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Vladan Milovanov, Yanko Petkov

ABSTRACT

Introduction: Congenital myotonic dystrophy type 1 (CDM1) is a trinucleotide repeat disorder with early onset of symptoms and high neonatal mortality. Most patients with CDM1 have >1000 CTG repeats; a high number of CTG repeats generally indicate severe disease. CDM1 complicated by persistent pulmonary hypertension in the newborn (PPHN) has seldom been reported, and all previously reported cases have resulted in neonatal death.

Case Report: We present a neonate with CDM1 complicated by PPHN with early onset of symptoms and severe course of disease as a result of anticipation by maternal transmission. A triplet repeat primed polymerase chain reaction (TP-PCR) analysis showed CDM1 with only 800 CTG repeats. The patient was successfully treated by inotropic support and mechanical ventilation.

Conclusion: This is the first reported case of CDM1 with PPHN that did not result in neonatal death. More information on association between PPHN and number of CTG repeats in neonates with CDM1 is needed.

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CASE REPORT

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Keywords: Congenital myotonic dystrophy, Newborn, PPHN, TP-PCR analysis, Neonatal death

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INTRODUCTION

Congenital myotonic dystrophy type 1 (CDM1) is a multisystem muscle disorder that can present prenatally with polyhydramnios and reduced fetal movements, or in the neonatal period with hypotonia, respiratory distress, facial muscle weakness and clubfoot. The estimated prevalence of CDM1 ranges from 1:10 000 to 1:100 000, depending on the geographic region [1]. CDM1 is caused by expansion of a CTG trinucleotide repeat in the non-coding region of the myotonic dystrophy protein kinase (DMPK) gene, located on chromosome 19q13.3 [2]. The normal CTG repeat size is 5–34, [1, 2] and most patients with CDM1 have more than 1000 CTG repeats [2]. There are no reported cases of CDM1 with PPHN, with a CTG repeats number <1000. We present a case of severe CDM1 complicated by PPHN, with only 800 CTG repeats.

CASE REPORT

The case concerns a male born by vaginal delivery with vacuum extraction at 38+3 weeks of gestation

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after a pregnancy complicated by polyhydramnios. His birth weight was 3292 g. His immediate Apgar score was 7, but after three minutes he became limp and cyanotic with feeble respiratory efforts. He was resuscitated by intubation and administration of 100% oxygen and surfactant in the delivery room. The initial examination showed profound hypotonia, facial diplegia and a triangular-shaped mouth. Laboratory evaluation revealed hydrogen ion (pH) 7.10, partial pressure of carbon dioxide ($p\text{CO}_2$) 11.7 kPa, hydrogen bicarbonate 19 mmol/l, base excess (BE) 0.6 mmol/l. Complete blood count, serum glucose and electrolyte, and infection parameters were normal. Chest radiography showed thin ribs and an elevated right hemidiaphragm, which are typical signs of CDM1 (Figure 1). Arterial mean blood pressure was 30 mmHg. Pre-ductal and post-ductal pulse oxygen saturation monitoring showed a difference of 10%. He developed PPHN, confirmed by echocardiographic examination. The PPHN was effectively treated by inotropic support and mechanical ventilation. He was extubated on day-four, and subsequently required intermittent administration of continuous positive airways pressure (CPAP) support during period of the infancy. Initial brain ultrasound showed mild bilateral ventricular dilation. The ventricular dilation gradually progressed to hydrocephalus (Figure 2), and he underwent ventriculoperitoneal shunt placement at age of four months. He had congenital bilateral clubfoot that was successfully treated by splinting. The ophthalmologic examination was normal. Muscle biopsy showed increased numbers of fibrous septa and ring fibers. The creatine kinase level was normal. A triplet repeat primed polymerase chain reaction (TP-PCR) analysis showed a CDM1 with 800 CTG repeats. Genetic testing of the parents showed that the mother had 125 CTG repeats.

Figure 2: Computed tomography scan of the head without contrast enhancement demonstrating hydrocephalus.

The mother had muscle weakness and fatigue, but was unaware of her disease. The parents had a healthy older daughter. Genetic counseling was recommended before family planning. The mother's older sister also had mild symptoms, and TP-PCR showed 64 CTG repeats. She has a 12-year-old son without any symptoms. No other family member were tested.

Our patient was discharged from hospital at fifth month after birth. Intermittent CPAP support by night at home was continued until the age of 14 months. Follow-up at age of 18 months showed neurodevelopmental delay. He started to crawl and was able to walk with support shortly. Physiotherapy and neurological follow-up have been proceeded.

DISCUSSION

CDM1 is associated with a poor prognosis, with an overall mortality rate of up to 50% in severely affected children [3]. The most commonly reported cause of death is respiratory failure, which occurs secondary to hypotonia and muscle weakness. Other factors associated with a lethal outcome are prematurity, low birth weight, prolonged mechanical ventilation and chylothorax [1, 4]. There is a well-established link between mechanical ventilation for more than four weeks and a lethal outcome [1, 4]. As with most severely affected neonates, our patient presented with generalized hypotonia and respiratory failure. He was resuscitated at birth and treated with mechanical ventilation for four days. This is significantly less than in previously reported cases [1, 4]. We have

Figure 1: Chest X-ray on day-1 showing thin ribs and a raised right hemidiaphragm.

speculated that the use of new techniques of mechanical ventilation resulted in fewer days on a ventilator and survival in our case.

PPHN has seldom been reported in neonates with CDM1, but contributes to the high mortality rate when present. Only three cases have been described, all with lethal outcomes during the neonatal period [5, 6]. Cantagrel et al. [6] reported a case of CDM1 with PPHN complicated by pneumothorax, pneumomediastinum and pneumopericardium, which resulted in death in the first day of life. In our case, there were no air trapping complications, which may explain respiratory stabilization and survival. Reis-Bahrami et al. [5] described two cases of CDM1 complicated by PPHN in premature neonates who were born at gestational ages of 35 and 36 weeks, respectively. They died at fourth day and ninth day, respectively, despite aggressive ventilator and pharmacological support. Neonatal death was probably determined by both CDM1 with PPHN and surfactant deficit due to prematurity. Neither of these two infants was treated by surfactant, in contrast to our case. To the best of our knowledge, this is the first reported non-fatal case of CDM1 complicated by PPHN.

Besides PPHN and respiratory compromise during infancy, our patient showed neurodevelopmental delay. He started to crawl at the age of 18 months. According to literature, surviving infants experience improvement in motor function and are usually able to walk [7]. However, affected children may develop weakness, myotonia, cardiac problems, impaired attention and autism spectrum disorder [7–9].

The diagnosis of CDM1 was confirmed by TP-PCR analysis. Molecular genetic testing of our patient showed 800 CTG repeats. On the other hand, his mother had 125 repeats and she presented with mild clinical signs. This case illustrates the well-reported phenomenon of anticipation by maternal transmission, in which the child has earlier onset of disease and more severe disease than the mother [2, 6].

All patients with CDM1 have an increased CTG repeat size in the DMPK gene. Most patients with CDM1 have > 1000 CTG repeats [2]. The severity of disease generally correlates well with the CTG repeat size and patients with a higher number of CTG repeats generally have more severe disease. Redman et al. [10] reported a few patients with CDM1 who had repeat sizes of between 730 and 1000. However, there is no data on severity of disease in these patients. Further investigation into the severity of CDM1 and CTG repeat sizes could be valuable for predicting outcomes. It is rare to find cases of CDM1 complicated by PPHN with only 800 CTG repeats in the DMPK gene.

CONCLUSION

We presented a case of congenital myotonic dystrophy type 1 (CDM1) complicated by PPHN that did not result

in death during the neonatal period. Further research is needed to elucidate the relationship between PPHN and the number of CTG repeats in patients with CDM1.

Author Contributions

Vladan Milovanov – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Yanko Petkov – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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