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CASE REPORT

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A Rare Cause of Neonatal Hypotonia: First Case of Autosomal Recessive Fast-Channel Congenital Myasthenic Syndrome Type 1B in Albania

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Abstract

Hypotonia is a concern, with high morbidity and poor outcomes in 10% of neonatal care cases. Neonatal hypotonia presents a diagnostic challenge for neonatologists, as it may be a sign of a central nervous disorder (hypoxic-ischemic insult, intracranial hemorrhage, cerebral palsy), inborn errors of metabolism, a primary neuromuscular disorder, or a genetic syndrome associated with hypotonia.

This clinical report presents a rare case of neonatal hypotonia caused by autosomal recessive fast-channel congenital myasthenic syndrome type 1B (FCCMS-1B). We describe the case of a newborn who presented with severe hypotonia, muscle weakness, respiratory insufficiency, and feeding difficulties. He was diagnosed with autosomal recessive FCCMS-1B in the presence of heterozygous pathogenic variants in the cholinergic receptor nicotinic alpha 1 subunit (*CHRNA1*) gene as determined by molecular genetic testing and suggestive clinical features. To our knowledge, this is the first FCCMS-1B report in Albania. (**International Journal of Biomedicine. 2024;15(1):215-217.**)

Keywords: neonatal hypotonia • congenital myasthenic syndrome • molecular genetic testing• muscular weakness

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Introduction

Hypotonia is a concern, with high morbidity and poor outcomes in 10% of neonatal care cases.[1] Neonatal hypotonia presents a diagnostic challenge for neonatologists, as it may be a sign of a central nervous disorder (hypoxic-ischemic insult, intracranial hemorrhage, cerebral palsy), inborn errors of metabolism, a primary neuromuscular disorder, or a genetic syndrome associated with hypotonia (Down syndrome, Prader-Willi syndrome, Sotos syndrome, congenital myasthenic syndrome).[2] However, hypotonia and weakness in ill-appearing babies can occur in other common neonatal conditions, such as neonatal sepsis, hypothermia, hypoglycemia, hypothyroidism, congenital infections, acute bilirubin encephalopathy, and drug toxicity.[3]

Early diagnosis of newborn hypotonia requires genetic testing, medical history, physical examination, laboratory tests, family history, and further genetic counseling.

Case Presentation

This case of a male newborn delivered by cesarean section at 39 weeks of gestation with polyhydramnios, but no other events were noted during pregnancy. At birth, the amniotic fluid was meconium-stained, and the birth weight was 2450 g. He failed to establish the first breath and needed resuscitation in the delivery room (the 1-minute and 5-minute Apgar scores were 3 and 6, respectively) and was immediately

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intubated and admitted to the neonatal intensive care unit for severe respiratory distress. Our newborn stayed on mechanical ventilation for 10 days and later was always oxygen-dependent. Hypotonia and muscle weakness were noted during ventilation, which became more evident after disconnection from the ventilator. Although lung auscultation was clear, the baby still manifested signs of respiratory distress, including shallow breathing, tachypnea, and suprasternal and subcostal retractions. Other clinical findings included profound muscular weakness, palpebral ptosis, pool of secretions, and feeding difficulties (feeding through a nasogastric tube). Subtle facial dysmorphism was noted, with micrognathia, palpebral ptosis, high-arched palate, and low-set ears.

Common causes of neonatal hypotonia, such as sepsis, hypoglycemia, hypothermia, hypothyroidism, and congenital infections, were excluded. CBC, biochemical and coagulation panel, thyroid gland function, and neonatal sepsis workup revealed normal results. In addition, the SARS-CoV-2 PCR, Toxoplasma IgM, CMV IgM, rubella IgM, and herpes simplex IgM were tested and found to be negative. The ammonia level was 89 µg/dL, creatine kinase - 29 UI/L, lactate dehydrogenase - 892.02 UI/L. Newborn screening tests for metabolic disorders were within normal limits.

A brain MRI detected no pathological signals related to the patient's neurological situation, no signs of intracranial hemorrhage or hypoxic lesions. Ophthalmological evaluations revealed no significant abnormalities.

We also performed a genetic molecular analysis. Genomic DNA was extracted from the peripheral blood in dried blood spots, a genetic test was developed, and its performance was validated using CENTOGENE AG. Molecular genetic testing identified a heterozygous pathogenic variant and a heterozygous variant of uncertain significance in the cholinergic receptor nicotinic alpha 1 subunit *(CHRNA1)* gene. The *CHRNA1* variant c.1072C>T (p.Arg358Trp) causes an amino acid change from Arg to Trp at position 358. This variant has also been detected in the mother in a heterozygous state. It is classified as a variant of uncertain significance (Class 3), according to the recommendations of CENTOGENE and ACMG. The *CHRNA1* variant c.1396G>A (p.Gly466Arg) causes an amino acid change from Gly to Arg at position 466. This variant was detected in the father in the heterozygous state and was classified as pathogenic (Class 1). Parental carrier testing confirmed the trans-state of the CHRNA1 variants. These molecular findings suggested the genetic diagnosis of autosomal recessive FCCMS-1B. After the genetic diagnosis of FCCMS-1B was made, treatment with pyridostigmine was recommended; however, the infant's clinical condition significantly deteriorated. The infant was transferred to the Pediatric Intensive Care Unit and the Pediatric Neurology Service after the neonatal period. During that period, he was intubated three times, fed through a nasogastric tube, and never discharged home. The patient died at four months of age.

Neonatal hypotonia presents a diagnostic challenge to neonatologists. Molecular genetic tests are crucial for early diagnosis, enabling patients to receive the best care and provide the best genetic counseling for their parents and relatives.

Discussion

While diagnosing neonatal hypotonia is difficult, determining the reason for this disease could also be difficult.[2] Neonatologists are helped in the early evaluation of neonatal hypotonia and its differential diagnosis by genetic testing, physical examination, medical history, laboratory testing, imaging, and family history.[2,4]

We excluded more common causes, such as sepsis, hypoglycemia, hypothyroidism, congenital infections, acute bilirubin encephalopathy, and drug toxicity.[3] We then focused on metabolic causes, and newborn screening for metabolic disorders was within the normal limits. A brain MRI detected no pathological signals related to the patient's neurological condition.

Our newborn presented with hypotonia, persistent respiratory failure without signs of infection, and feeding difficulties, symptoms that can be found in both neuromuscular and myopathic diseases. These symptoms, along with facial dysmorphism, palpebral ptosis, facial muscle atony, and obstetrical data, such as paucity of fetal movements, are suggestive of a myopathic cause.[5]

The whole exome analysis of our patient and his parents revealed the presence of a heterozygous pathogenic variant and a heterozygous variant of uncertain significance in the *CHRNA1* gene. The *CHRNA1* variant c.1396G>A (p.Gly466Arg) has previously been described as disease-causing for congenital myasthenic syndrome (CMS) by Neto et al..[6] This variant was detected in the father's heterozygous state. The *CHRNA1* variant c.1072C>T (p.Arg358Trp) was previously described as a disease-causing CMS by Masuda et al.[7] This variant was detected in the mother in the heterozygous state. No Class 1 or 2 variants were detected in genes for which secondary (incidental) findings were reported. These molecular findings were consistent with the genetic diagnosis of autosomal recessive FCCMS-1B.

Fast-channel myasthenic syndromes are caused by mutations that alter the kinetics of ion channels by reducing the time that the acetylcholine receptor channel is open, causing a reduction in postsynaptic depolarization and failure to trigger muscle action potentials.[8,9] In CMS, the severity of symptoms can significantly vary depending on the specific gene mutation.[4,10] The clinical features of hypotonia and muscle weakness are present in all subtypes of CMSs, a heterogeneous group of neuromuscular disorders affecting the muscles, central nervous system, and other organs.[4,10] The age at which symptoms of CMSs first appear and how they manifest are dependent on the molecular mechanism of the genetic defect. Some myasthenic symptoms are present at birth, and these neonates frequently exhibit respiratory insufficiency with cyanosis and sudden, episodic apnea.[11] Other important neonatal findings may be poor sucking and crying, choking episodes, eyelid ptosis, facial, bulbar, generalized weakness, and stridor, which may provide crucial information, as well as some joint contractures (also known as arthrogryposis multiplex congenital) due to insufficient fetal mobility during pregnancy. Some children may have a long face, a narrow jaw, and a high-arched palate.[4,5,12,13]

Our patient, the only child of non-consanguineous parents, presented most of these congenital myasthenic

syndromes, clinical characteristics as a severe clinical phenotype with hypotonia, feeding difficulties, and profound muscle weakness that was more evident without ventilation assistance. He required immediate intubation in the delivery room and required recurrent oxygen and ventilatory support by nasal cannula and mechanical ventilation. He was never able to feed by breast or bottle. Additionally, mild facial dysmorphism with low-set ears, a high-arched palate, palpebral ptosis, and micrognathia were observed. Reduced intrauterine fetal movements, meconium-stained amniotic fluid, and polyhydramnios were other data mentioned in our patient's history.

Our patient is the first case of autosomal recessive FCCMS in Albania. This is a rare case of autosomal recessive FCCMS heterozygous for two pathogenic variants of the *CHRNA1* gene with a severe and deadly neonatal phenotype. This case demonstrates the importance of considering subtypes of congenital myasthenic syndromes in diagnosing neonatal hypotonia.[14] CMS should generally be suspected if there is permanent weakness, most frequently in the ocular, facial, bulbar, respiratory, or limb muscles, with onset from birth to childhood. Because of the large number of mutations, genes, and muscular weakening patterns that might develop, and their intra- and interfamilial phenotypic heterogeneity, CMS diagnosis can be difficult, and differential diagnosis with many other disorders with similar presentations should be ruled out.[4,10,13] As genetic testing is the most important investigation for diagnosing CMS, we would also like to point out that finding disease-related genes via molecular genetic tests could help in early diagnosis, improve knowledge of the pathophysiology of the disease and genotype-phenotype correlation, and enable patients to receive the best care and provide the best genetic counseling for their parents and relatives.[4,10]

Ethical Considerations

The patient's parents gave informed consent to publish this case report.

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