Male neonatal death and progressive weakness and immune deficiency in females: an unknown X linked condition

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Abstract

We report a family with an undiagnosed X linked condition. The grandmother, two of her three daughters, and one of her granddaughters have a slowly progressive proximal weakness, brisk reflexes, poor bladder function, static reduced night vision, and IgG2 deficiency. The diagnosis of the three living symptomatic females was "hereditary spastic paraplegia plus". They have lost five male children who died in the neonatal period of severe hypotonia and were of low birth weight. Investigations have not led to a unifying diagnosis: myotonic dystrophy, NARP, and X linked hyper IgM were specifically eliminated. Using the hypothesis that the condition is X linked dominant, haplotype analysis of the family suggests that the disease locus is within Xq26-qter. This entity should be considered in the differential diagnosis of families presenting with severe neonatal hypotonia in males and females with symptoms suggestive of complex hereditary spastic paraplegia.

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It is unusual for both males and females to be consistently significantly symptomatic in an X linked disorder. We report such a family in which the affected males were severely hypotonic and died in the neonatal period and the affected females have a "complex hereditary spastic paraplegia".

Hereditary spastic paraplegia is a clinical diagnosis. Affected persons are spastic with little weakness. Pure forms of the condition are described, as are complex (plus) forms with additional features such as cerebellar ataxia, optic atrophy, deafness, and mental retardation. Most families exhibit either autosomal dominant or recessive inheritance; X linked hereditary spastic paraplegia is less common. The family described here is unusual because females are consistently affected and have the additional features of defective night vision and immune deficiency which are rarely described in hereditary spastic paraplegia.[1] The condition appears to be distinct when compared to other X linked complex hereditary spastic paraplegias such as MASA (mental retardation, adducted thumbs, shuffling gait, aphasia), Allan-Herndon syndrome (spastic paraplegia, mental retardation, and muscle

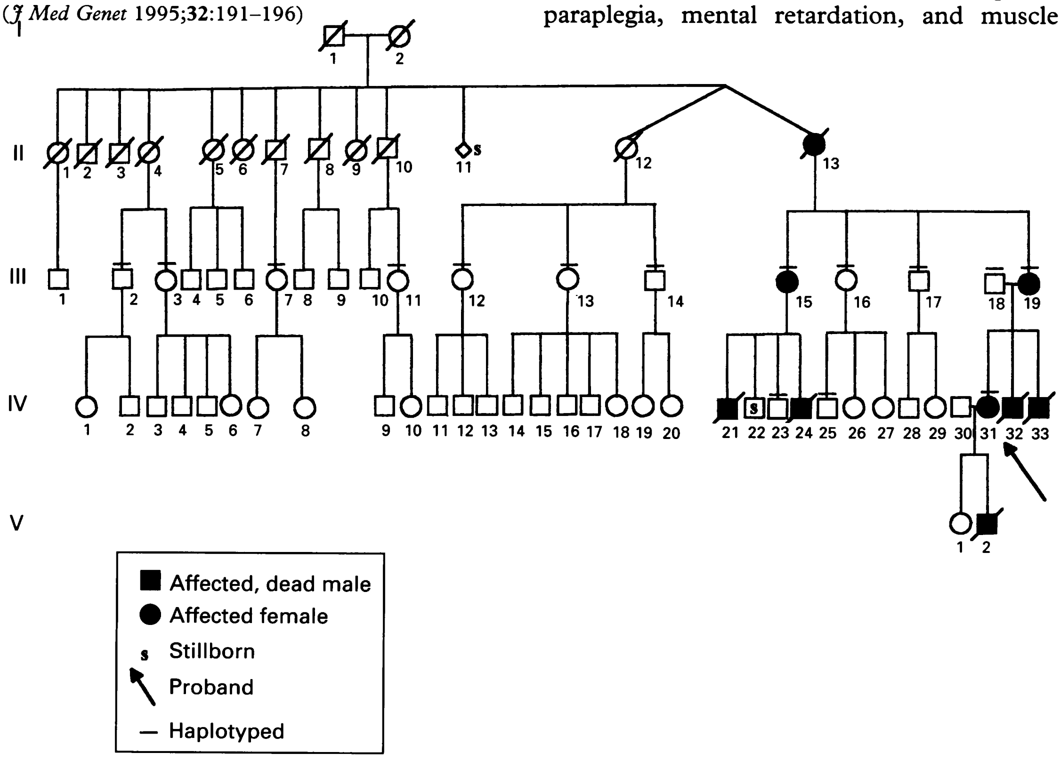

Figure 1 Pedigree showing birth order, symptomatic females and males, and persons from whom DNA was analysed.

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hypoplasia), and the family described by Kenwrick *et al* with mental retardation and optic atrophy.[2-4]

Subjects and methods

CLINICAL DETAILS

The pedigree is shown in fig 1. The index case, IV·31, was referred after the unsuccessful resuscitation of her son, V·2, at birth. Her mother III·19 and aunt III·15 had also lost male children in the neonatal period. All three women, and the maternal grandmother, II·13, had a "hereditary spastic paraplegia" with brisk deep tendon reflexes, slowly progressive weakness, poor bladder control, static poor night vision, and late onset immune deficiency. The maternal grandmother, II·13, was the last born of a sibship of 13. The condition has only occurred in her and her descendants.

Subjects III·19 and IV·31 were investigated in depth. Other family members were interviewed and blood samples obtained from III·2, 3, 7, 11, 12, 13, 14, 15, 16, 17, 18, and IV·23 and 25.

The clinical features of the four affected females were very similar. All had been ungainly as children and had been poor at sports in their youth. By the age of 30 they were noticeably unsteady on their feet and had frequent falls. Because of weakness II·13, III·15, and III·19 needed to use wheelchairs by their fifth decade. All had static poor night vision, first noted in the first decade, having great difficulty walking, reading, or driving at night. Acuity and colour vision were normal. All complained of a weak bladder with giggle and stress incontinence. This had been noticed in the first decade but had not progressed. All had an increased number of sinopulmonary infections starting in the third or fourth decade. III·19 had suffered three pneumothoraces, the last leading to a pleurodesis. Bilateral cataracts were removed from II·13 at the age of 70 years and III·19 at 51 years. II·13 died of a coronary thrombosis at the age of 75 years.

II·13 was examined at the age of 67 years, III·19 at 30 and 51 years, and IV·31 at 8, 18, and 27 years. All had lateral nystagmus. III·19 and IV·31 had mild facial and neck weakness. Their limb appearance was normal but by the second decade tone was increased in the legs but not the arms, power was reduced proximally in the legs, much more so than the arms, and hyperreflexia was found in the legs but not the arms. Upward plantar responses, slightly reduced proprioception, and pes cavus were present but peripheral coordination was normal. Knee and ankle clonus was elicited after the second decade. There were no abnormal peripheral cerebellar signs, myotonia, or contractures. When testable Romberg's sign was positive. Intellect and speech were normal in all four affected females. III·15 has not been examined.

III·15 had four pregnancies and all were males. Her third born child is now a healthy 22 year old. The other three males died within four hours of birth, were hypotonic, and unable to maintain respiration. The first pregnancy was complicated by pre-eclamptic toxaemia and polyhydramnios. Labour was induced at 38 weeks of gestation. The second pregnancy ended at 5 months with premature labour and a stillborn male child. The fourth pregnancy went to term.

III·19 had three pregnancies. Female IV·31 was her first child and she herself had a daughter by her first pregnancy, who is 6 years old and well. The second and third pregnancies of III·19 and the second pregnancy of IV·31 were complicated by polyhydramnios in the last two months, but fetal movements were reported to be normal. Deliveries occurred at term of males weighing 2500 g, 2700 g, and 2460 g who died within the first six hours.

CLINICAL INVESTIGATIONS

At necropsy V·2 had hypoplastic lungs (the left weighing 12 g and the right 15·2 g), a large left tension pneumothorax, bilateral talipes equinovarus, and a contracture of the right hand. All internal organs were normal including the brain. The dead males were of normal appearance but smaller than expected for their gestational age (<3rd centile).

Detailed cytogenetic analyses of blood from III·15, III·19, IV·31, and V·2 were normal. Creatinine kinase of III·15, III·19, and IV·31 was normal. A lipid profile, thyroid function and antibodies tests, serum phytanic acid, and very long chain fatty acids levels were normal in III·19 and IV·31.

A brain CT scan of III·19 at the age of 52 years was normal, and in particular there were no features of multiple sclerosis. At the age of 31 years, IV·31 had neurophysiological examinations performed. The nerve conduction velocities of the right and left posterior tibial nerve and right ulnar nerve showed no significant abnormalities. The findings on EMG were consistent with a chronic neurogenic lesion and did not support the diagnosis of a myopathy. Muscle biopsy of the left biceps of IV·31 was reported as showing "some non-specific changes which may represent those of a mild myopathy. Muscle fibres range in size from 55–62 μm with scattered atrophic fibres of types 1 and 2. No central nuclei, inclusions, or nemaline bodies. Connective tissue was not increased and there was no inflammation. A trichrome stain showed a few prominent mitochondria in a few fibres".

Immune studies showed that III·15, III·19, and IV·31 all had IgG2 subclass deficiencies (1·0 g/l, <0·08 g/l, <0·4 g/l respectively, the normal range being 1·2–6·6 g/l). All had low antibodies titres to diphtheria, Candida, and *Pneumococcus*. Levels of IgA, IgM, total IgG, IgG1, IgG3, and IgG4 were normal. Immunological studies of III·16 and III·17 (male and female sibs of the affected females III·15 and III·19) were normal. III·19 and IV·31 are successfully treated with three weekly gammaglobulin injections.

Ophthalmic assessment of IV·31 by slit lamp and shine through camera showed normal fundi and lens. In III·19 remnants of non-posterior pole cataracts were seen in both lenses. Neither

Table 1 Markers used in the haplotype investigation

Locus	*Type*	*Localisation*	*Annealing temperature*	*Reference*
DMD 5′	(AC)n	Xp21	55°C	7
DXS228	(AC)n	Xp11.4	53°C	8
DXS255	VNTR	Xp11.22		9
HUMARA	(CAG)n	Xq11	65°C	10
DXS456	(AC)n	Xq21-Xq22	55°C	11
DXS424	(AC)n	Xq24-Xq26	55°C	11
XHM	(AC)n	Xq26	55°C	12
HPRT	(AGAT)n	Xq26	60°C	13
FRAXAC2	(AC)n	Xq27.3	55°C	14
F8C	(AC)n	Xq28	53°C	15
DXS52	VNTR	Xq28		16
CKMM	VNTR	19q13.3		17
ApoC2	(AC)n	19q13.2	55°C	18
PH1100	VNTR	19q13.2		Korneluk, see below

PH1000 is an unpublished marker also known as pKH1.1 and is located 200 kb centromeric of the myotonic dystrophy gene, between it and ERCC1 (R Korneluk, personal communication).

had any findings suggestive of myotonic dystrophy. Electroretinograms were reported as showing "slight reduction of amplitude in photopic conditions, normal in scotopic" in both. Dark adaptation studies in III·19 showed an absent alpha point (break between rod and cone function) in the right eye and a normal result in the left; in IV·31 a bilaterally absent alpha point was found. These results are not typical of "stationary night blindness", but may represent a defect of rod/cone interaction. The significance of these results is unclear as is the cause of the reduced night vision.

PREPARATION OF GENOMIC DNA

DNA from peripheral blood was extracted by standard procedures.[5]

AMPLIFICATION OF SATELLITE REPEATS

PCR was carried out in 20 ml reaction volumes overlaid with paraffin oil. The reaction mix consisted of 100 to 200 ng of genomic DNA, 0·5 mmol/l of each primer, 2 ml of Perkin Elmer Cetus 10 × concentration reaction buffer, 0·2 mmol/l each of dGTP, dATP, dCTP, and dTTP, and 0·1 ml *Taq* polymerase (Perkin Elmer Cetus). Before amplification 50% of one primer was end labelled with T4 polynucleotide kinase (Boehringer Mannheim), and [^{32}P] ATP using standard procedures.[6] Samples were processed through 35 cycles of denaturation (94°C for 45 seconds), annealing (see table 1 for temperatures for 45 seconds), and elongation (72°C for one minute). For analysis, PCR products were run on 6% (w/v) polyacrylamide, 11% urea denaturing gels. For details of PCR probes, see table 1.

RFLP ANALYSIS

DNA samples were digested overnight with the appropriate restriction endonuclease (*Eco*RI at 37°C for DXS255, PH1100, and GB2·2; *Taq*I at 65°C for DXS52 and CKMM; and *Nco*I at 37°C for CKMM) and analysed by Southern blot hybridisation using probes labelled by random priming ("Multiprime", Amersham Biochemicals).

To assess X inactivation, probe DXS255 at Xp11.22 was used.[19] DNA samples were digested with *Pst*I, ethanol precipitated, and digested with *Msp*I or *Hpa*II (all enzymes from Boehringer Biochemicals).

NARP MUTATION DETECTION

The NARP mutation present at position 8993 in the ATPase subunit 6 of the mitochondrial genome was sought using polymerase chain reaction amplification followed by *Ava*I restriction.[20]

X LINKED HYPER IGM IMMUNODEFICIENCY (XHM)

The gene for X linked hyper IgM (XHM) has recently been cloned and the cDNA sequence published.[12] A polymorphic microsatelite (AC)n repeat in the 5′ untranslated region of the gene was amplified by polymerase chain reaction and used for both haplotype analysis and to attempt deletion detection.

MYOTONIC DYSTROPHY MUTATION EXPANSION DETECTION

The (CTG) expansion associated with myotonic dystrophy was sought both with the probe GB2.2 (a *Pst*I digest of probe GB2.6) digested with *Eco*RI by Southern blotting and agarose gel, and by PCR of the expansion analysed both by ethidium bromide staining and radiolabelled (CTG) probe.[21 22]

Results

X CHROMOSOME HAPLOTYPE ANALYSIS

Using the hypothesis that the family had an X

Table 2 Haplotype results of family members

Probe	*III·2*	*III·3*	*III·7*	*III·11*	*III·12*	*III·13*	*III·14*	*III·15*	*III·16*	*III·17*	*III·18*	*III·19*	*IV·23*	*IV·25*	*IV·31*
X chromosome															
DMD 5′	B	AB	CC	BC	AC	AC		AC	AB	C	C	AC	C		AC
1Aa6	A	AC	AA	AC	AA	AA	A	AB	AB	A	A	AB	A		AB
DXS255	B	DG	BH	EK	AD	AE	E	BD	BB	D	A	BD	D		AB
And Rec	D		AD	EF	BC	CE		AB	AD	B	C	AB	B		CC
DXS456	A	AB	CC	AC			A	AA	CC	A	A	AC	C		AC
DXS424	A	AB	AA	AC	AC	AC	A	AD	AD	A	A	AD	D		AD
XHM	C	AC	CC	CC	CC	CC	C	BC	BC	C	A	BC	B		AB
HPRT	A	BE	BE	CE	BE	AB	A	AB	BE	E	C	AB	B		BC
FRAXAC2	A	BB	BB	BB	BC	AC		AC	BC	B	B	AC	C		AB
DXS52	A	BD	BD	BC	CD	AD		AB	BC	C	B	AB	B		AB
F8C	C	CG	BC	BF	DF	CD		CD	DF	F	H	CD	D		CH
Chromosome 19															
ApoC2	13	13	34		34			36		23	36	36	67		34
CKMM-Ta	11	11	12		11	11	12	12		12	12	12	12	11	12
CKMM-Nc	22	12	12		22	22	22	22		12	22	12	22	22	22
PH1100	12	12	12		12	11	12	12		11	12	12	11	12	12

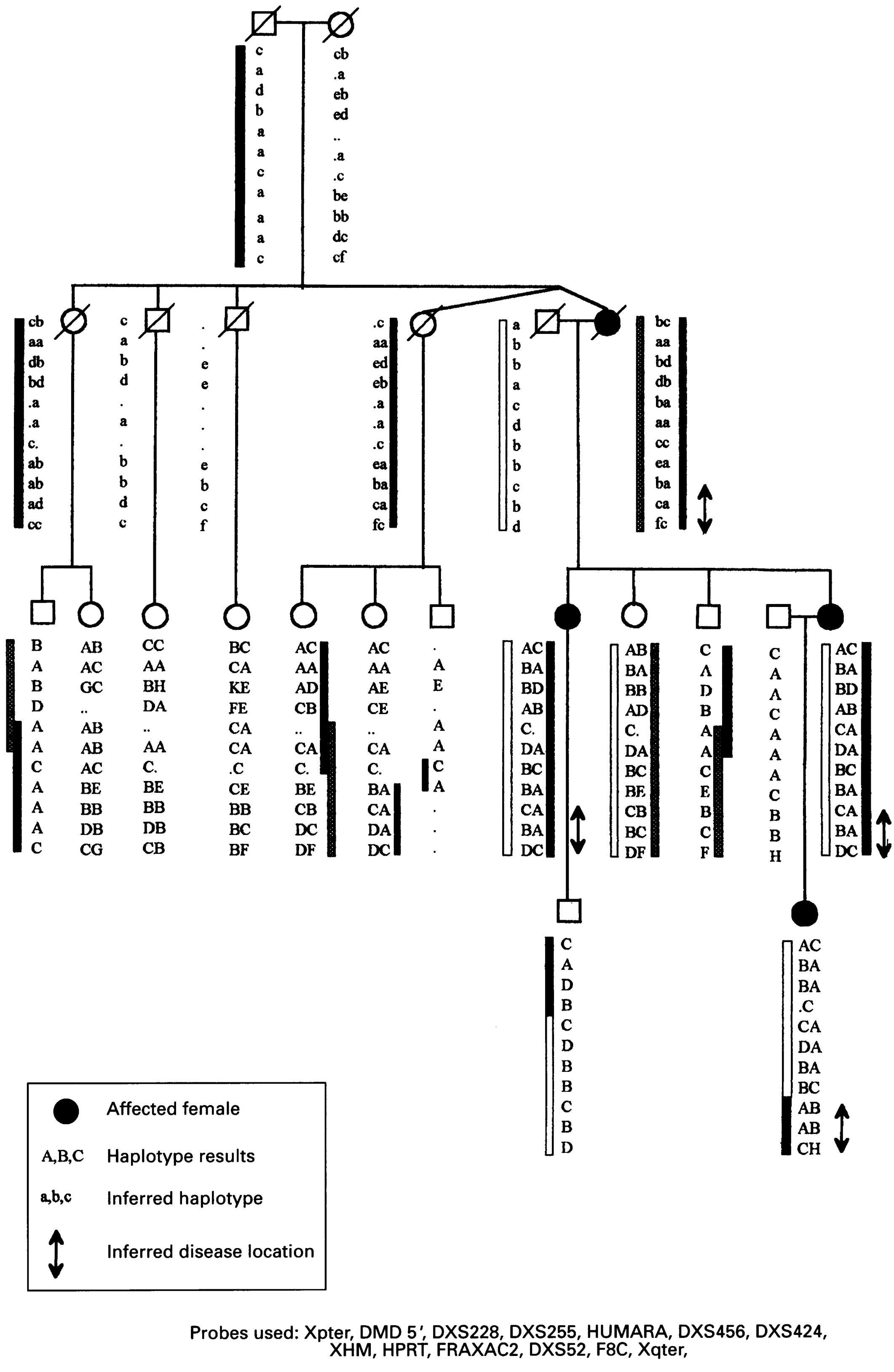

Figure 2 Reduced pedigree showing the probe results of the persons tested. Calculated and inferred haplotypes are shown. The X chromosome of I·1 is shown as a black bar. The region of this chromosome distal to HPRT is expected to contain the disease mutation (see text). It is also assumed that either I·1 is a germline mosaic for this mutation or it occurred in his last child, the female II·13.

linked dominant condition, we performed X chromosome haplotype analysis. We have assumed that living males and females aged over 20 years who have no neurological symptoms do not have the condition and that females with neurological and immunological features do have the condition.

Using 11 markers spaced along the length of the X chromosome we analysed the segregation of the X chromosomes in this family. The results are set out in table 2 and shown in fig 2. Within the nuclear family containing affected subjects (progeny of grandmother II·13), Xq26–Xqter is implicated as the region containing the disease associated mutation. The lod score for each marker is 1·5 at $\theta=0$ in this approximately 10–14 megabase segment of the X chromosome distal to the HPRT locus on Xq26.

Using all available family members, as shown in fig 2, and making the assumption that the calculated haplotypes are correct, the region that we hypothesise to carry the disease mutation in the grandmother II·13 has been passed to III·2 and III·13, while that region on her other X chromosome has been passed to III·12. All three and their offspring are well. The mutation bearing segment may have been derived from their grandfather, I·1, in which case he would have been a gonadal mosaic.

EXCLUSION OF DIFFERENTIAL DIAGNOSES: NARP (NEUROGENIC WEAKNESS, ATAXIA, RETINITIS PIGMENTOSA), X LINKED HYPER IGM IMMUNODEFICIENCY (XHM), AND MYOTONIC DYSTROPHY

Subjects III·19 and IV·31 did not have the NARP mutation. X linked hyper IgM immunodeficiency maps close to the HPRT locus on Xq26, within the disease bearing region of Xq defined by haplotype analysis.[23] If the locus were to be involved in this condition then it would probably be as part of a contiguous gene deletion. No deletion was detected in the affected females. Furthermore the locus segregates with HPRT, proximal to the recombination event in IV·31. On this basis, the XHM locus can be excluded as the origin of the immune deficiency in this family. We considered it important to exclude myotonic dystrophy as a possible diagnosis despite the detailed family clinical picture being unusual. Subjects III·15, III·19, and IV·31 had a normal myotonic dystrophy triplet repeat size. Using an autosomal dominant model of inheritance we were unable to show linkage between the disease and the 19q13.3 haplotype in family members using the probes ApoC2, CKMM, and pH1000 (table 2).

X INACTIVATION ANALYSIS

The putative mutation bearing X chromosome was determined by haplotype analysis. Subjects III·19 and IV·31 exhibited a skewed X inactivation pattern, 80% and 90% of the unaffected haplotype respectively, as determined with DXS255. As all three females had a similar degree and spectrum of symptoms we conclude that either X inactivation is not a significant factor in the phenotype of this condition or that we were measuring X inactivation in the wrong tissue.

Discussion

In this family five male children have died with severe hypotonia in the neonatal period. Diminished fetal movement in utero is suggested by their low birth weights, polyhydramnios in later pregnancy, and contractures present at birth. Necropsy examination was incomplete but no structural anomalies of the nervous system were seen. Of the four females affected by the condition, two women have been investigated in detail. Pertinent findings are: progressive proximal weakness, brisk reflexes, normal touch and proprioception, an increased incidence of sinopulmonary infections, and non-progressive difficulties with night vision and bladder control. Investigations showed an unusual cone/rod dark adaptation response and low IgG2. The original diagnosis made in the affected females of this family was hereditary spastic paraplegia.

This pattern of clinical features has not previously been reported. The family is too small to allow a definitive statement about the mode of inheritance. The best fit to the data is X linked dominant although X linked recessive and maternal/mitochondrial inheritance are also possible. We have attempted to define a group of diseases which represent the potential differential diagnoses as well as considering the possibility that the causative mutation is a deletion encompassing a number of genes and giving a compound phenotype.

The clinical features in our family are not typical of the several X linked conditions which cause night blindness, including retinitis pigmentosa, stationary night blindness (both of which show probable genetic heterogeneity), Aland eye disease, and deletions encompassing the chorioderaemia gene. As the IgG2 deficiency was associated with an increased number of sinopulmonary infections we considered it a significant finding. Although at least seven X linked immunodeficiency disorders exist, in none would the female carriers be consistently symptomatic. As X linked hyper IgM (XHM) causes similar immunological features we excluded this gene. Considering the conditions that can cause severe neonatal hypotonia, we excluded myotonic dystrophy by analysis of the triplet repeat mutation expansion. Although Barth syndrome (3-methylglutacaconic aciduria type 2) can cause severe male neonatal hypotonia and male neonatal death, the clinical picture seen in the affected females is atypical.[24 25] The family described by Zollino with an X linked dominant condition presenting in males with severe congenital hypotonia also seems distinct as the affected males were dysmorphic, hypogonadic, and had pachygyria.[26] The X linked form of myotubular myopathy (centronuclear myopathy) can cause male neonatal death but seems an unlikely diagnosis as females are usually asymptomatic and are not described to have visual and immune deficiencies.[27–30] Neurogenic weakness, ataxia, retinitis pigmentosa (NARP) was eliminated by direct mutation analysis.

By analysis of meiotic crossovers using an X linked dominant model the disease locus maps to the region Xq26 to Xqter. Linkage of pure hereditary spastic paraplegia has been to Xq21-22 in one family,[31] in a family with Allan-Herndon to Xq21,[3] in the family described by Kenwrick *et al*[4] to Xq28, and in MASA syndrome to Xq28.[2] Given the possible localisation of the condition we describe to Xq26-28 it may prove to be allelic to one of the latter two diseases. There was no evidence of skewed X inactivation in the blood of three obligate affected females, nor of an X chromosome deletion.

Two observations have previously been made which are pertinent to this report: (1) that Xqter seems to contain a disproportionate number of male lethal conditions, and (2) that families such as this may be unreported because of the small family size and difficulty in obtaining sufficient data.[32]

This disorder is important to consider in apparently X linked families where females present with progressive weakness or males with severe neonatal hypotonia or both. We suggest that this condition be known as Lindenbaum syndrome.

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