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Hypotonia and feeding problems in the newborn: a congenital myotonic dystrophy type 1 clinical case

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ABSTRACT

Introduction: Congenital myotonic dystrophy type 1 (DM1) is characterized by hypotonia and severe general weakness at birth, often with respiratory distress and even death.

Clinical report: A newborn male with prenatal diagnosis of ventriculomegaly and polyhydramnios was born at 39 weeks of gestation with no immediate occurrences and a maternal family history of two cases with unspecified neuromuscular conditions. The newborn was admitted in the second day of life due to feeding problems and desaturation episodes, presenting with hypotonia, non-vigorous crying, facial diplegia, and arthrogryposis of the lower limbs. A genetic study for myotonic dystrophy was requested, which revealed cytosine thiamine and guanine (CTG) expansion in the DMPK gene (1100–1400 repeats), confirming diagnosis of congenital DM1.

Discussion and conclusions: Despite the presence of congenital DM1, this newborn presents with a milder phenotype than expected for the condition. Symptom recognition, combined with family history, allowed an early diagnosis and adequate follow-up.

Keywords: Congenital myotonic dystrophy; DMPK gene; Hypotonia; Steinert's disease

HIPOTONIA E DIFICULDADES ALIMENTARES NO RECÉM-NASCIDO: UM CASO DE DISTROFIA MIOTÓNICA TIPO 1 CONGÉNITA

RESUMO

Introdução: A distrofia miotónica tipo 1 (DM1) congénita caracteriza-se por hipotonia e fraqueza generalizada grave ao nascimento. Frequentemente, apresenta-se com insuficiência respiratória, podendo ser fatal.

Caso Clínico: Um recém-nascido do sexo masculino, com diagnóstico pré-natal de ventriculomegalia e polihidrâmnio, nasceu às 39 semanas sem intercorrências. Dos antecedentes familiares, destacam-se dois elementos da linhagem materna com doença neuromuscular não esclarecida. O recém-nascido foi internado no segundo dia de vida devido a dificuldades alimentares e episódios de dessaturação, apresentando hipotonia, choro pouco vigoroso, diplegia facial e artrogripose dos membros inferiores. Foi solicitado estudo genético de distrofia miotónica, que revelou expansão de citosina, tiamina e guanina (CTG) no gene DMPK (1100–1400 repetições), confirmando o diagnóstico de DM1 congénita.

Discussão e conclusões: Apesar de se tratar de um caso de DM1 congénita, este recém-nascido apresenta um quadro menos grave do que o expectável. O reconhecimento da sintomatologia, aliado à história familiar, permitiu estabelecer um diagnóstico atempado e um plano de seguimento adequado.

Palavras-chave: Distrofia miotónica congénita; Doença de Steinert; Gene DMPK; Hipotonia

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INTRODUCTION

Myotonic dystrophy (DM) is a clinically and genetically heterogeneous disease, with autosomal dominant inheritance, presenting as two major types: myotonic dystrophy type 1 (DM1), the most common type, also known as Steinert's disease, and myotonic dystrophy type 2 (DM2), recognized in 1994 as a milder phenotype of the disease.

DM1 is a multisystemic disease, resulting from an expansion of cytosine, thiamine, and guanine (CTG) trinucleotides in the DMPK gene of chromosome 19q13.3. Its estimated prevalence is 1:20.000 and can be classified as mild, classic, or congenital according to phenotype and number of CTG repeats.[1]

Mild DM1 is diagnosed between 20 and 70 years of age, presenting with cataracts and mild myotonia, and has a normal life expectancy. Classic DM1 manifests earlier, in the second or third decades of life, and is characterized by general weakness (with distal predominance), myotonia, cataract, and often cardiac conduction abnormalities. These patients have a reduced life span, living until the age of 48–55. Congenital DM1 usually manifests in the neonate with hypotonia, severe weakness, and respiratory failure, and is frequently lethal.[2] Two different entities are recognized according to age of symptoms' onset: childhood-onset DM1 and juvenile DM1. Childhood-onset DM1 is commonly diagnosed on the first decade of life (one to 10 years of age) and predominantly affects muscle strength, cognition, and respiratory, central nervous and gastrointestinal systems, having a similar prognosis as congenital DM1. Juvenile DM1 manifests in the second decade of life (10 to 20 years of age), but has an unclear onset and symptoms overlap between childhood-onset and classic DM1.[3]

CASE REPORT

The case of a newborn male, resulting from a planned and supervised pregnancy and with prenatal diagnosis of mild polyhydramnios and ventriculomegaly, is described. Due to risk of preterm delivery, the mother was admitted at 33 weeks of gestation and pulmonary maturation and tocolysis were carried out. A fetal cerebral magnetic resonance was performed, confirming mild symmetric ventriculomegaly. Fetal echocardiogram was normal. Due to pelvic presentation, the baby was born by elective caesarean delivery at 39 weeks of gestation, with an Apgar score of 7 and 10 at the first and fifth minutes, respectively, and no need for resuscitation measures. This was the first child of young, non-consanguineous parents. A second-grade maternal aunt had died at the age of 60 due to complications from an unspecified neuromuscular disease and one of this aunt's sons also reported an unclear neuromuscular disease.

On the second day of life, the newborn was admitted to Neonatology Unit due to feeding problems, hypoglycemia, and desaturation episodes. At admission, hypotonia, low-pitched cry, facial diplegia with retrognathia, oval palate, and "inverted V-shaped" superior lip were confirmed. Furthermore, the child had a unilateral cryptorchidism, bilateral feet syndactyly, and arthrogryposis of the lower limbs. Analytical studies were performed, with no major abnormalities detected except for a creatine phosphokinase (CK) maximum value of 602 U/L on the third day of life. A cranial ultrasound confirmed symmetric ventriculomegaly (15 mm longer axis). Chest radiography was normal and echocardiogram revealed patent foramen ovale (PFO) and persistence of small and restrictive ductus arteriosus. Karyotype 46 XY was confirmed.

Due to hypotonia and facial diplegia associated with a family history of neuromuscular disease, DM hypothesis was considered. The mother was evaluated and revealed grip myotonia, supporting this hypothesis. Genetic study for DM was requested, revealing a CTG expansion (1100–1400 repeats [+/-70]) in the DMPK gene, confirming the diagnosis of congenital DM1.

During hospitalization, the newborn was hemodynamically stable, with spontaneous ventilation, requiring oxygen support until the fourth day of life, and with no signs of respiratory distress afterwards. Progressive feeding improvement was observed. Axial hypotonia showed a mild improvement, with no further complications. Ophthalmologic examination excluded the presence of cataracts or other abnormalities. The child was discharged on the 14th day of life with feeding autonomy and referred to a multidisciplinary, early intervention approach. Six months after discharge, the child maintained facial diplegia, with hypotonia improvement but pending head control. He currently maintains physical therapy, as well as clinical follow-up by Child Neurology, Pediatrics, Orthopedics, and Physical and Rehabilitation Medicine. Parents were referred for genetic counseling.

DISCUSSION AND CONCLUSIONS

Congenital DM1 is the most severe form of DM1. Despite of the limited number of studies and often small sample sizes, it has an estimated incidence of 2.1 to 28.6 new cases in 100.000 births.[4,5] DM1 may present during pregnancy with polyhydramnios (due to poor fetal swallowing) and decreased fetal movements, especially in most severe cases.[6] Prematurity is also frequent. In the neonate, main features consist of severe hypotonia, facial diplegia (with "inverted V-shaped" or "fish-shaped" superior lip), feeding problems, arthrogryposis (more pronounced in the limbs), and respiratory failure.[1] Although hypotonia and facial diplegia are most frequently reported, even in newborns with milder disease phenotypes, feeding problems are also common, with a significant proportion of newborns temporarily requiring tube feeding.[5] Respiratory compromise is also frequent, affecting 70–80% of newborns and requiring ventilation support. At this stage of life, this is the main cause of death.[5] Although usually requiring intensive care, most newborns survive the neonatal period. However, overall mortality rate remains at 15–20% and may be as high as 40% in severely affected infants.[7]

A gradual improvement of motor function is often observed in this condition. Some children are able to walk, although late. Nevertheless, some degree of hypotonia and general weakness with facial predominance persists. Between the age of three and five, foot deformities, learning problems, behavioral abnormalities, and delayed psychomotor development become the main problems. After that, intellectual disability associated with generalized cerebral atrophy is the predominant feature,

affecting 50–60% of children.[8] The Intelligence Quotient (IQ) usually ranges between 40 and 80, with an average of 70. A lower IQ seems to relate with more severe muscle weakness, longer CTG repeats, and maternal transmission.[9,10] Although there is a later development of classic DM1 complications – including distal muscle weakness, myotonia, cataracts, and electrocardiographic abnormalities – in these children, there is no apparent correlation with the severity of newborn presentation.[8]

The parent (usually the mother) is often diagnosed after the newborn, underscoring the potential subclinical presentation of the disorder. Although there are few reports of congenital DM1 with paternal transmission, men at risk appear to have smaller CTG repeats and/or be asymptomatic when the child is diagnosed.[11]

The gold-standard for diagnosing DM1 is genetic testing showing an expanded CTG repeat in the DMPK gene. Normal DMPK gene alleles contain five to 34 CTG repeats. Premutation alleles contain 35 to 49 repeats. Full penetrance alleles of ≥50 CTG repeats are associated with symptomatic disease. The three disease entities also seem to correlate with the extent of CTG repeats. In mild DM1, DMPK contains 50 to 100 CTG repeats and, in classic DM1, this number ranges from 100 to 1000. A CTG repeat number over 1000 indicates congenital DM1, as in the present clinical case, and over 2000 indicates a higher than 90% probability of developing a severe phenotype.[2]

DM1 is inherited in an autosomal dominant manner. Therefore, offspring of an individual with a premutation or mild DM1 have a 50% chance of inheriting the mutated allele. These children have a higher risk of inheriting longer CTG repeats and hence a more severe and earlier onset disease, due to a process known as anticipation.[1,2] The asymptomatic parents of an affected child must be referred for genetic counseling. Prenatal diagnosis of DM1 can be achieved by fetal cell DNA analysis, collected by amniocentesis at 15–18 weeks of gestation, or by chorionic villus sampling at 10–12 weeks of gestation.[12] When there is familiar history of DM, genetic counseling should be offered to parents – even in asymptomatic cases – before prenatal diagnosis, due to risk of subclinical disease (premutational variant).

Children affected by this condition should have a multidisciplinary follow-up and support treatment. Physiotherapy, occupational therapy, and orthopedic treatments are important to prevent complications and maximize muscle function. Many children will require special education due to intellectual disability. Respiratory and cardiac complications should be monitored, with periodic respiratory function tests, electrocardiography, echocardiography and Holter, according to the child's evolution.

Although the present case refers to congenital DM1, the infant presented with a milder disease than it would be expected, not requiring ventilatory support. Parents' genetic study was requested and, albeit with no results to date, clinical history suggests maternal transmission. The infant's diagnosis will allow for family genetic counseling and adequate follow-up of affected relatives.

This clinical case highlights the importance of considering congenital DM1 even in newborns with mild symptoms. Furthermore, it reinforces the relevance of family history, which allowed for an early diagnosis and adequate follow-up.

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