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Haddad Syndrome — more than don't forget to breathe

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Abstract: Congenital central hypoventilation syndrome (CCHS) and Hirschsprung's disease (HD) belong to neurocristopathies — autonomic nervous system defects caused by abnormal neural crest cells migration. Their co-occurrence defines Haddad Syndrome (HS) associated also with increased risk of neural crest origin tumors, mainly neuroblastoma (NBL), and PHOX2B gene mutation. This case concerns a male newborn presenting respiratory failure minutes after birth. Due to sleep apnea and increasing hypercapnia, he required intubation. Genetic testing revealed an anomaly in PHOX2B gene. In subsequent days, the patient did not pass the meconium, which, based on the imaging tests and biopsy, raised a suspicion of HD. The boy was diagnosed with HS and additional diagnostic measures, including cancer screening, were ordered, owing to the syndrome's characteristics. Awareness of such conditions enables clinicians to implement targeted management that may significantly improve long-term outcomes and quality of life for affected children.

Keywords: Haddad Syndrome, Hirschsprung's disease, congenital central hypoventilation syndrome, neurocristopathy.

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Introduction

The autonomic nervous system (ANS) plays a crucial role in controlling essential physiological functions, such as heart rate, blood pressure, pupil width, bowel movements and thermoregulation. [1, 2, 3, 4] Therefore, any damage to the ANS can result in malfunctioning of the body which, if left untreated, can be fatal. Neurocristopathies, such as CCHS and HD, are examples of congenital defects that arise from the disordered migration, differentiation, or destruction of neural crest cells (NCC) and lead to ANS impairment. [1, 2, 3] NCCs are multipotent neuroectodermal cells and can evolve into various cell types. They are only found in humans and tunicates. Prevention, prenatal detection, or complete cure remain elusive, as the disruptions occur during the initial stage of embryogenesis. Medical support therefore focuses on sustaining the patient's life by managing the affected body systems which is possible if the symptoms are detected relatively early after birth. Diseases resulting

from a defect in the ANS are rare in the population. However, if only one has been detected, it is necessary to consider further diagnostics for other ANS defects, because the co-occurrence of CCHS and HD is estimated at 16–20%, and CCHS and neuroblastoma at 5–10%. [1, 2]

Case presentation

A full-term male newborn from an uncomplicated pregnancy was observed to have respiratory failure soon after birth. A non-invasive CPAP ventilation was initiated, but due to sleep apnea and increasing carbon dioxide retention (checked by continuous monitoring of respiratory rate and by capnography), the child was intubated. An unsuccessful extubation attempt was made on the fifth day, and a further three attempts in the third month of life were, too. They resulted in cardiac arrest. Successful resuscitation was undertaken. Organic cases were ruled out via flexible bronchoscopy and brain MRI, which revealed cerebellar vermis hypoplasia and a brainstem cyst unrelated to the patient's condition. Genetic testing was performed revealing abnormalities in the PHOX2B gene. NPARM (Non PolyAlanine Repeat Mutations) was detected in Next-generation sequencing and was considered to be the cause of CCHS. Due to the results of the genetic test, a search for other congenital defects correlated with the detected mutation was initiated. After stabilizing the vital signs, it was decided to create a tracheostomy and to de-escalate respiratory support—furnishing independent breathing during wakefulness and home mechanical ventilation during sleep.

The newborn displayed symptoms of gastrointestinal obstruction, including a lack of meconium and dilated intestinal loops visible on abdominal X-ray, leading to suspicion of HD (Fig. 1). Additionally, a mutation in the PHOX2B gene was identified as a potential contributing factor to the disease. Rectal suction biopsy confirmed the diagnosis. Neural ganglia were located 40 cm ahead of the Bauhin's valve during gastrointestinal track mapping. An ileostomy was created at this point, with subsequent symptoms of short bowel syndrome, such as lack of expected body growth. While a modified diet was attempted, only partial improvement was achieved.

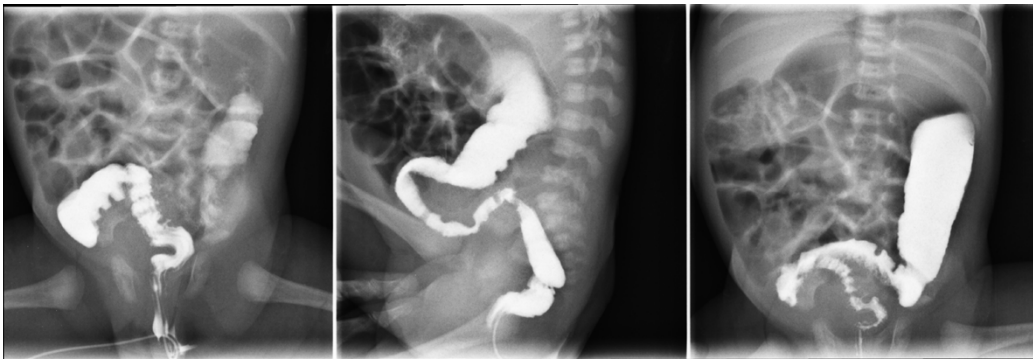

Fig. 1. Barium enema. Sign of HD.

The confirmation of a PHOX2B gene mutation in a patient who presented with both CCHS and HD led to a diagnosis of HS. Owing to the higher cancer risk associated with this syndrome, the patient underwent oncological screening tests at the age of 2 months. During an abdominal ultrasound, bilateral nodular lesions were found on the adrenal glands. A surgical biopsy subsequently confirmed them to be undifferentiated NBL with no expression of the N-MYC gene. Two cycles of

chemotherapy (etoposide + carboplatin) were performed, after which regression of changes was observed in the follow-up CT scan.

During hospitalization, the boy experienced two partial motor seizures (hemilateral facial right) with secondary generalization. Due to the child's anxiety, a valuable EEG test could not be conducted and an administration of carbamazepine was associated with excessive sleepiness.

During the examination, global psychomotor developmental delay, asymmetry in limb muscle tone and hypotonia of the midline were observed. A facial dysmorphia was not detected.

In follow-up imaging tests (transparietal ultrasound, head MRI) performed to check for brain defects detected after birth (cerebellar vermis hypoplasia, brainstem cyst), a gradual dilatation of the cerebral ventricular system was observed without signs of intracranial hypertension. Atrophic nature of the condition was most likely. It was decided to implant a ventriculoperitoneal shunt to prevent further loss of white matter.

Follow-up imaging tests (transparietal ultrasound, head MRI) were conducted to assess brain defects that were previously detected after birth (cerebellar vermis hypoplasia, brainstem cyst). The tests revealed a gradual dilatation of the cerebral ventricular system without signs of intracranial hypertension (Fig. 2). This condition was determined to be atrophic and to prevent further loss of white matter, a ventriculoperitoneal shunt was implanted.

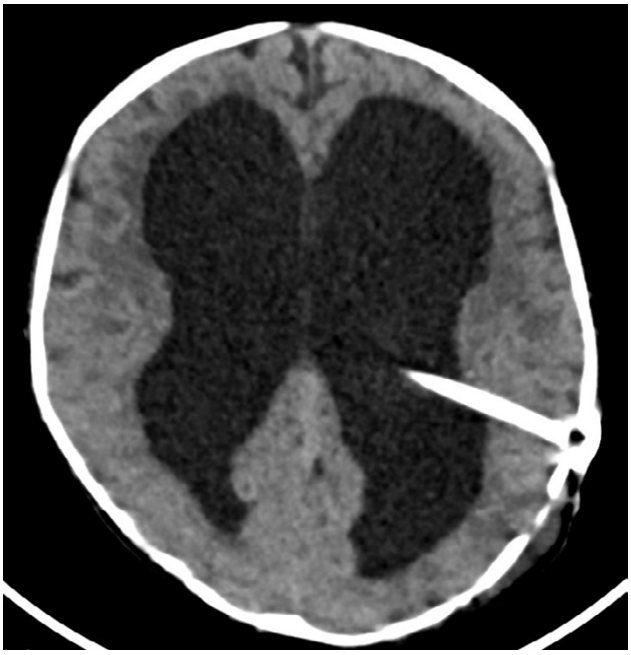

Fig. 2. Dilatation of the cerebral ventricular system without signs of active hydrocephalus. Properly-functioning ventriculoperitoneal shunt.

Due to possible cardiac arrhythmias in HS, a 24-hour Holter ECG monitoring was conducted. The results showed no abnormalities in heart rhythm.

The child underwent numerous hospitalizations complicated by generalized infections. Furthermore, the boy was diagnosed with atopic dermatitis.

The patient requires continuous treatment and life support measures.

Informed consent was obtained from the caregivers for the case report and its publication.

Discussion

Don't forget to breathe

CCHS is a rare condition also known as "Ondine's Curse." According to myth, a nymph cursed her human lover who betrayed her, causing him to forget to breathe whenever he fell asleep. [1] The estimated prevalence of CCHS is 1 in 200,000 live births. [2, 3, 4, 5] The condition is caused by ANS dysregulation, which weakens the response of chemoreceptors to increasing hypercapnia, resulting in central apnea. In the most common form of CCHS, ventilation is normal during wakefulness; but during sleep, especially in the NREM phase, apneas and carbon dioxide retention occur, leading to severe respiratory failure. [6] Typically the disease appears during the neonatal period and an infant will require mechanical ventilation and, over time, will be unable to extubate.

More than don't forget to breathe

The title "more" means that Ondine's Curse is accompanied by HD and a higher risk of cancer—mainly NBL—than in the general population. "more" is therefore HS (1 in 1,000,000 live births). [4]

HD, also called congenital aganglionic megacolon, is the most common of the above-mentioned diseases and affects one out of every 5000 live births. [3] HD is caused by the significant deficiency or absence of ganglion cells in the submucosal and intramuscular plexus of the intestine, causing a paralytic intestinal obstruction. This condition primarily affects the rectum and sigmoid colon, but it can also occur in the small intestine in rare cases. In HS, HD co-occurring with CCHS is more frequently associated with the long-segment form. Total colonic aganglionosis accounts for approximately 5% of HD cases is a rare form and can be difficult to differentiate from other forms of distal intestinal obstruction. [1] The root cause of HD is a disruption in the cranio-caudal migration of vagal crest cells in the intestine, which typically takes place between the fifth and 12th week of pregnancy.

NBL is a malignant tumor originating from neuroblasts. These are neural crest cells that physiologically form the ANS ganglia and the adrenal glands. While most cases of NBL are sporadic, there is also a familial form to which mutations in the PHOX2B and ALK genes are predisposed. The amplification of the N-MYC gene is an important prognostic factor. Patients at a young age (less than 90 days) and the absence of N-MYC gene amplification tend to have a better prognosis. Although NBL in newborns is frequently associated with a tendency toward spontaneous regression, in this case chemotherapy was initiated due to its occurrence within the context of a complex and rare genetic syndrome. This presentation requires a more individualized diagnostic and therapeutic approach compared to the "classic", isolated form of NBL. [7]

Facial dysmorphia is often observed in HS. There are also many defects directly related to ANS dysfunction, such as cardiac arrhythmias leading to bradycardia and even asystole, dysphagia, gastric motility malfunction, the risk of hypoglycemic episodes, thermoregulation disorder or abnormal pupillary light reflex. [4, 6, 8, 9, 10] Therefore, it is necessary to perform additional tests in every patient suspected of HS, aimed at "getting ahead of the diagnosis." For example, detecting life-threatening arrhythmias or hypoglycemia using simple and easily available tests such as ECG Holter or glycemia measurement. A summary of comprehensive assessment of autonomic dysfunctions associated with HS is provided in Table 1. [4, 6, 8, 9, 10]

Table 1. Comprehensive assess ment of autonomic dysfunction associated with HS, which should be undertaken at diagnosis using the methods outlined.

Autonomic dysfunction	Diagnostic methods	Case results
sleep apnea related to CCHS	polysomnography or cardiorespiratory polygraphy	CCHS diagnosed by continuous monitoring of respiratory rate and by capnography
cardiac arrhythmias leading to primarily sinus bradycardia, transient asystole, syncope	regular ECG Holter monitoring	no changes
hypotension	blood pressure monitoring	no changes
dysphagia	oesophageal manometry	no changes
gastric motility malfunction	rectal suction biopsy (the gold standard), contrast enema	HD
risk of hypoglycemia (asymptomatic or manifested by seizures)	glycemia measurement	no changes
thermoregulation disorder		no changes
ocular disorders	a complete ocular examination	no changes
face dysmorphia		no changes

The PHOX2B gene located in the 4p12 locus and plays crucial role in differentiation of the cells of ANS during the initial stages of embryogenesis. Therefore, it may contribute to severe diseases — also those mentioned in the case report. The most common type of PHOX2B abnormalities are PARMs (PolyAlanine Repeat Mutations). NPARMs (Non-PARMs) being frameshift, missense and nonsense mutations are in the minority. While PARMs are usually observed in isolated CCHS, NPARMs are associated with co-ocurance of CCHS, HD and neuroblastoma. Nevertheless, a wide range of phenotypes occurs in patients with HS corelated with NPARMs. [6] The majority of defective PHOX2B variants arise de novo, but around 10–25% of heterozygous asymptomatic carriers pass the mutation to their offspring. [8, 10]

The brain abnormalities detected in the MRI were considered uncorrelated with the patient's condition. They are most likely congenital defects. However, in other cases they may have an impact on the patient's condition. Especially if the changes involve areas responsible for chemoreception, the chemoreception may be impaired.

The title "more" is therefore a warning sign that should alert medical professionals to exercise heightened diagnostic vigilance when identifying only one of the components of the HS symptoms. For instance, in the case of late-onset CCHS, respiratory failure may not be evident, as was observed in the presented case. [6] However, when a pathological mass appears in the abdominal cavity of a patient diagnosed with HD, considering HS and anticipating the occurrence of the first symptoms of respiratory failure with appropriate actions is paramount. In such cases, readiness to provide respiratory support is essential and stoma creation may not be as urgent a procedure as intubation. Tracheotomy should be considered as soon as a diagnosis of CCHS is made, which indicates that extubation will not be possible in the future and that lifelong ventilatory support will be necessary for the patient. [7, 9] The combination of certain images may be key to diagnosing this rare syndrome. Children who exhibit unexplained central hypoventilation should undergo

evaluation for CCHS. [6] While genetic testing plays an important role in the correct diagnostic pathway, the readiness to implement mechanical ventilation seems to be more important in determining patient survival. [6] Currently, the optimal solution for most CCHS patients is a voluntary respirator, which detects episodes of apnea and turns on only when the break in the respiratory cycle is too long.

Conclusion

Children diagnosed with Haddad Syndrome require comprehensive, lifelong medical care due to the dual challenges posed by CCHS and HD, as well as the increased risk of tumors originating from neural crest cells. Early and accurate diagnosis — supported by genetic testing — and timely initiation of multidisciplinary treatment are crucial for improving both survival rates and long-term quality of life. Effective management relies on coordinated efforts from interdisciplinary medical team.

Beyond addressing immediate life-threatening symptoms, long-term care should prioritize routine oncological surveillance, monitoring of autonomic nervous system function, and psychosocial support for both patients and families. The dynamic nature of this rare syndrome also necessitates clinical vigilance and openness to evolving diagnostic and therapeutic strategies. With appropriate support and advances in medical care, patients with HS can experience significantly improved outcomes despite the complexity of their condition.

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Author's contribution

S.K. and O.M. conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript. K.K. designed the study, collected data and drafted the initial manuscript.

All authors approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

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Conflict of interest

None declared.

Abbreviations

ANS — autonomic nervous system
CCHS — congenital central hypoventilation syndrome

HD — Hirschsprung's disease
HS — Haddad Syndrome
NBL — neuroblastoma
NCC — neural crest cells
NPARM — Non PolyAlanine Repeat Mutations
PARMs — PolyAlanine Repeat Mutations
PEG — Percutaneous Endoscopic Gastrostomy

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