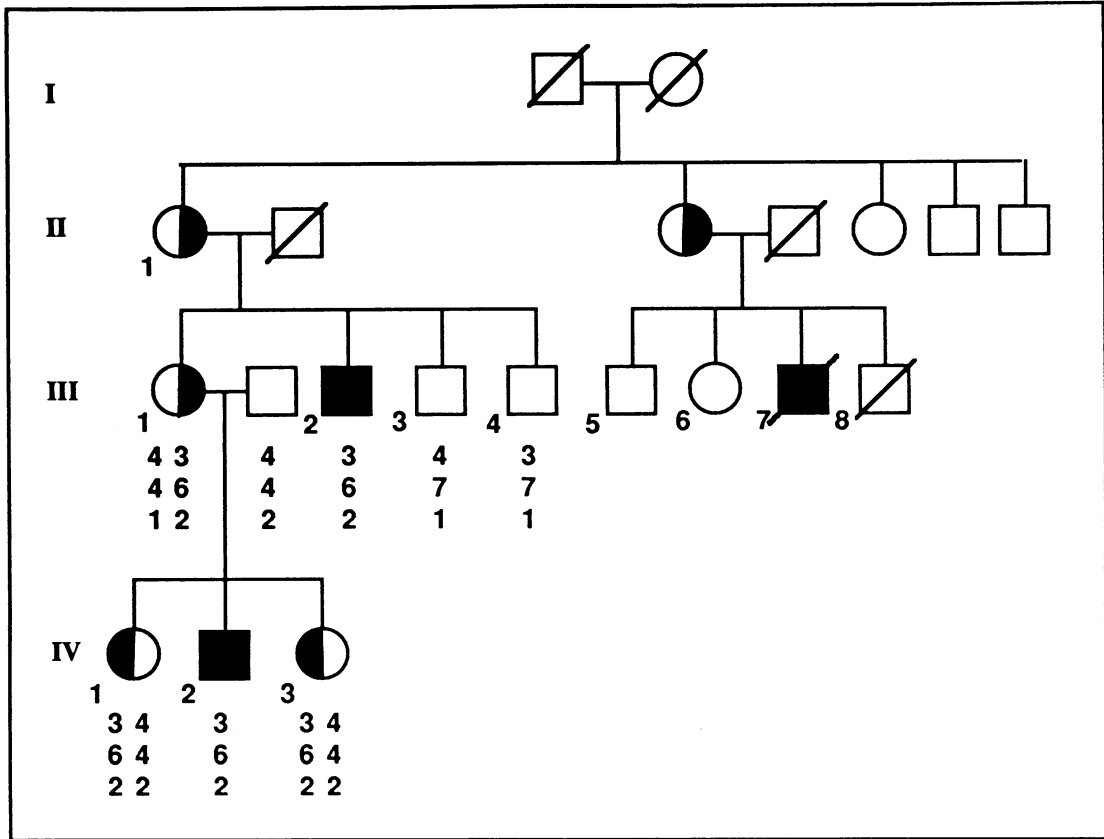


Figure 1 Pedigree of the family with informative DNA markers (F8C, St14, St35). The side of the shaded region in the female carriers' symbols corresponds to the parental origin (mother left, father right) of the haplotypes.

evaluation at the age of 5 years showed generally delayed development; the tendon reflexes were normal, including the plantar responses. EEG and EMG were normal. His IQ was 50. At the age of 6 years his reflexes were noted to be increased with an extensor plantar response.

Now, at the age of 19 years, he is a friendly, mildly retarded boy with a spastic gait. There is a remarkable general resemblance to his maternal uncle. He attends a special school and will soon be working in sheltered employment. Height is 165 cm, weight 85 kg, and OFC 58 cm (98th centile). Apart from epicanthic folds and relative macrocephaly, no facial dysmorphism is present. Both thumbs are flexed and adducted and the fingers show distal tapering. Neurological examination showed a spastic paraplegia of the legs. Electromyography of the thumb muscles showed adduction of the thumb when the abductor pollicis longus muscle was stimulated; CT scan of the forearm musculature, however, failed to show any abnormality.

On ophthalmological examination, myopia and

astigmatism were found and divergent strabismus of the left eye was present. The media and fundus of both eyes were normal. Chromosome study was normal (46,XY) and the fragile site at Xq27.3 was negative. CT scan of the brain showed the same abnormalities as seen in his maternal uncle but less pronounced.

CASE 3

Case 3 (III.7), a maternal cousin of case 1, was born in 1936 with apparent hydrocephalus. He had severe mental and motor retardation and died at the age of 15 years in an institute for severely retarded patients.

Family history

The family was examined when the older sister of case 2 presented for genetic counselling. The mother and maternal grandmother, both obligate heterozygotes, showed no signs of the syndrome and their neuro-



Figure 2 Case 1. Note the anteverted hips, bowed knees, and anteverted shoulders.

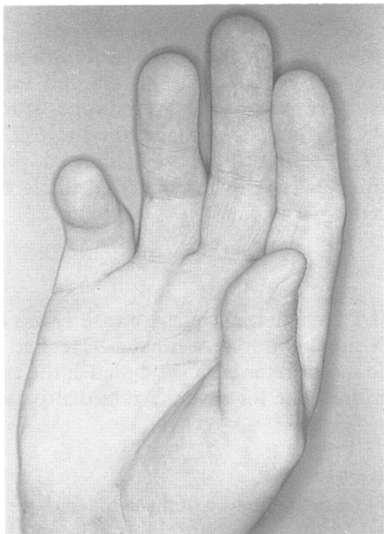


Figure 3 Hand of case 1 showing adducted and flexed thumbs, and camptodactyly of the fifth finger.

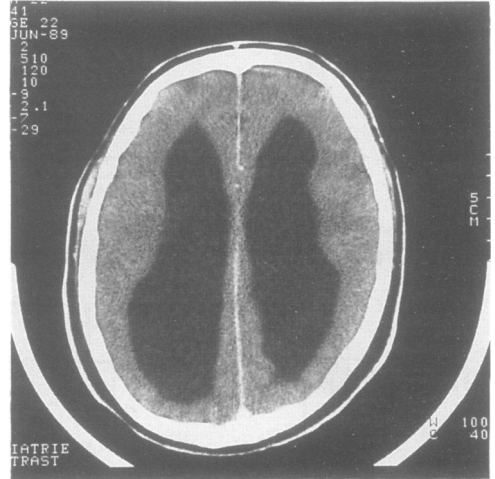


Figure 4 CT scan of the brain of case 1: note the irregularly shaped, wide ventricles.

logical reflexes were normal. Neither of the sisters of case 2 has any clinical signs of the syndrome.

DNA studies

DNA was extracted from peripheral venous blood samples. After restriction enzyme digestion the resulting fragments were size separated by agarose gel electrophoresis and alkali blotted on Hybrid N plus membranes. These membranes were hybridised with the following probes: F9, F8, pX58d11lc (*DX599*), U6.2 (*DXS304*), DX13 (*DXS15*), St14.1 (*DXS52*), and St35.691 (*DXS305*). The computer program MENDEL was used to compare lod scores (K Lange, D Weelss, Boenke). Only three markers were informative in all meioses: St14.1 (*DXS52*), St35.691 (*DXS305*), and *F8C* (*XbaI/KpnI* polymorphism) (fig 1). Lod scores for the present family and the families reported by Kenwick *et al*⁷ and Winter *et al*⁸ are given in the table.

MASA syndrome can be unambiguously assigned to Xq28 because there are no recombinations between St14.1 and MASA syndrome in the two reported families and in the present family. This gives a total lod score of 5.97 at $\theta=0.0$. Moreover a recombination apparently occurred in the meiosis of II.1 resulting in III.4 between the MASA locus and *F8C* but not *DXS52* or *DXS305*. This places the MASA locus on the same side of *F8C* as *DXS52* and *DXS305*, which are closely linked.⁹

Discussion

The two males in the present family show the clinical features of the MASA syndrome, an acronym for

Lod scores for MASA versus St14.

	Lod score (θ)					
	0.0	0.05	0.10	0.20	0.30	0.40
Present family	1.204	1.093	0.975	0.721	0.444	0.173
Three families combined	5.98*	—	4.85	3.64	2.33	0.95

*The 95% confidence limits for θ were between 0 and 0.09.

mental retardation, aphasia (delayed speech), shuffling gait (spastic paraplegia), and adducted thumbs. A third male relative died from congenital hydrocephalus. The mental retardation in the older male (case 1) is more severe than in the younger (case 2). It is not clear whether this is a real difference owing to variation within the syndrome, as the provision of special education for the mentally retarded in the 1940s was clearly different from the facilities that could now be offered to case 2. On the other hand, the neurological and brain abnormalities in case 1 are more severe than in case 2, and this may be an indication of a progression of the spastic paraplegia and CNS abnormalities with age. The lowest reported IQ in MASA syndrome is 40.⁷ A review of the clinical signs in the syndrome was recently reported by Winter *et al.*⁸ In the present patients, ocular findings were non-specific. Additional important findings in this family were the abnormal CT findings in the brain with gross enlargement of the lateral ventricles. So far, a CT scan of the brain in a male with MASA syndrome has been reported only once and was normal.⁶ This ventricular widening is an interesting finding in view of the dead male relative with congenital hydrocephalus. In the differential diagnosis of MASA syndrome, congenital hydrocephalus has to be considered; this can occur as an X linked recessive trait and is known to be associated with adducted thumbs in about 50% of cases.¹⁻¹⁰

The adducted thumbs in MASA syndrome are thought to be caused by hypoplasia or absence of the extensor pollicis longis and/or brevis muscles; this assumption has been proven once by surgical exploration.⁶ The clasped thumbs in X linked hydrocephalus are thought to be a developmental defect of the abductor and/or extensor muscles as well, shown by electrophysiological and surgical findings.¹¹ In the present case 2, electrophysiological examination of the thumb muscles showed evidence of an abnormality of the abductor pollicis longus muscles, which could not be confirmed on the CT scan of the forearm musculature. Pyramidal tract anomalies as seen in the present two males are a common finding in necropsy records of dead males with X linked hydrocephalus.¹⁰ In families with X linked hydrocephalus, surviving male relatives have been described with non-specific mental retardation with or without spastic paraplegia.¹² In the present family with two males with MASA

syndrome, a third male relative had congenital hydrocephalus.

On clinical grounds it is not clear whether the X linked hydrocephalus and the X linked MASA syndrome represent different entities; the present family illustrates the hypothesis that both disorders could be closely related. Moreover, the three patients reported by Winter *et al.*⁸ all showed marked macrocrania (OFC > 97th centile). Genetic linkage analysis in the present family supports close linkage with *DXS52* on Xq28 and more precisely locates MASA syndrome on the same side of *F8C* as *DXS52* and *DXS305*. The preliminary results of genetic linkage analysis in families with X linked congenital hydrocephalus also suggest linkage with Xq28 markers (*DXS52, F8C*).¹³ The results of the linkage analysis, together with the clinical findings (dilated ventricles, macrocrania, and lethal hydrocephalus) strongly suggest that MASA syndrome and X linked hydrocephalus are allelic variants.

The uncomplicated form of X linked spastic paraplegia is clinically different and linkage has been found with loci in the Xq21-22 region.¹⁴⁻¹⁵ Goldblatt *et al.*¹⁶ reported a family with the complex form of X linked spastic paraplegia with linkage to Xq13-21.2. The affected males in this family also presented varying degrees of mental retardation in addition to the spastic paraparesis, but abducted thumbs were absent and macrocrania was not mentioned. This indicates that the nosology of X linked spastic paraplegia, MASA syndrome, and X linked hydrocephalus still remains a difficult problem. This question may only be resolved by the study of more families, including DNA studies together with careful clinical descriptions.

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