Review Article

Distal myopathies a review: Highlights on distal myopathies with rimmed vacuoles

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Distal myopathies are a group of heterogeneous disorders classified into one broad category due to the presentation of weakness involving the distal skeletal muscles. The recent years have witnessed increasing efforts to identify the causative genes for distal myopathies. The identification of few causative genes made the broad classification of these diseases under "distal myopathies" disputable and added some enigma to why distal muscles are preferentially affected. Nevertheless, with the clarification of the molecular basis of specific conditions, additional clues have been uncovered to understand the mechanism of each condition. This review will give a synopsis of the common distal myopathies, presenting salient facts regarding the clinical, pathological, and molecular aspects of each disease. Distal myopathy with rimmed vacuoles, or Nonaka myopathy, will be discussed in more detail.

Key words: Amyloid, hIBM, sialic acid

Introduction

Although proximal muscles of the extremities are predominantly affected in most primary myopathies including muscular dystrophies, there are several diseases preferentially involving distal muscles from the early stage of the disease and thus have been labeled as distal myopathies. Classification of the distal myopathies was therefore a matter of dispute; most in the past were classified on the age of onset of the disease and mode of inheritance,[1-5] though recent studies have shown a large list of diseases based on molecular biologic aspects.[6] Despite that the term "distal myopathy" may not be exactly accurate, as some conditions included in this classification actually are characterized by dystrophic changes in the muscle, it is maintained for historical purposes and clinical classification.

Since the discovery of the gene loci for a number of distal myopathies, several diseases previously categorized as different disorders have now proven to be the same or allelic disorders (e.g. distal myopathy with rimmed vacuoles and hereditary inclusion body myopathy, Miyoshi myopathy and limb-girdle muscular dystrophy type 2B (LGMD 2B).

This review will focus on the most commonly known and distinct distal myopathies, using a simple classification: distal myopathies with known molecular defects [Table 1] and distal myopathies with unknown causative genes [Table 2]. The identification of the genes involved in distal myopathies has broadened this classification into sub-categories as to the location of encoded proteins: sarcomere (titin, myosin); plasma membrane (dysferlin, caveolin); cytoskeleton (rare; includes desmin, myotilin, αB-crystallin, ZASP, filamin C, nebulin); and cytosol (GNE).

Tibial Muscular Dystrophy (late onset, Type 2)

Clinical and pathologic characteristics

Udd *et al.*[7] first reported 66 patients from several Finnish families who had an autosomal dominantly inherited late adult onset distal leg myopathy with weakness confined mainly to the anterior tibial muscles. They named the disorder tibial muscular dystrophy (TMD), because they thought that the muscle pathology was similar to that seen in muscular dystrophy, including muscle fiber necrosis and fat tissue replacement, but serum creatine kinase (CK) levels were normal or slightly elevated.

The clinical phenotype presents after the age of 35 years, with almost selective involvement of the anterior tibial muscles and long toe extensors initially, resulting in moderate foot drop in 10-20 years. The disease severity varies from the absence of symptoms to marked difficulty in walking. Weakness may initially be

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Table 1: Distal myopathies with identified causative genes[6]

Disease	Onset	Weakness at initial presentation	CK	Gene	Locus	Inheritance pattern
Udd distal myopathy / Tibial muscular dystrophy (TMD)	2-15	Anterior lower leg	Normal to 4x elevated	TTN (titin)	2q31	AD
Distal nebulin myopathy	2-15	Anterior lower leg	Normal to 3x elevated	NEB (nebulin)	2q22	AR
Laing distal myopathy	35	Anterior lower leg	Normal to 8x elevated	MH7 (slow skeletal/ beta cardiac myosin)	14q12	AD
Miyoshi myopathy	15-30	Posterior lower leg, calf	Moderately to 100x elevated	DYSF (dysferlin)	2p13.3-p13.1	AR
Distal caveolinopathy	early	Hands	3x to 10x elevated	CAV3 (Caveolin-3)	3p25	AD
Nonaka/DMRV/ IBM2	15-30	Anterior lower leg	Normal to 5x elevated	GNE (UDP-N-acetyl glucosamine 2-epimerase/ N-acetylmannosamine kinase	9p12-p11	AR
Desminopathy MFM	15-40	Distal leg and forearm + cardiomyopathy	Normal to 3x elevated	DES (desmin)	2q35	AD
Myotilinopathy MFM	40-60	Lower legs and hands	Normal to 3x elevated	MYOT (Myotilin/TTID)	5q31	AD, sporadic
Alpha-B crystallinopathy MFM	adult	Distal leg and hands + cardiomyopathy	Variable	CRYAB (α-B crystallin)	11q22.3-q23.1	AD
ZASP-related MFM	40-60	Lower legs and hands	Normal to 3x elevated	LDB3/ZASP (Z-band alternatively spliced PDZ motif containing protein)	10q 22.2-q23.3	AD, sporadic

asymmetric; progression of symptoms is slow, whereby patients could develop proximal leg muscles at the age of 70. Affected individuals are usually ambulant; however, elderly patients may need walking aid. Cardiac, facial, and respiratory muscles are usually not affected.[6,7]

Biopsies of the affected tibialis anterior muscles show dystrophic changes of variable severity, including marked variation in fiber size, occasional fiber necrosis and regeneration, increased number of fibers with internal nuclei, and fiber splitting. Rimmed vacuoles (RVs) are present in the majority of patients, especially in the early stages, but muscle fibers are subsequently replaced by fat and fibrous tissue when the vacuoles are no longer discernible. Thus, the presence of RVs is not mandatory for this diagnosis. There was no immunoreactivity for tau, beta-amyloid or beta-amyloid precursor protein in the vacuolated fibers, in contrast to their positive immunoreactivity in distal myopathy with rimmed vacuoles (DMRV)/hereditary inclusion body myopathy (hIBM). These RVs in TMD are usually not membrane-bound and thus are not thought to fulfill the morphologic criteria of autophagic vacuoles, even though the vacuolar space contains numerous vesicles compatible with lysosomal autophagic components.[6]

Molecular aspects

The gene in TMD has been mapped to Chromosome 2q31[8,9] and mutations were found in a gene encoding a structural protein titin.[10] Deletion of 11 bp was initially found in the last exon encoding titin; later heterozygous missense mutations were also documented. Titin is the largest single polypeptide protein and each molecule spans over one half of the sarcomere from Z-disk to M-line interacting both with thin filaments and thick filaments.[6] Titin interacts repeatedly with myosin filaments in the A-band region; this gives the contractile system a strong positional fixation and keeps myosin-thick filaments always centered in the sarcomere.[6] Although TMD was initially identified among Finnish patients, recent reports show that this disease is also found in the French[11] and Belgian[12] population. After the discovery of *TTN* as the gene responsible for TMD, mutations in the same gene have also been shown to induce proximal muscle involvement of limb-girdle muscular dystrophy (LGMD 2J).[13]

Laing Distal Myopathy

Clinical and pathologic characteristics

Laing distal myopathy (MPD1) was originally described by Gowers in 1902, and was later reported by Laing *et al.*[14] It is an autosomal dominant distal myopathy with an onset as young as four or five years, although the disease onset varied from four to 25 years. It is a distinct condition characterized by weakness

Table 2: Distal myopathies without causative genes identified[6]

Disease	Onset	Initial weakness at presentation	CK	Locus	Inheritance pattern
Welander distal myopathy	>40	Hands, finger extensors (patient cannot extend index finger)	Normal to 4x elevated	2p13	AD
Distal myopathy with vocal cord paralysis /MPD2	35-60	Asymmetric lower leg and hands, dysphonia	Normal to 8x elevated	5q31	AD
Myoshi myopathy 2	25-30	Posterior lower leg, calf	Normal to 10x elevated	10p	AR
Autosomal dominant vacuolar myopathy with pes cavus and areflexia	15-50	Anterior and posterior lower leg and hands, dysphagia	2x to 6x elevated	19p13	AD
Adult onset distal myopathy /MPD3	>30	Hands or anterior lower leg	Normal to 4x elevated	8p22-q12 or 12q13-q22	AD
Juvenile onset distal myopathy /MPD3	10-40	Lateral and posterior lower leg	Normal to 2x elevated	12 genetic loci excluded	AD

affecting the anterior compartment of the lower leg and selective involvement of the toe extensors, giving rise to the characteristic hanging big toe sign. The disease is slowly progressive, i.e. a patient has been reported to maintain independent ambulation 23 years after the initial investigation, whereby patients gradually develop weakness of finger flexors and proximal muscles including neck flexors, shoulder, trunk, facial and tongue muscles. Cardiomyopathy is rare and severe respiratory problems have not been described. Serum CK levels are mildly elevated.

The pathological features are variable and there are no pathognomonic diagnostic features.[14,15] In general, fiber size distribution appears to be bimodal. Type I fibers are atrophic in 50% of the population and express both slow- and fast-type myosin. In tibialis anterior muscles, virtually all muscles abnormally express fast-type myosin. RVs are found in a minority of patients with MPD1, but not prominent. Immunohistochemical staining for slow and fast myosin showed co-expression of slow and fast myosin in some Type I fibers, possibly indicating fiber type switching. This finding seems to be a useful aid to diagnosis.

Molecular aspects

The gene for this myopathy is mapped to chromosome 14 and the mutations are found in the slow myosin heavy chain gene *MYH7*,[16] hence it is sometimes know as myosinopathy. Mutations have been discovered on the *MYH7* tail region, which is physically located in the M-line of the sarcomere, and where it was described to interact with myomesin and titin. Mutations in *MYH7* have also been reported in patients with hyaline body myopathy, suggesting that this myopathy is allelic with myosinopathy.

Distal Nebulin Myopathy

Clinical and pathological characteristics

Recently, four families of Finnish decent were described to have an early onset distal myopathy with remarkable involvement of the ankle dorsiflexors (foot drop); other muscles severely involved include finger extensors and neck flexors. In some of the older patients, mild proximal muscle weakness was noted. Moderate facial weakness was seen in few patients.[17]

The muscle biopsy can generally be described as myopathic, although the severity of the pathology varied remarkably. Chronic atrophy was suggested by the presence of large hypertrophic fibers with increase in internal nuclei and nuclear clumps that express neonatal MHC. Nemaline bodies were not observed on light microscopy histochemistry, but were seen in toluidine blue-stained semi-thin epon sections of some patients.

Molecular aspects

Extensive analysis of patients revealed an abnormal SSCP band in the nebulin gene *(NEB)*, in two of the four families. Gene sequencing revealed homozygous mutations in *NEB*.[17] This was rather surprising because recessive mutations in *NEB* have been associated with nemaline myopathy, clinical picture of which is similar to that of most congenital myopathy and presents with proximal myopathy. Actually, in nemaline myopathy, most of the mutations identified were either nonsense, frameshift, or splice-site mutations, while mutations in the distal myopathy phenotype are missense. Thus Wallgren-Petterson *et al*. concluded that homozygozity for *NEB* missense mutations causes a distinct type of recessively inherited distal myopathy,[17] albeit rarely.

Autosomal Recessive distal Muscular Dystrophy (Miyoshi myopathy; early adult onset, Type 2)

Clinical and pathological characteristics

Miyoshi myopathy (MM) is an adult-onset autosomal recessive condition characterized by preferential gastrocnemius muscle involvement and dystrophic muscle pathology.[18,19] MM seems to be widely distributed throughout the world, because many

similar patients have been described from various countries.[20-22]

The symptoms and the onset of the disease can be variable, but most patients become aware of difficulty in walking in early adulthood, from 20 to 40 years. In the early stages of the disease, patients have muscle atrophy and weakness in the distal parts of legs, predominantly of the gastrocnemius and soleus muscles, and therefore have difficulty in standing on tip-toe. The disease subsequently progresses rather rapidly and muscle atrophy/weakness becomes more prominent and may spread to the proximal muscles. A few patients become non-ambulant 10-20 years after onset of the disease. Cardiac and respiratory muscles are not involved. Serum CK levels are elevated to 20-100 times the normal value. Muscle computed tomography (CT) shows preferential soleus, gastrocnemius and occasionally paraspinal muscle involvement. Despite the characteristic involvement of the posterior lower leg muscles, there is a variant of MM which peculiarly involved the tibialis anterior among a Spanish population, and hence was called distal myopathy with anterior tibialis involvement (DMAT).[23]

Muscle biopsies show dystrophic changes with active fiber necrosis and regeneration, interstitial fibrosis, and fat tissue replacement,[18,19] similar to those seen in Duchenne or limb-girdle muscular dystrophy. Inflammatory cellular infiltration is commonly seen and could sometimes lead to misdiagnosis of polymyositis.[24]

Molecular aspects

The causative gene is *DYSF* gene in Chromosome 2p13.[25]

Mutations are variable and include insertions, deletions, altered splicing and point mutations. The exact function of dysferlin remains unknown, but it is thought to allow rapid membrane resealing of membranes disrupted by mechanical stress. Interestingly, patients with LGMD2B with gene locus at 2p13 also have mutations in *DYSF*, suggesting heterogeneous phenotypic expressions in the *DYSF* gene mutations.[26] This is not surprising, because MM patients occasionally show apparent proximal muscle involvement as the disease advances.

Caveolinopathy

Clinical and pathological characteristics

Caveolinopathy is known to cause LGMD1C, however, other phenotypes have been associated with this condition, including distal myopathy, rippling muscle disease, and hyperCKemia.[27] In the initial report of this caveolinopathy-associated distal myopathy, onset of weakness and atrophy was at 12 years of age, mainly involving the intrinsic muscles in the hands and feet, without involvement of the proximal muscles. The progression was slow. Muscle biopsy showed mild variation in fiber size, increased number of internalized nuclei, and predominance of Type 1 fibers.

Molecular aspects

The causative gene is *CAV3*, which encodes a protein that is implicated in the development of the T-tubule system in the skeletal muscle. Mutations are mostly heterozygous missense mutations, but one deletion mutation was also identified. Like in all caveolinopathies, the expression of caveolin 3 is reduced, however, it should be noted that caveolin 3 expression can also be secondarily reduced in some muscular dystrophies like sarcoglycanopathies and dytrophinopathies, underscoring the importance of genetic screening for final diagnosis.

Myofibrillar Myopathy

The term myofibrillar myopathy (MFM) was proposed by AG Engel's group in 1996 as a non-committal term for a pathologic pattern of myofibrillar dissolution associated with accumulation of myofibrillar degradation products and ectopic expression of multiple proteins including desmin, αB-crystallin, dystrophin and amyloid material.[28,29] This condition had previously been labeled as spheroid body myopathy, cytoplasmic body myopathy, Mallory body myopathy and desmin storage myopathy, among other names. In this review, some MFMs are included as patients can present with distal weakness, but it is important to note that both distal and proximal muscles can be involved.[30] In patients with MFM, mutations were found in *DES* (desmin), *CRYAB* (αB-crystallin), *MYOT* (myotilin), *LDB3* (Z-band alternatively spliced PDZ-containing protein; ZASP), and FLNC (filamin C). Accordingly, although MFM is morphologically distinct it is genetically and clinically heterogeneous.[30]

Only two of 63 patients had distal myopathy. Most patients with mutations in *DES* had dilated cardiomyopathy and generalized muscle weakness.[31] Although many patients with distal myopathy with desmin accumulation have been reported in the literature,[32] they were probably not common in desmin myopathy with *DES* mutation.

Distal dominant involvement seems to be rare in patients with *CRYAB*[33] and *ZASP*[34] mutations. Interestingly, a family with autosomal dominantly inherited distal myopathy first described by Markesbery *et al*.[35] is now proven to be caused by the *ZASP* mutation A165V.[36] Haplotype studies in this family and in five other families with European ancestry carrying the identical A165V mutation share common markers at the locus suggesting the existence of a founder mutation. Further study is necessary to determine whether *ZASP*

gene mutation commonly causes distal myopathy.

MYOT, the gene associated with autosomal dominantly inherited LGMD1A,[37,38] also causes distal myopathy.[39-42] Myotilin (myofibrillar protein with titin-like Ig domain) is a 57 kDa Z-disc component that interacts with alpha-actinin, filamin-C, FATZ (calsarcin) and actin. The onset of distal myopathy with myotilin gene mutation is in late adulthood ranging mostly from 50-75 years of age. In the lower legs, the soleus and gastrocnemius muscles are predominantly involved from the early stage,[40,41] extending to the anterior compartment with disease progression.[42] Electromyogram shows myopathic pattern with occasional neurogenic components. Serum CK levels are normal to slightly elevated.

Distal Myopathy with Rimmed Vacuoles (DMRV; Nonaka; early adult onset, Type 1)

Among the various forms of distal myopathies, DMRV has been regarded as a distinct disorder from both the clinical and pathologic aspects.[43-45] The disease is inherited as an autosomal recessive trait and characterized clinically by preferential muscle involvement of the anterior compartment of the lower legs, i.e. tibialis anterior muscle, beginning in young adulthood, and pathologically by the presence of RVs in muscle biopsies. We thought that distal muscle involvement was the initial important disease process, but Argov *et al.*[46] thought quadriceps sparing was the unique finding because the bulk and strength of quadriceps muscles were relatively preserved even in the advanced stages. Since pathologic findings are similar to sporadic inclusion body myositis (sIBM), Askanas *et al.* suggested the term "hereditary inclusion body myopathy (hIBM)" for these patients.[47,48] Subsequently, the term hIBM has been widely used usually when discussing the pathologic findings and DMRV when referring to patients clinically.

Clinical and pathologic findings

The age at onset of the disease ranges from 15 to 40 years, averaging 26 years.[43,45] Since the tibialis anterior muscle is preferentially involved from the early stage [Figure 1], the initial symptom is gait disturbance, usually with difficulty in climbing stairs and running. The disease is rather rapidly progressive.[48,49] Patients become non-ambulant between 26 and 57 years, average of 12 years after the onset of the disease.[43,49] Cardiac and respiratory muscles are less involved. Although the anterior tibial muscle is most significantly affected, gastrocnemius, hamstrings, paraspinal and sternocleidomastoid muscles are also involved from an early stage when one examines muscles by CT [Figure 2A and B]. Even in the advanced stages, quadriceps muscles are relatively spared [Figure 2C]. Serum CK levels are normal to mildly elevated.

In all muscle biopsies, there are myopathic changes with variation in size in both Type 1 and 2 fibers. RVs are present predominantly in atrophic fibers which are occasionally aggregated forming small groups [Figure 3A].[43,45] Necrotic and regenerating fibers can

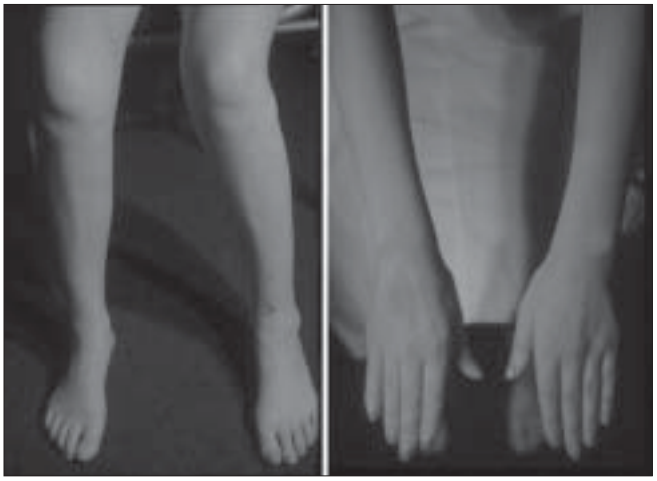

Figure 1: Characteristic findings in a DMRV patient on clinical examination. This patient is in the early stage of the disease showing marked atrophy of the anterior compartment of the lower legs and mild hand muscle atrophy

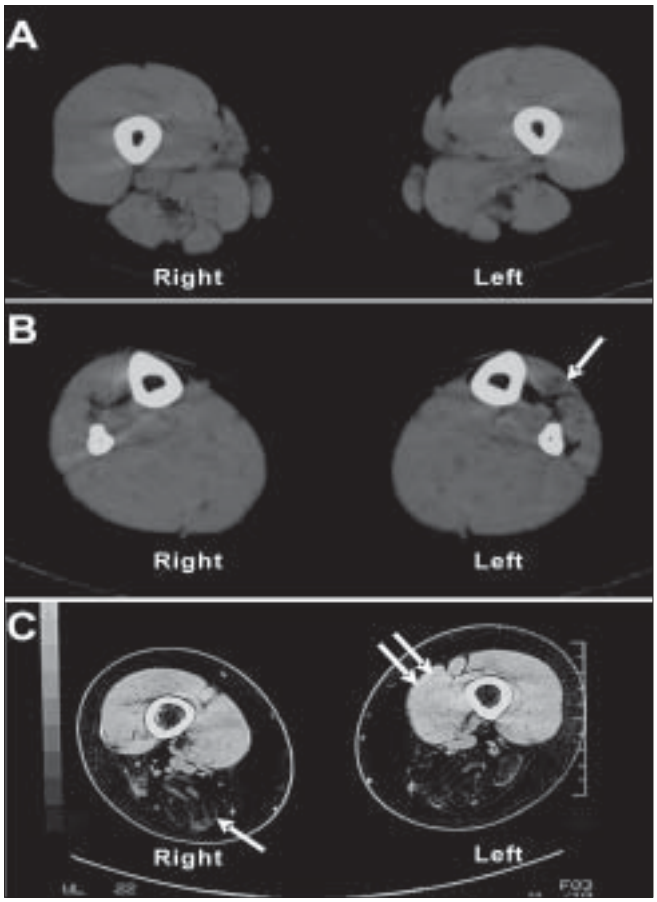

Figure 2: Muscle imaging in a DMRV patient. Muscle CT at mid-thigh (A) and mid-calf (B) levels; note mild muscle atrophy in the hamstring and marked atrophy with fat replacement in the tibialis anterior muscle (arrow). Muscle CT at mid-thigh level in the advanced stage (C); the bulk of the quadriceps femoris muscles (double arrows) is relatively preserved compared to the hamstring muscles (arrow).

be rarely seen. Type 1 fibers tend to predominate as the disease progresses.[43]

Process of muscle fiber degeneration

RV formation is thought to be the primary pathologic event which induces muscle fiber atrophy and loss in DMRV, but its exact significance remains uncertain. By electron microscopy, the RV consists of autophagic vacuoles and myeloid bodies [Figure 3B] . In the vicinity of the RVs, myofibrils are frequently disorganized, therefore degenerated contractile proteins and other cytoplasmic debris appear to activate the lysosome (autophagosome) to scavenge them.[50,51] In the myofibrillar degeneration pathways, non-lysosomal ATP-ubiquitin proteasome proteolysis was proposed to play a role as there is increased proteasome activity in and around RVs.[52] The RV itself is not specific for DMRV, but is also found in other disorders, including chronic muscular dystrophies, metabolic disorders, myotonic dystrophy,[45,53] oculopharyngeal muscular dystrophy, oculopharyngodistal myopathy, and Marinesco-Sjögren syndrome.[45]

RVs in muscle fibers in sIBM[48] and DMRV[54] occasionally contain congophilic deposits, which are also positively stained with β-amyloid protein precursor and tau protein antibodies.[48,53] This notion is further supported by the finding in the DMRV model mouse: amyloid deposits preceded myofibrillar degeneration and accumulation of the autophagic vacuoles suggesting that the autophagic phenomenon is not a primary pathologic event in DMRV.[55]

A common pathologic feature includes various nuclear inclusions and tubulofilamentous inclusions measuring 15-20 nm [Figure 4A] which are similar to 8-10 nm inclusions in oculopharyngeal muscular dystrophy. The nuclei with such inclusions are sometimes markedly degenerated and are surrounded by degenerated myofibrils, suggesting that nuclear degeneration precedes myofibrillar degeneration and autophagic phenomenon [Figure 4B]. Because some nuclei are stained positively with the TUNEL method, the nuclear change is thought to be related to apoptosis.[56]

A close relationship between nuclear change and RV formation has been suggested. In autosomal dominant inclusion body myopathy with Paget's disease of bone and frontal dementia (IBMPFD), mutations were

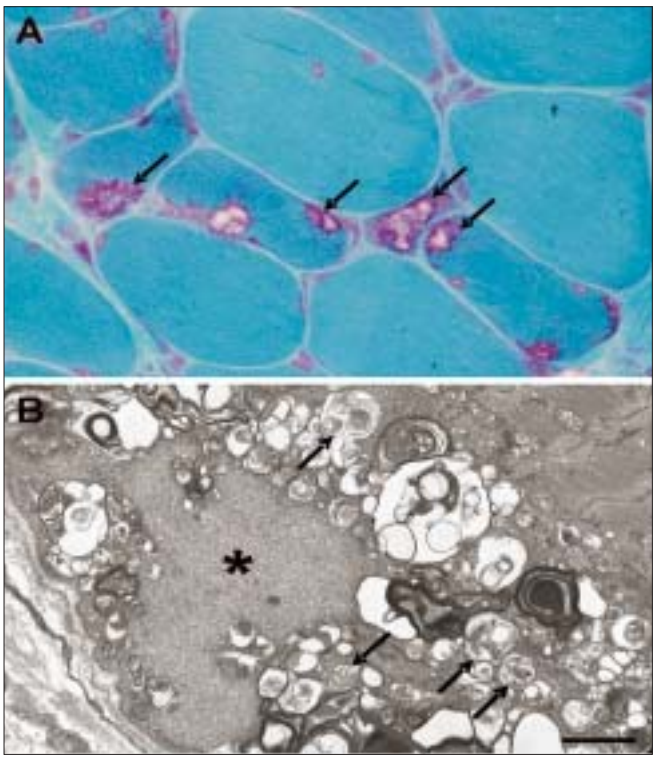

Figure 3: Typical muscle pathology seen in DMRV. Modified Gomori trichrome stain (A) shows moderate variation in fiber size with numerous rimmed vacuoles in atrophic fibers (arrows). On electron microscopy (B), rimmed vacuoles are actually clusters of autophagic vacuoles (arrows) and numerous myeloid bodies; markedly disorganized myofibrils are seen (asterisk). Scale bar in (B) denotes 1.0 micron

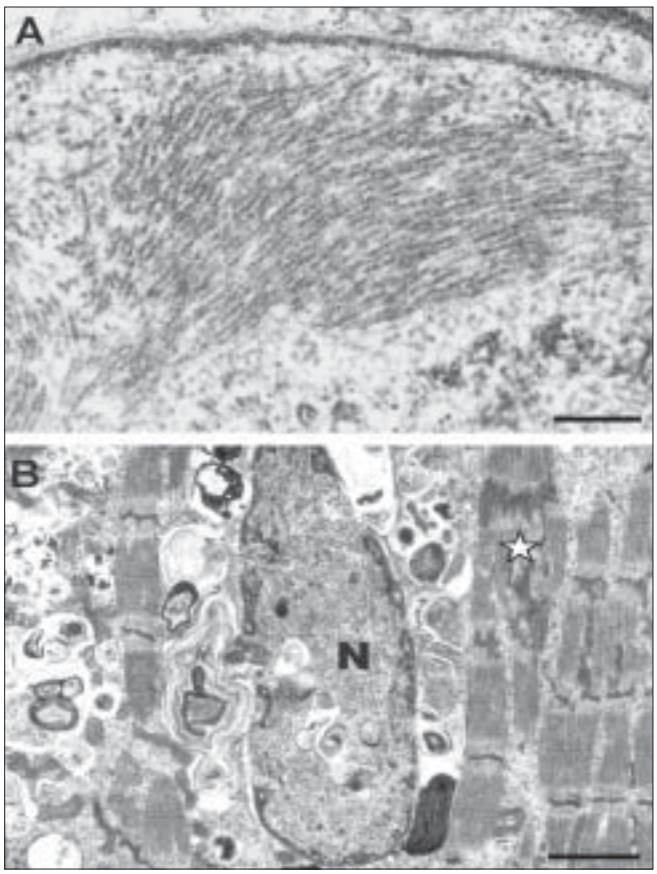

Figure 4: Pathologic hallmarks of DMRV on electron micrograph. Tubulofilamentous nuclear inclusions measuring 15-20 nm in diameter are usually seen in fibers with rimmed vacuoles (A); bar denotes 0.2 micron. In figure (B), myofibrillar degeneration (asterisk) and autophagic phenomenon are seen in the vicinity of an abnormal nucleus (N) filled with tubulofilamentous inclusion, suggesting a close relationship between nuclear change and myofibrillar degeneration; bar denotes 1.0 micron.

found in valosin-containing protein *(VCP)*.[57] The *VCP* is a polyglutamine (polyQ) interacting protein[58] and co-localizes with ubiquitin-containing inclusions in a number of neurodegenerative disorders including polyQ diseases, Parkinson, Alzheimer and Creutzfeldt-Jakob diseases.[59] Although nuclear inclusions in polyQ diseases are different from those in DMRV, nuclear degeneration probably precedes cytoplasmic vacuolar changes resulting in cell death (and probably apoptosis).

Molecular aspects

The gene for hIBM was first mapped to Chromosome 9 in 1996[60] and in DMRV in 1997.[61] The most epoch-making event in hIBM was the discovery of mutations in UDP-N acetylglucosamine 2-epimerase/N-acetylmannosamine kinase *(GNE)*,[62] a gene involved in sialic acid synthesis. *GNE* consists of an epimerase domain and a kinase domain [Figure 5]. The identification of *GNE* mutations among Japanese DMRV patients[63-66] confirmed that DMRV and hIBM are the same disorders. Almost all of the mutations associated with DMRV/hIBM are missense mutations scattered throughout the open reading frame and can be found either in the epimerase domain only, in the kinase domain only, or heterozygous mutations on each domain [Figure 5].[66]

The most common 2186T-to-C (M712T) mutation was initially thought to be restricted to Middle Eastern Jews including a large proband family analyzed by Dr Argov's group.[62] On the other hand, the most frequent mutation in Japanese DMRV patients was the 1714C-to-G (V572L) mutation which was found in more than 50% of patients.[64,66,67] To date, several mutations have also been reported in other populations throughout the world.[66-69]

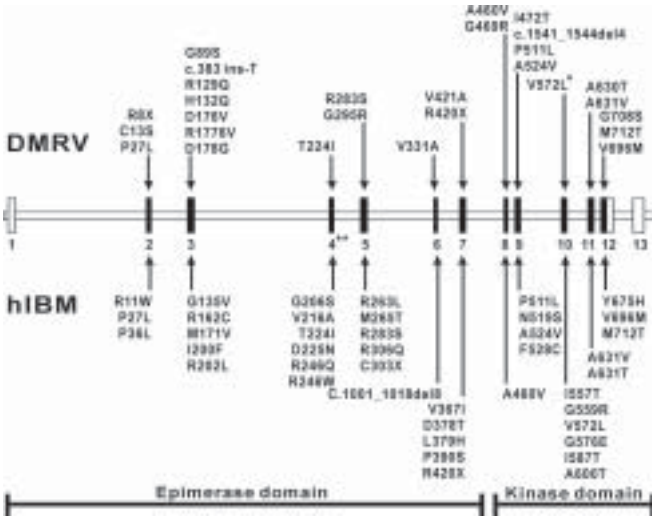

Figure 5: Schematic diagram of the *GNE* gene. Mutations are scattered throughout the open reading frame of the gene. Mutations found in Japan (DMRV) are shown in the upper panel. Mutations outside Japan (hIBM) are illustrated in the lower panel. V572L mutation (asterisk) accounts for 57% of cases in Japan

Genotype and phenotype correlation

Although homozygous V572L mutation was thought to present with the typical clinical features of DMRV,[64] further study is necessary to clarify the genotype/phenotype correlation. A previous study reported that there was an unusual patient with proximal muscle weakness.[67] Furthermore, we had an individual with a homozygous M721T mutation with no muscle symptom, suggesting an incomplete penetrance of the disease.[66]

Two patients had inflammatory cellular infiltration in muscle biopsies mimicking the pathology of sIBM.[70,71] The onset of DMRV is in young adulthood while sIBM becomes manifest after 50 years, therefore one can differentiate the two diseases with little difficulty although there may be patients with late onset DMRV with inflammation among patients clinically diagnosed as having sIBM.

Biochemical abnormalities

The GNE enzyme is a bifunctional enzyme catalyzing two initial steps in the biosynthesis of sialic acid. Sialic acids are present at the terminal ends of glycolipid or glycoprotein on the cell surface, and are thought to contribute to glycoprotein stability, in addition to other various cellular functions. Since *GNE* knockout is lethal in the mouse embryo this suggests that the GNE plays a crucial role in organ synthesis.[72] Moreover, as GNE is ubiquitously expressed, mutations in the gene are thought to induce more serious disorders than DMRV in which only the muscle is affected. Nevertheless, the epimerase activity in patients was markedly reduced in white blood cells[66,73] and lymphoblastoid cell lines,[74] suggesting that the mutations are responsible for decreased or loss of the GNE gene function. It should be noted that most mutations are missense, thus a complete loss of enzyme function may not be expected.

Altered cellular sialylation has been controversial. Hinderlich et al. found no abnormalities in patient-derived lymphoblastoid cell lines with the M712T mutation,[74] although Noguchi *et al.*,[73] found sialic acid levels reduced to 60-70% of control in biopsied and cultured muscle cells, and variable lectin binding reactivities from fiber to fiber. Other reports also described defective glycosylation of skeletal muscle glycoproteins,[75] including α-dystroglycan which is known to be a hyperglycosylated cell membrane protein.[76] The concept of hyposialylation was further supported by the only existing model of DMRV, the *Gne* knockout mouse expressing human *GNE* D176V mutation, wherein marked hyposialylation in serum, muscle and other organs was seen.[55]

It is still unknown how *GNE* mutations induce nuclear inclusion bodies and degeneration followed by amyloid accumulation and myofibrillar degeneration. O-GlcNacylation is a form not only of cytoplasmic but

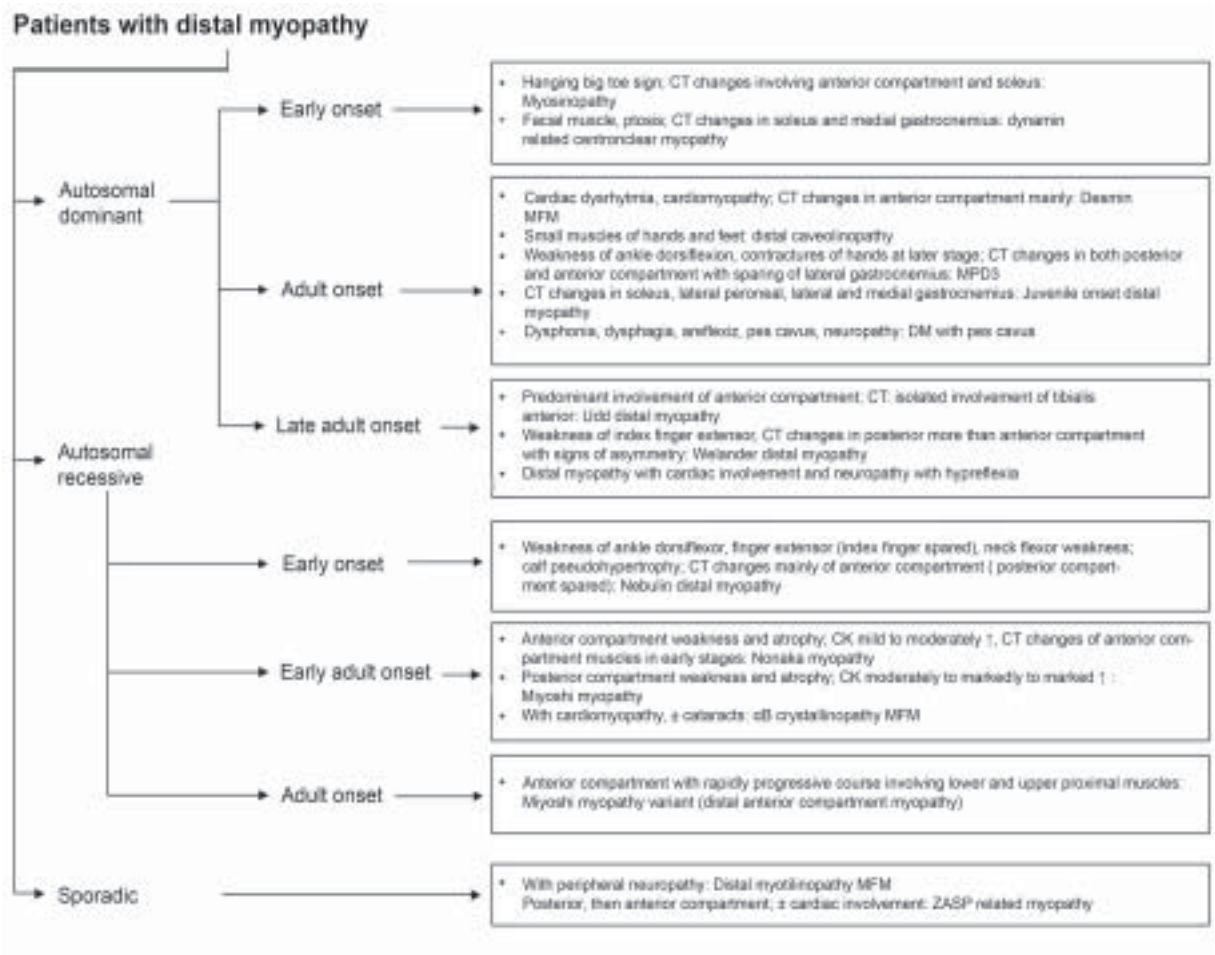

Figure 6: A simple algorithm for the diagnosis of patients with muscle weakness predominantly involving the distal extremities

also of nuclear glycosylation and is present on RNA polymerase II and its associated transcriptional factors, nucleoporins etc[77] and could probably influence signal transduction.[78] Defective nuclear glycosylation may alter nuclear function which results in various defects in protein metabolism inducing amyloid deposition and protein misfolding.[55]

Welander Distal Myopathy (late onset, Type 1)

Welander described 249 patients from 72 pedigrees with autosomal dominant inheritance exclusively among the Swedish population.[79,80] Onset is late, usually after the age of 40 years, and muscle weakness initially involves the distal extensor muscles of the hands and feet, and later the arms and legs. Symptoms are slowly progressive but can be detected earlier in young middle-aged relatives of the patients.[79,81] Serum CK levels are normal or mildly elevated. On linkage analysis, Welander distal myopathy (WDM) was clearly separated from other distal myopathies and the gene was mapped to Chromosome 2p13,[82] but specific causative gene still awaits identification up to this time.

Pathological features in WDM include both myopathic and neuropathic changes, with RVs as the most striking finding.[83,84] On electron microscopy, there is focal myofibrillar degeneration, autophagic vacuoles and nuclear inclusions with tubulofilamentous structure measuring 15-20 nm in diameter,[79] similar to those seen in DMRV/hIBM. RVs are abundant in muscle biopsies from patients with moderate to severe symptoms, but are absent in the early stages of the disease. It is therefore still uncertain whether RV formation is a primary pathologic event that induces muscle fiber atrophy and loss, or is a secondary change associated with the primary dystrophic process.[83] Decreased numbers of myelinated fibers were found in some sural nerve biopsies, suggesting that there is also peripheral nerve involvement.[84]

Vocal cord and Pharyngeal weakness with Autosomal Dominant Distal Myopathy (MPD2)

A unique distal myopathy with vocal cord and pharyngeal weakness inherited as an autosomal dominant trait has been reported in a Caucasian family from Southern Tennessee.[85] The gene has been mapped Chromosome 5q31. The onset of the disease ranged from

35 t0 57 years, averaging 45.7 years. Muscle weakness usually involves the feet and ankles, often in a peroneal distribution, and the hands. Vocal cord and pharyngeal weakness can be present at the onset of the distal extremity weakness. Serum CK levels are normal to mildly elevated. Muscle biopsies in six patients showed a noninflammatory myopathy with RVs, and groups of atrophic fibers consistent with denervation. No nuclear inclusions were found.

Oculopharyngodistal Myopathy

There are two categories of this disorder with different modes of inheritance, autosomal dominant[86,87] and recessive.[88] Four families with autosomal dominant inheritance who were first described by Satoyoshi *et al.*,[86] had late onset external ophthalmoplegia, facial and bulbar muscle weakness, and distally dominant limb muscle weakness. Leg muscle weakness usually precedes ocular and pharyngeal symptoms. The disease is slowly progressive. It remains to be determined whether oculopharyngodistal myopathy is a variant form of oculopharyngeal muscular dystrophy, because distal weakness has also been described in some oculopharyngeal muscular dystrophy families. Recently, we examined five patients with the clinical characteristics of oculopharyngodistal myopathy for GCG expansion in poly(A)-binding protein nuclear 1 gene, the causative gene defect for oculopharyngeal muscular dystrophy. Since only one of our five patients had the significant GCG expansion, oculopharyngodistal myopathy is concluded to be a genetically heterogeneous disorder.[89]

Oculopharyngodistal myopathy with an autosomal recessive inheritance has been reported in two patients from a Japanese family who had anterior tibial muscle weakness beginning after the age of 40 and 50 years respectively.[88] Distal upper extremity weakness and drooping eyes gradually became evident. In their muscle biopsies, there were myopathic changes with RVs in atrophic fibers and cytoplasmic filaments measuring 16-18 nm in diameter.

Conclusion

Precise diagnosis in distal myopathies remains as a challenge to clinicians, but some clues from the clinical history could be used for differential diagnosis [Figure 6]. The classification of distal myopathies would need some clarifications in the near future, especially that the molecular bases for such diseases are just starting to be clarified. More importantly, further analyses of the biological and molecular aspects of this disease in correlation to the clinical data, which are ongoing for some of the established entities , is expected to provide clues for understanding the mechanism behind why distal muscles are affected.

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