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Case Report

Erosive Arthritis Associated with Limb-Girdle Muscular Dystrophy: Clinical Case and Literature Review

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Abstract

Limb-Girdle Muscular Dystrophy (LGMD) are a group of hereditary muscular dystrophy that primarily affect skeletal muscle, leading to progressive muscular weakness. Among LGMD, autosomal dominant forms are relatively rare and represent about 10% of reported cases. Classification of LGMD is complex, based upon specific mutations. Currently, there are 6 reported families world- wide with LGMD with mutations in heterogeneous nuclear ribonucleoprotein D like (HNRPNDL) gene. In this report, we describe an Argentinian family with HNRPNDL mutation associated LGMDD3 with clinical differences compared to previous reports, presented with myalgia, muscle weakness and arthritis compromising carpus and metacarpophalangeal joints. This report is relevant because of the description of a new clinical manifestation in LGMD not previously reported: erosive arthritis. This might expand the understanding of this infrequent disease and reports a third affected family from Argentina. In our country, the study of muscular dystrophy is scarce and usually performed by disperse uncoordinated research teams. This report may shed new light to an unusual manifestation and may incentivize future research.

List of Abbreviations

1. Limb-Girdle Muscular Dystrophy (LGMD).
2. Heterogeneous nuclear ribonucleoprotein D like (HNRPNDL).
3. Muscle magnetic resonance (Muscle MRI).
4. Creatine phosphokinase (CPK).
5. Lactate dehydrogenase (LDH).
6. Erythrocyte sedimentation rate (ERS).
7. Antinuclear antibodies (ANA).
8. Anti-neutrophil cytoplasmic antibodies (ANCA).
9. Anti-Sjögren's syndrome related antigen A (Anti-Ro)
10. Anti- double stranded DNA (Anti dsDNA).
11. Anti-DNA topoisomerase I antibodies (Anti Scl-70).
12. Small nuclear ribonucleoprotein antibodies (Anti Smith).
13. Hematocrit (HCT).
14. White Blood cells (WBC).
15. Platelets (PLT).
16. C reactive protein (CRP).
17. Glutamic oxaloacetic transaminase/pyruvic transaminase (TGO/TGP).

Introduction

Limb-Girdle Muscular Dystrophy (LGMD) are a group of hereditary muscular dystrophy that primarily affect skeletal muscle, leading to progressive muscular weakness. Among LGMD, autosomal dominant forms are relatively rare and represent about 10% of reported cases. Classification of LGMD is complex, based upon specific mutations [1,2].

Currently, there are 6 reported families world-wide with LGMD with mutations in heterogeneous nuclear ribonucleoprotein D like (HNRPNDL) gene; one in Brazil, one in China, one in Uruguay and two in Argentina [2,3]. A wide phenotypic spectrum is described among the cases, including oligosymptomatic scapular and pelvic girdle compromise and phenotypes affecting distal muscles. Winged scapula is the most common feature in all patients, but differences have been reported regarding age at onset, evolution, CPK levels and clinical findings, including muscle cramps and early apparition of cataracts [2,3].

The table [1] and figures [1-4] shows the value given by each company's model, the number of penalty kicks that are supposed to be scored according to the model, and the accuracy rate of each model in predicting each season individually and for the total of the five seasons compared to the realistic numbers.

In this report, we describe an Argentinian family with HNRPNDL mutation associated LGMDD3 with clinical differences compared to previous reports.

Clinical Case

A 38 years-old male patient was admitted in our center for study of a suspected myopathy. At age 25, he started with difficulties during recreational sports practice and, by age 33, arthralgia and arthritis were added, compromising carpus and metacarpophalangeal joints, which were treated with betamethasone 0.6mg. No muscle biopsy was performed.

At admission, myalgia and muscle weakness in the pelvic region and left hand were assessed, along with hypomimia face, seborrheic dermatitis and arthritis in the left carpus. No scoliosis, winged scapula nor dyspnea were found. A history of monophasic Raynaud's phenomenon was reported by the patient, without digital ulcers.

A four limbs electromyogram was performed, informing moderate myopathic involvement with distal predominance in upper limbs and proximal predominance in lower libs. Muscle MRI showed fatty replacement predominantly in proximal and posterior muscles, with augmented signal in muscle fibers in distal zones. Laboratory showed CPK 947.2 U/L (32-294), LDH 676.1 U/L (50-150), ESR 25mm/h and ANA 1/80 with a spotted pattern. ANCA, Rheumatoid Factor, ACPA, anti dsDNA, anti-cardiolipins, Scl-70, Ro, La, Smith, U1-RNP and myositis specific antibodies (Jo-1, PL-7, PL-12, Mi- 2SRP, Ku, PM/SCL) were all negative. Laboratory results along time are shown in table and figure

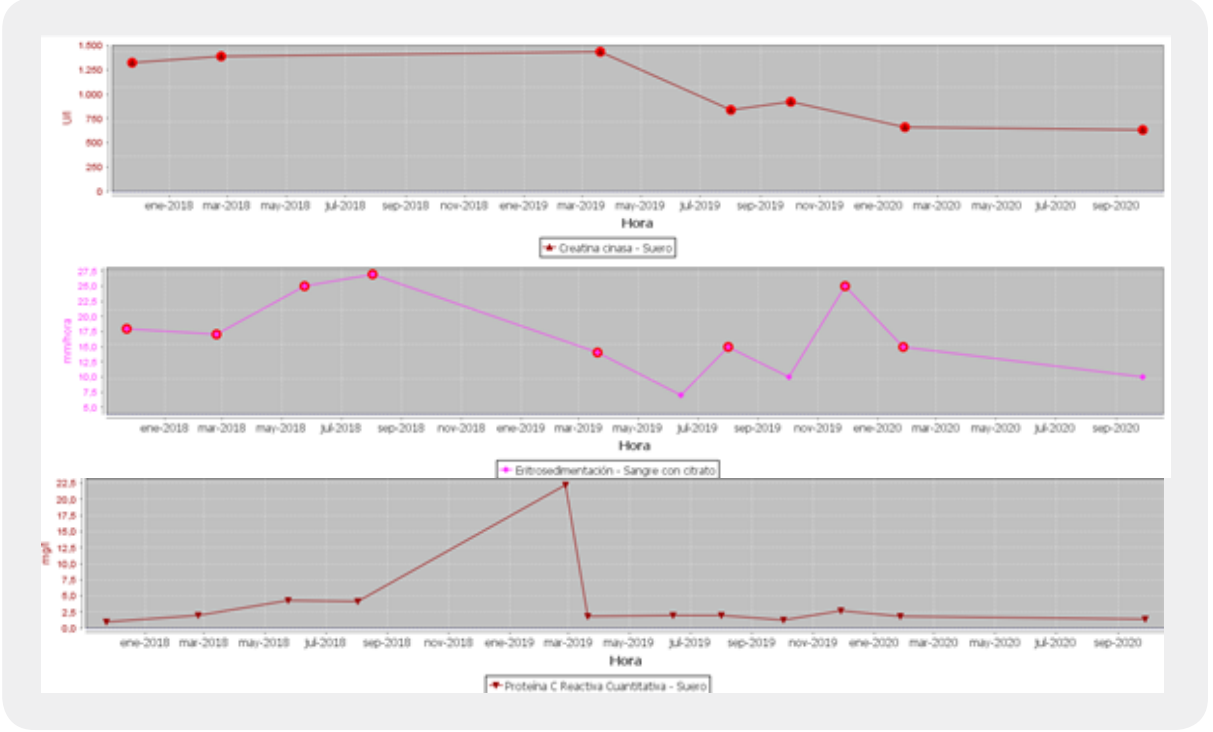

Figure 1: *Laboratory findings along time*

Table 1: *Laboratory findings along time Tamic oxaloacetic*

	11/11/2015	**23/11/2017**	**23/02/2018**	**20/03/2019**	**13/06/19**
HCT%/WBC celsx10^3/ PLT		46/9150/222	46/7780/222	37/9460/231	39/7070/226
ESR mm/h /CRP mg/dl		18/0.93	17/2.02	14/ 22.26	7/1.9
TGO/TGP U/L		49/70	37/48	45/60	46/60
CPK U/L	947.2	1322	1386	1434	835
Aldolase U/L		11	11	14	9
LDH U/L	676.1			339	245

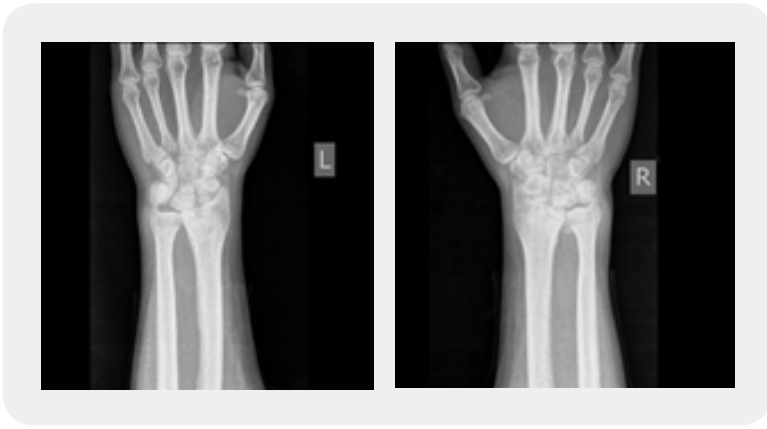

Figure 2: *Wrist radiography. Bilateral radio-carpal joint space narrowing is shown. Cubital distal erosions can be seen in the right hand.*

1. A bilateral joint space narrowing was found in radio-carpal joints and second carpal-metacarpal joints along with right cubital erosions in plain radiography (Figure 3). A scintigram was performed, showing accumulation in carpus, shoulders, and sternal-clavicular joints (Figure 3).

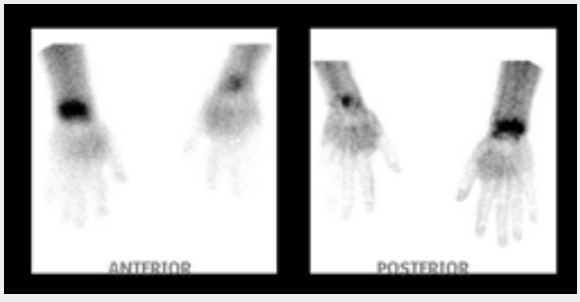

Figure 3: *Cumulation in both wrists*

Suspecting a muscle dystrophy, a NGS genetic study was performed, evidencing C.1132G>C (P.D378H) heterozygous mutation in HNRPDL gene.

The case was interpreted as LGMD associated with erosive seronegative arthritis and prednisone 5mg daily and methotrexate 15 mg weekly was initiated in February 2019, tailoring dose to 25mg SC weekly with resolution of articular symptoms.

By medical recommendation, two cousins of the patient were evaluated. One of them had neither muscle nor articular symptoms, with normal ESR and muscle enzymes. The other had arthralgia in the right carpus with MRI showing focal tenosynovitis and laboratory showed persistent elevated acute phase reactants and CPK (ESR 40mm/hora, CRP 16.32mg/L, CPK 283 U/L, ANA negative, myositis autoantibodies negative). This patient presented persistent arthritis in the ankle, requiring initiation of prednisone treatment and is currently in plan of starting a DMARD.

Discussion

According to the definition established by experts from the 22nd International Workshop of the European Neuro Muscular Center (ENMC) in 2017, LGMD are a group of hereditary muscle dystrophy affecting skeletal muscle and causing a progressive, predominantly proximal, muscle weakness. Autosomal dominant forms are rare, representing 10% of LGMD. According to the new classification, based on specific gene mutations, this includes: LGMDD1 related to mutations in DNAJB6, LGMDD2 related to mutations in TNPO3, LGMDD3 related to mutations in HNRPNPDL and LGMDD4 related to mutations in CAPM3 [1]. Clinical manifestations typically consist of progressive limb weakness and may include "waddling" gait, muscle pain during exercise, deltoid and quadriceps hypertrophy and muscle atrophy affecting pelvic and or scapular girdles. Facial muscles are usually respected or minimally affected [1,2].

HNRNPDL is an DNA/RNA binding protein which associate with pre-mRNAs in the nucleus and appear to influence pre-mRNA processing and aspects of mRNA metabolism and transport. It is believed that HNRNPDL mutations cause defects in biogenesis and mRNA metabolism [4]. Data published by Vieira et al [5] suggest that protein translocation from the cytoplasm to the nucleus might be affected by p(Asp378Asn) mutation. This might prevent HNRNPDL protein access to the nucleus, disrupting its function in Pre-mRNA maturation. Several HNRPNPs have been associated with diseases, because of their crucial role regulating gene expression. Mutations in prion-like dominions (PrLDs) in HNRNPA1 and HNRNPA2B1 cause a multisystem proteinopathy, a hereditary degenerative affection with involvement of the muscle, bone and central nervous system. However, isolated myopathy has also been described for HNRNPA1 mutations. Tissue inclusions composed by ubiquitin have been shown in samples from tissues affected by multisystem proteinopathy, including ARN binding proteins like HNRNPA1 and HNRNPA2B1 and proteins that mediate in ubiquitin-dependent autophagy [6].

Currently, there are 6 reported families world-wide with LGMD associated with HNRNPDL mutations (LGMDD3); one from Brazil, one from China, one from Uruguay, two from Argentina and one from Italy [2,3]. The first description of the disease was in 2004 in a Brazilian-Caucasian family with 12 affected

individuals among three generations. Age of onset was 30-47 years old, and the disease was a slowly progressive proximal muscle weakness affecting the lower limbs and progressing to upper limbs with muscle cramps and limitation of finger flexion. CPK was usually normal or slightly elevated. Histology was available for one patient, describing a "myopathic pattern" [7]. In 2014, affection in 18 individuals from a Uruguayan family was reported, with onset between 15 and 55 years old and a similar phenotype to the previously described, except for upper limbs onset in 8 of the patients and early onset cataracts as an additional manifestation [8]. In both families, genome sequencing identified mutations in HNRNPDL in chromosome 4q21, both heterozygous and affecting the same aminoacyl: p(Asp378Asn) in the Brazilian family and p(Asp378His) in the Uruguayan one.

Ten individuals from three generations with LGMDD3 were reported in China, with the same mutation as in the Brazilian family: p(Asp378Asn). Muscle biopsy showed similar characteristics to the previously described, however the clinical phenotype was different, with half of the patients presenting proximal weakness and half with distal weakness. Limitation of finger flexion was not reported [9].

Recently, two unrelated families from Argentina were reported with LGMDD3 with HNRNPDL mutations2. One from Buenos Aires, with 10 affected individuals among 3 generations, with onset at 38-48 years old, with proximal muscle weakness in the lower limbs in two patients associated with distal muscle weakness in one of them. Winged scapula and anterior thigh atrophy were common findings in all patients. Muscle cramps and early onset cataracts were also reported. The second family from Entre Rios Province with Vasque French heritage presented 5 affected individuals among 3 generations, with onset at 41-63 years old and proximal muscle weakness in the lower limbs. Neither finger flexion limitation nor early onset cataracts were reported in this family.

In the patient reported from Italy, diaphragmatic muscle compromise leading to hemidiaphragm elevation was reported, a novel manifestation in HNRNPDL so far [3,10].

Conclusions

The current case presents a patient with upper limbs proximal and distal muscular involvement, similar to the phenotype described for the Uruguayan family, but with carpus arthritis. Neither finger flexion limitation nor early onset cataracts nor muscle cramps were present in this patient [2,3]. Erosive articular involvement has not been described so far in LMGDD3 and, having no other plausible alternative diagnosis, we believe it is associated with the muscle dystrophy. The mutation present in our patient matches the one reported in the Uruguayan family and in the two Argentinian families [2]. Having neither family history of muscle weakness nor diagnosis of muscle dystrophy, we believe this is a new affected family.

We consider this report to be relevant because of the description of a new clinical manifestation in LGMD not previously reported: erosive arthritis. This might expand the understanding of this infrequent disease and reports a third affected family from Argentina. In our country, the study of muscular dystrophy is scarce and usually performed by disperse uncoordinated research teams. This report may shed new light to an unusual manifestation and may incentivize future research.

Conflicts of Interests

There are no conflicts of interest.

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