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Ondine's syndrome: Central hypoventilation syndrome. A case

Síndrome de ondine. A propósito de un caso

Dear Editor:

We present the case of a female term newborn with an unremarkable prenatal history and no risk factors for infection. Labour was induced due to maternal disease and premature rupture of membranes of 8 h' duration with leakage of thick meconium-stained fluid, and the patient was delivered by vacuum extraction to shorten the expulsion stage. At birth, the Apgar score was 8/9/9 and the cord blood pH 7.34, and the patient required suctioning and intermittent positive pressure ventilation at 1 min post birth, with a favourable response, but she was admitted to the neonatal unit because she still needed supplemental oxygen to maintain an adequate oxygen saturation.

In the first hours of life, the patient exhibited hypotonia, a fluctuating level of consciousness and a tendency to oversleep and bradypnoea. She had no dysmorphic features. She required respiratory support with bilevel positive airway pressure (BiPAP). Attempts to discontinue BiPAP or switch to continuous positive airway pressure (CPAP) triggered desaturation episodes. Her blood gas values fluctuated, with the partial pressure of carbon dioxide (pCO_2) at times in the normal range and at other times abnormal, to the point that the patient required intubation in the first 48 h post birth due to severe respiratory acidosis (pCO_2 of 80 mmHg).

This presentation prompted screening for metabolic diseases, starting with hyperammonaemia, and subsequently testing for inborn errors of amino acid metabolism (urea cycle disorders), fatty acid oxidation disorders and inborn errors of carbohydrate metabolism, including testing for Pompe disease, none of which identified any abnormalities. The evaluation was completed with brain imaging studies: an ultrasound examination, computed tomography (CT) angiography to rule out potential acute changes, such as haemorrhage, as the cause of the symptoms, and magnetic resonance imaging, which ruled out the presence of malformations and ischaemic lesions in the brain. Electroencephalographic monitoring evinced a normal pattern, with no electrographic or clinical seizures.

After being extubated at 4 days post birth, the patient required ongoing respiratory support with BIPAP, especially in periods of deep sleep, when she exhibited bradypnoea and, in the absence of respiratory support, marked desaturation, a clinical presentation compatible with central sleep apnoea. Her hypotonia persisted and she was fed through a nasogastric tube. The evaluation was expanded with karyotyping, array-based comparative genomic hybridization and genetic testing for Prader-Willi syndrome, spinal muscular atrophy and Steinert myotropic dystrophy, the results of which were negative. In light of these findings, a genetic study of diseases that manifest with central hypoventilation was conducted, which resulted in diagnosis of Ondine's curse due to the detection of a heterozygous variant of

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the *PHOX2B* gene, a polyalanine repeat expansion with 25 repeats. Segregation analysis in the parents demonstrated that this was a de novo mutation. However, the risk of recurrence for this disease has been found to be greater than the usual 1% for de novo mutations, due to the high prevalence of germline or somatic mosaicism (5%–25%), so the family was advised to seek prenatal genetic screening in future pregnancies.

The patient was discharged home at age 1.5 months with prescription of BiPAP non-invasive ventilation for sleep of any duration, and is currently in follow-up in the departments of pulmonology, paediatric gastroenterology, paediatric physical therapy and rehabilitation. Adequate nutrition has been achieved, with consumption of maternal milk with a bottle and at the breast and fair tolerance of introduced complementary foods, accompanied by adequate weight gain and linear growth. Her psychomotor development is adequate. In the first year of life, she has continued to receive non-invasive ventilation during sleep and has only required hospital admission once at 10 months of age due to a cold whose management required supplemental oxygen and that resolved well.

Our patient has exhibited a more favourable course of disease compared to the classical description of the syndrome in the literature,[1] probably because she had a more benign genetic variant, with only 25 triplets in the *PHOX-2B* gene, an early diagnosis and optimised respiratory therapy that prevented episodes of clinically significant hypoxia and hypercapnia, which are usually the events that determine the course of the disease.[2–4]

Ondine's curse, also known as congenital central hypoventilation syndrome (CCHS), is a rare genetic disorder (incidence of 1 case in 200 000 births)[5] in which the central ventilatory controller is damaged or impaired, which results in alveolar hypoventilation, mainly during slow-wave non-rapid eye movement (NREM) sleep, due impaired autonomic control of ventilation. A heterozygous change in the *PHOX-2B* gene is identified in 90% of cases, usually de novo and less frequently with dominant autosomal inheritance. It may be associated with other manifestations of autonomic dysfunction, Hirschsprung disease or neural crest tumours. Its prognosis varies, although it is generally poor, with a high mortality and lifelong dependence on mechanical ventilation, especially during sleep.[6,7]

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