Review article

The myotubular myopathies: differential diagnosis of the X linked recessive, autosomal dominant, and autosomal recessive forms and present state of DNA studies

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Abstract

Clinical differences exist between the three forms of myotubular myopathy. They differ regarding age at onset, severity of the disease, and prognosis, and also regarding some of the clinical characteristics. The autosomal dominant form mostly has a later onset and milder course than the X linked form, and the autosomal recessive form is intermediate in both respects. These differences are, however, quantitative rather than qualitative. Muscle biopsy studies of family members are useful in some cases, and immunohistochemical staining of desmin and vimentin may help distinguish between the X linked and autosomal forms. Determining the mode of inheritance and prognosis in individual families, especially those with a single male patient, still poses a problem.

Current molecular genetic results indicate that the gene for the X linked form is located in the proximal Xq28 region. Further molecular genetic studies are needed to examine the existence of genetic heterogeneity in myotubular myopathy and to facilitate diagnosis.

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The X linked recessive form of myotubular myopathy (XMTM) is well documented (McKusick *310400).¹ An autosomal dominant form (McKusick *160150)¹ and an autosomal recessive form (McKusick 255200)¹ have been described, although to our knowledge only two reports include verified cases of male to male transmission, and we have found no reports of fully examined families with healthy parents of affected children of both sexes.

No clear consensus exists regarding the use of the alternative names myotubular or centronuclear myopathies. Some authors, including one of us (MF), prefer the descriptive term centronuclear myopathy for the autosomal forms.² Further studies are needed to resolve this pathogenetic debate.

The myotubular or centronuclear myopathies are among the group of rare myopathies called the congenital myopathies. In addition, a form with hypotrophy of type 1 fibres has been described.³ Type 1 hypotrophy is, however, a common feature in the congenital myopathies and this is not likely to be a distinct condition.

No definite morphological differences have been found on histological examination of muscle biopsies between the autosomal and X linked forms. They are all characterised by smallness of muscle fibres and centrally placed myofibre nuclei. The central areas of the muscle fibres are devoid of myofibrils, with aggregation of mitochondria. This is reflected by the oxidative enzyme reactions showing central density of staining, and, correspondingly, the ATPase reaction showing central lack of staining. The resemblance to fetal myotubes has been thought to reflect an arrest in morphogenesis of the muscle fibres, a hypothesis corroborated by the results of Sarnat,⁴ who found persistence of desmin and vimentin staining in the myofibres of patients with XMTM. A similar persistence was not found in late onset cases,^{5,6} with one exception.⁷

The aim of this review is to outline the features of the different forms of myotubular myopathy. The basis of the paper is data on families seen by members of the International XMTM consortium and published familial cases. In addition to previous suggestions of immunohistochemical differences between XMTM and the autosomal forms, some differences are suggested in clinical features such as age at onset and severity of the disease.

The X linked form

Data on 37 families with confirmed or likely X linked inheritance were presented at the first International ENMC Sponsored Workshop on Myotubular Myopathy.⁸ At the time of the Workshop, most of the patients had died and information on clinical and histological details was not always complete. Therefore, in the following, the numbers of patients with in-

formation available on the detail discussed will be stated.

The clinical features included polyhydramnios in 17/36 cases. Ten out of 23 boys were born prematurely. They were mostly long and light for both length and gestational age with large heads. Almost all had severe hypotonia and generalised muscle weakness, at least half of them totally lacking spontaneous antigravity movements at birth. Facial weakness was noted in 20/21 boys and ophthalmoplegia in 10/13. At birth, only three boys established normal respiration, and in 17/40 respiration was completely lacking. Cardiac problems were rare and mostly attributable to respiratory difficulties. Many had a weak cry, swallowing difficulties, recurrent respiratory infections, and absent tendon reflexes. Cryptorchidism was noted in nine, three of whom were born prematurely. Six boys had hip contractures and six had knee contractures, the contractures tending to be less severe than in myotonic dystrophy.

Serum concentrations of creatine kinase were normal or only slightly raised. Electromyography mostly gave normal results, whereas a few patients showed small polyphasic motor unit potentials, and fibrillation potentials were occasionally seen.

Muscle samples from the quadriceps femoris, biceps, deltoid, diaphragm, intercostal, tongue, and psoas muscles taken during life or post mortem all showed characteristic findings (figs 1 to 3). The fibres were usually small for age and rounded in shape. Ten out of 17 had predominance of type 1 fibres, which were

Figure 2 Paraffin embedded section of muscle biopsy from the same patient as in fig 1, showing a longitudinal fibre with "empty" central tube-like structure, containing a row of nuclei (Masson trichrome, $\times 1200$).

often more hypotrophic than type 2 fibres. There were central nuclei, central areas devoid of myofibrils with the ATPase reaction, and a

Figure 1 Semithin (1 μ m) toluidine blue stained transverse Epon section of skeletal muscle from a neonate with X linked myotubular myopathy. Most fibres shown are abnormal with large central "empty" spaces devoid of myofibrils. Some of these empty spaces contain a nucleus depending on the plane of section ($\times 528$).

Figure 3 Muscle biopsy of 2 month old male patient with myotubular myopathy. Transverse cryostat section stained for NADH-oxidoreductase activity. Activity is concentrated in the inner parts of the fibres. Type 1 fibres, containing the highest activity, are generally smaller than type 2 fibres ($\times 300$).

corresponding central aggregation of mitochondria with the oxidative enzyme stains. The proportion of these myotube-like fibres varied widely.

In most of the patients the disease followed a fatal course. The boys died of respiratory or cardiac failure, in some combined with pneumonia, at ages ranging from 3 hours to 3 years (mean 4.8 months). Family histories often included stillbirths and miscarriages. The boy who survived up to the age of 3 years needed mechanical ventilation all his life.

Six boys were alive at ages of 6 months to 27 years (mean 10 years). Although all but one had respiratory difficulties at birth, respiration later became normal in four of the boys, but two still needed mechanical ventilation at the ages of 8 and 10 years, respectively. One was severely disabled and dependent on others for the activities of daily living, being able to move only his hands to use a computer. Four out of five learned to walk although later than normal, and two of these later began to use a wheelchair. Three had no significant disability at the ages of 6 months, 5 years, and 7 years, respectively.

In summary, the clinical picture in XMTM is quite consistent, with perinatal onset of severe generalised muscle weakness and hypotonia, often accompanied by ventilatory insufficiency. Nevertheless, care has to be taken in interpreting the mode of inheritance and prognosis in families with a single male patient. In particular, the prognosis in the X linked form is not always poor and survival into adulthood cannot be regarded as proof of autosomal inheritance.

Sarnat⁴⁹ has shown that muscle biopsies of boys with XMTM show a persistence of desmin and vimentin. Recent studies of a family with autosomal dominant inheritance⁵ and three solitary adult onset male cases⁶ did not show a similar persistence, whereas one adult onset male case did.⁷

FINDINGS IN CARRIERS

Reports of clinical symptoms and signs in carriers are few and far between. Mild facial weakness has been noted in one obligate carrier and one possible carrier.^{10 11}

Results of muscle biopsy studies of female relatives of patients with XMTM have been reported in 15 families.¹¹⁻²² By analysis of the original pedigrees, the females have been designated as obligate or possible carriers. Obligate carriers were defined as females who had two sons with histologically verified diagnoses of XMTM, or one affected son and affected male relatives with histologically verified diagnoses, related to the carrier through the maternal line. Possible carriers were females with one son affected or females related to affected males through the maternal line.

Out of 12 obligate carriers, six showed fibres with central nuclei resembling fetal myotubes (fig 4), one showed other abnormalities and five showed normal findings. Out of 13 possible carriers, four showed fibres with central nuclei resembling myotubes, six showed other abnormalities, and three showed normal findings.

Results of further muscle biopsy studies of obligate or possible carriers were presented at the International ENMC sponsored Workshop on Myotubular Myopathy. In six of the French families presented, muscle biopsies had been obtained from 12 possible carriers. None of the biopsies showed myotube-like fibres, but biopsies in five possible carriers showed central nuclei in more than 3% of the fibres. An additional predominance of type 1 fibres (70 to 80%) was seen in three of the possible carriers. In a large Welsh kindred, muscle biopsy studies had been performed in two obligate and five possible carriers. Neither of the obligate carriers but two of the possible carriers showed central nuclei. In one possible carrier muscle morphology was completely normal, whereas both obligate carriers and the remaining four possible carriers showed other abnormalities, such as abnormally high variability of fibre size or high atrophy factors.

Thus, adding published data and those presented at the Workshop together, six out of 14 obligate carriers showed fibres with central nuclei resembling fetal myotubes, three showed other abnormalities, and five showed normal findings.

The interpretation of the biopsy results warrants some caution. Clearly, one needs to distinguish between definitely central, often enlarged nuclei in fibres centrally devoid of myofibrils, and internal nuclei, that is, non-subsarcolemmal nuclei, located somewhere inside the myofibre, a feature quite commonly encountered in myopathies. It seems reas-

Figure 4 Muscle biopsy of female carrier of X linked myotubular myopathy. Transverse section of vastus lateralis muscle stained for NADH-oxidoreductase activity. Between normal type 1 and type 2 fibres a very small longitudinally oriented "myotube" is seen with enzyme activity concentrated in the centre of the myofibre ($\times 330$).

unable to interpret the former as expressions of the XMTM gene, whereas the latter are too non-specific to warrant any firm conclusion. Neither can it be said with any confidence that other abnormalities reported, such as abnormal variability in fibre size or predominance of type 1 fibres, constitute definite proof of the person being a carrier. One of the problems in this context is the lack of a true, sufficiently large normal control series for various ages.

The combined data of studies of obligate carriers suggest that definite exclusion of carrier risk is not possible by muscle biopsy, whereas about half of carriers may have their high risk verified. The number of muscle biopsy studies done in obligate carriers is, however, not sufficiently high to permit more exact risk calculation for individual possible carriers.

There are suggestions, however, that immunohistochemical studies of desmin and vimentin might be helpful in carrier diagnosis. The study of biopsies from two possible carriers suggests persistence of these proteins in the muscle tissue of carriers of XMTM.⁹ These results await confirmation through studies of further, obligate carriers.

In pedigrees where X linked inheritance is not certain, it is important to keep in mind

the possibility that abnormal muscle biopsy findings in parents might be the result of expression of an autosomal gene.

DNA STUDIES

Current molecular genetic results indicate that the XMTM1 gene is likely to be located in the proximal Xq28 region between the markers DXS369 and DXS15.^{19,23-28} Determining the breakpoints of a deletion in a female patient with XMTM and linkage analysis in three families showing informative meiotic recombination events has narrowed the region of interest to a 600 kb interval.²⁹⁻³¹ This should greatly accelerate the cloning of the XMTM1 gene. Prenatal diagnosis still relies on linkage analysis.³² The microsatellite markers DXS1113 and DXS1684 are the closest flanking markers, and the highly polymorphic marker DXS455 (which requires Southern blot analysis) is located within the 600 kb candidate region.³⁰

However, in a French family with apparently X linked myotubular myopathy, linkage to Xq28 markers has been excluded.³³ This is the first suggestion to date of genetic heterogeneity in this condition.

Data on pedigrees compatible with autosomal dominant transmission

To our knowledge, there have been only two reports of families with histologically verified male to male transmission of MTM^{34,35} but at least 11 other reported pedigrees are compatible with autosomal dominant transmission (fig 5).^{5,36-45}

In these 13 families, there were 26 patients altogether in whom the diagnosis had been histologically verified and 28 other family members with probable MTM, some of whom had muscle biopsies showing central nuclei but no clinical signs or symptoms of MTM. Among the patients with verified diagnoses, the sex ratio (male:female) was 0.86. When the family members with probable MTM were included, the sex ratio was 1.16, which is in keeping with autosomal dominant inheritance.

In nine patients, the onset of symptoms was in the first decade, in four patients in the second decade, and in 12 it was later. In two affected brothers,⁴³ the onset was prenatal, but the possibility remains that these boys actually were affected by the X linked form and the clinically mildly affected mother was in fact a manifesting carrier of XMTM.

The clinical features are generalised muscle weakness, often predominantly proximal, but some patients show a definite additional distal involvement. A few patients have calf hypertrophy. The facial muscles may also be involved and some patients have ptosis or ophthalmoplegia. Electromyographic findings may be normal or "myopathic", that is, consist of small polyphasic motor unit potentials and a full interference pattern during weak effort. Serum concentrations of creatine kinase are mostly normal.

Progression is usually slow. Twenty-four of the 26 patients were alive at the time of writing

Figure 5 Pedigrees compatible with autosomal dominant transmission. Black symbols represent patients whose diagnoses have been histologically verified, hatched symbols persons thought to be affected but whose diagnoses have not been histologically verified, and white symbols represent healthy family members. A dash through a symbol indicates that the person is dead. B=biopsy showing central nuclei. E=pathological findings at electromyography. ?=slight clinical symptoms of uncertain significance.

Figure 6 Pedigrees compatible with autosomal recessive inheritance. Symbols as for fig 5.

the reports, at ages ranging from 11 months to 68 years (mean 37 years). One patient⁵ had died at the age of 57 years of cardiorespiratory failure and another at 5 years.⁴³

In summary, the autosomal dominant form mostly has a later onset and a milder course than the X linked form, but the clinical features do not seem to be qualitatively different.

Data on pedigrees compatible with autosomal recessive transmission

At least 11 MTM families with pedigrees compatible with autosomal recessive inheritance have been reported (fig 6).⁴⁶⁻⁵⁴ The family reported by Verhiest *et al*⁴⁸ could, however, represent X linked recessive inheritance; examination of the parents was not reported. At the first International Workshop on Myotubular Myopathy, a twelfth, Welsh family was presented. In addition, there have been reports of sporadic late onset female cases and two sporadic cases of male patients with consanguineous parents.

In the 12 families, there were 21 patients with histologically verified diagnoses of MTM. The sex ratio (male:female) was 0.62. This may well reflect an ascertainment bias since families with male sibs affected may not readily be reported as recessive.

In six of the patients, the onset of the disease was in infancy, in seven it was in early childhood, and in a further eight it was between 8 and 30 years.

Clinical features commonly included ophthalmoplegia, ptosis, and facial weakness. Six of the patients were reported to have feeding difficulties, two were floppy at birth, and two had asphyxia at birth. Muscle weakness was often most pronounced proximally, but some showed an additional distal involvement. Electromyography was normal or showed non-specifically abnormal or "myopathic" features.

In three of the families the parents were consanguineous. Muscle biopsy findings were reported in four of the mothers, all of whom had central nuclei. We found only one report of a biopsy in a father.⁵⁵ In this family, one son and one daughter were affected and the parents were healthy (although the mother said she had been thin and weak in her youth) with muscle biopsy findings within normal limits. The interpretation of the biopsy findings is, however, somewhat difficult because histochemical staining methods were not used.

No clinically detectable weakness has been reported in the parents, but not all have been examined. Both parents in one family reportedly showed abnormalities on electromyography.⁵³

The pedigree described by Sher *et al*⁴⁶ warrants a few comments. The clinically healthy mother of two affected girls showed central nuclei in her muscle biopsy. No biopsy was done in the father. If the two affected children had been boys, the mode of inheritance would be interpreted as X linked recessive and the biopsy findings as indicative of heterozygosity for the X chromosomal gene. One possibility is that an autosomal dominant gene with variable penetrance is segregating in this family. Another possibility is that the central nuclei are a manifestation of heterozygosity for an autosomal recessive gene, an interpretation difficult to verify in the absence of results of biopsies from both parents in this and other families. Suggestions of such heterozygote manifestations at biopsy of clinically healthy parents have been reported for another congenital myopathy, nemaline myopathy.⁵⁶ One could also interpret the pathological findings at electromyography in both (clinically healthy) parents and a clinically healthy sib of an affected boy⁵³ as examples of heterozygote manifestations.

All but one of the 21 patients whose diagnoses had been histologically verified were alive at the time of reporting, at ages between 3 and 32 years (mean 18 years). One patient had died from heart failure at the age of 16 years.

In summary, the age at onset is generally later than in the X linked form and earlier than in the autosomal dominant form. The severity of the disease also seems to be intermediate between that in the other two forms.

Comments and conclusions

Clinical differences exist between the various forms of MTM. The age at onset, severity of

the disease, and prognosis differ, as do some of the clinical characteristics. These differences are, however, quantitative rather than qualitative. Thus, determining the mode of inheritance in sporadic cases still poses a problem. An example is survival into adulthood of male patients, often accepted as definite proof of autosomal inheritance, but compatible also with X linked inheritance. It is hoped that further molecular genetic studies will help resolve some of these questions and provide additional diagnostic tools.

The role of muscle biopsy studies in establishing the mode of inheritance in singleton families remains to be determined.

Care has to be taken in interpreting biopsy findings in one clinically healthy parent, especially if the other has not undergone muscle biopsy. It is clear that in XMTM, some carriers will manifest histological abnormalities, but it is unclear whether similar manifestations occur in heterozygotes for the autosomal recessive gene or in subclinical cases of the autosomal dominant form. Studies of desmin and vimentin might facilitate these distinctions.

An important differential diagnosis to bear in mind is myotonic dystrophy. The congenital form is clinically and histologically very similar to severe XMTM. Molecular genetic exclusion of myotonic dystrophy (or electromyography in the mother) should be performed in all cases of XMTM.

To sum up, some clinical and histological differences exist between the autosomal dominant, autosomal recessive, and X linked forms of MTM. However, as these differences are mostly quantitative rather than qualitative, further studies are needed to permit definite distinction, especially in singleton cases. The role of immunohistochemical studies of desmin and vimentin needs to be elucidated further. Molecular genetic studies are necessary to confirm the existence of genetic heterogeneity in MTM and to facilitate diagnosis.

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