Dysregulated glucose homeostasis in Congenital Central Hypoventilation Syndrome

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OBJECTIVE

Congenital Central Hypoventilation Syndrome (CCHS) is a rare disorder of respiratory control resulting from heterozygous polyalanine repeat expansions within the Paired-Like Homeobox 2B (*PHOX2B*) gene. A hypoglycaemic seizure in a 4 year old girl with CCHS, led to a more detailed examination of glycaemic control in a cohort of children with CCHS.

Objective: To describe glucose homeostasis in children with CCHS.

METHODS

An observational cross-sectional cohort study of glucose homeostasis in seven children (11 months to 12 years) with genetically confirmed CCHS was conducted. Glycaemic profiles were evaluated using a combination of Dexcom™ G4 continuous glucose monitoring (CGM), fasting studies and an oral glucose tolerance test (OGTT). CGM was also used to compare the response to Diazoxide and dietary intervention in the patient who presented with a hypoglycaemic seizure.

Human Research Ethics Council Reference number 17/QRCH/233

RESULTS

Table 1. Clinical characteristics of participants

	Age, Sex	Genotype[a]	Respiratory support	Cardiac dysautonomia	CNS disorders	GI dysmotility	Neural crest tumours
PT1	4y, F	20/28	Sleep-Trach	Yes[b]	No	Yes[e]	No
PT2	1y, F	20/24	Sleep-Trach	No	No	No	No
PT3	10y, F	20/24	Sleep-NIV	No	No	No	No
PT4	9y, M	20/24	Sleep-NIV	No	No	No	No
PT5	5y, M	20/24	Sleep-Trach	No	Yes[c]	No	No
PT6	8y, F	20/25	Sleep-NIV	No	Yes[c,d]	No	No
PT7	3m, F	20/24	Sleep-Trach	No	No	No	No

[a]Number of polyalanine repeats [b] Cardiac Pacemaker [c]Speech delay [d]Autistic Spectrum Disorder [e]Hirschsprung disease Trach= tracheostomy

Table 2. Summary of findings from inpatient formal fasting study

	Duration	BGL[a] nadir mmol/l)	Final BGL[a] (mmol/l)	Insulin mU/L)	FFA[b] (mmol/l)
PT1	20 hours	3.0	4.2	1.4	1
PT2	12 hours	3.1	3.1	1.3	1.2

[a]BGL = Blood glucose level [b]FFA = Free Fatty Acids (0.1 - 0.6 mmol/l)
Insulin and FFA measured at BGL nadir

Table 3. Summary of postprandial glucose fluctuations using Continuous glucose monitoring (CGM)

	Postprandial Glucose[a] Peak (mmol/l)	Postprandial Glucose[b] Nadir (mmol/l)
PT1	8.3	2.2
PT2	9.3	2.4
PT3	11.1	3.8
PT4	8.4	4.0
PT5	16.7	4.4
PT6	8.0	3.3
PT7	10.3	3.3

[a]Peak levels 1-2 hours post-prandially; [b]nadir levels 2-4 hours post-prandially.
Postprandial Hypoglycaemia = BGL ≤ 2.8mmol/L, Hypoglycaemia within 2-4 hours after a meal.
Postprandial hyperglycaemia = BGL of >7.8 mmol/L within first 2 hours after a meal.

Table 4. Oral glucose tolerance test

	Time (mins)	BGL[a] (mmol/L)	Insulin (mU/L)	Acylcarnitine profile	BOHB[b] (mmol/l)	FFA[c] (mmol/l)
PT 1	0	3.6		normal		
	60	5.7				
	120	2.2	2.4		0.27	0.57
PT 2	0	5.6		normal		
	60	10.1				
	120	2.6	1.1		0.11	

[a]BGL = Blood glucose level [b]BOHB = Beta Hydroxy Butyrate (<1.1mmol/l)
[c]FFA = Free Fatty Acids (0.1 - 0.6 mmol/l) OGTT performed with prescription of 1.75 g of Glucose/kg of body weight (maximum of 75 g) consumed < 5mins. Normal glucose tolerance = BGL <7.8 mmol/l at 120 minutes, glucose intolerance = BGL 7.8-11.0 mmol/l at 120 minutes.

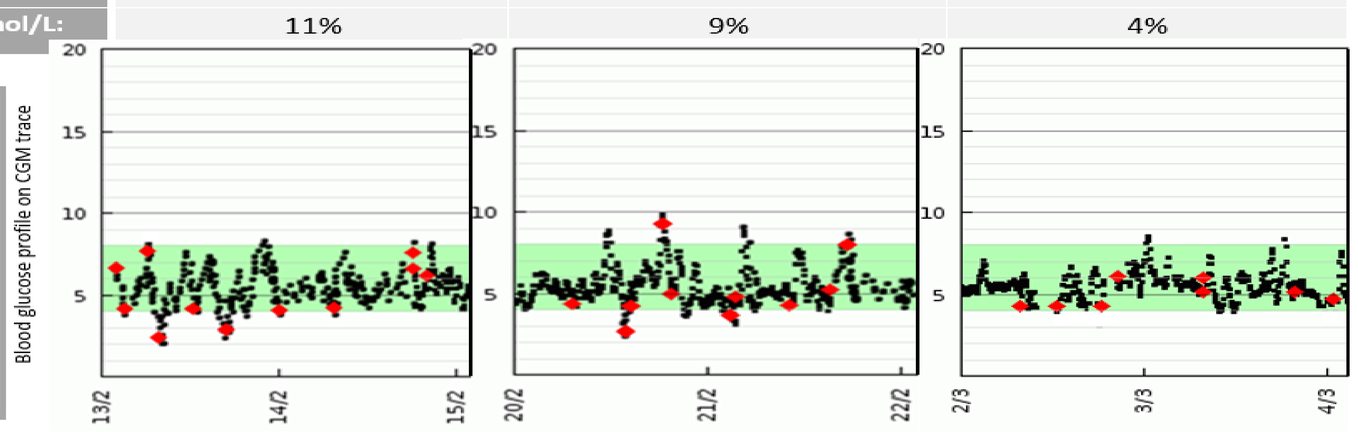
Table 5. Continuous Glucose Monitor Metrics

BLOOD GLUCOSE LEVEL	(A) BASELINE	(B) DIAZOXIDE	(C) LOW GI[a] DIET ONLY
Highest value (mmol/L):	8.3	11.7	9.7
Lowest value (mmol/L):	2.2	2.3	2.2
Period average (mmol/L):	4.6	6.2	5.4
Values > 7.8 mmol/L:	3%	15%	4%
Values 4-8 mmol/L:	86%	76%	92%
Values < 2.8 mmol/L:	11%	9%	4%

[a]GI, Glycaemic index

Definitions
•Hypoglycaemia = BGL ≤2.8mmol/L
•Postprandial hyperglycaemia = 1-2 hour postprandial BGL >7.8 mmol /l

OGTT
•Normal = BGL< 7.8 mmol/l at 120 mins
•IGT = BGL 7.8-11.0 mmol /l



Fasting study: PT1 and PT2 demonstrated normal blood glucose concentrations during fasting studies conducted in hospital and after an overnight fast prior to an OGTT. The remaining patients also had normal blood glucose levels after overnight fasting of at least 12 hours (4.1 – 5.3 mmol/L). *(Table 2 and 3)*

Continuous Glucose Monitor (CGM): Asymptomatic postprandial hypoglycaemia validated by glucometer readings (2.1mmol/L and 2.5mmol/L respectively) was detected in PT1 and PT2, occurring 2-4 hours following typical meals. *(Table 2 and 5).* Immediate postprandial hyperglycaemia was also demonstrated 1-2 hours following meals on CGM, with validation by glucometer testing (8 – 16.7 mmol/L) in 7/7 patients.

Oral Glucose Tolerance Test (OGTT): PT1 and PT2 underwent an OGTT at the cessation of their fasting study that demonstrated asymptomatic non-ketotic hypoglycaemia at 120 mins in the presence of detectable insulin levels. PT2 displayed initial hyperglycaemia (BGL 10.1mmol/L at 60 minutes). *(Table 4)*

Intervention: A low Glycaemic Index dietary intervention was associated with a reduction in the proportion of CGM readings < 2.8mmol/L when compared with baseline (4% versus 11%), without having an obvious effect on the proportion of CGM readings above 8mmol/L (4% versus 3%). Diazoxide (10mg/kg/day) treatment was also associated with a slight reduction in the proportion of CGM readings < 2.8 mmol/L when compared with baseline (9% versus 11%) however the proportion of CGM readings above 8 mmol/L increased (15% versus 3%). *(Table 5)*

CONCLUSIONS

Glucose variability may be unrecognised in CCHS, particularly in children with features of Autonomic nervous system dysfunction (ANSD). This report highlights the occurrence of hyperglycaemia as well as hypoglycaemia in CCHS. Given the challenges of recognising hypoglycaemia based on clinical symptomatology the use of CGM may be an appropriate method of screening. The observed normoglycaemia during fasting with increased post-prandial BGL variability is consistent with a dynamic dysregulation in the central autonomic control of insulin secretion. ANSD is likely to be influencing the responses that co-ordinate glucose delivery across the gut and peripheral insulin mediated glucose disposal. Dietary modifications may be more effective than Diazoxide in managing hypoglycaemia. The long-term consequences of dysregulated glucose homeostasis in this group are unknown.

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