Review article

Nemaline myopathy: current concepts

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Definition

Nemaline (rod) myopathy, first described in 1963 by Shy *et al*[1] and Conen *et al*,[2] is assigned to the group of congenital myopathies. These muscle disorders are defined on the basis of structural abnormalities of the muscle fibres, visible after staining of muscle biopsy sections with histochemical methods. The histological definition of nemaline myopathy is based on the presence of thread- or rod-like bodies, the nemaline (rod) bodies in the muscle fibres of patients.

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Nemaline myopathy, first described in 1963,[1] [2] is a neuromuscular disorder characterised by muscle weakness and the presence of rod shaped structures (synonym: rods) in the muscle fibres. The term nemaline was applied by Shy *et al*[1] because of the thread-like appearance of the rod bodies (Greek nema=thread). This is a rare form of congenital myopathy with an estimated incidence of 0.02 per 1000 live births.[3]

Incidence

To our knowledge, the only published incidence figure, based on ascertainment through a number of sources in a small geographical area in Finland, gives an estimate of the incidence of congenital nemaline myopathy of 1 per 500 000.[3]

Classification

Classification of nemaline myopathy into subtypes has been attempted on the basis of clinical features such as the pattern of weakness and age of onset. Three subtypes have been suggested: severe neonatal onset, a milder congenital, non-progressive or slowly progressive nemaline myopathy, and a slowly progressive late or adult onset form[4–6]; however, there is marked overlap between each of these groups. The large kindred described by Laing *et al*[7] does not fall into any of these subtypes and probably warrants the inclusion of an additional "childhood onset" group. With the recent confirmation of both autosomal dominant and recessive forms of nemaline myopathy, and the discovery of two genetic loci for the disorder (see below), further molecular studies may eventually result in a meaningful classification which permits

prediction of prognosis or determination of the mode of inheritance in singleton cases. The diagnostic criteria for nemaline myopathy are summarised in table 1.

The severe neonatal form presents at birth with severe hypotonia and muscle weakness, little spontaneous movement, difficulties with sucking and swallowing, gastro-oesophageal reflux, and respiratory insufficiency. Decreased fetal movements and rarely polyhydramnios may complicate the pregnancy.[8] Dilated cardiomyopathy and arthrogryposis occur infrequently.[9] [10] Death from respiratory insufficiency or recurrent pneumonia is common during the first weeks or months of life.[8] However, even patients with severe floppiness and lack of spontaneous respiration at birth have been known to survive, some of them with little residual disability.[11–13]

The mild congenital or "classic" form of nemaline myopathy usually presents at birth or during the first year of life with hypotonia, weakness, and feeding difficulties; however, the severity of muscle involvement is often less marked than in the severe neonatal form. Some cases present later with delayed attainment of motor milestones, a waddling gait, or speech abnormalities. There is commonly distal involvement in addition to the proximal muscle weakness, and some patients have initially been thought to have peroneal paresis because of their foot drop. The respiratory muscles are always involved although hypoventilation may not be clinically obvious; cardiac involvement is rare. The course of the disease is often static or only very slowly progressive and most patients will be able to lead an active life. Others may experience deterioration during the prepubertal period of rapid growth and some will start using a wheelchair at this time.[14]

The childhood onset form of nemaline myopathy occurred in a large Australian kindred described by Laing *et al*,[7] in which inheritance was autosomal dominant. Onset of weakness occurred late in the first or early in the second decade and was slowly progressive. Early motor development was normal with the development of symmetrical weakness of ankle dorsiflexion in the late first or early second decade. Weakness was slowly progressive with eventual involvement of all ankle movements and more proximal limb musculature. Two older family members were wheelchair bound

Table 1 Criteria for diagnosis of nemaline myopathy

Definition
Neuromuscular disorder producing weakness and associated with nemaline bodies in the absence of other known conditions
    sometimes associated with nemaline bodies (see exclusion criteria).
Features
    (A) Clinical features
        (1) Patterns of weakness:
            (a) Predominantly proximal limb/neck muscles (including diaphragm)
            (b) Diffuse (proximal and distal muscles equally weak)
            (c) Selective patterns: scapuloperoneal, scapulohumeral, distal
            (d) Facial with a, b, or c
            (e) Note: extraocular muscles usually not involved
        (2) Onset
            (a) Infantile: birth or within first year
            (b) Childhood
            (c) Adult
        (3) Inheritance
            (a) AR, NEM2, and other
            (b) AD, NEM1, and other
    (B) Laboratory findings
        (1) CK normal or mildly raised
        (2) EMG:
            (a) Early: normal or "myopathic"
            (b) Late: can be "neuropathic" in distal muscles
        (3) Nerve conduction studies:
            (a) Normal motor and sensory conduction velocities and latencies
            (b) Normal sensory amplitudes
            (c) Distal compound muscle action potential amplitudes can be decreased when distal atrophy is present
    (C) Muscle histology
        (1) Light microscopy:
        Nemaline bodies visible with Gomori trichrome in subsarcolemmal or sarcoplasmic regions, rarely intranuclear
        Other common features: type 1 predominance, poor fibre type differentiation, fibre type disproportion
        (2) Electron microscopy:
        Nemaline bodies in cytoplasm resemble Z disc with periodic lattice pattern
        (3) Immunohistochemistry:
        Nemaline bodies positive for α-actinin
    Exclusion criteria
    (A) Sensory symptoms or signs
    (B) Other known conditions sometimes associated with nemaline bodies, eg mitochondrial myopathy, HIV infection,
        inflammatory myopathy, central core disease, toxic myopathies

Table compiled by Dr Richard Barohn, Dallas, Texas, USA.

by 40 years of age. Cardiac muscle was spared, although the proband had achalasia and chronic intestinal pseudo-obstruction.

The late onset or adult onset form of nemaline myopathy is heterogeneous in terms of clinical presentation and disease progression. In patients with a true isolated adult onset form of nemaline myopathy, there is no family history and no preceding symptoms and onset of proximal and distal weakness is in the third to sixth decade.[15] In some patients there is minimal skeletal muscle involvement and presentation is with a cardiomyopathy[16 17] or as part of the investigation of other family members.[18 19] Respiratory and cardiac involvement occurs in the minority of cases, but in these patients the disease often follows a clearly progressive course.[20-27] A few patients have shown monoclonal gammopathy[20 28 29] and others have had muscle pain,[22 30] paraesthesias,[20] or inflammation.[20 31]

Clinical features

The cardinal features of nemaline myopathy are weakness and hypotonia. Muscle weakness is usually most severe in the face, the neck flexors, and the proximal limb muscles. In some patients there is an additional distal involvement. The extraocular muscles are spared. Rarely, the muscle weakness in sporadic cases has shown a scapulohumeral distribution, with "terracing" of the shoulders.[32]

In congenital onset forms of nemaline myopathy, the face is often elongated and expressionless, the mouth tent shaped, and the palate high arched (a myopathic facies, fig 1).
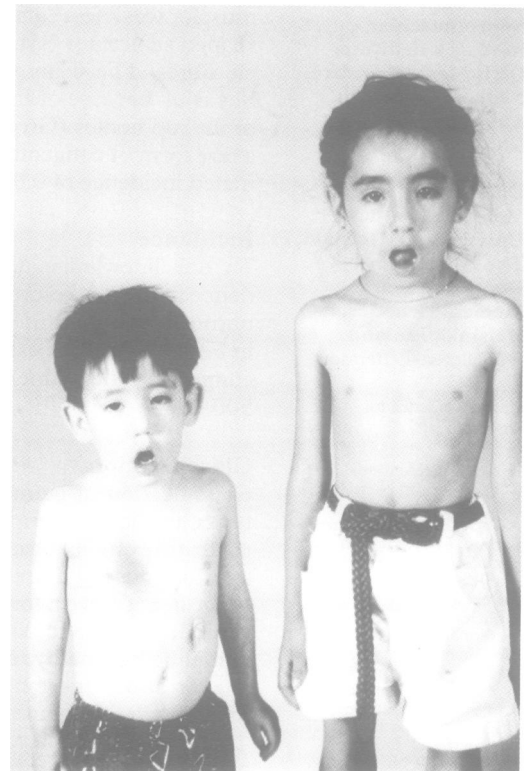

Figure 1 A brother and sister (aged 3 and 7 years, respectively) with classical congenital onset nemaline myopathy. Both sibs had dysphagia and respiratory distress at birth (note gastrostomy scar and pectus excavatum in the male sib); age at walking was 13 months in the male and 24 months in the female. Note proximal muscle wasting and facial diplegia ("myopathic facies") in both children. (Photograph reproduced with permission, courtesy of Dr Susan Iannaccone, Dallas, Texas, USA.)
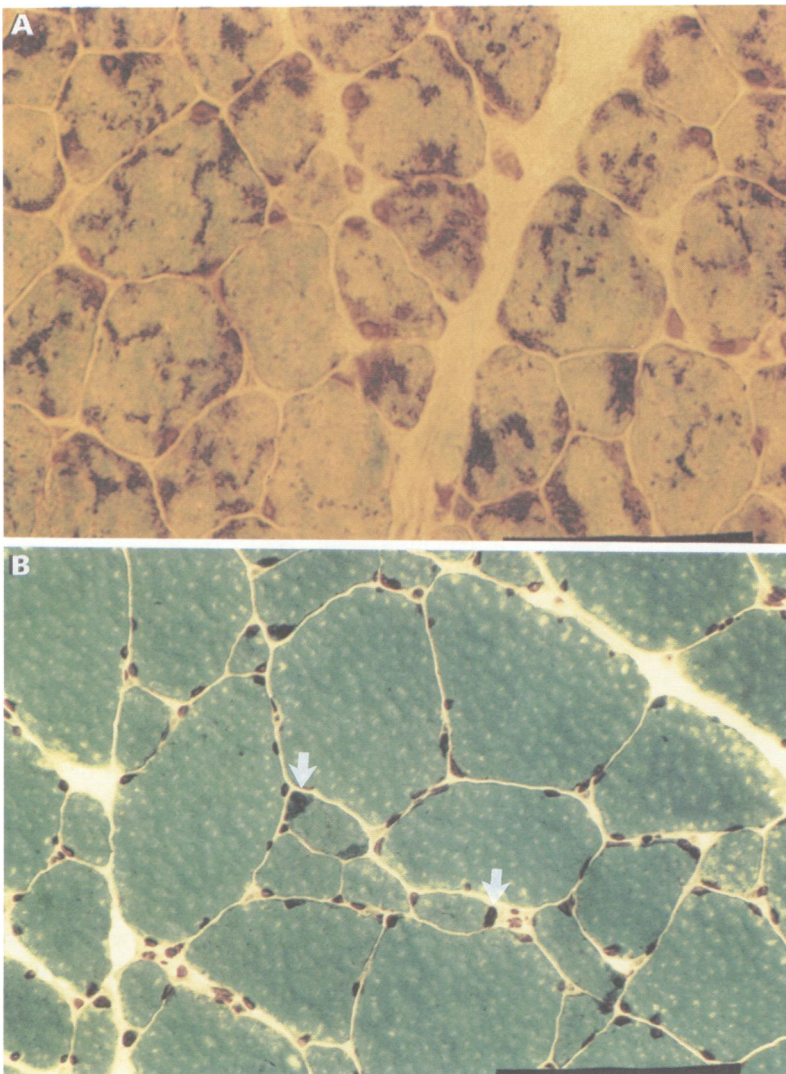
Figure 2 Light microscopy in nemaline myopathy (Gomori trichrome stain). Sections for muscle biopsies of two patients showing variability in the number of nemaline bodies (rods) that may be present. In muscle from patient 1 (A) rods were present and multiple in almost all fibres. Note aggregation of rods under the sarcolemmal membrane. In muscle from patient 2 (B) rods are only present in occasional fibres (arrow).

There may be retrognathia and later jaw lock. The patients commonly have a nasal voice or even dysarthria, the palatal reflex is usually absent, the tongue is often small and furrowed, and most patients are unable to lift their heads in the supine position.

The gait is usually waddling. The build is slender but muscle bulk is not necessarily reduced, especially in young children. The spine is hyperlordotic and sometimes rigid.[12 33-36] In some patients, chest deformity is evident at birth. Tendon reflexes are weak or absent. Gross motor activity is slow whereas fine motor activity is normal. Many patients have hypermobility of joints, and contractures and deformities of the joints commonly develop with time. Severe arthrogryposis is not a characteristic feature of the mainstream form of nemaline myopathy, but there have been a few descriptions of patients with congenital arthrogryposis and nemaline bodies in their muscle fibres.[10 37-39]

Respiratory problems are a common feature of congenital nemaline myopathy, not only in the neonatal period but throughout life. The degree of skeletal muscle weakness does not necessarily reflect the degree of respiratory muscle involvement. Although symptom free, most patients will show restriction of their respiratory capacity on testing. The patients run a great risk of insidious nocturnal hypoxia even in the absence of morning symptoms, and several patients have experienced sudden respiratory failure.[12 40-42] While infants with the congenital onset form of nemaline myopathy commonly have feeding difficulties, older patients may present with isolated swallowing difficulties.

Cardiac contractility is usually normal in congenital nemaline myopathy.[43] However, cardiac involvement, particularly dilated cardiomyopathy, may occur.[9 17 44] The central nervous system is not usually affected in nemaline myopathy and intelligence is usually normal.[12] However, Sewry and Dubowitz[39] reported two infants with arthrogryposis and a histological diagnosis of nemaline myopathy who were unresponsive to external stimuli from birth. Absence of fetal movements, polyhydramnios, and the development of seizures were suggestive of clinical involvement of the central nervous system.

Investigations

Laboratory examinations are of little help in making the diagnosis of nemaline myopathy. Serum concentrations of creatine kinase are mostly normal or slightly raised (up to five times higher than normal). Electromyography may be normal in young patients and mild cases, but usually shows polyphasic motor unit potentials with small amplitude, a full interference pattern during weak effort, and normal fibre density.[45 46] In addition to these "myopathic" features, electromyographic signs often interpreted as neurogenic (large motor unit potentials with discrete pattern on full effort, abnormal jitter, and increased fibre density) may develop with time, especially in distal muscles.[46-48] Although a variety of abnormalities interpreted as neurogenic have been reported,[49 50] most patients will have normal findings on examination of peripheral nerves, including normal conduction velocities.

Ultrasonography often shows abnormally high echogenicity in affected muscles, computed tomography will show low density of muscles with preservation of volume, and magnetic resonance imaging will commonly show fatty infiltration of the muscle tissue.[51-53]

Muscle pathology

NEMALINE BODIES (RODS)

The pathological changes of nemaline myopathy are much the same irrespective of the severity of the clinical manifestations or the age of onset.[54] Nemaline bodies or rods are the pathological hallmark of the disorder. The rods are only readily visible after staining with the Gomori trichrome method and appear red or purple against the blue-green myofibrillar background[55 56] (fig 2). The distribution of rods within myofibres may be random, but they show a tendency to cluster under the sarcolemma and around nuclei. The proportion of fibres containing rods varies from case to case
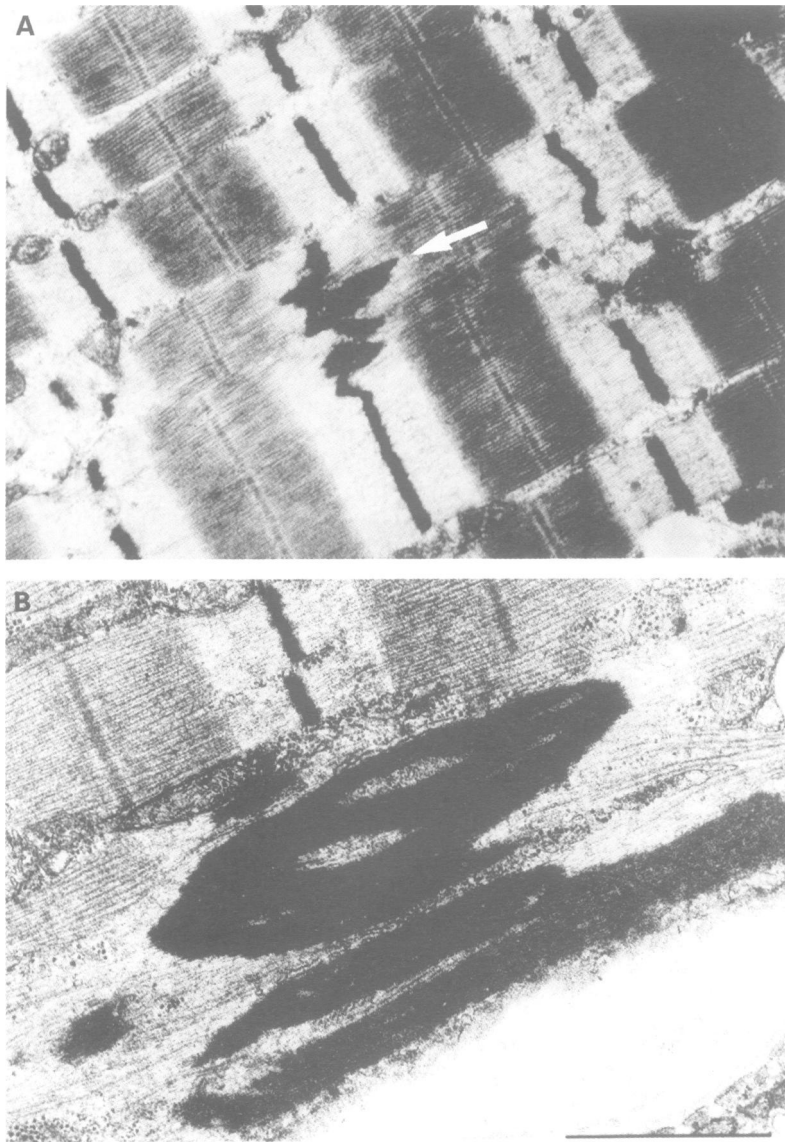
Figure 3 Electron microscopy of nemaline bodies. Note that nemaline bodies appear to be in structural continuity with the Z disk (A) and the lattice pattern of the rod ultrastructure at higher magnification (B).

filaments, is accumulated at the periphery of Z discs and of nemaline bodies.[62]

It is important to note that nemaline bodies are not specific to congenital nemaline myopathy, but have been described in a number of probably unrelated conditions, such as in tenotomised rat muscle,[64] haemodialysis,[65] and HIV infection.[66] Combinations of histological abnormalities characteristic for different congenital myopathies, particularly cores, have been encountered within families, sometimes even in the same patient.[30 67-70] Nemaline bodies may also occur in the setting of a mitochondrial myopathy.[71 72] It is not justified, therefore, to make the diagnosis of hereditary nemaline myopathy in the absence of a typical clinical picture.

OTHER HISTOLOGICAL FEATURES
On staining with H&E (haematoxylin and eosin) the changes characterising the disorder are difficult to detect. Replacement of muscle fibres by fat and fibrous tissue may be seen in advanced cases, but necrotic and regenerating fibres are uncommon. Inflammation is not a feature. There may be internal nuclei and occasional fibre splitting.[57] There is often focal disruption of the myofibrillar pattern on EM. Goebel *et al*[73] described necropsy findings in one case of the severe neonatal form of nemaline myopathy and in one boy with the milder form. They found large areas in both diaphragm and skeletal muscle where contractile material was deficient and there was excess formation of thin filaments, suggesting that disorganisation of the sarcomere may be part of the pathogenesis of the disorder. In older patients, there is usually an abnormal variability in fibre size, reflecting the presence of one population of small fibres and one of large fibres. Follow up biopsies of 11 out of 13 patients showed increase in internal nuclei, fibrosis, or fibre splitting which is suggestive of a continuing disease process.[48]

FIBRE TYPING
Predominance of type I fibres is a common feature of nemaline myopathy and some patients show exclusively type I fibres or poor fibre type differentiation. In many biopsies, the mean diameter of the type I fibres is smaller than that of the type II fibres. Fibre type I predominance and atrophy tend to become more prominent with age and there is often a complete deficiency of type IIB (fast glycolytic) fibres and an increase in undifferentiated type IIC fibres.[48 74 75] Volpe *et al*[74] showed a lack of myosin light fast chains in muscle from three patients with nemaline myopathy, reflecting a depletion of type II (fast) fibres. They suggested that there was delayed muscle fibre type differentiation in the severe neonatal form of nemaline myopathies and that, in other forms, there was active transformation of type II (fast) to type I (slow) fibres as part of the disease process. This hypothesis has been supported by the morphometric studies of Miike *et al*[75] who suggested the following sequence of events: (1) atrophy of type I fibres, (2) transformation of IIB to IIA fibres resulting in deficiency of IIB

and from muscle to muscle; in many patients they are present in every extrafusal fibre. However, in some patients the rods occur only in type I fibres (which are usually smaller) and, in the minority of patients, rods occur in only a small proportion of fibres. Some patients with nemaline myopathy have shown nemaline bodies only in their second muscle biopsy,[48 57 58] whereas fibre type disproportion was evident already in the first biopsy.

On electron microscopy, nemaline bodies are electron dense and measure 1-7 μm in length and 0.3-2 μm in width (fig 3). For several reasons they are considered to be derived from the lateral expansion of Z disks. On EM, the nemaline bodies are in structural continuity with Z disks, their ultrastructure resembles the lattice pattern of the Z disk,[59 60] and they are penetrated by thin filaments which run parallel to their long axis and which behave like actin filaments.[61] α-actinin, the main component of Z disks (see below), is also a major component of nemaline bodies,[62 63] and desmin, the structural component of muscle specific intermediate
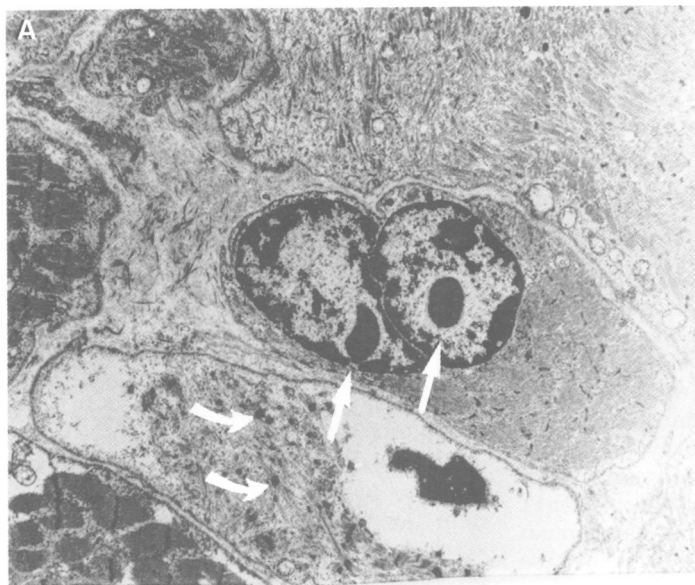
Figure 4 (A) Electron micrograph showing intranuclear rods in two nuclei (straight arrows). Intranuclear rods are at least 10 times larger than cytoplasmic rods (curved arrows) which are present in areas of myofibrillar disarray. (B) Higher magnification of intranuclear rod. Note lattice pattern of rod ultrastructure. (Courtesy of Dr Richard Barohn, Dallas, Texas, USA.)
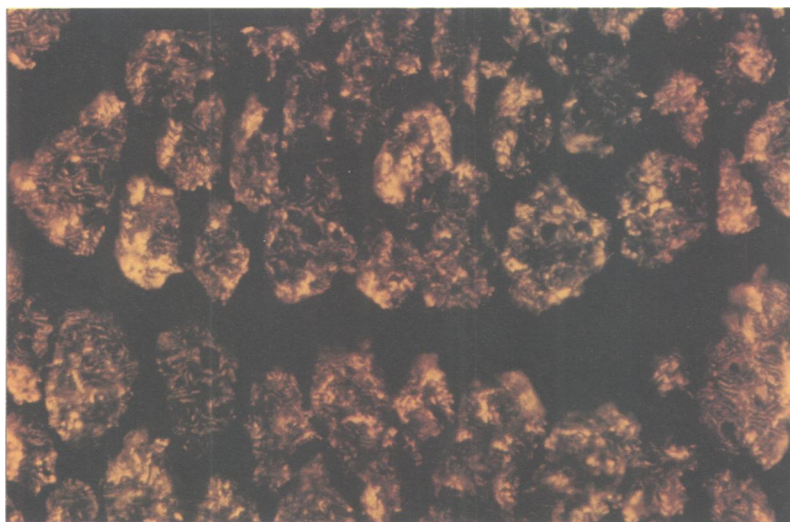

Figure 5 Immunocytochemistry of muscle biopsy shown in fig 2A, using antibody to α-actinin-2. With antibody to α-actinin-2 all muscle fibres show positive staining (α-actinin is localised in the Z disk of the sarcomere). Nemaline bodies (rods) show strongly positive staining.

fibres, (3) type I predominance and IIA hypertrophy, (4) transformation of IIA to type I fibres resulting in marked type I fibre predominance. It is not known whether this progressive type I fibre predominance is part of the primary disease process or a compensatory mechanism. Intrafusal muscle fibres are normally differentiated even when there is a marked type I fibre predominance.

INTRANUCLEAR RODS

Whereas nemaline bodies typically occur in the sarcoplasm of the muscle fibre, intranuclear nemaline bodies (fig 4) have been observed in muscle biopsies from patients with severe neonatal myopathy[38 76] and in some adult onset cases, with a progressive course.[77] Nuclear rods tend to be larger than sarcoplasmic rods, are usually solitary, may be formed in the absence of sarcoplasmic rods, and have a crystalline appearance with an ultrastructural pattern typical of Z discs.[73] By immunocytochemistry, they consist mainly of α-actinin (see below).

Intranuclear rods have generally been considered to be associated with more severe muscle involvement and a worse prognosis.[38 76] Goebel et al[73] reported clinical and pathological findings in four patients with intranuclear rods and summarised eight of nine published cases for whom clinical data were available. Onset of symptoms was at birth in 8/12 cases, in childhood in one case, and in adulthood (fourth to sixth decade) in three cases. Seven of the 12 patients developed respiratory insufficiency (including two with adult onset disease) and two of the infantile onset patients had cardiac involvement. Mortality was high at all ages of onset; 6/8 patients with onset at birth died in the first year of life and 2/3 adult onset patients died four years and seven years after onset, respectively.

CLINICOPATHOLOGICAL CORRELATES

To date, no histological means of distinguishing between the various forms of nemaline myopathy has been found. Shimomura and Nonaka[54] performed comparative muscle histochemistry in the severe neonatal (n=6), moderate congenital (n=13), and adult onset (n=3) forms of nemaline myopathy. Although the number of rods appeared to increase with age, there was no correlation between the number of rods and the severity or age of onset of the myopathy.

Wallgren-Pettersson et al[48] performed repeat biopsies in 13 patients with the moderate childhood form of nemaline myopathy (time of follow up biopsy five to 18 years after the first biopsy); 10/12 patients (for whom clinical data were available) had become weaker with time. Type I fibre predominance (>55%) was evident in 12/13 follow up biopsies and eight patients had exclusively type I fibres. Type I fibres were small and numerous; type II fibres, where present, were large. Compared to earlier biopsies, the following changes were noted at follow up: there was an increase in mean fibre diameter, a decrease in the number of type II fibres, and an increase in number of nemaline bodies. Again, there was no correlation be-

tween the number of rods and the severity of disease. Fibrosis was evident in some biopsies, suggestive of a continuing pathological process, but there was no evidence of necrosis or regeneration. In two patients, fibre type distribution was normal, raising the possibility that these represent a genetically distinct form of nemaline myopathy.

IMMUNOCYTOCHEMISTRY

α-actinin is the main constituent of the nemaline bodies (fig 5); rods also contain actin and are surrounded by an outer layer of desmin.[62][63] α-actinin-2 is present in rods in all fibres, but the other skeletal muscle isoform α-actinin-3, which is specific for type II fibres, is only present in rods in type II muscle fibres (North and Beggs, unpublished observations). Although rods contain actin and may contain tropomyosin, staining with antibodies to these proteins did not show any increase in fluorescence at the site of rods.[62] Yamaguchi et al[60] suggested that the antibodies to these proteins do not sufficiently penetrate the electron dense material (presumably α-actinin).

Sewry and Dubowitz[39] found that rods were negative for titin (Novocastra) and nebulin (Sigma) but otherwise staining with antibodies to these proteins showed no difference between control muscle and muscle from patients with nemaline myopathy. Desmin (Amersham) was not present in rods but staining with an antibody to this protein showed disruption of myofibrillar pattern. Expression of the sarcolemmal proteins dystrophin, dystroglycan, and the extracellular matrix protein α2-laminin was normal. Fibre type I predominance in nemaline myopathy was associated with abnormally high expression of fetal myosin (usually not expressed after 6 months of age) and coexpression of fast and slow myosin in some muscle fibres.

Pathological studies of other tissues

Involvement of cardiac muscle is unusual in nemaline myopathy.[9][78][79] In the majority of necropsy studies, nemaline bodies are not present in heart muscle.[49][58][59][80-85] However, one case of congenital nemaline myopathy, with onset of cardiac symptoms in childhood, had dilated cardiomyopathy with nemaline bodies verified histologically.[9] In two atypical cases, rods have been observed in both the diaphragm and cardiac muscle[86] and there are also reports of cases with cardiac involvement but no muscle weakness.[16][87]

The central nervous system appears normal in necropsy studies of congenital nemaline myopathy. Two studies have identified a decrease in size or number of motor neurones in the spinal cord but it is not known whether this represents a primary or secondary phenomenon.[49][50] There is no evidence for abnormalities of smooth muscle[88] or of the contractile elements (especially actin and α-actinin) in non-muscle cells, for example, fibroblasts, axons, Schwann cells, and white blood cells.[89]

Inheritance

Nemaline myopathy is genetically heterogeneous with both autosomal dominant (MIM *161800[90]) and autosomal recessive (MIM *256030[90]) forms now identified. In a review by Kondo and Yuasa,[91] it was concluded that nemaline myopathy was an autosomal dominant condition with reduced penetrance, but reanalysis of the 44 pedigrees included in the review indicated that most of them were compatible with a recessive mode of inheritance.[92] There have been further reports of familial cases with probable autosomal recessive inheritance.[54][92-95] A segregation analysis performed on a further 46 families presented at the ENMC Workshop on Nemaline Myopathy in The Netherlands (2-4 February 1996) and analysed by Alan Emery gave a segregation ratio of p=0.23 ± 0.05, consistent with autosomal recessive inheritance. Moreover, the high proportion (5/43) of consanguinity among parents of patients with congenital nemaline myopathy also supports a recessive mode of inheritance.[96] Only one pedigree with histologically verified male to male transmission of nemaline myopathy has been described,[7] although a number of reported families are clearly compatible with autosomal dominant inheritance.[18][80][97] The proportion of new mutations and the incidence of germline mosaicism is as yet uncertain.

The autosomal dominant and autosomal recessive forms are clinically and histologically similar, although the family reported by Laing et al[7] had onset of muscle weakness in childhood, rather than the congenital onset seen in many families with verified autosomal recessive inheritance. It remains to be determined whether adult onset cases represent a uniform disease entity, and whether they are genetic in origin.

When only one person in a family is affected by nemaline myopathy, determining the mode of inheritance can be a problem. Clinical evaluation of both parents is necessary to rule out minor muscle weakness. Muscle biopsy of parents may be useful, but interpretation of abnormal findings can be difficult. In some families both clinically healthy parents have shown abnormalities on muscle biopsy, suggesting a manifesting heterozygote state for a recessive gene.[18][92] This means that if only one parent undergoes muscle biopsy and shows abnormalities, these are not in themselves definite proof of the person manifesting a dominant gene. If one parent shows overt disease clinically and typical histological abnormalities on muscle biopsy, while the other parent is healthy and shows normal findings on muscle biopsy, the likely mode of inheritance is autosomal dominant. If both parents are clinically healthy and show no abnormality on muscle biopsy, dominant transmission from one of the parents is unlikely, leaving the possibility of a new dominant mutation (the proportion of which remains to be determined) in the child, germline mosaicism in one of the parents (the role of which has also yet to be determined), or recessive inheritance with a 25% recurrence risk. As the molecular genetics

of the disorder are clarified (see below), some of these diagnostic issues may be resolved.

Molecular genetics

To date, two genetic loci for nemaline myopathy have been identified. Laing *et al*[7] found linkage to chromosome 1 (NEM1 at 1q22-q23) in the large Australian kindred with childhood onset autosomal dominant nemaline myopathy. Wallgren-Pettersson and *et al*[8] subsequently discovered the locus for a congenital onset autosomal recessive form of nemaline myopathy (NEM2 at 2q21.2-2q22) using samples from seven European multiplex families. A candidate gene in this region is the gene for the thin filament protein nebulin. The autosomal recessive form of the disease may be genetically heterogeneous and other loci may be found. Laing *et al*[9] have recently identified α-tropomyosin$_{SLOW}$ (TPM3) as the disease gene on chromosome 1 causing an autosomal dominant form of nemaline myopathy. α-tropomyosin is a component of thin filaments of the sarcomere; the two muscle specific isoforms (α-Tm$_{SLOW}$ and α-Tm$_{FAST}$, depending on the muscle fibre type, and β-Tm) form an α-helical dimer, bind head to tail, and lie in the major groove of filamentous actin with each tropomyosin molecule binding to seven actin molecules. The mutation described in TPM3 is a point mutation (Met9Arg) close to the N-terminal end of the protein. This region may be important for assembly of dimers and actin binding. It is not yet known how the mutation in TPM3 results in rod formation or muscle weakness. Interestingly α-tropomyosin$_{SLOW}$ is specific for type I (slow) fibres and nemaline bodies in patients with the TPM3 mutation occur preferentially in type I fibres (K N North, unpublished observations).

The TPM3 gene has been screened for mutations in 45 other nemaline myopathy patients and a mutation has been identified in one additional case, in which inheritance appears to be autosomal recessive (N G Laing, unpublished observations). The other three human tropomyosin genes, TPM1 at 15q22,[100] TPM2 at 9p13,[101] and TPM4 at 19p13.1,[102] must all be considered as candidate genes for other forms of nemaline myopathy. However, the majority of the recessive cases of nemaline myopathy studied to date appear to localise to chromosome 2q (see above), thus excluding the tropomyosin genes. In one family not showing evidence of linkage to chromosome 2q, linkage to TPM1 and TPM2 has been ruled out, but definite exclusion of TPM3 and TPM4 is not currently possible as their localisation on the genetic maps remains imprecise (C Wallgren-Pettersson, unpublished observations). TPM1 mutations have been identified in patients with familial hypertrophic cardiomyopathy,[103 104] indicating that mutations in other tropomyosin genes may produce a completely different phenotype.

Management

No curative treatment is currently available for the congenital myopathies. However, a multidisciplinary approach to management can offer much to the individual patient in terms of quality of life (reviewed in Wallgren-Pettersson and Clarke[14]). The main factors influencing prognosis seem to be respiratory capacity and the development of scoliosis[12 40 41]; the monitoring of respiratory function and of the spine are essential elements in the ongoing care of these patients.

The need for intermittent or permanent use of a mechanical ventilator should be evaluated at an early stage because of the risk of insidious nocturnal hypoxia and sudden respiratory failure.[41 105] Follow up care should include the assessment of cardiac status because of the risk of cardiomyopathy or cor pulmonale[41] and involvement, as needed, of physiotherapy, speech therapy, and orthopaedics. Malignant hyperthermia has not been clearly associated with nemaline myopathy, although one report describes three children with nemaline myopathy in whom the heart rate decreased during induction of anaesthesia for cardiac surgery, and body temperature increased during or after surgery.[106] If surgery is planned, the anaesthetist should be aware of the patient's diagnosis.[107 108]

Future prospects

The pathogenesis of nemaline myopathy, in terms of the clinical and histopathological phenotype, is not well understood. Questions arise in three main areas. (1) What is the mechanism of rod formation in nemaline myopathy? (2) What is the mechanism of suggested type I fibre predominance in nemaline myopathy? Is progressive type I fibre predominance part of the primary disease process or a compensatory mechanism? (3) What is the mechanism of weakness in nemaline myopathy apart from type I predominance, and what factors influence the severity of phenotype (age of onset, rate of progression, and severity of muscle weakness)?

The identification of two genetic loci for nemaline myopathy, and the recent identification of a mutation in α-tropomyosin$_{SLOW}$ in childhood onset nemaline myopathy are the first steps towards understanding the pathogenesis of this disorder.

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