Reproductive counselling for women with myotonic dystrophy

A C Magee, A E Hughes, A Kidd, A Lopez de Munain, A M Cobo, K Kelly, J Dean, N C Nevin

METHODS AND RESULTS

Full clinical information was obtained from DM1 pedigrees in Northern Ireland, the Basque area of Spain, and the Grampian region of Scotland. The patients were classified as classical (onset of clinical symptoms from 16 years or older), juvenile (onset of symptoms such as muscle weakness, learning difficulties, or myotonia between 1 and 16 years), and congenital (symptomatic from birth). Genomic DNA was isolated from peripheral blood leukocytes by standard procedures. Molecular genetic analysis of the CTG trinucleotide expansion associated with DM1 was performed. Polymerase chain reaction (PCR) was carried out using fluorescent primers and subsequent analysis on an automated sequencer with Genescanner software. Southern blotting was performed on samples showing a single sized allele. Digest was with BglII and hybridisation with probe pB1.4 and cDNA25 and pGB2.6. The expansion size was determined by the midpoint of the smear.

A total of 30 offspring had CDM (group 1), with expansion size ranging from 1.6 to 6.5 kb, mean 3.9 kb. There were no cases of paternally inherited CDM. The mothers of the CDM children had expansions ranging from 0.23 to 5 kb, mean 1.98 kb. Sixty-two offspring had either juvenile onset DM1 or classical DM1 (group 2). In this group, the expansion size ranged from 0.129 to 4 kb (mean 2.17 kb). Their mothers had expansions ranging from 0.12 to 3.5 kb, mean 0.71 kb. All sibships except two (from the Aberdeen group) showed exclusive CDM or DM1 phenotypes.

One of the CDM offspring showed a contraction in the DM1 mutation inherited from his mother. The contraction was just over 1 kb, from 3.83 kb to 2.73 kb. One stable transmission was seen where the mother had a large amplification of ~5 kb, as did her son. The mothers of CDM offspring have a DM1 expansion which is on average 1.27 kb greater than the expansion in mothers of the milder classical form. On transmission to their offspring, the expansion undergoes greater amplification in the CDM mothers, by approximately 0.56 kb (table 1). The distribution of transmitted expansions shows a much higher concentration of CDM once the maternal expansion exceeds 1 kb. Five stable transmissions (8%) and two contractions (3%) of 1 kb each were observed in the non-CDM offspring.

DISCUSSION

The neonatal period can be critical for CDM babies. If they establish respiration and feeding successfully, muscular hypotonia improves. The highest risk of death is in the neonatal period. Harper reported a death rate of 66% for this stage. As CDM was only described as recently as 1960, the clinical phenotype of adult CDM patients is still evolving.

The sex of the affected grandparent in CDM sibships was male in 57 of the 69 sibships where the grandparental sex was known (82.6%). Our findings support those of previous studies, but only the study of Lopez de Munain et al included mutational analysis.

When classically affected women are divided into those who have CDM offspring and those who have non-CDM offspring, the more severely affected mothers of the CDM children transmit a larger increase in the mutation. Koch et al published genetic risks for children of women with myotonic dystrophy, but this was before the advent of direct mutational analysis. Our observations certainly support the findings of Koch et al in that the risks are different for two groups of women. The mean expansion size in mothers of CDM offspring is almost twice that seen in the mothers of non-CDM offspring.

There are definite differences observed between mothers of CDM offspring and mothers of non-CDM offspring. The mothers of CDM offspring have smaller families, possibly

Abbreviations: DM1; myotonic dystrophy; CDM, congenital myotonic dystrophy
because their disease severity and earlier age of onset naturally limits fertility or because of reproductive choices after the birth of a CDM child.

Our results suggest that if her DM1 expansion is >1 kb, then her risk of a CDM child in the first affected pregnancy is 59%. If her expansion is ≤ 1 kb, the risk of a CDM child is 17% (table 2). However, the risk is almost 100% if there is a sib with CDM.

A DM1 mother in her first pregnancy is more likely to have a CDM child if: (1) she has multisystem clinical signs at the time of pregnancy; (2) her age of onset is less than 30 years; (3) her affected parent is her father; and (4) her DM1 expansion is >1 kb.

Segregation distortion in DM1 must also be considered, and would suggest that there may be preferential transmission of the DM1 allele, resulting in a greater than 50% risk of an affected child in any pregnancy. Further data will help refine these risks. It is also important to note that the DM1 repeat is expansion with age.

This provides further information for counselling of women with DM1 who are contemplating pregnancy. It is now clear that they can no longer be considered as a single entity, but must be differentiated into high risk or low risk, regarding congenital myotonic dystrophy. Molecular genetic analysis of the DM1 expansion will enable the genetic counsellor to give more detailed information.

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Table 1 Increase in the DM1 expansion on transmission to CDM/non-CDM offspring

<table>
<thead>
<tr>
<th>Maternal DM1 repeat size</th>
<th>Classical onset DM1 mothers (n=30)</th>
<th>Non-CDM offspring (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in repeat size on transmission</td>
<td>1.98 kb (0.23-5 kb)</td>
<td>0.71 kb (0.12-3.5 kb)</td>
</tr>
<tr>
<td>1.88 kb (1.1-5.1 kb)</td>
<td>1.32 kb (1.0-3.775 kb)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Risk of CDM with different cut offs of expansion size

<table>
<thead>
<tr>
<th>Maternal expansion cut off (kb)</th>
<th>Chance of child having CDM if expansion &gt; cut off (%)</th>
<th>Chance of a child having CDM if expansion ≤ cut off (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>49</td>
<td>16</td>
</tr>
<tr>
<td>1</td>
<td>59</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>31</td>
</tr>
</tbody>
</table>
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