Confirmation of Clinical Diagnosis in Requests for Prenatal Prediction of SMA Type I

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LESSON OF THE MONTH

Confirmation of clinical diagnosis in requests for prenatal prediction of SMA type I

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Abstract

The recent discovery of a major SMA-locus in the chromosomal region 5q makes it possible to carry out prenatal DNA studies in families in which a child with SMA type I has been born. Since direct mutation analysis is not yet possible, the reliability of prenatal prediction of SMA type I usually depends on the certainty of the clinical diagnosis in the index patient. Sixteen requests were received for DNA studies in couples who had had a previous child with SMA type I. After re-evaluation, the performance of prenatal diagnosis was rejected in four cases. Among the other twelve families prenatal DNA analysis of chorion villus biopsies has been carried out in three families. In all three cases the fetus had inherited the high-risk haplotypes from both parents, and the parents chose to terminate the pregnancy. An illustration of the prenatal DNA studies in one family is given. The importance of confirmation of the diagnosis SMA type I before performing DNA studies is emphasised.

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Proximal spinal muscular atrophies (SMA) of childhood can be classified into three types on the basis of clinical criteria, SMA type I (Werdnig-Hoffmann disease), SMA type II (intermediate SMA) and SMA type III (Kugelberg-Welander disease).[1] SMA type I is a lethal, autosomal recessive disease with a gene frequency of approximately 4–5/100,000.[2] The clinical picture is characterised by onset of hypotonia, progressive weakness, wasting of limb and trunk muscles and areflexia before six months of age. Children with classic SMA type I never gain the ability to sit, and death usually occurs within two years due to respiratory insufficiency. The diagnosis is based on the characteristic clinical picture, on signs of denervation in EMG studies and on the histopathological picture, that is, groups of atrophic muscle fibres of either type in conjunction with hypertrophic, usually predominantly type I, fibres. Inclusion and exclusion criteria for the diagnosis of SMA type I have recently been formulated.[3] (Table)

In 1990 a major gene for the autosomal recessive types of SMA type I, II and III was localised in the chromosomal region 5q12-q13.[4–9] The availability of several highly polymorphic DNA-markers in this region permits prenatal prediction of SMA type I by DNA studies of chorionic villus or amniotic fluid cells in families with an affected child, making use of DNA from the affected child.[10,11] Caution is necessary, however, because of the probable genetic heterogeneity of SMA.[5,8,12]

We analysed the process of confirmation of the clinical diagnosis in requests for prenatal diagnosis of SMA type I.

Methods

We restricted prenatal diagnosis to cases with an unequivocal diagnosis of SMA type I because of the reported genetic heterogeneity of SMA types II and III.[12] In all cases the diagnosis SMA type I was evaluated by careful analysis of clinical data and re-evaluation of all available muscle biopsies.

When there was no doubt about the diagnosis of SMA type I, DNA from the parents and all healthy siblings was isolated by routine procedures, and DNA analysis was carried out with markers available for the chromosomal region 5q12-q13.[13,14–17]

When both parents were informative for

Table Criteria for diagnosis of SMA type I

1 Clinical symptoms of anterior horn cell disease
  a-/hyporeflexia
  muscle atrophy
  fasciculations
2 Early onset and progressive course
  age at onset < 1/2 year
  age at death < 4 year
  never able to sit unsupported
3 Creatine kinase normal
  CK <10x higher reference value)
4 Electromyographic study showing signs of anterior horn cell involvement
5 Muscle biopsy compatible with anterior horn cell disease
6 Exclusion criteria:
  no symptoms of other neurological systems
    no sensory loss
    no central motor neuron symptoms
    no mental retardation
  no arthrogryposis
  no evident facial involvement
  no other major organ involvement

In an isolated case all criteria except number 4 are obligate. In a familial case only criteria 1, 2, 3 and 6 are obligate, while at least one affected family member (sibling) must meet the criteria for an isolated case.

markers on both sides of the SMA-locus, located between D5S6 and D5S112, the family was informed that prenatal diagnosis was possible with a specified reliability, dependent on the recombination distances of informative probes, the number of investigated affected and healthy siblings and the presence or absence of consanguinity. We incorporated in the calculations the current best estimate of 5% for the proportion of SMA type I families, which may not be due to an autosomal recessive gene on 5q12-q13. In a particular family this a priori estimated figure of 5% was further modified for additional support for 5q-linkage, derived from the family itself. Finally, the chance of errors resulting from single and double recombinations between the SMA-locus and the informative DNA-markers was incorporated.

Results

Sixteen requests for prenatal diagnosis of SMA type I were received by our centre. In 4/16 cases prenatal diagnosis was declined because the diagnosis did not fit classical SMA type I. We describe these 4 cases, indicating the differential diagnosis in the discussion.

Case 1

Case 1 was a male infant born with congenital contractures of all joints, telecanthus, generalised hypotonia and signs of respiratory insufficiency. EMG-studies showed lively spontaneous muscle activity. Muscle biopsy revealed extensive endomysial fibrosis. After extensive clinical and biochemical studies bacteriology and virology, chromosome studies, radiological and ultrasound examinations, ECG and CT scanning of the cerebrum), no diagnosis could be made and the child died at the age of two months. Necropsy revealed an obvious decrease in the anterior horn cells with calcium deposits in these cells and the diagnosis of Werdnig-Hoffmann disease was made.

Case 2

Case 2 was a female infant born with congenital contractures of arms and legs, hygroma colli, a large atrial septal defect and generalised hypotonia with fasciculation of the tongue. She died when she was seven days old of respiratory insufficiency. Necropsy showed clear signs of anterior horn cell involvement, and it was concluded that the child had Werdnig-Hoffmann disease.

Case 3

This male child appeared normal at birth, but in the first year hypotonia became evident. The child could not sit unsupported. At one year EMG-studies were normal, but a muscle biopsy revealed groups of atrophic muscle fibres, lying amidst groups of normal to large calibre, predominantly type I, fibres. The diagnosis of spinal muscular atrophy was then made. At the age of 5, the child survived, but had respiratory insufficiency.

Case 4

Case 4 was a male infant, noted to be progressively hypotonic at age one. There was decreased facial muscle activity and knee jerks were preserved. EMG studies revealed no abnormalities. A muscle biopsy was performed and a diagnosis of Werdnig-Hoffmann disease was made. Re-evaluation of the muscle biopsy, however, showed only a slight variation in the size of the individual muscle fibres, without groups of atrophic fibres or other signs indicative of spinal muscular atrophy.

In the remaining 12 families DNA-studies were completed. In all families the parents were informative for DNA-markers flanking the SMA-gene. In 3 of the 12 families prenatal diagnosis by DNA-analysis of chorionic villus biopsy material was performed. In all three cases the fetus was probably affected with SMA type I (with a risk of 90%, 92–93% and 94% respectively). The couples opted for selective abortion before the fifteenth week of pregnancy. An example of one family in which prenatal diagnosis was actually performed is represented in the figure.

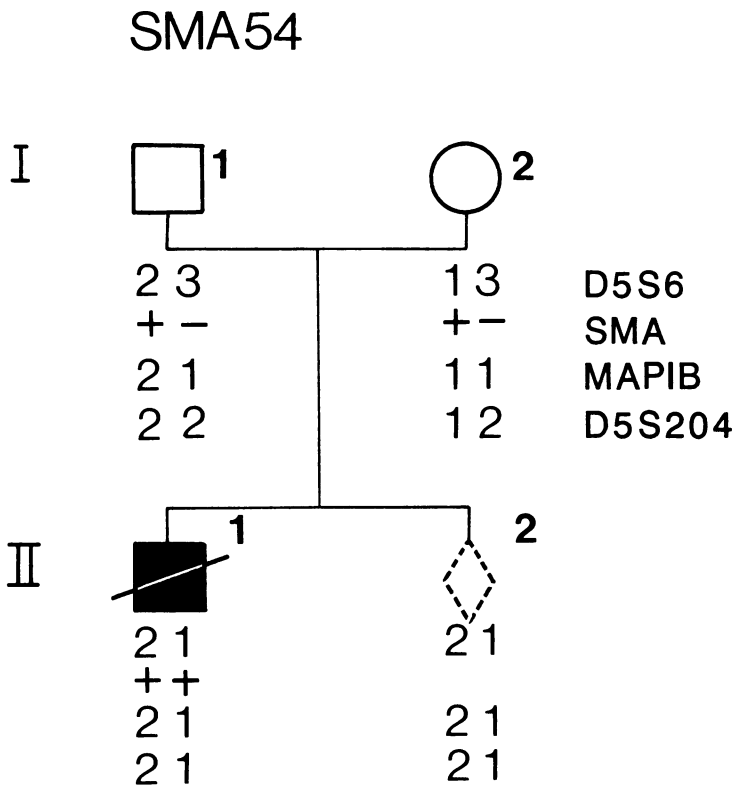

Figure Prenatal diagnosis in family SMA54. II-1 was a boy with SMA type I, who died in 1987. DNA was extracted from a frozen muscle biopsy, which had been stored. Both parents were informative for D5S6, the father informative for MAP1B and the mother for D5S204. The fetus I-2 inherited the same haplotype from the parents as the affected child. Assuming a genetic distance between D5S6 and MAP1B of 2–4cM and between MAP1B and 6741 of 4–6cM, and taking into account a 5% proportion of a priori non-5q-linked SMA I-families, the risk of the fetus being affected with SMA type I was calculated to be 92–93%. The parents chose to terminate the pregnancy. ■ = male with SMA I. ○ = female, healthy. ◇ = chorionic villus biopsy. + = SMA-allele. -=normal allele.

Discussion

It is important to confirm the clinical diagnosis of SMA type I by all available methods to

avoid errors in prenatal diagnosis of this disease. The SMA gene itself has not yet been found, so direct mutation DNA analysis is impossible.

The four cases in the families not offered prenatal diagnosis were considered not to have classic SMA type I.

Although contractures may develop during the course of SMA type I (case 1), the association of spinal muscular atrophy in children with congenital arthrogryposis may represent a separate disease entity.[18]

The congenital contractures, cardiac defect, hygroma colli and facial dysmorphia in case 2 are all unusual signs in SMA type I. Case 2 possibly represents a unique syndrome with signs of anterior horn disease, and resembles another case which has been documented.[19] Although the first pathologist had diagnosed "Werdnig-Hoffmann disease" this term is often used erroneously, as a synonym for anterior horn cell disease.[20]

The clinical course in case 3 does not fit a diagnosis of SMA type I but could be consistent with SMA type II. Genetic heterogeneity for SMA type II is described with a proportion of cases not autosomal recessive inherited but either due to phenocopies or to autosomal dominant mutations.[12] Progressive hypotonia in infancy (case 4) has a wide differential diagnosis and the diagnosis in this child is not yet clear.

The importance of confirming the clinical diagnosis SMA before embarking on DNA studies has recently been emphasised.[3 20] It is difficult to define rigid diagnostic criteria. There will always be cases on which every expert agrees that it must be SMA type I, even though not all criteria (table 1) are met.

With the current availability of highly informative CA- or GT-repeat DNA-markers, parental uniformativeness for all markers in the 5q12–13 region will be rare, and did not occur in our cases. The DNA-studies will therefore reveal whether or not the fetus has inherited the same relevant portion of the parental chromosomes 5 as the preceding child with SMA did. A complicating factor is that a recombinant between the flanking markers of one or both parents may be detected in prenatal DNA-studies. A single recombination can greatly influence the risk of the fetus being affected. Before prenatal diagnosis, parents should be informed of the possibility and probability of results like these. The probabilities differ from family to family, depending on the precise family situation and on which DNA-markers are informative. In most families, however, as long as the gene has not been found, the reliability of prenatal testing for SMA type I is mainly dependent on the certainty of the clinical diagnosis in the index patient.

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