NERVE AND MUSCLE (L WEIMER, SECTION EDITOR)

Distal Myopathies

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Abstract Advanced molecular genetic possibilities have made it possible to clarify and delineate an ever growing number of distinct new disease entities in the group of distal myopathies. These diseases share the clinical features of preferential muscle weakness in the feet and/or hands, and as they are genetic disorders that lead to progressive loss of muscle tissue they can also be called distal muscular dystrophies. More than 20 entities are currently identified and many are still waiting for genetic characterisation. No final diagnosis can be made on other grounds than by the molecular genetic defect. Besides the usual investigations, including electromyography and muscle biopsy, muscle imaging is very important in defining the precise pattern of muscle involvement. Based on the combination of age at onset, mode of inheritance, pathology and muscle imaging, the list of possible underlying genes can be tracked down to minimal number allowing for specific genetic testing.

Keywords Distal myopathy · Distal muscular dystrophy · Classification · Molecular genetics · Pathogenesis · Diagnostics · MRI · Muscle pathology

Introduction

In the distal myopathies the molecular genetic era started in 1995 with linkage of an early-onset autosomal dominant distal myopathy to chromosome 14 in an Australian family [1]. The history before molecular genetics includes clinical descriptions of four different distal myopathies occurring in multiple families: autosomal dominant Welander distal myopathy (WDM) [2], recessive Miyoshi myopathy [3, 4], recessive distal myopathy with rimmed vacuoles (Nonaka, DMRV) [5], and dominant tibial muscular dystrophy (Udd, TMD) [6]. In addition to these, a few disorders described later in single families also proved to represent separate entities by molecular genetics: early adult-onset dominant distal myopathy [7] and late-onset dominant distal myopathy [8] (Table 1).

All these entities currently have their causative gene identified: *dysferlin* for MM in 1998 [9, 10], *desmin* in the Milhorat family 1998 [11], C-terminal mutations in *M-line titin* as the cause of TMD in 2002 [12, 13], mutations in *GNE* for DMRV the same year [14, 15], mutations in slow myosin *MYH7* for Laing myopathy in 2004 [16], *ZASP* mutations responsible for Markesbery–Griggs myopathy in 2007 [17] and *TIA1* mutation in WDM in 2013 [18, 19••].

Recent developments have increased the number of separate diseases identified by molecular genetics to more than 20 different entities [20••]. For clinicians, this means more demanding diagnostic challenges requiring an updated classification and differential diagnostic algorithms to increase the possibilities of reaching a final genetic diagnosis for the patient. Moreover, distal muscle weakness and atrophy frequently occurs in other disorders, which needs to be considered in the differential diagnostic work-up (Table 2).

Clinical Classification

Late Onset Autosomal Dominant Distal Myopathies

WDM

Index finger extension weakness is usually the first symptom and sign, followed by extension deficit in the other fingers.

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Table 1 Distal myopathies with identified genetic cause

	Gene	Protein
1. Late adult-onset autosomal dominant forms		
a. Welander distal myopathy	TIA1	TIA1
b. Tibial muscular dystrophy (Udd myopathy)	TTN	Titin
c. Distal myotilinopathy	TTID	Myotilin
d. ZASPopathy (Markesbery–Griggs)	LDB3	ZASP
e. Matrin3 distal myopathy (VCPDM, MPD2)	MATR3	Matrin3
f. VCP-mutated distal myopathy	VCP	VCP
g. Alpha-B crystallin-mutated distal myopathy	CRYAB	αB-crystallin
2. Adult-onset autosomal dominant forms		
a. Desminopathy	DESM	desmin
b. Distal ABD-filaminopathy	FLNC	Filamin-C
3. Early-onset autosomal dominant forms		
a. Laing distal myopathy (MPD1)	MYH7	beta-MyHC
b. KLHL9 mutated distal myopathy	KLHL9	KLHL9
4. Early onset autosomal recessive forms		
a. Distal nebulin myopathy	NEB	Nebulin
5. Early adult-onset autosomal recessive forms		
a. Miyoshi myopathy	DYSF	Dysferlin
b. Distal anoctaminopathy	ANO5	Anoctamin-5
c. Distal myopathy with rimmed vacuoles (GNE-myopathy)	GNE	GNE

ABD actin binding domain

Wrist flexor weakness, atrophy of hand muscles, and weakness in toe and ankle extensors are usually the next steps in the disease evolution. Most patients have onset of weakness in the fifth–sixth decade, but there are also earlier or later onsets. A minority of patients do not have onset of weakness in the upper limbs, but in the lower leg muscles with later involvement of the hands. Neuropathic sensory involvement has been suggested, but definite neuropathy has not been confirmed by electrophysiology measurements [21]. Disease progression is very slow; patients remain ambulatory and have a normal life span. The main disability relates to hand weakness and foot drop. Electromyography (EMG) reveals myopathic changes in the target muscles and creatine kinase (CK) levels are normal or slightly elevated. Muscle biopsy taken from a target muscle, such as tibialis anterior, shows rimmed vacuoles with degenerated atrophic fibres. Muscle imaging of lower limbs by magnetic resonance imaging (MRI) is useful and shows advanced fatty degenerative changes in the anterior compartment of the lower legs, but also marked involvement of posterior calf muscles, despite good plantar flexion [22].

Molecular Pathology The genetic defect causing WDM has recently been identified as a missense mutation in the *TIA1* gene [19••]. As expected from previous linkage studies [18] there is one single founder mutation accounting for the disease in the Scandinavian families linked to chromosome 2p13. One UK family proved to have the same mutation on the same haplotype, suggesting remote ancestry [19••]. TIA1 is an RNA binding protein involved in regulation of translation via splicing machinery and protein complexes called stress granules capable of halting transcripts from translation; the mutation causes alteration of the stress granule dynamics [19••].
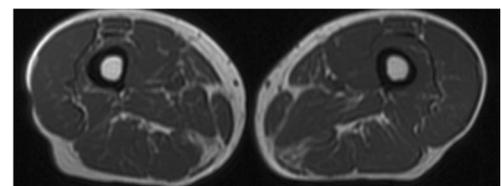
Table 2 Other muscle diseases that may present with a distal phenotype

1. FSHD
2. Nemaline myopathy
3. DNM2-mutated centronuclear myopathy
4. HMERF titinopathy
5. DNAJB6-mutated LGMD1D
6. Myotonic dystrophy type 1
7. Metabolic myopathies
  a. Branching glycogenosis
  b. Debrancher glycogenosis
  c. Phosphorylase b kinase deficiency
  d. PNPLA2 lipidosis
8. Caveolinopathy
9. Telethoninopathy
10. Sporadic inclusion body myositis
11. Scapuloperoneal syndromes
12. Nephropathic cystinosis
13. Amyloid myopathy (myeloma-induced)
14. POLG1 mitochondrial myopathy

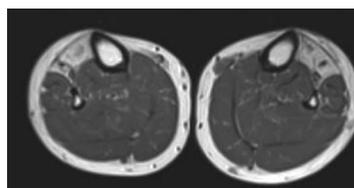*FSHD* facioscapulohumeral muscular dystrophy

Epidemiology The numbers of the patients in Sweden and Finland are in the hundreds, but so far molecularly diagnosed patients outside Sweden and Finland are very rare.

TMD (Udd Myopathy)

In contrast to WDM this disease does not involve the upper limbs. There is insidious onset of decreased ankle dorsiflexion typically after the age of 35–40 years. Later onset after the age of 60 years may occur and in so far exceptionally rare recessive forms the onset may be earlier, after the age of 20 years, but childhood onset forms are not known. Asymmetric weakness for many years is not unusual. In the typical patient moderate proximal weakness of lower limbs, mainly in the hamstring muscles, occurs after the age of 65–70 years, and patients remain ambulant. Extensor digitorum brevis and hand muscles are spared [6]. Variations of the phenotype are observed even within a family [22, 23]. Muscle MRI is very helpful with highly selective fatty degeneration in the anterior compartment muscles of the lower legs starting in tibialis anterior (Fig. 1). Hamstring and gluteus minimus muscles are involved later, and focal changes can be observed in other muscles, such as soleus and medial gastrocnemius [24, 25]. Muscle pathology findings depend largely on the muscle targeted for biopsy. In the most affected tibialis anterior muscle rimmed vacuoles in atrophic fibres are frequent, while necrotic fibres are rare [24].

Molecular Pathology The cause of this relatively mild disease is mutations identified in the far C-terminus of the huge sarcomeric protein, titin. The first mutation in Finnish patients (FINmaj) was a complex insertion–deletion mutation in the last exon, 363, causing an in-frame exchange of four amino acids [13]. Why the mutant titin causes a dominant autophagic fibre degeneration in selective muscles is not known. Other c-terminal mutations causing the same phenotype occur in other populations in French, Belgian, Spanish, Italian, Portuguese and Swiss TMD families [20••, 26–29]. For exact molecular diagnosis, sequencing the last three exons is recommended.

Epidemiology TMD is a very common muscle disease in Finland with a prevalence of 20/100,000, whereas only rare families are known in other countries [20••, 26–29].

ZASPopathy (Markesbery–Griggs Late-Onset Distal Myopathy)

The disease has a late onset, with ankle weakness after the age of 40–50 years. The slow progression later involves weakness of finger and wrist extensors, with moderate muscle atrophy. Proximal limb muscle weakness is a late feature and may cause loss of walking capacity after 15 or 20 years' disease duration in severe cases. CK levels are usually slightly elevated. Cardiomyopathy and heart block have been reported late in the disease course and may require a pacemaker [8]. Muscle MRI reveals early fatty degenerative changes in medial gastrocnemius and soleus. Later on, all lower leg muscles are severely involved, while proximal lower limb muscles show mild or moderate involvement. Muscle biopsy shows extensive myofibrillar abnormalities with dark and hyaline structures in trichrome stain. These correspond to myofibrillar disintegration on EM and protein aggregations on immunohistochemistry, which contain ectopic dystrophin, desmin, myotilin and alphaB-crystallin, among others. These cause autophagic abnormalities with rimmed and non-rimmed vacuoles [17].

Molecular Pathology Two ancient European founder mutations, A165V and A147T, in ZASP (Z-disc alternatively spliced PDZ-domain containing protein) are the most frequent cause of the disease [20••]. The protein is encoded by the *LDB3* gene, and only very rare other mutations have been identified. Mutant ZASP destabilises Z-disc structures leading to Z-disc streaming and later larger disintegration, but why ZASP itself is not part of the secondary protein aggregations has not yet been clarified [17].

Epidemiology Most patients identified are of Caucasian–European origin in accordance with the identified founder mutations.

Fig. 1 Magnetic resonance image of the lower limb muscles in a 60-year-old woman showing selective fatty degenerative changes in the anterior compartment muscles of the lower legs (tibialis anterior, extensor hallucis and extensor digitorum longus). At the thigh level most muscles are within normal range, but for semimembranosus with fatty degeneration and vastus intermedius on the right showing atrophy

Distal Myotilinopathy

Most patient have a very late onset of ankle weakness after the age of 45–60 years [30]. Contrary to the other late-onset distal myopathies the disease may show unusual progression and lead to loss of ambulation less than 10 years after onset, including upper limb and proximal leg muscle weakness [31, 32]. On muscle MRI the pattern of fatty degenerative changes is very similar to ZASPopathy, appearing first in calf muscles followed by all lower leg muscles and milder involvement of proximal lower limb muscles. Muscle biopsy findings correspond to myofibrillar myopathology, similar to findings in ZASPopathy [32]. The myotilin aggregates may also be compact and circumscribed, pathologically defined as spheroid bodies [33]. CK levels are only mildly elevated.

Molecular Pathology Almost all myotilin mutations are located within the second exon of the gene, coding for a serine-rich domain of the Z-disc protein. The mutant protein affects actin filament bundling; disruptions of the Z-disc structure are very similar to those in ZASPopathy, with secondary autophagic abnormality [34, 35].

Epidemiology Myotilinopathy was first reported to cause a LGMD1A phenotype in two families. However, later experience suggests that myotilinopathy in most patients presents with the late-onset distal phenotype. No exact frequency of the disease is known, but it could be in the range of 1/million [20••].

Vocal Cord and Pharyngeal Distal Myopathy

The combination of late-onset distal weakness in lower and upper limbs, combined with bulbar symptoms, should lead to considering this disease in the diagnostic work-up. However, not all patients have marked bulbar symptoms. The onset of muscle weakness may be either in the ankle and toe extensors, or in the fingers. Serum CK levels are normal or elevated up to eightfold. Muscle pathology findings are consistent with a rimmed vacuolar myopathy without marked myofibrillar protein aggregation [36, 37]. Muscle MRI shows clearly more fatty degenerative changes in the posterior calf muscles than in the anterior compartment [37], despite the clinical reports on ankle and toe extensor weakness as the clinical hallmark.

Molecular Pathology and Epidemiology The disease is caused by a unique missense mutation in the nuclear matrix gene *MATR3*, reported primarily only in the originally linked US family and independently occurring in one Bulgarian family [38]. A recent report identifies additional families and patients with the same mutation, and apparently patients with a WDM phenotype might also be considered regarding this disease [35]. How this mutational defect is able to cause

rimmed vacuolar pathology and the distal phenotype is not understood.

VCP-Mutated Distal Myopathy

Mutations in VCP are reported with different neuromuscular disorders. The more common outcome is adult-onset proximal or scapuloperoneal myopathy with variable penetrance of Paget and frontotemporal dementia [39]. However, familial ALS has also been associated with VCP mutations [40], and we have identified a late-onset distal myopathy phenotype clinically very similar to WDM or TMD [41]. Paget disease was not part of the distal phenotype and the progressive lethal frontotemporal dementia occurred very late, 20–25 years after onset of the muscle weakness. Distal weakness was slowly progressive leading to foot drop and hand weakness, but did not cause scapular winging. Muscle pathology findings consisted of rimmed vacuoles and peculiar multi-loculated ring fibres [41]. Muscle MRI showed fatty degenerative changes in the anterior compartment of the lower legs, and CK levels were mildly or moderately elevated.

Alpha-B Crystallin Mutated Distal Myopathy

Similar to VCP myopathy, mutations in CRYAB usually cause a more proximo-distal muscle phenotype and may be combined with dilated cardiomyopathy and cataracts [42]. However, distinct late-onset distal myopathy is also part of the disease spectrum and occurs without cardiomyopathy, respiratory insufficiency or cataracts [43]. Muscle pathology findings, consistent with myofibrillar myopathy, and muscle changes in MRI on the lower legs are similar to the findings in desminopathy.

Adult-Onset Dominant Distal Myopathies

Desminopathy

Distal leg muscle weakness combined with dilated cardiomyopathy with or without conduction defects or respiratory failure are the typical features in desminopathy [11]. In case of onset in early adulthood the progression can be rather severe, leading to disability and a need for cardiac and respiratory intervention. Typical muscle pathology includes excess accumulation of desmin and myotilin, Z-disc alterations and myofibrillar disintegration with autophagic components, although these findings may be inconsistent; one family reported as a neurogenic scapulo-peroneal syndrome proved to be desminopathy [44]. Muscle MRI findings may provide important guidance with unusually more fatty degeneration in the lateral peroneal muscles of the lower legs compared with the anterior compartment and medial gastrocnemius or soleus muscles. If this is associated with particular involvement of

semitendinosus muscle on the thigh, the combination can be diagnostic [45, 46].

Molecular Pathology and Epidemiology Mutations are located over large parts of the gene with no certain genotype–phenotype correlation. Desmin forms intermediate filaments linking the Z-disc of the sarcomeres to the costameres on the sarcolemma. Some, but not all, of the mutations have aggregational properties by themselves [45]. No clear epidemiological data are available, but the general frequency is probably in the magnitude of 1–3/million.

Distal Actin Binding Domain Filaminopathy

Muscle weakness is usually first noted as reduced handgrip strength in early adulthood. Later in the slowly progressive disease, after the age of 40 years, calf muscles get weak, and at that stage atrophy of thenar muscles is also evident [47]. Muscle pathology is not specific and the myofibrillar and rimmed vacuolated pathology caused by other FLNC mutations is not observed. Muscle imaging MRI shows large scale fatty-fibrous replacement in all calf muscles, but the anterior and lateral compartments are spared.

Molecular Pathology and Epidemiology Mutations in other parts of FLNC, in the central or C-terminal regions cause a different phenotype: axial and proximo-distal weakness with a myofibrillar histopathology. In contrast, the N-terminal part of FLNC contains the actin binding domain, where the mutations cause this different distal myopathy disease [48••]. Currently, only a few families, all of European descent, are known.

Early-Onset Dominant Distal Myopathies

Laing Distal Myopathy (MPD1)

Ankle dorsiflexion weakness is commonly observed from early childhood, although onset later in life has been reported. Combined with neck flexor and finger extensor weakness, and a hanging big toe, the clinical picture is rather pathognomonic for an early-onset myopathy. Progression is slow and most patients remain ambulant, but more severe disease evolution with shoulder muscle weakness, scoliosis and proximal lower limb weakness may occur [49]. EMG findings have frequently been misinterpreted, and CK is normal or slightly elevated. The most consistent muscle pathology finding is that of hypotrophic type 1 fibres compatible with congenital fibre type disproportion. Cores are frequently found, while rimmed vacuoles and aggregates are exceptional [50].

Molecular Pathology Laing distal myopathy is caused by mutations in the *MYH7* gene, which codes for slow myosin heavy chain, the isoform of myosin present in slow type 1

muscle fibres and in the heart muscle. Usually, cardiomyopathy is not part of the phenotype but may, nevertheless, occasionally occur. More than 30 mutations causing the disease are known and all are positioned in the C-terminal tail region of the rod domain of MYH7 heavy chain, whereas mutations causing cardiomyopathy are more frequent in the head, neck and central rod regions of the protein. Many patients are sporadic cases because a substantial proportion of mutations are *de novo*, which makes it difficult for the clinician to consider a dominant disease [51, P. Lamont, W. Wallefeld, D.Hilton-Jones et al., submitted].

Epidemiology Increasing numbers of families and sporadic de novo patients have been identified, and the disease should be present in all populations based on the experience with different mutations, even in smaller populations from Western Australia, Finland, Valencia (Spain) and Norway. The overall prevalence is likely higher than 1/million [51, P. Lamont, W. Wallefeld, D.Hilton-Jones et al., submitted].

KHLH9 Mutated Distal Myopathy

This is an early childhood-onset distal myopathy with first signs in the lower legs causing ankle dorsiflexion weakness. Patients eventually develop atrophy of intrinsic hand muscles, and proximal upper and lower limb muscle weakness. The disease was identified in one German family, but no further families have been reported [52]. CK is mildly or moderately elevated, electrophysiological muscle findings were mostly myopathic and muscle pathology showed non-specific myopathy.

Molecular Pathology The protein affected is a kelch-like homologue encoded by the *KHLH9* gene. The protein has associations with degradation pathways, but further understanding of the pathomechanisms is not available [52].

Early-Onset Recessive Distal Myopathies

Distal Nebulin Myopathy

First symptoms, usually in the childhood, are weakness of ankle dorsiflexion, and, soon after, weakness of extensors of fingers and hands. The progression of the disease is slow and includes neck flexor weakness and moderate proximal weakness, but patients remain ambulant [53]. CK is normal on slightly elevated consistent with the slow evolution. EMG shows mixed findings, but with clearly low motor unit potentials in the affected muscles. CK is normal or mildly elevated. Muscle MRI reveals myopathic selective fatty degeneration in the anterior compartment muscles of the lower legs. Muscle pathology has also been repeatedly misinterpreted because of some grouped atrophic fibres mimicking neurogenic changes. Nemaline rods have not been observed on light microscopy,

whereas very rare small rod structures may be found at the ultrastructural level [53].

Molecular Pathology and Epidemiology Mutations in nebulin cause this distal myopathy [53]. Recessive mutations in nebulin usually cause the more severe congenital nemaline myopathy with rod pathology. There is some genotype–phenotype correlation, as the first families identified with distal myopathy had missense mutations on both chromosomes, while the severe nemaline myopathy is caused by more disruptive nebulin mutations [53]. Recently, the distal myopathy phenotype has also been associated with nonsense mutations on one allele and causing nemaline myopathology [54].

Early Adult-Onset Recessive Distal Myopathies

GNE Myopathy (DMRV, Nonaka Myopathy)

The patients usually show first symptoms of ankle dorsiflexion and toe extensor weakness in early adulthood. There is moderate-to-severe progression within 5–10 years, with foot drop, steppage gait and knee flexion weakness with relative sparing of quadriceps muscles. Most patients lose their ambulation after 10–15 years of disease evolution [5]. However, current genetic testing also identifies patients with later onset and variations of the phenotype. CK levels are moderately increased and EMG shows myopathic changes with spontaneous activity and complex repetitive discharges. Muscle biopsy findings are dominated by autophagic rimmed vacuoles [5].

Molecular Pathology GNE is double enzyme, UDP-N-acetylglucosamine 2 epimerase/N-acetyl mannosamine kinase, in the sialic acid pathway, and mutations in the *GNE* gene cause hyposialylation in the muscle. Mutations are located in both enzyme domains and were first identified in quadriceps-sparing myopathy patients from Middle East [55]. Both diseases are now called GNE myopathy. The hyposialylation is currently targeted for corrective therapeutic intervention in early patient trials.

Epidemiology In Japan and Middle Eastern populations founder mutations cause a higher frequency prevalence of the disease. In other populations, GNE-mutated patients are increasingly identified, but the total numbers of patients are still low, indicating a prevalence of <1/million outside the endemic populations.

MM

First symptoms in MM appear in the calf muscles in early adulthood with plantar flexion weakness and calf muscle atrophy, preceded in some patients by calf muscle pain and swelling [3, 4]. The disease is slowly progressive, including proximal limb muscles. There are two phenotypes in the early course

of dysferlinopathy, Miyoshi myopathy and LGMD2B, but the phenotypes cannot be clearly distinguished 20 years after onset [56, 57]. Occasionally, anterior lower leg muscles are also affected early on [58]. In contrast to most other distal myopathies CK levels are very high: 20–150-fold normal values. Myopathic changes and spontaneous activity are recorded on EMG, and scattered fibre necrosis is the main finding on muscle biopsy with variable degrees of other dystrophic features. Diagnosis can be made based on loss of dysferlin staining on immunohistochemistry and Western blotting. Monocytes can also be used for assessment of dysferlin protein.

Molecular Pathology MM is caused by mutations in the *dysferlin* gene [9, 10]. Dysferlin protein is located in the sarcolemma and has been associated with sarcolemmal repair mechanisms.

Epidemiology Patients with MM are identified in many populations, although first reported in Japan. No exact data on prevalence are available, but the overall frequency of MM and LGMD1B dysferlinopathies is in the range of 1–2/million.

Distal Anoctaminopathy

Anoctaminopathy is one of the recent muscular dystrophies and may present as an early adult-onset distal myopathy with asymmetric calf involvement. Exercise calf pain and hypertrophy may precede atrophic changes [59, 60••]. Progression of the disease is slow, and patients remain walking until very old age. Patients have the very high CK levels, comparable to dysferlinopathy. Muscle biopsy findings consist of scattered fibre necrosis.

Molecular Genetics and Epidemiology Mutations of all kinds and all over the *ANO5 (TMEM16E)* gene are the cause of the disease, but the exact functions of the protein are not well understood. The structure suggests a calcium-activated chloride channel possibly in the cytosolic membranes. Anoctaminopathy is one of the most frequent muscular dystrophies in northern Europe [60••]. Diagnostic protein assessment is not available and molecular genetics is needed for final diagnosis.

Oculopharyngeal Distal Myopathy

Both juvenile-onset sporadic/recessive forms and adult-onset dominant forms of oculopharyngodistal myopathy have been described, although the underlying molecular genetic defects are still unknown [61].

Other Distal Myopathies

Single families with distal myopathy apparently distinct from the other entities have been reported:

- distal neuromyopathy with pes cavus (MIM 601846) [62];
- autosomal dominant distal myopathy in a Polish–USA family [63];
- adult-onset dominant distal myopathy, MPD3 (MIM 610099) [64, 65];
- later-onset recessive calf distal myopathy [66].

Management

There is no curative treatment as yet for any of the distal myopathies. Advanced trials are ongoing in GNE myopathy and may eventually change the scenario. Associated cardiomyopathy and respiratory involvement in desminopathy needs monitoring and therapy. Cardiomyopathy at older age is also possible in ZASPopathy. In VCP distal myopathy there was no Paget disease in the first described distal myopathy family, but is certainly possible. Foot drop and wrist weakness can be helped by different forms of suitable orthoses, and surgical treatment can be needed for scoliosis and ankle contractures in severe forms of Laing distal myopathy. Muscle biopsies in distal myopathies may show inflammatory infiltrates and full diagnostic workup to reach a final diagnosis is essential to avoid immune suppressive treatments because of incorrect diagnosis. Algorithms to help the diagnostic work have been published [20••].

Conclusions

The increasing number of families identified with various forms of distal myopathy show that the group has not been well understood in the past. Benign late-onset forms with distal leg atrophies have usually been diagnosed with Charcot-Marie-Tooth neuropathy without comprehensive investigations. A new aspect further emphasising the need for final molecular diagnosis has recently been shown in the case of distal titinopathy (TMD, Udd myopathy): some patients carrying the familial mutation for the mild distal myopathy may have another titin defect on the other allele and then get a more severe form of muscular dystrophy [67••].

Compliance with Ethics Guidelines

Conflict of Interest   Bjarne Udd declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent   This article does not contain any studies with human or animal subjects performed by any of the authors.

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