Familial manifestation of limb-girdle muscular dystrophy associated with FKTN gene: a case report

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Abstract

Introduction: to report a familial case of Limb-girdle muscular dystrophy, type C, 4 (MDDGC4) associated with a homozygous mutation in FKTN gene, highlighting phenotypic variability, diagnostic delay, and atypical clinical features described in the pediatric literature.

Description: two siblings were evaluated due to persistent hypertransaminasemia and markedly elevated creatine kinase (CK). Both underwent detailed clinical assessment, laboratorial and imaging exams, hepatologic investigation, and neuromuscular genetic panel testing for diseases. The older sibling, currently 10 years old, had been investigated since birth for hepatomegaly, direct hyperbilirubinemia, and elevated liver and muscle enzymes. After years of unfruitful hepatological investigation, a diagnosis of muscular dystrophy associated with FKTN gene was established by a genetic panel. The patient presented muscle hypertrophy and sleep-disorder, with significant clinical improvement after the use of continuous positive airway pressure. His 5-year-old brother presented a similar clinical presentation, and the same homozygous genetic pattern was identified. Bothpresented cognition with good academic performance.

Discussion: this report highlights the importance of creatine kinase (CK) doseage in children with elevated transaminases to prevent diagnostic delay. In addition, it describes clinical manifestations that are poorly documented in pediatric patients with FKTN gene mutations.

Key words *Limb-girdle muscular dystrophies, Inheritance patterns, Dystroglycans*

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http://dx.doi.org/10.1590/1806-9304202600000109-en

Introduction

Limb-girdle muscular dystrophies (LGMDs) constitute a heterogeneous group of genetic myopathies characterized by progressive muscle weakness predominantly affecting the proximal muscles of the shoulder and pelvic girdles. Currently, around 30 genetically distinct subtypes are recognized, classified according to the inheritance pattern, the affected protein, and the order of identification.[1,2]

Diagnosing LGMDs is challenging due to the broad phenotypic variability. The initial investigation is based on the age of symptom onset, pattern of weakness, family history, creatine kinase (CK) levels, muscle imaging exams, and, in some cases, muscle biopsy, which subsequently directed to genetic analysis.[1,2]

Among the genes involved, SGCB, CAPN3, DYSF, and FKTN are notable. Mutations in the FKTN gene are associated with dystroglycanopathies, including a limb-girdle muscular dystrophy, type C 4 (MDDGC4), an autosomal recessive condition caused by defects in the glycosylation of α-dystroglycan.[3] Although classically described with proximal muscle involvement, MDDGC4 can involve respiratory and cardiac complications, generally maintaining preserved cognition.[3]

This study was previously approved by the Permanent Committee for Ethics in Research with Human Beings (COPEP), under the number 86853425.2.0000.0104, with authorization from parents via Informed Consent Form (ICF) and from patients via Assent Form, and aims to highlight the rarity of MDDGC4 and analyze its clinical variable presentation, justifying the importance of case reports to expand knowledge about its different phenotypes and diagnostic pitfalls.

Descri ption

Patient 1

A 10-year-old boy, followed up since the neonatal period due to hepatomegaly and persistently elevated transaminases (AST 262 U/L; ALT 283 U/L), creatine kinase (CK 6,721 U/L), and lactate dehydrogenase (LDH 963 U/L). Born at 36 weeks of gestation, weighing 2,365 g, with an Apgar score of 9/10, remained under neonatal observation for jaundice with a predominance of direct bilirubin and elevated muscle enzymes. Throughout childhood, he experienced difficulty with weight gain, recurrent episodes of vomiting, a single febrile epileptic seizure at the age of 2, and repeated upper respiratory tract infections. Initially, he was followed by a hepatologist, with hypotheses of hepatitis and hereditary cholestasis (PFIC and BRIC), which were later ruled out by a specific genetic panel. At 9 years of age, due to myalgia, he was referred to pediatric neurology. The neurological examination revealed preserved muscle strength, normal reflexes, and moderate muscle hypertrophy, particularly in the shoulders and quadriceps. The genetic panel for neuromuscular diseases identified a pathogenic homozygous mutation in the FKTN gene (OMIM*607440), specifically the missense variant c.1270G>A (p.Gly424Ser). After the diagnosis, multidisciplinary follow-up was initiated. Polysomnography revealed a sleep-related breathing disorder with desaturations and an apnea index greater than ten, showing significant improvement after using continuous positive airway pressure (CPAP) at 9.5 cmH_2O. Echocardiogram and abdominal ultrasound have remained normal up to date. A Videofluoroscopic Swallowing Study showed no alterations. He has presented several respiratory tract infections but hospitalization was not required (Table 1).

Patient 2

A five-year-old brother, referred due to significantly elevated CK (11,055 U/L), LDH, and transaminases detected in the first year of life, began follow-up shortly after birth because of his brother's history. He was born at 40 weeks via cesarean section, with an Apgar score of 9/9, and remained hospitalized for 15 days in the neonatal ICU due to early respiratory distress. The pregnancy required bed rest due to premature labor. He was followed by a hepatologist for the same suspected diagnosis as his brother. The neurological examination revealed global muscle strength grade 5, pronounced muscle hypertrophy (shoulders, quadriceps, and rectus abdominis), normal reflexes, and no motor complaints. The genetic panel revealed the same homozygous mutation in the FKTN gene. Abdominal ultrasound showed grade I hepatic steatosis. The initial cardiological evaluation showed no alterations. Over a one-year of follow-up period, he developed arthralgia and episodes of chest pain associated with tachycardia and dyspnea. A new echocardiogram and cardiological evaluation were performed, which remained with no alterations. Polysomnography demonstrated a pattern similar to his older brother's, with clinical improvement after starting nocturnal CPAP. He continues with follow-up at the pediatric neurology, pediatric cardiology, pediatric pulmonology, pediatric nephrology, and clinical genetics. Both brothers attend regular school, presenting good academic performance, and do not take continuous medication (Table 1).

Table 1

Summary of information regarding each patient, including birth data, symptom onset, complementary exams requested for case investigation, as well as referrals, interventions, and current approach.

	Patient 1	Patient 2
Birth	36 weeks	40 weeks
Onset of symptoms	At birth	At birth
Initial laboratorial tests	AST 262 / ALT 283 / LDH 963/ CK 6.721	CK 11055
Referrals	Initially to a hepatologist and, at 9 years old, to a pediatric neurologist	Followed by a pediatric neurologist since birth
Complementary exams	-P-Polysomnography: sleep-disordered breathing with desaturations and apnea–hypopnea index (AHI) >10 -Echocardiogram and abdominal ultrasound: normal findings -Videofluoroscopic swallow study: no alterations	-Polysomnography: sleep-disordered breathing with desaturations and apnea–hypopnea index (AHI) >10 -Echocardiogram and cardiological evaluation: no alterations
Diagnostic hypotheses	Hepatitis. Hereditary cholestasis (PFIC and BRIC).	Due to the brother's clinical picture, the initial suspicion was MDDGC4
Genetic diagnosis	Homozygosity in the FKTN gene (OMIM*607440), missense variant c.1270G>A (p.Gly424Ser)	Homozygosity in the FKTN gene (OMIM*607440), missense variant c.1270G>A (p.Gly424Ser)
Interventions	Nocturnal CPAP	Nocturnal CPAP
Follow-up	Multidisciplinary	Multidisciplinary

Discussion

Clinical manifestations associated with FKTN mutations present broad phenotypic variability depending on the genetic alteration. They range from severe congenital forms with central nervous system involvement, as described in the compound variant p.Ala170Glu/p.Tyr371Cys. This variant leads to cerebellar vermis hypoplasia, cysts, polymicrogyria, cerebral atrophy, epilepsy, and severe cardiac and respiratory compromise, in addition to muscle impact.[4]

On the other hand, milder limb-girdle muscular dystrophy phenotypes may also occur without cognitive alteration. These milder forms have been described in compound heterozygous variants (3kb with c.527T>C, c.340G>A, and c.536G>C (p.R179T)) and in homozygosity, such as p.Arg307Gln and the variant described herein (p.Gly424Ser), which mainly involves motor delay and proximal weakness without cognitive impact.[4,5,6]

MDDGC4 typically manifests in childhood, although cases have been reported from the neonatal period to adulthood.[4,7] An important point is paternal consanguinity in cases of FKTN gene mutations. Although some studies on homozygous cases do not make this clear, others highlight family consanguinity, given that, due to its recessive inheritance pattern, the probability increases with the degree of kinship. This is the case in this study, in which the parents of the described patients are first-degree cousins.[4]

A relevant aspect of this report is the initial presentation with persistent hypertransaminasemia, mimicking primary liver disease. It is known that elevated AST and ALT can reflect muscle damage, underscoring the importance of measuring CK in children with elevated transaminases without a defined hepatic cause.[8]

Another rarely described finding was early respiratory impairment, evidenced by sleep disorders in both patients during childhood. Although the literature reports the presence of dyspnea, it occurred as a consequence of cardiac impairment.[7,9] Thus, such a finding broadens the spectrum of symptoms that these patients may present. This finding diverges from other variants of the FKTN gene, which have manifested progressive respiratory impairment requiring non-invasive mechanical ventilation and even tracheostomy.[4]

Therefore, the subtle manifestation observed in this study points to the inclusion of genetic causes in the investigation of childhood sleep disorders after excluding the most frequent etiologies, particularly obstructive sleep apnea, for which adenotonsillar hypertrophy is the primary cause in children.[10] In the present case, this differential diagnosis showed to be limited, as adenotonsillar hypertrophy was identified only in patient 2, following evaluation by otorhinolaryngology. Nevertheless, both patients exhibited similar alterations on polysomnography and showed a good response to nocturnal CPAP, a finding that precludes the complete exclusion of a genetic cause or interference.

The phenotypic variant p.Gly424Ser, inherited in homozygosity as in this case, has already been described in association with dilated cardiomyopathy in adults as a late manifestation. However, other studies have shown decompensated heart failure with cardiac remodeling, biventricular dysfunction, and even diffuse fibrosis with septal predominance, resulting in cardiogenic shock or sudden death before 22 years of age.[7,9] These findings converge with the need for cardiac transplantation in an adolescent, which was observed in the phenotypic variant of the FKTN gene with compound heterozygous mutations FKTN 3kb/c.1073A>C (p.Q358P), as well as with early death due to rapidly progressive heart failure in a 12-year-old individual carrying the variant 3kb/c.536G>C (p.R179T).[6]

In the present report, both patients maintain preserved cardiac function and remain under continuous follow-up with a cardiologist. To date, this is the first report of the homozygous variant p.Gly424Ser in Brazil, with previous reports in Mexico and Spain.[7,9] The search strategy focused on the variant, with the term: (p.Gly424Ser OR c.1270G>A OR rs752358445) AND FKTN queried in the PubMed, LILACS, and SciELO databases, resulting in only two articles from the previously mentioned countries. This fact suggests the possibility of a founder variant of Iberian origin. It has been described exclusively in populations with Iberian or Ibero-American ancestry. Therefore, it is pertinent to note that this probable interaction presents a new research field for future studies.

Nevertheless, this study presented limitations regarding the data and the sample analysis time. In the population defined for the study, during the follow-up of the cases, some complementary tests for diagnosing the condition were not performed, namely muscle biopsy for histopathological evaluation and magnetic resonance imaging for assessment by imaging examination. Furthermore, there is no complete description of the polysomnography exam, as it does not specify if there is a dominance in relation to the central, obstructive, mixed, or hypoventilatory component.

The sample analysis time also does not permit a precise determination of the complications and prognosis regarding the cardiac condition. Therefore, it is not possible to predict long-term progression, especially concerning the fatal cardiomyopathy associated with this variant in other reports.

This report describes two siblings with, MDDGC4 associated with the homozygous p.Gly424Ser phenotypic mutation in the FKTN gene. Despite the small number of cases, the article raises the possibility of suspecting genetic myopathy in the presence of persistent hypertransaminasemia and highlights the importance of early respiratory and cardiac monitoring in these patients in order to anticipate future complications.

Authors' contribution

Babugia Pinto M: data curation (Lead), formal analysis (Lead), funding acquisition (Lead), investigation (Lead), methodology (Lead), writing - original draft (Lead), writing - review & editing (Equal)

Magalhães FIM: data curation(Equal), formal analysis (Equal), investigation (Equal), methodology (Equal), writing - original draft (Equal)

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Périco AA: formal analysis (Equal),project administration (Equal), supervision (Equal), Conceptualization (Equal), project administration (Lead), supervision (Lead), writing - original draft (Supporting), writing - review & editing (Lead)

Ferarri Strang AGG: conceptualization (Equal), project administration (Lead), supervision (Lead), writing - original draft (Supporting), writing - review & editing (Lead)

All authors approved the final version of the article and declare no conflict of the interest.

Use of artificial intelligence

The authors declare that they used artificial intelligence tools as a support for translating the manuscript into English, with the aim of adapting it to the grammatical norms required by international scientific writing.

Data availability

The data used in this study are available upon request from the corresponding author(s).

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Received on February 28, 2026
Final version presented on June 4, 2026
Approved on June 8, 2026

Associated Editor: Melania Amorim