Central Hypoventilation Syndrome and Hyperinsulinaemic Hypoglycaemia

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BACKGROUND

- Congenital central hypoventilation syndrome (CCHS) is a rare autosomal dominant condition due to transcription factor *PHOX2B* mutations.
- Characterised by alveolar hypoventilation, with symptoms of autonomic nervous system dysfunction, both hyperglycaemia and hyperinsulinaemic hypoglycaemia (HH) have also been reported.
- The mechanism of the dysglycaemia is unclear; autonomic dysfunction may underlie this dysregulation of glucose homeostasis.
- Studies in mouses showed that *PHOX2B* and *NKX2.2* form a non-cell-autonomous feedback loop that links the neural crest with the pancreatic epithelium, regulates the size of the beta-cell population, and impacts insulin-secretory capacity and energy homeostasis.

OBJECTIVE: To highlight the phenotype and treatment outcome of HH in children with CCHS.

METHODS: We report three children diagnosed with CCHS and HH and the challenges of their management.

	Case 1	Case 2	Case 3
Gestation and birth weight	40.3 weeks, BW = 2.81Kg	39.5 weeks, BW = 3.16 kg	39.8 weeks, BW = 3.375 kg
Sex	Female	Female	Female
Other clinical features	Continuous ventilation via tracheostomy, Hirschprung disease, ileostomy	Continuous ventilation via tracheostomy, tracheomalacia, ompalocele, GORD, autoimmune dysfunction (may not mount fever response)	Continuous ventilation via tracheostomy, seizures
Genetics	*PHOX2B*-expansion mutation of 7 alanines (dad mosaic carrier of *PHOX2B* alteration) Microarray: deletion within long arm of chr 6 -arr 6q14.1 (79,426,597-79,600,904)x1	*PHOX2B* mutation	*PHOX2B* mutation (20/27)
Age at diagnosis of HH	80 days	36 days	240 days
Results of hypoglycaemia screen	Glucose 2.5mmol/l Insulin <2mU/l C peptide 237 pmol/l NEFA 0.22 mmol/l BHOB 0.92 mmol/l	Glucose 1.6 mmol/l Insulin 28 mU/l C peptide 482 pmol/l NEFA <0.1mmol/l BHOB 0.3 mmol/l	Glucose 2.1 mmol/l Insulin 1.7 mU/l C peptide 147 pmol/l NEFA 0.52mmol/l BHOB <0.05 mmol/l
HH medications (max dose)	Diazoxide (6 mg/kg/day) Chlorothiazide (7.5mg/kg/day)	Diazoxide (3.4 mg/kg/day) Chlorothiazide (7.5mg/kg/day)	Diazoxide (11.3 mg/kg/day) Chlorothiazide (5.6 mg/kg/day)
Feeding regime at discharge	3 hourly	3 hourly	On demand
Age of last clinic review	2.74 years	1.1 years	8.83 years
HH medications at the last clinic review	Diazoxide (4.32 mg/kg/day) Chlorothiazide (3.6mg/kg/day)	Diazoxide (7.31 mg/kg/day) Chlorothiazide (7.3mg/kg/day)	Mediactions stopped at 5.5 years
Feeding regime at last clinic visit	On demand	Daytime: 4hourly Overnight: 7 hours continuous via gastrostomy	Regular diet
Fasting tolerance at last clinic visit	12.5 hours	8 hours	11 hours at 5.5 years

RESULTS

- All our cases had confirmed mutations in *PHOX2B,* two of whom were heterozygous for polyalanine repeat expansions (20/27).
- HH presented in infancy (range 30-240 days of life) with fasting hypoglycaemia; one case also demonstrated episodic post-prandial hypoglycaemia.
- All were diazoxide-responsive, dose range 5-11.3 mg/kg/day
- The case with post-prandial hypoglycaemia (case 2) required overnight gastrostomy feeds.
- Two cases remain on diazoxide at 1.1 and 2.7 years, while a third case was gradually weaned off by 5.5 years.
- All cases required long-term ventilation via tracheostomy had other characteristics of CCHS (Hirschsprung disease, autoimmune dysfunction) as well as other features (tracheomalacia, omphalocele, seizures).

CONCLUSIONS

- Dysregulated glucose homeostasis may be under recognised in CCHS.
- Both fasting and post-prandial hypoglycaemia can occur in children with CCHS.
- Our cases of CCHS-associated HH exhibited predominantly fasting hypoglycaemia, which could be related to the severity of their CCHS based on mutation status or may be directly related to mutation.
- Children with CCHS must be monitored closely for symptoms of hypoglycaemia and investigated for HH, including for post-prandial hypoglycaemia if concerns arise.
- Our case series highlights that diazoxide can be effective treatment; however dietary intervention may nonetheless still be necessary

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