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UNVEILING LIMB-GIRDLE MUSCULAR DYSTROPHY: A CASE STUDY OF AN EIGHT-YEAR-OLD BOY

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Abstract

We report a case of an 8-year-old boy with autosomal recessive limb-girdle muscular dystrophy (LGMD), characterized by a history of global developmental delay and progressive weakness of all four limbs since birth. The child also exhibited thinning of the shoulders, arms, and thighs. Neurological examination revealed shoulder atrophy, deltoid muscle wasting, and thigh thinning, along with hypertonia in all four limbs. Muscle strength was graded as 3/5 at the shoulders, elbows, wrists, hip joints, knees, and ankles. All superficial reflexes were present and deep tendon reflexes were exaggerated, with bilateral extensor plantar responses.

Keywords: Muscular Dystrophy, Global Developmental Delay, Genetic Testing.

INTRODUCTION

Limb-girdle muscular dystrophy (LGMD) comprises a spectrum of conditions characterized by muscle weakness, primarily impacting the shoulder and hip girdles. These conditions include Duchenne and Becker muscular dystrophies, facioscapulohumeral muscular dystrophies, and myotonic muscular dystrophies [1]. They stem from mutations in various genes encoding muscle proteins, resulting in roughly 30 identified subtypes to date.

The origins of LGMD can be traced back to observations made in the early 1800s by Erb and Leyden-Mobius, who noted weakness in the shoulder and hip girdles while facial muscles remained unaffected. The term "limb-girdle dystrophy" was coined in 1954 by Walton and Nattrass, highlighting its equal occurrence among both genders. LGMD is divided into two primary groups: LGMD 1 (autosomal dominant) and LGMD 2 (autosomal recessive).

Among the recognized forms of LGMD is Calpainopathy (LGMD 2A), arising from mutations in the CAPN 3 gene, resulting in calpain deficiency. Dysferlinopathy arises from mutations in the DYSF gene, leading to dysferlin deficiency, while Duchenne muscular dystrophy results from dystrophin gene mutations, causing dystrophin deficiency and subsequent muscle fibrosis [2].

The age of onset varies, with Duchenne muscular dystrophy typically appearing in childhood and other forms like Calpainopathy and Dysferlinopathy emerging later in adulthood. Symptoms include progressive weakness in proximal muscles, difficulty in tasks such as stair climbing and rising from squatting positions, with lower limbs often affected earlier than upper limbs.

The severity and inheritance patterns of LGMD vary, with most cases inherited in an autosomal recessive manner. Recent findings indicate a higher prevalence in communities practicing consanguineous marriages, underscoring the importance of avoiding such unions to prevent the inheritance of LGMD [3,4].

Case report

An 8-year-old boy, the first child of a non-consanguineous marriage, presented with a history of gradual thinning in both upper and lower limbs since 1 year of age. Currently, the child was brought in with complaints of increased thinning in both upper and lower limbs. The history further revealed global developmental delay, with gross motor function being the most affected.

During the mother's pregnancy, she had history of varicella infection in the first trimester (at 14 weeks gestation). The baby was delivered prematurely at 34 weeks due to severe oligohydramnios and fetal distress via emergency caesarean section. He weighed 1.6kg and was categorized as small for gestational age. Following delivery, he was kept in the neonatal intensive care unit due to low birth weight and prematurity, with no instances of neonatal sepsis, seizures, or the need for assisted ventilation .

Examination of the child after birth revealed a flat occiput and a wide-open anterior fontanelle measuring 3x3cm. His blood investigations, including Vitamin D and thyroid function tests, were within normal ranges. An MRI brain scan done after birth revealed features of bilateral supratentorial cerebral white matter hyperintensity in T2W and FLAIR sequences, along with hyperintensity in the internal capsule and corticospinal tract in the medulla. MR angiography results were normal.

Physiotherapy was recommended for his poor muscle tone and was carried out for the initial 4 years of his life, after which it was discontinued by the parents due to family constraints. This cessation in physiotherapy resulted in increased stiffness of the limbs, leading to joint contractures at the elbow, knee, and ankle, and diminished mobility in these joints.

Currently, the examination of the child showed thinning of the shoulders, arms, and thighs. There was no history of distal muscle weakness, muscle twitching, limb pain, breathlessness, cranial nerve involvement, sensory symptoms, or bladder and bowel disturbances. The child was found to be severely stunted with severe muscle wasting, with all anthropometric measurements below the third percentile for his age.

The general physical examination was normal. Neurological examination revealed severe thinning of both upper and lower limbs (Fig-1). He couldn't lift his head from the bed, indicating weakness of neck muscles and Muscle strength was found to be 3/5 at the shoulders, elbows, wrists, hip joints, knees, and ankles. All deep tendon reflexes were exaggerated, with an absence of clonus, and superficial reflexes were present with bilateral extensor plantar responses. Sensory system and spine examination was found to be normal. Respiratory, cardiovascular, and abdominal examinations were unremarkable.

Figure 1: Severe wasting and thinning of limbs

Investigations showed normal results for hemogram, liver function, renal function, serum electrolytes, thyroid function tests, serum cortisol, serum LDH, and serum PTH. Creatinine phosphokinase was 59 IU/L (reference: 24-190 IU/L). Urine routine and urine myoglobin tests were negative. ECG, chest X-ray, echocardiography, and abdominal ultrasound were normal. Nerve conduction studies were normal. A recent MRI brain study revealed diffuse bilateral symmetrical confluent areas showing iso-hypointensities in T1 and T2/FLAIR hyperintensities involving the subcortical and deep white matter of the bilateral fronto-temporo-parietal lobe and periventricular region.

Genetic studies were conducted as a last resort to identify the cause of the child's gradual deterioration. Whole exome sequencing identified an abnormality in the LAMA2 gene, specifically in exon 35 variant c.5018_5019delp.Thr1673LysfsTer10, indicative of autosomal recessive limb-girdle muscular dystrophy 23 (Fig-2). Genetic testing has also identified a mutation in the ASH1L (NM_018489.3) gene, specifically on Exon 3, presenting as the c.1997C>Tp.Thr666Ile [41X/83X] variant. This variant displays heterozygosity with uncertain classification and is associated with autosomal dominant inheritance of intellectual developmental disorder, specifically autosomal dominant 52. This mutation may have contributed to the observed global developmental delay (Fig-3). Based on the history, proximal muscle weakness, and whole exome sequencing results, a diagnosis of LGMD with associated intellectual developmental disorder was made.

Summary of Variants

Gene and Transcript	Exon/Intron Number	Variant Nomenclature [Variant depth/ Total depth]	Zygosity	Classification	OMIM Phenotype	Inheritance
LAMA2 (NM_000426.4)	Exon 35	c.5018_5019del p.Thr1673LysfsTer10 [47X/90X]	Heterozygous	Uncertain significance	Muscular dystrophy, limb-girdle, autosomal recessive 23	Autosomal recessive

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Figure 2: LAMA2 gene mutation)

Summary of Variants

Gene and Transcript	Exon/Intron Number	Variant Nomenclature [Variant depth/ Total depth]	Zygosity	Classification	OMIM Phenotype	Inheritance
ASH1L (NM_018489.3)	Exon 3	c.1997C>T p.Thr666Ile [41X/83X]	Heterozygous	Uncertain significance	Intellectual developmental disorder, autosomal dominant 52	Autosomal dominant

Figure 3 Intellectual developmental disorder gene mutation

DISCUSSION

Limb-girdle muscular dystrophy (LGMD) represents a rare genetic condition marked by muscle weakness and deterioration, notably affecting muscles around the shoulders and hips, profoundly affecting one's quality of life. Recognizing its genetic underpinnings is paramount, given LGMD's hereditary nature and the varied gene mutations involved, highlighting the necessity of genetic testing and counseling for those impacted and their families [5,6].

Managing symptoms takes precedence, as no cure currently exists; therapies like physical rehabilitation, assistive technologies, and prescribed medications aim to mitigate discomfort such as pain and stiffness, offering crucial insights to affected individuals.

While clinical and molecular genetic assessments often suffice for precise diagnosis in numerous instances, the inclusion of imaging and histopathological analyses remains crucial, if not indispensable, for evaluation in select cases [7].

Living with LGMD poses multifaceted challenges, both physically and emotionally, ranging from limitations in movement to adapting daily routines, accentuating the importance of developing coping mechanisms and supportive networks [7,8].

The reverberations of LGMD permeate various spheres of life, including daily activities, professional pursuits, education, and interpersonal relationships, underscoring the imperative of fostering understanding and empathy. Tackling obstacles in education and employment becomes imperative to ensure equitable opportunities for individuals with LGMD, necessitating tailored approaches for accommodation and inclusivity [9].

Moreover, recognizing the psychological toll of LGMD, avenues for psychosocial support like counseling and peer groups are indispensable for navigating the emotional complexities associated with the condition, acknowledging its profound impact on mental well-being [10].

CONCLUSION

In conclusion, diagnosing an eight-year-old male child with limb girdle muscular dystrophy (LGMD) inherited as autosomal recessive and global developmental delay presents a challenging clinical scenario [8]. The added complexity of global

developmental delay necessitates a comprehensive, multidisciplinary approach to care.

The autosomal recessive inheritance suggests both parents are likely carriers of the mutation, which is important for genetic counseling and future family planning considerations [9]. Early identification of the condition is crucial to start supportive therapies, such as physical and occupational therapy, aimed at preserving mobility and enhancing the child's quality of life.

Regular monitoring and assessments are necessary to manage the progressive nature of LGMD and to address potential complications like respiratory or cardiac issues [8-10]. Effective care requires a team of specialists, including neurologists, geneticists, physiotherapists, and developmental pediatricians, to provide personalized, holistic support.

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