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Case study

Apneic crises: A clue for MECP2 testing in severe neonatal hypotonia-respiratory failure

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ABSTRACT

Males with methyl-CpG-binding protein 2 (*MECP2*) mutations may present with neonatal encephalopathy. We report on an infant with a *MECP2* mutation who exhibited complex constellation of symptoms, including severe hypotonia, respiratory failure, and apneic episodes. In the neonatal period these symptoms are common to other disorders, including Ondine syndrome. Our observation confirms that the triad of severe hypotonia, apneic episodes, and respiratory failure may be caused by *MECP2* mutations. Neonatologist and neuropediatricians must be alert to the presence of these symptoms to exclude this rare but severe disorder. Clinical suspicion and molecular confirmation of MECP2 mutation is of great importance for defining the diagnosis of this rare affection.

1. Introduction

Mutations in methyl-CpG-binding protein 2 (*MECP2*) have been reported in males with a phenotype that overlaps clinically with affected females that have classical or atypical forms. One of the last manifestations of *MECP2* mutations is severe encephalopathy and exitus, which most often occur before 2 years of age. *MECP2* mutations also occur in males with mild or severe mental retardation, and recently, males with autistic spectrum disorders.[1]

We report an infant with a *MECP2* mutation who presented with respiratory failure, severe hypotonia, and apneic crises that were consistent with Ondine syndrome and other similar neurologic disorders.

2. Case report

This 18-month-old boy was born at term after an uneventful pregnancy. Family history was unremarkable. His mother denied any infectious diseases during pregnancy or having used drugs or alcohol. The mother felt regular fetal movements. The baby was delivered vaginally with a birth weight of 2900 g, a height of 50 cm, and a head circumference of 34 cm. Apgar scores were 8 and 9 at 1 and 5 min, respectively. A few hours after birth, he experienced feeding difficulties and respiratory failure. Blood gas analysis showed a high CO_2 level (54 mm/Hg) with a normal pH. The neonatal period was characterized by apneic crises, respiratory failure, and severe hypotonia with episodes of arching and stiffness. During

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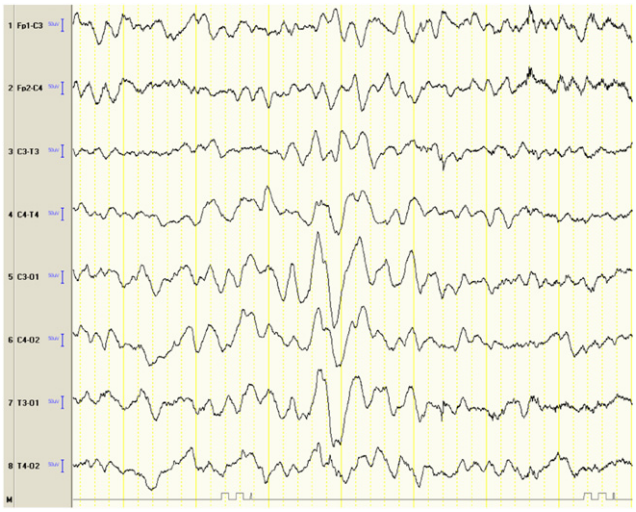

Fig. 1 – EEG performed at the age of 3 months: high-voltage theta activity predominant over the central-occipital areas of left hemisphere, but no paroxysmal activity.

these episodes the baby was treated with non-invasive positive pressure ventilation in bilevel mode. Routine laboratory investigations, including a hemogram, and blood glucose, NO_2, blood amino acids, urine organic acids, and blood ammonia levels, were normal. An abdominal ultrasonogram, electrocardiogram, and echo and cranial ultrasonography were also normal. At 1 month of age, there was persistent severe hypotonia, patellar tendon hyperreflexia, lethargy, and weak sucking. Milk was administered by nasogastric feeding and episodes of apnea were monitored.

At 3 months of age the boy had the first episode of pneumonia, which was treated with hydration, antibiotics, and cortisone. At this time gastroesophageal reflux was diagnosed and appropriately treated.

At 6 months of age, after a severe episode of hypercapnic respiratory failure during the feeding, failure to thrive, and inability to suck, a gastrostomic tube was placed. Two months later, the infant had an episode of mixed respiratory insufficiency, which was treated similar to the previous episodes, with an improvement in lung function (SaO_2, 97%). The patient weighed 6.4 kg. Head circumference was 42 cm (<3rd percentile). Neurologic examination revealed intermittent episodes of arching and stiffness, severe hypotonia, inability to hold the head, poor general movements, patellar hyperreflexia, lethargy, and intermittent crises of apnea/hypopnea.

Neurological examination has been slightly but, progressively worsened. At the age of 19-months, the boy displayed generalized hypotonia and weakness, with marked muscles wasting. He was unable to hold his head, and to sitting up. The cry was weak and respiration shallow. He was able to follow the objects, but not to grasp them. He suffered from frequent respiratory infections, and apneic crises which required 3 admissions in the intensive care unit. Feeding was parenteral. Recently he has been tracheotomized and submitted to mechanical pulmonary ventilation. Routine laboratory investigations, including hemogram, blood glucose, NO_2, CK, thyroid function, lactate, blood ammonia levels, were normal. Brain MRI, and an abdominal ultrasonography, electrocardiogram were also normal. EEG performed at the age of 3and 8 months showed a pattern of rhythmic, high-voltage theta activity predominant over the central-occipital areas of left hemisphere but no paroxysmal activity (Fig. 1). Polysomnography at the age of 3 months and again at 8 months, showed periodic cerebral irregulation breathing apnea–hypopnea (Fig. 2).

Initially the frequent apneic episodes raised suspicion of Ondine syndrome but molecular testing for the PHOX2B gene was negative. Therefore, due to the association of severe hypotonia, apneic crises with respiratory failures MECP2 gene sequencing was performed revealing a *de novo* deletion in exon 4 (c.803del G or G269fs). Analysis of

Fig. 2 – Polysomnography at the age of 3 months revealed periodic central irregular breathing with apnea–hypopnea.