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Case Report

Recurrent apnea in an infant: Lessons for the clinician

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Introduction

Recurrent apneas in an infant can be a frightening event for the parents and have a broad differential diagnosis. We describe one such infant, who posed a diagnostic dilemma, to highlight the important issues in care.

Case report

A 30-day-old male infant was admitted to the neonatal intensive care unit with shallow breathing, bradycardia, shock, and severe hypothermia (axillary temperature <94°F).

The infant was born late preterm (35_{4/7} weeks) and low birth weight (2.1 kg) by emergency caesarean (indication: severe maternal preeclampsia) to a 28-year-old booked primigravida with preeclampsia and cholestasis of pregnancy in the antenatal period. The infant had poor feeding with coryza for 2 days and breathing difficulty 6 h before admission. The blood sugar (glucometer) at admission was 69 mg/dl, and venous blood gas revealed pH 6.2, pCO₂ 110 mm Hg, and pO₂ 73 mm Hg. The infant required cardiopulmonary resuscitation, intravenous fluid boluses, and mechanical ventilation. Intravenous antibiotics were begun for suspect community-acquired late-onset sepsis along with inotropes and supportive care. The laboratory evaluation and chest radiograph were normal. The blood culture (after 48 h) grew *Escherichia coli* sensitive to meropenem, amikacin, and imipenem. A cerebrospinal fluid study revealed no organism on gram stain; white blood cells, nil; red blood cells, 02; glucose, 43 mg/dl; proteins, 38 mg/dl; and cerebrospinal fluid culture was sterile. Intravenous antibiotics were continued for a total duration of 2 weeks. The infant gradually improved over the next 7 days and was extubated to nasal intermittent mandatory ventilation after 10 days.

However, in view of shallow breathing efforts and hypercarbia (pCO₂ 110 mm Hg), the infant required reintubation with minimal pressure and FiO₂ requirements. A loading dose of injection caffeine citrate (20 mg/kg/day) was given followed by a maintenance dose (10 mg/kg/day) for the next 2 weeks with no significant clinical benefit.

Over the next 4 weeks, the infant failed five attempts at extubation—each event preceded by hypoventilation during

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sleep and hypercarbia. There were three episodes of multifocal seizures (? hypoxic/? late-onset hypocalcaemia) during this period, managed with intravenous calcium, phenobarbitone, and evaluation revealed hypocalcemia with a normal intact parathyroid hormone. There was no axial or appendicular hypotonia, dysmorphic features, or clinical features suggestive of neuromuscular disease. The further workup (Table 1) including a bedside 12-lead electrocardiogram, 2D echocardiogram, and fluoroscopy for diaphragmatic function, metabolic workup including blood tandem mass spectrometry, serum aminoacidogram and urine gas chromatography mass spectrometry, electroencephalogram, magnetic resonance imaging brain, nerve conduction studies, and a muscle biopsy were normal.

Having ruled out cardiac, respiratory, neurological, and metabolic causes of recurrent apnea in this infant, genetic testing for paired-like homeobox 2B (PHOX2B) gene mutation was sent (repeated episodes of intermittent hypoventilation during sleep and hypercarbia). The patient tested positive for 27 ± 2 alanine repeats, that is, polyalanine repeat expansion mutation (PARM) in the 20 alanine stretch of the PHOX2B gene, confirming the diagnosis of congenital central hypoventilation syndrome (CCHS).

The further hospital course was complicated by culture positive meningitis (acinetobacter), and the infant received a further 3-week course of intravenous antibiotics (colistin and meropenem). Having confirmed the diagnosis of CCHS, the parents were counseled about the possible need for tracheostomy and long-term home ventilation. However, in view of lifelong nature of illness and guarded future outcome, the parents declined further treatment and

requested discharge against medical advice. The parents underwent a genetic counseling before discharge and were advised testing for PHOX2B gene mutation before the next pregnancy.

Discussion

Recurrent apneas in a neonate or infant can pose a difficult diagnostic challenge.^{1,2} Clinical evaluation is guided by the gestational age, postnatal age, and the clinical setting, with the investigations tailored to the individual patient. In our index case, the infant had previously been well and gaining weight on exclusive breast feeds and presented with apnea, bradycardia, hypothermia, and required aggressive resuscitation and mechanical ventilation.

CCHS, also known as Ondine's Curse is a rare genetic disorder (estimated prevalence of 1 in 2,00,000 live births) with a primary failure of the autonomic nervous system control of breathing due to a mutation in the PHOX2B gene. First reported by Mellins et al., it presents in the neonatal period with hypoventilation more marked during non-rapid eye movement (REM) sleep, hypoxemia, and hypercarbia without clinical features of respiratory distress.² Some patients with a milder phenotype present later in older childhood or adulthood (late-onset CCHS), with hypoventilation following a pneumonia or general anesthesia.³ The hallmark of CCHS is alveolar hypoventilation with absent physiologic responses to hypoxemia and hypercarbia, thus delaying the diagnosis only when severe cyanosis and central nervous system depression have set in. There can be associated arrhythmias, reduced

Table 1 – List of investigations.

Investigation	Result	Remarks
Serum calcium	1.02 mmol/L (1.16–1.32 mmol/L)	Hypocalcemia with normal serum phosphorus, magnesium, vitamin D, and i PTH level
Serum phosphorus	3.14 mg/dl (2.40–4.40 mg/dl)	
Serum magnesium	1.80 mg/dl (1.80–2.60 mg/dl)	
Vitamin D	54 nmol/L	
i PTH	23 pg/ml (14–72 pg/ml)	Normal
FT3	3.50 pg/ml (2.3–4.2 pg/ml)	
FT4	1.27 ng/dl (0.89–1.76 ng/dl)	
TSH	2.285 micro IU/ml (0.55–4.78 micro IU/ml)	
Serum creatine kinase	Normal	Normal
TORCH IgG/IgM	Negative	Normal report
Blood TMS	Normal levels of all metabolites tested	Normal
Serum aminoacidogram		
Urine GCMS	Normal levels of metabolites tested	Normal
12-lead ECG	Normal axis, heart rate 130/min, normal PR, QRS interval, no ST segment, or T wave changes	Normal
Bedside 2D echo	Normal structure and function of all 4 chambers. No evidence of ventricular dysfunction	Normal
Fluoroscopy	Normal diaphragmatic function	Normal
Nerve conduction studies	Normal	Normal
Muscle biopsy	Normal histology	Normal
EEG	Normal background, no abnormal waves	Normal
MRI brain and cervical spine	Mild cerebral atrophy	Normal
PHOX2B gene study	Positive for 27 ± 2 alanine repeats, that is, PARM in the 20 alanine stretch of the PHOX2B gene	Confirms diagnosis of congenital central hypoventilation syndrome

ECG, electrocardiogram; EEG, electroencephalogram; GCMS, gas chromatography mass spectrometry; MRI, magnetic resonance imaging; PARM, polyalanine repeat expansion mutation; TMS, tandem mass spectrometry.

heart rate variability, decreased basal body temperature, seizures, and developmental delay.

A transcription factor encoded by the PHOX2B gene plays an important role in the early development of the autonomic nervous system. PHOX2B normally contains a repeat sequence of 20 alanines in exon 3. Most patients of CCHS have 24–33 PARMs in exon 3 of the PHOX2B gene. Around 10% have non-PARMs (NPARMs), that include missense, nonsense, or frameshift mutations. In general, milder disease course is expected with fewer PARMs (20/25 or 20/26), whereas those with genotypes 20/27–20/33 usually require continuous ventilatory support.^{4,5} The majority of NPARMs occur de novo and have been associated with severe phenotypes, Hirschsprung's disease, need for continuous ventilatory support, and increased risk of neural crest cell tumors.

Diagnosis requires a high index of suspicion and exclusion of cardiac, respiratory, metabolic, and neurological causes of central apnea or hypoventilation.⁶ CCHS is a lifelong disease with no response to pharmacologic therapies. Management is extremely challenging with need for lifelong home ventilation and tracheostomy in the severe phenotypes. Non-invasive ventilation and diaphragm pacing have been tried in select children with less severe manifestations. Long-term survivors are at risk for developmental delay, neural crest tumors, and cardiac arrhythmias.

Repeated extubation failures, need for long-term ventilation, parental anxiety, and the diagnostic uncertainty/challenge (the PHOX2B gene study result took 4 weeks) with the attendant risks of prolonged hospitalization (nosocomial infections and other complications) overwhelmed the parents. We addressed parental concerns by repeated counseling and held regular team meetings to plan further evaluation and care of the baby.

Before the advent of genetic and metabolic testing, many of these infants would have been labeled as sepsis or meningitis.

The clinical picture of intermittent hypoventilation during sleep with hypercarbia and the methodical exclusion of other causes led to a diagnosis of CCHS in this infant. The alert clinician must consider the possibility of rare causes when the clinical course is not consistent with sepsis.

Conflicts of interest

The authors have none to declare

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