© Pediatr Med Rodz 2021, 17 (4), p. 350–353
DOI: 10.15557/PiMR.2021.0056

Natalia Gołuchowska[1], Piotr Rzepniewski[1], Oliver Jendro[1], Karol Taradaj[2], Tomasz Ginda[2], Joanna Schreiber-Zamora[2], Bożena Kociszewska-Najman[3]

Received: 10.10.2021
Accepted: 10.11.2021
Published: 31.12.2021

Haddad syndrome: a case report

Zespół Haddada – opis przypadku

[1] ProNeo Students' Science Club, Department of Neonatology, Medical University of Warsaw, Warsaw, Poland
[2] Department of Neonatology, University Clinical Centre, Medical University of Warsaw, Warsaw, Poland
[3] Head of Department of Neonatology, University Clinical Centre, Medical University of Warsaw, Warsaw, Poland
Correspondence: Natalia Gołuchowska, Danków 39, 26-021 Daleszyce, Poland, e-mail: goluchowskan@gmail.com

Abstract

Congenital central hypoventilation syndrome is a very rare genetic disorder. The disease involves respiratory failure associated with impaired central control of the breathing process. Hirschsprung's disease is the cause of congenital intestinal obstruction as a result of the agenesis of ganglion cells in the submucosal and myenteric plexuses. If congenital central hypoventilation syndrome and Hirschsprung's disease occur simultaneously, Haddad syndrome is diagnosed. A male infant was born at 37 weeks of gestation in a moderate general condition. Due to increasing respiratory effort and increased demand for oxygen, the newborn was intubated and mechanically ventilated. During an extubation attempt, respiratory symptoms intensified, and CO_2 was accumulating on blood gas test. Genetic tests revealed a mutation in the *PHOX2B* gene, which confirmed congenital central hypoventilation syndrome. Lack of meconium and enteral nutrition intolerance were observed. Hirschsprung's disease was diagnosed on the basis of intestinal biopsy. Loop ileostomy was created at 5 weeks of life. Due to coexistence of congenital central hypoventilation syndrome and Hirschsprung's disease, Haddad syndrome was diagnosed.

Keywords: Hirschsprung's disease, Ondine's curse, Haddad syndrome, breathing disorders, neurocristopathy

Streszczenie

Zespół wrodzonej ośrodkowej hipowentylacji jest rzadkim zaburzeniem genetycznym, polegającym na nieprawidłowej wentylacji prowadzącej do niewydolności oddechowej w przebiegu upośledzonej ośrodkowej kontroli procesu oddychania. Choroba Hirschsprunga to częsta przyczyna wrodzonej niedrożności jelit, której istotą jest agenezja komórek zwojowych w splotach śródściennych jelita. Jeśli zespół wrodzonej ośrodkowej hipowentylacji i choroba Hirschsprunga występują jednoczasowo, rozpoznaje się zespół Haddada. W pracy opisano przypadek chłopca urodzonego w 37. tygodniu ciąży, w stanie ogólnym średnim. Ze względu na wysiłek oddechowy, słaby napęd oddechowy i wzrost zapotrzebowania na tlen pacjent został zaintubowany i był wentylowany mechanicznie. Przy próbach ekstubacji utrzymywał się słaby napęd oddechowy. We śnie głębokim występowała zmniejszona liczba oddechów, a w gazometrii kumulacja CO_2. W badaniu genetycznym stwierdzono mutację w genie *PHOX2B*, co potwierdziło zespół wrodzonej ośrodkowej hipowentylacji. Pacjent nie tolerował żywienia enteralnego oraz nie oddawał smółki. Wykonano biopsję jelita, na podstawie której rozpoznano chorobę Hirschsprunga. Chłopiec został zoperowany z wyłonieniem ileostomii w 5. tygodniu życia. Wobec współwystępowania zespołu wrodzonej ośrodkowej hipowentylacji i choroby Hirschsprunga stwierdzono zespół Haddada.

Słowa kluczowe: choroba Hirschsprunga, klątwa Ondyny, zespół Haddada, zaburzenia oddychania, neurokrystopatia

INTRODUCTION

Congenital central hypoventilation syndrome (CCHS), which is also known as Ondine's curse, is a rare genetic disorder characterised by inadequate ventilation that leads to respiratory failure associated with impaired central control of the breathing process. The primary manifestation of the disease is hypoventilation during sleep, which can result in extremely low pulmonary ventilation or complete respiratory arrest. In CCHS, there is a relationship between the degree of hypoventilation and the phase of sleep. In NREM (non-rapid eye movement) sleep, respiratory symptoms are much more severe than during REM (rapid eye movement) sleep[1]. The majority of patients are found to have a *PHOX2B* (paired-like homeobox 2B) mutation[2]. According to the research available, the global incidence of CCHS ranges between 1/148,000 and 1/1,200,000 live births[3,4]. CCHS is one of neurocristopathies, i.e. a group of disorders occurring in vertebrates, particularly humans, which are associated with abnormal migration, differentiation and death of neural crest cells during embryogenesis[5].

Neurocristopathies also include Hirschsprung's disease (HD), which is a congenital developmental defect of the colon characterised by the absence of parasympathetic ganglion cells in the submucosal and myenteric plexuses, and of interneurons in the distal colon. HD is considered to be a consequence of premature arrest of craniocaudal migration of vagal neural crest cells in the hindgut, which takes place between 5 and 12 weeks of gestation to form the enteric nervous system[6].

Unlike in a number of developmental anatomical defects of the intestines, HD is rarely diagnosed antenatally[7]. In the majority of cases, the condition is diagnosed during the neonatal period. A sign that should raise the suspicion of HD is delayed passage of meconium, which is caused by paralytic ileus. Other manifestations include abdominal distension, which can be mitigated by rectal stimulation or enema, and vomiting[6]. The incidence of HD is approximately 1/5,000 live births, with a male-to-female ratio of 3.2:1.1[8]. If CCHS and HD are concurrent, Haddad syndrome is diagnosed. Despite a low number of documented cases of the syndrome, a common aetiology is suggested for CCHS and HD, which is associated with impaired development of the neural crest[9]. In this paper, we present the case of a newborn transferred to the Department of Neonatology of the Paediatric Teaching Hospital, University Clinical Centre, Medical University of Warsaw (DSK UCK WUM) from a different centre for diagnostic investigation and treatment of impaired breathing.

CASE REPORT

A male infant was born at 37 weeks of gestation by caesarean section. On the day before delivery, abnormal blood flow was found in the umbilical vessels and intrauterine growth restriction was suspected. A decision was made to end the pregnancy earlier by caesarean section. The child was born in a moderate general condition with 6–7–9–8 Apgar scores and a birth weight of 2,260 g (13th percentile).

Breathing problems

During the first hour of the infant's life, impaired breathing was observed: shallow breaths, falling oxygen saturation and cyanosis. Supplemental oxygen therapy was initially used. Due to lack of improvement, non-invasive nasal continuous positive airway pressure (n-CPAP) treatment was applied. Since ventilation support was not effective (when oxygen delivery was increased to 80%, a maximum SpO_2 level of 85% was achieved), the neonate was intubated and mechanical ventilation was started. The child required a high oxygen delivery (fraction of inspired oxygen, FiO_2: 0.6–0.8).

Upon admission to the Department of Neonatology of DSK UCK WUM, the newborn was in a severe general condition with a decreased muscle tone. His heart rate was regular at 130 bpm. The first blood gas test revealed signs of respiratory acidosis with a pH level of 7.0 and excessive accumulation of CO_2 (partial pressure of carbon dioxide, pCO_2: 117 mm Hg). In the beginning, mechanical synchronised intermittent mandatory ventilation (SIMV) was applied with the following initial ventilator settings: f 27, PIP 17, PEEP 6, PS +11, Ti 0.8 with oxygen delivery at FiO_2 0.4–0.5. Ventilator settings were modified based on blood gas and saturation values. Periodic episodes of decreased heart rate down to 80 bpm were observed. Due to bradycardia, continuous infusion of pressor amines: dobutamine (at 5–10 μg/kg/min) and dopamine (at 5 μg/kg/min) was administered. During extubation attempts, persistently weak respiratory drive was observed with up to 27 spontaneous breaths per minute. The neonate remained on DuoPAP ventilatory support only periodically, for 2–3 days.

Due to deteriorating respiratory failure (decreased breathing rate during periods of reduced activity, down to as few as 20 breaths per minute in deep sleep) and pCO_2 accumulation (pCO_2 of 73.9 mm Hg on blood gas test), the child required reintubation. Based on decreased respiratory drive being the dominant problem, congenital central hypoventilation syndrome was suspected. During hospitalisation, genetic testing was conducted: a mutation in the *PHOX2B* gene was detected, which confirmed the diagnosis of CCHS.

Due to the need for prolonged mechanical ventilation, on day 50 of the child's life a tracheotomy procedure was performed and a tracheostomy tube was placed. This made it possible for the boy to breathe spontaneously during periods of activity. During sleep, the patient's respiration was supported with DuoPAP without oxygen therapy, with a guaranteed number of breaths at 30–35/min. The child also required ventilation support during feeding and after it due to increased fatigability.

 DOI: 10.15557/PiMR.2021.0056

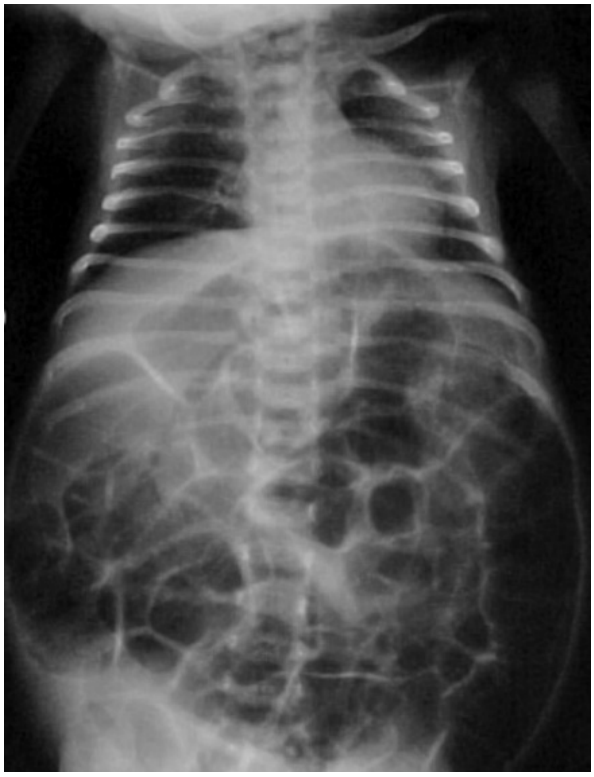

Fig. 1. Colonic ileus associated with HD on abdominal radiography

Gastrointestinal problems

Other dominant problems during the first days of the patient's life included increasing abdominal distension and lack of spontaneous passage of stool. The neonate also did not tolerate enteral nutrition. The child did not pass meconium, and this was achieved only after the administration of enemas. Initially, total parenteral nutrition was provided through a central line.

On day 6 of the newborn's life, a plain abdominal radiograph was taken due to persistent abdominal distension (Fig. 1). A large, distended sigmoid (sentinel loop) was visualised. Abdominal ultrasound examination revealed a locally distended bowel with a normal image and peristalsis in the remaining part of the intestine, which indicated the presence of paralytic ileus.

On day 16 of the neonate's life, a lower gastrointestinal tract series and subsequently colonic mucosal biopsy were performed. Based on their results, HD was diagnosed.

At 5 weeks of life, ileostomy surgery was performed. From day 5 after the operation, enteral nutrition was gradually introduced, which became the only form of nutrition for the boy from day 14. The mother's milk was given, and if it was absent, an infant formula was administered. The child was initially fed through a nasogastric tube; subsequently, a dummy was also used (up to 70–90 mL). It was not possible to increase the amount of food taken by mouth due to significant fatigability of the child during feeding and increasing respiratory failure.

Since the patient was diagnosed with HD, he required further care and surgical intervention at 10 months of age. Under general anaesthesia, the transperineal stage of HD treatment was performed. A 20 cm long fragment of the abnormal intestine was resected. The level of normal innervation was determined intraoperatively, which made it possible to establish the level of anastomosis. Based on the coexistence of CCHS and HD, Haddad syndrome was diagnosed.

Neurological problems

In the first weeks of his life, the newborn was apathetic with a decreased muscle tone. The patient was seen by a neurologist and neurological examination revealed a very low activity level of the child. The boy had a globally decreased muscle tone and bilateral foot clonus. The neonate did not follow objects with his eyes and did not fix his gaze on them. Magnetic resonance imaging of the central nervous system revealed signs of demyelination.

In the first month of the boy's life, a hyperreaction to sedatives was observed. During hospitalisation, the child had one tonic-clonic seizure that required anticonvulsant treatment (the child received a single 2.5 mg dose of diazepam rectally).

The child's activity, responsiveness to stimuli and muscle tone were observed to gradually and slowly improve. A follow-up electroencephalography did not record a pattern characteristic for neonatal seizures.

Haematological problems

The patient was diagnosed with anaemia based on complete blood count values: haemoglobin (HGB) – 8.2 g/dL (normal range: 13.5–16.5 g/dL), red blood cells (RBC) – 2.75 × 10^6/μL (normal range: 3.9–5.5 × 10^6/μL) and mean corpuscular volume (MCV) – 92.0 fl (normal range: 87–113 fl). During hospitalisation, the child received filtered and irradiated packed red blood cells (15 ml/kg) three times.

In the second month of the infant's life, supplementation of iron (5 mg/kg of body mass daily) and erythropoietic vitamins (folic acid: 1 × 2.5 mg daily and vitamin B_6 1 × 25 mg daily) was started.

From 7 weeks of life, erythropoiesis was stimulated by using epoetin beta (250 IU/kg of body weight 3 times a week). As a result of the treatment, gradual improvement of red blood cell values was observed on complete blood count (CBC): HGB – 11.3 g/dL (normal range: 10.0–13.5 g/dL), RBC – 3.92 × 10^6/μL (normal range: 3.7–5.0 × 10^6/μL) and MCV – 86.2 fl (normal range: 80–96 fl).

***

At 3 months of age, the patient was transferred to a centre which provided home ventilation support services. The boy remains under multispecialist care and undergoes regular examinations at ENT (ear, nose and throat) and surgical clinics.

DOI: 10.15557/PiMR.2021.0056

The child requires long-term physiotherapy. The parents were instructed on taking care of a child with a tracheostomy tube.

DISCUSSION

Haddad syndrome is a very rare condition, which occurs at a rate of less than 1/1,000,000 live births[3]. Haddad syndrome is diagnosed when two syndromes are found to coexist: HD and CCHS. Diagnostic investigation of HD should take into account not only its characteristic clinical presentation and typical abnormalities on physical examination, but also imaging and anal manometry findings. A diagnosis of HD can only be made with confidence on the basis of histopathological examination of colonic mucosal aspiration biopsy specimens[10].

CCHS is suspected when hypoventilation is observed in a neonate. Genetic testing confirms the diagnosis. As in the present case, patients with suspected CCHS need to be tested for a *PHOX2B* gene mutation. Due to the fact that the present patient's respiratory centre does not respond to increased carbon dioxide pressure in the blood, he will require breathing support to the end of his life. For this purpose, non-invasive DuoPAP ventilation through a tracheostomy tube was used during sleep. It also allowed the patient to breathe spontaneously during periods of activity. In patients with CCHS, ventilatory support is always required during sleep. It can also be considered for the time of activity depending on the severity of the disease. Observations show that a patient may require breathing support not only at night, but during the day as well[11].

Gastrointestinal problems are another important aspect of Haddad syndrome patient care. HD is associated with nutrition disorders leading to developmental problems. It is important to balance nutritional deficiencies, including with parenteral nutrition, if necessary. Ileostomy surgery is also performed in order to decompress the aganglionic segment of the colon. The next stage of surgical treatment involves the excision of that segment and attachment of the colon stump to the rectum[12], as was done in the present case. After the procedure, parenteral nutrition should be replaced with enteral nutrition via a nasogastric tube or by mouth.

Complications of CCHS include cardiological problems associated with hypoventilation, which leads to hypoxia. As a result, patients have episodes of bradycardia, asystole, low daytime blood pressure, orthostatic hypotension and syncope[13]. Due to these complications, patients require specialist cardiological care, including cardiac stimulator implantation in some cases.

CONCLUSIONS

Haddad syndrome is a very rare disorder. However, it needs to be taken into account in all neonates and infants with persistent respiratory failure, constipation and delayed passage of meconium, especially if no pulmonary manifestations, congenital heart defects and muscular or neural pathologies are involved. A clinical diagnosis is difficult to make; however, genetic testing provides an answer in the majority of cases. Currently, it is not possible to cure Haddad syndrome. Further research to develop new therapeutic methods is necessary, which could contribute to increased survival of children with this condition.

Conflict of interest

The authors do not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

References

1. Zaidi S, Gandhi J, Vatsia S et al.: Congenital central hypoventilation syndrome: an overview of etiopathogenesis, associated pathologies, clinical presentation, and management. Auton Neurosci 2018; 210: 1–9.
2. Trang H, Samuels M, Ceccherini I et al.: Guidelines for diagnosis and management of congenital central hypoventilation syndrome. Orphanet J Rare Dis 2020; 15: 252.
3. Trang H, Dehan M, Beaufils F et al.; French CCHS Working Group: The French Congenital Central Hypoventilation Syndrome Registry: general data, phenotype, and genotype. Chest 2005; 127: 72–79.
4. Shimokaze T, Sasaki A, Meguro T et al.: Genotype-phenotype relationship in Japanese patients with congenital central hypoventilation syndrome. J Hum Genet 2015; 60: 473–477.
5. Vega-Lopez GA, Cerrizuela S, Tribulo C et al.: Neurocristopathies: new insights 150 years after the neural crest discovery. Dev Biol 2018; 444 Suppl 1: S110–S143.
6. Amiel J, Lyonnet S: Hirschsprung disease, associated syndromes, and genetics: a review. J Med Genet 2001; 38: 729–739.
7. Das K, Mohanty S: Hirschsprung disease – current diagnosis and management. Indian J Pediatr 2017; 84: 618–623.
8. Wester T, Granström AL: Hirschsprung disease – bowel function beyond childhood. Semin Pediatr Surg 2017; 26: 322–327.
9. Shuman L, Youmans D: Haddad syndrome: a case study. Neonatal Netw 2005; 24: 41–44.
10. Kessmann J: Hirschsprung's disease: diagnosis and management. Am Fam Physician 2006; 74: 1319–1322.
11. Kasi AS, Perez IA, Kun SS et al.: Congenital central hypoventilation syndrome: diagnostic and management challenges. Pediatric Health Med Ther 2016; 7: 99–107.
12. Smith C, Ambartsumyan L, Kapur RP: Surgery, surgical pathology, and postoperative management of patients with Hirschsprung disease. Pediatr Dev Pathol 2020; 23: 23–39.
13. Bishara J, Keens TG, Perez IA: The genetics of congenital central hypoventilation syndrome: clinical implications. Appl Clin Genet 2018; 11: 135–144.