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 excluded. 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.

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. 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...
hypoplasia), and the family described by Ken-
wick et al with mental retardation and optic
atrophy.54

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
depression deep tendon reflexes, slowly progressive weak-
ness, 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 inter-
viewed 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 num-
ber 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 progressive 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 prox-
imally 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 propriocception, and pes cavus were
present but peripheral coordination was nor-
mal. Knee and ankle clonus was elicited after
the second decade. There were no abnormal
peripheral cerebellar signs, myotonia, or con-
tractures. 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 toxemia
and polyhydramnios. Labour was induced at
38 weeks of gestation. The second pregnancy
ended at 5 months with prematurity and a
stillborn male child. The fourth pregnancy
got 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 2200g, 2700g, and 2460g who died
within the first six hours.

CLINICAL INVESTIGATIONS

At necropsy V-2 had hypoplastic lungs (the left
weighing 12g and the right 15:2g), a large left
tension pneumothorax, bilateral talipes equino-
varus, and a contracture of the right hand.
All internal organs were normal including the
brain. The dead males were of normal ap-
pearance 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 pyhtcic 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 ex-
aminations performed. The nerve conduction
velocities of the right and left posterior tibial
nerve and right ulnar nerve showed no sig-
nificant abnormalities. The findings on EMG
were consistent with a chronic neurogenic le-
sion 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 55-250m and contain 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 mito-
ochondria in a few fibres".

Immune studies showed that III-15, III-19,
and IV-31 all had IgG subclass deficiencies
(1-0g/l, <0-08g/l, <0-4g/l respectively, the nor-
mal range being 1-2-6-6g/l). All had low anti-
bodies titres to diphtheria, Candida, and
Pneumococcus. Levels of IgA, IgM, total IgG,
IgG1, IgG3, and IgG4 were normal. Im-
munological 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 gamma-
globulin 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
had any findings suggestive of myotonic dystrophy. Electoretinograms 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 20ml reaction volumes overlaid with paraffin oil. The reaction mix consisted of 100 to 200ng of genomic DNA, 0.5 mmol/l of each primer, 2ml of Perkin Elmer Cetus 10 × concentration reaction buffer, 0.2 mmol/l of 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 [3P] 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.

FRLP ANALYSIS
DNA samples were digested overnight with the appropriate restriction endonuclease (EcoRI at 37°C for DXS255, PH1100, and GB2-2; TaqI at 65°C for DXS52 and CKMM; and NeoI 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 PstI, ethanol precipitated, and digested with MspI or HpaII (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 Avel 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 microsatellite (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 PstI digest of probe GB2.6) digested with EcoRI by Southern blotting and agarose gel, and by PCR of the expansion analysed both by ethidium bromide staining and radiolabelled (CTG) probe.21

Results
X CHROMOSOME HAPLOTYPE ANALYSIS
Using the hypothesis that the family had an X

Table 1 Markers used in the haplotype investigation

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PH1100 is an unpublished marker also known as pKH 1.1 and is located 200kb centromeric of the myotonic dystrophy gene, between it and EBC1 (R Korneluk, personal communication).

Table 2 Haplotype results of family members

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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 θ = 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. 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-methylglutaconic aciduria type 2) can cause severe male neonatal hypotonia and male neonatal death, the clinical picture seen in the affected females is atypical. 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. 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. 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, in a family with Allan-Herndon to Xq21, in the family described by Kenrick et al. to Xq28, and in MASA syndrome to Xq28. Given the possible localisation of the condition we describe to Xq26-28 it may prove to be allelic to one of the latter two disorders. 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.

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 Lin- denbaum syndrome.

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