Prenatal diagnosis in laminin α2 chain (merosin)-deficient congenital muscular dystrophy: A collective experience of five international centers

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Received 2 February 2005; received in revised form 30 March 2005; accepted 22 April 2005

Abstract

The congenital muscular dystrophies (CMD) are clinically and genetically heterogeneous. The merosin (laminin α2 chain) deficient form (MDC1A), is characterized clinically by neonatal hypotonia, delayed motor milestones and associated contractures. It is caused by deficiency in the basal lamina of muscle fibers of the α2 chain of laminins 2 and 4 (LAMA2 gene at 6q22–23). Laminin α2 chain is also expressed in fetal trophoblast, which provides a suitable tissue for prenatal diagnosis in families where the index case has total deficiency of the protein. This article reports the collective experience of five centers over the past 10 years in 114 prenatal diagnostic studies using either protein analysis of the chorionic villus (CV) of the trophoblast plus DNA molecular studies with markers flanking the 6q22–23 region and intragenic polymorphisms (n = 58), or using only DNA (n = 44) or only protein (n = 12) approaches. Of the 102 fetuses studied by molecular genetics, 27 (26%) were predicted to be affected while 75 (74%) were considered as unaffected, with 52 (51%) being heterozygous, thus conforming closely to an autosomal recessive inheritance. In 18 of the 27 affected fetuses, the trophoblast was studied by immunocytochemistry and there was a total or only traces deficiency of the protein in CV basement membrane in all. In 10 cases material from the presumably affected fetus was available for analysis after termination of the pregnancy and immunohistochemical study confirmed the diagnosis in all of them. Prenatal studies of ‘at risk’ pregnancies in the five centers produced neither false negative (merosin-deficiency in CVs in a normal fetus), nor false positive (normal merosin expression in CVs and affected child), indicating the reliability of the technique, when all the necessary controls are done. Our experience suggests that protein and DNA analysis can be used either independently or combined, according to the facilities of each center, to provide accurate prenatal diagnosis of the MDC1A, and have an essential role in genetic counseling.

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Keywords: MDC1A; α2-laminin; Merosin; Prenatal diagnosis

1. Introduction

The congenital muscular dystrophies (CMD) are clinically heterogeneous disorders characterized by the presence of hypotonia from infancy, generalized muscle weakness and joint contractures to variable degrees, as well as a possible association with central nervous system and eye abnormalities. Electromyography reveals a myopathic
pattern; serum creatine-kinase is usually elevated in the early phases of the disease and muscle biopsy shows pathological changes consistent with a dystrophic process [1–4].

To date, 10 genetically different forms have been identified [4]. The most common form, MDC1A, accounts for about 40% of cases, and is due to mutations in the LAMA2 gene on chromosome 6q22–23 [5,6], which codes for the α2 chain of laminin 2 (merosin) and laminin 4 (s-merosin) [7]. The LAMA2 gene is composed of 65 exons and at least 90 different mutations have been described in affected patients (http://www.dmd.nl/), but, as there are neither common mutations nor hot spots for mutations, the identification of causative genetic abnormality is laborious, expensive and time consuming. In this respect, the immunohistochemical analysis of the protein in the muscle biopsies is a powerful diagnostic tool, since the great majority of patients with complete laminin α2 chain deficiency have shown gene mutations when they have been searched for systematically [8–10].

Laminins are glycoproteins that are an integral component of basement membranes. They are composed of three subunits: one heavy and two light chains. The main heterotrimers of mature skeletal muscle fibres are α2–β1–γ1 (laminin 2) and α2–β2–γ1 (laminin 4), both of which contain the α2 chain [7,11]. Laminin α2 chain binds to α dystroglycan, linking the dystrophin–glycoprotein complex to the extracellular matrix [12,13]. In addition, it binds to integrin α7β1D [13].

The laminin α2 chain is expressed in several tissues in addition to muscle, including skin and trophoblast [14–18]. Thus, immunohistochemical detection of laminin α2 chain can be used for prenatal assessment of trophoblast samples from fetuses at risk for MCD1A, using specific antibodies.

Additionally, genotype analysis and determination of ‘at-risk’ haplotypes, using chromosome 6q22–23 microsatellite markers flanking the LAMA2 gene and various intragenic polymorphisms, have also been used for prenatal diagnosis [17,19–23]. The reliability of this diagnosis depends on the information yielded by the markers and the accuracy of the diagnosis in the index patients.

The first prenatal diagnoses through the study of the protein in the trophoblast were done in Germany in 1994 by Voit [15,24] and shortly afterwards in UK [16] and in France (Fardeau and Tomé, in January 1995, unpublished observation), following the suggestion made by Voit et al. [15] that direct assessment of merosin from chorionic villous (CV) might provide a rapid and straightforward approach to determine laminin α2 chain expression in a fetus ‘at risk’. Since then, several laboratories have performed prenatal diagnosis of MDC1A, and the purpose of this report is to summarize the data of 114 prenatal tests performed in five reference neuromuscular centers worldwide.

2. Patients and methods

The chorionic villus (112 cases) or amniotic fluid samples (two cases) of 114 ‘at risk’ fetuses of MDC1A were collected for prenatal diagnosis at 9–12 weeks of gestation, according to routine procedures (Table 1). The criteria for doing this were an unequivocal diagnosis of MDC1A in at least one member of the family, that was based on the clinical features (hypotonia in infancy, presence of white matter hypodensity determined by brain magnetic resonance imaging) and muscle biopsy showing absence or drastic reduction of laminin α2 chain by immunocytochemistry. A muscle sample from each index patient was studied generally using at least two antibodies against laminin α2 chain. The antibodies were directed against the N-terminal (300 kDa) and C-terminal (80 kDa) epitopes.

Where a pregnancy was terminated because the fetus carried the at risk haplotypes and/or the CVs showed absence of laminin α2 chain, the fetal muscle, when it could be obtained (10 cases), was studied for laminin α2 chain expression.

3. Protein studies

CV samples were frozen in isopentane cooled in liquid nitrogen. Frozen sections were immunolabelled using routine methodologies, having as secondary antibodies anti-mouse labeled with fluorescein, biotin–streptavidin-Texas-Red or Alexa 594, according to the methodologies used in each laboratory [5,25,26].

Immunohistochemical analyses were performed as previously described using the following antibodies: against the laminin α2 chain 80 kDa fragment (Gibco; mAb1922 Chemicon), Mer3/22B2, kindly provided by Dr L.V.B. Anderson and commercially available from Novocastra, and 4H8 (Alexis). The two antibodies, Mer3/22B2 and 4H8, detect mild reduction of the protein more easily than the mAb1922, although they react with different domains of the protein: the C terminal globular domain (Mer3/22B2) and the N-terminal globular IVa domain (4H8), as reported by He et al. [27]. The epitope of the Novocastra antibody is not known but it behaves like the Alexis antibody. Additional monoclonal antibodies against the α5, β1 and γ1 laminin chains (Gibco; Chemicon) were also used as positive markers for the CV sample labeling. Control CV samples from fetuses not ‘at risk’ for MDC1A were studied in parallel.

4. Genetic studies

DNA was extracted from the CV and more recently from 20 ml of amniotic fluid cells (two cases) according to standard techniques. In a few cases with known LAMA2
gene mutations a direct diagnosis was performed by sequencing the mutated exons. In all other cases the genotype analysis was performed to identify the ‘at-risk’ haplotypes. The chromosome 6q22–23 microsatellite markers D6S1715, D6S407, upstream of the LAMA2 gene, and D6S1620, D6S1572, D6S262, downstream of the LAMA2 gene, and the intragenic polymorphisms G1905A (exon 12), A2848G (exon 19), and G5515A, A5551G and C5579A (exon 37) and G6286A (exon 42) were used for this purpose, according to the methodologies described by Guicheney et al. [22] and Helbling-Leclerc and Guicheney [28]. The microsatellite markers (amplified by PCR using fluorescent-labeled primers, or revealed by peroxidase-labeled CA-repeat probe) were first tested in parents and the affected child to establish if they were informative. If all the markers were heterozygous in parents, the three closest to the gene were kept for the prenatal diagnosis (D6S407–D6S1620–D6S1705). At least one informative intragenic polymorphism should be informative in both parents. In the case that one of the parents showed homozygosity for all the markers, an indirect genetic prenatal diagnosis could not be accurately made and the study of the trophoblast by immunocytochemistry with appropriate antibodies remained as the only informative strategy.

5. Results

The examination of 112 CVs and of two samples of cells from the amniotic fluid of ‘at-risk’ fetuses of laminin α2 chain deficiency, using DNA molecular studies using markers flanking the 6q22–23 region and intragenic polymorphisms (n=44) or protein analysis (n=12) or both methods (n=58), allowed the identification of 27 affected fetuses, while the remaining 87 were considered as unaffected (Table 1).

Among the 70 CV samples assessed for the presence of the laminin α2 chain, 18 showed total deficiency or only traces of this protein in the CV basement membrane, and 52 showed an expression of the laminin α2 chain identical to that in controls (Fig. 1, Table 1). Labeling of CVs for α5, β1 and γ1 laminins chains was similar in all samples and showed no abnormalities, indicating that there was good preservation of the basement membrane, and that these chains were normal in the trophoblasts of affected fetuses (Fig. 1).

DNA haplotyping with microsatellite markers, performed in 102 samples, identified the ‘at risk’ chromosomes inherited from each parent in 27 (26.4%) fetuses, while 52 (50.9%) were heterozygous for one of the at-risk alleles. Twenty-three (22.5%) were normal for both alleles.

In the French group a genetic evaluation was performed in all cases but one (Table 1), either by an indirect approach using microsatellite and intragenic marker analysis (47 cases) or by a direct approach where the mutations of the index case were known (10 cases). Analysis of the parental haplotypes was informative in most cases. In 17 cases protein study was performed concomitantly with the genetic study. A crossing-over between one of the closest markers and the gene were detected in three fetuses out of 47 indirect diagnoses. Nevertheless, in all three cases an accurate diagnosis was possible due to information revealed by the intragenic markers (Fig. 2). From all those seeking advice in France, in only five families were the markers not sufficiently informative in one of the parents, and genetic evaluation was declined.

In the British group, in most cases the genetic analysis was performed with only microsatellite markers, but immunocytochemical studies of trophoblast were concomitantly done in most cases (25 out of 29). In the German, Turkish and Brazilian groups an approach similar to that of the British was used and trophoblast immunostaining was performed in all cases (Table 1).

In the French, British, German and Turkish groups more than one prenatal diagnosis (2–4) was done in the same family.

There was total concordance between the results of the protein analysis and DNA studies in CV samples in cases studied by both techniques.

A total of 10 (five in Essen, three in London and two in Paris) fetal muscle samples could be studied after termination of the pregnancy, owing to the presence of the at-risk haplotype in the fetus and lack of laminin α2 chain expression in the CVs sample. In nine, the fetal muscle

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**Table 1**

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Chorionic villus (CV); Heterozygote carriers (heteroz.).
showed absence of laminin α2 chain expression and in one case studied in London there were traces of this protein.

6. Discussion

The data presented here show that immunohistochemical analysis of CV samples, substantiated in most cases by molecular analysis, provided the correct diagnosis in all 70 fetuses ‘at risk’ of laminin α2 chain deficiency tested for protein deficiency. The method is therefore very reliable. It is essential, however, that the diagnostic criteria for MDC1A in the proband are fulfilled, since the trophoblasts from cases with partial laminin α2 chain deficiency have not been studied by this method and partial reduction of laminin α2 chain may also occur as a secondary feature in other forms of CMD, such as MDC1B, 1C, 1D, FCMD, MEB or WWS (reviewed in [4]).

The LAMA2 gene codes for a protein of 390 kDa, and under reducing conditions, the laminin α2 chain migrates as an N-terminal fragment of approximately 300 kDa and a C-terminal fragment of 80 kDa. Immunohistochemical studies have shown that partial deficiencies of laminin α2 chain are more easily detected with the 300 kDa antibody than with the antibody against the 80 kDa fragment [18,29]. The use of more than one antibody is therefore recommended for diagnostic purposes.

In case of absence of labeling with antibodies against the laminin α2 chain, an adequate control for the integrity and identification of proteins from the basement membrane is necessary. All laminin variants are heterotrimers with an α, β, and γ chain and each chain can be studied with specific antibodies. Secondary changes in other chains occur in muscle when laminin α2 chain is absent [5,25,30] and also in other disorders [31]. The basement membrane of normal muscle fibers and of normal CVs contains α5, β1 and γ1 chains. Antibodies against these chains can be used to control the good preservation of the basement membrane in CV samples and muscle fibers of fetuses affected by laminin α2 chain deficient CMD.

The reliability of prenatal diagnosis by microsatellite analysis is dependent on the absence of locus heterogeneity.
for the disease [28]. In families with a single child having complete merosin deficient CMD and white matter hypodensity determined by brain imaging, microsatellite analysis can be used for prenatal diagnosis with confidence. The issue is more complex for patients with partial laminin \(\alpha_2\) deficiency, as it can be primary and secondary [3,4]. The prenatal diagnosis by microsatellite markers in cases of partial merosin deficiency therefore needs to be interpreted very cautiously, as results in cases of secondary protein deficiencies can be misleading.

Prenatal diagnosis can be made by direct DNA analysis of CV material, as first reported by Guicheney et al. [22]. In the present study, indirect DNA analysis was used in the majority of the cases from France, Germany and UK. Among the 102 ‘at-risk’ fetuses tested, 27 affected were identified. This diagnosis was confirmed, after the interruption of the pregnancy, by immunohistochemical analysis of the muscle in all 10 affected fetuses that could be examined.

Considering the total of DNA studies reported here the transmission of the mutations is in accordance with Mendelian inheritance: 26.4% affected fetuses, 50.9% heterozygous carriers and 22.5% fetuses with normal alleles (Table 1). A heterozygote advantage has been reported in a study of 29 informative families with merosin deficient CMD done in UK [32] but such abnormal transmission was not confirmed in the present larger data set.

A potential risk of error through double crossing-over, if haplotyping alone is made, has been suggested [3]. Nevertheless, by using intragenic markers, single crossings were observed in three fetuses in this series and an accurate interpretation was always possible.

In families with a high degree of consanguinity, not only did the parents show the same ‘at-risk’ haplotype, but the examination of the fetal DNA samples may reveal the same haplotypes as those of the mother. In such cases, to exclude the risk of misinterpretation owing to a maternal DNA contamination, a paternity testing has to be performed (four in the French experience) to verify the presence of paternal alleles at different chromosomal loci in fetal DNA.

Differences in the transcriptional control of the expression of laminin \(\alpha_2\) chain between the skeletal muscle and peripheral nerve have been observed [33,34] but no difference in the expression pattern of laminin \(\alpha_2\) chain was reported between skeletal muscle and trophoblast. In our five different centers, no discordance was observed between the results obtained by study of trophoblast by immunocytochemistry and those provided by molecular genetic techniques. In addition, when only the immunocytochemical study of the trophoblast was done and showed normal presence of laminin \(\alpha_2\) chain in CV basement membrane, the children have always been healthy.

In the Brazilian family studied by molecular genetics, the majority of the microsatellite markers were informative, allowing the identification of the ‘at-risk’ haplotype inherited from each parent [35]. However, the known LAMA2 gene polymorphisms located in exons 12, 19, 37

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**Fig. 2. Importance of intragenic markers for the interpretation of indirect genetic diagnosis.** Pedigree A shows a molecular diagnosis done on the basis of single nucleotide polymorphisms (SNP) since the distal markers were non-informative in the mother. Pedigrees B and C show families with crossing-overs (arrows) occurring between the microsatellite markers and the LAMA2 gene. The intragenic SNP were used to determine on which haplotype and where the recombinations occurred. B: crossing-overs (arrows) occurred on both paternal and maternal alleles. SNP analysis allowed determining that the fetus was carrier of the two parental mutations. C: crossing-over (arrow) occurred on the paternal allele. SNP analysis allowed determining that no mutation was transmitted to the fetus.
and 42, which have been described as highly polymorphic in
the European population [28] were not informative in
Brazilian families, suggesting that appropriate intragenic
markers, such as new microsatellites, should be developed
for each population.

On such rare occasions (five in the French experience)
when the markers are not sufficiently informative in one of
the parents, the genetic evaluation alone could not be used,
and immunocytochemical analysis of the trophoblast should
be favored.

In conclusion, haplotyping and immunohistochemistry,
independently or combined (to avoid potential methodo-
logical pitfalls), are powerful tools which provide accurate
prenatal diagnosis of this form of congenital muscular
dystrophy (MDC1A) and play an essential role in genetic
counseling, but accurate diagnosis of the index patient is
mandatory for such indirect approaches.

Acknowledgements

Special thanks to Profs. Victor Dubowitz and Michel
Fardeau, whose initiatives lead the way to a better
understanding of congenital muscular dystrophies and to
the studies here reported. The collaboration of the follow-
ing persons is gratefully acknowledged: Thomas
R. Gollop, Nadyr F. Naccache, Dra. Rita de Cassia,
M. Pavanello, Prof. Dr G. Gillessen-Kaesbach, Dr D.
Wahl, Dr J. Colomer and Dr B. Cormand for samples
collection. We would also like to thank very much the
following researchers, who kindly provided us with
specific antibodies: Dr L.V.B. Anderson, Newcastle
upon Tyne, Prof. Dr U. Wewer, and Dr J. Chamberlain.
This work was supported by MDC (Muscular Dystrophy
Campaign) and NSCAG (support to FM), the Hammer-
smith Hospital Neuromuscular Unit, and grants from
FAPESP-CEPID, PRONEX and CNPq, by IMPULS e.V.

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laminin a 2-chain (or merosina) deficient congenital muscular
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