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Case report

Diaphragmatic hernia in a term newborn with congenital myotonic dystrophy: case report

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Abstract. *Background and aim:* Myotonic dystrophy (DM) is a genetic disorder determined by an amplified trinucleotide CTG repeat in the untranslated region of the DMPK gene on chromosome 19q13.3. The incidence of the congenital form is 1 in 47619 live births and the mortality in the neonatal period is up to 40%. *Methods:* We report a case of congenital DM (CDM, also designated Myotonic Dystrophy Type 1), presented with congenital right diaphragmatic hernia and cerebral bilateral ventricular dilatation, genetically diagnosed. *Conclusions:* Since no case of congenital diaphragmatic hernia associated with CDM is reported, the present case report could be considered of particular interest. (www.actabiomedica.it)

Key words: Congenital myotonic dystrophy, diaphragmatic hernia, cerebral ventricular dilatation

Introduction

Myotonic dystrophy type 1 (DM1; OMIM # 160900) is an autosomal dominant neuromuscular disorder with variable penetrance. It is the most prevalent myopathy in adults, representing a multisystemic disorder with dysfunction of virtually all organs and tissues and a great phenotypical variability, which implies that it has to be addressed by different specialties with experience in the disease.

The congenital form, named Congenital Myotonic Dystrophy (CDM1), represents the most severe form of the disease with prenatal onset, symptoms distinct from adult onset DM1 and a high rate of perinatal mortality. The incidence of the congenital form is 1 in 47619 live births; mortality in the neonatal period is up to 40% (1).

The DM1 genetic abnormality is an amplified trinucleotide CTG repeat in the 3'-Untranslated region (3'-UTR) of the DMPK gene on chromosome 19q13.3 (1). Like frequently observed in trinucleotide repeat expansion diseases, the severity and age of onset is directly proportional to the triplet repeat number.

DM1-affected individuals frequently show the involvement of other organs aside from muscles; the most frequently reported in literature are cataracts (2), cardiac conduction anomalies (3,4), developmental disabilities (2) and endocrine dysfunctions (hypogonadism, diabetes and hyperparathyroidism) (5).

We report a case of CDM1, who presented with prenatal diagnosis of right congenital diaphragmatic hernia (CDH) and cerebral bilateral ventricular dilatation. Reviewing the literature regarding CDM1, we could find only one case report of disease presenting with both cerebral ventricular dilatation and diaphragmatic elevation (6) and one case of CDM associated with eventration of the diaphragm (7). Since no case

of CDH associated with CDM is reported, the present case report could be considered of particular interest.

Case report

A 37+2 week female baby, conceived through homologous in vitro fertilization, was born to a 39-year-old woman and a 45-year-old man of Italian origin, not consanguineous. No congenital diseases were reported in family history. Pregnancy was complicated by gestational diabetes and polyhydramnios (detected since 30 weeks of pregnancy); moreover, the baby was diagnosed with borderline ventriculomegaly at 32 weeks. Fetal magnetic resonance (MR) performed at 35 weeks showed bilateral club feet and raised the suspect of right CDH. Invasive antenatal genetic investigation was not performed.

The baby was born from an emergency cesarean section for non-reassuring cardiotocographic trace. She weighed 2374 grams at birth (13th percentile) and head circumference was 35 cm (100th percentile). On physical examination, she presented equine posture and plantar cavity of both feet, as well as flexion of elbow and wrist. Due to the prenatal diagnosis of right CDH, she was electively intubated and ventilated. Apgar scores were 4 and 7 at 1 and 5 min, respectively. She was transferred to the neonatal intensive care unit and remained hemodynamically stable: her heart rate was 120/min with normal sinus rhythm and blood pressure was 65/40 mmHg.

Cerebral ultrasound (US) confirmed the bilateral ventriculomegaly without any sign of hydrocephalus, and a thin corpus callosum was also documented; those findings were subsequently confirmed by a brain MR. Chest and abdomen X-rays were compatible with right CDH or right diaphragmatic relaxation (Figure 1).

Thoracoscopy, performed during the second day of life, confirmed the diagnosis of right CDH with hernia sac. The sac was resected and the diaphragm was repaired primarily. Histology did not show muscle component in the resected sac. After sedation interruption, mechanical ventilation weaning was attempted repeatedly, without success. The baby was hypotonic and poorly reactive, with paucity of facial and limb movements and an insufficient respiratory drive. After ten days of mechanical ventilation the patient was finally extubated but required 7 more days of non-invasive ventilation (NIV).

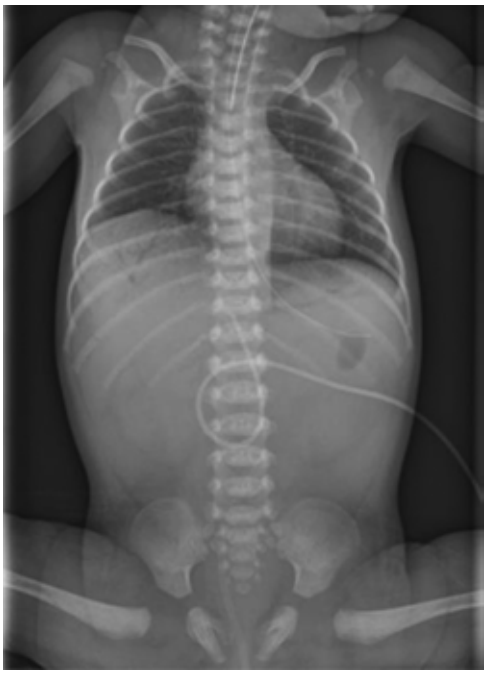

Figure 1. Chest and abdomen X-rays compatible with right congenital diaphragmatic hernia or right diaphragmatic relaxation.

Twelve days after surgery, given the persistent necessity of NIV, chest X-rays and chest US were performed, showing right pleural effusion. Subsequent drainage revealed a chylothorax. No further drainage was required.

Given the persistent hypotonus and feeding difficulties, together with the neuromuscular disorders features, diagnostic genetic exams were undertaken; testing of the myotonic dystrophy protein kinase (DMPK) gene demonstrated >50 CTG repeats. Diagnosis of CMD1 was therefore confirmed. Segregation analysis documented a number of CTG repeats >50 also in patient's mother. Clinical examination of the mother by a clinical geneticist highlighted mild ptosis and upper limbs myotonias; at the moment, she has no further symptoms and has been referred to neurology.

The patient was discharged at home at 65 days of life; she was hemodynamically stable in spontaneous breathing and able to oral feeding.

Neurodevelopmental and physiatric follow-up is currently ongoing; at 10 months of age the patient showed social smile and vocalization. Motor initiative for manipulating objects with both upper limbs was found; lower limbs were kept adducted and flexed. Uncertainty in holding the head and brachycephaly persisted.

Discussion

CDM1 is a hereditary muscle dystrophy, accompanied by muscle atrophy and characteristic myotonia. It is caused by the expansion, typically over 1000 repeats, of the CTG trinucleotide located in the 3'UTR of *DMPK* gene, which encodes for the DMPK protein (1), and the severity of the disease correlates with the number of repeats. Fully penetrant alleles (more than 50 CTG) are associated with disease manifestations. In CMD1, CTG repeats are usually more than 1000, compared to less than 37 in normal individuals, and 38-49 in premutation allele patients (asymptomatic) (1). As DMPK alleles of CTG length greater than 34 repeats are unstable, they may expand in length during meiosis; as a consequence, at-risk offspring may inherit repeat lengths considerably longer than those present in the transmitting parent. This phenomenon results in anticipation, which is the occurrence of increasing disease severity and decreasing age of onset in successive generations. As for CMD1, the condition is most often transmitted from the mother (8), who may present with very subtle manifestations, or even any at all, of the condition; however, anticipation with paternal transmission is possible (9). In our case, clinical examination of the mother brought on typical signs of myotonic dystrophy.

Many features are associated with CDM1: in the prenatal period, polyhydramnios and reduced fetal movements can be found; preterm delivery is also common (1). The newborn often presents with hypotonia, hyporeflexia, muscle weakness (proximal muscle weakness indicates a poor prognosis), myopathic facies (ptosis, facial diplegia), cataract, feeding difficulties and early death; during childhood the patient is usually able to walk with improvement in motor function, however progressive weakness restarts in the 2nd decade; myotonia (by 10 years of age), intellectual disability (mean IQ 70), excessive daytime sleepiness, cardiac and endocrine complications are also common (1). Gastrointestinal manifestation can vary from constipation (the most common and less severe) to feeding difficulties, gastroesophageal reflux and dysphagia (2).

In literature, diaphragm alterations presenting during the neonatal period described in CDM are mainly two: diaphragmatic elevation, possibly consequent to paresis and/or hypoplasia, was found on chest X-rays in 42% of 14 CMD patients in one study (10); diaphragmatic eventration was described in one CDM case report associated with cardiac conduction defects (7). Only recently chylothorax was included as a possible complication of CDM (11). To our knowledge, CDH has never been reported as part of the CDM clinical picture, although we cannot exclude that in our patient the right CDH with the hernia sac was actually an extreme form of diaphragmatic eventration due to a lack of right diaphragmatic muscle function related with the primary disease. The progressive increase of right diaphragm elevation during pregnancy may support this view. On the other hand, the lack of muscle components in the resected sac supports the diagnosis of right CDH. In our patient, right CDH contributed to pulmonary hypoplasia; the non-persistent chylothorax might have been secondary to surgery and recovered after single pleural drainage, or be a complication of CDM (11).

In the literature, respiratory difficulties are found in 50% of neonates with CDM and represent the main cause of neonatal mortality; for this reason, they are used to distinguish between mild and severe CDM (1). Our patient required mechanical ventilation for 10 days and non-invasive respiratory support for 7 more days; at discharge, she was hemodynamically stable in spontaneous breathing. Respiratory distress, weak cough, sleep apnea, pulmonary hypoplasia, bronchopulmonary dysplasia, raised right hemidiaphragm and pneumothorax are also reported as clinical features or complications associated with CDM. In our patient, pulmonary hypoplasia was probably due to diaphragmatic hernia, as already mentioned above; none of the other reported features was found in our case.

Moreover, our patient presented bilateral brain ventricular dilatation, detected in the prenatal period by fetal US and MR. Ventricular enlargement is the most common neuropathological finding in CDM. Ventricular dilatation, without any clinical sign of increased intracranial pressure, was found frequently: Garcia-Alix et al report brain ventricular dilatation in 11/14 affected infants (12), Tanabe and coworkers in 3/7 patients (13), Hageman et al. in 9/13 patients (14) and Hashimoto and coworkers in all their 13 patients (15). The reason underlying this condition is not quite clear. In some cases, an intraventricular haemorrhage preceded the hydrocephalus, while in others, a cerebral dysgenesis with neuronal migrational disturbance was suspected (16). Our patient performed a brain MR, which showed ventricular enlargement and thin corpus callosum, without further pathological findings.

In summary, CDM can severely affect infants born to mothers presenting little to no symptoms. This can cause a delay in the diagnosis, also given the numerous clinical features possibly found in CDM. Based on this experience, CDH and cerebral ventricular dilatation can represent the initial clinical presentation of a DM case. We cannot yet provide a long term follow-up of the patients, since she is actually 11 months-old, and this is a limitation of the present paper.

Ethics and Informed Consent: The study was conducted in accordance with the Declaration of Helsinki. Written informed consent for scientific use of data and images of the patient was given by the parents.

Conflict of Interest: No author declares any commercial associations that might pose a conflict of interest in connection with this article.

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