

A Case Report on CLCN1- Related Myotonia Congenita

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Date of Submission: 01-10-2026

Date of Acceptance: 11-10-2026

ABSTRACT

Myotonia congenita is an inherited skeletal-muscle channelopathy caused by pathogenic variants in the CLCN1 gene, resulting in muscle stiffness and delayed muscle relaxation. We report a 29-year-old pregnant woman with a painful muscle stiffness since early childhood and proximal muscle weakness. Based on the clinical suspicion of myotonia congenita or another muscle channelopathy, whole-exome sequencing was performed and identified a homozygous CLCN1 c.1667T>A (p.Ile556Asn) missense variant in exon 15, classified as likely pathogenic and associated with autosomal-recessive myotonia congenita. During pregnancy, non-invasive prenatal testing (NIPT) at 11 weeks and 6 days showed low-risk results for trisomies 13, 18, and 21 and the tested sex-chromosome aneuploidies. First-trimester ultrasound demonstrated a singleton live intrauterine pregnancy without reported aneuploidy markers. At 16 weeks and 6 days, ultrasound demonstrated a regular cardiac activity, active fetal movements, adequate liquor, a posterior placenta, a cervical length of 4 cm, and no structural abnormality. This case highlights the value of integrating clinical findings, molecular genetic testing and obstetric assessment in diagnosing CLCN1 related myotonia congenital during pregnancy.

KEY WORDS: Myotonia congenital, CLCN1, p.Ile556Asn, whole-exome sequencing, pregnancy, genetic diagnosis.

I. INTRODUCTION

Myotonia congenita is a rare inherited disorder of skeletal-muscle channelopathy caused by pathogenic variants in CLCN1, the gene encoding the CLC-1 voltage-gated chloride channel. CLC-1 plays an important role in maintaining the electrical stability of skeletal-muscle cell membranes following muscle contraction. Abnormal function of

this chloride channel results in increased muscle membrane excitability and repetitive electrical activity, leading to delayed muscle relaxation, muscle stiffness. It can be inherited in either an autosomal-dominant or autosomal-recessive manner. The autosomal-dominant form is also known as Thomsen disease, whereas the autosomal-recessive form is commonly referred to as Becker disease. Symptoms commonly begin during childhood or adolescence and may include muscle stiffness after voluntary movement, difficulty relaxing contracted muscles, and, in some patients, muscle pain and weakness. The muscles commonly affected include the limbs, trunk, and facial muscles, although the distribution and severity of symptoms can vary. Some individuals may develop muscle hypertrophy because of persistent muscle activity. Symptoms can be influenced by factors such as sudden movement, prolonged rest, or cold temperatures. The diagnosis is based on the clinical phenotype and may be supported by electromyography (EMG), which can demonstrate characteristic myotonic discharges. Molecular genetic testing provides a definitive etiological diagnosis when pathogenic or likely pathogenic variants in CLCN1 are identified. Identification of biallelic pathogenic variants supports the diagnosis of autosomal-recessive myotonia congenita, while a heterozygous pathogenic variant may establish autosomal-dominant disease in the appropriate clinical context. The CLCN1 c.1667T>A (p.Ile556Asn) variant identified in the present patient has previously been reported in association with myotonia congenita.

II. CASE REPORT

The report investigate a case of myotonia congenita. A 29-year-old pregnant woman underwent clinical and genetic evaluation for a history of muscle symptoms dating back to childhood. She had experienced painful muscle

stiffness beginning in early childhood along with proximal muscle weakness, raising clinical suspicion of myotonia congenita or another muscle channelopathy. The patient was born to a non-consanguineous marriage. Based on her clinical presentation, further molecular genetic evaluation was undertaken to determine the underlying cause of her symptoms. Whole-exome sequencing was performed using a blood sample. The genetic analysis identified a homozygous missense variant in the CLCN1 gene. The identified variant was c.1667T>A, resulting in an amino-acid substitution of p.Ile556Asn (I556N). The variant is located in exon 15 of the CLCN1 gene. The reported mode of inheritance was autosomal recessive, and the associated condition was identified as myotonia congenita, autosomal recessive. The genetic report also documented that the variant was a missense variant, meaning that the nucleotide change results in substitution of one amino acid for another in the resulting protein. The specific change, p.Ile556Asn, involves replacement of isoleucine by asparagine at position 556 of the CLCN1 protein. At the time of evaluation, the patient was carrying a singleton pregnancy. During the first trimester, at approximately 11 weeks and 6 days of gestation, non-invasive prenatal testing (NIPT) was performed. The test documented a singleton pregnancy and reported low-risk results for chromosomes 13, 18, and 21, as well as low-risk results for the tested sex-chromosome aneuploidies. A second-trimester obstetric Doppler ultrasound was subsequently performed at approximately 16 weeks and 6 days of gestation. The examination demonstrated a single live intrauterine fetus in cephalic presentation with regular cardiac activity. The fetal heart rate was approximately 158 beats per minute, and active fetal movements were observed. The placenta was located posteriorly, and the liquor was adequate. The cervical length was approximately 4 cm, and there was no obvious intra- or retroplacental bleed. The estimated fetal weight was approximately 169g. Doppler assessment of the ductus venosus demonstrated a normal waveform without evidence of flow reversal. Overall, the ultrasound findings were consistent with a single live intrauterine pregnancy corresponding to approximately 16 weeks and 6 days of gestation. A detailed anomaly scan at approximately 20 weeks was recommended.

III. DISCUSSION

The present case illustrates the molecular diagnosis of CLCN1-related myotonia congenita in

a pregnant woman with a childhood-onset myotonic phenotype. The CLCN1 gene encodes the skeletal-muscle chloride channel CLC-1, which plays an important role in maintaining muscle membrane stability. Reduced chloride conductance can increase membrane excitability, resulting in repetitive depolarization and delayed muscle relaxation, clinically manifesting as myotonia. In this patient, the history of painful muscle stiffness beginning in childhood along with proximal muscle weakness prompted genetic evaluation, and the identification of a homozygous CLCN1 variant provided a molecular explanation for the clinical presentation. In the present pregnancy, routine obstetric imaging and aneuploidy screening were reassuring for the abnormalities assessed; however, these investigations do not determine whether the fetus has inherited a familial CLCN1 variant, as routine non-invasive prenatal testing primarily evaluates chromosomal abnormalities rather than single-gene disorders. Myotonia congenita is also clinically important during pregnancy and delivery because certain medications, anesthetic agents, and physiological stresses may aggravate myotonia; therefore, appropriate obstetric, anesthetic, and neonatal planning is important. Genetic counseling is recommended because the patient carries a homozygous variant associated with an autosomal-recessive condition. Although assessment of the reproductive partner could help clarify the potential genetic risk to the offspring, partner testing.

IV. CONCLUSION

This case highlights a CLCN1-related myotonia congenita in a 29-year-old pregnant woman presenting with childhood-onset painful muscle stiffness and proximal muscle weakness. Whole-exome sequencing identified a homozygous CLCN1 c.1667T>A (p.Ile556Asn) missense variant in exon 15, supporting the diagnosis of autosomal-recessive myotonia congenita. The pregnancy was monitored with appropriate antenatal investigations. NIPT performed at 11 weeks and 6 days showed low-risk results for trisomies 13, 18, and 21 and the tested sex-chromosome aneuploidies. Subsequent ultrasound and Doppler assessment at 16 weeks and 6 days demonstrated a single live intrauterine fetus with regular cardiac activity, active fetal movements, adequate liquor, normal ductus venosus Doppler, and no obvious structural abnormality on the examination performed. A detailed anomaly scan at approximately 20 weeks was recommended for further fetal assessment. Overall, this case demonstrates the importance of integrating clinical

presentation with molecular genetic testing and antenatal assessment in pregnant women with suspected inherited neuromuscular disorders. Identification of the homozygous CLCN1 variant enabled confirmation of the underlying genetic diagnosis and emphasizes the importance of appropriate genetic counselling and multidisciplinary obstetric, neurological, and anaesthetic planning during pregnancy.

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