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Case Report

Autosomal Recessive ANO5-Related Disorder in a Child with Persistently Raised CK Levels

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Abstract

The anoctamin-5 (ANO5) gene, located on chromosome 11, encodes a calcium-activated chloride channel involved in the function of the musculoskeletal and cardiovascular systems. Autosomal recessive mutations in ANO5 are associated with limb-girdle muscular dystrophy (LGMDR12), Miyoshi Myopathy (MMD3), and isolated hyperCKaemia. This case report describes a boy in early childhood with heterozygous ANO5 mutations, identified after persistently elevated creatine kinase (CK) levels were discovered incidentally during an evaluation for olanzapine overdose.

Initially, he presented with drowsiness after accidentally ingesting his mother's olanzapine. His CK level peaked at 908 IU but remained elevated on follow-up, prompting further metabolic work-up and genetic testing. Despite unremarkable physical exams and normal developmental milestones, genetic testing revealed heterozygous pathogenic ANO5 variants.

This case highlights the significance of careful follow-up for persistently elevated CK levels, even in the presence of alternative explanations. Early genetic diagnosis facilitated proper referrals and monitoring, ultimately protecting patient outcomes. Proactive assessment offers reassurance to families and enables timely intervention to address potential complications.

Background

The anoctamin-5 (ANO5) gene, located on chromosome 11, encodes a calcium-activated protein that plays a critical role in bone, skeletal, and cardiac muscle function.1,2 Autosomal dominant mutations in this gene are associated with gnathodiaphyseal dysplasia, a rare bone dysplasia characterized by cemento-osseous lesions of the jaw, sclerosis of long bones, and generalized osteopenia, which predispose patients to recurrent fractures.3 In contrast, autosomal recessive mutations in ANO5 are implicated in limb-girdle muscular dystrophy and Miyoshi Myopathy, particularly in individuals of Northern European descent.4 An additional phenotype linked to ANO5 mutations is persistently elevated creatine kinase (CK) levels, which may occur with or without overt clinical symptoms.

The prevalence of ANO5 mutations is not yet known, however limb-girdle dystrophies encompassing a variety of mutations, including ANO5, are estimated to have a worldwide prevalence of 0.8 and 6.9 per 100,000. 10 It is noteworthy that the child described in this case report had no symptoms at the time of diagnosis.

Case Presentation

In April 2023, a boy in early childhood was brought in by ambulance to the Emergency Department of a regional hospital following an olanzapine overdose. He was found drowsy and unable to speak, discovered beside his mother's olanzapine tablets, which she takes as treatment for a psychiatric condition. As part of his clinical evaluation, serum creatine kinase (CK) levels were checked, revealing an elevation to 656 IU. His physical examination was unremarkable, and other blood investigations were within normal limits. By the following day, his CK levels had decreased to 346 IU. He was subsequently discharged with a follow-up plan to reassess CK levels in two weeks to ensure normalization.

In May 2023, repeat testing revealed a persistently elevated CK level of 531 IU. Consequently, he was referred to General Paediatrics' clinic in August 2023 for further assessment. At this time, physical examination was again unremarkable, with no abnormalities noted in muscle bulk, tone, or strength, and Garrow's sign was negative. There were no reported concerns regarding his developmental milestones. However, given the persistent hyperCKaemia, a comprehensive metabolic work-up was conducted, including assessments of ammonia, lactate, urine organic acids, acylcarnitine profiles, and chromosomal microarray analysis, all of which returned normal results.

Due to the absence of a clear metabolic explanation, Trio Based Exome sequencing was performed in February 2024 using CeGAT genetic sequencing via the Illumina NovaSeq 6000/NovaSeq X plus system. This revealed heterozygous pathogenic variants in the ANO5 gene. Following this diagnosis, the patient was referred to neurology and genetic counselling services. Genetic testing of both parents, who are separated, is pending at the time of this report, and both were provided with appropriate genetic counselling and support.

The patient was evaluated in the neurology clinic at a Tertiary Children's hospital following his diagnosis. A comprehensive neurological examination revealed normal findings, including appropriate muscle bulk, tone, power, reflexes, and gait bilaterally. His motor skills were developmentally appropriate for a boy in early childhood, as evidenced by his ability to cycle with stabilizers, kick a ball, and navigate stairs independently. His mother reported occasional unsteadiness, minor falls, and complaints of muscle pain following prolonged walking, leading him to request being carried. Overall, his physical abilities appeared on par with his peers.

Outcome and Follow-Up

The child was seen by a Geneticist in August 2024. They explained the likely disease progression and the recurrence risk, as well as linking them in with up-to-date research on the condition through the Orphanet leaflet. 11

He is currently being followed up on a yearly basis in the paediatric clinic in the regional hospital. He was last reviewed in clinic in August 2024, at which point parental genetic testing was pending for both his parents. There were no concerns identified at this appointment.

He is due to see a neurologist in a Tertiary Centre once the results of his parents' Trio Based Exome sequencing have returned.

Table 1: Patient's CK values over time

Date	19/04/23	20/04/23	10/05/23	21/08/23	24/10/23	13/12/23	14/03/24
CK Level (ref. 25-172 IU)	656	346	531	908	346	248	372

Discussion

Recessive ANO5-related anoctaminopathy manifests clinically in three distinct phenotypes: Proximal Limb Girdle Myopathy (LGMDR12), distal Myoshi Myopathy (MMD3) and hyperCKaemia, which may be associated with exercise intolerance. 5

LGMDR12 is characterised by weakness predominantly in the quadriceps and biceps muscle groups, accompanied by asymmetrical atrophy. Symptoms have a mean onset age of 35 years, with a wide range of presentation spanning form childhood to the sixth decade of life. Notably, the condition is frequently preceded by asymptomatic hyperCKaemia. 6 Calf atrophy or pseudohypertrophy is a common examination finding, despite the proximal distribution of muscle involvement. Winging of the scapula may also be present. Patients with this phenotype typically present with myalgia, cramps, exercise intolerance, and rhabdomyolysis. Dysphagia has also been reported in approximately 46% of patients.7 LGMDR12 is a slowly progressive muscular dystrophy, with most patients remaining ambulatory several decades after symptom onset.

Patients with MMD3 exhibit distal muscle weakness and calf pseudohypertrophy, often followed by atrophy, presenting as difficulty walking on tiptoes. Over time, the disease may involve the hip and shoulder girdle muscles, although it retains a slow progression similar to LGMDR12. Weakness is usually asymmetrical, although rare cases of symmetrical involvement have been reported. The mean age of onset for MMD3 is 33 years, with a reported range of 15 to 51 years.

Both LGMDR12 and MMD3 are associated with persistently elevated CK levels, which may precede symptom onset by decades. In some cases, ANO5-related anoctaminopathy may present as isolated hyperCKaemia without overt symptoms or with mild myalgia in the absence of muscle weakness. This milder phenotype tends to be more prevalent in female patients.8

Furthermore, approximately 30% of patients with recessive ANO5 mutations develop cardiac abnormalities, including arrhythmias and cardiomyopathy. Interestingly, about half of affected individuals exhibit skeletal muscle amyloid deposition without evidence of systemic amyloidosis. However, this isolated amyloidosis appears unrelated to cardiac abnormalities or specific muscular phenotypes.

Despite advances in our understanding of ANO5-related conditions, there are currently no disease-modifying treatments available. Nevertheless, moderate aerobic exercise has been shown to enhance cardiovascular fitness and prevent contractures without exacerbating CK levels, myalgia, or rhabdomyolysis.5,7

The youngest reported case of ANO5-related disease involved a 4-year-old female with CK levels exceeding 3000 IU, who presented with myalgia and exercise intolerance.9 By comparison, the patient described in this case report was also first identified in early childhood, although his CK levels were significantly lower, and the initial elevation was attributed to olanzapine overdose. This case underscores the importance of diligent follow-up for abnormal laboratory results, even when alternative explanations exist. Such follow-up allowed for early diagnosis and referral to appropriate medical teams before symptom onset. Although the necessity of extensive investigations in asymptomatic individuals remains debatable—particularly in cases where clinical symptoms may never manifest—the reassurance provided by proactive monitoring is invaluable. This approach ensures timely identification and management of potential complications, including rhabdomyolysis and arrhythmias, ultimately safeguarding patient outcomes.

Learning Points/Take Home Messages

This case delineates the importance of careful evaluation and follow-up in the context of persistently elevated CK levels, even when an initial precipitating factor, such as an overdose, appears to explain the abnormality. Early identification of pathogenic ANO5 mutations through genetic testing allowed for prompt referral to neurology and genetic services, ensuring ongoing monitoring and multidisciplinary management to mitigate potential complications, such as rhabdomyolysis, cardiomyopathy, or arrhythmias. While this child remains asymptomatic and developmentally appropriate, the case underscores the wide phenotypic variability of ANO5-related conditions, ranging from mild hyperCKaemia to progressive myopathies. This emphasizes the value of proactive follow-up in asymptomatic patients with hyperCKaemia, particularly in paediatric populations. Although the utility of extensive diagnostic work-up in asymptomatic individuals remains a topic

of debate, this case demonstrates how diligent monitoring and early diagnosis can facilitate timely interventions and provide reassurance to patients and families.

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