PERGAMON

Genotype–phenotype correlations in X-linked myotubular myopathy

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Abstract

X-linked myotubular myopathy is a severe congenital myopathy that presents in the neonatal period with profound hypotonia and an inability to establish spontaneous respiration. Usually death occurs in infancy from respiratory failure. However, there is phenotypic variability; a number of affected boys have achieved respiratory independence and become ambulatory. Disease-causing mutations have been identified throughout the MTM1 gene on Xq28. MTM1 encodes the protein myotubularin, which is expressed ubiquitously. The main objectives of this study were to establish whether the nature or site of the mutation in the MTM1 gene could predict severity of the disease and to investigate whether early intensive clinical intervention facilitated survival until spontaneous improvement occurred. An association was demonstrated between the presence of a non-truncating mutation of the MTM1 gene and the mild phenotype. However, many non-truncating mutations were also seen in association with the severe phenotype and these were not confined to recognized functional domains of the protein. This suggests that the use of mutation analysis to predict prognosis in the early period following diagnosis is limited. Unexpectedly, over 50 patients surviving for more than 1 year were identified in this study. Further information obtained on 40 of these cases revealed that 50% were receiving 24-h ventilatory support, while 27% were ventilated at night only. The high survival rate for this disorder therefore reflects intensive medical intervention without which the majority of these boys would not survive. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: X-linked; Myotubular myopathy; Genotype–phenotype correlation

1. Introduction

The myotubular (centronuclear) myopathies are a group of rare congenital myopathies characterized histologically by the presence of small rounded muscle fibres, with centrally located nuclei, which resemble fetal myotubes. This finding suggests that the disorders result from a defect in the structural organization or in the development of muscle fibres [1]. The X-linked recessive form of myotubular myopathy (XMTM; MIM 310400) is a severe congenital myopathy affecting approximately 1 in 50 000 males [2]. Typically affected males present in the neonatal period with

profound hypotonia and an inability to establish spontaneous respiration. Death usually occurs in infancy or early childhood from respiratory failure. There is often a prenatal history of polyhydramnios and weak or infrequent fetal movements. Female carriers of the disorder have a high incidence of miscarriages and stillbirths. The autosomal dominant and recessive forms of myotubular myopathy have mostly a later age of onset and a milder clinical course [3].

As yet there is no evidence for heterogeneity in the X-linked form of this disease and mutations in the MTM1 gene located at Xq28 have been identified in the majority of XMTM cases [4]. The mutations are evenly distributed throughout the gene, with no hotspots and few recurrent changes [2,5,6]. MTM1 is highly conserved throughout evolution down to yeast and belongs to a newly defined

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Table 1
One hundred and sixteen individuals were identified in whom a phenotypic category and mutation type could be assigned

	Mild: Respiratory independence	Intermediate: Respiratory support < 12 h per day	Severe: Respiratory support > 12 h per day or deceased due to respiratory failure
Truncating mutation	3	4	60
Non-truncating mutation	14	3	32

family of phosphatases [2]. The gene has at least two functional domains, a phosphatase domain and a SET-interacting domain. Myotubularin, the protein product of MTM1, has recently been shown to function as a lipid phosphatase which acts on the phosphatidylinositol 3-phosphate pathway [7,8]. This pathway is important in regulating intracellular membrane trafficking and vesicular transport processes. Thus it has been suggested that mutations of MTM1 may interfere with the pathways involved in the regulation of myogenesis [7].

XMTM families with surviving affected boys have been reported where the X-linked nature of the disorder was evident from pedigree analysis [9]. Where family history was uninformative characterization of the causative gene for this condition has permitted the identification of MTM1 mutations in a number of boys displaying a milder phenotype and the typical features on muscle biopsy, thus clearly distinguishing these cases from autosomal forms of the disorder. Previous studies have suggested that there might be a correlation between the presence of missense mutations of the MTM1 gene and a milder phenotype [2,6,10].

A United States study suggests that long-term survivors of XMTM usually have prolonged ventilator dependence and grossly delayed motor milestones [11]. However, a small number of individuals do improve, establish respiratory independence and become ambulatory. Respiratory management decisions in this disorder are particularly challenging as it is difficult to identify those affected boys who will go on to establish independent respiration. These difficulties, and the observation that missense mutations might be associated with a milder phenotype [2,6,10], prompted the European Neuromuscular Centre (ENMC) consortium for XMTM to use its previously established international database of clinical and mutation data to carry out a more detailed analysis of the genotype–phenotype relationship in this condition.

Our objectives were to establish whether (1) there is a relationship between the site or nature (truncating or non-truncating) of the mutation of the MTM1 gene and the severity of the phenotype, (2) early intensive clinical intervention facilitates survival until spontaneous improvement occurs, and (3) there is a correlation between prognostic indicators in the antenatal/neonatal period and clinical outcome.

2. Methods

Clinical and mutation data were sought on affected male

cases via questionnaires circulated to physicians and clinical scientists that were known to the consortium in Europe, the United States and Japan. In addition to requesting the nature of the mutation, the questionnaire included 35 questions aimed at establishing a profile of the antenatal and neonatal course, developmental progress, the level of medical intervention provided, and survival in each individual. Mutation analysis has been reported previously for the majority of cases studied [2,5,6,10–12]. In accordance with the predicted protein, mutations were classified into two groups: truncating (nonsense, frameshift, large deletion) or non-truncating (missense, in-frame insertion/deletion). The effect of splicing mutations was predicted either by reverse transcription–polymerase chain reaction or by whether the mutations affected essential nucleotides of a donor or acceptor splice site.

Based on the level of ventilatory support required, each patient was classified as having either a mild, intermediate or severe phenotype (Table 1). Deceased individuals were classified as having the severe form as the majority had died of respiratory failure, either while under treatment or when respiratory support had been withdrawn. A perinatal evaluation score (PES) was devised as the sum of individual scores based on six findings in the antenatal and neonatal period that might predict prognosis (Table 2).

The chi-squared (χ^2) test was used to test for a significant association between phenotypic classification and the presence of a truncating or non-truncating mutation. As the distribution of PES in each group was non-normal, the Kruskal–Wallis test was used to analyse the association between PES and phenotype. This test is the non-parametric equivalent of analysis of variance. Survival analysis was performed using Kaplan–Meier life tables. The log-rank test was used to compare selected factors. Multivariate analysis was carried out using Cox regression analysis. All statistical tests were performed using SPSS version 9.0.

As 53 surviving patients were identified, a brief follow-up

Table 2
Definition of perinatal evaluation score (sum range: 0–6 points)

	1 point	0 points
Polyhydramnios	No	Yes
Fetal movements	Normal	Weak/absent
Delivery	Normal	Abnormal
Tendon reflexes	Present	Absent
Joint contractures	No	Yes
Intubation at birth	No	Yes

Table 3
Intrafamilial variability of XMTM phenotype

Mutation	Exon	Family	Phenotype
Del exon 1	1	A. Two brothers	1 mild, 1 severe
Del exons 1–7	1–7	B. Three brothers	All severe
R241C	9	C. Two brothers	1 intermediate, 1 severe
E404K	11	D. Uncle, nephew	Both mild
1503 delA	13	E. Two brothers, male maternal cousin	All severe

questionnaire was designed to obtain information on the quality of life of these individuals.

3. Results

3.1. Patients

A total of 168 questionnaires were returned. Mutations in MTM1 had been documented in 138 affected males. The analysis in this study was based on data available on these 138 mutation proven cases. Not all questionnaires had been completed in their entirety, so the total number of cases varied for different sections of the data analysed.

3.2. Genotype–phenotype correlation

One hundred and sixteen individuals were identified in whom a phenotypic classification and a truncating or non-truncating type of mutation could be assigned. Amongst these were 53 living patients, with a median age of 4.5 years (6 months to 40 years). Sixty-three individuals were deceased with a median age at death of 2.5 months (range 0 months to 12 years).

Of the 116 cases, the disease was classified as mild in 17 individuals, as intermediate in seven and as severe in 92. As expected, mutations were spread evenly throughout the gene and comprised 19 nonsense, 38 missense, 38 deletion, 14 splicing and seven insertion mutations. A total of 83 different mutations were present with 17 mutations occurring more than once. Mutations were predicted to be non-truncating in 49 and truncating in 67 cases (Table 1). A significant correlation was noted between the presence of a non-truncating mutation and the mild, as opposed to the intermediate/severe, phenotype ($\chi^2 = 13.17$, 1 df, $P < 0.001$). Exon 11 encodes the PTP domain of myotubularin and exons 12 and 13 encode the SET-interacting domain. Non-truncating mutations in cases with the severe phenotype affected exons 3, 8, 9, 10, 11, 12 and 14. The non-truncating mutations associated with the mild phenotype were similarly distributed in exons 4, 8, 9, 10 and 11. By contrast, truncating mutations occurred in all exons.

3.2.1. Intrafamilial variability of phenotype

Intrafamilial variability of phenotype has been reported in association with XMTM [9]. Our findings in this cohort of patients confirm this observation but the numbers are small. Five families were identified where two or more individuals were affected by the condition (Table 3). In three of these families (B, D and E) there was consistency of phenotype in all affected persons. However the phenotype in the other two families was found to vary. In family A, affected by a deletion of exon 1 in MTM1, one brother manifested the mild phenotype while the other's myopathy was classified as severe. The latter however had been considered mildly affected until he suffered a respiratory arrest and seizures in the first year after which he was ventilator dependent. Central nervous system damage cannot be ruled out in this case. In family C, one brother had an intermediate phenotype while the other was classified as severe.

3.2.2. Variability of phenotype in association with recurrent mutations

Four mutations (141–144delAGAA, 139–142delAAAG, insFIQ and R241C) were identified that affected four or more unrelated cases (Table 4). The first three mutations were all associated with a severe phenotype. The 141–144delAGAA and 139–142delAAAG mutations were predicted to cause a truncating mutation in exon 4 at codon 48. All cases reported to date carrying insFIQ have had a severe phenotype, and this was also the case for the boys documented in this report. Variation in phenotype was seen in association with R241C. Six boys with this mutation were documented, two of whom had severe, one had intermediate and three had mild disease.

3.2.3. Phenotypic effect of mutations associated with preservation or loss of recognized functional domains

Exons 11, 12 and 13 of the MTM1 gene encode the putative catalytic site and the SET-interacting domain of myotubularin. Missense (non-truncating) mutations associated with the severe phenotype were clustered around exons 8, 9, 10, 11, 12 and 14. Only a small number of these mutations altered an amino acid within the active domains, and all were associated with a severe phenotype. It is interesting to note that the splicing mutation in intron 11 (1261-10A > G) that causes insertion of three amino acids (FIQ) into the protein between the functional domains invariably resulted in a severe phenotype. The missense mutations that were associated with a mild phenotype showed a similar distribution in exons 4, 8, 9, 10 and 11. None result, in

Table 4
Phenotypic variability with recurrent mutations

Mutation	Exon	Phenotype
141–144delAGAA	4	4 severe
139–142delAAAG	4	4 severe
R241C	9	2 severe, 1 intermediate, 3 mild
Insertion FIQ	11	6 severe

alterations of amino acids within the putative functional domains.

All but two of the truncating mutations documented here were associated with a severe phenotype. One of these two, resulted in deletion of the terminal exon 15 while the other resulted in deletion of exon 1. Deletion of exon 15 may allow production of a stable shortened protein that retains some function due to preservation of the active sites. Exon 1 is non-coding although its functional importance is clear from the fact that deletion of this exon has been documented previously in severe and mild cases [2]. Initial data submitted to the XMTM database, suggested that a third truncating mutation (286–287insA) affecting codon 96 in exon 5 was also associated with a mild phenotype. It has since transpired that this patient died at the age of 5 months following episodes of aspiration pneumonia and apnoea. His severe phenotype is in keeping with the history reported in other patients with this mutation [2].

The missense mutations identified in cases with the intermediate phenotype did not interfere with the functional domains of the protein and were located in exons 5, 9 and 14.

3.3. Clinical intervention

3.3.1. Respiratory support (Fig. 1)

Data on respiratory intervention was available on 120 patients, 101 of whom were ventilated at birth (85%). Forty-five out of these 101 (44.5%) individuals were still alive at the time of circulating the questionnaire. Thirty-two (71%) were on full ventilatory support, six (13%) received ventilatory support for < 12 h per day and a further seven (15%) had achieved respiratory independence.

Fifty-six out of the 101 (55.5%) were deceased. Of this group, 30 never achieved independent ventilation and died within the first year of life, the majority in the neonatal period. Nineteen did achieve a period of independent

respiration and death occurred at a median age of 1 year. Two-thirds of those who died within the first year were 6 months of age or less. Two-thirds of those surviving past the first year died before their third birthday. For many patients, detailed information on ventilatory history was not available, although comments from clinicians suggest there that was an elective decision in a significant number of cases not to re-ventilate because of the poor prognosis.

Nineteen out of 120 patients had not been ventilated at birth. Eight of these were deceased, five of them despite subsequent ventilatory assistance. The median age of death was 7.5 months. Of the 11 surviving individuals who were not ventilated at birth, ten had retained respiratory independence and one required ventilatory support for < 12 h per day.

3.3.2. Gastrostomy/tracheostomy

As an indicator of the level of medical intervention, information was also collected on the number of cases who had had either gastrostomy or tracheostomy carried out at any point. Sixty-three of 113 cases where the question was answered had undergone gastrostomy (56%). Fifty-nine of 117 cases had had tracheostomy (50%). As would be expected, the majority of boys who had undergone these procedures were in the severe phenotype group. Gastrostomy insertion was more common in the United States cohort, which may reflect a difference in management policies.

3.4. Perinatal evaluation score (PES) and outcome

Detection of the following features in the perinatal period are considered a sign of significant neurological/neuromuscular disease: polyhydramnios, absent fetal movements, absent reflexes, joint contractures and the need for intubation at birth. The need for assisted delivery for fetal distress
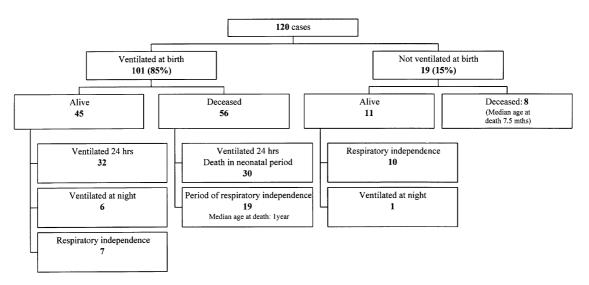
Fig. 1. Flow diagram of respiratory support provided from birth and patient outcome.

may also be a sign of neurological disease in a newborn. A PES was devised based on these six features (Table 2).

All six questions were answered for 42 cases; the severe form of the disease affected 38 of these while four showed the mild phenotype. The median score in the severely affected group was 2/6 (range 0–5/6) while the median score in the mildly affected group was 5/6 (range 3–6/6). A total of 110 cases with a designated phenotype were identified in whom at least 2/6 PES questions had been answered. The median scores observed in the three groups were compared by calculating the percentage of the number of questions answered for each case (e.g. 2/4 = 50%). A significant difference was observed between the three groups ($\chi^2 = 13.2$, 2 df, $P = 0.001$) and there was an appropriate trend downwards in score from mild to severe (Fig. 2).

3.5. Evaluation of common clinical features

3.5.1. Gestational data

Gestational age was documented on 121 individuals. The median gestation at birth was 38 weeks (range 29–43 weeks). The prevalence of prematurity (gestation < 36 weeks) was 30.5%.

3.5.2. Growth

Previous reports on boys affected by XMTM have frequently commented that measurements for length and head circumference (OFC) fall on the upper centiles of the growth charts [11,13]. OFC measurements were available on 70 cases and 51% of these were on or above the 75th centile while 27% were on or above the 91st centile. Length measurements were available on 74 cases and again 56% were on or above the 75th centile while 36% were on or above the 91st centile. All measurements analysed were those documented at birth. No correlation was found
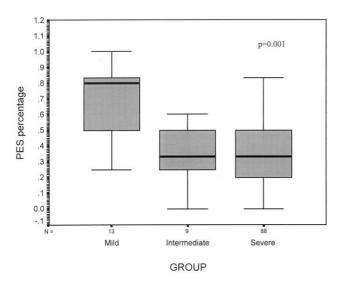

Fig. 2. Box plot indicating median PES percentage for each group (heavy lines). Each box represents the interquartile range and the error bars represent the range.

between growth patterns and truncating or non-truncating mutations of the MTM1 gene.

3.5.3. Genital development

Cryptorchidism has been associated with XMTM. A United States study previously reported bilateral undescended testes in 57% but this figure was not corrected for prematurity [11]. Evaluation of 57 European cases in our study identified the presence of cryptorchidism in 58% of affected males. Of those born prematurely, i.e. before 36 weeks, 63% had undescended testes, while the corresponding number for those born after the 36th week was 55%. Ambiguous genitalia have also been described as a feature in this condition, but it is now known that several such cases had large deletions consistent with a contiguous gene deletion syndrome [14,15]. In our study, no cases of ambiguous genitalia were identified as being associated with intragenic mutations of MTM1.

3.6. Follow-up data/quality of life data

Fifty-six surviving patients were identified through circulation of the initial questionnaire. A follow-up questionnaire was sent to the physicians caring for these boys in an attempt to glean more detailed information on their development and quality of life. Forty-two quality-of-life questionnaires were returned; 40 patients were still alive while two had died. Of these 40 surviving boys, 15 were from Europe, one from Japan and 24 from the United States. Twenty were classified as severely affected, 11 as intermediate and nine as mildly affected. The four additional intermediate cases identified were not included in the genotype-phenotype analysis in Section 3.2, as the initial data submitted was insufficient for assigning the phenotypic category in three cases, and the mutation type in the fourth. The median age overall was 6 years 2 months (range 1–41 years) and was similar in the group from the United States and Europe.

Motor development was virtually universally delayed. Some 23 boys learned to sit at a median age of 18 months (range 6 months to 5 years) while only 12 learned to walk at a median age of 23 months (range 12 months to 3 years). Of those in the severe group who were on full ventilatory support only ten (50%) achieved sitting and none walked. These boys' failure to progress in motor development was judged by their physicians to result from the patient's global weakness and was not felt to be due to restricted opportunities resulting from ventilator dependence. The majority of boys in the intermediate group learned to sit and five of 11 achieved walking, three of them independently. All of the boys in the mild group learned to walk and only one used a wheelchair regularly.

Information on speech development was obtained in 36 cases, reporting delay in 22 and normal development in 14. The median age at which first words were spoken was 21 months (range 9 months to 3.5 years, $n = 18$). The median age at which boys spoke in sentences was 3.5 years (range 2

years to 5 years, $n = 13$). It was felt that cognitive function of most boys was normal but in many cases dysarthria and tracheostomy made speaking difficult; a number of boys learned to communicate by signing.

Thirty-one of the boys were receiving some form of ventilatory support, 20 on a 24-h basis and 11 at night only. Four of the boys had had an initial period of respiratory independence but then required support at varying ages (10 months, 1 year, 3.5 years and 12 years). All but three boys had tracheostomies; these three used nasal masks. Nine out of 15 of the European patients receive ventilatory support, representing 36%, while 21/24 of the cases from the United States receive assisted ventilation, representing 87%. This marked difference is likely to result from divergent treatment policies in the United States and Europe with a greater proportion of the severely affected boys in the United States receiving more active treatment. Eleven boys were able to feed themselves, the remainder all received supplementary feeding via gastrostomy or naso-gastric tube.

All but two boys lived at home with their families (one is in foster care). The two who did not live at home were aged 11 years and 16 years and lived in hospital, with the occasional overnight stay at home. Almost all of those at school age, including those in hospital, attended school. Eighteen received tuition in a regular school while eight attended schools for children with disabilities. A small number of boys received tuition at home. Where comment about this was made, intelligence was noted to be average or above average. Boys with the mild phenotype were involved in activities such as horse riding, swimming and dancing. Most surviving boys were still at school, four were 18 years or older. Of these, one owns his own business and two intend to go to university and are involved in journalism.

3.7. Survival analyses

The age at death was documented in 72 cases. Survival durations available on 51 living cases were censored at the

Fig. 4. Kaplan–Meier plot comparing survival for cohorts harbouring truncating and non-truncating mutations in MTM1.

age attained at the time of completion of the study in September 2000. Fig. 3 shows the overall unadjusted survival curve for these subjects. The overall median survival is 29 months (95% confidence interval 0.1–63.8). Fig. 4 compares survival in cases harbouring a truncating versus a non-truncating mutation. Survival was greater in subjects with a non-truncating mutation. At 18 months 70% of cases with a non-truncating mutation were still alive compared with only 43% of cases in the truncating group ($P = 0.015$). Fig. 5 shows the variation in survival across the three phenotypic groups. Fig. 6 demonstrates the influence on survival of the country in which the subject received medical care. Treatment policies in the United States and Japan were considered similar and therefore subjects treated in these countries were grouped together. The remaining subjects were all treated in European countries. The cohort of patients from the United States and Japan has a greatly
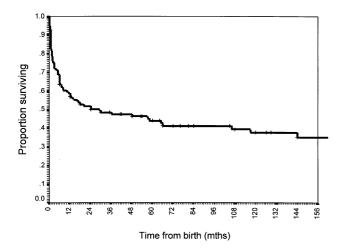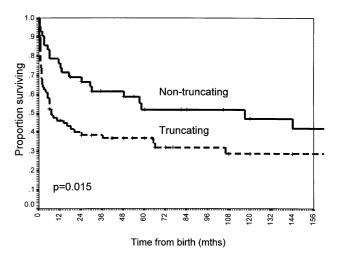

Fig. 3. Kaplan–Meier plot illustrating unadjusted survival for the full cohort of XMTM cases. Eighteen months survival was 54%.
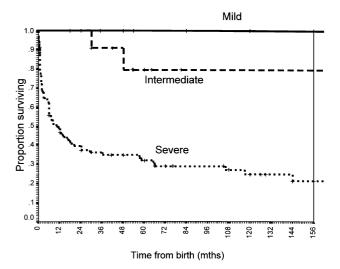

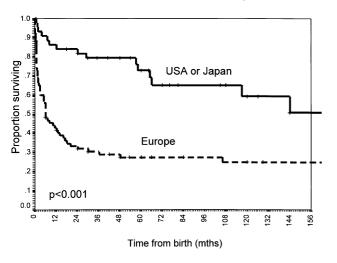Fig. 5. Kaplan–Meier plot comparing survival in mild, intermediate and severe phenotypic groups.

Fig. 6. Kaplan–Meier plot for cohorts treated in the United States and Japan versus Europe.

increased chance of survival. Cox regression analysis was used to evaluate the influence on survival of gestation, PES, mutation type and the country in which the affected case was treated. The country ($P < 0.0001$) and mutation type ($P < 0.005$) were independent predictors of mortality.

4. Discussion

XMTM has generally been considered a severe and frequently lethal disorder. The cause of death is usually respiratory failure. In the current study affected males had a 46% risk of death by 18 months (Fig. 3). This compares with a 25% risk of death before the age of 18 months in cases of congenital myotonic dystrophy [16]. The identification of boys with milder manifestation of XMTM [9,11] and the recent isolation of the causative gene, MTM1, has provided an opportunity to evaluate whether the nature of the mutation in MTM1, or the presence/absence of early prognostic markers on clinical evaluation, could be used to predict a mild or severe outcome.

In the current study evaluating 116 males affected by this condition, we have confirmed a previously discerned association between the presence of a non-truncating mutation of the MTM1 gene and the mild phenotype [2,6,10]. However, extensive mutational heterogeneity is known to occur in this disorder and it should be noted that 83 different mutations were found during the course of our study. Many non-truncating mutations were also seen in association with the severe phenotype and these were not confined to recognized functional domains of the protein. Furthermore, intrafamilial variability of phenotype was observed and the analysis of recurrent mutations in unrelated individuals also revealed variable phenotypes. These observations suggest that the use of mutation analysis to predict prognosis in the early period following diagnosis is very limited.

Detection of polyhydramnios, absent fetal movements,

absent reflexes, joint contractures and the need for intubation at birth in the perinatal period are considered signs of significant neurological/neuromuscular disease. Assisted delivery for fetal distress may also be a sign of neurological disease in a newborn. All cases in this study were assigned a perinatal evaluation score (PES) based on these six features (Table 2). An association was identified between the presence of a higher PES and a mild phenotype. This suggests that affected males who later develop a mild phenotype show milder signs of the disorder from the outset. However, it is important to note that seven boys in this study who manifest the mild phenotype did require a period of ventilatory support in the early neonatal period before they went on to establish respiratory independence. Moreover, although there was an association between PES and phenotypic group, the variability from case to case was too wide for the PES as such to be considered a robust indicator of the patient's future requirement for ventilatory support.

The number of survivors in our study was higher than expected. It is noteworthy however that 75% of the surviving cases receive some level of regular ventilatory support therefore reaffirming that this is a severe congenital myopathy. Breakdown of the data by the rate of ventilation in cases from Europe versus the United States reveals that a much higher percentage of cases in the United States receive assisted ventilation. It is presumably this high level of medical intervention that has increased survival in cases treated in the United States. This is reflected in the overall survival figures for XMTM. Home ventilation has become a reality in recent years for a number of respiratory and neuromuscular conditions; therefore we may expect to see more boys affected by XMTM surviving for longer periods.

XMTM appears to be genetically a homogeneous disease and the mutation detection rate is high. The failure to identify mutations in the occasional classical case may reflect limitations of the techniques used. The greatest value of mutation detection in this disorder is in confirming the diagnosis and determining carrier status. It is important to note that a number of cases of maternal and grand-paternal germline mosaicism for this condition have been described [2,17]. The precise incidence of germline mosaicism in XMTM is not known, but in Duchenne muscular dystrophy, another X-linked recessive condition, it is in the order of 20% [18]. Therefore it is advisable to offer prenatal diagnostic testing to all women who have had an affected boy.

In boys in whom a mutation has not been detected, determining the mode of inheritance and recurrence risk is difficult as these patients may be affected by one of the autosomal forms of the disorder, the genes for which have not yet been identified. Recently, Laporte et al. [19] described a method of immunoprecipitation to detect the presence or absence of myotubularin in cell lines (cultured lymphocytes and fibroblasts). Myotubularin was reduced or absent in known cases of XMTM whereas levels were normal in four presumed autosomal cases of the disorder.

Moreover, myotubularin was undetectable in one patient for whom no MTM1 mutation could be identified thereby perhaps providing another method of establishing the diagnosis of XMTM. Further studies will be needed to determine if the level of myotubularin expression is related to the observed phenotype in XMTM and to confirm that it is indeed normal in the autosomal forms of this condition. At present however the limitations of using the mutation type or the level of myotubularin expression to predict the likely phenotype in XMTM are clear and physicians will need to continue to rely on clinical judgment in making difficult management decisions.

Myotubularin is ubiquitously expressed and although it is known to function as a phosphatase implicated in the phosphatidylinositol 3-kinase pathway, the pathophysiology of this disorder is not understood [7,8]. The phosphatidylinositol 3-kinase pathway is important in regulating intracellular membrane trafficking and vesicular transport processes and a role for myotubularin in myogenesis has been suggested. Functional studies of the myotubularin protein are needed to determine if this is the case and a mouse model of XMTM has been designed to this end [20]. Such work may also reveal how mutations in this gene result in the non-neuromuscular manifestations of this disease, specifically the tall stature and the high incidence of hepatic peliosis, a rare disorder previously associated with wasting conditions [11].

Acknowledgements

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