CASE REPORT

More than meets the eye: infant presenting with hypoxic ischaemic encephalopathy

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SUMMARY

We report a newborn infant who presented with poor Apgar scores and umbilical artery acidosis leading to the diagnosis of hypoxic ischaemic encephalopathy. During the course of the infant's hospitalisation, subsequent workup revealed an underlying genetic cause that masqueraded as hypoxic ischaemic encephalopathy.

BACKGROUND

Several genetic and inherited metabolic diseases may present with clinical features that overlap with more common disease processes. The awareness of these inherited disease states as well as clinical and biochemical clues may assist the clinician in suspicion and evaluation of these rare conditions. An early diagnosis is important for appropriate treatment and prognostication and enables genetic counselling and potential in utero diagnosis in the appropriate scenario.

CASE PRESENTATION

A 1-day-old baby girl was admitted to the neonatal intensive care unit for acute respiratory failure. The patient was born at term to a 24-year-old primigravida after an uneventful pregnancy. She was delivered by caesarean section due to failure to progress. At the time of birth, the baby was noted to be limp and was intubated for poor respiratory drive. Apgar scores were 2, 6 and 7 at 1, 5 and 10 min, respectively. The pH of the cord blood was 7.1 with a base deficit of 10 mEq/L. Based on the clinical presentation, neurological exam and umbilical artery acidemia, she was diagnosed with hypoxic ischaemic encephalopathy (HIE) and received therapeutic hypothermia per protocol.

The patient's growth parameters were appropriate for gestational age. No facial dysmorphism was seen. Neurological exam on second day of life showed hypotonia with poor suck. Palmar and plantar grasps were present; Moro reflex was symmetrically elicitable. Funduscopic examination was normal. Cardiac auscultation revealed normal heart sounds without presence of a murmur. Abdomen was soft to palpation without presence of hepatosplenomegaly. During her stay, she developed recurrent episodes of apnoea leading to several failed extubation attempts. Nonetheless, she only required minimal ventilator settings; hence, we suspected a central cause of apnoea and ventilator dependence.

INVESTIGATIONS

Brain MRI revealed signal abnormalities in the thalamus and basal ganglia consistent with HIE (figure 1). Electroencephalogram (EEG) did not show signs of seizures. Metabolic workup including serum ammonia, lactic acid, acylcarnitine profile, urine organic acids and plasma amino acids was unremarkable. Testing for congenital disorders of glycosylation and peroxisomal defects was negative. Genetic testing showed a mutation in the *PHOX2B* gene, and thereby the diagnosis of congenital central hypoventilation syndrome (CCHS) was made.

DIFFERENTIAL DIAGNOSIS

In addition to CCHS, there is an array of other genetic and inherited metabolic conditions that can cause neonatal respiratory depression and masquerade as HIE. A list of some of such conditions which should be borne in mind is included in table 1.

OUTCOME AND FOLLOW-UP

On day 20 of life, she underwent a tracheostomy and was discharged home shortly on a home ventilator.

DISCUSSION

CCHS is a rare genetic disorder of respiratory and autonomic regulation that usually presents in the newborn period. It is characterised by a lack of normal ventilatory and arousal responses to hypercarbia and hypoxaemia. It presents with apnoea or hypoventilation either exclusively during sleep or both awake and sleep. CCHS is also known as Ondine's curse based on a famous French folklore. In addition to respiratory issues, CCHS can be associated with other systemic manifestations.¹ Patients can have prolonged sinus pauses, attenuated heart rate response as well as gastrointestinal features such as oesophageal dysmotility and Hirschsprung's disease. Tumours of neural crest origin including neuroblastoma, ganglioneuroma and ganglioneuroblastoma have been described in 5%–6% of the patients. These tumours present at different ages but deaths from them are not usual. Chronic hypoxaemia may lead to secondary complications like polycythaemia, cor pulmonale and neurocognitive dysfunction. A characteristic dysmorphic phenotype has been reported in which the facies are shorter and flatter and typically show an inferior inflection of the lateral segment of vermilion border on the upper lip.

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Figure 1 MRI brain showing signal changes in bilateral thalamus and basal ganglia consistent with HIE. (A) Axial T1 image shows hyperintensity in the ventrolateral thalami, internal capsule and posterior basal ganglia bilaterally (black arrows). (B) Axial T2 image shows hypointensity in the same regions as 1, better seen on the right side (white arrows). HIE, hypoxic ischaemic encephalopathy.

When clinically suspected, the diagnosis of CCHS is made by molecular genetic testing. Newborns with CCHS may often show clinical features that can be attributed to HIE. The hypotonia and poor suck seen in our patient, as well as the abnormalities in the basal ganglia and thalamus on MRI, are in most likelihood secondary to HIE. Routine structural neuroimaging in patients with CCHS is usually normal; however, advanced MRI techniques using diffusion tensor imaging and T2-relaxometry have shown changes in forebrain, brainstem and cerebellum.² Liver and kidney function tests, ammonia, lactic acid and other biochemical parameters are typically unremarkable in children with CCHS. EEG is usually negative or may show signs of neuronal dysfunction secondary to HIE. In our patient, the presence of recurrent apnoeas and inability to extubate were unusual for HIE, thus leading to further evaluation. As noted in [table 1](#), various metabolic and genetic disorders can masquerade as HIE, and even though their clinical features are hugely overlapping, many of these conditions have biochemical markers which can lead the clinician to a definitive diagnostic evaluation. When the metabolic derangements are persistent and excessive, an inborn error of metabolism becomes a diagnostic possibility. However, CCHS is a unique entity in which there are no specific laboratory abnormalities that lead to its suspicion. And as aforementioned, brain imaging may show non-specific features secondary to the effects of the disease which can further mask the underlying aetiology and mislead the clinician. Thus, a high index of suspicion is necessary to suspect CCHS and to avoid delay in diagnosis and appropriate intervention.

CCHS is a neurocristopathy leading to an abnormal development of the embryonic progenitor cells that form the neural crest. It is typically caused by a de novo mutation in the *PHOX2B* gene located on chromosome 4p13. Most pathogenic variants result in the classic neonatal presentation but less severe mutations may cause clinical symptoms only when respiratory control is challenged, for example, during an infection or during a procedure requiring anaesthesia. Unlike classical CCHS, these individuals may present in childhood or even as adults. The *PHOX2B* contains 20 polyalanine repeats in exon 3, which is represented as 20/20 for the two normal alleles in general population. The most common abnormality in CCHS is polyalanine repeat expansion mutation, resulting in expansion of the polyalanine repeats from 20 to a broad range between 24 to 33 repeats (indicated as 20/24 to 20/33). The presence of non-neurological involvement

Table 1 Selected metabolic disorders that may present with features of HIE

Disorder	Clinical or neuroradiological features which may be seen, in addition to neonatal encephalopathy or seizures	Biochemical abnormalities which may raise suspicion of a metabolic disorder
1. Fatty acid oxidation disorders	► Cardiomyopathy	► Abnormal acylcarnitine profile ► Elevated CPK
2. Urea cycle defects	► Cerebral oedema on neuroimaging	► Elevated ammonia ► Abnormal plasma amino acids
3. Glycine encephalopathy	► Hiccups present in utero or in the neonatal age	► Non-ketotic hypoglycaemia ► Elevated glycine in serum and cerebrospinal fluid
4. Peroxisomal disorders	► Dysmorphic features ► Hypotonia	► Abnormal very long-chain fatty acids
5. Organic acidaemias	► Abnormal odour ('sweaty feet') in isovaleric acidemia ► Pancytopenia	► Abnormal urine organic acids
6. Congenital disorders of glycosylation	► Hypotonia ► Inverted nipples ► Dysmorphic facies ► Cerebellar atrophy	► Abnormal carbohydrate-deficient transferrin panel
7. Mitochondrial disorders	► Multisystem involvement (cardiomyopathy, hearing impairment, pancreatitis) ► MRI may show specific distribution of lesions, mostly involving the basal ganglia ► MR spectroscopy may show lactate peak	► Elevated cerebrospinal fluid and serum lactate
8. Sulfite oxidase deficiency	► Dysmorphic features ► Lens dislocation (may develop in infancy) ► MRI brain may show cystic lesions in basal ganglia and thalamus	► Elevated urine thiosulfate level
9. GLUT-1 deficiency	► Refractory neonatal seizures	► Normal blood glucose with low cerebrospinal fluid glucose ► Low to low normal cerebrospinal lactate

CPK, creatine phosphokinase; GLUT-1, glucose transporter 1; HIE, hypoxic ischaemic encephalopathy.

is at least in part determined by the underlying mutation seen in the *PHOX2B* gene. Based on the number of repeats, genotype-phenotype correlations have also been established which help predict the comorbidities and the risk of developing tumours of neural crest origin in an individual patient with CCHS. Our patient had a 20/27 polyalanine repeat mutation, putting her at a lower risk of neural crest tumours compared with individuals with higher repeats (20/28 and more). She was also diagnosed with Hirschsprung disease which is seen in repeats 20/26 and higher. CCHS is an autosomal dominant condition, thus, an affected individual has a 50% chance of passing the mutated gene to his/her offspring.

The crux of management of CCHS lies in providing optimal respiratory support. Tracheostomy and home ventilator are offered to infants with apnoea who require continuous support. Diaphragm pacing by phrenic nerve stimulation or negative pressure ventilation can be considered in older children and adults requiring support during sleep only. Cardiac pacemaker is recommended for those with prolonged sinus pauses. Swimming, breath holding contests, alcohol as well as certain sedatives and anaesthetics should be avoided as they could induce respiratory depression and death. Regular surveillance for comorbid conditions as well as secondary complications should be undertaken as per published guidelines by American Thoracic Society.³ Screening should be undertaken

for prolonged sinus pauses by yearly 72hours Holter and right ventricular hypertrophy or cor pulmonale by yearly echocardiogram. Complete blood counts should be done at least yearly for evaluation of polycythaemia. A multidisciplinary team involving the primary care paediatrician, pulmonologist, cardiologist, gastroenterologist and developmental paediatrician is required for optimal management of these patients. Prenatal testing is an option which permits informed decisions regarding the pregnancy and a planned transition after birth.

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Learning points

- Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder that may present with respiratory failure and unexplained apnoeas in the newborn period.
- A high index of suspicion is necessary for suspecting CCHS in neonates as clinical and radiological features of hypoxic ischaemic encephalopathy (HIE) may dominate the patient's presentation.
- Timely recognition of the disorder may prevent unnecessary diagnostic pursuits and interventions and aid in appropriate management and counselling.
- In addition to metabolic and neuromuscular diseases, which are often included in the differential diagnoses of neonates with HIE without a clear sentinel event, clinicians should also consider rarer genetic syndromes even in a non-dysmorphic child.

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