Elevated transaminases in congenital central hypoventilation syndrome

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To the Editor:

Congenital central hypoventilation syndrome (CCHS) is a rare autosomal dominant genetic disorder of autonomic nervous system (ANS) dysfunction which affects approximately one in 148 000 to 200 000 live births [1, 2]. It arises from a mutation in the *PHOX2B* gene, typically involving polyalanine repeat expansion mutations or, less commonly, nonpolyalanine repeat expansion mutations [3]. People with CCHS are at risk of disorders affecting organs controlled by the ANS [4–8]. While the role of the ANS in liver function has been described previously [9, 10], to our knowledge, there is limited information on the association between CCHS and hepatic dysfunction. This study aims to describe the presence and clinical presentation of hepatic dysfunction in patients with CCHS. We hypothesise that patients with CCHS are at risk of hepatic dysfunction due to autonomic dysregulation.

We conducted a retrospective study on patients with confirmed diagnosis of CCHS at Children's Hospital Los Angeles (CHLA) from 2004 to 2021. The following data were collected: 1) demographics; 2) *PHOX2B* genotype; 3) clinical course; 4) associated ANS dysfunction; 5) liver function tests (total, direct and indirect serum bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (GGT)); and 6) liver synthetic function tests (prothrombin time, partial thromboplastin time, international normalised ratio and hypoalbuminaemia).

Patients who had any abnormal liver function or liver synthetic function tests were included in the initial analysis. None had previous diagnoses of inborn errors of metabolism, autoimmune or nonaccidental events that predisposed them to liver function abnormalities. The study was approved by the CHLA institutional review board (IRB). This was an observational study, and CHLA IRB confirmed that no consent to participate was required.

Of the 64 people with CCHS, 28 had liver function tests and 16 (57%) out of 28 had abnormal laboratory findings in at least one parameter. We defined ALT elevation ⩾1.3 times the upper limit of normal (ULN) as a significant marker of liver dysfunction, as this is considered abnormal in the clinical care setting. Of the 16 patients, three had a significant ALT elevation, six had elevated transaminases without a significant ALT elevation and seven did not have elevated transaminases. Clinical characteristics of the nine patients with elevations in ALT and/or AST are described in table 1.

The clinical courses of the three patients with ALT ⩾1.3×ULN are as follows.

Patient 1. This patient displayed an elevated ALT 1.4×ULN accompanied by elevated ALP and prothrombin time at age 3.5 years at hospital admission for increased ostomy output and dehydration. Although ALT and ALP resolved, elevated AST persisted upon discharge a week later. On readmission 2 weeks later for ileostomy stricture and partial small bowel obstruction, he had AST 1.2×ULN, ALT 1.2×ULN and elevated ALP which resolved after corrective stricture surgery. He was readmitted at 3 years 8 months for another stricture surgery, and post-operative labs showed AST 1.3×ULN, ALT 1.1×ULN and elevated ALP and hypoalbuminaemia that was not followed-up until 6 months later, at which time they had resolved. The patient continued to have occasional ALT or AST elevations up to 1.1×ULN with interval resolution for the next 13 years, during which his body mass index (BMI) percentile decreased steadily to the 6th percentile.

Shareable abstract (@ERSpublications)
Patients with CCHS who also have Hirschsprung disease, elevated or low BMI, or pulmonary hypertension may be predisposed to elevated transaminases and may need periodic follow-up of their hepatic function https://bit.ly/3uW7AUG

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TABLE 1 Clinical characteristics of subjects with abnormal elevations in transaminases (n=9)

Subject	Age at first abnormal lab test years	*PHOX2B* gene mutation	WFL/ BMI percentile	Ventilator support	Associated disorders	Condition at the time of liver function tests	ALT/AST	Time to normal labs
1	2.6	20/27 PARM	7	PPV (full-time)	Dysphagia, ocular abnormality, Hirschsprung disease	Presumed tracheitis (stool culture positive for adenovirus), ileostomy strictures	ALT 1.4×ULN AST 1.5×ULN	1 year
2	14.2	c.A945G NPARM	99	PPV (sleep only)	Constipation, NAFLD, diabetes, hypothyroidism, Hirschsprung disease	Stable; fatty liver on ultrasound	ALT 3.4×ULN AST 1.8×ULN	Did not resolve
3	0.4	20/25 PARM	84	PPV (sleep only)	Constipation, dysphagia, pulmonary hypertension	Pulmonary hypertension; on antibiotics for presumed sepsis	ALT 1.9×ULN AST 2.3×ULN	2 weeks
4	1.8	20/27 PARM	82	PPV (full-time)	Dysphagia, ocular abnormality, arrhythmia, hyperinsulinism, Hirschsprung disease	Found on pre-operative labs for diaphragm pacer surgery; stable	ALT 1.1×ULN	3 months
5	1.2	20/25 PARM	95	PPV (full-time)	Ocular abnormality, Hirschsprung disease	Hypoxic event (tracheostomy obstruction)	ALT 1.1×ULN	No repeat labs
6	2.3	20/27 PARM	42	PPV (full-time)	GORD, pulmonary hypertension, hyperinsulinism	Stable; admitted for management of CCHS	AST 1.1× ULN	No repeat labs
7	17.9	20/33 PARM	1	PPV (sleep only)	None	Seizure and hyponatraemia	AST 1.3×ULN	1 month
8	1.1	20/26 PARM	93	PPV (full-time)	Pulmonary hypertension, Hirschsprung disease	Pneumonia (*Pseudomonas* and *Serratia* cultures)	AST 2.0×ULN	3 years
9	1.1	20/25 PARM	88	PPV (sleep only)	Constipation, dysphagia, arrhythmia	Acute respiratory distress syndrome, parainfluenza, disseminated intravascular coagulation	AST 1.1× ULN	6 days

WFL: weight-for-length; BMI: body mass index; ALT: alanine transaminase; AST: aspartate transaminase; PARM: polyalanine repeat expansion mutations; PPV: positive pressure ventilation; ULN: upper limit of normal; NPARM: nonpolyalanine repeat expansion mutations; NAFLD: nonalcoholic fatty liver disease; GORD: gastro-oesophageal reflux disase; CCHS: congenital central hypoventilation syndrome.

Patient 2. At age 14 years, this patient's labs showed ALT 3.4×ULN, AST 1.8×ULN and elevated GGT during hospitalisation for a pulmonary exacerbation. She had a BMI in the 99th percentile, evidence of fatty liver on ultrasound and was diagnosed with nonalcoholic fatty liver disease (NAFLD) by magnetic resonance imaging elastography and liver biopsy. Over that year, she had three readmissions for pulmonary exacerbations, all with elevated transaminases. The abnormalities persisted for 1 year and did not show any interval resolution at the time of data collection.

Patient 3. The patient was diagnosed with CCHS at 5 months when he presented with hypoxic respiratory failure. He was on total parenteral nutrition and intralipid for 2 weeks and was previously on ceftriaxone for presumed sepsis. His admission weight-for-length was in the 3rd percentile. He had pulmonary hypertension on echocardiography. His initial tests were ALT 1.2×ULN and AST 1.4×ULN, which climbed to ALT 1.7×ULN and AST 1.8×ULN over the next few days. After 2 weeks, interval resolution of elevated transaminases occurred, but transaminases increased again a few days later, reaching ALT 1.9×ULN and AST 2.3×ULN. At that time, his weight-for-length was in the 84th percentile. His pulmonary hypertension resolved by age 6.5 months, and he was discharged with abnormal transaminases without follow-up liver function tests. At the time of data collection, his BMI was in the 99th percentile.

Preliminary observations show that Hirschsprung disease, abnormal BMI and pulmonary hypertension could be causing persistently elevated transaminases in people with CCHS. Patient 1 and patient 2 had Hirschsprung disease. Patient 2 developed NAFLD alongside a high BMI. Patient 3 had pulmonary hypertension, presented as underweight, and became obese over time.

In liver innervation in humans, sympathetic nerve fibres course into liver sinusoids while parasympathetic and sympathetic fibres surround the portal area [9, 10]. CCHS is a genetic disorder of ANS dysfunction and there have been reports of hyperinsulinism and dysregulation of glucose metabolism in these patients [8]. Polygenic ANS dysfunction has been linked to Hirschsprung disease [11]. Of the nine patients with elevated ALT and/or AST, five had Hirschsprung disease and two had hyperinsulinism. Two of the three patients with elevated ALT $\geqslant$1.3×ULN had Hirschsprung disease. We speculate that the dysfunction in the ANS in CCHS could contribute to the abnormal liver function.

Obesity is a recognised NAFLD risk factor, and abnormally low BMI has been linked to nonalcoholic steatohepatitis (NASH) and NAFLD [12, 13]. Abnormal BMI was seen in six of the nine patients with elevated transaminases. Of the three patients with ALT $\geqslant$1.3×ULN, one had BMI in the 99th percentile throughout the study, one presented with BMI in the 3rd percentile and became obese over time, and one maintained normal BMI but had a gradual decline to the 6th percentile. CCHS is a disease of ANS dysfunction, and the ANS is crucial for the regulation of bodyweight, as it mediates the sense of satiety after gastric distension [14]. The abnormal BMIs in our cohort could indicate evidence of ANS regulatory dysfunction leading to NASH-like liver disease.

Hypoxia, associated with pulmonary exacerbation and pulmonary hypertension, may elevate ALT/AST. Hypoxia signalling plays a role in hepatic lipid metabolism regulation, with some experiments indicating that hypoxia induces lipid accumulation in hepatocytes [15]. Some patients with persistently elevated transaminases presented during periods of pulmonary exacerbation; notably, their abnormal liver values did not always normalise before discharge. One-third of patients with elevated transaminases had pulmonary hypertension at the time of their elevated transaminases, and one patient had significantly elevated ALT $\geqslant$1.3×ULN.

A limitation of this study is that abnormal liver function tests were taken during acute illnesses. Many patients did not have follow-up labs, so it is possible that mildly elevated transaminases may have worsened, and that more significant elevations may have resolved. In addition, the cut-off for abnormal liver function was lower than what is usually used in clinical drug trials.

In summary, our study showed that some CCHS patients may have persistently elevated transaminases. Hirschsprung disease, abnormal BMI, and pulmonary hypertension may predispose these patients to continued liver function abnormalities, highlighting the importance of periodic follow-up of hepatic function.

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