Case Report

Neonate with Congenital Myotonic Dystrophy Conceived via In Vitro Fertilisation by an Asymptomatic Mother

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Abstract

Congenital myotonic dystrophy 1 (CDM1) is characterised by severe hypotonia with difficulty in swallowing and respiration, facial diplegia, and increased risk of prematurity. We report a neonate with CDM1 born to an asymptomatic mother after in vitro fertilisation. Molecular analysis for the cytosine-thymine-guanine (CTG) triplet related DM1 was carried out and revealed over 1,000 CTG repeats, which was consistent with the clinical impression of CDM1. Gene analysis was carried out on the proband's family. In this family, the expanded CTG repeats were transmitted maternally, and earlier age of onset and increasing severity of the disease occurred in following generations.

Key words

Congenital myotonic dystrophy

Introduction

Myotonic dystrophy is an autosomal dominant, multisystemic disorder characterised by myotonia, progressive muscle weakness and atrophy, disturbances of heart rhythms, hypogonadism, frontal balding, and cataracts.1 Usually there is weakness of distal muscles, especially those of face, ankle, and feet. The two types of myotonic dystrophy (DM1 and DM2) are both caused by gene mutations. DM1 results from an expansion of a cytosine-thymine-guanine (CTG) trinucleotide repeat in the 3'-untranslated region of the dystrophia myotonica protein kinase gene (DMPK gene) on chromosome 19q13.3. DM2 is due to mutations in the cellular nucleic acid-binding protein gene (CNBP gene) on chromosome 3q21.3 and generally milder. Myotonic dystrophy has heterogeneous clinical phenotype, ranging from the congenital form to an asymptomatic form. We report a neonate with congenital myotonic dystrophy 1 (CDM1) born to an asymptomatic mother after in vitro fertilisation (IVF) for a history of infertility.

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The male proband was born via Caesarean section to non-consanguineous parents at 37+1 weeks of gestation and his birth weight was 2,960 g. He was admitted to the neonatal intensive care unit with mild respiratory distress, increased sleep duration, arthrogryposis, and decreased movements. Physical examination revealed bradycardia, respiratory problems, poor feeding, narrow palpebral fissure with antimongoloid slant. The patient had several episodes of bradycardia (70-90 beats per minute) most frequently in the first few days, but he was haemodynamically stable. He lay in a frog-like position and showed weak spontaneous movements and developmental reflexes such as Moro, grasp and sucking. He showed profound hypotonia (e.g., head lagging, inverted U posture in prone suspension). Deep tendon reflexes were normal and no fasciculation of the tongue was seen. Owing to transient tachypnoea with mild chest wall retraction, assisted oxygen via nasal prong was
Blood parameters including creatine kinase, lactate, ammonia, serum amino acids, urine organic acids, and thyroid function tests were all within normal range. Echocardiogram showed no abnormality. Holter monitoring revealed evidence of cataracts. Brain magnetic resonance imaging and electroencephalography were normal for the gestational age.

Electromyography and nerve conduction velocity done at 18 days of age showed no evidence of a myopathic process.

Main problems were global hypotonia, along with insufficient sucking and swallowing, which required gavage feeding in the first week. He was discharged after 23 days without gavage tube and with consistent weight gain. During early infancy, he showed gradual improvement of motor function and was able to sit without support at 12 months of age. Walking was accomplished at the age of 19 months and the proband's speech was limited to pronouncing just his parent's names at the age of 20 months.

Blood karyotype with G-banding and a genomic microarray showed no abnormalities. FMR1 mutations for the fragile X syndrome were not detected and the Prader-Willi methylation test was normal. Molecular analysis for the CTG triplet related DM1 was carried out and revealed over 1,000 CTG repeats, consistent with the clinical impression of CDM1.

There was no striking family history of any neuromuscular disease reported by his parents up to this point. They were both unaware of muscle weakness or myotonia. However, on examination, the mother had minimal evidence of muscle wasting in the face. Characteristically she had mild symptoms and was not diagnosed until after the birth of the affected baby. She menstruated irregularly once every 2-3 months. The pregnancy was achieved by IVF owing to fertility problems. Grip myotonia and percussion myotonia were not observed in the hands. She had no history of frontal balding, fatigue, or developmental delay. However, she revealed exercise intolerance. Photographs at age of 36 showed clear evidence of wasted facial and bitemporal muscles and ptosis (Figure 1). The electromyography demonstrated myotonia and myopathic changes and cataracts were not detected.

The grandmother (I-2) developed cataracts and mild weakness of hands later in life. Being diagnosed at age of 28, the 1st uncle (II-3) denied any symptoms of hand or wrist weakness or myotonia. Ophthalmological assessment and echocardiogram were normal. He was able to finish college as a normal person without any problems. His face showed some wasting facial muscles but no apparent signs of DM1. The detailed neurological test of the patient (II-3) was completely normal. At age of 25, he (2nd uncle, II-4) was unaware of muscle weakness or myotonia. Neither the patient's father nor grandfather exhibited any signs of DM1.

The family was referred for medical genetic consultation for screening and counselling. Several family members were identified as carriers of the mutation (Figure 2). The presence of a pathological expansion of CTG repeats was revealed in the proband, mother, grandmother, and the 1st uncle. The mother (II-2) had 400 repeats, grandmother (I-2) had 160 repeats, and 1st uncle (II-3) had 220 repeats. But the father (II-1) and 2nd uncle (II-4) were within the normal range at 20 to 25.
Discussion

CDM1 is characterised by severe hypotonia with difficulty in swallowing and respiration, facial diplegia, and prematurity after birth. Overall perinatal mortality is 11% and mortality is associated with cardiorespiratory complications. Children who survive the critical neonatal period later show improved motor functions, but typically still have global developmental delay compared to normal children. Clinical myotonia do not appear until late in childhood although electromyographic myotonia may develop after the first year. CDM1 is therefore a biphasic disease and should be considered as a possible diagnosis to neonates with hypotonia. Previous studies have documented a general tendency for the repeat number to increase with passage of generations because instability of the expanded CTG repeat during gametogenesis, which results in larger repeat size in the progeny. Moreover, there is a fairly strong correlation between earlier onset/greater severity and increasing repeat size. Normal populations have 5 to about 30 CTG repeats, whereas DM1 patients have 50-2,000 repeats. Patients with a CTG repeat size of 100 or less are likely to be either asymptomatic or only mild symptomatic. Neonatal form is associated with hypotonia, cardiorespiratory and feeding problems and may showed 1,000-2,500 CTG repeats. Although repeat size does seem to play a decisive role in the aetiology of the DM1 phenotype, it does not entirely explain it. The variability of the CTG repeat sizes among different tissues resulting from the somatic instability provides a basis for heterogenous expressivity of this pleiotropic disease. Inheritance of CDM1 is overwhelmingly maternal. This phenomenon emerges from the much greater likelihood for anticipation (e.g., expansion of CTG repeats) to occur in maternal compared with paternal transmission.

There is a 50% risk of the offspring being affected and 3-9% chance of having a severely affected child. The estimated incidence of CDM1 is very broad, ranging from 2.1 to 28.6 per 100,000 live births. In this family, the expanded CTG repeats were transmitted maternally, and earlier age of onset and increasing severity of the disease occurred in following generations. The proband’s echocardiography revealed intermittent bradycardia and PR interval prolongation. Conduction delays are seen from 5 to 25% in DM1 patients.

Because DM1 is a known aetiology of infertility and is one of the most frequent adult myopathies, our experience shows the need to consider DM1 in infertility clinic. DM1 patients of both sexes can suffer from problems of infertility due to different causes, which are at times concomitant (ovarian dysfunction, multiple miscarriages, or azoospermia). About 20% of affected females show menstrual irregularities, infertility, miscarriage or early menopause. The development and generalisation of reproductive techniques have opened the possibility that asymptomatic carriers of the disease can conceive fetuses affected by more serious clinical phenotypes. Therefore, infertility clinics should test for DM1 with detailed history and exact physical examination of the couples.

Declare of Interest

None to declare.

Declaration of Informed Consent

We obtained informed consent to include photographs in this case report.

References