



Central Congenital Hypoventilation Syndrome associated with hypoglycemia and seizure



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ABSTRACT

Central Congenital Hypoventilation Syndrome (CCHS) is a rare diagnosis that presents with various forms of autonomic dysfunction. The disease is characterized by reduced chemoreflexes and severe hypoventilation during sleep. Several case reports have noted that patients with CCHS have been found to suffer from hypoglycemic episodes, which frequently present as a seizure. In this report, we will review previous case presentations to alert the physicians about this association with hypoglycemic episodes. Early treatment and monitoring of hypoglycemia will prevent further complications for these populations.

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1. Case report

The patient was born by repeat Cesarean section at 37 weeks and 2 days, weighing 2960 g. There were no complications during the pregnancy or labor. Apgars were 7 and 9 at 1 and 5 minutes respectively. On day of life 1, the patient began having apneic episodes, which required intubation. By 12 days of life she continued experiencing episodes of apnea and hypercapnia and was diagnosed as having PHOX2B expansion of polyalanine repeats 20/27. Patient underwent tracheostomy at 13 weeks of life. In addition, she was diagnosed with Hirschsprungs disease and underwent a Soave pull through at 15 days of life as well as gastrostomy placement. After discharge from the NICU at 4 months of age, the patient was readmitted at 5 months of age for episodes of hypersomnolence followed by seizure-like episodes. Those episodes involved choking, desaturation to 80%, as well as staring off with arms and legs outstretched. The patient was found to have Enterococcus UTI and MDR Serratia marcescens and Stenotrophomonas tracheitis, both of which were treated with a 10 day course of levofloxacin. Six days into admission, the patient continued experiencing multiple episodes of hypersomnolence and she had another seizure-like episode with eye deviation to the left. Patient was on an EEG at that time and was found to have no epileptiform activity. It was

discovered that the patient was consistently hypoglycemic with blood glucose as low as 30 mg/dl. Patient was started on continuous feeds and D10 1/4 NS at 5 cc/hr. In addition, patient was given diazoxide 10mg/kg times two doses for concern of hyperinsulinemia. While receiving diazoxide, the patient experienced another episode of hypoglycemia of 41 mg/dl, which was noted after holding feeds for only 10 minutes. At that time, diazoxide was discontinued. On abdominal US, the pancreas was found to be normal, and insulin levels, drawn during hypoglycemic episodes while on diazoxide and after its discontinuation, were found to be within normal limits at 0.6 uIU/ml and <0.5 uIU/ml. Patient was discharged home on continuous feeds with q6h glucose checks and glucagon to be used as needed. At home the hypoglycemia symptoms have been well controlled with continuous feeds; however, if the feeds are interrupted for more than 15 minutes the serum glucose level decreases to less than 30 mg/dl.

2. Review of previous cases

Several authors have reported cases of hypoglycemia in patients with known CCHS (Table 1). One case report noted a patient who was found to have episodes of hypoglycemia at 6 weeks of life. In addition, that patient was found to have hyperinsulinemia as a root cause of the hypoglycemia [2]. At the time of their publication, there had only been one other report of hyperinsulinemia associated with CCHS. In that case report, a patient with severe CCHS was found to have hyperinsulinemia, which was controlled with

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Table 1
Previous case report patient presentations.

	Hennewig et al.	Meissner et al.	Farina et al-Patient 1	Farina et al-Patient 2	Farina et al-Patient 3	Marics et al.
Age at presentation	6 weeks	15 months	13 days	8 months	15 months	14 days
Symptoms	Episodes of sweating	–	Seizures	Seizures (first at 4 months)	Seizures (first at 9 months)	Detected on screening
Glucose (mg/dl)	27 Repeat 16	32	20–17	11 Repeat 17 Repeat 14	36 Repeat 53 Repeat 51 Repeat 46	48
Insulin level (mU/l)	9.2 Repeat 19.9	8.5	2.9	37.4	19.2 Repeat 12.9 Repeat 7.8 Repeat 12	43

diazoxide [3]. Since the case report put forth by Hennewig et al., two subsequent publications have reported cases of hypoglycemia associated with hyperinsulinemia. In one case series, three patient presentations with first time seizures with associated hypoglycemia were noted. In one case, the patient's insulin level was normal [4]. In one final case report put forward by Marics et al., another case of hyperinsulinemia was reported. However, that time the patient was noted to have hypoglycemia in routine screening at 14 days of life and avoided any seizure activity due to sustained hypoglycemia [5]. Also of note, none of the previous case presentations reported associated Hirschsprungs disease.

3. Review of mechanisms and discussion

Several mechanisms pointing to the root cause of hypoglycemia in patients who have been diagnosed with CCHS have been proposed in previous publications. As noted above, most of the case reports reviewed have shown hypoglycemia associated with hyperinsulinemia. The most common mutation seen in CCHS is a PHOX2B expansion associated with hyperalanine [2]. In patients with this mutation, hypoglycemia stems from a genetic co-expression of Dopamine beta hydroxylase precursor (DBH). DBH causes an impaired trans-activation when associated with a Phox2b mutation, which leads to an abnormally low stimulation of the promoter. Overall, this leads to a decreased amount of DBH being transcribed [4]. In a study of DBH knockout mice, the animals did not exhibit an appropriate stress response. They demonstrated recurrent hypoglycemia, which was associated with hyperinsulinemia, much like those patients seen in the cases listed above [8]. Another proposed mechanism involves the function of the carotid body and glucose homeostasis. The carotid bodies contain neuroendocrine cells which function in maintaining glucose homeostasis. These cells, known as glomus cells, have been extensively studied and shown to influence blood glucose levels by means of autonomic control [6]. In the case of CCHS, glucose homeostasis appears to be effected due to the autonomic control of the carotid body being under regulation of the Phox2b gene [1]. The Phox2b gene controls a great amount of the visceral nervous system as well as certain areas of the CNS such as the retrotrapezoid nucleus, which is highly involved with the abnormal CO₂ sensation seen in CCHS. Due to that association, many of the regulatory functions of the autonomic nervous system are compromised when a mutation is present in the Phox2b gene [1]. Therefore, as to be expected, when the carotid body was removed in a group of dogs the result is hypoglycemia with associated hyperinsulinemia [5]. However, based on literature review, it appears that there have been no reports of human subjects who have undergone carotid body removal for various reasons who have exhibited signs of

recurrent hypoglycemia. In addition, there have been reports of two patients with CCHS who were shown to have physically small carotid bodies with a decreased number of glucose sensing cells [5].

Another topic of discussion is that of the coexistence of Hirschsprungs disease in the CCHS population and its potential association with underlying hypoglycemia. Hirschsprungs is commonly seen in association with CCHS when there is a non-polyalanyne expansion mutation. Among those patients with the most common mutation, polyalanine expansion of 20/27, only 20% have associated Hirschsprungs disease [7]. While in the previously presented case reports none of the patients were reported to have Hirschsprungs, an additional case report of a 39 week infant with both CCHS and Hirschsprungs, associated hypoglycemia was found [7]. No clear association of stand-alone Hirschsprungs with recurrent hypoglycemia appears to exist and this may prove be an area to further investigate.

4. Conclusion

While the underlying mechanism of hypoglycemia in patients with CCHS has not been determined, it is clear that there is an association with these diagnoses. It has now been reported that 6 patients, with the rare diagnosis of CCHS, have suffered from hypoglycemia associated with seizure on some occasion. This report should serve as a reminder to clinicians giving care to patients with CCHS that screening for hypoglycemia could prevent the patient from suffering from symptomatic hypoglycemia (seizures) and provide necessary treatment and monitoring for this complication.

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