ACTA RADIOLÓGICA PORTUGUESA
May-August 2019 | Vol 31 nº 2 | 15-17

Radiological Case Report / Caso Clínico

Bethlem Myopathy and the Importance of Whole-Body Magnetic Resonance Imaging in the Evaluation of Myopathies

Miopatia de Bethlem e a Importância da Ressonância Magnética de Corpo Inteiro na Avaliação de Miopatias

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Abstract

Bethlem myopathy is a congenital muscular dystrophy associated with collagen VI dysfunction that courses with contractures and progressive muscle weakness. Clinical and histopathological findings may be similar to other myopathic disorders, thus making it necessary to employ alternative diagnostic tools to establish a definitive diagnosis. Recently, magnetic resonance imaging has shown promise in helping with diagnosis and follow-up of myopathic disorders and, specifically with regards to collagen-related disorders, some characteristic muscle changes may be present in such patients.
We report a case of a patient with Bethlem myopathy and describe the characteristic radiological findings specific of this disorder, thus demonstrating the role of magnetic resonance imaging in the evaluation of myopathies.

Keywords

Myopathy; Neuromuscular disorder; Magnetic resonance imaging; Bethlem myopathy; Collagen VI.

Resumo

A miopatia de Bethlem é uma distrofia muscular congénita associada a alterações da proteína de colagénio VI, que cursa com contracturas e fraqueza muscular progressiva. Os achados clínicos e histopatológicos podem ser semelhantes a outras doenças miopáticas e são necessários meios complementares para estabelecer o diagnóstico definitivo. Recentemente, a ressonância magnética tem revelado um papel crescente no diagnóstico e seguimento desta doença e, a respeito das colageniopatias, podem estar presentes alterações distróficas características.
Reportamos um caso de miopatia de Bethlem onde descrevemos os principais achados radiológicos característicos desta doença e salientamos o papel promissor da ressonância magnética na avaliação de miopatias.

Palavras-chave

Miopatia; Doença neuromuscular; Ressonância magnética; Miopatia de Bethlem; Colagénio VI.

Introduction

Congenital muscular dystrophies are a heterogeneous group of diseases that occur at birth or during the first months of life with hypotonia, muscle weakness, contractures and delayed motor development. These diseases are progressive and typically associated with other organic findings in addition to muscular dystrophic changes.[1]
The key structure affected in most muscular dystrophies is the cell membrane or sarcolemma, in particular the interaction between the intracellular myofibrillar structures and the extracellular matrix through a system of proteins termed dystrophin-associated glycoprotein complex (DAGP). This complex ensures stability of the sarcolemma during muscle contraction and relaxation.[2]
Type VI collagen is found in the extracellular matrix of various structures, such as muscles, tendons, skin and vessels and is part of the DAGP elements. This molecule is composed of three α chains, which are encoded by three distinct genes. The occurrence of mutations in such genes is responsible for the development of muscular diseases termed collagen VI-related myopathies. Clinical presentation shows various degrees of penetrance ranging from the most severe (Ullrich congenital muscular dystrophy) to more insidious phenotypes such as Bethlem myopathy (BM).[3,4]
For the last two decades, the role of imaging and, particularly, magnetic resonance imaging (MRI), in the diagnosis and follow-up of myopathic diseases has grown considerably, especially for evaluation of congenital myopathies and limb-girdle muscular dystrophies, which present similar histopathological patterns.[5,6]

Clinical Case

A 46-year-old woman presented with progressive abnormal gait for the last 12 months, with greater difficulty in walking and climbing up or down stairs. She had a clinical history of multiple sclerosis diagnosed 20 years ago, currently under fingolimod therapy (last outbreak 1 year ago and an average of 1 outbreak every 2 years), and cutaneous psoriasis. The patient also mentioned a previous diagnosis of nonspecific myopathy during infancy, without any additional follow-up or investigation. Physical examination did not reveal gait abnormalities but there was evidence of difficulty changing from sitting to standing position without help and paresis of the thigh

muscles more accentuated on the right lower limb.
The patient underwent further examinations such as electromyography (which revealed changes suggestive of myopathy), whole-body MRI and genetic evaluation that confirmed the final diagnosis of BM due to heterozygosity in exon 12 of the COL6A3 gene.
Whole-body MRI revealed generalized skeletal muscle fatty infiltration, most severe in the abdominal wall, pelvic girdle, thigh and leg muscle groups. The pattern of involvement of the thigh muscle bellies was suggestive of collagen-associated myopathy, with peripheral involvement sparing the central region, with the exception of the rectus femoris muscle which presented the reverse pattern (peri-tendinous involvement sparing the periphery of the muscular body, i. e., antero-central or U-shaped involvement) (Figure 1). There was also a marked and generalized increase in subcutaneous fat.

Discussion

BM is a rare disease first described in 1976 by Bethlem and Wijngaarden (7), with a slow and insidious progression in the lighter spectrum of myopathies associated with collagen VI mutations. Clinical findings include contractures, hypermobility, muscle weakness and hypotonia, associated with articular laxity of the distal joints and formation of keloid scars. There is also risk of progression to respiratory failure, a complication that is more frequent in severe forms.[1]
We describe a case of BM that illustrates the importance of MRI evaluation and the main findings to consider in patients with a suspected myopathy (Table 1). Our patient showed dystrophic changes (muscle fatty infiltration) with diffuse symmetrical distribution. At the thigh level, there was multi-compartmental involvement and a characteristic pattern of muscular atrophy suggesting collagen-associated myopathy, as described in the literature.[8,9]
The body composition of patients with collagen VI-associated disease is also frequently affected, with an increase in all parameters of adipose mass in both severe and intermediate phenotypes.[10] These changes were also present in our case and well depicted with whole-body MRI(Figure 1).

Table 1 – Summary of key changes and patterns to be assessed when performing a whole-body MRI in a patient with suspected myopathy

Main changes and patterns to evaluate in case of suspected myopathy
Symmetrical / asymmetrical distribution
Edema / dystrophy (predominance)
Posterior / anterior involvement of the thighs and legs (predominance)
Proximal / distal involvement of the limbs (predominance)
Involvement of pelvic or scapular girdle
Involvement of paravertebral muscles
Involvement of the head and neck muscles
Muscles or muscle segments selectively spared or involved (tibialis anterior, rectus femoris, sartorius, other)
Pattern of adipose infiltration in the muscle bellies (centripetal, diffuse, mottled, other)

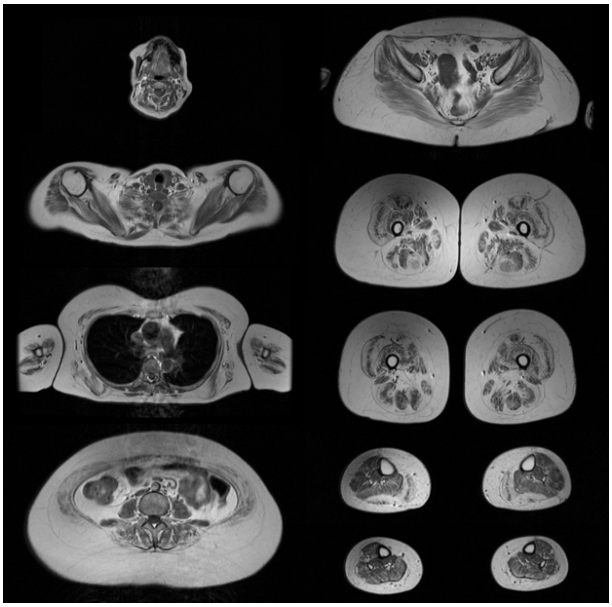

Figure 1 – Whole-body magnetic resonance imaging, T1 weighted sequence, axial slices. Moderate to advanced diffuse muscular atrophy (grade 2 or 3 on the Mercuri scale), with significantly increased subcutaneous fat. There is characteristic involvement at the level of the thighs, with centripetal atrophy of the vasti and U-shaped antero-central involvement of the rectus femoris. In the legs, predominant involvement of the posterior compartment (mainly the gastrocnemii) with centripetal distribution is observed.

Table 2 – Mercuri et al. (2002) scale to evaluate the degree of muscular degeneration. CT - computed tomography. MRI - magnetic resonance imaging

Mercuri et al. (2002) scale to evaluate the degree of muscular degeneration	
Stage	**Findings**
0	Normal appearance
1	Early moth-eaten appearance with scattered areas of hypodensity on CT or hyperintensity on MR (T1-weighted sequences)
2a	Late moth-eaten appearance with numerous discrete areas of hypodensity on CT or hyperintensity on MR (T1-weighted sequences), with beginning confluence, comprising less than 30% of the volume of the individual muscle
2b	Late moth-eaten appearance with numerous discrete areas of hypodensity on CT or hyperintensity on MR (T1-weighted sequences), with beginning confluence, comprising 30%-60% of the volume of the individual muscle
3	Washed-out appearance, fuzzy appearance due to confluent areas of increased signal
4	End stage appearance, muscle replaced by increased density of connective tissue and fat, with only a rim of fascia and neurovascular tissue distinguishable

The semi-quantitative assessment of the degree of muscular atrophy can be made using the Mercuri scale (Table 2),[11] which presents 4 degrees of severity. Such evaluation is essential to determine the most affected areas and progression of the disease in subsequent examinations. Our patient had a moderate to advanced degree of muscular atrophy (grade 2 or 3, depending on the muscle body in question).
The imaging findings described are characteristic of adult-onset collagen VI-related myopathy,[12] however there are other diseases that should be ruled out, namely Emery Dreifuss muscular dystrophy and some variants of limb-

girdle muscular dystrophies, which may have the same clinical presentation when the pattern of muscle weakness is proximal. The combination of clinical findings, lab-work and imaging evaluation narrows down the differential diagnoses, guides further testing (e. g. genetic evaluation) and allows for follow-up of such patients.

Conclusion

Myopathic diseases are rare and often challenging to diagnose. Collagen VI-related myopathies should be suspected in adult patients with history of contractures, pelvic girdle muscle weakness and dermatological changes such as hyperkeratosis. Major imaging findings are often characteristic and whole-body MRI plays an important role in diagnosis and monitoring the disease.

Received / Recebido 12/11/2018
Acceptance / Aceite 31/05/2019

Ethical disclosures / Divulgações Éticas
Conflicts of interest: The authors have no conflicts of interest to declare.
Conflitos de interesse: Os autores declaram não possuir conflitos de interesse.
Financing Support: This work has not received any contribution, grant or scholarship.
Suporte financeiro: O presente trabalho não foi suportado por nenhum subsídio ou bolsa.
Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Confidencialidade dos dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.
Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).
Protecção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

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