BILATERAL DISTAL LOWER LIMB MUSCLE WEAKNESS: DIAGNOSTIC APPROACH.

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Abstract

Background: Patients with pure distal weakness represent a diagnostic challenge. Most of them prove to have a peripheral neuropathic condition, either neuropathy or radiculopathy, but other diagnoses less common, should be considered as well.

Methods: We report a case of a young woman with bilateral drop foot and describe the diagnostic approach, that led to the final diagnosis.

Results: Electrodiagnostic studies limited the diagnostic umbrella, and with the help of muscle biopsy and genetic testing, she was identified as suffering from Nonaka myopathy, one of the five classic distal myopathies.

Discussion: Distal myopathies, neuromuscular junction disorders and central nervous system lesions are rare but nevertheless possible causes of distal limb weakness. In this review article, these conditions are discussed in the light of electrodiagnostic studies, that are a valuable diagnostic tool in investigating these cases and help distinguish one from the other.

Keywords: distal myopathy; electrodiagnostic studies; Nonaka myopathy

ΑΜΦΟΤΕΡΟΠΛΕΥΡΗ ΠΕΡΙΦΕΡΙΚΗ ΜΥΪΚΗ ΑΔΥΝΑΜΙΑ ΚΑΤΩ ΑΚΡΩΝ: ΔΙΑΓΝΩΣΤΙΚΗ ΠΡΟΣΕΓΓΙΣΗ

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Περίληψη

Οι ασθενείς με αμιγή μυϊκή περιφερική αδυναμία αποτελούν μία διαγνωστική πρόκληση Οι περισσότεροι από αυτούς αποδεικνύεται ότι έχουν προσβολή είτε νεύρων είτε ριζών, αλλά και άλλες λιγότερο συχνές διαγνώσεις πρέπει να λαμβάνονται υπόψη. Αναφέρουμε την περίπτωση νεαρής γυναίκας με αμφοτερόπλευρη πτώση άκρου ποδός και περιγράφουμε τη διαγνωστική προσέγγιση που οδήγησε στην τελική διάγνωση. Ο νευροφυσιολογικός έλεγχος περιόρισε τις πιθανές διαγνώσεις και με τη βοήθεια της βιοψίας μυός και του γενετικού ελέγχου ετέθη η διάγνωση της μυοπάθειας Nonaka, μίας εκ των πέντε κλασσικών περιφερικών μυοπαθειών. Οι περιφερικές μυοπάθειες, οι νόσοι νευρομυϊκής σύναψης και οι βλάβες του Κεντρικού Νευρικού Συστήματος αποτελούν σπάνιες αλλά υπαρκτές πιθανές αιτίες περιφερικής μυϊκής αδυναμίας. Σε αυτό το άρθρο ανασκόπησης, περιγράφονται αυτά τα σπάνια αίτια υπό το πρίμα του νευροφυσιολογικού ελέγχου, που αποτελεί πολύτιμο διαγνωστικό εργαλείο στη διερεύνηση αυτών των περιστατικών και στη διάκριση μεταξύ τους.

Λέξεις-κλειδιά: distal myopathy; electrodiagnostic studies; Nonaka myopathy

Introduction

Certain conditions should be considered when evaluating a patient with distal weakness. If there are no sensory abnormalities, the differential diagnosis is further limited to diseases affecting the muscles, neuromuscular junction, motor nerves, anterior roots, and motor neurons, either lower or upper (figure 1).

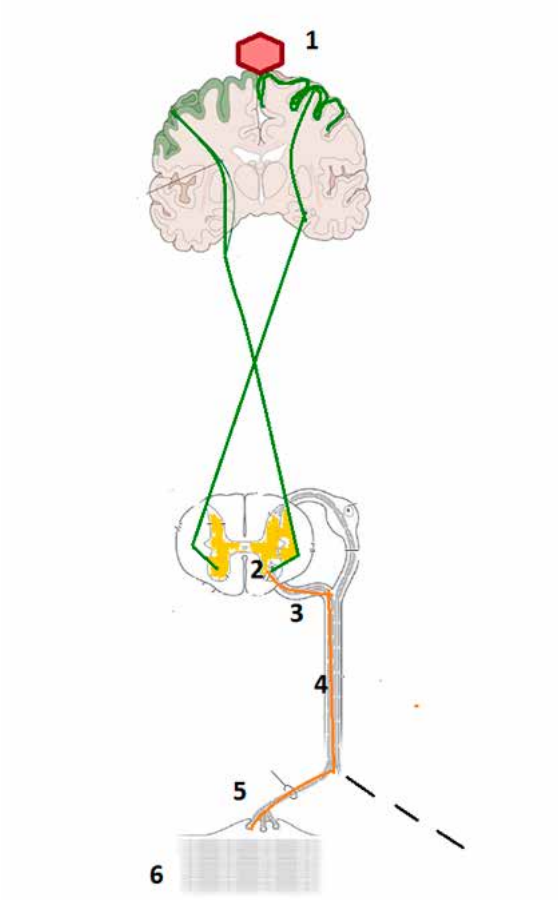

Figure 1: 1. Parasaggital lessions 2. Lower motor neuron diseases 3. Anterior root lesions 4. Peripheral neuropathy (motor) 5. Neuromuscular junction disorders 6. Myopathies

Patients with peripheral weakness are mostly thought to have a peripheral neuropathic condition. However, less common causes should be considered. Beginning from the most distal part, myopathies only rarely affect distal parts. Most myopathies affect proximal muscles of the legs and arms, or the so-called "limb-girdle" distribution. Barohn et al [1] describes 10 distinctive patterns of muscle weakness. Pattern 2 (Distal Weakness), pattern 3 (Proximal Arm/Distal Leg Weakness (Scapuloperoneal) and pattern 4 (Distal Arm/Proximal Leg Weakness) include those myopathies that affect exclusively or concomitantly distal muscles.

Five distinct predominantly distal myopathies have been identified [2]: Welander myopathy (late adult onset, type 1), Markesbery–Griggs/Udd myopathies (late adult onset, type 2), Nonaka myopathy (early adult onset, type 1), Miyoshi myopathy (early adult onset, type 2) and Laing myopathy (early onset, type 3) [3]. Other less common distal myopathies are listed in Table 1. Apart from these classic forms, other myopathies may occasionally present with distal weakness (Table 2).

Neuromuscular junction diseases, namely Myasthenia Gravis, present with purely motor symptoms but with a distinct pattern. Patients with Myasthenia Gravis (MG) typically present with fatigable muscle weakness, involving the facial and bulbar muscles, the neck and trunk muscles and the proximal limbs, the upper limbs affected more severely than the lower limbs. Distal extremity muscles are typically spared. However, predominance of muscle weakness and fatigability in distal limb muscles should not be ignored and might be more frequent than suspected [4]. Hand muscles, particularly finger extensors, are more frequently involved than were distal leg muscles [5].

Most peripheral neuropathies involve mainly sensory fibers. Pure motor neuropathies are much less common. Multifocal motor neuropathy with conduction block [6] is a rare, slowly progressive, asymmetric distal limb motor neuropathy with an upper limb predilection. Hereditary neuropathy with liability to pressure palsy (HNPP) may present with unilateral or bilateral drop foot [7]. Spinal root compression, is a common medical condition, caused most often by disc degeneration and herniation and spondylosis. Posterior (sensory) roots are more often injured, resulting in pain and numbness in the corresponding dermatomes. Pure motor weakness due to L5 and less commonly L4 radiculopathy, rarely occurs, and bilateral presentation is considered extremely rare. The same applies for bilateral sciatic and peroneal neuropathy, bilateral lumbosacral plexopathy, cauda equina and conus medullaris lesion [7]. Anterior compartmental syndrome of the leg may result to distal weakness but bilateral presentation is a rarity.

Anterior horn diseases lead to pure motor weakness sparing sensory system. Spinal Muscular Atrophy (SMA), present from early childhood is characterized by degeneration and loss of motor neurons in the anterior horn of the spinal cord, leading to progressive muscle weakness. Depending on age of onset, severity and life expectancy may vary. Proximal muscles are preferentially affected, as are lower more than upper extremities. Adult-onset Type IV SMA presents as mild proximal muscle weakness with normal expectancy [8].

Amyotrophic Lateral Sclerosis (ALS), the most common motor neuron disease, is characterized by progressive degeneration of upper (UMN) and lower

(LMN) motor neurons in the brain and spinal cord. ALS leads to progressive muscle weakness leading to death, usually from respiratory failure. ALS most often affects the limbs at onset, and symptoms are unilateral. Sensory system is spared. UMN features, like pyramidal signs, accompany those of LMN involvement [9].

Lastly, distal motor weakness, may occur in cases of selective involvement of pyramidal tract. Cortical lesion may mimic peripheral injury, especially when lesion is situated in interhemispheric fissure, such as a parasagittal meningioma, that may even affect both primary motor cortices [10]. In those cases, drop foot with UMN signs, should raise the suspicion of central origin of distal weakness.

Case Description

We report a case of a young woman 22 years old, who developed a slowly progressive distal weakness in the lower limbs since last year. She didn't report pain or sensory disturbances nor bulbar symptoms. She didn't report cramps, myalgia or fatigue. Her medical history consisted of adrenal hyperplasia, for which she was under prezolon 5 mg/d. On physical examination she had symmetrical weakness on walking on heels (MRC grade 3/5 for foot extension), while she could walk on toes. She had no difficulty in arising from a squatted or supine position. She had mild weakness in adduction and abduction of thighs (MRC grade 4+/5). Deep tendon reflexes were elicited symmetrically with the exception of achilles reflexes that were abolished. Sensation to touch, pain, vibration and joint position sense was normal as was cranial nerve examination. Muscle tone was normal and had a bilateral flexor plantar response.

Bloods tests were normal or negative for the following investigations: Full blood count, urea and electrolytes, liver function tests, vitamin D, B12 and folate, creatine kinase (CK) 335 U/L, normal range 26–192), lactate dehydrogenase 223 U/L (normal range 133–225 U/L), antinuclear antibodies 9.99 U/ml (normal range <12 U/ml), immunoglobulin and protein electrophoresis. Only creatine kinase (CK) 335 U/L (normal range 26–192) was slightly elevated. CSF was normal.

Based on the clinical picture and physical examination, which showed symmetrical distal weakness in the lower extremities, the differential diagnosis showed mainly a peripheral nerve disorder with a predisposition to motor fibers. Second, the history of chronic steroid intake raised the hypothesis of an underlying myopathy, even though the distribution of weakness did not fit the more common proximal pattern. As for the other possible causes of distal weakness, they were considered more remote, based on specific features: too young for ALS, no pyramidal signs for parasaggital lesions, symmetrical occurrence not common in radiculopathies, no fatigue as expected in MG.

She underwent neurophysiological investigation. Nerve conduction studies (NCS) were normal in upper and lower limbs. Needle electromyography (EMG) revealed fibrillation and positive potential in all examined muscles in lower limbs, sparing quadriceps and low-amplitude and short-duration polyphasic motor units action potentials (MUAPs) in several muscles in upper and lower limbs (Figure 2).

Figure 2

MUSCLE	FIBRILLATIONS / POSITIVE WAVES	MUAP MORPHOLOGY	RECRUITMENT
Extensor Digitorum Communis R	0/10	Normal	Normal
Biceps R	0/10	Normal	Normal
Trapezius R	0/10	Normal	Normal
Deltoid R	0/10	Short duration, low amplitude, polyphasic	Early
Tibialis Posterior R	3/10	Short duration, low amplitude, polyphasic	Early
Gastrocnemius Medial Head R	5/10	Short duration, low amplitude, polyphasic	Early
Gastrocnemius Medial Head L	3/10	Short duration, low amplitude, polyphasic	Early
Tibialis Anterior R	6/10	Short duration, low amplitude, polyphasic	Early
Tibialis Anterior L	5/10	Short duration, low amplitude, polyphasic	Early
Vastus Lateralis R	0/10	Normal	Normal
Tensor Fasciae Latae R	3/10	Short duration, low amplitude, polyphasic	Early
Biceps R	2/10	Short duration, low amplitude, polyphasic	Early

R: right, L: Left

Figure 2: EMG findings

MRI lumbosacral spine was normal. Cerebrospinal fluid (CSF) examination was unremarkable apart from positive oligoclonal bands with normal IgG index 0.5 (normal range <0.8).

SMA gene testing for type 3 and 4 was negative. Muscle biopsy from left gastrocnemius muscle revealed rimmed vacuoles and eosinophilic inclusions (figure 3).

Figure 3

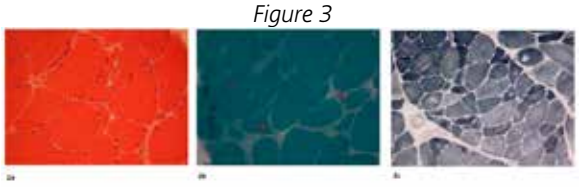

Figure 3: HE: increased muscle fiber diameter variability - in the center of the slide, there is a muscle fiber with multiple irregular-shaped rimmed vacuoles
GMT: multiple muscle fibers with rimmed vacuoles and eosinophilic inclusions
NADH: disruption of intermyofibrillar network in multiple muscle fibers and unevenness of oxidative staining in some of them resembling core-like areas

Whole Exome sequencing showed the c.1985C>T (p.A662V) GNE pathogenic variant (previously referred to as p.A631V) that has been reported in individuals with GNE-related [11].

Discussion

This is a case of a symmetrical distal pure motor weakness, that was complicated by the EMG findings. The first hypothesis of peripheral nerve disorder was ruled out, since NCS were totally normal. On the other hand, EMG findings were consistent with neurogenic (acute denervation) and myopathic (small polyphasic motor units) lesion simultaneously, in a wide distribution, mainly distally.

Acute denervation

Acute denervation is the hallmark of lower motor neuron diseases and is associated with neuropathic disorders (neuropathies, radiculopathies). A fibrillation potential (FP), which is a spontaneous depolarization of a muscle fiber, is derived from the extracellular recording of a single muscle fiber. Positive sharp waves (PW) have the same significance as FP: they are the spontaneous depolarization of a muscle fibers. The mechanism by which a single muscle fiber action potential can assume either a FP (i.e., brief spike) or a PW morphology is not completely agreed upon [12]. They both represent the spontaneous firing of a single muscle fiber with an unstable resting membrane. FP/PWs occur in any muscle fiber that is not innervated, due to neurogenic or myopathic processes.

In neurogenic disorders, such as radiculopathies, mononeuropathies, or motor neuron disease, loss or degeneration of axons leads to denervated muscle fibers. Although FP/PW are typically associated with neuropathic disorders, they also may be seen in some muscle disorders (especially the inflammatory myopathies and dystrophies) and rarely in severe diseases of the Neuromuscular Junction (NMJ), especially botulism [12]. In myopathic diseases, that produce pathologic changes of muscle fiber necrosis, fiber splitting, functional denervation of individual or segments of muscle fibers, occurs as the fiber becomes separated from the end plate zone [1] [3]. The presence of FP/PW potentials in myopathic disorders probably relates to isolation of part of the muscle fibers from their endplates, so that they are denervated functionally (Figure 4) [14].

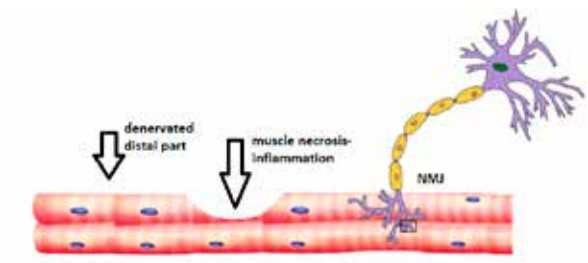

Figure 4: Generation of fibrillation potentials / positive sharp waves in injured muscle fibers

They are thought to most likely occur as a consequence of segmental inflammation or necrosis of muscle fibers, separating a distal, healthy portion of the muscle fiber from the part attached to the endplate. Infarction of small intramuscular nerve twigs by surrounding interstitial inflammation also is speculated to be a possible cause of denervation in inflammatory myopathies. Although the presence of denervating potentials in a patient with myopathy often suggests the diagnosis of an inflammatory myopathy, denervating potentials can occur in a variety of myopathies. In chronic myopathies, complex repetitive discharges may also be seen.

Inflammatory myopathies (Polymyositis, Dermatomyositis, Inclusion Body Myositis) are characterized by tenderness and weakness. Proximal muscles are preferably affected. Spontaneous activity is generally profuse. However, in one large study of 98 patients with myositis, a distal-to-proximal gradient of abnormalities was found in the lower limbs, which might lead to confusion with neurogenic diseases [15], as it happened in our case. In Muscular Dystrophies FP, PW and complex repetitive discharges may be found because of segmental necrosis of muscle fibers or the presence of regenerating fibers. In hypothyroidism spontaneous FP/PW and fasciculation potentials, together with trains of complex repetitive discharges, may also be found in rare instances [14]. It must be remembered that in cases of endocrine myopathies, other types of neuromuscular disorders may coexist, and that these may complicate the EMG findings. Patients with hypothyroidism are liable to develop peripheral nerve entrapment syndromes. Similar findings are encountered in cases of hyperkalemic or normokalemic periodic paralysis and in patients with acid maltase deficiency, where spontaneous FP/PW, myotonic discharges, and complex repetitive potentials may be found. However, the motor unit action potentials are similar in character to those seen in other myopathies, that is motor unit action potentials are reduced in duration and number [14].

Myopathy is a rare manifestation of primary systemic amyloidosis. Needle EMG reveals findings similar to those of a chronic inflammatory myopathy. FP/PW potentials are common, most often in the gluteus medius and paraspinal muscles. Motor unit action potentials may be of short duration and low amplitude, especially in proximal muscles; however, long-duration large potentials sometimes are found, and occasionally a mixed population of motor units is encountered [16].

In chronic alcoholics, EMG typically reveals FP/PW and motor unit action potentials that are small and of short duration [14]. In Critical Illness Myopathy the EMG findings include small, short duration, polyphasic, motor unit action potentials and early

recruitment of motor units; FP/PW is sometimes conspicuous and cannot be used to distinguish critical illness neuropathy from myopathy [17],[18].

FP/PW are rarely seen in MG or botulism [19]. They are usually inconspicuous and present mostly in proximal muscles, most commonly in bulbar and paraspinal muscles of patients with late-onset disease. Their presence should raise the suspicion of an alternate diagnosis or associated illness. The mechanism of FP/PW in NMJ disorders is likely persistent transmission block, resulting in ''effective'' denervation of individual muscle fibers. A full report of myopathies and NMJ diseases with FP/PW is presented in table 3.

MUAPs morphology

The second main finding of EMG was short duration, small amplitude, polyphasic MUAPs. In most myopathies, there is dropout or dysfunction of individual muscle fibers that effectively decreases the size of the motor unit whereas the actual number of motor units does not change, as it happens in motor neuron diseases.

MUAP amplitude depends on just the few muscle fibers that are very close to the needle electrode. MUAP phases often are increased (>4 phases) in myopathy, but this is a nonspecific finding. The number of phases is primarily a measure of synchrony, and polyphasia may be seen in both myopathic and neuropathic disorders.

MUAP duration is the most important parameter to measure in myopathy as it reflects the total number of muscle fibers in a motor unit. In myopathy and myositis duration characteristically decreases, explained by the random dropout of muscle fibers. Short-duration MUAPs often have low amplitude and early (rapid) recruitment because small MUAPs generate a small amount of force. Hence, early recruitment refers to inappropriate firing of many small MUAPs to overcome the handicap. However, because each motor unit has fewer fibers than normal, it can generate less force.

Brief-duration MUAPs may be seen in conditions other than myopathy, whenever a disorder causes loss or dysfunction of individual muscle fibers (e.g., myopathy, NMJ disorders with block, disorders of the terminal axon) without affecting the motor neuron and its main axon [12].

In ALS, when early reinnervation occurs after severe denervation, only a few fibers may be successfully reinnervated, resulting in nascent (early reinnervated) motor unit potentials, which are also short and small [20].

In NMJ disorders, conventional needle EMG is usually normal. However, non-specific changes are often observed, like FP/PW discussed earlier. Short duration, low amplitude, and polyphasic MUAPs in proximal muscles, similar to those seen in myopathies are occasionally found. Those small MUAPs are caused by physiological blocking and slowing of neuromuscular transmission at many end plates during voluntary activation. This leads to exclusion of many muscle fiber action potential from the MUAP (hence the short duration and low amplitude) and delay of neuromuscular transmission of other fibers (hence the polyphasia) [19].

In periodic paralysis, during paralytic attack show low CMAPs, decrease insertional activity, and short-duration, low-amplitude, and polyphasic MUAPs [7]. Lastly, in paraneoplastic syndromes, antibodies may selectively attack terminal axons resulting in small MUAPs [21].

Table 4 shows all non-myopathic disorders showing "myopathic" MUAPs.

Interference Pattern (IP)

Interference Pattern depends on recruitment and activation of MUAPs. Recruitment refers to the ability to add MUAPs as the firing rate increases**.** Recruitment is altered in peripheral disorders. It is reduced in neuropathic diseases due to loss of MUAPs. In the case of myopathies, where there is loss of muscle fibers, MUAPs become smaller, and generate less force. As a consequence, many small MUAPs must fire almost simultaneously to generate a small amount of force, and this phenomenon is called "early recruitment". Early recruitment might also be seen in NJM disorders. However, in chronic myopathies, where most muscle fibers in many motor units are lost, the number of MUAPs decreases. This results in decreased recruitment which may be confused with a neurogenic disorder [7]. Activation refers to the ability to increase firing rate and is a central process. Poor activation is seen in diseases that affect Central Nervous System or may reflect poor cooperation due to pain or functional disorders [12]

Diagnostic Approach

In this case of bilateral distal lower limb muscle weakness, several possible diagnoses should be considered, as discussed in the Introduction section. Electrodiagnostic studies is the main tool to support or rule out each of them. Distal lower limb weakness caused by central lesions, situated in the parasaggital area, would not have elicited acute denervation, nor small MUAPs. The main finding would have been poor activation of MUAPs resulting in poor IP. Lower motor neuron diseases, ALS and SMA, can elicit both acute denervation and small MUAPs. ALS was ruled out due to patient's

Table 1. Classic and Less Common Distal Myopathies [1,3,32]

TYPE	INHERITANCE	INITIAL WEAKNESS	BIOPSY
CLASSIC DISTAL MYOPATHIES			
Welander— late adult type 1	AD	Hands, fingers, wrist extensors	Myopathic; rimmed vacuoles in some
Udd—late adult type 2a	AD	Legs, anterior compartment	Myopathic; rimmed vacuoles in some
Markesbery—Griggs late adult type 2b	AD	Legs, anterior compartment	Vacuolar myopathy; myofibrillar features
Nonaka—early adult onset or sporadic type 1 (h IBM2)	AR	Legs, anterior compartment	Vacuolar myopathy
Miyoshi—early adult onset type 2 (LGMD 2B)	AR or sporadic	Legs, posterior compartment	Myopathic, usually no vacuoles; "endstage" gastrocnemius
Laing—early adult onset type 3 (MPD1)	AD	Legs, anterior compartment, neck flexors	Moderate myopathic changes; no vacuoles in most
LESS COMMON DISTAL MYOPTHIES			
Myopathy with anterior leg sparing	AD	Calf & hands	Fiber size variability
Myopathy with Paget's & dementia young adult	AD	Proximal & distal leg	Myopathy with vacuoles
Distal Myopathy with vocal cord & pharyngeal weakness, MPD2 – late adult onset	AD	Legs, hands or vocal cords	Myopathy with vacuoles
Miyoshi-like myopathy 3 early adult onset	AR	Posterior legs	Myopathy with sarcolemmal lesion
Distal nebulin myopathy -child or adult	AR	Toe & finger extensor	Myopathy with small rods
limb girdle muscular dystrophy 2G puberty onset	AR	Leg: proximal & anterior distal	Myopathy, rimmed vacuoles
Distal myopathy type 3 (MPD3) early adult onset	AD	Asymmetric distal leg & hand	Myopathy with vacuoles

young age and the lack of pyramidal signs. SMA type III, IV was considered as a possible diagnosis and genetic testing was ordered, but the diagnosis was not confirmed. Lesions in anterior roots could have given rise to FP/PW but not to small MUAPs, nor to early recruitment. Motor neuropathies were ruled out since motor conduction studies were normal. NMJ disorders might have had FP/PW and small MUAPs, but clinically no fatigue was documented. Finally, distal myopathy**,** is the last possible explanation of the electrophysiological findings. A biopsy was performed from left gastrocnemius (lateral head muscle) that showed myofribillar inclusions (figure 2). Genetic testing confirmed the diagnosis of Nonaka myopathy.

Nonaka Myopathy

Nonaka myopathy, described in 1981 by Nonaka[22]is a distal myopathy with rimmed vacuoles and lamellar (myeloid) body deposits cause by mutations in gene GNE which encodes for the N-acetylglucosamine epimerase/N-acetylmannosamine kinase (GNE) [23]. This myopathy is also called "Quadriceps Sparing Myopathy" and "Hereditary Inclusion Body Myopathy", due to histological similarities to Inclusion Body Myositis. GNE myopathy has an estimated worldwide prevalence of 1/1.000.000 [24]. Symptoms occur most frequently in the third decade of life, although, few early and late onset cases have been reported [25]. The typical clinical presentation begins with distal weakness in the legs (foot drop). Progressive muscle weakness and atrophy follows in lower and upper limbs, with relative sparing of quadriceps. Simultaneous involvement of posterior thigh muscles and tibialis anterior point towards GNE myopathy [26]. Neurological examination is otherwise normal, as it is with cognition.

Routine blood tests reveal mild to moderate CK elevation and probable mild ALT elevation. Muscle imaging is a non-invasive tool helping to diagnose patients in early stages. MRI shows preferable muscle damage in distal legs (anterior compartment) and posterior thigh compartment while quadriceps remains unaffected [27]. Muscles in younger patients that appear normal in T1, occasionally show hyperintensities in T2-weighted sequences, which may indicate a degree of edema.

There are limited number of studies assessing cardiac involvement in GNE myopathy and did not show any specific abnormality linking GNE myopathy to heart disease. It is also generally considered that GNE myopathy does not predispose to respiratory failure [28].

EMG in patients with Nonaka myopathy correlate with clinical presentation and show myopathic

Table 2. Other myopathies that can have distal weakness [3,32]

	TYPE	WEAKNESS
Myotonic dystrophy (DM)		
	Facioscapulohumeral dystrophy (FSH) [1]	Scapuloperoneal distribution
	Scapuloperoneal syndromes	
	Oculopharyngeal dystrophy	
	Oculopharyngodistal myopathy (recessive)	
	Emery-Dreifuss humeroperonal dystrophy	
Inflammatory myopathy		
	Inclusion body myositis (IBM) [1]	Wrist and finger flexors
	Polymyositis [1]	Wrist and finger flexors
Metabolic myopathy		
	Debrancher deficiency [33]	Scapuloperoneal distribution
	Acid-maltase deficiency [34]	Scapuloperoneal distribution
Congenital myopathy		
	Nemaline myopathy [35]	Ankle dorsiflexion weakness
	Central core myopathy [36]	Weakness of the great toe and ankle dorsiflexors
	Centronuclear myopathy type 2 (Dynamin 2; 19p13)[37]	distal upper and lower limbs weakness
Nephropathic cystinosis [3]		Distal myopathy and dysphagia
Cytoplasmic body myopathy (Myofibrillary inclusions in Type I muscle fibers; Dominant)		
Hyperthyroid myopathy		
hIBM3 (Myosin heavy chain IIa; Chromosome 17p13; Dominant)		
hIBM and respiratory failure (6q27; Dominant)		
Distal weakness (distal myopathy or motor neuropathy; KLHL9; Chromosome 9p22; Dominant)		
Distal weakness, hoarseness & hearing loss (MYH14; Chromosome 19q13.33; Dominant)		

changes and spontaneous activity [22]. Muscle biopsies are characterized by small angular fibers, rimmed vacuoles, deposition of various proteins and intracellular Congo red-positive depositions in vacuolated or non-vacuolated fibers. Inflammatory cell infiltration can occasionally be detected. Finally, the GNE gene is located on chromosome 9 and consists of 13 exons. Spectrum of disease-causing mutations is wide and constantly growing. Currently, over 150 mutations are known to be causative for GNE myopathy [29].

There is no approved treatment for GNE myopathy to date. Current patient management is focused on improving quality of life by addressing major symptoms. It is known that the disease gene GNE, encodes glucosamine (UDP-N-acetyl)-2-epimerase and N-acetylmannosamine kinase, two essential enzymes in sialic acid biosynthesis. Muscle atrophy and weakness were completely prevented in a mouse model after treatment with sialic acid metabolites orally, thus providing evidence that hyposialylation might be one of the key factors in the pathomechanism of GNE myopathy [30]. IVIG therapy was tried in a small group of patients with modest results. However, Immunohistochemical staining and immunoblotting of muscle biopsies for alpha-dystroglycan and NCAM did not show that IVIG treatment improves muscle syalilation, and therefore, IVIG therapy was abandoned [31]. The intermediate of the sialic acid biosynthesis pathway - N-acetyl-D-mannosamine (ManNAc) is another potential therapeutic option. ManNAc is reported to be safe with recent publications suggesting that ManNAc restores the intracellular biosynthesis of sialic acid [22]. Patients suffering from GNE may benefit of consumption of food rich in sialic acid, such as milk and dairy products (e.g. whey) but no research has been conducted yet to support this. On the other hand, physical therapy is strongly recommended to patients to help them maintain functioning.

Conclusions

GNE myopathy is a rare disease, discovered relatively recently, 40 years ago, with a unique presentation, affecting mainly distal limbs and with a unique neurophysiological picture, i.e. small MUAPs and active denervation at the same time. However, when assessing a patient with distal limb weakness without sensory disturbances, among other diagnostic thoughts, GNE myopathy should always be considered.

Table 3 Myopathies with FP/PW [7,12,13]

Inflammatory
Polymyositis / Dermatomyositis, Inclusion Body Myositis, HIV associated myopathy, Human T-cell lymphotropic virus-1 myopathy/polymyositis
Infiltrative
Sarcoid Myopathy, Amyloid
Muscular dystrophies
Dystrophin deficiency (Duchenne and Becker), Facioscapulohumeral muscular dystrophy, Autosomal recessive distal muscular dystrophy, Emery–Dreifuss muscular dystrophy, Oculopharyngeal muscular dystrophy, Limbe-girdle
Myotonic Dystrophies
Metabolic myopathies
Acid maltase deficiency myopathy, Carnitine deficiency myopathy, Debrancher deficiency myopathy
Hypothyroidism
Critical Illness Myopathy
Congenital myopathies
Centronuclear/Myotubular myopathy, Nemaline rod myopathy
Infectious myopathy
Trichinosis, Toxoplasmosis
Muscle trauma and Acute rhabdomyolisis
Toxic myopathies
Colchicine, azidothymidine (AZT), alcohol, chloroquine, hydroxychloroquine, pentazocine, clofibrate, ε-aminocaproic acid, cholesterol-lowering agents, Lipid lowering agents
Neuromuscular Junction Diseases
Myasthenia Gravis, Lambert-Eaton Myasthenic Syndrome, Botulinum intoxication

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