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Prenatal Prediction of Spinal Muscular Atrophy

Experience with Linkage Studies and Consequences of Present SMN Deletion Analysis

Abstract

With the localisation of the gene for the autosomal recessive forms of proximal spinal muscular atrophies (SMA) to the chromosomal region 5q13 and the later detection of homozygous deletions of the SMN gene located in this region, prenatal prediction of SMA has become feasible and is widely applied now. In our experience with 77 prenatal predictions of SMA, follow-up of the 39 liveborn children from these pregnancies never led to a false-negative result. Application of SMN deletion analysis has consequences for prenatal prediction of SMA. When the index patient has a homozygously deleted exon 7 of the SMN gene, prenatal prediction and interpretation of results are straightforward. In families in which no DNA from the index patient is available, prenatal detection of a homozygous SMN deletion may be considered almost proof of SMA in the fetus. Absence of a deletion, however, will not guarantee an unaffected child. A real problem exists if the index patient does not show a homozygous deletion of SMN exon 7. In such cases with non-homozygous SMN deletions, one cannot be certain of 5q linkage and autosomal recessive inheritance until other SMN mutations are detected. This is an argument to abstain from prenatal diagnosis by linkage analysis in these families.

Key Words

Spinal muscular atrophy
Chromosome 5
Prenatal diagnosis
SMN deletion

Introduction

Proximal spinal muscular atrophies (SMA) are incurable, mostly heritable, lower motor neuron diseases. SMA can be classified on clinical grounds into three subtypes: SMA I or Werdnig-Hoffmann disease, SMA II or intermediate type SMA and SMA III or Kugelberg-Welander disease [1, 2]. In SMA I, death usually occurs before the age of 2 years. In SMA type II survival is longer, but patients are never able to walk. SMA type III is a relatively milder clinical subtype, in which walking ability is achieved at some point in life, although most patients become wheelchair-bound at a later date. SMA appears to be one of the most frequent severe autosomal recessive diseases in man: the birth prevalence of all types of SMA is estimated to be between 1/5,000 and 1/10,000 births for most European countries [3, 4]. A gene for all three subtypes of autosomal recessive SMA has been assigned to chromosomal region 5q13 [5–8]. This allowed prenatal prediction of SMA by means of closely linked flanking DNA markers

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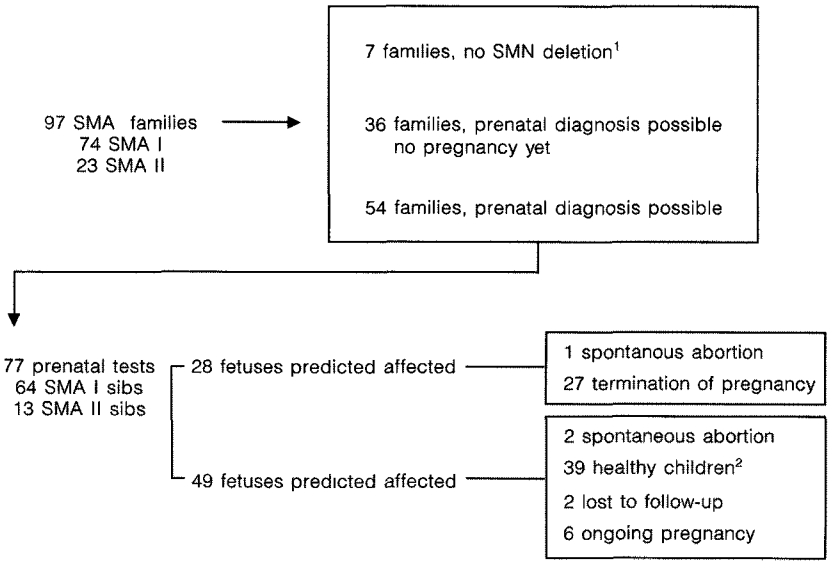

Fig. 1. Results of DNA-analyses in preparation of prenatal prediction in 97 SMA families and outcome of prenatal prediction in 54 families. All families had been referred for prenatal prediction during the period 1990–1995. A further 21 other families which did not meet the diagnostic criteria are excluded from this summary.

[1] SMN delection analyses have been carried out retrospectively in most cases. In 1 of these 7 non-SMN deleted SMA families, prenatal prediction had been performed earlier by means of linkage analysis. The fetus was predicted to be unaffected and a healthy child was born, which was 2 years old at the time of completion of this study.

[2] Healthy as far as SMA is concerned (see figure 2 for details on the age distribution at the time of completion of this study). Three of these 39 children had another congenital abnormality: coarctation of the aorta, a club foot and cleft lip/palate, respectively.

[9, 10]. More recently, homozygosity for deletions of SMN, which is the telomeric copy of a duplicated gene in this chromosomal region, was found to be strongly associated with the disease [11]. We described a simple DNA test to detect homozygous SMN deletions, which can easily be applied prenatally [12]. A complication in prenatal application may be the most recent finding of homozygous SMN deletions in unaffected siblings (and one parent) of patients affected with SMA type II or III [13, 14].

We report our experience in the prenatal prediction of SMA using DNA markers and SMN deletion analysis and discuss the consequences of the present knowledge of SMN deletions in SMA for prenatal prediction.

Materials and Methods

Clinical Data

A total of 118 families were referred to our Department in Groningen with a request for prenatal diagnosis in an ongoing or future pregnancy. Our data cover the period May 1990–September 1995. Clinical data of all index patients were reviewed. In unclear cases, muscle biopsies were examined by one of us (MdV). After excluding 21 families in which the index case did not meet the internationally agreed diagnostic criteria [15, 16], 97 families (74 SMA I and 23 SMA II families) remained for preliminary DNA analyses. After the prenatal prediction, follow-up data on the outcome of the pregnancy were ascertained through the gynecologist and/or the general practitioner involved. In September 1995, all parents were approached by telephone and interviewed on the health status of their children born after prenatal prediction.

DNA Analysis

DNA from most index cases was routinely obtained from blood or fibroblasts. However, in 4 cases only a frozen muscle biopsy, in 5 cases paraffin-fixed muscle tissue, in 3 cases a slide with cryostat-sectioned unfixed muscle and in 3 cases a Guthrie card were available. In all cases, sufficient DNA could be retrieved to analyse at least 10 different CA repeat markers and screen for a homozygous deletion of SMN exon 7.

Before 1995, prenatal prediction was based on linkage analysis with closely flanking informative DNA markers. From spring 1995 on, SMN deletion analyses were performed as well. In all families, the SMN deletion status of the index case was assessed retrospectively. We could not look for SMN deletions in terminated pregnancies that had been investigated with closely flanked markers only, as we had decided earlier not to store DNA from aborted fetuses predicted to be most likely affected.

SMN deletions were searched for according to previously described procedures [12]. Linkage studies using D5S76, D5S6, D5S125, D5S435, D5S629 and D5S823 on the proximal side of the SMA-locus and D5S557, D5S610, D5S637, D5S351 and D5S112 on the distal side were performed using standard methods.

Results

Preliminary DNA Analysis

Prior to prenatal DNA analyses, the 97 families included in this study were investigated with DNA markers flanking the SMA 5q region. Retrospectively, SMN deletion analyses were carried out in all families. In 90 families, the index case showed homozygosity for a deletion of exon 7 of SMN and the parents were informative for

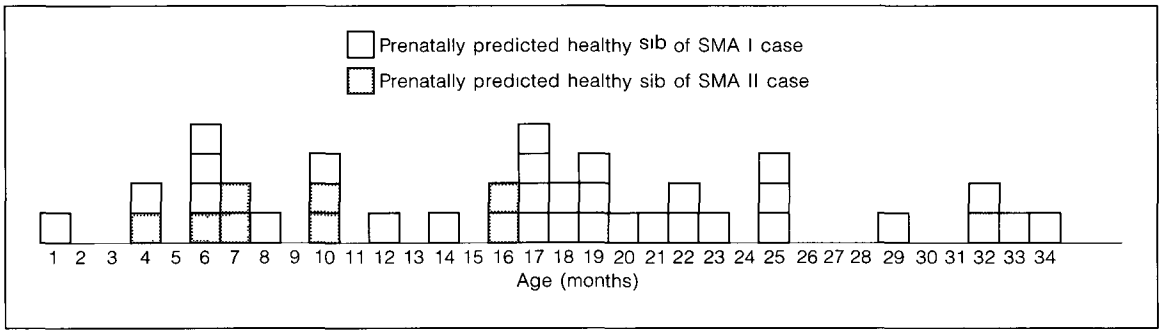

Fig. 2. Age distribution at the end of the follow-up period of 39 healthy sibs of SMA patients, prenatally predicted to be unaffected.

DNA markers closely flanking the SMA locus. In the remaining 7 families, no homozygosity for a deletion of SMN exon 7 could be detected. In 1 of these 7 families prenatal analysis with DNA markers had been carried out before SMN deletion analysis was possible. The fetus was predicted to be unaffected and a healthy child was born; it was 2.5 years old in March 1996.

Prenatal DNA Analysis

In 54 families with exon 7 homozygously deleted in the index case, prenatal DNA-analysis was performed predicting the disease status for a total of 77 fetuses. The outcome of the preliminary DNA analysis of all 97 referred families and of the 77 prenatal predictions is listed in figure 1. Using linkage analysis only, we never had a case where the prenatal test predicted a fetus to be unaffected, whereas after birth the child appeared to be affected (fig. 2).

Cases with Non-Homozygous Deletions

As stated above, in 7 out of 97 families referred for prenatal prediction no homozygosity for a deletion of SMN exon 7 could be detected in the index case. All 7 index patients had their diagnosis confirmed by a muscle biopsy and conformed to the current clinical diagnostic criteria [15, 17]. In 4 of these 7 families without deletions, the index case was the first and only child in the sibship, so that linkage analysis was impossible. In each of the remaining 3 families, a sibling appeared to be healthy and available for blood sampling. Linkage analysis in these 3 families without SMN deletions was informative and showed that in 2 out of 3 sibships without SMN deletions the healthy sib had inherited the same 5q13 haplotype as the sibling affected with SMA (type I in all three families). In the remaining family the healthy sib had inherited a 5q13 haplotype different from that of the affected child.

Discussion

With the localisation of autosomal recessive SMA to the chromosomal region 5q13, prenatal diagnosis of these forms of SMA has become feasible in most families with a previous affected child. As yet, a diagnosis of SMA in a fetus aborted before the 20th week of pregnancy cannot be confirmed. Therefore, the term prenatal prediction rather than prenatal diagnosis seems appropriate. We and other groups [9, 10, 18] did not experience any false-negative prenatal prediction so far. Thus, linkage analysis seems reliable enough to at least exclude SMA in the fetus. False-positive prenatal predictions of SMA, however, have been reported [19].

Figure 1 shows that investigation of 77 pregnancies resulted in 28 (36%) high-risk outcomes. This percentage is significantly above the expected 25% ($p < 0.05$ by two-tailed and one-tailed χ^2 testing, respectively). Wirth et al. [18] found 36/109 (33%) fetuses at a high risk of being affected. This high percentage, however, was partly due to recombination events in 7 of their 36 high-risk predictions. Two other series of prenatal linkage analysis in SMA families also showed a higher than expected rate of affected sibs, but the numbers are too small to be significant (number of fetuses predicted to be affected 10/32 (31%) and 3/9 (33%), respectively [20, 21]. We think that investigation of larger series is needed before a distorted segregation in SMA families can be postulated. Since the reporting of SMN deletions in a large majority of all SMA patients in various populations [11, 13, 18, 22–25], one can distinguish different groups of families that request prenatal diagnosis:

(1) Families in which the index patient is shown to have a homozygous deletion in exon 7 of the SMN gene. These will form the large majority of families referred for

prenatal diagnosis. Strict documentation of the clinical diagnosis in the index patient is still important, but not as obligatory as in the following groups (2) and (3): although SMN deletions have rarely been described in healthy subjects [13, 14], clinical symptoms of SMA (without confirmation by EMG studies or a muscle biopsy) in combination with an SMN deletion can be considered as sufficient proof for the diagnosis. At prenatal testing, the interpretation of SMN deletion status in the fetus is straightforward. Of course, as a general precaution, one should still haplotype parental and fetal material in order to confirm the fetal origin of the tissue investigated.

(2) Families in which there is no DNA from the index case. First, one should always try to retrieve DNA from the deceased child from whatever source: Paraffin-embedded or frozen muscle tissue and Guthrie spots, even mummified umbilical cord [26], can all reliably be used for PCR-based DNA analyses. In all cases, one should always check by analysing DNA from the parents, that the DNA retrieved is indeed from the deceased child. In case DNA of the affected child is definitely not available, one needs to be as sure as possible of the diagnosis in the index case before embarking on prenatal diagnosis, since SMA has not been confirmed by the demonstration of a homozygous SMN deletion. At prenatal diagnosis one can look for SMN deletions. Parents in these families have to be aware, however, that whereas the presence of an SMN deletion at prenatal diagnosis may be considered almost proof of SMA in the fetus, the absence of an SMN deletion in the fetus cannot guarantee an unaffected child. In different studies [11, 13, 14, 22–25], the frequency of homozygous SMN deletions varies between 0.9 and 0.99, so the risk of an affected child will vary between 0.25 and 2.5% when no SMN deletion is found at prenatal diagnosis in families without DNA of the child affected with SMA. These risk figures should only be used when the clinical diagnosis leaves no doubt. From a pragmatic point of view, DNA analyses of healthy sibs will not lead to important additional information in SMA families in which there is no DNA of an affected child: prenatal DNA analysis will or will not demonstrate homozygosity for an SMN deletion, and this will determine the decision to continue the pregnancy or not. There will be no useful additional information in knowing, whether a healthy sib proves to be SMN deleted or not. When the fetus has an SMN deletion, haplotype information on healthy sibs is irrelevant. When the fetus has no SMN deletion, the knowledge whether a healthy sib is haplo-identical or not is of doubtful relevance, as this will hardly influence the estimated risk of the fetus being affected with SMA. In most families in this group (2), prenatal diagnosis will be considerably improved when detection of heterozygotes by DNA analysis becomes possible.

(3) Families in which the index patient does not show a homozygous SMN deletion. These families pose a problem in view of the prenatal prediction of SMA. One should realise that SMA is known to be heterogeneous, with an estimated 5% of SMA families probably not fitting simple autosomal recessive inheritance and/or not being 5Q-linked [27, 28]. In 7 of our families referred for prenatal prediction we did not find a homozygous SMN deletion retrospectively (fig. 1): in 2 out of 3 of these families haplo-identity of the index case and a healthy sib was observed. Taking them as a subgroup, the odds of the SMA disease gene being linked to 5q in these families are very low, but spontaneous point mutations in the SMN gene cannot be ruled out in these families. In fact, there are several possible explanations for SMA without deletions of SMN:

(a) clinical misdiagnosis;

(b) undetected (de novo) mutations in the SMN gene;

(c) autosomal dominant SMA;

(d) another locus for (autosomal recessive) SMA.

ad (a). One should be very alert to the possibility of a diagnosis different from SMA in an index case with non-homozygous SMN deletions. The importance of the certainty of the clinical diagnosis SMA before embarking on prenatal diagnosis has been stressed by several authors [16, 29].

ad (b). In a proportion of cases with non-homozygous SMN deletions, a point mutation might be present in one SMN allele in addition to a mutation in the other allele such as an SMN deletion, which cannot be demonstrated in a heterozygous state at this moment. Evidence for spontaneous mutations in SMA is well-documented in the literature [19, 22, 30]. Thus, spontaneous mutations (or phenocopies or uniparental disomy [25]) may account for some of the cases with non-homozygous SMN deletions.

identical

ad (c). The locus for autosomal dominant SMA is outside the 5q region [31]. Especially in more chronic types of SMA one should be aware of the possibility of a mildly affected parent, but even when the parents are clinically normal, a de novo mutation cannot be completely excluded.

ad (d). In the literature and from our own data there is no clear indication for another locus for autosomal recessive SMA outside the 5q region. We reported earlier on a consanguineous family in which a boy with SMA I and his healthy sib were haplo-identical for markers surrounding the SMA locus [32]. A recent SMN deletion analysis

revealed that the SMA I in this family is not due to a homozygous SMN deletion. To our knowledge, sibs with SMA type I, II or III who inherited different 5q haplotypes, have never been reported. Non-5q-haplo-identical sibs with variants of SMA (SMA with diaphragmatic paralysis, SMA with olivopontocerebellar atrophy and a form of SMA with arthrogryposis) have been described, but these variants are apparently not linked to 5q [33–35]. In our opinion, the possibility of another autosomal recessive locus for SMA proper is mainly a theoretical one.

In conclusion, although there is no direct evidence for non-5q-linked SMA, it is likely that a proportion of non-SMN-deleted SMA is not simply autosomal recessively inherited and/or not even 5q-linked at all. In non-homozygously-SMN-deleted SMA there is no proven 25% recurrence risk. If the proportion of potentially de novo mutation or phenocopies were not negligible in this group, then the risk of a false-positive result of prenatal prediction by means of linkage analysis might be unacceptably high. This is an argument for not performing prenatal DNA analysis in SMA families with non-homozygous SMN deletions until both SMN mutations (one of them might be an SMN deletion) have been demonstrated in the index case.

A last point of discussion is the possibility to perform direct prenatal diagnosis when one of the parents is at an increased risk of being a carrier, for instance because of being a sibling or an uncle or aunt of an affected patient. In our opinion, as long as carrier detection is not possible, prenatal testing for a homozygous SMN deletion is not warranted in such cases: firstly, their risk of having an affected child (1/270–1/360 with an estimated carrier frequency of 1/45) is lower than the risk of iatrogenic abortion after prenatal sampling (about 1%). Secondly, although the presence of a homozygous SMN deletion can be considered proof of SMA in a clinically affected individual [12], this does not hold true in the absence of a clinical picture (as in prenatal testing), because SMN deletions have been described to occur in healthy SMA family members as well [13, 14]. At the low a priori risk of having an affected child for couples in which one of the parents is at an increased risk of being a carrier, even a small frequency of homozygous SMN deletions in healthy SMA family members might dramatically influence the predictive value of a prenatally demonstrated SMN deletion.

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