PAPER

Laing early onset distal myopathy: slow myosin defect with variable abnormalities on muscle biopsy

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Background: Laing early onset distal myopathy (MPD1) is an autosomal dominant myopathy caused by mutations within the slow skeletal muscle fibre myosin heavy chain gene, *MYH7*. It is allelic with myosin storage myopathy, with the commonest form of familial hypertrophic cardiomyopathy, and with one form of dilated cardiomyopathy. However, the clinical picture of MPD1 is distinct from these three conditions.
Objective: To collate and discuss the histological features reported in the muscle biopsies of MPD1 patients and to outline the clinical features.
Results: The phenotype of MPD1 was consistent, with initial weakness of great toe/ankle dorsiflexion, and later development of weakness of finger extension and neck flexion. Age of onset was the only variable, being from birth up to the 20s, but progression was always very slow. The pathological features were variable. In this retrospective series, there were no pathognomonic diagnostic features, although atrophic type I fibres were found in half the families. Rimmed vacuoles are consistently seen in all other distal myopathies with the exception of Myoshi distal myopathy. However, they were found in a minority of patients with MPD1, and were not prominent when present. Immunohistochemical staining for slow and fast myosin showed co-expression of slow and fast myosin in some type I fibres, possibly indicating a switch to type II status. This may be a useful aid to diagnosis.
Conclusions: The pathological findings in MPD1 are variable and appear to be affected by factors such as the specific muscle biopsied, the age of the patient at biopsy, and the duration of disease manifestations.

It was recently demonstrated that the cause of Laing early onset distal myopathy (MPD1) was mutations within the c-terminal part of slow skeletal muscle fibre myosin heavy chain gene (*MYH7*).[1] Analysis of these patients reveals that, with the exception of age of onset, the clinical features are relatively consistent. It is an autosomal dominant myopathy with a recognisable pattern of muscle weakness and atrophy, emerging in a reliable sequence. However, muscle morphology can be extremely variable, even within a single family.[2] The purpose of this paper is to collate and discuss the pleomorphic histological features reported in the muscle biopsies of MPD1 patients, as well as outlining the clinical features.

METHODS

The clinical features of all 34 patients were summarised, both by reference to original reports, and also updates from ongoing clinical follow up.

The methods used to obtain and process the muscle biopsies were outlined in the original reports in families 1 to 5.[2–6] In family 6, the muscle biopsy was taken from the proband at the age of 32 years from the vastus lateralis muscle. The NCL-SPEC1 antibody (Novocastra, Newcastle upon Tyne, UK) was used against β-spectrin, employing the indirect horseradish peroxidase technique. The unfixed cryostat section was preincubated with TENG-T (10 mM Tris, 5 mM EDTA, 150 mM NaCl, 0.25% gelatin, 0.05% Tween-20, pH = 8.0) for 30 minutes to reduce non-specific binding. Upon incubation of the pretreated tissue section with the primary antibody the subsequent detection involved binding with a peroxidase conjugated second antibody (rabbit anti-mouse Ig, Dako P260, Glostrup, Denmark). Sera were diluted in phosphate buffered saline (PBS). All incubations were followed by three washes in PBS for five minutes. The immunocomplex formation was visualised by incubating the sections in 0.5 mg/ml 3.3 diaminobenzidine, 0.01% hydrogen peroxidase, 30 mM imidazole, 1 mM EDTA (pH = 7.0). Sections were mounted in Entellan (Merck, Germany).

In family 7, the proband had a biopsy of the vastus lateralis muscle carried out at the age of 11 years. Routine processing of the sample and histochemical techniques have been published previously.[7] Immunoperoxidase staining using desmin (Dako M0724) at a dilution of 1:200 was done using the streptavidin-biotin method (Dako LSAB 2 system). Antigen retrieval was in EDTA pH 8 and incubation times were 10 minutes in the primary and 10 minutes in the LSAB. The colour indicator was liquid diaminobenzidine (case III:5) or 3-amino-9-ethyl-carbozide (cases III:1, IV:5). A similar immunoperoxidase technique was used for the muscle proteins, namely, dystrophin (rod domain, C-terminal, and N-terminal), α, β, γ, and δ sarcoglycans, and dysferlin (all from Novocastra), and nebulin M-176 (a gift from S Labeit). Spectrin (Novocastra) was demonstrated as a monitor of sarcolemmal integrity.

The proband of family 8 had the tibialis anterior muscle biopsied at the age of 12 years. The biopsy had serial transverse muscle cryostat sections cut, 6 and 10 μm thick, for immunohistochemical (IHC) and routine histochemical staining, respectively. The 10 μm sections were stained with haematoxylin and eosin (H&E), Gomori's trichrome, and NADH tetrazolium reductase 19. Determination of muscle fibre types 1 (slow) and 2 (fast) was based on enzyme histochemical activity in all muscle samples, and also immunohistochemical methods. A standard myofibrillar ATPase staining protocol was used after preincubation at

Abbreviations: IHC, immunohistochemical; MPD1, Laing early onset distal myopathy

pH 4.3, pH 4.6, and pH 9.4 or 10.4. A Ventana Nexes automated immunostainer (Ventana Medical Systems, Tucson, Arizona, USA) was employed for immunohistochemistry, with the avidin-biotin-complex method followed by DAB detection. Monoclonal primary antibodies against different myosin heavy chain (MHC) isotypes were used at the following dilutions: MHCf 1:400 (Sigma anti-skeletal myosin fast, clone My-32); MHCs 1:5000 (Sigma anti-skeletal myosin slow, clone NOQ7.5.4D); MHCd 1:10 (Novocastra myosin heavy chain developmental, clone RNMy2/9D2).

RESULTS

Clinical phenotype

The clinical phenotypes are detailed in table 1. The age of onset of weakness varied. In some families, onset was so early as to delay walking, but in other cases symptoms were not evident until the late teens to late 20s. The initial symptom in all patients was weakness of great toe and ankle dorsiflexion, leading to a high stepping gait, and secondary tightening of the tendo achilles (fig 1).

Weakness of finger extensors usually followed, within months to years (fig 2). This was often accompanied by a tremor of the hands, both postural and action related. Mild involvement of the face occurred, with weakness of orbicularis oculi and orbicularis oris. In all families, patients developed definite weakness of neck flexion. However, in one family this was not seen until the patients were in their seventh decade of life (Hedera P, personal communication). Computed tomography (CT) or magnetic resonance imaging (MRI) of the neck musculature in families 6 and 8 showed loss of bulk of the sternocleidomastoid muscles, with minimal involvement of other neck flexors, and signal change in the deep paravertebral muscles with some hypertrophy of the other neck extensors. With the passage of time in more severe cases, the axial weakness progressed to involve the truncal muscles, as well as proximal leg muscles. However, overwhelmingly the deterioration in strength was very gradual, over the course of many years. There were no reports of any affected person being confined to a wheelchair.

Echocardiography was undertaken in seven patients, with normal results in five. Two patients (father and son) in family 5 developed a dilated cardiomyopathy, for which no other cause was found.[6] No cardiac abnormalities were reported in the remaining 32 patients. The serum creatine kinase level was often normal, but was occasionally as high as eight times the normal upper limit (table 1).

Nerve conduction studies were reported in all 34 cases, and showed normal nerve conduction velocities. Electromyography (EMG) did not show any large prolonged motor unit potentials to indicate a definite underlying denervation of muscle. Two studies did report fibrillation potentials, often seen in myopathies. Unequivocal pathological evidence of peripheral nerve involvement was seen in one patient in family 4.[5] This patient had a sural nerve biopsy which demonstrated hypomyelination (results below).

Muscle biopsy

The pathology findings are summarised in table 2. Excessive variation in fibre size was seen in all but one biopsy. Two patients in family 5 demonstrated minimal fibre size variability. In four families (1, 2, 7, 8) the type I fibres were abnormally small. One of these families had small type II fibres, as well as type I fibres. The presence of predominance of one fibre type over another was not commented on in three families (3,4,5). In families 1, 7 and 8, type II predominance was observed, and families 2 and 6 there was type I fibre predominance.

Necrotic and regenerating fibres were seen in five of eight families, but they were not prominent. Angulated fibres typical of an underlying neurogenic component were not seen in any of the biopsies, although angulated fibres secondary to regeneration were seen in four families (table 2). The oldest member of family 3 was examined was in the seventh decade of life and had many atrophic changes consistent with age. The muscle appearances were described as ''end stage'', and were accompanied by replacement of the muscles by fat and fibrous tissue. Excessive central nucleation was reported in four of eight families, with Z disc streaming in two and nuclear clumps in three families.

As opposed to myosin storage myopathy (hyaline body myopathy), sarcoplasmic bodies were prominent in only one MPD1 family. Figure 3 illustrates the muscle pathology from family 6. Vacuoles were present, and they were seen in both fibre types. Eosinophilic debris was observed within some of these vacuoles. Immunohistochemically, numerous membrane bound vacuoles were visualised using an antibody to spectrin (fig 3, middle panel). Electron microscopy showed many areas consistent with autophagic vacuoles, with debris and myelin figures (fig 3, bottom panel). In two other families, vacuoles were seen but were not prominent. In family 3, one patient had very occasional sarcoplasmic bodies, positioned laterally. In family 4, the father had some cytoplasmic bodies, but these were not seen in his daughter's biopsy. The tubulofilamentous inclusions seen on electron microscopy were observed in the muscle nuclei as well.[5]

Two families had occasional ''motheaten'' fibres, three families had a minor degree of fibre splitting, three had occasional ''whorled fibres'', four showed occasional ring fibres, but cores were not reported in any of the families. ''Routine'' immunohistochemistry for dystrophin domains, sarcoglycans, dysferlin, laminins, desmin, and spectrin was normal.

Immunohistochemistry for slow and fast myosins was carried out in three patients (families 6, 7, and 8), and was abnormal in all three. In family 6 (fig 4) immunohistochemical staining for fast-skeletal myosin on paraffin sections showed vacuoles in both type I and type II fibres. Some intermediate fibres can be seen suggesting switching of fibre type. In family 7 (fig 5) all atrophic fibres were of type I. As illustrated in fig 6, there were fibres showing co-expression of fast and slow myosins and an intermediate staining at pH 9.5. This may indicate that these fibres are in the process of switching from type I to type II. In family 8 (fig 6), there were almost no normally sized slow myosin fibres, and with only a couple of exceptions, all showed conversion to fast myosin. The muscle biopsied in patient 8 was the tibialis anterior, which usually has type I fibre predominance. However, most fibres, both normal sized and atrophic, expressed both myosin types.

Nerve biopsy

The older member of family 4 had a sural nerve biopsy which showed hypomyelination of large nerve fibres without onion bulb formation.[5] There were no degenerating or demyelinated nerve fibres, and no myelin degradation products at the light microscopic level. At electron microscopic level, empty Schwann cell processes without axons were detected around myelinated fibres, indicating past demyelination and remyelination episodes.

DISCUSSION

The discovery that mutations of the slow skeletal muscle fibre myosin heavy chain gene (*MYH7*) caused MPD1 meant that this disease was allelic with myosin storage myopathy (formally known as hyaline body myopathy)[8] and common forms of both hypertrophic and dilated cardiomyopathy.[19]

Table 1 Clinical characteristics of patients with Laing distal myopathy

	Family							
Feature	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Reference	Laing/Mastaglia, 1995/2002[3 15]	Scoppetta, 1995[2]	Zimprich, 2000[4]	Voit, 2001[5]	Hedera, 2003[6]	de Visser (Meredith, 2004[1])	Lamont (Meredith *et al* 2004[1])	Udd B (unpublished)
Number of affected persons reported	9	3	3	4	12	One – sporadic	One – sporadic	One – sporadic
Age of onset	4-25 years	All late to start walking (18 months)	Mid to late teens	Late to walk, to onset at 18 months	14-34 years	5 years	4 years	Toe walking at 12 months
Site of initial weakness	Toe and ankle dorsiflexion	Toe and ankle dorsiflexion	Toe and ankle dorsiflexion	Toe and ankle dorsiflexion	Toe and ankle dorsiflexion	Toe and ankle dorsiflexion	Toe and ankle dorsiflexion	Toe and ankle dorsiflexion
Later weakness	Finger extensors in most subjects; mild proximal leg weakness in most	Lumbar hyperlordosis	Finger extensors	All leg muscles, finger and wrist extensors,	Proximal leg in 3 of 12	Proximal leg muscles, finger extensors	Finger extensors aged 11 years, proximal limbs	Neck flexors, Scapular and pectoral muscles
Neck flexion weakness	All cases	All cases	Index case only	Index case only (other 3 cases too young)	No	Yes; also neck rigidity	Yes	Yes – severe
Truncal weakness	1 of 9 cases	2 of 3 cases	No	Index case only	No	No	Yes	Yes
Tremor	Not reported	Postural tremor in 2 of 3	Not reported	Postural tremor in all 4 cases	Not reported	Yes	Yes	Mild
''Hanging big toe'' sign	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Drop foot
Facial weakness	Most	All 3 members	No	No	No	No	Yes	Yes
''End stage'' signs	Shoulder girdle weakness	Upper and lower limb girdle weakness	Nil	Gower's manoeuvre	Mild progression, still walking	Weakness hip girdle and upper leg muscles	Still young	Scoliosis surgery, neck, achilles, and elbow contractures
Cardiomyopathy	Nil	Nil	Nil	Nil	One subject developed cardiomegaly aged 32 years	Nil	Nil	Nil
Peripheral neuropathy	Occasional fibrillation potentials on EMG	Nil	Occasional fibrillation potential on EMG	Hypomyelinated neuropathy in one case (sural nerve biopsy)	No, mild myopathic changes on EMG	Normal NCVs; spontaneous muscle fibre activity plus myopathic features in the leg muscles	EMG normal	Normal NCVs and no neurogenic large MUPs on EMG
CK	Raised (216–531; N<180)	Normal	Raised (115–543; N<70)	Elevated in index case only (200–450; N<120)	Normal in 11; (200–400 in one subject (N<70)	Raised (324; N<150)	Normal	Normal during first 15 years, later 3× elevated
MYH7 mutation	c.A1663P	None identified	c.K1617del	c.K1617del	c.K1729del	c.L1706P	c.R1500P	c.K1617del

CK, creatine kinase, EMG, electromyography; N, normal; NCV, nerve conduction velocity.

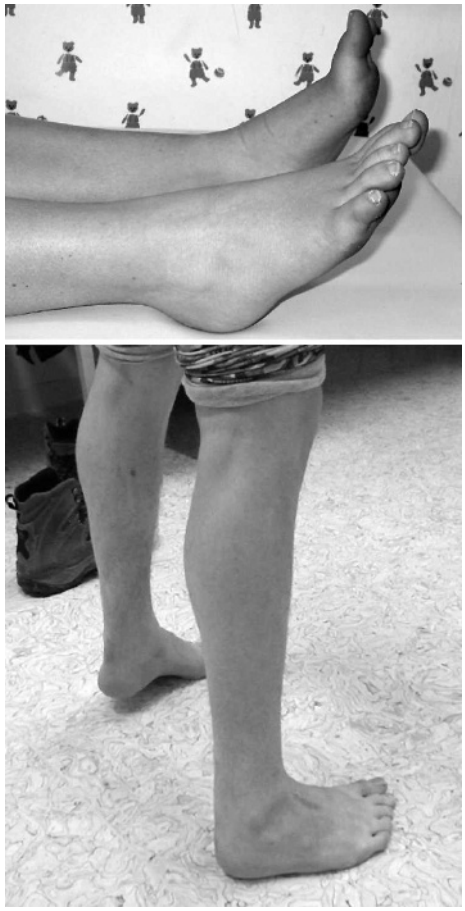

Figure 1 Top: Proband of family 7 aged 13 years, attempting to dorsiflex both ankles; she is unable to dorsiflex the ankle and great toe any further because of weakness of tibialis anterior muscle and long extensors of the toe. Bottom: proband of family 8 aged 14 years; weakness of anterior compartment muscles has led to marked tightening of the tendo achilles bilaterally, right more than left, leading to an inability to place the heels on the ground. Consent was obtained for publication of this figure

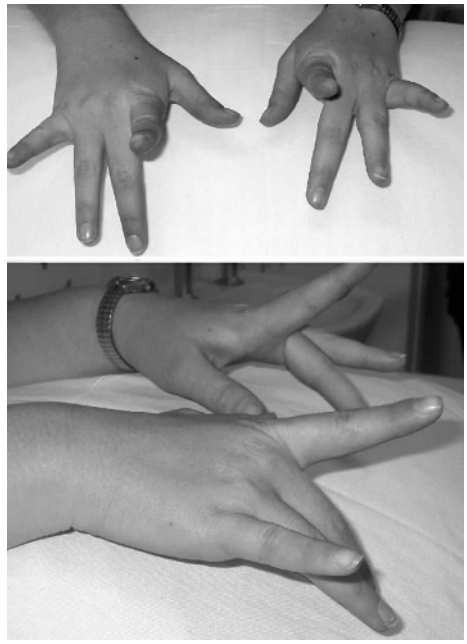

Figure 2 Proband of family 7 at age 13 years, attempting to fully extend her fingers; there is weakness and marked loss of extension of the third and fourth fingers, with a lesser degree of weakness in the remainder of the fingers. Consent was obtained for publication of this figure

The emerging clinical phenotype of MPD1 is reasonably consistent, as detailed in table 1. In some families the onset was so early as to delay walking, but in others was not evident until the late teens, or even the late 20s. Whatever the age of onset, progression was very gradual. The initial symptom in all reported patients was weakness of great toe or ankle dorsiflexion, or both. Weakness of finger extension was common, as was weakness of neck flexion where the disease had been manifest for a few years. The proband of family 6 developed rigidity of the neck. The emerging clinical phenotype is extremely similar to that described by Gowers in 1902.[10]

The clinical phenotype of hyaline body myopathy is distinct to that of MPD1. The distribution of weakness in hyaline body myopathy is either scapuloperoneal or scapulopelvic, and the subsarcolemmal hyaline bodies are present on muscle biopsy. Arrhythmias reported in two subjects with hyaline body myopathy were thought to be incidental, and there was no sign of cardiomyopathy.[11] Similarly, patients with a primary cardiomyopathy caused by *MYH7* gene mutations have not had skeletal muscle weakness reported. However, histological skeletal muscle abnormalities such as central cores, selective atrophy of type I fibres, and mitochondrial abnormalities in type I fibres have been reported in cardiomyopathy patients in the absence of clinical skeletal muscle weakness.[12 13] In a study of 11 patients with hypertrophic cardiomyopathy, EMG findings in keeping with a myopathic process were reported, namely short, small, and polyphasic motor potentials.[14] Biopsy abnormalities were also found in these patients' muscles, including central cores, target fibres, and subsarcolemmal mitochondrial proliferation. Only one of these 11 patients had mild muscle weakness in a limb girdle distribution.

It was recognised with the earliest reports of MPD1 that the muscle biopsy findings were variable and non-specifically myopathic.[2 3] The summary of pathological findings in the 34 patients presented in this paper confirms this observation. The distal myopathies, except for Miyoshi myopathy, have prominent rimmed vacuolated fibres. However, this was not the case in MPD1. In earlier reports, it was postulated that the lack of rimmed vacuoles may have reflected the small number of biopsies, or the muscles sampled,[15] but this would not appear to be the case. When autophagic rimmed vacuoles were seen ultrastructurally, it was in older patients who had manifested the disease for many years. It would appear they are a late pathological change, as has been suggested previously.[5]

Some of the variability in histopathological findings can be attributed to the muscle sampled. Foot drop is an early sign clinically, and this correlates with the tibialis anterior muscle being affected early and severely. Figure 7 is of the tibialis anterior muscle, sampled in a patient from family 8 when he was 12 years of age. The changes were ''end stage'', revealing marked secondary fibrosis but no rimmed vacuoles. The tibialis anterior muscle normally has marked type I fibre predominance, but ATPase staining of this muscle shows very few type I fibres, and those remaining are markedly atrophic (fig 7). In contrast, figs 3, 4, and 5 illustrate pathology from the quadriceps femoris muscle of two other families. Clinically, the quadriceps is affected late and not severely. In particular, fig 5 was from a member of family 7, biopsied at the age of 11 years. There was minimal fibrosis, with no necrotic or regenerating fibres, and no central nucleation or

Table 2 Pathology of muscle biopsies from patients with Laing distal myopathy

	Family							
	1	2	3	4	5	6	7	8
Muscle biopsied	TA, Quads	TA	TA	Quads	Quads	Quads	Quads	TA
Reference	Laing/Mastaglia, 1995/2002[3 15]	Scoppetta, 1995[2]	Zimprich, 2000[4]	Voit, 2001[5]	Hedera, 2003[6]	De Visser (Meredith, 2004[1])	Lamont (Meredith, 2004[1])	Udd B (unpublished)
Abnormal fibre size	Excessive variation; mainly type I fibres are small, although a few small type II fibres in older subjects	Type I fibres small; type II fibres normal although few in number	Prominent variation in fibre size	Increased variation (10–120 μm at age 34 y), scattered atrophic fibres	Minimal fibre size variability; infrequent hypotrophic fibres	Prominent variation in fibre size; atrophic fibres of both type I and 2	Wide variation in fibre size; atrophy of type I fibres but not type II fibres	Highly increased size variation. Atrophic type I fibres. Large type II fibres.
Fibre type grouping	None seen	NR	NR	NR	NR	None seen	None seen	No
Fibre type predominance	Type II fibre predominance (81%)	Type I fibre predominance (80%)	NR	NR	NR	Type I fibre predominance	Type II fibre predominance	Type II fibre predominance
Necrotic/regenerating fibres	Occasional	NR	Present	NR	None seen	Present in both fibre types	None seen	Occasional
Angulated fibres	Occasional	NR	Markedly increased in older case	NR	None seen	Present	None seen	Occasional type I fibres
Central nucleation	Increased	NR	Increased	Increased	NR	Increased	Not increased	No
Z disc streaming	None seen		Present	NR	NR	Present	None seen	No
Nuclear clumps	Increased	NR	NR	NR	NR	Present	Present	No
Endomysium and perimysium	Normal	Slightly increased in some areas	Increased in older case	Increased endomysial and perimysial connective tissue	NR	Increased endomysial and perimysial connective tissue	Focal mononuclear cell infiltration; no increase in collagen	Increased endomysial and perimysial connective tissue. Parts of the muscle end stage
Sarcoplasmic inclusion bodies	None seen	NR	Rare lateral sarcoplasmic bodies	Present	None seen	Present	None seen	None seen
Rimmed vacuoles	None seen		Suggested on EM; no tubulofilamentous inclusion bodies	Numerous on Gomori Trichrome stain	None seen	Present in both fibre types	None seen	No
''Motheaten'' fibres	Occasional	NR		NR	None seen	Occasional	None seen	No
Ring fibres	None seen	NR	Occasional (positive for desmin)	Ringbinden fibres	None seen	Present	None seen	Occasional
''Whorled'' fibres	None seen	Few	None seen	NR	None seen	Present	None seen	Occasional
Cores	None seen	NR	NR	NR	NR	None seen	None seen	
Fibre splitting	None seen	NR	Present	Present	NR	Present	None seen	No
Histochemistry	Increased NADH-TR activity in angulated fibres	Normal	NR		Normal	Increased NADH-TR activity in angulated fibres; increased acid phosphatase	Nor	Normal
Immunohistochemistry	Normal (myosins not done)	NR	Normal (myosins not done)	Normal (myosins not done)	NR	Vacuoles using membrane markers	Co-expression of fast and slow myosin in some fibres, some of which appear intermediate between type I and 2 on ATPase staining	Abnormal with few normal sized slow myosin fibres and conversion to fast myosin; almost all atrophic fibres express both
Electron microscopy	Minor non-specific changes; non-specific honeycomb bodies and granulofilamentous inclusions	NR	Autophagic vacuoles containing myelin figures	Cytoplasmic bodies, tubulofilamentous inclusions (see text)	NR	Atrophic fibres, rod-like bands, autophagic vacuoles containing cellular debris	Atrophic fibres, lymphocytes, macrophages	NR

EM, electron microscopy; NR, not reported; Quads, quadriceps femoris; TA, tibialis anterior; y, years.

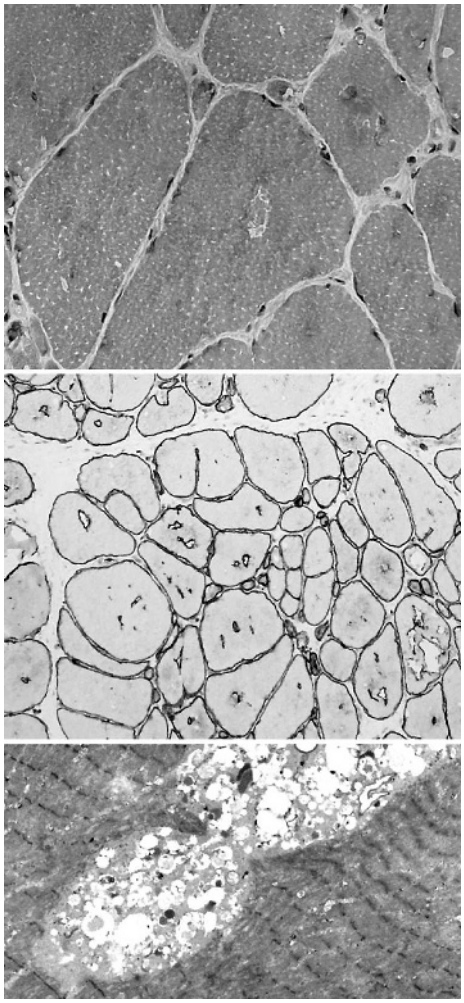

Figure 3 Biopsy of vastus lateralis muscle from proband of family 6 at age 32 years. Top: Haematoxylin and eosin stain showing vacuoles containing debris. Middle: Immunohistochemical staining for spectrin, showing inclusions to be membrane bound. Bottom: Electron microscopy of an area with myelin figures and debris, consistent with autophagic vacuoles.

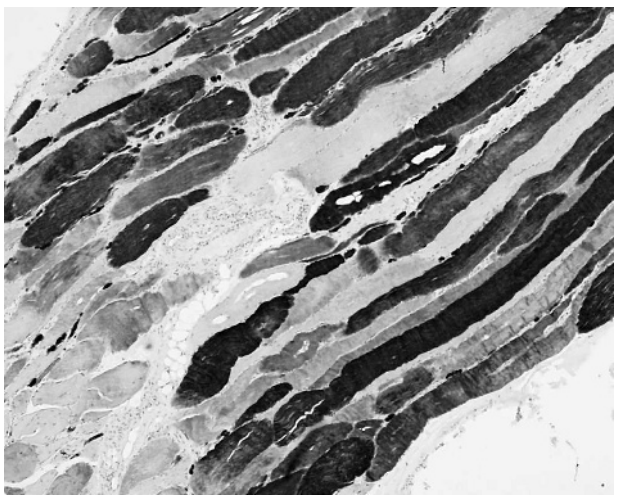

Figure 4 Biopsy of quadriceps femoris from proband of family 6 at 32 years of age. Immunohistochemical staining for fast-skeletal myosin on a paraffin section shows vacuoles in both type I and type II fibres. Some intermediate fibres can be seen suggesting switching from type I to type II.

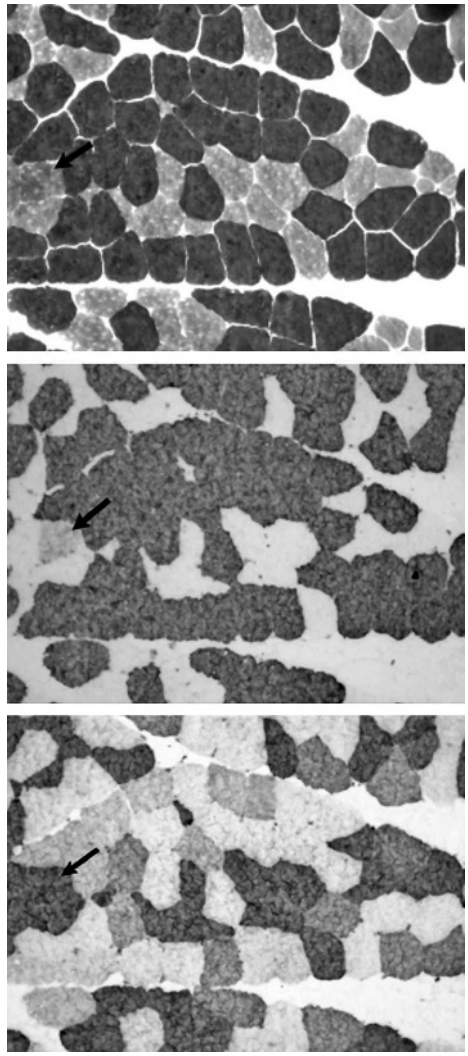

Figure 5 Biopsy of lateral quadriceps muscle from proband of family 7 at 11 years of age; the arrowed muscle fibre is type I on ATPase histochemistry and by staining on slow myosin immunohistochemistry, but is slightly darker than the other type I fibres and shows partial staining for the fast myosin. Top: Myosin ATPase at pH 9.4. Middle: Fast myosin staining. Bottom: Slow myosin staining.

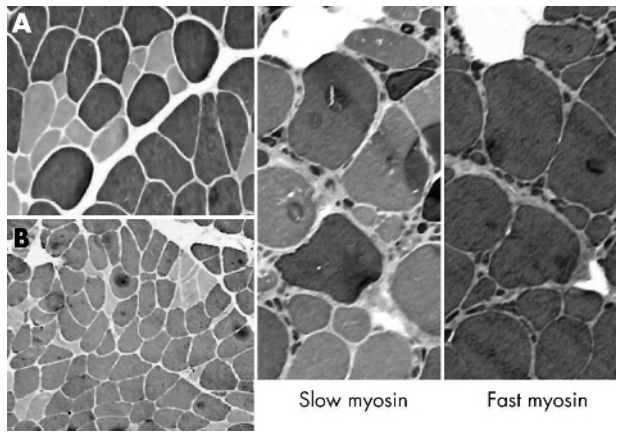

Figure 6 Left: ATPase staining at pH 9.4 of the quadriceps muscle from the probands of family 1 (A) and family 7 (B) (reproduced from Meredith et al (2004)[1] with permission of the *American Journal of Human Genetics*). Right: Slow myosin staining (middle) and fast myosin immunostaining (far right) of tibialis anterior muscle from proband of family 8 at 12 years, showing conversion to type 2 fibre predominance.

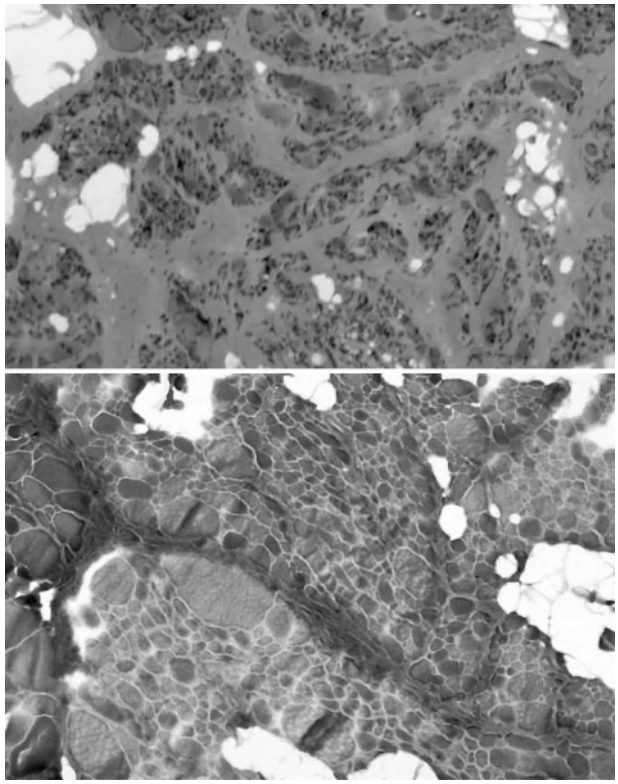

Figure 7 Biopsy of the tibialis anterior muscle from the proband of family 8 at the age 12 years. The muscle is ''end stage'', but does show marked secondary fibrosis, fatty replacement, marked atrophy of some fibres, no rimmed vacuoles, and occasional necrotic fibres. Top, haematoxylin and eosin stain; bottom, Gomori trichrome stain.

angulated fibres. In contrast to the marked differences in pathology, the phenotypes in patients 7 and 8 were similar with respect to age at onset and progression. Thus the site of muscle biopsy has a significant impact on the pathology seen.

The lack of rimmed vacuoles or any other consistent histochemical feature leads to difficulty in making a pathological diagnosis in MPD1. *MYH7* codes for the isoform of myosin present in slow (type I) muscle fibres. One would predict from this that pathological changes in MPD1 should be confined (or most prominent in) type I fibres. However, pathological changes were not consistently confined to type I fibres. Atrophic type II fibres were reported in some families, and fibre type predominance could be of type I or type II, or be normal. Therefore, routine histochemical features of the muscle biopsy do not seem to hold the key to diagnosis in MPD1.

Immunohistochemical staining for slow and fast myosins was done in two biopsies, and for fast myosin alone in family 6, and was abnormal in all three. In case 6 (fig 4), immunohistochemical staining for fast-skeletal myosin on paraffin section showed vacuoles in both type I and type II fibres. Some intermediate fibres were also seen which suggested a switch from type I to type II. In case 7 (fig 5), all the atrophic fibres expressed slow myosin and there were fibres in which myosin ATPase staining intensity was intermediate between type I and type II. The ''intermediate'' fibres seen may represent conversion from slow to fast myosin. This conversion to fast myosin expression is consistent with a mutation in a gene responsible for slow myosin protein generation. In case 8 (fig 6), most of the fibres expressing slow myosin appeared atrophic and also expressed fast myosin. The tibialis anterior muscle is normally programmed to have type I fibre predominance. In contrast to the normal picture, the tibialis anterior muscle biopsied in case 8 had few type I fibres, and almost all fibres expressed fast myosin. Once again, this conversion to fast myosin is consistent with a slow myosin defect. It may also explain why the tibialis anterior is the first and most affected muscle in MPD1. The quadriceps muscle has either equal proportions of type I and type II fibres, or even type II predominance in the deeper regions of the muscle. This may ''protect'' it from severe disease in a slow myosin defect.

One patient in the present study had definite changes on sural nerve biopsy. No other patients had pathological examination of a peripheral nerve. Fibre type grouping or targetoid fibres, as typically seen in peripheral neuropathies, was not reported in any of the eight cases and not even in the patient with the abnormal nerve biopsy. Thus the single neuropathic finding may represent an incidental finding, and neuropathy seems not to be a definite component of MPD1 disease.

The pathological findings in MPD1 are variable and appear to be affected by factors such as the specific muscle biopsied, the age of the patient at the time of biopsy, and the duration of disease manifestations. Myosin immunohistochemistry not only aided diagnosis, but in the future may also provide insight into the pathogenesis of the *MYH7* gene mutation. In contrast to the inconsistency of pathological findings, the clinical phenotype is far more consistent, only varying as to the age of onset. So far, onset after the third decade has not been reported. Also notable is the extremely slow progression of the disease, with cases with onset in the first decade still ambulant in the sixth decade of life.

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REFERENCES

1 **Meredith C**, Herrmann R, Parry C, *et al*. Mutations in the slow skeletal muscle fiber myosin heavy chain gene (*MYH7*) cause Laing early-onset distal myopathy (MPD1). *Am J Hum Genet* 2004;**75**:703–8.
2 **Scoppetta C**, Casali C, la Cesa I, *et al*. Infantile autosomal dominant distal myopathy. *Acta Neurol Scand* 1995;**92**:122–6.
3 **Laing NG**, Laing BA, Meredith C, *et al*. Autosomal dominant distal myopathy: linkage to chromosome 14. *Am J Hum Genet* 1995;**56**:422–7.
4 **Zimprich F**, Djamshidian A, Hainfellner JA, *et al*. An autosomal dominant early adult-onset distal muscular dystrophy. *Muscle Nerve* 2000;**23**:1876–9.
5 **Voit T**, Kutz P, Leube B, *et al*. Autosomal dominant distal myopathy: further evidence of a chromosome 14 locus. *Neuromusc Disord* 2001;**11**:11–19.
6 **Hedera P**, Petty EM, Bui MR, *et al*. The second kindred with autosomal dominant distal myopathy linked to chromosome 14q. *Arch Neurol* 2003;**60**:1321–5.
7 **Lamont PJ**, Thorburn D, Fabian V, *et al*. Complex I deficiency and nemaline rods in three infants with hypotonia and motor delay. *Neuropediatrics* 2004;**35**:302–6.

8 **Bonnemann CG**, Laing NG. Myopathies resulting from mutations in sarcomeric proteins. *Curr Opin Neurol* 2004;**17**:529–37.
9 **Richard P**, Charron P, Carrier L, for the EUROGENE Heart Failure Project, *et al*. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation* 2003;**107**:2227–32.
10 **Gowers WR**. Myopathy and a distal form. *BMJ*, 1902;ii, 89–92.
11 **Tajsharghi H**, Thornell L-E, Lindberg C, *et al*. Myosin storage myopathy associated with a heterozygous missense mutations in *MYH7*. *Ann Neurol* 2003;**54**:494–500.
12 **Fananapazir L**, Dalakas MC, Cyran F, *et al*. Missense mutations in the β-myosin heavy-chain gene cause central core disease in hypertrophic cardiomyopathy. *Proc Natl Acad Sci USA* 1993;**90**:3993–7.
13 **Caforio ALP**, Rossi B, Risaliti R, *et al*. Type 1 fiber abnormalities in skeletal muscle of patients with hypertrophic and dilated cardiomyopathy: evidence of subclinical myogenic myopathy. *J Am Coll Cardiol* 1989;**14**:1464–73.
14 **Smith ER**, Heffernan LP, Sangalang VE, *et al*. Voluntary muscle involvement in hypertrophic cardiomyopathy. *Ann Intern Med* 1976;**85**:566–72.
15 **Mastaglia FL**, Phillips BA, Cala LA, *et al*. Early onset chromosome 14 linked distal myopathy (Laing). *Neuromusc Disord* 2001;**12**:350–7.

NEUROLOGICAL PICTURE

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Medial medullary infarction

A 60 year old man with hypertension and diabetes mellitus sought neurological consultation for sudden onset of numbness over the left side of body. On examination, he was conscious and had dysarthria. Right lingual paresis was observed on tongue protrusion (fig 1A). The other neurological findings included left lemniscal sensory impairment and mild left haemiparesis without facial involvement (fig 1B). The presence of crossed neurological signs—right (ipsilateral) hypoglossal palsy and left (contralateral) sensorimotor haemiparesis (with facial sparing)—localised the lesion to right medial medulla. Cranial magnetic resonance imaging (MRI) confirmed the clinical localisation (fig 2A, B). Intracranial portion of right vertebral artery was not visualised on the magnetic resonance angiogram (fig 2C). The topography of the lesion and the absence of flow in the right vertebral artery favoured infarction over demyelination as the likely aetiology. The neurological problem was ascribed to right medial medullary infarction due to occlusion of antero-medial medullary artery, originating from right vertebral artery. He eventually made good clinical recovery.

Our patient presented with the classical clinical triad of Dejerine's syndrome, that includes ipsilateral hypoglossal palsy, contralateral haemiparesis, and lemniscal sensory loss.[1] Involvement of right hypoglossal nucleus and nerve fibres in the dorsomedial portion of upper medulla, right pyramid, and medial lemniscus rostral to the motor and sensory decussations contributed to the observed neurological signs. Intracranial vertebral artery occlusion more often manifests with lateral medullary syndrome. Rarely does it produce medial medullary infarction as observed in our patient.

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Consent has been obtained for figure 1.

Reference

1 **Bassetti C**, Bogousslavsky J, Mattle H, *et al*. Medial medullary stroke: Report of seven patients and review of the literature. *Neurology* 1997;**48**:882–90.

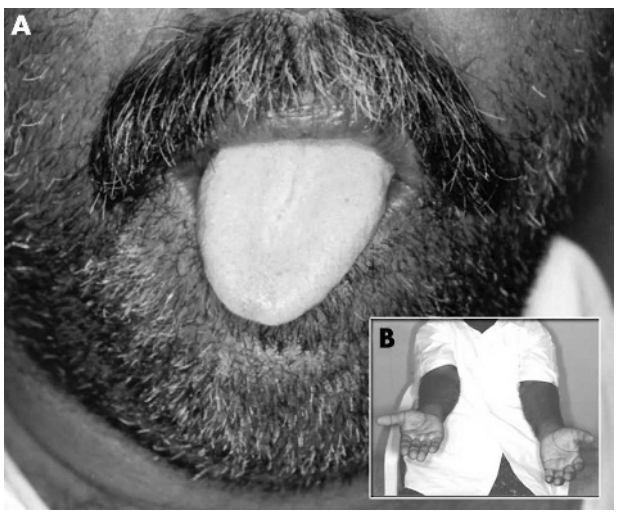

Figure 1 (A) Right hypoglossal palsy elicited on tongue protrusion; (B) Left pronator drift evident on forward arm abduction.

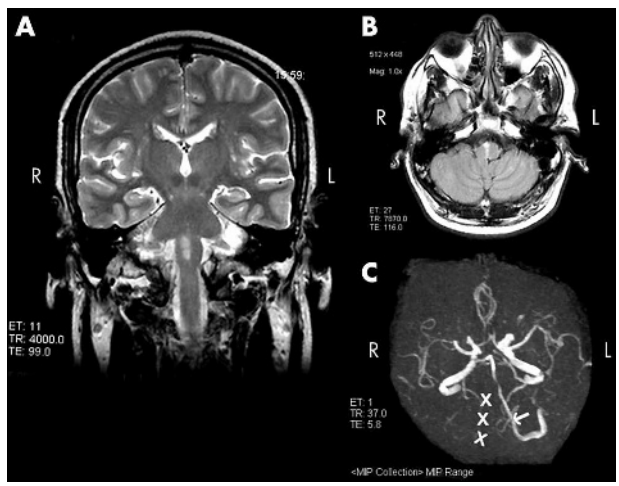

Figure 2 (A) Right medial medullary infarction seen on the T2 weighted coronal magnetic resonance imaging; (B) The same lesion in transaxial fluid attenuated inversion recovery sequence; (C) Magnetic resonance angiogram showing normal flow in the left vertebral artery (arrow). Note the absence of flow in the right vertebral artery (cross).