CASE REPORT

Ventilator respiratory graphic diagnosis of hiccupping in non-ketotic hyperglycinaemia

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SUMMARY

A neonate presented with early encephalopathy deteriorated and was intubated and ventilated. Ventilator data were monitored and recorded at 100 Hz for 24 hours.

The infant had many sudden deep inspirations during this time which were initially thought to be seizures. These were characterised by short, rapid, large inspirations when the airway pressure was reduced well below the positive end expiratory pressure level. Analysis of the ventilator data showed that these were hiccupping episodes misinterpreted by the ventilator as spontaneous breaths and triggering ventilator inflations. The expired tidal volumes during the hiccupping episodes were more than double the set 4.5 mL/kg. During these episodes, there was no change in the level of consciousness or in the amplitude-integrated electroencephalogram signal. Detailed respiratory recording of pathological hiccups has not been reported.

Metabolic screening diagnosed non-ketotic hyperglycinaemia. Hiccups commonly occur in this condition and should not be misinterpreted as seizures, spontaneous breaths or gasps.

BACKGROUND

Non-ketotic hyperglycinaemia (NKH) presents in the neonatal period with severe neurological abnormalities including encephalopathy, seizures and hiccupping.^{1 2}

Frequent hiccups are associated with a poor outcome.³

NKH is a rare genetic disorder of metabolism with autosomal-recessive inheritance. A mutation in the gene that encodes the glycine cleavage enzyme leads to abnormal metabolism and accumulation of glycine in the brain and other body tissues. The majority (80%) of mutations are in glycine decarboxylase (*GLDC* gene); in the remaining cases, the mutations affect the *aminomethyltransferase* or *glycine cleavage system H protein* gene.⁴ The accrual of glycine to toxic levels results in symptoms usually in the neonatal period and presents with a progressive encephalopathy, resulting in coma and death within the first few days to weeks of life.

Hiccupping in the neonatal period is usually normal, however, pathological causes should be considered with persistent hiccups accompanied by lethargy, hypotonia, poor suck and feeding, seizures and apnoea. In an encephalopathic infant, hiccups may be interpreted by parents and clinicians as seizures or as spontaneous breathing efforts rather

than as abnormal diaphragmatic contractions, therefore influencing perceptions of prognosis. Tidal volume-targeted ventilation can be influenced by hiccupping as the ventilator misinterprets the hiccups as spontaneous breaths. Understanding the influence of these factors will aid in both management of such ventilator-dependent infants and appropriate communication with parents.

CASE PRESENTATION

A male infant was born following an uneventful pregnancy at term. There was no family history of metabolic disease or parental consanguinity. He was delivered following two previous pregnancies: an early miscarriage and a normal healthy daughter born at term. During this pregnancy, his mother consistently felt increased fetal movements. He was born by normal vaginal delivery in good condition, following induction of labour for gestational diabetes. He did not require any resuscitation.

Shortly after his birth, he was noted to be hypotonic with poor feeding. On day 2 of life, neonatal sepsis was suspected and he was treated with intravenous antibiotics. On day 3, he developed cyanotic episodes and poor respiratory effort, leading to admission to the local neonatal unit. He was intubated, ventilated and transferred to the regional neonatal intensive care unit (NICU). Prior to transfer he was noted to have unusual gasping movements and hiccups. In the referring hospital these were interpreted as seizures despite a cerebral function monitor (CFM) recording showing no evidence of this. He was treated with phenobarbitone. During his admission to NICU, mechanical ventilation was complicated by ongoing hiccupping. Clinically, the abnormal movements were felt to be ongoing seizures and further phenobarbitone was administered with no improvement in neurological status.

INVESTIGATIONS

In NICU, a CFM showed a persistent abnormally wide trace with no signs of seizure activity. The electroencephalogram was also discontinuous with bursts of mixed frequency interspersed with periods of low amplitude (burst-suppression). The spasmodic breathing episodes were not associated with electrographic seizures on the CFM (figure 1).

A cranial MRI was normal except for a small subdural haemorrhage.

He was ventilated with a Babylog VN500 Ventilator (Dräger) using the synchronised intermittent

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Figure 1 CFM recording. Persistent abnormally wide trace with no evidence of seizures. The infant had two hiccupping episodes over this period (triangles). CFM, cerebral function monitor.

mandatory ventilation with volume guarantee mode. During the observation period, the target expired tidal volume was 15 mL (4.5 mL/kg), mandatory ventilator rate 40/min, later reduced to 35/min, inspiratory time 0.35 s, positive end expiratory pressure (PEEP) 4 cmH₂O and pressure limit ($P_{\max}$) 17 cmH₂O and flow triggering with a trigger sensitivity of 0.2 L/min.

Ventilator data were downloaded to a laptop via a cable attached to a communication port of the Dräger Babylog VN500 Ventilator. Airway pressure (paw), flow and tidal volume data were downloaded with at a sampling rate of 100 Hz. Other ventilatory parameters were recorded at 1 Hz. To analyse and

visualise data, we have built software using the freely available Python computer language (V.3.4.3–0, <https://www.python.org>).

We recorded detailed ventilator parameters for 24 hours. The infant had several episodes lasting 5–10 min of short sharp inspirations which reduced the airway pressure well below the PEEP level and sometimes down to -10 cmH₂O (figure 2). The abnormal inspirations were interpreted by the ventilator as spontaneous breaths which then triggered inflations. Their maximum inspiratory flow exceeded 20 L/min. This was approximately five times the flow during ventilator inflations. The tidal volumes exceeded 10 mL/kg and as this was >130% of the set tidal volume, a safety mechanism of the ventilator stopped further inflation for each high inspiration. These large tidal volume breaths alternated with ventilator backup inflations at the set 4.5 mL/kg expired tidal volume (figure 3). Between episodes, the baby was apnoeic. During episodes with large tidal volumes, the minute ventilation doubled (figure 2).

Careful analysis of the ventilator recordings of these episodes showed that they were hiccups. Respiratory recording of pathological hiccups in a ventilated baby has not been reported before.

Metabolic analysis of the plasma and cerebrospinal fluid (CSF) showed a CSF glycine of 358 μ mol/L (normal: 0–10

Figure 2 Recording of the minimum airway pressure ($P_{\min}$) and the expiratory minute volume (MVe) over ~24 hours. Each point on the graph represents the median value of 60 measurements taken at 1 Hz. Between ~16:00 and 18:00 hours, the infant had an MRI, therefore recording was paused (dashed arrow). (Upper panel) $P_{\min}$, the lowest pressure during each 1 s window. The PEEP was set at 4 cmH₂O. During the hiccupping periods (each marked by a solid arrow), the minimum airway pressure dropped below zero, reaching -10 cmH₂O. (Lower panel) MVe, the expiratory minute volume. Minute ventilation was very high during some hiccupping periods. PEEP, positive end expiratory pressure.

Figure 3 Ventilatory pressure, flow and volume curves during the 30 s hiccupping period marked by rectangle early on figure 2. During the hiccupping episodes, high tidal volume hiccups (arrows) alternate with backup ventilator inflations. The hiccupping is characterised by high inspiratory flow (>20 L/min) and negative pressure during inspiration resulting in >40 mL tidal volume. The inflation time are shortened by the ventilator when the tidal volume is 130% of the target tidal volume. Outside the hiccupping periods, the infant is apnoeic.

$\mu\text{mol/L}$) and a plasma glycine of $1050 \mu\text{mol/L}$ (normal: $160\text{--}304 \mu\text{mol/L}$). The CSF/plasma glycine ratio was 0.34 (normal: <0.08). These values established the diagnosis of NKH. Genetic analysis of a blood sample identified a homozygous pathogenic variant (c.1545G>C) in the *GLDC* gene consistent with the diagnosis of NKH.

OUTCOME AND FOLLOW-UP

The infant's neurological status further deteriorated with lack of spontaneous breathing and frequent hiccupping episodes. He remained ventilator-dependent and comatose. There was no clinical improvement over the next 10 days. Extensive, detailed discussions were held with his parents and the paediatric metabolic team. NKH presenting in the neonatal period is a devastating neurological condition. Most patients die soon after birth, and those who survive manifest severe neurological deficits. Given the extremely poor neurodevelopmental prognosis, intensive support was withdrawn.

DISCUSSION

NKH is a very rare condition that should be considered in a neonate presenting with evolving encephalopathy and hiccups. Assessing encephalopathic infants is challenging, and as in this case, hiccupping can be misinterpreted as seizures.

Diagnosis of NKH relies on paired CSF and plasma glycine measurements with an elevated ratio being pathognomonic for the condition.^{2,5} Early consideration of NKH in infants presenting with hypotonia, apnoea and hiccups may enable an early diagnosis.

Learning points

- ▶ Pathological hiccups can be diagnosed early by careful physical examination in combination with the interpretation of ventilator signals of tidal volume, flow and pressure.
- ▶ The excessive tidal volumes trigger ventilator alarms which may mislead staff and parents who may interpret them as signs of neurological improvement with a return of spontaneous breathing.
- ▶ Hiccupping may also be interpreted as seizure activity and treated as such with sedating antiepileptic medications, making assessment of neurological status difficult.
- ▶ It is important that the clinicians consider hiccupping as part of the metabolic encephalopathy accompanying this rare condition and appreciate the associated ventilation pattern they can see on a modern ventilator screen.

Contributors GB: collected and analysed the data. KS: provided the CFM data. EP, CM and GB: wrote the case report.

Competing interests None declared.

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