REVISTA NEUROCIÊNCIAS

Hereditary inclusion body myopathy: a clinical and genetic review

Miopatia com corpos de Inclusão hereditária: revisão clínica e genética

Miopatía por cuerpos de inclusión hereditária: revisión clínica y genética

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Resumo

Introdução. Miosite com corpos de inclusão representa a miopatia adquirida mais comum na prática clínica de início após os 50 anos. Apesar da abordagem clássica de tal miopatia como condição clínica inflamatória, a base degenerativa muscular é considerada atualmente o principal mecanismo ligado a tais miopatias vacuolares. Formas hereditárias, embora raras, representam um grupo em expansão e pouco reconhecido na prática clínica. **Objetivo.** realizar revisão estruturada da literatura atual a respeito das formas hereditárias de miopatia com corpos de inclusão. **Método.** revisão das bases de dados da U.S. NLM PubMed e MEDLINE para análise de artigos originais, relatos de casos, series de casos e artigos de revisão incluindo os termos-chave "inclusion body myositis" OR "inclusion body myopathy" AND "genetics" OR "hereditary". **Resultados.** Este manuscrito oferece amplo artigo de revisão da literatura a respeito dos principais aspectos clínicos, de imagem, fisiopatológicos, genéticos e terapêuticos relacionados a miopatias hereditárias ligadas a 7 apresentações clínicas e genéticas diferentes (*GNE, MATR3, VCP, SQSTM1, MYH2, HNRNPA2B1* e *HNRNPA1*). **Conclusão.** Miopatia com corpo de inclusão hereditária se associa atualmente a pelo menos 7 formas clínico-genéticas monogênicas distintas.

Unitermos. Miopatia com corpos de inclusão; neurogenética; miopatia vacuolar; miosite

Abstract

Introduction. Inclusion body myositis represents the most common acquired myopathy in clinical practice in patients over 50 years old. Despite classical approach to this myopathy as an inflammatory disorder, a muscle degenerative disorder is now considered the main mechanism linked to these vacuolar myopathies. Hereditary presentations, although quite rare, represent an expanding and underrecognized group in clinical practice. **Objective.** perform a structured review of the current literature regarding hereditary inclusion body myopathies. **Method.** review of U.S. NLM PubMed and MEDLINE database of original articles, case reports, case series and review articles including the terms "inclusion body myositis" OR "inclusion body myopathy" AND "genetics" OR "hereditary". **Results.** We present in this article a wide review regarding the main clinical, imaging, pathophysiological, genetic and therapeutic aspects related to hereditary myopathies linked to seven different clinical and genetic presentations (*GNE, MATR3, VCP, SQSTM1, MYH2, HNRNPA2B1* and *HNRNPA1*). **Conclusion.** Hereditary inclusion body myopathy is associated with at least 7 distinct clinic and genetic monogenic forms.

Keywords. inclusion body myopathy; neurogenetics; vacuolar myopathy; myositis

Resumen

Introducción. Miosite com corpos de inclusão representa a miopatia adquirida mais comum na prática clínica de início após os 50 anos. Apesar da abordagem clássica de tal miopatia como condição clínica inflamatória, a base degenerativa muscular é considerada atualmente o principal mecanismo ligado a tais miopatias vacuolares. Formas hereditárias, embora raras, representam um grupo em expansão e pouco reconhecido na prática clínica. **Objetivo.** realizar revisão estruturada da literatura atual a respeito das formas hereditárias de miopatia com corpos de inclusão. **Método.** revisão das bases de dados da U.S. NLM PubMed e MEDLINE para análise de artigos originais, relatos de casos, series de casos e artigos de revisão incluindo os termos-chave "inclusion body myositis" OR "inclusion body myopathy" AND "genetics" OR "hereditary". **Resultados.** Este manuscrito oferece amplo artigo de revisão da literatura a respeito dos principais aspectos clínicos, de imagem, fisiopatológicos, genéticos e terapêuticos relacionados a miopatias hereditárias ligadas a 7 apresentações clínicas e genéticas diferentes (*GNE, MATR3, VCP, SQSTM1, MYH2, HNRNPA2B1* e *HNRNPA1*). **Conclusão.** Miopatia com corpo de inclusão hereditária se associa atualmente a pelo menos 7 formas clínico-genéticas monogênicas distintas.

Palabras clave. Miopatia com corpos de inclusão; neurogenética; miopatia vacuolar; miosite

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INTRODUCTION

Inflammatory myopathies represent the main group of acquired myopathies in clinical practice with well-established clinical, laboratorial, imaging and therapeutical aspects related to idiopathic and paraneoplastic polymyositis and dermatomyositis[1]. Despite its designation and classification as an inflammatory myopathy by most authors in the past[1], Inclusion body myopathy or myositis (IBM) has been progressively recognized as a chronic degenerative muscle disease[2,3]. The frequent changes regarding pathophysiological processes[4-6], the absence of clinical response to a definite specific therapeutic approach[7,8] and the recognition of new sporadic and hereditary clinical

presentations[1,9,10] are disclosing several heterogeneous facets about IBM complexity.

Sporadic IBM (sIBM) represents the main acquired myopathy in patients over the age of 50 years, being frequently underdiagnosed, especially in the early stages of clinical compromise in which there is a clear predominance of selective weakness in long flexors of the fingers and forearms and quadriceps femoris before progression to scapular girdle, lower limb distal groups and bulbar regions[4,10,11]. There are well-established clinico-pathological diagnostic criteria described by the European Neuromuscular Centre in 2011[5] which are currently used to diagnose sIBM with clinical and research purposes.

A complex association of pathophysiological processes occur in sIBM involving abnormal muscle autophagic mechanisms, nitric oxide and class I MHC (major histocompatibility complex) pathway-induced cellular stress responses, prolonged inflammation, proteostasis defects with diverse protein aggregates accumulation, and excessive release of proinflammatory cytokines (highlighting gamma-interferon and interleukin-1β)[1]. There is no doubt that individual or familial genetic predisposing factors are involved in sIBM pathophysiology, including polymorphisms in several genes (including *NOTCH4*) and in different components of the major histocompatibility complex[4,8,12]. As the only therapeutic approach with well-documented efficacy and safety, intravenous immunoglobulin has been used with partial benefit in cases of IBM with dysphagia[7].

Even though sharing some features with sIBM, atypical and heterogeneous clinical early-onset presentations with some distinct pathological features and new neurogenetic patterns, eventually familial, have been described in the last decade and characterize hereditary IBM (hIBM). In this perspective, it has become complex the comprehension of clinical, pathophysiological, radiological and genetic aspects associated with such hereditary myopathies and a wide clinical and genetic review of these new presentations is extremely necessary and presented herein.

METHOD

Looking for a wide review of the current knowledge on the clinical and genetic presentation of hIBM, a wide review of the literature was performed using a structured search in the database of article citations for medical and biomedical current literature from PubMed/MEDLINE and PubMed Central (PMC) (U.S. Department of Health and Human Services, U.S. National Institutes of Health-NIH biomedical research agency, National Center for Biotechnology Information-NCBI, U.S. National Library of Medicine) database, based on MeSH (Medical Subject Heading) vocabulary used for indexing article propose. The used terms in search included "inclusion body myositis" (introduced in 1996 in MeSH) and "inclusion body myopathy" (introduced in 2010 and 2012 in MeSH), including autosomal dominant or recessive inherited presentations. The search strategy used included all case reports, case series, review and

original articles involving: (i) (inclusion body myositis) AND (hereditary); (ii) (inclusion body myositis) AND (genetics); (iii) (inclusion body myopathy) AND (hereditary). Search strategies were updated until 10th July, 2020, and included studies since the first description of sIBM in 1971. All genetic presentations observed were individualized and carefully evaluated and the authors personal experience (including photos and videos from examination studies) was included to improve clinical characterization.

RESULTS AND DISCUSSION

The strategy used in the referred database searching engine provided 1899 distinct manuscripts during the described period for "inclusion body myositis", including 510 review manuscripts, 11 systematic review, 323 case reports and 20 randomized controlled trials. The strategy including "genetics" restricted 641 articles (293 in the last decade), involving 170 review manuscripts, 81 case reports and 2 systematic reviews. Instead of "genetics", the same strategy with "hereditary" brought, since the first result in 1980, 164 results (48 in the last decade), involving 35 reviews and 28 case reports. Using the new proper nomenclature "inclusion body myopathy" and "genetics" in the search resulted 306 results (with 115 in the last decade), including 62 reviews, 60 case reports and 1 systematic review. There was overlap of 365 manuscripts using the referred group strategies and unappropriated manuscripts were also excluded due to low quality of descriptions (i.e. genetic methods, absence of

definite diagnosis, presence of polymorphisms or variants of uncertain significance, conclusion not properly supported by the results, cases with familial sIBM or with confusing classification between sIBM, familial sIBM and hIBM), leading to a final number of 63 studies of interest for this review purposes.

Hereditary Inclusion Body Myopathy (hIBM)

Classification and genetic basis of hereditary Inclusion body myopathy (hIBM)

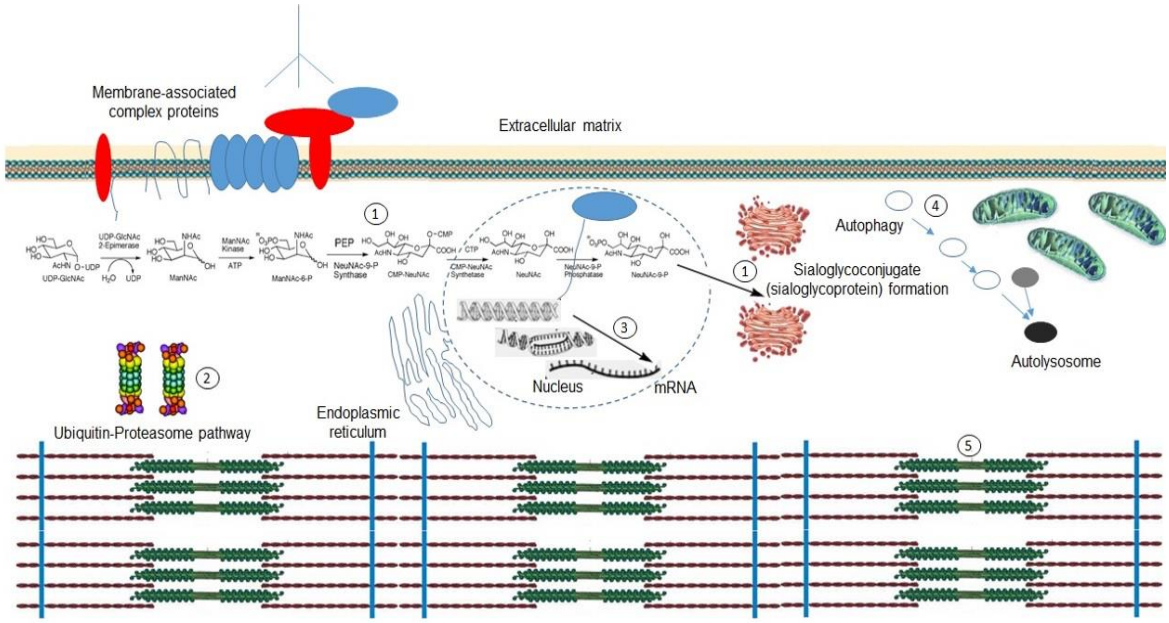
The main current classification regarding hIBM correlates the major genetic presentations associated with autosomal dominant or recessive inheritance pattern and histopathological features with intracytoplasmic or intranuclear tubulo-filamentous inclusions. There are different clinical and genetic forms of hIBM (Table 1), mainly represented by *GNE*-related disorders (Nonaka distal myopathy, former hIBM type 2), *VCP*-associated disorders (former chromosome 9-related hIBM or multisystem proteinopathy type 1), *HNRPA2B1* gene mutations (former multisystem proteinopathy type 2), *SQSTM1* gene mutations, *HNRNPA1* gene mutations (former multisystem proteinopathy type 3), and *MYH2* gene mutations (former hIBM type 3 or chromosome 17-related hIBM)[13-19]. This complex and heterogeneous genetic basis correlates with complex pathophysiological mechanisms in hIBM (Figure 1).

Table 1. Genetic classification and clinical and pathological findings of hIBM[13-15,17-22].

Nomenclature (hIBM type)	Gene (inheritance; locus)	Clinical and pathological hallmarks	Other systemic and neurodegenerative allelic disorders
Nonaka distal myopathy (*GNE*-related disorders; hIBM type 2)	*GNE* (AR; 9p13.3)	Starting in the third to fourth decade; distal and symmetrical in the legs; quadriceps-sparing myopathy phenotype; moderate/severe proximal compromise of the lower limbs and Iliopsoas	Allelic to AD Sialuria (French type)
IBMPFD1 (chromosome 9-related hIBM; multisystem proteinopathy type 1)	*VCP* (AD; 9p13.3)	Starting in the third to seventh decade; limb-girdle proximal, VCP-positive inclusions; one third with early-onset FTLD; early-onset PDB	Allelic to familial ALS type 14, hereditary spastic paraparesis (variant) and CMT type 2Y
IBMPFD2 (multisystem proteinopathy type 2)	*HNRNPA2B1* (AD; 7p15.2)	Starting in the third to fourth decade; scapuloperoneal phenotype; PDB; lower motor neuron disease (rare), FTLD (rare)	------
IBMPFD3 (multisystem proteinopathy type 3)	*HNRNPA1* (AD; 12q13.13)	Starting in the fourth to fifth decade; slowly progressive limb-girdle phenotype, severe involvement of Iliopsoas and abdominal wall; PDB	Allelic to familial ALS type 20
***SQSTM1*-associated hIBM**	*SQSTM1* (AD; 5q35.3)	Late-onset distal myopathy with rimmed vacuoles (TDP-43 and SQSTM1 positive inclusions), PDB	Allelic to FTLD with ALS type 3, PDB type 3
hIBM type 3 (MYPOP; chromosome 17-related hIBM)	*MYH2* (AD/AR*; 17p13.1)	Infancy-onset proximal myopathy (quadriceps femoris, pectoralis major and minor), congenital joint contractures, external ophthalmoplegia, rimmed vacuoles; variable scoliosis and ptosis	Allelic to distal arthrogryposis type 5
MATR3*-associated hIBM (distal myopathy type 2)*	*MATR3* (AD; 5q31.2)	Distal myopathy with vocal cord and pharyngeal dysfunction	Allelic to familial ALS type 21

AD: autosomal dominant; ALS: amyotrophic lateral sclerosis; AR: autosomal recessive; CMT: Charcot-Marie-Tooth disease; FTLD: frontotemporal lobar degeneration; IBMPFD: inclusion body myopathy with early-onset Paget disease of bone with or without frontotemporal dementia; PDB: Paget disease of bone; *: in rare presentations; **: not described separately in the text.

Figure 1. Pathophysiological mechanisms involved in the different hIBM subtypes. The abnormal formation of rimmed vacuoles and intracellular cytoplasmic aggregates depends on the existence of mutations in genes involved in different cell mechanisms: (1) abnormal sialic acid biosynthesis and disruption of sialyation (sialoglycoconjugation) and post-translational changes in intracellular proteins involved in basic homeostasis (i.e. *GNE*); (2) ubiquitin-proteasome system dysfunction; (3) abnormal mRNA metabolism processes and abnormal transcription; (4) abnormal autophagy and autolysosome formation; and (5) abnormal actin-myosin interaction and excitation-contraction coupling (i.e. *MYH2*)[19,21].



Also in the group of vacuolar myopathies with inclusion bodies, heterozygous mutations in *MATR3* gene (5q31.2), typically associated with familial ALS type 21 and distal myopathy with vocal cord and pharyngeal dysfunction (former "distal myopathy type 2"), can present in some cases as IBM phenotype starting in the fourth to sixth decade of life with marked asymmetric involvement of the lower limbs, sparing the gastrocnemius, but also involving hand and shoulder girdle in asymmetrical pattern and bulbar dysfunction[20]. Some authors currently include *MATR3*-related vacuolar myopathy as a cause of hIBM, while others

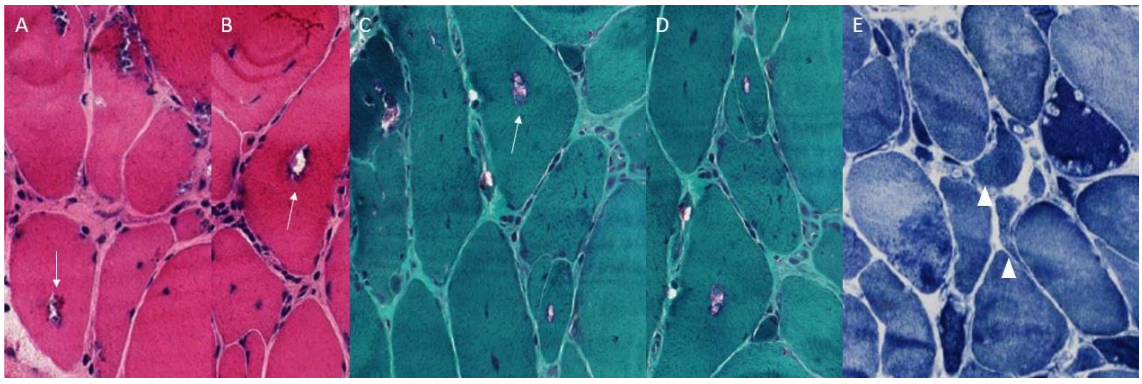
prefer to classify this condition in the distal myopathy group. Classically included in the group of hIBM, the former autosomal dominant IBM type 1 (hIBM type 1), related to homozygous or compound heterozygous mutations in the *DES* gene (2q35), has been classified in the last few years in the group of myofibrillar myopathies (MM), being currently known as MM type 1 (MFM1), as a consequence of direct dysfunction of Z-disk structure by abnormal coding of desmin. However, many authors still classify desminopathies as a cause of hIBM due to the common presence of red rimmed vacuoles in myopathic fascicles[4,8,12-14,17,21].

It is essential to differentiate hIBM from familial IBM (fIBM). Despite nomenclature represents a common final pathway in classification in some neuromuscular disorders, fIBM represents a definition limited to cases in which clinical and histopathological findings of sIBM occur in two or more patients from the same generation from a family or in cases with definite autosomal dominant inheritance pattern. Thus, there are different clinical and muscle histopathological patterns in fIBM when compared to hIBM[12]. It has been well-described several familial aggregates of fIBM with genetic association with specific HLA (human leukocyte antigen) alleles, highlighting DR3 (DRB1*0301/0302) and DR15(2)/4 (DRB1*1502/0405), both which were previously described in cases of sIBM and not correlated with hIBM[4,12,21].

Muscle pathology findings in hIBM

In hIBM, as well as in sIBM, muscle pathology hallmark is the finding of rimmed vacuoles (authophagic vacuoles) (Figure 2), without immunoexpression of MHC class I in muscle fibers, without the presence of congophilic-positive amyloid deposits in vacuoles and without the presence of TCD8+ lymphocytes[1,19]. However, also as well as in sIBM, there are cases of hIBM in which there are no rimmed vacuoles, but rather the presence of a highly suggestive phenotype for hIBM diagnosis with the existence of chronic myopathic findings without necrosis and only mild lymphocytic infiltrate with *ragged-red fibers* (or *ragged-blue fibers*) in modified Gomori trichrome stain and negative staining for cytochrome *c*-oxidase expression, suggestive of the diagnosis of the some different subtypes of hIBM[1,19].

Figure 2. Muscle pathology findings in hIBM associated with *VCP* gene mutations. Histopathological study disclosing rimmed vacuoles (white arrow) in hematoxylin-eosin (A,B) and modified Gömöri trichrome staining (C,D) associated with moderate neurogenic changes with angulated fibers (white arrow-head) in NADH-TR staining (E). No marked inflammatory infiltration is observed. Source: first author own archive (reproduced with the patient's permission and informed consent).



Inclusion body in rimmed vacuoles in hIBM exhibits a complex content of protein aggregates, such as in sIBM and in senile plaques in Alzheimer's disease, including beta-amyloid, tau-hyperphosphorylated, presenilin-1, alpha-synuclein, alpha1-antichemotrypsin, beta-amyloid precursor protein, p62 (sequestosome 1), TDP-43 (transactive response DNA-binding protein 43 kDa), apolipoprotein-E, gamma-tubulin, gelsolin, apoptosis regulatory proteins (Bcl-2, BAX, Bcl-x), oxidative stress proteins (including superoxide dysmutase), clusterin, prion protein, ubiquitin and proteosomal catalytic core proteins. It is essential to make differential diagnosis with other disorders which originate rimmed vacuoles, including oculopharyngeal muscular dystrophy, X-linked Emery-Dreifuss muscular dystrophy, congenital muscular dystrophy with rigid spine syndrome, some forms of limb-girdle muscular dystrophies (including LGMD1A, LGMD1G and LGMD2G), some rare mutations in *LAMA2* gene and chronic denervation (such as in spinal muscular atrophies and previous acute poliomyelitis)[1,4,12]. A summary of the main clinical, pathological, laboratorial and therapeutic aspects of sIBM and hIBM is presented in Table 2.

Table 2. Practical comparison of clinical, pathological, laboratorial and therapeutic aspects between sIBM and hIBM[1,12].

Parameter	sIBM	hIBM
I. Clinical hallmarks		
Age at onset	Late-onset (most cases after the fifth to sixth decade of life)	Earlier-onset than sIBM (most cases varying from the third to fifth decade of life)
Male-to-female ratio	3:1	1:1 (AD and AR cases)
Pattern of muscle involvement	Quadriceps and asymmetric distal arm and finger flexor weakness (mainly nondominant side); dysphagia (late); rare facial and extrinsic ocular muscle groups involvement	Variable; symmetric; distal myopathy; limb-girdle muscle weakness; scapuloperoneal myopathy; ophthalmoparesis, ptosis; vocal cord paresis; abdominal wall weakness
Concurrent disorders	Chronic viral infections (e.g. HIV/AIDS, hepatitis C, HTLV-I), monoclonal gammopathies, chronic lymphocytic leukemia, T cell large granular lymphocytic leukemia, paraneoplastic, variable common immunodeficiency, sarcoidosis, other connective tissue disorders	Amyotrophic lateral sclerosis, Paget disease of bone, Frontotemporal lobar degeneration
II. Muscle pathology findings		
General findings	Inflammatory myopathy with rimmed vacuoles, aggregates and mitochondrial pathology; prominent endomysial infiltration by mononuclear cells, focal invasion of non-necrotic muscle fibers by CD8+ T cells and macrophages; MHC-I expression on surface of muscle fibers	Unspecific chronic myopathic findings with rimmed vacuoles (rarely mild and scarce lymphomonocyte infiltrates)
Specific findings	Rimmed vacuoles with congophilic positive inclusions and granular material in aggregates (e.g. desmin, beta-amyloid, clusterin, beta-synuclein, beta-tubulin, gelsolin, Tau phosphorylated, TDP-43, SQSTM1, presenilin-1, apolipoprotein-B and ubiquitin); non-vacuolated aggregates stain with LC-3 and SMI-31 antibody; increased number of COX negative and SDH positive muscle fibers for age; mononuclear endomisial foci with CD20 positive cells in chronic lymphocytic leukemia (reports)	Each genetic subtype with specific testing for antibody expression in the muscle fiber and their coupled proteins (e.g. VCP/p97, SQSTM1/p62); no congophilic inclusions; rarely without vacuoles and with mitochondrial myopathic findings
III. Laboratorial findings		
Biological markers	Positive anti-cN1A antibodies (up to 75% of cases); serum CK raised less than 10-15 times de ULN or normal; Specific HLA alleles association in familial IBM (e.g. DRB1*0301/0302, DR15(2)/4 (DRB1*1502/0405)) or sIBM (e.g. DRB1*0101/0202, DQB1*0201); DQ2 haplotype in early-onset cases	Specific genetic testing (e.g. *GNE, VCP, MYH2, SQSTM1, HNRPA2B1, HNRNPA1*); no serum specific biochemical markers
Muscle MRI	Involvement of flexor digitorum profundus in the arms and marked compromise of the lower leg (mainly the medial head of the gastrocnemius) and the anterior muscles of the thigh (with relative sparing of the rectus femoris)	*GNE* myopathy: quadriceps-sparing (mainly vastus lateralis) in late stages, and biceps femoris short head, gluteus minimus, tibialis anterior, extensor hallucis, soleus and gastrocnemius medialis in early phases; *VCP* myopathy: widespread changes with patchy distribution; *MYH2* myopathy: marked involvement of the medial gastrocnemius, semitendinosus, gracilis and vastus lateralis
IV. Therapeutic aspects		
Immunoglobulin (IV)	Partial response for dysphagia (not clinically significant)	No response
Bimagrumab BYM338 and other immunosuppressive therapies	No response	Not potentially useful

AD: autosomal dominant; AR: autosomal recessive; CK: creatine kinase; COX: cytochrome oxidase; IV: intravenous; SDH: succinate dehydrogenase; ULN: upper limit value of normality.

Clinical characterization of hIBM subtypes

Despite the genetic and pathophysiological heterogeneity associated with hIBM, it is a common characteristic for all subtypes the adult-onset of slowly progressive distal myopathy mainly at feet dorsiflexion, evolving later to proximal appendicular and axial (paravertebral) muscle groups, in association with rimmed vacuoles and filamentous cytoplasmic inclusions in muscle biopsy. Distal upper limb weakness occurs mainly in deep finger and forefinger flexors muscle groups. There is no marked facial involvement as it occurs in advanced stages of sIBM patients over 50 years. In hIBM, there has been no cases with positive serum anti-cN1A antibodies (cytosolic anti-5'nucleotidase 1A), which are found in up to 70% of sIBM cases. However, serum creatine kinase (CK) elevations are commonly observed, but generally mildly (less than 10 times the upper limit of normality) or even with normal values. Regarding neurophysiological studies, in hIBM and sIBM, chronic and active myopathic and neurogenic findings are frequently found concomitantly[1,22].

1.Nonaka distal myopathy with rimmed vacuoles

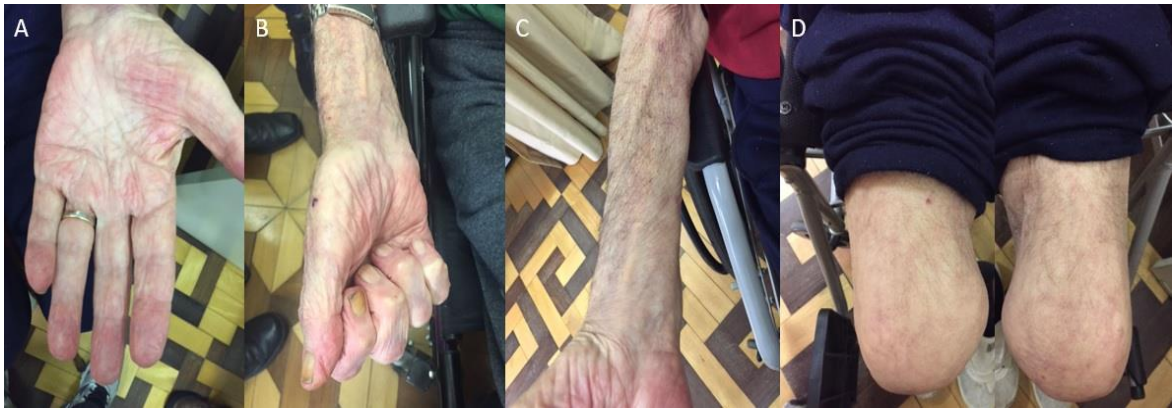
Typical hIBM (MIM #605820) or Nonaka distal myopathy associated with the *GNE* gene (9p13.3) is characterized by the presence of autosomal recessive progressive myopathy starting in the third to fourth decade of life, first distally and symmetrically in the legs and then evolving with moderate to severe compromise of the

proximal lower limb muscle groups and the Iliopsoas, but sparing the quadriceps femoris (the so-called "quadriceps sparing myopathy"). Rare variants with facial and quadriceps femoris involvement and minor distal myopathy have also been described. Cases have been more commonly described in some populations, such as Iranian jews, Japanese, Palestinian and Middle East muslim. Despite its neurometabolic dysfunction of sialic acid biosynthesis, the replacement of such acid has not disclosed significant clinical and functional evidence of improvement in patients with hIBM. It has not been established also the reason there is no multisystem involvement in such disorder as defective enzyme expression also occurs in central nervous system and other systems. Some authors still consider *GNE*-related myopathy mainly as a distal myopathy, thus maintaining the use of its former designation as Nonaka distal myopathy. A key differential diagnosis in rapidly progressive phenotypes is represented by Autosomal Dominant Myopathy with Early Respiratory Failure (ADMERF/HMERF) or Edstrom myopathy, a *TTN*-related distal myopathy, currently classified in the myofibrillar myopathy group, presenting with symmetric distal and proximal involvement of the lower limbs, mainly of the anterior tibial group, and early progressive respiratory failure and cardiac conduction block. Allelic disorder to *GNE* includes autosomal dominant sialuria (French type)[4,12,14,23]. There is no expectancy in such hIBM presentations of benefit with Bimagrumab monoclonal antibody or other imunossupressive agents, previously studied for sIBM[24].

2.Inclusion body myopathy with early-onset Paget disease of bone with or without Frontotemporal Dementia type 1 (IBMPFD1)

IBMPFD1 (MIM #167320) associated with *VCP* (9p13.3) gene mutations is characterized by a wide and complex autosomal dominant spectrum of neurodegenerative disorders with incomplete penetrance. Clinical picture (Figure 3) is dominated by a myopathic phenotype starting between the third and seventh decade of life in a limb-girdle proximal pattern of involvement with typical VCP-positive inclusion bodies on muscle biopsy, osteolytic and sclerotic bone lesions diagnostic of early-onset Paget disease of bone (mainly in the spine, hip and skull), and one third of patients with frontotemporal lobar degeneration with early frontotemporal atrophy on neuroimaging studies. A pure myopathic phenotype with mild CK elevation and proximal and distal involvement is also eventually found. Atypical presentations with parkinsonism, dystonia, sensorimotor polyneuropathy and cataracts have rarely been described. Muscle MR imaging shows diffuse widespread fatty degeneration involving most thigh muscle groups and axial musculature. There is typical genotype-phenotype correlation in such cases, including the R155C mutation which gives rise to the most severe and earlier myopathic phenotypes and to earlier presentations of Paget disease of bone. Allelic disorders include familial ALS type 14, Charcot-Marie-Tooth type 2Y, and hereditary spastic paraparesis[12,17].

Figure 3. Clinical examination findings in a patient with *VCP* gene mutation. Examination showing mild tenar hypotrophy (A), fist sign resulting from finger flexor muscle group weakness (B), marked atrophy of medial forearm muscle groups (C), and severe bilateral amyotrophy of the quadriceps femoris muscle, more severe in the left thigh (D). Source: first author own archive (reproduced with patient's permission and informed consent).



3.Inclusion body myopathy with early-onset Paget disease of bone with or without Frontotemporal Dementia type 2 (IBMPFD2)

IBMPFD2 (MIM #615422) associated with *HNRPA2B1* gene (7p15.2) mutations is characterized by autosomal dominant hereditary myopathy with scapuloperoneal phenotype starting in the third to fourth decades of life and Paget disease of bone involving the long bones, and eventually evolving with lower motor neuron disease, frontotemporal lobar degeneration and mild CK elevation. Rimmed vacuoles and high degree of nuclear centralization are frequently found in muscle biopsy[12,16]. Due to the rarity of this condition, specific muscle MR imaging findings are yet unknown. This genetic subtype seems more uncommon and rarely found when compared to *VCP*-related hIBM.

4.Inclusion body myopathy with early-onset Paget disease of bone with or without Frontotemporal Dementia type 3 (IBMPFD3)

IBMPFD3 (MIM #615424) associated with *HNRNPA1* gene (12q13.13) mutations is characterized by autosomal dominant chronic hereditary myopathy starting in the fourth to fifth decade of life with slowly progressive limb-girdle phenotype and severe involvement of Iliopsoas and abdominal wall muscle groups with mild serum CK levels and mild to moderate serum phosphatase alkaline levels with Paget disease of bone, mainly found in the epiphyseal portion of the femur and in the lumbar vertebral bodies. Allelic condition includes familial ALS type 20 and rarely familial Flail-arm syndrome[12,16]. As it occurs with IBMPFD2, this hIBM genetic subtype represents a rare cause of hIBM when compared with *VCP* gene mutations, however without marked clinical association with FTD.

5.Myopathy with congenital joint contractures, ophthalmoplegia, and rimmed vacuoles

Proximal myopathy with congenital joint contractures, external ophthalmoplegia, and rimmed vacuoles (MYPOP; MIM #605637) is associated with *MYH2* (17p13.1) gene mutations and characterized by slowly progressive or nonprogressive autosomal dominant myopathy starting in infancy, presenting mainly with muscle atrophy of the

quadriceps femoris and pectoralis major and minor muscles. Variable involvement with eyelid ptosis, ophthalmoparesis and scoliosis is also described. Muscle biopsy discloses type 1 predominance with type 2A muscle atrophy and high degree of nuclear centralization and commonly the finding of rimmed vacuoles in affected muscle groups. In cases with marked eyelid ptosis and ophthalmoplegia, mitochondrial myopathy makes the most important differential diagnosis, being frequently misdiagnosed as chronic progressive external ophthalmoplegia. Rare familial presentations with autosomal recessive inheritance pattern have also been described[12,15].

6.SQSTM1-related hIBM

hIBM has also been described in association with heterozygous mutations in the *SQSTM1* gene (5q35.3; sequestosome 1), coding the p62 protein (sequestosome 1), involved in NFκB1 signaling pathway, neuronal apoptosis, nuclear transcription regulation and mainly in ubiquitin-mediated autophagy by shuttling aggregated and ubiquitinated proteins to the forming autophagosome. Most cases of hIBM related to *SQSTM1* gene mutations occurred in the context of an autosomal dominant multisystem familial proteinopathy, involving IBM, FTD, Paget disease of bone and ALS. However, splice site mutation in *SQSTM1* has been described in patients from a United States family with autosomal dominant late-onset distal lower extremity

myopathy with rimmed vacuoles with TDP-43 and SQSTM1 positive inclusions. Allelic disorders include Paget disease of bone type 3 and FTD with ALS type 3[18,25,26].

hIBM: a key clinical and genetic model to understand neurodegenerative processes

As genetic and metabolic basis related to hIBM were being established, different studies involving intraneuronal and muscle intracellular microenvironment have been carried out and revealed a complex range of pathological mechanisms. Thus, disorders related to the biosynthesis of sialic acid in the *GNE* gene mutations with deficiency of UDP-N-acetylglucosamine 2-epimerase with reduction of post-translational changes in glycoproteins and glycolipids proved a key mechanism in the main presentation of hIBM in clinical practice with dysfunction of adhesion molecules (notably NCAM) and surface and nuclear glycoproteins (alpha-dystroglycan and neprilysin-1, respectively)[4,12]. However, it is not yet understood why such enzyme deficiencies give rise to a marked isolated myopathic phenotype without multisystem or neurodegenerative associated disorders.

There is marked pathophysiological overlap between genetic mechanisms common to hIBM subtypes and familial ALS involving multisystem proteinopathies and intracytoplasmic system of ubiquitin-proteosome networks[16,27,28]. Thereby, *VCP* gene mutations result from complex dysfunctions in the biogenesis of the Golgi apparatus, ubiquitin-proteosome system, protein

degradation of external mitochondrial membrane, establishment and maturation of the autophagosome, clathrin-mediated membrane endocytosis and cell cycle regulation[29].

Dysfunctions involving the ribonucleoproteins A1 and B1 originate intracellular defects related to splicing and processing of messenger preRNA and interaction with RNA polymerase II[29], being, thus, a pathophysiological mechanism not restricted to skeletal muscle groups or to the central nervous system. Regarding other hIBM subtypes, it has not been well-defined if mutations in the gene coding heavy myosin chain IIa could be associated with non-myopathic complex neurodegenerative spectrum of disorders or with multisystem proteinopathy phenotype[15]. This complex multisystem disorders have also been linked to other genes involved with similar pathophysiological mechanisms, including *OPTN, DNAJB6 and HNRNPDL*, thus, disclosing a complex network of proteins involved in intracellular protein homeostasis and related with the same mechanisms previously described in ALS, FTLD and other degenerative disorders[3,27,29,30].

There is a lot of expectancy that the knowledge related to hIBM etiopathogenesis can represent the basis to understand properly the mechanisms of IBM and other clinically significant neuromuscular and neurodegenerative disorders (including ALS, parkinsonian syndromes and frontotemporal lobar degeneration) and systemic diseases (such as Paget disease of bone), as well as the foundation in

the development of common specific therapeutic modalities for such multisystem disorders[29,30].

CONCLUSIONS

hIBM represents a rare and heterogeneous hereditary myopathy group, certainly underdiagnosed, and associated with complex neurogenetic and pathophysiological dysfunctions with proper clinical and pathological hallmarks depending on the metabolic or degenerative basis involved. Previously considered merely an extension of sporadic IBM, hIBM is distinct in different aspects (Table 2) and represents a widening and noteworthy group of hereditary vacuolar myopathies, which makes them difficult to classify as a group, but also acts as a prototype of broadening neurogenetic spectrum of clinical conditions and offers a great opportunity to provide proper development of targeted therapies based in molecular and genetic approaches.

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