EDITORIAL

Distal myopathies: clinical and molecular diagnosis and classification

The distal myopathies are a clinically and pathologically heterogeneous group of genetic disorders in which the distal muscles of the upper or lower limbs are selectively or disproportionately affected. Although there is some uncertainty as to the actual diagnosis, the first case description of distal myopathy is usually attributed to Gowers in 1902.¹ However, it was not until the landmark publication by Welander in 1951² describing a large cohort of patients with a dominantly transmitted late onset familial form of distal myopathy in Sweden, that this group of disorders became firmly established. Other dominant and recessive forms with distinctive clinical phenotypes and muscle pathology have since been recognised, particularly in Finland and Japan.³⁻⁶ Linkage to chromosome 14q11 was first reported in an Australian family with early onset autosomal dominant distal myopathy in 1995⁷ and genetic linkage has since also been described in the other five major forms of distal myopathy⁸⁻¹¹ (table 1). To date, the responsible gene has been identified in only one of these (Miyoshi myopathy), in which mutations have been found in the dysferlin gene at chromosome 2p12-14.¹³

Comparison of the different forms of distal myopathy has shown considerable phenotypic variability, both in terms of the age at which symptoms first develop and the pattern of differential involvement of the limb muscles and of other muscle groups such as those of the neck and face. Moreover, it has been recognised that similar phenotypes

may result from different genetic defects and conversely, that certain defects such as the dysferlin gene mutations may be associated with different clinical phenotypes including one form of limb girdle muscular dystrophy (LGMD2B).^{12 13} At the histological level, several of the distal myopathies are characterised by the presence of rimmed vacuoles and tubulofilamentous inclusions and therefore also fall within the range of inclusion body myopathies.^{4 10 14}

Although the diagnosis in an individual patient from a family with a well established form of distal myopathy may be relatively straightforward, the diagnostic classification of apparently sporadic cases¹⁵ or of undiagnosed familial cases with a distal pattern of muscle weakness presents a challenge to the clinician.

Classification

The distal myopathies may be classified in several ways.^{11 16 17} A classification based on the mode of inheritance and clinical syndrome is shown in table 1. They have also been classified on the basis of the age at onset into early and late onset forms (figure). A further basis for classification is with reference to the muscle groups which are most severely affected—for example, cases with onset in the hands versus onset in the legs; cases involving the anterior tibial versus the posterior calf muscles; cases with additional involvement of the ocular and pharyngeal muscles (oculopharyngodistal myopathy). Lastly, as shown in

Table 1 Classification and distinguishing features of the major forms of distal myopathies

	<i>Nonaka</i>	<i>Miyoshi</i>	<i>Laing</i>	<i>Welander</i>	<i>Finnish (Udd)</i>	<i>Markesbery-Griggs</i>
Inheritance	AR/sporadic	AR/sporadic	AD	AD	AD	AD
Gene loci	9p1-q1	2p12-14	14q11	2p13	2q31-33	2q31-33
Age at onset (y)	20-30	15-30	4-25	>40	>35	25-50
Site of onset	Legs	Legs	Legs	Hands	Legs	Legs
Leg compartment	Anterior > posterior	Posterior	Anterior	Anterior	Anterior	Anterior
Proximal weakness	+ (late)	+ (late)*	+	+†	+ (late)‡	+ (late)
Neck weakness	+	+ (late)	+	+	+	+
Serum creatine kinase	<X5 N	X10-100 N	<X3 N	N or mild ↑	N or mild ↑	X2-5 N
EMG:						
Myopathic	+	+	+	+	+	+
Spontaneous activity	+	+	+	+	+	+
Biopsy:						
RVs and TFIs	+	-	-	+	+	?
Fibre necrosis	-	+	+	-	+	+

*Allelic with LGMD2B.

†Some families.

‡Limb girdle phenotype in some individuals.

RVs=Rimmed vacuoles, TFIs=tubulofilamentous inclusions, AR=autosomal recessive, AD=autosomal dominant, N= normal.

Algorithm for the diagnosis and classification of the distal myopathies.

table 1, a classification based on the gene locus is now also possible for all of the major forms of distal myopathy. The classification of cases with a distal or scapuloperoneal pattern of muscle involvement and desmin accumulation in muscle fibres¹⁸⁻²⁰ and of unusual cases with mitochondrial abnormalities²¹⁻²² remains uncertain.

Clinical aspects

The age at which symptoms first develop, whether the onset is in the upper or lower limbs, and the pattern of muscle involvement provide clues to the diagnostic category into which an individual patient or family falls. In the recessive varieties (Nonaka and Miyoshi myopathies), symptoms usually develop in early adult life whereas in the dominant Scandinavian and Markesbery-Griggs varieties the onset is usually later.¹¹ However, in some dominant families (for example, Laing myopathy) the onset may be during childhood, and even in infancy,²³ but may be variable even within the same family.⁷ Whether or not all such early onset cases are of this type remains unclear. With the exception of the Welander variety, in which the muscles of the hands are affected first, and involvement of the lower limb muscles only occurs at a later stage,²⁻¹⁴ in most of the other forms the leg muscles are affected first. Weakness of the forearm and hand muscles usually develops subsequently, but in the Finnish form (Udd myopathy) the condition usually remains confined to the lower limbs.¹⁰ The other distinction, which is helpful clinically in cases with lower limb onset, is between those forms in which there is selective involvement of the anterior tibial muscles (tibial myopathies), as occurs in the Nonaka, Laing, Udd,

and Markesbery-Griggs forms, and the Miyoshi form in which the posterior calf muscles are usually more severely affected.

Proximal muscle involvement also occurs in some forms of distal myopathy, particularly in Miyoshi myopathy in which the glutei and biceps brachii are commonly affected.⁵⁻²⁴ More generalised and severe involvement of the limb muscles may occur in the later stages of both the Miyoshi and Nonaka recessive forms and the patient may become wheelchair dependent.²⁴⁻²⁵ In the Laing myopathy there is selective involvement of some proximal muscle groups such as the hip abductors and adductors, iliopsoas, and hamstrings in the lower limbs and the infraspinatus and supraspinatus in the upper limbs, and mild weakness of these muscles may be detected as early as the second decade of life.⁷ Weakness and atrophy of the sternomastoid muscles also occur in this form of myopathy and in the Nonaka and Miyoshi myopathies⁴⁻⁵ (table 1). In the Laing myopathy, there is also mild weakness of the facial muscles.⁷

In oculopharyngodistal myopathy (Satoyoshi myopathy) both recessive²⁶ and dominant inheritance²⁷ has been reported. The onset is usually in the 30s or 40s, with involvement of the anterior tibial or forearm muscles, followed by the development of progressive ptosis, external ophthalmoplegia, and dysphagia, although in some of the dominant cases the extraocular muscles were affected first. In dominant cases with an oculobulbar onset the clinical phenotype may closely resemble that of oculopharyngeal muscular dystrophy.²⁷ The relation between the two conditions remains unclear as distal limb muscle involvement is also known to occur in some cases of

Table 2 Differential diagnosis of distal myopathies

Neurogenic:
HMSN II (CMT-2)
Distal SMA
Scapuloperoneal syndrome
Myopathic:
Myotonic dystrophy
Facioscapulohumeral dystrophy
Desminopathy
Mitochondrial myopathy
Congenital myopathies
Glycogen storage disease
Inclusion body myositis

oculopharyngeal muscular dystrophy, although it is unusual.²⁸

Although there have been reports of sporadic cases of distal myopathy with cardiac involvement, and one of the patients originally described by Markesbery *et al*³ had an associated cardiomyopathy, this is not a consistent feature of any of the major forms of distal myopathy. Cardiomyopathy has, however, been reported in some cases of oculopharyngodistal myopathy²⁹ and has been a frequent finding in some families with autosomal dominant distal myopathy with desmin storage,¹⁹ although not in others.²⁰

Investigation

Investigations in patients with a clinical picture suggestive of a distal myopathy should be directed firstly towards confirming the presence of an underlying myopathic process and excluding a primary neurogenic disorder such as a motor neuropathy or neuronopathy or other more specific forms of myopathy (table 2), and then to define the particular form of distal myopathy.

CREATINE KINASE

The serum creatine kinase concentration may be helpful if it is increased but it may be normal or only mildly raised in some forms of distal myopathy (table 1). The highest concentrations are found in the Miyoshi form in which up to 100-fold increases may occur.⁵ Creatine kinase concentrations of up to five times the normal upper limit have been reported in the Nonaka and Markesbery-Griggs varieties.^{3, 4}

ELECTROMYOGRAPHY

Electromyographic studies will allow confirmation of a primary myopathic disorder and exclusion of a myotonic disorder and of neurogenic conditions such as motor neuropathies and neuronopathies. Needle examination shows the characteristic early recruiting, low amplitude, short duration motor unit potentials, especially in the most severely affected muscles, but also in muscles which may be normal clinically, indicating the diffuse nature of the myopathic process. Spontaneous activity such as fibrillation potentials and positive waves may be found in any of the forms of distal myopathy and may be prominent especially in the more severely affected muscles.¹⁵ These findings may be related to functional denervation of muscle fibres undergoing segmental necrosis or degeneration (myogenic denervation). The finding of increased jitter and blocking and increased fibre density in some cases of Laing myopathy (FL Mastaglia, unpublished observations) is also compatible with a process of denervation and reinnervation of muscle fibres as a result of terminal sprouting of motor axons³⁰ with resulting remodelling of the motor unit architecture, as occurs in other forms of muscular dystrophy.³¹ However, the possibility that in some forms of distal myopathy there is primary involvement of motor nerve terminals cannot be excluded, particularly in the Welander

form in which changes in sensory and autonomic nerve function and a reduction in myelinated fibre numbers in the sural nerve have been found.¹⁴

MUSCLE BIOPSY

A biopsy is indicated in sporadic or familial cases in which the diagnosis has not been established and will allow exclusion of other myopathies with distinctive histological changes such as mitochondrial myopathy, glycogen, lipid, or desmin storage myopathies, congenital myopathies such as nemaline, or core myopathies and inclusion body myositis, as well as chronic neurogenic disorders (table 2).

The distal myopathies fall broadly into two groups in terms of histological changes: firstly, those in which the major changes comprise muscle fibre necrosis and regeneration with dystrophic changes of variable degree, as in the Miyoshi and Markesbery-Griggs varieties^{3, 5}; and secondly, those characterised by the presence in muscle fibres of rimmed vacuoles and tubulo-filamentous inclusions of the type found in inclusion body myositis and the hereditary inclusion body myopathies. The latter findings were first recognised as the histological hallmark of the autosomal recessive Japanese form of distal myopathy (Nonaka)^{4, 32} but have since also been found in the Scandinavian forms^{10, 14} but not to date in the Laing myopathy.⁷ Rimmed vacuoles and 16–18 nm filamentous inclusions have also been reported in cases of recessive oculopharyngodistal myopathy but the 8.5 nm intranuclear inclusions which are characteristically found in oculopharyngeal muscular dystrophy were not present in these cases.³³

Rimmed vacuoles are more likely to be found in clinically affected distal limb muscles, such as the anterior tibial muscles, and may be absent in proximal muscles such as the vastus lateralis. The most appropriate muscle to biopsy is therefore one of the calf or forearm extensor muscles, provided that it is not too severely atrophied, in which case the biopsy may show little or no residual muscle tissue and may be inconclusive. Magnetic resonance imaging or CT has, in our experience, been useful in assessing the degree of involvement of the calf and forearm muscles and may be helpful in selecting a muscle for biopsy. If the distal muscles are too severely affected, it is preferable to biopsy a proximal muscle such as the vastus lateralis, rectus femoris, or biceps brachii

MOLECULAR GENETIC STUDIES

Linkage studies

Since 1995, genes for each of the six major recognised forms of the distal myopathies have been localised in the human genome (table 1). These include childhood onset distal myopathy (MPD1) to 14q,⁷ Miyoshi myopathy to 2p12–14,⁸ Nonaka myopathy (distal myopathy with rimmed vacuoles) to 9p1–q1,⁹ tibial muscular dystrophy (Udd myopathy) to 2q31,³⁴ and Welander distal myopathy to 2p13.³⁵ In addition, the Markesbery-Griggs distal myopathy has been mapped to the same locus as the Udd tibial muscular dystrophy^{36, 37} and thus the two disorders are probably allelic with the obvious candidate gene in the linkage region being the gene for the giant muscle protein titin.³⁴ Nonaka myopathy is linked⁹ to a similar region of chromosome 9 as hereditary inclusion body myopathy with quadriceps sparing (hIBM)³⁸ and these two disorders are therefore probably also allelic. The loci for Welander and Miyoshi myopathy are very close and these two conditions may also be allelic despite their very different clinical and pathological phenotypes. Genetic heterogeneity has been established for the Miyoshi myopathy phenotype.³⁹ Linssen *et al*³⁹ showed that some families with a Miyoshi phenotype did not show linkage to the known chromosome 2 gene region. They demonstrated probable linkage to a 23 cM

region on chromosome 10 between the markers D10S189 and D10S1423 in two of these families. However, the linkage was not significant (LOD 2.57) because of the small size of the families. The authors also suggested that there may be a third locus for the Miyoshi phenotype, as one of their four families did not show linkage to either the chromosome 2 or chromosome 10 loci.³⁹

There have been no published linkage studies in families with oculopharyngodistal myopathy. However, linkage to 5q31 has recently been demonstrated in a family with dominantly transmitted distal myopathy associated with vocal cord and pharyngeal weakness but without involvement of the ocular muscles.⁴⁰

There remain some distal myopathy families which are not linked to any of the known loci.⁴¹ The obvious relation between the distal myopathies and hereditary inclusion body myopathies (hIBM) means that all loci identified for hIBM should also be screened for linkage in distal myopathy families which do not show linkage to the other known loci. Some of these hIBM loci may seem unlikely candidates—for example, the recently described locus for autosomal dominant myopathy with congenital joint contractures, ophthalmoplegia, and rimmed vacuoles⁴²—as the clinical picture, which includes proximal weakness, is so different from the classic distal myopathies. However, the pleiotropic nature of the dysferlin phenotype and the chromosome 2q (Udd/Markesbery/Griggs) phenotype would suggest that multiple phenotypes may also be associated with other distal myopathy/hIBM loci.

As the responsible genes have yet to be identified in most of the distal myopathies, only linkage studies for the known dominant and recessive distal myopathy loci are at present possible for these conditions in new families. Significant linkage requires a reasonably large number of affected members in dominant and recessive families: greater than 10 for “an affecteds only” analysis in dominant disease, and single families segregating recessive disease are unlikely to produce a significant LOD score unless there is considerable consanguinity. Therefore, it is likely that most individual families will not be large enough to generate a significant LOD score and it will only be possible to show that linkage is compatible with the clinically diagnosed disease in most families.

Mutation analysis

At present, only the dysferlin gene can be screened for mutations. However, before embarking on mutation analysis in any patient with a Miyoshi phenotype the identified genetic heterogeneity in Miyoshi myopathy³⁹ would mandate linkage analysis for the chromosome 2p dysferlin locus. The dysferlin gene is large, consisting of 55 exons, a cDNA of 6.9 kb, and mutations are distributed along the length of the cDNA, with no apparent hotspots of mutation as yet identified.^{12–13} Although all cases associated with mutations of the dysferlin gene show raised creatine kinase concentrations, the clinical phenotypes are highly variable. Mostly there is predominant calf weakness but in some cases the anterior tibial muscles are more severely affected. In view of this variability in phenotype, it may be reasonable to screen all patients with a high creatine kinase concentration for dysferlin gene mutations irrespective of the distal myopathy phenotype.

The mutated gene responsible for the Laing myopathy has yet to be identified. Although the linkage region on 14q11.2-q13 is known to include the oculopharyngeal dystrophy locus, neither the triplet repeat expansion in the PABP2 gene which is associated with oculopharyngeal dystrophy⁴³ nor a point mutation in the gene have been identified in Laing myopathy (NG Laing, unpublished observations). Similarly, mutations have not been found in

the PAB2 gene in Japanese cases of oculopharyngodistal myopathy (I Nonaka, unpublished observations).

Ultimately, as has occurred in the limb girdle dystrophies,⁴⁴ once the responsible genes are identified molecular diagnosis of the distal myopathies should be greatly aided by immunohistochemical studies using antibodies to the gene products.

Future studies

The distribution of affected muscles is very similar in the Laing and Udd/Markesbery/Griggs myopathies despite the difference in age of onset. It will be interesting to see in the future whether the proteins mutated in these and the other distal myopathies interact, just as so many of the proteins mutated or missing in the muscular dystrophies interact.⁴⁵ Two-hybrid studies using dysferlin may help identify other distal myopathy genes if this is so.

Conclusions

Since the first report by Gowers, it has become apparent that the distal myopathies are a genetically and phenotypically diverse group of disorders which are more prevalent in certain racial groups. The classification of these disorders has been greatly aided during the past 5 years by the application of modern molecular genetic techniques which have disclosed a degree of genetic heterogeneity comparable to that which has been found in the limb-girdle dystrophies and have led to the recognition of an overlap between these two groups of myopathies. It has also been recognised that the distal myopathies are pathologically diverse and that some varieties overlap the hereditary inclusion body myopathies.

It seems likely that the genes causing disease will be identified in all of the major forms of distal myopathy in the foreseeable future and that once their products are identified these disorders will be classified on a molecular basis in the same way as the dystrophinopathies and sarcoglycanopathies. Moreover, once the molecular defects have been identified, it will then be possible, through the use of transgenic animal models and transfected cell lines, to investigate the ways in which the normal structure and function of the muscle fibre is deranged and the mechanisms leading to necrosis or to the formation of rimmed vacuoles and tubulofilamentous inclusions. In addition, identification of the underlying molecular defects and mechanisms of muscle fibre damage will bring gene replacement or other therapeutic interventions within the realms of possibility.

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EDITORIAL COMMENTARY

Vigabatrin associated visual field constriction

Peripheral visual field defects in patients taking vigabatrin seem to arise in a proportion of patients. Typically a concentric narrowing of the field is seen with preservation of central acuity and colour vision. Case definition remains poorly defined and prevalence figures ranging from as low as 0.14% to as high as 39% have appeared.^{1,2} The high figures reported by Lawden *et al.*, this issue, pp 716–722,³ reflect a definition which includes any bilateral field defect that could not be explained in terms of other retinal or neurological pathology regardless of severity of symptomatology. This clearly highlights the problem but leaves more work to be done.

Visual field testing alone does not give any insights into pathogenesis as both cortical and retinal effects could cause the same result. The ocular examination is usually normal, although optic disc pallor is sometimes seen. However subtle electrophysiological abnormalities which include electro-oculogram light rise reductions, loss of oscillatory potentials on the Ganzfeld electroretinogram

and focal ERG changes do point to a retinal origin of the visual loss.⁴ The inhibitory neurotransmitter GABA is found in retinal ganglion and amacrine cells and it is a plausible hypothesis that anticonvulsants which irreversibly inhibit GABA amino-transferase such as vigabatrin will impair retinal function.

The natural history of this effect is a concern. In an audit from our own department we found five cases with major field defects (no responses to the Goldmann 1/4e isopter outside 25 degrees nasally and 40 degrees temporally) and in only three of these did the visual field improve after withdrawal or reduction of the medication. This seems to be consistent with anecdotal reports elsewhere.

It has been suggested that epileptic patients taking other anticonvulsant drugs might show similar field abnormalities if they were tested in the same way. Lawden *et al.* have dispelled this by showing that 16 controls taking a range of other anticonvulsant drugs all had normal fields.

Prescribers and patients now face a range of practical difficulties. Firstly, there are patients whose seizure control is good enough for them to apply for a driving licence, but whose visual fields may disqualify them. Then there are other patients who have mild field defects of no great clinical relevance. They need simple reassurance that there is no reason to change their medication on visual grounds. A further group are young children and adults of cognitive age of less than 9 years who cannot reliably perform perimetry testing. Prescribers should beware false positive field abnormalities and appreciate the overall limitations of perimetry here.⁵ Unfortunately standard clinical electrophysiology on its own will not provide an alternative in practice as both electro-oculography and electroretinography performed to the reliability standards of the International Society for the Electrophysiology of Vision are not widely available. Cognitively impaired people in whom there are no occupational consequences from having reduced fields may not be helped by referrals to ophthalmology clinics to diagnose field defects which are too subtle to detect by simple confrontation techniques,

especially when the benefits of good seizure control may outweigh the risks of mild field loss. Clinical guidelines for the visual assessment of these patients will need to be developed jointly by neurologists and ophthalmologists according to local circumstances. In the meantime, more data on the prevalence of both mild and severe field defects and on the natural history will be helpful.

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EDITORIAL COMMENTARY

Axonal loss and demyelination in multiple sclerosis

In the paper by Davie *et al* in this issue (pp 710–715),¹ proton magnetic resonance spectroscopy and magnetisation transfer imaging were combined in a study of 18 patients with multiple sclerosis to determine whether the axonal loss in lesions of multiple sclerosis is correlated with the extent of demyelination.

Axonal damage is now often discussed as a likely cause of chronic disability in multiple sclerosis.^{2,3} But what is the cause of the axonal damage itself? It is tempting to speculate that it arises from injury secondary to a primary inflammatory response against myelin, but axonal injury in primary progressive multiple sclerosis occurs with relatively little demyelination. There is considerable heterogeneity of pathology in multiple sclerosis.⁴ It is possible that different mechanisms predominate in different patients (or perhaps at different stages of the disease). Central to understanding mechanisms of damage is to understand whether axonal damage occurs in parallel with demyelination.

Magnetic resonance imaging can be used as a non-invasive probe of the pathology of multiple sclerosis as well as a clinical diagnostic tool. Although conventional MRI is relatively non-specific in the pathological information provided, newer techniques provide more specific information. Magnetisation transfer (MT) imaging generates contrast dependent on the association of brain water with macromolecular proteins particularly in myelin.⁴ It is a sensitive marker of demyelination in animal models. One useful contribution of Davie *et al*¹ is to give evidence that this is true in humans as well with the demonstration that

reversible MT ratio changes occur with the reversible demyelinating pathology associated with central pontine myelinolysis.

Magnetic resonance spectroscopy allows measurement of relative concentrations of the acetylated amino acid N-acetylaspartate (NAA), a marker of axonal density and integrity in the brain.² Davie *et al* demonstrate that there is a significant correlation between the reduction in MT ratio and the reduction in NAA in the lesions of multiple sclerosis, particularly in patients with secondary progressive disease. This suggests a tight coupling between damage to myelin and damage to axons. The particularly strong correlation in patients with secondary progressive disease may be a consequence of the larger magnitude of changes in both perimeters in these patients rather than there being a fundamentally different mechanism in the operating in the patients with relapsing-remitting disease, although this cannot be clearly demonstrated with the data available. It is tempting to speculate that the extent of loss of NAA per unit change in the normalised MT ratio might be used to define the severity of damage in lesions and could be clinically predictive of progression of disease.

Although the authors are rightly cautious in suggesting that their data allow strong inferences to be made regarding the mechanism of damage to axons, the results are consistent with the coupling of axonal injury and demyelination. Longitudinal studies of new lesions could provide more direct information relevant to the question of mechanism by defining the relative time course of

changes. In emphasising the potential usefulness of integrating data from multiple new imaging methods to describe pathology of multiple sclerosis, Davie *et al* point the way forward for a whole new phase of imaging research in multiple sclerosis.

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- 5 McGowan JC, Filippi M, Campi A, *et al*. Magnetisation transfer imaging: theory and application to multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1998;**64**(suppl 1):S66–9.