Apparent SMA I unlinked to 5q

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Abstract

A proband with a clinical picture indistinguishable from SMA type I is described. The parents are second cousins. On DNA analysis it appeared that the proband and his healthy 2 year old sib had inherited the same haplotypes for DNA markers flanking the SMA locus on 5q. This supports non-linkage of SMA to chromosome 5q in this family. The consanguinity of the parents raises the possibility of a second locus for autosomal recessive SMA type I outside the 5q12-13 region. This may have implications for genetic counselling after prenatal diagnosis in consanguineous families. Furthermore, this case illustrates the importance of the inclusion of all healthy sibs in prenatal DNA studies for SMA type I.

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Spinal muscular atrophy type I (SMA I) is generally considered to be an autosomal recessive disease.¹² Recently, linkage has been described of a major gene for SMA I (and for autosomal recessive SMA II and III) with DNA markers in the chromosomal region 5q12-13.³⁻⁶ Some authors^{7,8} estimated that an a priori proportion of 5% of all SMA I families are not linked to the 5q12-13 region, probably because of misdiagnosis, phenocopies, or spontaneous dominant mutation, but proof for this is lacking. Other authors do not consider a minority of SMA I cases to be unlinked to 5q.⁹ We report a family which suggests the existence of another locus for autosomal recessive SMA I.

Case report

A male infant was born by caesarean section because of intrauterine fetal distress. Apgar scores were 1, 7, and 8 at one, five, and 10 minutes respectively. The child was hypotonic, had a weak cry, and had a simian crease on both palms. Otherwise no abnormalities were noted at the age of 1 day. In particular, there were normal tendon reflexes and no contractures. The child was discharged from hospital. At a routine check up at the age of 7 weeks the paediatrician noted that the hypotonia was more severe than immediately after birth. At this time there was proximal and distal paresis of the limbs, a weak cry, and slight fibrillations of the tongue but otherwise a normal face with full eye movements, areflexia, slight contractures of the elbows and wrists, and signs of

respiratory distress. The child was referred to our hospital. Electrophysiological studies showed spontaneous positive potentials and fibrillations at rest. Conduction velocities were normal. A muscle biopsy showed large groups of atrophic fibres with some smaller groups of hypertrophic fibres (fig 1). For technical reasons, no histochemical studies were performed. The child died of respiratory insufficiency at the age of 8 weeks.

The family history was negative for neuromuscular disease and there is one healthy brother, aged 2½ years. The parents are second cousins (fig 2).

Informed of a 25% recurrence risk, the parents wanted prenatal diagnosis in a future pregnancy. DNA analysis of the parents, the healthy sib, and of a paraffin fixed muscle biopsy of the patient was carried out with DNA markers in the chromosomal region 5q12-13. The order of loci is cen-D5S76-D5S6-D5S125-D5S435-SMA-D5S357-D5S112.^{7,10} The results of the DNA analysis are shown in fig 2. The healthy sib and the patient have inherited the same haplotypes from their parents.

The parents decided to refrain from having another child in view of the probable 25% recurrence risk and the impossibility of prenatal diagnosis.

Discussion

In this family no linkage of the apparent SMA I with DNA markers on 5q could be found. One explanation for these results is that another locus for autosomal recessive SMA I exists outside the 5q12-13 region.

There are, however, alternative explanations for the results of the DNA studies. Non-paternity does not seem likely in view of the parents' attitude towards the 25% recurrence risk and prenatal diagnosis. Furthermore, non-paternity of the healthy sib could be excluded with a probability of >99% after testing with several DNA markers on other chromosomes (this could not be tested in the affected sib as there was no DNA left). The possibility of misdiagnosis in the child seems unlikely as the clinical symptoms were in complete agreement with the diagnostic criteria for SMA I,¹⁵ except for the slight contractures of the elbows and wrist. The clinical picture is incompatible with the type of X linked SMA described by Greenberg *et al*,¹⁶ which presents with severe congenital contractures and fractures. The consanguinity of the parents argues against other explanations, such as a phenocopy or a spontaneous mutation in the patient. Moreover, segregation ratios for SMA I do not deviate significantly from the expected 25%.^{17,18} In contrast, some authors found a

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Figure 1 Muscle biopsy of the proband at the age of 8 weeks, largely composed of small, atrophic fibres with scattered hypertrophic fibres (H × E).

Figure 2 Pedigree and DNA results in family SMA64. The numbers beneath the pedigree symbols refer to alleles for the DNA markers D5S76, D5S6, D5S125, D5S435, D5S351, and D5S112.¹⁰⁻¹⁴ The SMA locus on 5q is located between D5S435 and D5S351.

relatively low segregation ratio for SMA II in population studies, suggesting that a proportion of SMA II cases are not the result of homozygosity for an autosomal recessive gene.¹⁹ There is the possibility that the healthy sib is affected with SMA, but he shows no sign of muscle weakness at the age of 2½ years and simultaneous occurrence of SMA type I and chronic SMA type III has never been reported within the same sibship. A final alternative explanation is a double crossover (or two single crossovers) between flanking markers in the paternal or maternal haplotype, either in the patient or the healthy sib, although the chance of this is <1%. Moreover, the fact that the index patient is not homozygous for the flanking DNA markers investigated while his parents are consanguineous itself argues against location of the SMA gene on 5q in this family. It is interesting to note that two multiplex families have been described with SMA type III, in which the disease does not seem to be linked to the 5q region.^{20,21}

It is generally concluded that the vast majority of SMA I is linked to 5q^{7,9} and SMA I resulting from homozygosity at a locus different from 5q would be a rare event. As homozygosity for rare disease alleles occurs relatively more often in children of consanguineous parents than is the case for diseases with a higher carrier frequency, parental consanguinity can be expected to be relatively more frequent in non-5q autosomal recessive SMA I than in 5q linked SMA I.

Our observation of a case, diagnostically indistinguishable from SMA I, probably autosomal recessive but unlinked to 5q markers, has implications for DNA linkage studies aimed at the identification of the gene. It may have consequences for genetic counselling and risk calculation at prenatal diagnosis. For the large majority of SMA I families, prenatal risk calculation is feasible according to accepted procedures,⁷ but it appears that one should take special care in interpreting results from DNA studies in consanguineous SMA I families. Our case is a good example of the necessity to include all available healthy sibs in a DNA analysis to investigate the feasibility of prenatal diagnosis for a given couple.

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