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Genetic Risks for Children of Women with Myotonic Dystrophy

Manuela C. Koch,* Tiemo Grimm,† Helen G. Harley,‡ and Peter S. Harper‡

*Institut für Humangenetik, Universität Marburg, Marburg, Germany; †Institut für Humangenetik, Universität Würzburg, Würzburg; and ‡Institute of Medical Genetics, University of Wales College of Medicine, Cardiff

Summary

In genetic counseling, the recommended risk estimate that any heterozygous woman with myotonic dystrophy (DM) will have a congenitally affected child is 3%–9%. However, after already having had such an offspring, a DM mother's risk increases to 20%–37%. The risks of 10% and 41%, respectively, calculated in this study are similar to the estimates in the literature. However, our data on clinical status of the mothers demonstrate that only women with multisystem effects of the disorder at the time of pregnancy and delivery are likely to have congenitally affected offspring. No heterozygous woman with polychromatic lens changes but no other clinically detectable multisystem involvement had a congenitally affected child. In addition, our data suggest that the chance of having a more severely affected child increases with greater severity of maternal disease. The findings of this study are relevant for genetic counseling, as the risk of having a congenitally affected child for women with classical manifestations of the disease is shown to be higher than predicted by the overall risk estimate for any heterozygous woman. We consider it appropriate to give these classically affected women risk figures which approach the recurrence risk given to mothers with congenitally affected children. However, the risk of having a congenitally affected child for heterozygous women with no multisystem involvement appears to be minimal. Our findings support the earlier proposed hypothesis of maternal metabolites acting on a heterozygous offspring. Neither genomic imprinting nor mitochondrial inheritance is able to explain the correlation between the clinical status of heterozygous mothers and that of their children.

Introduction

Myotonic dystrophy (DM) is a progressive autosomal dominant multisystem disorder. Estimates of prevalence rates are 2.4–5.5/100,000 in most populations (Klein 1958; Grimm 1975; Takeshita et al. 1981). Like many other pleiotropic, autosomal dominantly inherited diseases, DM exhibits marked variability in age at symptom onset and in degree of involvement of different organ systems. Nonpenetrance of the defective allele is thought to be exceptional if careful attention is paid to minor diagnostic signs, especially in individuals in the older age groups. To date, no individual with a proved new mutation has been reported.

The gene has been localized on the long arm of chromosome 19 (Eiberg et al. 1983; Shaw et al. 1985; Korneluk et al. 1989). Linkage analyses provide no evidence that DM is determined by more than one locus, although the existence of different allelic mutations has not been ruled out.

Despite extended clinical studies which mentioned a high infant mortality rate and individuals affected from childhood (Fleischer 1918; Thomasen 1948; Klein 1958) the neonatal form of DM—congenital myotonic dystrophy (CMD)—was not convincingly described until 1960 (Vanier 1960). The exclusive inheritance of the congenital form through a mother carrying the mutant gene was finally shown in 1972 by Harper and Dyken (1972). To explain the severely affected neonate, Harper and Dyken put forward the hypothesis of a maternal intrauterine factor acting on a heterozygous fetus.

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Address for correspondence and reprints: Manuela C. Koch, M.D., Institut für Humangenetik, Universität Marburg, Bahnhofstrasse 7, 3550 Marburg, Germany.

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As the proposed abnormal maternal product has not yet been identified (Silver et al. 1985), other models—more than one locus for the disease (Bundey and Carter 1972; Bundey 1982), mitochondrial inheritance (Merril and Harrington 1985; Poulton 1988), and chromosomal imprinting (Erickson 1985; Swain et al. 1987; Reik 1988)—have been considered to explain the severely affected neonate.

In this context the question arises of whether all women carrying the mutant gene have a risk of a congenitally affected child. Risk figures—of 3%–9% for any carrier woman having a neonatally affected child and of 20%–37% after a carrier woman has had a CMD child—have been reported by previous investigators (Bundey 1982; Grimm and Harper 1983; Glanz and Fraser 1984; Harper 1989). Bundey (1982), in addition, put forward the hypothesis that the propensity to have neonatally affected offspring is familial. In order to evaluate the risk that a heterozygous woman in a DM family will have a congenitally affected child, the present study was carried out.

Methods

Ascertainment and Data Collection

Main study.—Families were ascertained through the clinical register of the Institute of Medical Genetics in Cardiff. Altogether, 88 pedigrees were chosen from the records, with regard to having female family members of known or unknown disease status. Individuals from 28 families were investigated on an outpatient basis or were visited at home by one of the authors (M.C.K.). Those family members not affected by the age of 18 years were asked to cooperate by also having an ophthalmological and EMG assessment.

For 60 families, only the records were comprehensively reviewed. Either the families had been visited by two of the authors (Harper 1975*a*, 1975*b*; Grimm and Harper 1983) in earlier years (40 families) or the records were sufficiently informative (20 families). All 88 family records were updated, with the objective of assessing the disease status of the family members by grading of severity; age at onset, presence of affected parent, affected and nonaffected sibs, or affected and nonaffected offspring; and total number of pregnancies. Neonatal death with recorded signs in agreement with CMD were counted as affected.

Outside the main study.—In addition, data on 13 Dutch families from a report in the literature (Höweler 1986; Höweler et al. 1989) have been included in the analysis. The study by Höweler was chosen because the mode of ascertainment is clearly described and because both full pedigree information and detailed clinical features of affected and nonaffected individuals are given.

Diagnostic Criteria

It was considered essential for the purpose of the study to use a well-defined terminology for the different phenotypes of DM. Subclassifications for the disease have been used (Dyken 1969; Bundey 1982; Höweler 1986), but only the term *congenital myotonic dystrophy* (CMD) has been widely accepted by clinicians and geneticists.

DM-adult (age at onset 21–40 years).—These individuals had the classical or adult form of DM, either on examination, clinical record, or a convincing description from a family member. The signs constitute the typical pattern of wasting and weakness of the voluntary muscles, clinical myotonia, and involvement of other organ systems. The presence of lens changes was not obligatory for diagnosis as positive.

DM-Eadult (age at onset 11–20 years).—This subgroup comprised individuals with early-adulthood onset.

DM-mild.—These patients had either polychromatic lens changes or presenile cataracts. They might have experienced minor muscle problems such as jaw tightness or cramps in their hands. Individuals might show myotonic discharges on EMG, but the pathognomonic pattern of voluntary muscle involvement was not seen on clinical examination.

CMD (age at onset < 1 year).—For congenital myotonic dystrophy the mother gave a history of polyhydramnios and reduced fetal movements. Children had severe neonatal hypotonia, a typical facial expression, and, often, skeletal deformities. Developmental delay and mental retardation became obvious in the first year of life, but clinical myotonia was not clinically detectable before school age.

DM-ch (age at onset 1–10 years).—These children had an uneventful pre- and neonatal history and normal development within the first year of life. However, they exhibited increasing problems as toddlers, such as (*a*) failure to thrive, accompanied by abdominal symptoms, (*b*) variable degree of mental retardation, and (*c*) muscle hypotonia. Again, clinical myotonia was not observed before school age.

At risk.—Because EMG and lens changes are difficult to assess, it was found more appropriate to classify asymptomatic individuals as being at risk, instead of labeling them "nonaffected."

Table 1

Data on Offspring of Affected and Nonaffected Mothers and Fathers

Status of Parent (*n*)	No. of Offspring (no. of probands)							
	Status Unknown	CMD	DM-ch	DM-Eadult	DM-adult	DM-mild	At Risk	Total
Mothers (184):								
CMD (1)	. . .	1	. . .	. . .	. . .	. . .	. . .	1
DM-ch (4)	. . .	4	. . .	. . .	. . .	. . .	. . .	4
DM-Eadult (41)	2	63 (26)	8	. . .	. . .	. . .	35	108
DM-adult (87)	8	112 (37)	17 (5)	8	3	. . .	84	232
DM-mild (30)	1	. . .	2	6	21	3	52	85
At risk (21)	1	. . .	. . .	. . .	. . .	. . .	52	53
Fathers (80):								
DM-adult (21)	. . .	. . .	6	15	17	1	23	62
DM-mild (41)	. . .	. . .	3	28	42	11	52	136
At risk (18)	. . .	. . .	. . .	. . .	. . .	. . .	34	34

Statistical Evaluation

To test the hypothesis proposed for the study data, a segregation analysis was done in 81 informative sibships, each of which had at least one CMD child, by using the method of Fisher (1934) by assuming single incomplete acertainment for the data.

Results

Data were obtained from 101 DM families. Sixty-seven families were ascertained through children classified as CMD or DM-ch, 32 families through an affected or at-risk individual over 20 years of age and seeking professional advice, and two families through a mildly affected family member with a presenile cataract.

One hundred sixty-three heterozygous mothers had 430 offspring (average 2.6 children), and 62 heterozygous fathers had 198 offspring (average 3.2 children). The early-pregnancy loss rate of 16.5% is in agreement with results of previous investigations (for review, see Harper 1989). The age range for all recorded offspring (affected and nonaffected) was 15 mo–39 years; the youngest clinically nonaffected offspring was 4 years old.

Table 1 summarizes the data obtained for affected and nonaffected mothers and fathers and their offspring. Mothers classified as CMD (one), DM-ch (four), or DM-Eadult (41) had only (*a*) children affected under the age of 11 years or (*b*) children who had to be scored as being at risk. Even when CMD probands were excluded, the overwhelming majority of affected offspring of DM-adult mothers (mean age at onset 26.9 years) had a neonatal (75) or DM-ch (12) onset and only 11 offspring were later affected. Five of these 11 offspring (three DM-Eadult and 2 DM-adult) had younger sibs classified as DM-ch and CMD. For the remaining six offspring (five DM-Eadult and one DM-adult), the recorded age at onset for the four mothers was in the second half of the fourth decade. Only one of these mothers had, after the birth of the affected child, two additional children, both scored as being at risk.

None of the mothers was asymptomatic at the time of birth of her congenitally affected child. All mothers had obvious involvement of voluntary muscles that were detectable solely by clinical examination. Typically, most of these women had neglected their symptoms.

Of the 32 affected children of the 30 mothers classified as DM-mild (mean age at onset 49.3 years), none was neonatally affected. None of the 21 classically affected fathers could retrospectively be categorized as CMD or DM-ch. The mean age at onset for DM-adult fathers was 27.1 years, and that for DM-mild fathers was 55.5 years. DM-ch offspring were observed for all male age groups. Although the figures are small, table 1 shows that offspring of DM-mild mothers, of DM-adult fathers, and of DM-mild fathers have the same distribution for age at onset, with a strong tendency to postchildhood onset. This is in sharp contrast to the data for offspring of CMD, DM-ch, DM-Eadult, and DM-adult mothers. The overall risk that a DM-mild woman will have a DM-ch child is 2.5%, and that for any heterozygous man is 4.5%.

Table 2

Sibships of Index Mothers

Status of Grandparent (n)	No. of Offspring							
	Status Unknown	CMD	DM-ch	DM-Eadult	DM-adult	DM-mild	At Risk	Total
Grandmothers (35):								
DM-adult (12)	2	8	6	9	. . .	. . .	11	36
DM-mild (23)	1	. . .	2	9	40	5	29	86
Grandfathers (46):								
DM-adult (23)	. . .	. . .	. . .	6	37	8	32	83
DM-mild (23)	. . .	. . .	. . .	8	52	1	38	99
Grandparents phenotypically normal (23)	. . .	. . .	. . .	3	37	11	27	78

There were 32 heterozygous sisters (eight DM-Eadult, 17 DM-adult, and seven DM-mild) of 131 index women. In 20 sibships, sisters had an age at onset similar to that of the index mother; in 11 sibships, age at onset was significantly different. Only sisters classified as DM-Eadult and DM-adult had CMD offspring (n = 31) and DM-ch offspring (n = 3), but none of the DM-mild sisters did.

There were 81 three-generation families for which the affected ancestor was not in doubt. Grandfathers and grandmothers were approximately equally the affected ancestor; respective offspring data are summarized in table 2. None of the grandmothers gave a reliable history for age at onset under 21 years of age. Only DM-adult grandmothers had CMD children. A CMD child was always the last in the sibship, giving evidence of a birth-order effect for affected offspring (table 3). Neither grandmothers classified as DM-mild nor heterozygous grandfathers had neonatally affected children. From these data can be derived the risk estimate (10%) that any heterozygous grandmother will have a CMD child. Finally, for 23 grandparental couples, it could not decided who was the affected ancestor. A CMD child was not observed in any of these sibships (table 2).

A segregation analysis was performed in 81 informative families with an index mother classified as DM-ch, DM-Eadult, or DM-adult and having at least one CMD child. The results are shown in table 4. Under the assumption of single incomplete ascertainment, 41% of the offspring were affected at birth, 8% under the age of 11 years and 1% above the age of 11 years. Forty-four percent are at-risk children, and for 6% the status was unknown. The observed 1:1 pro-

Table 3

Thirteen CMD Sibships in Which Both Congenital and Other Types of DM Occur, Showing Evidence of Birth-Order Effect

Family	Sibship Birth Order
3	DM-ch, CMD, CMD
25	DM-ch, CMD
29a	DM-ch, CMD
29b	At risk, DM-ch, DM-ch, CMD, CMD
30	At risk, DM-ch, CMD, CMD
44	DM-ch, CMD
45	DM-ch, CMD
55	DM-ch, CMD, at risk, CMD, at risk
58	DM-ch, CMD, CMD, CMD
59	DM-adult, CMD
75	DM-ch, DM-ch, CMD
86	DM-adult, CMD, CMD
91	DM-ch, CMD, at risk

Table 4

Segregation Analysis of 81 Informative CMD Sibships by Method of Single Incomplete Ascertainment for Data

Sib Status (n[a])	p
Unknown (5)	.06
CMD (145[57])	.41[b]
DM-Ch (12[4])	.08[c]
DM-Eadult (. . .)	. . .
DM-adult (2)	.01
DM-mild (. . .)	. . .
At risk (72)	.44
Total (236)	1.00

[a] Numbers in square brackets are number of probands.

[b] $p \pm 1.96$ s/(CMD) = .41 ± .08.

[c] $p \pm 1.96$ s/(CMD+DM-ch) = .49 ± .08.

portion of affected to at-risk children is in good agreement with the figure expected according to autosomal dominant transmission. In 13 sibships with CMD children, offspring were differently affected. The less severely affected offspring was the older sib, whereas the more severely afflicted was later born (table 3).

An overall incidence rate of 3×10^{-6} for CMD was calculated indirectly via the offspring data on all heterozygous grandmothers, as there was no ascertainment bias. The figure is slightly less than previous estimates (Grimm and Harper 1983; O'Brien and Harper 1984), but an accurate figure is difficult to determine, as not all individuals will receive the correct diagnosis.

Discussion

Since the report by Vanier (1960) and the subsequently extended family studies (Dyken and Harper 1973; Harper 1975*a*, 1975*b*), it has been well recognized that CMD must be considered in the differential diagnosis of infants who have a complicated neonatal course and severe hypotonia. The diagnosis is best confirmed by an examination of the mother, who is in all cases the affected parent. The experience in genetic counseling shows that not every affected child of a heterozygous DM woman has CMD. But after she has had a congenitally affected child, a woman's risk of having another CMD offspring is greatly increased. When the precise age at onset and the phenotype of the woman are not taken into account, the risk estimate that any DM woman will have a CMD child is 3%–9% (Grimm and Harper 1983; Glanz and Fraser 1984; Harper 1989). So far, these figures are recommended in genetic counseling. The 10% risk figure calculated for all heterozygous grandmothers in the present study is in good agreement with the cited data. After she has had a CMD child, a DM woman's risk of having a similarly afflicted child has been estimated to be 20%–37% (Bundey 1982; Grimm and Harper 1983; Glanz and Fraser 1984; Harper 1989).

Combined data of the studies by Harper (1975*b*) and Glanz and Fraser (1984), which include neonatal deaths, show that offspring in CMD sibships will be 40% CMD, 14.5% DM-ch, and 47% nonaffected (Harper 1989). The segregation data in the present study of such DM women are not different from the above-cited figures.

The important unanswered question is whether it is reasonable to give different risk figures to a woman before and after she has had a CMD child—and whether a woman at risk for neonatally affected children can be identified beforehand. Bundey (1982) and Harper (1989) categorized DM women according to status of voluntary muscle involvement. Both failed to show that a certain muscle pattern and the propensity to have CMD children were related. To show that certain DM women indeed have a propensity to have CMD children, the present study used a different approach. Affected family members were categorized into different groups of manifestation by taking into account the clinical phenotype and the age at onset. Offspring data were analyzed separately for each group (table 1).

Analysis of the findings presented here show that a heterozygous mother of a CMD child exhibits, both before and at the time of birth, clinically detectable multisystem signs of DM. The symptoms might be mild, but they are present and easy to assess. The degree of manifestation and the age of the DM mother always justified her classification into the category DM-adult, with a mean age at onset of 26.9 years. For some of these mothers it was possible to trace the age at onset back to less than 20 years of age, and one mother was herself classified as CMD.

A critical review of reports in the literature supports these findings (Davis 1958; Vanier 1960; Dodge et al. 1965; Calderon 1966; Pruzanski 1966; Watters and Williams 1967; Bell and Smith 1972; Dyken and Harper 1973; Fried et al. 1975; Harper 1975*a*, 1975*b*; Simpson 1975; Sarnat et al. 1976; Webb et al. 1978; Pearse and Höweler 1979; Takeshita et al. 1981; Broekhuisen et al. 1983; Betremieux et al. 1985; Jaffe et al. 1986; Kimura et al. 1987; Curry et al. 1988; Farkas-Bargeton et al. 1988; Rutherford et al. 1989). In none of these studies was a mother with a CMD child asymptomatic either at the time of pregnancy or at the birth of her afflicted child. The conclusion of the present study is that women who are classified as CMD, DM-ch, DM-Eadult, or DM-adult both before and at the time of pregnancy before having had a CMD child should be assigned the same risk of having a neonatally affected child as is assigned to a mother who has previously had a CMD child. The 3%–9% risk figures given to a clinically affected woman who has not had a CMD child are underestimating her risk, which might lead her to have too much hope of bearing an unaffected child—and even to avoid prenatal diagnostic tests. There is no doubt that only a prospective study of DM mothers and their children will give definitive risk estimates. But the ex-

perience in counseling DM families shows that the high-risk group will rarely ask for genetic counseling before embarking on a pregnancy. Those four DM-adult mothers in the study who did not have CMD children had a multisystem-manifestation disease onset in their late thirties, several years after they had completed their families. In the present study none of the mothers classified as either DM-mild or at risk had a neonatally affected child, but Höweler and Bush (1990) recently reported an apparently asymptomatic mother who has two CMD children, the only such case fully described. Well-documented cases of DM-mild mothers and their offspring are rare (Sun and Streib 1983; Harper 1989), as there is undoubtedly an ascertainment bias toward examining families that have DM-adult mothers. An ascertainment bias which could not be overcome in the present study was that the number of DM-mild mothers is significantly lower. The age-at-onset distribution for children of DM-mild mothers is similar to that for children of affected fathers with a strong tendency to either adulthood onset or DM-mild onset (table 1). As derived from the data of the present study, the overall risks that DM-mild females and DM males will have DM-ch offspring are 2.5% and 4.5%, respectively. The risk of having male probands is similar to the 5.8% risk figure by Harper (1989). Both female and male risk figures will inevitably be underestimates and are not useful for genetic counseling. The experience from this study and in genetic counseling shows that DM-ch offspring of a DM-mild parent will only be correctly diagnosed in connection with other typically affected family members.

Another interesting finding is the age at onset for DM in offspring of 23 phenotypically normal parents. In none of these sibships were CMD children observed. Extremely late onset of DM, new mutation, or parental germ-line mosaicism might be an explanation for the phenomenon.

In the present study, there was no family in which an offspring with CMD was followed by others with DM-ch, DM-Eadult, or DM-adult onset. If such a combination existed, it should have been described in one of the numerous reports about DM mothers; but there is no such observation (for review, see Thomasen 1948; Klein 1958; Takeshita et al. 1981; Höweler 1986; Harper 1989). The conclusion is that obviously unaffected sibs born after a CMD child have a minimal risk of developing the disease later in life. More difficult is the situation for children born prior to a CMD child. Data in table 3 show that, in CMD sibships, (*a*) a prior-born and less severely affected offspring will mainly have the DM-ch phenotype and (*b*) the risk of being affected later in life is minimal. This view is supported by the derived segregation data on the present study and by a life-table curve for such sibships (O'Brien et al. 1983; Harper 1989). The two female offspring classified DM-adult (table 3) were diagnosed with their CMD children, at the age of 22 and 24 years, making it very likely that age at onset was under the age of 21 years. The hypothesis that within families there is a propensity to have congenitally affected children (Bundey 1982) could not be supported by this study or by those of Glanz and Fraser (1984) and Harper (1989). Carrier sisters have a risk of having CMD children that is appropriate to their own disease status, a situation comparable with findings in index mothers.

As the pathophysiology of DM is not well understood, it is difficult to assess the role of etiological factors in severely affected offspring of clinically affected DM mothers. At this stage of knowledge, the postulated maternal factor model of Harper and Dyken (1972) can account for all findings noted in DM women and in their offspring. In assessing DM patients who have involvement of voluntary muscles, one has to keep in mind that the afflicted muscles only reflect one sign of the multisystem disorder. At that stage of the disease, more organ systems are involved, and related metabolic disturbances might give rise to altered metabolic products. In the case of an affected woman, abnormal products might cross the placenta, harming the child in utero. As congenital malformations in children of affected mothers are not increased, the postulated substances might not interfere with the embryonal metabolism at the time of organogenesis, or the essential fetal uptake could reach its maximum only after this sensitive period. With increased uptake in advanced gestation, the heterozygous fetus might be unable to metabolize the pathologic products sufficiently and therefore become affected. A progression of the disease in the mother might imply that the postulated substances either increase in quantity or change in integrity. Either could lead to more severely affected children, as observed for 13 sibships in the present study (table 3) and in comparable situations in the literature (Dyken and Harper 1973; Sarnat et al. 1976; Betremieux et al. 1985).

In contrast, the child who does not inherit the DM gene will be able to metabolize the abnormal substances completely and therefore will be born without any effects. A woman classified as DM-mild does not

have a multisystem manifestation of the disease and might not produce enough of the propagated metabolites, and therefore neither she nor her child will be harmed. The child is born without symptoms but has a 50% risk of developing DM later in life.

Offspring phenotypic differences depending on the parent involved might also be explained by two other theories. In the first theory, an interaction between the mitochondrial genome, which is exclusively inherited by the mother, and the autosomal gene product could be responsible for the findings (Merril and Harrington 1985; Poulton 1988). The second theory interprets the anticipation in DM as being determined by an epigenetic change related to the pattern of methylation of DNA (Erickson 1985; Swain et al. 1987; Reik 1988). Neither theory is consistent with the clinical observations in DM families, and both fail to explain the following findings: (1) congenitally affected children born to heterozygous women classified DM-mild are the exception; (2) the segregation ratio of affected to nonaffected children is 1:1; (3) there is increasing severity in affected children, correlating with increasing severity in the affected mother; and (4) for females within a family, there is a lack of correlation with regard to having CMD children or CMD grandchildren.

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