Becker muscular dystrophy (BMD) and Klinefelter's syndrome: a possible cause of variable expression of BMD within a pedigree

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SUMMARY We describe a man with Becker muscular dystrophy whose weakness was minimal in contrast to that of his more severely affected nephews. This man had a Klinefelter karyotype (47,XXY) and his mild symptoms may be attributed to him being heterozygous for the muscular dystrophy gene. This is the first report of a person with both Klinefelter's syndrome and Becker muscular dystrophy. This combination may be one explanation for the variable expression of X linked muscular dystrophy noted in some pedigrees.

Becker and Duchenne muscular dystrophies are X linked disorders. Both conditions are caused by mutations or deletions in a single gene located at Xp21.1. Deletions which result in a shift of the translational open reading frame of the gene cause the Duchenne phenotype with severe muscle weakness and respiratory muscle failure by 20 years of age. The much milder Becker phenotype is the result of deletions or mutations which maintain the open reading frame of the gene.^{1,2}

Boys with Duchenne muscular dystrophy have a uniformly severe clinical course.³ In contrast, Becker muscular dystrophy displays a wide range of clinical expression in affected males as measured by age of onset (first to third decade), age of becoming wheelchairbound (second to sixth decade), or age at death (second to seventh decade).³ Variation in the expression of Becker muscular dystrophy in different pedigrees may reflect the extent or location of different deletions in the gene.¹ However, similar variation may occur within a family³ and may be sufficiently great to suggest the diagnosis of both Becker and Duchenne muscular dystrophies within the same pedigree.⁴⁻⁷ The cause of this variation is not known.

We describe a man with Becker muscular dystrophy whose weakness was minimal in contrast to that of his affected nephews. He had a Klinefelter karyotype (47,XXY) and his mild weakness may be

attributed to him being heterozygous for the muscular dystrophy gene.

Case reports

The proband (III.1, fig 1) was the nephew of the subject of this report and had presented at the age of eight years with a history of not walking until 24 months, weakness from the age of two years, and global developmental delay. He had proximal muscle wasting and calf hypertrophy with marked

FIG 1 Pedigree of the family. The letters j/J refer to DXS206 (XJ2.3) alleles (6.4/7.8 kb respectively). The numbers s4/6/8 refer to DXS52 (St14) alleles (4.5/4.0/3.4 kb respectively).

FIG 2 Quadriceps muscle biopsy (haematoxylin/eosin stain) from III.1 showing variation in fibre size, fibre necrosis, and phagocytosis.

weakness of hip flexion bilaterally. His serum creatine kinase level was 8770 IU/l (normal range 25 to 200 IU/l). His electromyogram was abnormal with low amplitude action potentials; motor and sensory nerve conduction velocities were normal. Histological examination of a quadriceps muscle biopsy showed increased variation in muscle fibre size, occasional necrotic fibres undergoing phagocytosis, numerous scattered atrophic fibres, and a mild increase in endomysial and perimysial fibrous tissue (fig 2). His ECG was normal with the algebraic sum of R-S in V₁ being -2.0 mm (normal for age).² When reviewed at the age of 12 years he was still ambulant but had a wide based gait with marked lumbar lordosis and tight heel cords. He had marked pectoral and pelvic girdle weakness and used Gower's manoeuvre to rise from sitting. On formal psychometric testing he had poor verbal skills with normal non-verbal skills, giving an overall IQ of 70 (WISC-R, Peabody Picture Vocabulary Test).

After some delay his two younger brothers (III.2 and III.3) were examined and were found to be affected. At the ages of 10 and eight years they had proximal muscle wasting and calf hypertrophy. Their serum creatine kinase levels were 11 450 IU/l and 16 025 IU/l respectively. The karyotypes of the three brothers were normal.

The boys' mother (II.1) had no muscle weakness but did have slight prominence of her calves. At the age of 24 years her serum creatine kinase level was mildly raised once (212 IU/l) and normal on three other occasions (135, 137, and 145 IU/l). Her sister

(II.2) and brother (II.3) were asymptomatic and had normal serum creatine kinase levels. The grandmother (I.2) was not weak and at the age of 43 years had normal serum creatine kinase levels. She did not have calf hypertrophy.

The boys' maternal uncle (II.4) is the subject of this report. When ascertained at the age of 18 years he complained of difficulty in lifting heavy objects and slightly reduced exercise tolerance. On clinical examination he had a normal gait, slight wasting of his triceps muscles bilaterally, and marked hypertrophy of his gastrocnemii. Apart from mild weakness of elbow and hip extension his muscle power was normal. Deep tendon reflexes were normal with the exception of the triceps, which could not be elicited. His height (172 cm) was on the 50th centile. He had Tanner stage IV pubic hair, soft 4 ml testes, a normal penis, and sparse facial and body hair; he did not have gynaecomastia. He had borderline intellectual handicap with impaired verbal and non-verbal skills (WAIS-R), and was illiterate without basic arithmetic skills. His serum creatine kinase levels on three occasions were 2665, 3225 and 5753 IU/l. His karyotype was 47,XXY in each of 43 cells examined.

The segregation of two DNA markers within the muscular dystrophy locus was examined in this family (fig 1). The women I.2 and II.1 were uninformative for the DNA marker *DXS164* (pERT87-15), but were informative for *DXS206* (XJ2.3). The affected males and the carrier female II.1 had inherited the same grandmaternal *DXS206* allele. The normal man II.3 and the woman II.2 carried the other grandmaternal *DXS206* allele. The highly polymorphic X chromosome marker *DXS52* (St14) was used to determine the parental origin of the second X chromosome in the man II.4; he received the second X chromosome from his father. His sister (II.1) had inherited the same *DXS52* alleles as her brother.

Discussion

As far as we are aware this is the first report of a man with Klinefelter's syndrome and X linked muscular dystrophy. This contrasts with reports of Klinefelter's syndrome with an autosomal muscular dystrophy⁸ and Turner's syndrome with X linked muscular dystrophy⁹ which date back to the 1950s. Klinefelter's syndrome is a common X aneuploidy syndrome with a prevalence among males of 0.1%. The lack of other reports of Klinefelter's syndrome and X linked muscular dystrophy probably reflects an ascertainment bias. The clinical manifestations of an inherited muscular dystrophy gene in a man with Klinefelter's syndrome would depend on the

origin of the second X chromosome. If the second X chromosome were the result of non-disjunction at the second maternal meiotic division or at an early zygotic mitotic division, the affected male would be homozygous at the muscular dystrophy locus and would presumably have the same phenotype as hemizygous males. However, if the second X chromosome was paternally derived or the result of non-disjunction at the first maternal meiotic division, the affected male would be heterozygous at the muscular dystrophy locus and be less severely affected. Hence he would be unlikely to come to the attention of clinicians.

The late presentation, normal ECG, and persisting ambulation at the age of 12 years of the proband (III.1) suggested that he had Becker rather than Duchenne muscular dystrophy.^{2,3} His pattern of intellectual handicap (verbal skills worse than non-verbal skills) has been noted in boys with both Becker and Duchenne muscular dystrophies.¹⁰ The three affected brothers (III.1, III.2, III.3) had similar ages of onset and degrees of weakness.

Their maternal uncle (II.4) also carried the Becker muscular dystrophy gene but had remarkably mild muscle weakness. The presence of a second paternally derived X chromosome made him heterozygous at the Becker muscular dystrophy locus. One might have anticipated that his clinical and laboratory features would have been similar to those noted in Becker muscular dystrophy carriers (that is, serum creatine kinase level up to 200 IU/l and minimal or no weakness).^{11,12} On the one hand, his degree of weakness and serum creatine kinase level were significantly less than those of his nephews, and this could be attributed to him being heterozygous. On the other hand, his calf hypertrophy and raised serum creatine kinase level were in marked contrast to the clinical and laboratory features of his heterozygous sister (II.1). It is striking that the man II.4 had inherited the same muscular dystrophy alleles as his sister yet there was a 10 to 30-fold difference in their serum creatine kinase levels.

There are at least three possible explanations for this discordance. The most likely possibility is that II.4 randomly inactivated a greater proportion of his paternal X loci than did his sister. The occasional mild clinical manifestations of X linked muscular dystrophy in karyotypically normal heterozygotes is the result of a majority of normal alleles being randomly inactivated during Lyonisation.² Women who are heterozygous but have non-random X inactivation, for example as a consequence of an X;autosome translocation¹³ or in association with monozygotic twinning,¹⁴ may have full expression of the muscular dystrophy gene. Some of the clinical

features of II.4 were not typical of a Becker muscular dystrophy carrier and raised the possibility of non-random inactivation of his paternally derived X chromosome. However, it is difficult to suggest a mechanism for selective paternal X inactivation in this case. There is no reason to suspect non-random X inactivation on the basis of a Klinefelter karyotype alone. He did not have a structural X chromosome abnormality as has been described in other cases of manifesting heterozygotes.¹³ There has been one report of a manifesting Becker muscular dystrophy heterozygote who had a normal karyotype.¹⁵ Her raised serum creatine kinase level, generalised hypotonia, and proximal muscle weakness were attributed to random inactivation of the normal alleles in her skeletal muscle. Thus it is not necessary to invoke non-random X inactivation to explain the features of the man II.4.

A second possibility is that the man II.4 had a mosaic Klinefelter karyotype (46,XY/47,XXY) and was hemizygous for muscular dystrophy in a proportion of his cells. Mosaic karyotypes are common in Klinefelter's syndrome, occurring in approximately 10% of cases.¹⁶ All of the lymphocyte metaphases studied in II.4 had two X chromosomes, but the possibility that he had a mosaic karyotype in skeletal muscle cells was not excluded. One mechanism which might account for a mosaic Klinefelter karyotype is mitotic non-disjunction in the zygote,¹⁶ in which case the resulting two X chromosomes would be genetically identical. The two X chromosomes of II.4 had different alleles at *DXS206* and *DXS52* (fig 1), indicating that non-disjunction had been a prezygotic event. Therefore the man II.4 could not have had a mosaic karyotype in his skeletal muscle on the basis of mitotic non-disjunction. The other mechanism which might account for a mosaic Klinefelter karyotype is meiotic non-disjunction and subsequent elimination of one X chromosome through lagging at anaphase during mitosis.¹⁶ This mechanism is also very unlikely in the case we describe as it would require selective elimination of the paternal X chromosome in his progenitor skeletal muscle cells while retaining two X chromosomes in his progenitor haemopoietic stem cells.

The variable phenotype of Becker muscular dystrophy raises a third possibility. The clinical spectrum of Becker muscular dystrophy is reported to be sufficiently wide in individual families³⁻⁷ that the difference in weakness between II.4 and his nephews could be attributed to variable gene expression alone. Before considering this possibility, it would be important to know whether mildly affected males in the reported pedigrees had normal karyotypes or not. In view of the prevalence of

Klinefelter's syndrome, men with X linked muscular dystrophy whose weakness is markedly less than that of affected relatives could have both Klinefelter's syndrome and muscular dystrophy. On the other hand, related males may appear to have the same DNA deletion within the muscular dystrophy gene (thereby excluding heterozygosity at that locus) yet have very different degrees of muscle weakness.^{17 18}

The clinical diagnosis of Klinefelter's syndrome may be difficult, as in the case we describe. One man with Becker muscular dystrophy, hypergonadotrophism, and testicular atrophy has already been described¹⁹ but his karyotype was not reported. Men with Klinefelter's syndrome would be readily identified during family studies with highly polymorphic X chromosome markers. It should be noted that the DNA markers commonly used in X linked muscular dystrophy studies have only two alleles and the presence of two X chromosomes in a male could be missed. As more families with muscular dystrophy are studied with highly polymorphic markers, more males with X linked muscular dystrophy and Klinefelter's syndrome may come to light.

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