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CASE REPORT

Congenital central hypoventilation syndrome associated with Hirschsprung's Disease: case report and literature review

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KEYWORDS
Congenital central hypoventilation syndrome;
Ondine syndrome;
Hirschsprung's disease;
Haddad syndrome;
PHOX2B gene

Abstract
Objective: To report the case of a newborn with recurrent episodes of apnea, diagnosed with Congenital Central hypoventilation syndrome (CCHS) associated with Hirschsprung's disease (HD), configuring Haddad syndrome.
Case description: Third child born at full-term to a non-consanguineous couple through normal delivery without complications, with appropriate weight and length for gestational age. Soon after birth he started to show bradypnea, bradycardia and cyanosis, being submitted to tracheal intubation and started empiric antibiotic therapy for suspected early neonatal sepsis. During hospitalization in the NICU, he showed difficulty to undergo extubation due to episodes of desaturation during sleep and wakefulness. He had recurrent episodes of hypoglycemia, hyperglycemia, metabolic acidosis, abdominal distension, leukocytosis, increase in C-reactive protein levels, with negative blood cultures and suspected inborn error of metabolism. At 2 months of age he was diagnosed with long-segment Hirschsprung's disease and was submitted to segment resection and colostomy through Hartmann's procedure. A genetic research was performed by polymerase chain reaction for CCHS screening, which showed the mutated allele of PHOX2B gene, confirming the diagnosis.
Comments: This is a rare genetic, autosomal dominant disease, caused by mutation in PHOX2B gene, located in chromosome band 4p12, which results in autonomic nervous system dysfunction. CCHS can also occur with Hirschsprung's disease and tumors derived from the neural crest.

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There is a correlation between phenotype and genotype, as well as high intrafamilial phenotypic variability. In the neonatal period it can simulate cases of sepsis and inborn errors of metabolism.
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PALAVRAS-CHAVE
Síndrome de hipoventilação central congênita;
Síndrome de Ondine;
Doença de Hirschsprung;
Síndrome de Haddad;
Gene *PHOX2B*

Síndrome de hipoventilação central congênita associada à doença de Hirschsprung: relato de caso e revisão de literatura

Resumo

Objetivo: Relatar caso de neonato com episódios de apneias recorrentes, diagnosticado com síndrome de hipoventilação central congênita (SHCC) associada à doença de Hirschsprung (DH), o que configurou síndrome de Haddad.

Descrição do caso: Terceiro filho de casal não consanguíneo, nascido a termo, parto normal sem intercorrências, peso e comprimento adequados para idade gestacional. Logo após o nascimento apresentou bradipneia, bradicardia e cianose, foi submetido à intubação orotraqueal e iniciada antibioticoterapia empírica devido à suspeita de sepse neonatal precoce. Durante internação em UTI neonatal evoluiu com dificuldade de extubação devido a episódios de dessaturação durante sono e vigília. Apresentou quadros recorrentes de hipoglicemia, hiperglicemia, acidose metabólica, distensão abdominal, leucocitose, aumento de proteína C reativa, com hemoculturas negativas e suspeita de erro inato do metabolismo. Aos dois meses foi diagnosticada doença de Hirschsprung de segmento longo, foi submetido à ressecção do segmento e colostomia à Hartmann. Feita pesquisa genética por reação em cadeia da polimerase para pesquisa de SHCC, que evidenciou alelo mutado do gene *PHOX2B* e confirmou o diagnóstico.

Comentários: Trata-se de doença genética rara, de herança autossômica dominante, causada por mutação no gene *PHOX2B*, localizado na banda cromossômica 4p12, que resulta em disfunção do sistema nervoso autônomo. A SHCC também pode cursar com doença de Hirschsprung e tumores derivados da crista neural. Há correlação entre fenótipo e genótipo, além de grande variabilidade fenotípica intrafamiliar. No período neonatal pode simular quadros de sepse e erros inatos do metabolismo.

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Introduction

Congenital central hypoventilation syndrome (CCHS) was first described by Robert Mellins et al. in 1970.[1] It is characterized by central apnea crises due to autonomic nervous system dysfunction.[2–5] Central nervous system malformations, as well as lung and heart disease, should be ruled out. Hypoventilation is accentuated during sleep, particularly in the non-REM phase, in which the autonomic control of breathing predominates.[6] For this reason it was called Ondine's curse syndrome, based on the Norse myth of Ondine (1811) by Friedrich La Motte Fouque, which tells the story of a nymph who gives up immortality to live a human love; however, when she is betrayed, she curses her faithless lover to forget to breathe while sleeping.[7]

In 1978, Gabriel Haddad was the first author to describe the association between CCHS, Hirschsprung's disease and tumors derived from the neural crest, in addition to hypothesize the familial character of the disease.[8] Approximately 15–20% of cases of CCHS have Hirschsprung's disease; short segment involvement (rectosigmoid) is more common, but long-segment aganglionosis is also described.[4,9–11] Tumors derived from the neural crest (neuroblastoma, ganglioneuroma, ganglioneuroblastoma) occur in 5–10% of cases, especially in the first two years of life.[12]

Initially only cases of severely affected newborns were reported in the scientific literature. However, from 1992 on, cohort studies started to be published, which broadened the scope of the syndrome through new evidence such as clinical variants of later onset and autonomic nervous system involvement in other organs, which expands the possibilities of associated clinical manifestations (cardiac arrhythmias, orthostatic hypotension, abnormal pupillary reflex, esophageal dysmotility, diaphoresis, decreased heart rate variability, chronic constipation, excessive drowsiness after use of sedatives and antihistamines). Confirmation of familial recurrence emphasized the genetic component and the broad phenotypic spectrum.[3,9–11,13–17]

In 2003, *PHOX2B* gene mutations were identified as responsible for CCHS. The *PHOX2B* gene (paired-like homeobox gene), located on chromosome 4p12, encodes a transcription factor responsible for the regulation of genes involved in the development of the autonomic nervous system.[15] The most frequently found mutation is a polyalanine expansion in exon 3. More than 90% of affected individuals are heterozygous for this mutation. The normal genotype has a sequence of 20 alanines (20/20 genotype). CCHS occurs from four extra alanines in one of the alleles (20/24 genotype). There is a correlation between genotype and phenotype, i.e., the higher the number of alanines, the greater the severity of clinical findings. The presence of a

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