

## Haddad syndrome

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### Abstract

Haddad syndrome is a rare genetically conditioned disease. We present a female newborn with congenital central hypoventilation syndrome associated with Hirschprung`s disease. The infant is mechanically ventilated and parentally fed in a home setting. The diagnosis has been confirmed by the presence of 20/26 PHOX2B genetic mutation.

**Key words:** congenital central hypoventilation syndrome, Ondine`s curse, Haddad syndrome, Hirschsprung`s disease, long-term home ventilation, long-term home parenteral nutrition

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Congenital central hypoventilation syndrome (CCHS) is a rare genetically conditioned disorder. Its incidence is estimated at 1:50.000–200.000 live births; 16–20% of such cases are accompanied by Hirschprung`s disease (HD). CCHS occurring concurrently with HD is known as Haddad syndrome [1]. The diagnosis is based on the presence of PHOX2B genetic mutation and the absence of diseases of the central and peripheral nervous system, muscular diseases, metabolic disorders and other genetic syndromes [2]. In most cases, congenital central hypoventilation syndrome manifests itself immediately after birth within the first month of life. CCHS diagnosed in older children is considered a mild (late-onset) form and is rarer [3].

### CASE REPORT

A female newborn, the first full-term pregnancy, young and healthy parents, was delivered spontaneously through natural passages with the initial Apgar score of 10. In the tenth minute of life, the respiration became shallow, the skin turned grey, and decreased muscle tone as well as apnoea were observed. The newborn required oxygen therapy; due to hypercapnia (pCO<sub>2</sub> 99.1 mm Hg), she was intubated and mechanical lung ventilation was initiated. The child with a suspicion of congenital cytomegaly was transferred to the Department of Neonatology.

After the 12-hour therapy in the Department, she was extubated and n-CPAP started. The newborn was quiet, without clinical features of dyspnoea. The abdominal breathing and no enhanced respiratory effort was observed yet the repeated acid-base balance testing showed the retention of CO<sub>2</sub> (91.2 mm Hg). The child was re-intubated and mechanically ventilated for several subsequent days. The pre-intubation physical examination revealed generalised hypotonia, most pronounced in the upper limbs and nuchal muscles, and shallow respiration.

The attempts to wean from ventilation failed due to apnoea or increased CO<sub>2</sub> pressure accompanied by decreases in pO<sub>2</sub> pressure. The newborn was periodically active, which led to self-extubation; however, the features of respiratory failure increased at various times (from several minutes to 48 hours). Due to chronic respiratory failure, the child underwent classical tracheostomy during the second month of life. The differential diagnosis excluded pulmonary diseases, heart defects, defects and tumours of the central nervous system, neuromuscular and metabolic diseases, as well as congenital or acquired infections. No dysmorphic features were observed, a normal female karyotype was confirmed.

Frequent burping was noted; enteral feeding was poorly tolerated from the very beginning. Imaging results confirmed the gastro-oesophageal outflow. Additionally,

angio-CT showed the left-sided aortic arch with the vascular ring crossing posteriorly the oesophagus of the right subclavian artery, which did not require surgical treatment repair. The newborn had to be parenterally fed until day 27.

During the ninth month of life, the symptoms of alimentary obstruction with generalized infection rapidly developed. Laparotomy was performed and ileostomy created. Based on the intraoperative inspection and histological biopsies, total colonic aganglionosis was diagnosed.

Since the cause of respiratory failure increasing during sleep was unclear, CCHS was suspected and genetic tests for the PHOX 2B mutation were performed. The findings demonstrated the 20/26 PHOX2B mutation confirming congenital central hypoventilation syndrome. CCHS was accompanied by Hirschprung's disease; therefore, Haddad syndrome was diagnosed.

The child was assigned to receive mechanical ventilation in a home setting; once the Broviac catheter was inserted, she was included in the home parental feeding program. The aganglionic colon was excised as scheduled and the continuity of the gastrointestinal tract reconstructed.

At present, the child breaths spontaneously through the tracheostomy tube during the waking state and mechanical ventilation is required during sleep, infections and vehicle transportation. The patient defecates abundantly about 8–10 times a day; the stools strongly irritate the skin leading to problems with proper care of the anal region. The child is now fed enterally and her weight gains are satisfactory.

The 72-hour Holter ECG recording showed two RR pauses in the mechanism of sinus inhibition to 2.15 s.

The child's psychomotor development is slightly delayed. The girl produces sounds and starts saying single words via the inserted tracheostomy tube with a phonation valve. Thanks to early motor rehabilitation started at month 20, the child can walk unaided.

## DISCUSSION

Haddad syndrome is a rare genetic disorder. Proper diagnosis requires genetic testing and identification of a mutation facilitates the treatment. In the case reported, the girl had the 20/26 PHOX2B mutation [2]; in such cases the clinical picture of disease is less severe and its course milder. Mechanical ventilation is required mainly during sleep and infections. In our patient, respiratory failure (whose cause is not fully clear) is additionally observed during vehicle transport; therefore, mechanical respiratory support is required.

According to the present knowledge, the disease is incurable. All patients with congenital central hypoventilation syndrome require lifetime respiratory support as they lack physiological reactions to increased pressure of carbon dioxide in the blood [3]. In our patient, invasive mechanical ventilation is provided through the phoniatic tracheostomy

tube, which is to accelerate the development of speaking skills. The characteristic feature of CCHS is coexistence with autonomic nervous system dysfunction, which also impairs the function of many systems and organs regulated by this system, e.g. the function of the cardiovascular system. Since vegetative disorders are the essential risk factor of sudden cardiac death, periodic, long-term monitoring of continuous ECG Holter recordings is necessary or implantation of cardiac electrotherapy devices [2, 4]. The 72-hour Holter recording of our patient demonstrated two RR pauses in the mechanism of sinus inhibition to 2.15 s. The child is under continuous care of the cardiac arrhythmia outpatient clinic; most likely, a cardiac pacemaker will have to be inserted in future.

Patients with Haddad syndrome can develop eating disorders resulting from concomitant Hirschprung's disease and impaired autonomic regulation of gastrointestinal functions [5]. Despite the excision of aganglionic bowel, our patient does not have eating disorders; on the other hand, frequent, abundant and strongly irritating stools (8–12 a day) as well as rectal prolapse causing huge discomfort pose relevant problems. Children with tracheostomy frequently have problems with proper biting and swallowing. Our patient started to swallow early, eats unaided and has a good appetite.

Autonomic dysregulation of the skin impairs natural mechanisms of thermoregulation; as a result, even during severe infections, children can remain afebrile. In our case, the body temperature is constantly reduced, yet during the infection episodes, the child has a fever. Since her discharge home, infections have been rare. Despite parenteral feeding through the Broviac catheter, no catheter-associated infections have developed.

Another marker of autonomic disorders is frequent coexistence of neoplasms originating from the nervous system, mainly neuroblastoma [6]; thus, the girl undergoes regular ultrasound examinations.

The child's psychomotor development depends on early diagnosis, mechanical ventilation instituted to prevent the incidents of hypoxia and hypercapnia and multi-profile rehabilitation [7]. In our patient, the change into non-invasive ventilation was abandoned, although parents entreated. The early-school period is the best time for such a change as the child can consciously cooperate; therefore, the change into non-invasive ventilation is planned for this period.

Another method of CCHS treatment is the implantation of a diaphragmatic pacemaker [8]. The method is recommended for patients dependent on ventilation 24 h a day; in our case, only periodic respiratory support is needed, therefore, another surgery seems ungrounded. The ongoing studies demonstrating resorted sensitivity of the respiratory centre in patients receiving desogestrel are promising [9]. The above method has not been applied in

our patient. When its efficacy is confirmed and desogestrel included, the respiratory support requirements of our patient are likely to decrease or mechanical ventilation will be eliminated.

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