

Full title: Post-prandial hyperinsulinaemic hypoglycaemia after oesophageal surgery in children

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Established facts

- Post-prandial hyperinsulinaemic hypoglycaemia (PPHH) or late dumping syndrome is a recognised complication of various gastric surgeries.
- In children, PPHH has been described almost exclusively as a postoperative complication of gastric fundoplication.
- There are very few paediatric case reports to confirm PPHH post esophageal repair, without any known precipitating factors such as gastroesophageal reflux surgery or associated microgastria.

Novel Insights

- PPHH is an unrecognised complication in children undergoing oesophageal atresia repair and hence it is important to be aware of this rare complication and screen these patients when are symptomatic.
- Continuous feeds might be the only option for PPHH if it is unresponsive to medical therapy, until it gradually lessens in intensity over time.

Abstract

Introduction: Post-prandial hyperinsulinaemic hypoglycaemia (PPHH) is a recognised complication of various gastric surgeries in children, but rarely reported after oesophageal atresia repair. We report two children diagnosed with PPHH post-oesophageal surgery and the challenges of their management.

Case 1: A 2-year-old boy diagnosed with oesophageal atresia at birth, was surgically repaired requiring six oesophageal dilatations the first year of life. At 11-months of age he manifested hypoglycaemic seizures and investigations confirmed PPHH. Acarbose and diazoxide trials failed. He was managed with 17-hours continuous gastrostomy feeds. Currently, he is 28-months-old with euglycaemia on daytime bolus gastrostomy feeds and overnight 12-hours continuous gastrostomy feeds.

Case 2: A 6-month-old girl diagnosed with Wolf-Hirschhorn syndrome and tracheo-oesophageal fistula, was surgically repaired, requiring monthly oesophageal dilatations. At 5-months of age she was reported to have hypoglycaemia and PPHH was confirmed. She responded to diazoxide and continuous nasogastric tube feeds, but developed pulmonary hypertension possibly diazoxide-induced. Subsequently diazoxide was stopped and normoglycaemia was secured via 20-hours continuous gastrostomy feeds.

Conclusion: PPHH may be an under-diagnosed complication in children undergoing surgery for oesophageal atresia. These children must be monitored closely for symptoms of hypoglycaemia and if there are concerns must be screened for possible PPHH. Our cases demonstrate that continuous feeding regimens might be the only therapeutic option, until PPHH gradually lessens in intensity over time.

Introduction:

Post-prandial hyperinsulinaemic hypoglycaemia (PPHH) or “Late Dumping Syndrome” is the effect of altered gastric reservoir function, abnormal post-operative gastric motor function and/or abnormal pyloric emptying mechanism. PPHH is a recognized complication observed after a variety of gastric surgical procedures such as vagotomy, pyloroplasty, gastrojejunostomy and laparoscopic Nissen’s fundoplication [1,2].

In childhood, the surgical treatment of gastroesophageal reflux by gastric fundoplication is the main cause of PPHH [2,3,4,5]. PPHH after oesophageal atresia repair without anti-reflux surgery is rare. In the literature there are three published cases [6,7] of children with oesophageal atresia who presented with PPHH without any known precipitating factors, such as gastroesophageal reflux surgery or associated microgastria. The possible mechanism is a disorder of gastric motor activity in patients following operative repair of oesophageal atresia [8,9].

In this article we report the initial symptoms, investigations and the therapeutic challenges in two children diagnosed with PPHH post-surgical repair of oesophageal atresia without anti-reflux surgery.

Case 1

An 11-month-old boy presented with an episode of seizure due to hypoglycaemia and consequently a head injury, with normal CT scan of the head. He was the first child of healthy, unrelated parents, with no family history of hypoglycaemia. Scans at 12 and 20 weeks were normal, but polyhydramnios was diagnosed at 32 weeks gestation. He was delivered by normal vaginal delivery at 38 weeks gestation weighing 2.5 kg (-1.9 SDS). He was found to have a long gap esophageal atresia (without fistula) and on day 3 of life, a gastrostomy was performed to facilitate feeding. At his first assessment, the gap was estimated to be 4.5 vertebral bodies and a second gap assessment at the age of 40 days confirmed a gap of 3 vertebral bodies. At the age of 3 months, the

oesophageal atresia was repaired. Furthermore, the baby was diagnosed with patent ductus arteriosus, which was medically treated. During the first year of life, he required six esophageal dilatations for strictures and was entirely gastrostomy fed.

Further biochemical investigations (table 1) at the age of 11-months, when he presented with hypoglycaemic seizures, confirmed PPHH as he developed hypoglycaemia (capillary glucose 2.6 mmol/l and laboratory glucose of 2.3 mmol/l), preceded by detectable insulin of 3.0 mU/L at 90 minutes of a mixed meal test. However, the child had a normal fast tolerance and no hypoglycaemia on protein load test. His metabolic screen (including acylcarnitine profile, plasma amino acids and urine organic acids) and Array-CGH chromosomes were normal.

Initially he was treated with acarbose, which was gradually increased up to a maximum dose of 75mg in three divided doses, and a feeding regimen of 3 hourly bolus gastrostomy feeds during the daytime and continuous feeds overnight. He showed no response and therefore acarbose was stopped and he was commenced on diazoxide, but unfortunately he was unresponsive to this. Finally, he was managed with eighteen hours of continuous gastrostomy feeds and two breaks of three hours during the day.

He is currently asymptomatic after 16 months of follow-up, with normal growth and developmental progress. He is on 12-hours continuous feeds overnight, with two small bolus feeds (100ml) during the day given over an hour, and solid food on demand orally. On this feeding regimen, he achieves normoglycaemia during a 24-hour glucose profile (capillary glucose ranges from 3.5-5.0 mmol/l) and he is able to fast for 10 hours.

Case 2

A 6-month-old female was antenatally diagnosed with Wolf-Hirschhorn syndrome. She was born at 38⁺³ weeks of gestation, with birth weight of 2040 grams (-2.72 SDS) by an elective C-section in poor condition, requiring resuscitation. At birth she was found to have oesophageal atresia and tracheoesophageal fistula that was surgically repaired on the second day of life. A prolonged stay in the neonatal unit followed this in order to establish oral feeds. Meanwhile she was diagnosed with a duplicated gall bladder, short long bones, double superior vena cava with atrial septal defect and hypoplastic kidneys; all of these features were consistent with Wolf-Hirschhorn syndrome, which was confirmed by microarray whereby a micro-deletion of the short (p) arm of chromosome 4 was found [4p16.3p 16.2 (51,120-5,150,630)x1].

Over the following months she developed strictures at the anastomosis site, requiring oesophageal dilatation. During the post-operative period she exhibited increased sleepiness and, when tested at the age of 5 months, she was found to be hypoglycaemic.

Further biochemical investigations (table 1) confirmed PPHH as she developed hypoglycaemia (laboratory glucose of 1.9 mmol/l), along with high insulin of 17.6 mU/L and high C-peptide of 2439 pmol/L, at 60 minutes post bolus NGT feed. She was able to fast 8 hours without developing hypoglycaemia and this ruled out fasting hyperinsulinaemic hypoglycaemia. Her metabolic screen (including acylcarnitine profile, plasma amino acids and urine organic acids) was normal. She had a gastric emptying study that was reported as normal.

Initially, she was commenced on diazoxide (maximum dose of 7mg/kg/day in three divided doses), and showed a good response to it. However this triggered pulmonary hypertension and eventually diazoxide had to be stopped. Finally, a gastrostomy was performed and PPHH was managed with 20 hours continuous gastrostomy feeds and 2 hourly breaks twice per day, while she was allowed small amounts of puree orally in order to preserve her orality. Her repeat Echocardiogram after 2 weeks showed complete resolution of pulmonary hypertension.

On her most recent visit at the age of 9 months, she has stable blood glucose concentrations on 20 hours continuous gastrostomy feeds and she is thriving well. She has been thoroughly investigated for severe and persistent GORD symptoms by an impedance study that showed non-acid GORD and an oesophagogastrroduodenoscopy that confirmed gastritis with eosinophilic

infiltration. Finally, her symptoms were controlled with prokinetic therapy and currently she requires fewer oesophageal dilatations.

Discussion

PPHH or late dumping syndrome manifests as non-specific symptoms 1-3 hours after a meal, with signs and symptoms of hypoglycaemia. The pathogenesis is likely related to the early development of hyperinsulinaemic (reactive) hypoglycaemia [1]. Calabria *et al* demonstrated that the exaggerated insulin response to a meal, seen in children with post prandial hypoglycaemia after gastric surgery, is at least in part due to the effects of GLP-1 on the pancreatic β -cell, as the blockade of the GLP-1 receptor with exendin(9–39) blunted the insulin response even in the presence of hyperglycaemia (2).

In childhood, the surgical treatment of gastroesophageal reflux remains the commonest cause of PPHH [3,4,5,10]. Other causes of PPHH in children caused by abnormal gastrointestinal anatomy are very rare and include congenital microgastria, partial or total gastrectomy, accidental intraduodenal or jejunal administration of bolus feeding, or inadequate meals with high osmolarity, as well as rare cases of generalized autonomic dysfunction [3, 11]. It is also rarely described as idiopathic PPHH in children without a known underlying cause [12].

In children with oesophageal atresia, most reported cases of PPHH have been related to the surgical treatment of associated gastroesophageal reflux [13,14]. There are very few paediatric case reports that report PPHH post-oesophageal repair without any known precipitating factors such as gastroesophageal reflux surgery or associated microgastria [6,7]. In those children PPHH can appear either acutely, with life threatening symptoms such as hypoglycaemic seizures. Thus, it is important to screen children at risk in the postoperative period. Early detection can lead to earlier treatment and prevention of brain damage from severe hypoglycaemia.

Management of PPHH in childhood continues to be challenging as a variety of therapies have been used including uncooked cornstarch [15], pectin [5], octreotide [16], acarbose [3], diazoxide [17], and change of feeding regimens (pertaining composition, volume and rate) [18]. All of these therapeutic options have limited responses as observed in our first case, or have side effects as observed in our second case that developed diazoxide-induced pulmonary hypertension [19]. Therefore, children with PPHH may require continuous feeds to achieve glycaemic control, until this condition becomes milder and improves over time, as shown by our first case.

PPHH can occur after surgical repair of oesophageal atresia without anti-reflux surgery and it may present postprandially with classical hypoglycaemic symptoms or may be asymptomatic. Also, both cases presented with hypoglycaemia after esophageal dilatation, we do not know whether there will be any long-term impact on precipitating hypoglycaemia. Thus, it is important to monitor closely for symptoms of hypoglycaemia children treated surgically for oesophageal atresia in the postoperative period, in order to rapidly identify those affected with PPHH and consequently commence treatment and thereby prevent potential brain injury due to severe hypoglycaemia.

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Table 1. Clinical features, biochemical investigations and treatment response in two patients with PPHH.

	Case 1	Case 2
Type of gastrointestinal malformation	Oesophageal atresia (Long gap) No fistula	Oesophageal atresia Tracheoesophageal fistula
Age at surgery (days)	90	2
Type of surgical procedures	Delayed primary repair following Replogle suction/irrigation of the upper pouch, gap assessments, gastrostomy insertion. Six oesophageal dilatations the first year of life	Closure of tracheo-oesophageal fistula Repair of oesophageal atresia Monthly oesophageal dilatations
Dysmorphic features	None	Wolf-Hirschhorn Syndrome
Age at presentation	11 months	5 months
Symptoms at presentation	Hypoglycaemic seizure	Incidental episode of hypoglycaemia
Feeding plan at presentation	3 hourly bolus feeds of 100ml (CHO content: 7.7%)	1-2 hourly bolus NGT feeds (CHO content: 7.7%)
Provocation test. Time of hypoglycaemia. Results.	Mixed meal test 90 minutes capillary glucose 2.6mmol/L, Insulin 3.0mU/L	Mixed meal test 60 minutes capillary glucose 1.9mmol/L, insulin 17.9mU/L
Response to Acarbose (max dose)	Unresponsive (25mgrams every 8 hours)	Not tried (due to maternal concerns regarding side effects)
Response to Diazoxide (max dose)	Unresponsive (5 mg/kg/day)	Responsive (7 mg/kg/day) Discontinued due to Pulmonary hypertension
Response to Continuous Feeds	Yes	Yes
Feeding regimen	12 hours continuous feed 3hourly breaks twice a day	20 hours continuous feeds Very small oral intake day time 2hourly breaks twice a day