RELATO DE CASO

SÍNDROME DE HIPOVENTILAÇÃO CENTRAL CONGÊNITA ASSOCIADO A DOENÇA DE HIRSCHSPRUNG: UM RELATO DE CASO NO TOCANTINS

CONGENITAL CENTRAL HYPOVENTILATION SYNDROME ASSOCIATED WITH HIRSCHSPRUNG'S DISEASE: A CASE REPORT IN TOCANTINS

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RESUMO

A síndrome de hipoventilação central congênita (SHCC) é uma desordem genética rara, associada a mutações no gene paired-like homeobox 2B (PHOX2B), caracterizada por disautonomia e apneia central. A doença de Hirschsprung (DH) está presente em cerca de 20% dos casos de SHCC. Este estudo objetiva relatar o caso de um neonato que apresentou apneia central recorrente, eliminação tardia de mecônio e distensão abdominal diagnosticado com DH associada a SHCC, comparando-se os aspectos clínicos esperados e os encontrados pela equipe que assistiu a criança. Nota-se um retardo no diagnóstico principalmente pela raridade da síndrome e ao seu desconhecimento por parte dos profissionais da saúde. Sendo assim, conclui-se ser imprescindível medidas de suporte, diagnóstico e tratamento precoces pelo risco de complicações graves que ambas as doenças podem acarretar ao recém nascido.

Palavras-chave: Síndrome de hipoventilação central congênita, síndrome de Ondine, gene PHOX2B, doença de Hirschsprung, síndrome de Haddad.

ABSTRACT

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder associated with mutations in paired-like homeobox 2B gene (PHOX2B), characterized by dysautonomia and central sleep apnea. Hirschsprung's disease (HD) is present in about 20% of CCHS cases. This study aims to report the case of a neonate who presented with sleep apnea, late elimination of meconium and abdominal distension diagnosed with CCHS associated with HD, comparing the clinical aspects expected and those found by the medical team that attended the child. There was a delay in the diagnosis, mainly due to the rarity of the syndrome and the lack of knowledge about the disease by health professionals. Therefore, it is concluded that life support, early diagnosis, and treatment are essential due to the risk of serious complications that both diseases can cause to the newborn.

Keywords: Congenital central hypoventilation syndrome, Ondine's curse, PHOX2B gene, Hirschsprung's disease, Haddad syndrome.

Citação: Tavares NNP, Lima DJS, Alcantara LS, Pereira LC, Amaral AS (2018) Síndrome de Hipoventilação Central Congênita associado a doença de Hirschsprung: um relato de caso no Tocantins. Revista de Patologia do Tocantins, 5(3): 32-36.

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Editor: Guedes V. R. Medicina, Universidade Federal do Tocantins, Brasil.

Publicado: 09 de setembro de 2018.

Conflito de interesses: os autores declararam que não existem conflitos de interesses.

INTRODUCTION

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder associated with mutations in paired-like homeobox 2B gene (PHOX2B), characterized by autonomic nervous system (ANS) dysfunction. It causes central sleep apnea mainly during non-rapid eye movement sleep, in which breath autonomic control predominates.[1-4] Patients do not show normal physiological responses to hypoxia or hypercapnia, leading to alveolar hypoventilation. The voluntary breathing control remains intact.[2,5,6] The diagnosis is made by discarding other pathologies such as central neurological lesions or neuromuscular injuries, neurological malformations, cardiopathies and pneumopathies.[7]

Robert Mellins et al. published the first description of CCHS in 1970.[8] It was named after "Ondine", a theatrical play Jean Giraudoux wrote in 1938. The plot says Ondine was a water nymph from Norse mythology who married Hans. After he betrayed her, he is condemned to live awake so that he could breathe.[1,5]

Until 2009, more than 1,000 cases of the disease with the PHOX2B mutation were diagnosed and documented. In Japan, the estimated incidence is 1 per 148,000 live births and 1 per 200,000 live births in France.[2,6,8,9] In Brazil, there are publications reporting isolated cases, but there is no defined epidemiology.[1]

In 2003, mutations in PHOX2B were identified as responsible for the syndrome.[10] This gene is located on chromosome 4p13 and its expression pattern involves the development of central autonomic circuits as well as of peripheral neural crest derivatives.[1,2,10-14] Heterozygous mutations are known to occur in more than 90% of CCHS cases.[15] The normal genotype shows a sequence of 20 polyalanines, designated as "20/20 genotype", there being an equivalence relation between the number of alanines added through the mutation and the severity of the syndrome phenotype.[1,8] In patients with CCHS, polyalanine repeat expansion mutations (PARM) may manifest genotypes 20/24 to 20/33 (with 24 to 33 alanines).[2,16] The presence of these mutations is evidenced by using genetic tests with polymerase chain reaction (PCR).[1,17] Other types of mutations may occur; they are known as non-polyalanine repeat expansion mutations (NPARM) of missense, frameshift or nonsense types.[2,10] They are diagnosed through genetic sequencing.[1]

Apnea, cyanosis, and hypercapnia are some of the manifestations of CCHS shown in the immediate postpartum.[2] In newborns with CCHS, hypoventilation can be imperceptible until they present with recurrent apnea episodes because they fail the normal physiological reaction to hypoxia or hypercapnia. Hypoglycemia and hyperinsulinemia are also reported frequently.[1,2,12,13]

Since 1992, studies have shown there is a late onset of the syndrome and diffuse impairment of ANS, which increases the range of clinical manifestations, such as arrhythmias, changes in heart rate, gastroesophageal reflux, baroreflex dysfunction, decreased intestinal motility and chronic constipation, diaphoresis, orthostatic hypotension, pupillary reflex abnormalities and excessive drowsiness.[1,5] Some patients with late onset of the disease may manifest symptoms only when submitted to anesthetics or other drugs that depress the central nervous system, or after respiratory tract infections.[2,6,16]

Shorter PARMs (20/24 or 20/25) may present late-onset CCHS and rarely rely on continuous ventilatory support, unlike patients with longer repetitions (20/27 to 20/33) or NPARM.[2]

Genetic studies found out mutations in PHOX2B gene also occur in individuals with complex neural-crest involvement including CCHS and Hirschsprung disease (HD) as well as early-onset neuroblastoma and other neural crest tumors.[10] It is known that approximately 15-20% of CCHS cases are associated with HD; this association configures the Haddad syndrome.[1]

HD or congenital megacolon incidence estimate is 1 per 5,000 live births. It is usually diagnosed during the neonatal period after delayed elimination of meconium (> 48 hours), abdominal distension, and food intolerance. It is characterized by aganglionosis in a variable long or short segment of the large intestine. Short segment aganglionosis happens more frequently, especially in the rectum and sigmoid. Due to the involvement of the enteric nervous system, symptoms such as intestinal obstruction arise with a variation on the degree of constipation. The barium enema is the most commonly noninvasive method used to exclude other causes of bowel obstruction in neonates prior to rectal biopsy.[2,18,19]

Tumors derived from neural crest typically manifest in the second year of life. Among all CCHS patients, 5-6% have these tumors, but the incidence may reach 50% in NPARM patients. They are tumors composed of immature neural cells, such as the neuroblastoma, ganglioneuroma, and ganglioneuroblastoma.[1,15]

This study aims to report the case of a newborn diagnosed with HD associated with CCHS in Tocantins, comparing the clinical aspects expected and those found by the medical team that attended the child.

CASE REPORT

Male neonate born by cesarean section without complications. Full-term pregnancy (gestational age 38 weeks and 5 days), weighing 2,765 g, a stature of 48 cm, a cephalic perimeter of 34.5 cm, a thoracic perimeter of 33 cm, Apgar score in the first minute of 4 and in the fifth minute of 8. Son of non-consanguineous couple . The mother was 26 years old, second gestation, a prior cesarean section, no abortion. She attended to a full prenatal care, had normal serologies, and "O positive" blood type. The membranes were ruptured during the c-section with clear oligohydramnios. The investigation of infectious foci in the mother was negative. She was hydrated and denied vaginal losses.

The newborn wept after birth but within the first hour presented irregular breathing and bradycardia, requiring supplemental oxygen and positive pressure ventilation (PPV) with a mask. The patient evolved with a saturation drop, was submitted to orotracheal intubation and referred to the neonatal intensive care unit (ICU) with a suspected cardiopathy. He was admitted to the ICU with PPV, a heart

rate of 120 bpm, a temperature of 36.4ºC, an oxygen saturation of 92% and glycemia of 54 mg/dl. In the ICU, antibiotic therapy was started due to presumptive early neonatal sepsis and the newborn was maintained in invasive mechanical ventilation (IMV) with low parameters.

At the neonatal ICU, extubation was attempted numerous times, but it was unsuccessful due to recurrent episodes of apnea without a definite cause.

Within 48 hours a transthoracic Doppler echocardiogram revealed a patent foramen ovale of 1.6 mm with no hemodynamic repercussions. A transfontanelle ultrasonography showed hyperechogenicity in the left periventricular white matter with normal Doppler.

The patient eliminated meconium only on his third day of life after rectal stimulation. He evolved with progressive abdominal distension; parenteral nutrition was initiated and maintained for 5 days. Other causes of intestinal obstruction were excluded through imaging and rectal examination; then, HD was suggested as a hypothesis by the pediatric surgery team, who requested an barium enema performed on his 20th day of life. It revealed normal colon size with small retention of contrast. Then it was performed a rectal biopsy through sphincterotomy, on the 28th day. No ganglion cells were observed in the submucosal and myenteric plexuses of the biopsied segment, confirming the diagnosis of congenital megacolon. Once HD was diagnosed, a loop colostomy was scheduled after resolution of the infectious condition.

Antibiotic therapy was maintained due to the presence of *Staphylococcus haemolyticus* in blood culture. Clinical improvement was shown; however, five days after the end of the antimicrobial regimen, the patient presented clinical worsening. In a new blood culture, the growth of *Klebsiella pneumoniae* was evidenced and an uroculture had the presence of fungi; thus, amphotericin B and ampicillin with sulbactam were started. After the antibiogram detected sensitivity to meropenem, it was initiated. Later ultrasonography of the urinary tract presented bilateral small renal hydronephrosis; there was no microbial growth in a new uroculture.

Suspicion was raised for CCHS and innate metabolism error. An expanded neonatal screening test was performed, which did not prove any alterations, neither did the study of organic acids in the urine show any abnormalities, discarding the last hypothesis. The karyotype of peripheral blood did not reveal abnormalities. Subsequently, a molecular biology test was performed with PCR followed by fragments analysis. It showed the presence of polyalanine allele expansion in the PHOX2B gene with 26 repetitions at the 4p13 locus, confirming the diagnosis of CCHS.

On day 46, the patient was transferred to the pediatric ICU where tracheostomy and colostomy were performed. The sigmoid colon biopsy revealed dilation of the intestinal lumen with narrowing in the adjacent segment, thinning of the wall and reactive epithelial changes in addition to an apparent reduction in the number of ganglion cells in the myenteric plexus.

The patient presented convulsive tonic-clonic seizures throughout hospitalization. A electroencephalogram showed epileptogenic activity in the right frontocentral region. Phenytoin was indicated for seizures prophylaxis.

Since then, the child has been maintained in VMI during sleep and using oxygen mask during the waking period, feeding on breast milk and milk formula by gavage, using domperidone and omeprazole for gastroesophageal reflux.

DISCUSSION

The Brazilian Ministry of Health (MH) never registered the number of CCHS cases in Brazil. Based on the estimated incidence of CCHS on newborns in France[2] and the number of live births MH reported through the Live Birth Information System (in Portuguese: *Sistema de Informações sobre Nascidos Vivos*), about 14 Brazilians with the disease were born in 2016.

CCHS is a rare entity, however it is notably underdiagnosed. To justify this fact, two aspects call attention: the variety of phenotypes already described in the literature[14] and the lack of knowledge about the pathology by health professionals. Phenotypes vary according to mutations, and range from newborns requiring continuous assisted ventilation to elderly patients with mild sleep apnea.[1] Its rarity and relatively recent discovery, the numerous differential diagnoses, the difficulty of access to the necessary tests, and many other factors, hamper the dissemination of acknowledgement about Ondine's curse among health professionals.

The patient's diagnosis was delayed due to these difficulties. Initially, early neonatal sepsis and cardiopathy were assumed, two important differential diagnoses that should be considered in this case.[1] Although, even before the diagnosis of CCHS, therapeutic management was started to guarantee adequate ventilation and oxygenation to the patient.

These patients require full-time care with oxygen saturation monitoring and ventilation, mainly during sleep. A multi-professional team trained and experienced in the management of the disease and its complications must assist them (pediatricians, pediatric surgeons, nurses, physiotherapists, nutritionists, speech therapists).[1,2,8,9,14]

Some pediatric patients will depend on continuous ventilatory support, while others will need support only during sleep.[8,14] The detailed patient previously, needed ventilatory support during sleep and in some instances during the waking period, such as after physical exertion, probably because of the shorter PARM (genotype 20/26).

It was decided to perform PPV by tracheostomy because it ensures better oxygenation and ventilation efficiency in the sleep-wake cycle in neonates and infants. Other ventilation options include noninvasive positive pressure ventilation (NIPPV) or diaphragm stimulation. NIPPV is recommended for older children with less severe phenotypes, as it is performed via a nasal catheter, nasal mask or face mask. The stimulation of the diaphragm is mainly performed in patients who require continuous ventilatory support, allowing greater mobility and better life quality.[2,14]

As the symptoms of HD emerged, obstructive causes were excluded through imaging and rectal examination. The

rectal biopsy through sphincterotomy identified aganglionosis of parasympathetic plexuses of the rectal segment. Subsequent sigmoid colon biopsy identified only hypoganglionosis, confirming the extension as a short segment disease.[20]

It is known that the absence of cells in the parasympathetic submucous and myenteric plexus causes the HD clinical features, such as the lack of motility in the intestinal tract it affects. This shortage of plexuses can lead to important complications like functional obstruction, enterocolitis or even intestinal perforation. To avoid the mentioned complications, it should be diagnosed and treated as early as possible. The cure for HD is the excision of the aganglionic intestinal segments with reconstruction of the intestinal transit.[20] The surgeons who attended the detailed patient, opted to perform the surgery in two times: firstly a loop colostomy, and secondly the reconstruction of the intestinal traffic.

The rectal biopsy is the gold standard for HD confirmation or exclusion. One of the tests that may be done is the barium enema, despite its sensitivity being low, due to recurrent failure to identify transition zone in newborns. Our patient had an inconclusive test as the transition zone was not visualized, although small retention of intestinal contents was identified. Children who have a very short aganglionic segment sometimes do not show an obvious transitional zone on radiography.[20]

In the literature, some isolated cases are described in which the patient presented at least one convulsive crisis due to acute episodes of hypoxia. Marcus et al. reported children who had persistent seizures and required prophylactic treatment; they had severe CCHS and received ventilatory support in wakefulness. Hopkins et al. addresses seizures in CCHS patients to episodes of sustained hypoglycemia and hyperinsulinemia.[17,12,21]

After positive uroculture for fungi, it was necessary to investigate malformations of the genitourinary tract. The ultrasonography showed only mild bilateral hydronephrosis was identified; no malformations were seen. The patient evolved with good diuresis, without related signs or symptoms, nor renal scales after the third day of life that justified the need for further investigation.[22]

CONCLUSION

CCHS should be suspected when a newborn presents with sleep apnea with no apparent cause. HD should be considered as a diagnosis in pediatric patients with abdominal distension associated with the late elimination of meconium during the neonatal period, and after exclusion of other causes of bowel obstruction. As soon as differential diagnoses have been suspected and discarded, confirmatory tests should be requested to conclude the diagnosis and initiate early management.

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