ELECTRONIC LETTER

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

J Med Genet 2002;**39**:e15 (http://www.jmedgenet.com/cgi/content/full/39/3/e15)

Myotonic dystrophy type 1 is the commonest neuromuscular disease affecting adults. It is inherited in an autosomal dominant manner, and is linked to a dynamic expansion of a CTG triplet repeat localised to chromosome 19q13.3. The phenotype can be divided into four main groups: mild, juvenile, classical, and congenital. The most severe form of the condition is observed in congenitally affected infants usually born to classically affected mothers. Recently, the nomenclature has been revised and myotonic dystrophy is referred to as DM1.[1]

Congenital myotonic dystrophy (CDM) was first described in 1960[2] and is the most severe phenotypic expression of DM1. It represents the final stage in the typical three generation anticipation cascade observed in this condition.[3] The symptoms may present late in pregnancy with reduced fetal movements, polyhydramnios, or hydrops fetalis.[4–6] Often the birth of a severely affected child identifies an extensive DM1 pedigree. The reasons for the almost exclusive maternal transmission of CDM are not clearly understood. There are no particular clinical features in the mothers of CDM children to account for this, but, from earlier studies, all the women exhibited clinical myotonia[7] and CDM cases were confined to the offspring of clinically affected women.[8] Koch *et al*[9] found that only women with multisystem signs of DM1 at the time of pregnancy and delivery were likely to have congenitally affected offspring and that the chance of having a more severely affected child increased with maternal disease severity. These observations have been given support by more recent molecular studies; infants with CDM and their mothers had greater amplification of the CTG repeat than those with non-CDM and their mothers[10] and the maternal expansion was three times greater in the CDM group than in the non-CDM group.[11] We present data to allow estimation of risk, based on maternal and fetal genotypes.

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 leucocytes 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 *Bgl*I and hybridisation with probe pB1.4[12 13] or cDNA25 and pGB2.6.[14] 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.[5 15] The highest risk of death is in the neonatal period. Harper[4] reported a death rate of 66% for this stage. As CDM was only described as recently as 1960,[2] 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,[5 9 15] but only the study of Lopez de Munain *et al*[15] 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*[9] 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*,[9] 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

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

	Classical onset DM1 mothers	
	CDM offspring (n=30)	Non-CDM offspring (n=62)
Maternal DM1 repeat size	1.98 kb (0.23–5 kb)	0.71 kb (0.12–3.5 kb)
Increase in repeat size on transmission	1.88 kb (–1.1–5.1 kb)	1.32 kb (–1.0–3.775 kb)

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

Maternal expansion cut off (kb)	Chance of child having CDM if expansion >cut off (%)	Chance of a child having CDM if expansion ≤cut off (%)
0.5	49	16
1	59	17
2	71	24
3	75	29
4	100	31

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[9]; (2) her age of onset is less than 30 years[16]; (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.[17] Further data will help refine these risks. It is also important to note that the DM1 repeat is somatically unstable, and there is a trend towards an increase in the expansion with age.[18 19] This would appear to account for the intragenerational anticipation seen among affected sibs, where those born later in the family, and therefore to older parents with larger expansions, tend to have an earlier age of onset and a greater degree of clinical severity. Somatic instability also reflects the need to assess the maternal progenitor allele accurately, either by measuring the base of an expanded smear or by expansion estimation taken in early childhood.

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.

Authors' affiliations
A C Magee, N C Nevin, Regional Genetics Service, A Floor, Belfast City Hospital Trust, Lisburn Road, Belfast BT9 7AB, Northern Ireland
A E Hughes, N C Nevin, Department of Medical Genetics, The Queen's University of Belfast, Lisburn Road, Belfast BT9 7AB, Northern Ireland
A Kidd*, K Kelly, J Dean, Department of Medical Genetics, Medical School, Foresterhill, Aberdeen AB25 2ZD, UK
A Lopez de Munain, A M Cobo, Neurology and Clinical Epidemiology Departments, Hospital Ntra Sra Aranzazu, San Sebastian, Basque Country, Spain

Correspondence to: Dr A Magee, Regional Genetics Service, A Floor, Belfast City Hospital Trust, Lisburn Road, Belfast BT9 7AB, Northern Ireland, Alex.Magee@bch.n-i.nhs.uk

*Present address: Central Regional Genetic Service, Wellington Hospital, Wellington South, New Zealand

REFERENCES

1 **Ashizawa T (The International Myotonic Dystrophy Consortium)**. New nomenclature and DNA testing guidelines fro myotonic dystrophy type 1 (DM1). *Neurology* 2000;**54**:1218-21.
2 **Vanier TM**. Dystrophia myotonica in childhood. *BMJ* 1960;**i**:1284-9.
3 **Harper PS**. *Myotonic dystrophy*. Major problems in neurology vol 21. 2nd ed. London: Saunders, 1989.
4 **Harper PS**. Congenital myotonic dystrophy in Britain. I. Clinical aspects. *Arch Dis Child* 1975;**50**:505-13.
5 **Reardon W**, Newcombe R, Fenton I, Sibert J, Harper PS. The natural history of congenital myotonic dystrophy: mortality and long term clinical aspects. *Arch Dis Child* 1993;**68**:177-81.
6 **Erikson A**, Forsberg H, Drugge U, Holmgren G. Outcome of pregnancy in women with myotonic dystrophy and analysis of CTG expansion. *Acta Paediatr* 1995;**84**:416-18.
7 **Harper PS**. Congenital myotonic dystrophy in Britain. II. Genetic basis. *Arch Dis Child* 1975;**50**:514-21.
8 **Bundey S**. Clinical evidence for heterogeneity in myotonic dystrophy. *J Med Genet* 1982;**19**:341-8.
9 **Koch MC**, Grimm T, Harley HG, Harper PS. Genetic risks for children of women with myotonic dystrophy. *Am J Hum Genet* 1991;**48**:1084-91.
10 **Tsilfidis C**, MacKenzie AE, Mettler G, Barceló J, Korneluk RG. Correlation between CTG trinucleotide repeat length and frequency of severe congenital myotonic dystrophy. *Nat Genet* 1992;**1**:192-5.
11 **Cobo A**, Poza JJ, Martorell L, Lopez de Munain A, Emparanza JI, Baiget M. Contribution of molecular analyses to the estimation of the risk of congenital myotonic dystrophy. *J Med Genet* 1995;**32**:105-8.
12 **Magee AC**. *The epidemiology and genetics of myotonic dystrophy in Northern Ireland*. Thesis, The Queen's University of Belfast, 1996.
13 **Shelbourne P**, Winqvist R, Kunert E, Davies J, Leisti J, Thiele H, Bachmann H, Buxton J, Williamson B, Johnson K. Unstable DNA may be responsible for the incomplete penetrance of the myotonic dystrophy phenotype. *Hum Mol Genet* 1992;**1**:467-73.
14 **Turnpenny P**, Clark C, Kelly K. Intelligence quotient profile in myotonic dystrophy, intergenerational deficit, and correlation with CTG amplification. *J Med Genet* 1994;**31**:300-5.
15 **López de Munain A**, Cobo AM, Poza JJ, Navarrete D, Martorell L, Palau F, Emparanza JI, Baiget M. Influence of the sex of the transmitting grandparent in congenital myotonic dystrophy. *J Med Genet* 1995;**32**:689-91.
16 **Wesström G**, Bensch J, Schollin J. Congenital myotonic dystrophy. Incidence, clinical aspects and early prognosis. *Acta Paediatr Scand* 1986;**75**:849-54.
17 **Magee AC**, Hughes AE. Segregation distortion in myotonic dystrophy. *J Med Genet* 1998;**35**:1045-6.
18 **Wong LJC**, Ashizawa T, Monckton DG, Casley CT, Richards CS. Somatic heterogeneity of the CTG repeat in myotonic dystrophy is age and size dependent. *Am J Hum Genet* 1995;**56**:114-22.
19 **Martorell L**, Monckton DG, Gamez J, Johnson KJ, Gich I, Lopez de Munain A, Baiget M. Progression of somatic CTG repeat length heterogeneity in the blood cells of myotonic dystrophy patients. *Hum Mol Genet* 1998;**7**:307-12.