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Frequency of Abnormal Glucose Tolerance Test Suggestive of Dumping Syndrome Following Oesophageal Atresia Repair

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ABSTRACT

Objectives: Dumping syndrome (DS) is mostly described as a complication of antireflux surgery in oesophageal atresia (OA) but we previously reported 2 cases of DS before any other surgery in infants operated at birth for OA. The objectives of the present study were to assess the prevalence of abnormal oral glucose tolerance test (OGTT) at 3 months of age in infants operated at birth with type C OA, to describe symptoms and clinical features, and to assess risk factors in infants presenting with abnormal OGTT suggestive of DS.

Methods: A prospective case series study including infants with type C OA without fundoplication, born between 2013 and 2016 in 8 centres was conducted. An OGTT was performed between 2.5 and 3.5 months. Abnormal OGTT was defined as early hyperglycaemia (>1.8 g/L until 30 minutes; >1.7 g/L between 30 minutes and 2 hours; and >1.4 g/L between 2 and 3 hours) and/or late hypoglycaemia (<0.6 g/L after 2 hours).

Results: Eleven of the 38 OGTT (29%) showed abnormalities. None of the patients' demographics (birth weight, sex, prematurity, associated malformation, use of enteral nutrition) or conditions of the surgery tested was associated with abnormal OGTT. No clinical sign was specific for it.

Conclusions: DS should be considered in every infant operated at birth for OA presenting with digestive symptoms. No risk factor was predictive for abnormal OGTT. An OGTT to screen for potential DS around 3 months of age should be considered in infants born with EA.

Clinical Trial name and registration number: DUMPING NCT02525705

Key Words: early or late dumping, infants, oral glucose tolerance test, postprandial hyperglycaemia, postprandial hypoglycaemia

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What Is Known

- Abnormalities of oral glucose tolerance test and dumping syndrome in children are mostly described after fundoplication.
- We previously reported 2 cases of infants operated at birth for oesophageal atresia and who presented with dumping syndrome before any fundoplication.
- The frequency of abnormal oral glucose tolerance test in this population is unknown.

What Is New

- Prevalence of abnormal oral glucose tolerance test was 29% in infants operated at birth for oesophageal atresia.
- Dumping syndrome is a frequent early complication of oesophageal atresia and should be systematically screened.

Although rare, oesophageal atresia (OA) is the most frequent malformation of the oesophagus (1/4000 live births in France) (1). OA is classified into 5 different types depending on the existence or localization of the tracheo-oesophageal fistula (TOF). Type C is the most frequent type (approximately 85%) where the upper oesophageal pouch is blind and TOF is situated between the lower pouch and the trachea. Complications occurring early after surgical repair of OA include anastomotic leakage, anastomotic stricture, gastro-oesophageal reflux disease (GORD), growth failure, recurrent TOF, and tracheal and respiratory complications (2–4).

Abnormal oral glucose tolerance test (OGTT) is a well-known complication of fundoplication in children with GORD (5,6). To date, abnormal OGTT in children with OA has only been described as a postoperative complication of fundoplication (7). We previously reported 2 cases of dumping syndrome (DS) with abnormal OGTT in infants operated at birth for type C OA who had no history of fundoplication. They presented with watery stools containing glucose at the age of 3 months and with hypoglycaemic seizures at 6 months of age, respectively (8). Dastamani et al also reported 2 cases of postprandial hypoglycaemia after OA repair (9). DS is important to recognize because it can lead to failure to thrive, discomfort, pain, refusal to eat, hypotonia, or seizure.

We aimed to test the hypothesis that abnormal OGTT is frequent in patients operated at birth for OA but who did not undergo antireflux surgery. The main objective of our study was

to assess the frequency of abnormal OGTT at the age of 3 months in a population of patients operated at birth for a type C OA. The secondary objectives were to describe symptoms and clinical characteristics of patients with abnormal OGTT and to assess risk factors.

METHODS

This was a multicentre prospective study, conducted from March 2013 to September 2016 in 7 French University tertiary centres affiliated to the French Reference Center of Chronic and Malformative Esophageal Diseases (Grenoble, Lille, Lyon, Nantes, Paris, Rennes, and Strasbourg) and 1 Australian Reference University Centre (Sydney).

To be eligible for the study, patients had to be operated at birth for type C OA in 1 of the 8 aforementioned centres between March 2013 and June 2016; to be aged 3 months \pm 2 weeks and to weigh \geq 4.150 kg at the time of OGTT (to remain below the maximal blood volume withdraws allowed for infant); to be off any prokinetic treatment for at least 72 hours before OGTT. Patients with conditions potentially associated with DS (microgastria, dysautonomia, small bowel surgery) or affecting glycaemic regulation (neonatal diabetes, hyperinsulinism), and patients treated with a drug that could modify gastric motility (domperidone, erythromycin, baclofen) and that was not discontinued at least 72 hours before OGTT were not included in the study. If previously taken, acid suppressive medication (proton pump inhibitors/H2 antagonists) was continued during the study.

Every consecutive patient, born in 1 of the 8 participating centres, who accepted to participate in the study were included. At inclusion, information about the perinatal period, personal and family history, esophageal malformation characteristics, and OA surgery and peri- and postoperative complications were collected.

The evaluation visit was planned between 2.5 and 3.5 months. Clinical history from the inclusion visit, feeding type, and current or previous treatment were collected; a clinical examination was carried out including anthropometric measurements (weight, height, and head circumference).

Parents were asked for the presence of unspecific gastrointestinal symptoms that were presented by their child: clinical signs of oesophagitis (pain during a meal seen by irritability, crying, back arching); colic (inconsolable crying $>$ 3 hours a day, $>$ 3 days a week, during $>$ 3 weeks (10,11)). We also recorded clinical signs suggestive of early hyperglycaemia (occurring in the first hour after oral intake): postprandial diarrhoea (occurrence of liquid stools within 1 hour following meal), abdominal pain, bloating, and clinical signs suggestive of late hypoglycaemia (occurring between 1 and 3 hours after oral intake): pallor, hypotonia, agitation, seizures, somnolence, sweating. The latter are related to a reactive hypoglycaemia.

OGTT was performed after a minimum of 4 hours fasting. A dose of 1.75 g/kg of glucose was given orally. Capillary blood glucose concentration was measured every 30 minutes from T₀ to T₁₂₀ (2 hours) then every hour until T₂₄₀ (4 hours). To assess reliability of capillary blood glucose concentration, a venous blood glucose concentration (COBAS 8000, Roche Diagnostics, Meylan, France) was simultaneously sampled at the same time of the 2 first measures. OGTT was interrupted if the patient had hypoglycaemia on blood testing ($<$ 0.6 g/L), clinical signs of hypoglycaemia, or discomfort. DS was defined by the occurrence of an early hyperglycaemia ($>$ 1.8 g/L from ingestion to 30 minutes; $>$ 1.7 g/L between 30 and 60 minutes; and/or late hypoglycaemia [$<$ 0.6 g/L] according to Guthrie et al (12). If OGTT showed DS, patients were prescribed cornstarch for at least 6 months to control blood glucose concentration before discharge from hospital.

The pain due to blood sampling was controlled by sampling while in parents' arms, giving glucose or using anaesthetic cream (EMLA). Volume and number of blood samples were restricted to 9 mL/kg (13).

Data were reported in case report forms and anonymized, monitored and centrally analyzed by the Paediatric Clinical Investigation Center of the Lille University Hospital.

Statistical Analysis

The number of patients to include—calculated a priori—was 40 to get enough statistical power (ie, 85%), based on a 30% expected prevalence of DS in infants with OA (6). Statistical analyses were performed using GraphPad Prism 7.

Results were expressed as mean \pm standard deviation (SD). Characteristics of each group were compared using Student *t* tests or Mann-Whitney test for quantitative values and Fisher exact test or Chi-square test for qualitative values. *P* values $<$ 0.05 were considered statistically significant. OGTT with at least 5 out of 6 glycaemia results were considered in the analysis.

Ethics

The study was approved by the Ethical Committee in France (Comité de Protection des Personnes Nord-Ouest France and in Australia (Sydney Children's Hospital Network Human Research Ethics Committee), and received authorization no 2010-A00217-32 of the French Agency for Drug Safety. It is recorded with number NCT02525705 in the *ClinicalTrials.gov* Web site. Written informed consent was obtained from parents. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

RESULTS

Population Characteristics

None of the screened patients had any exclusion criteria. Forty-one infants were included, of whom 38 completed OGTT. No OGTT had $>$ 1 glycaemia result missing. The characteristics of the study population are detailed in Table 1. OGTT could not be performed in 3 patients because of failure of complete ingestion of the glucose solution ($n=1$) and blood sampling failure ($n=2$). None of the 38 included patients developed symptoms during OGTT.

Frequency of Abnormal Oral Glucose Tolerance Test

Eleven of the 38 infants (29%) had abnormal OGTT: 5 had early hyperglycaemia (Fig. 1A), 4 had late hypoglycaemia (Fig. 1B), and 2 had both early hyperglycaemia and late hypoglycaemia (Fig. 1C).

Characteristics of Infants With Abnormal Oral Glucose Tolerance Test ($n=11$)

Mean (\pm SD) gestational age was 38 ± 1.7 weeks. Mean (\pm SD) weight at OGTT was 5.4 kg (± 0.64) which was not different from mean weight of patients with normal OGTT: 5.1 kg (± 0.76) ($P=0.18$) (Table 1). At least 1 associated malformation was present in 6 infants (Table 1), including 2 VACTERL syndromes. Considering surgery, none of the 11 patients had late or difficult

TABLE 1. Clinical characteristics of the population

	Total population (n = 38)	DS+ (n = 11)	DS- (n = 27)	P
Birth weight, kg (mean ± SD)	2.8 (±0.58)	2.8 (±0.56)	2.8 (±0.69)	0.98
Prematurity (GA <37 wk)	10	1	9	0.11
Associated malformation, s	20	6	14	0.99
Enteral bolus nutrition	4	3	1	0.065
Clinical signs suggestive of early or late DS	20	7	13	0.38
Age at OGTT, days (mean ± SD)	93.5 (±12.3)	96.5 (±7.4)	93.5 (±17.9)	0.67
Weight at OGTT, kg (mean ± SD)	5.16 (±0.74)	5.4 (±0.64)	5.1 (±0.76)	0.18

DS+ = patients with dumping syndrome, DS- = patients without dumping syndrome, OGTT = oral glucose tolerance test, SD = standard deviation.

anastomosis, 2 patients were considered as anastomosis under tension by their surgeon. Postoperative course was complicated for only one of them who presented with anastomotic leakage. In the 11 patients with abnormal OGTT, 4 were asymptomatic, including 3 with late hypoglycaemia underlying that frequency and severity of symptoms were not higher in the OGTT+ group. Both of the 2 patients with early/late DS were symptomatic, 4 of the 5 patients with early hyperglycaemia had at least 1 clinical sign suggestive of late hypoglycaemia and none suggestive of early hyperglycaemia, and the only symptomatic patient with late hypoglycaemia had clinical signs suggestive of it and inconsolable crying.

n = 14 patients, including 3 VACTERL syndromes. Considering surgery, 1 of the 27 patients had a late anastomosis, 1 had a difficult anastomosis, and 4 patients' anastomoses were considered under tension by the surgeon. Postoperative course was complicated for 5 of the patients of whom 2 presented with anastomotic leakage. Thirteen of the infants with normal OGTT (48%) had clinical signs, of whom 5 had signs suggestive of early hyperglycaemia, 1 had only signs suggestive of late hypoglycaemia, and the 7 others had a combination of signs suggestive of both. None of these 27 infants had any discomfort, symptoms, complication, or trouble to tolerate the prolonged fasting induced by OGTT.

Characteristics of Infants With Normal Oral Glucose Tolerance Test (n = 27)

Nine infants were preterm and mean gestational age was 37 ± 2.5 weeks. At least 1 associated malformation was present in

Factors Associated With Abnormal Oral Glucose Tolerance Test

In our population, no significant difference was found between the 2 groups—with or without abnormal OGTT—with

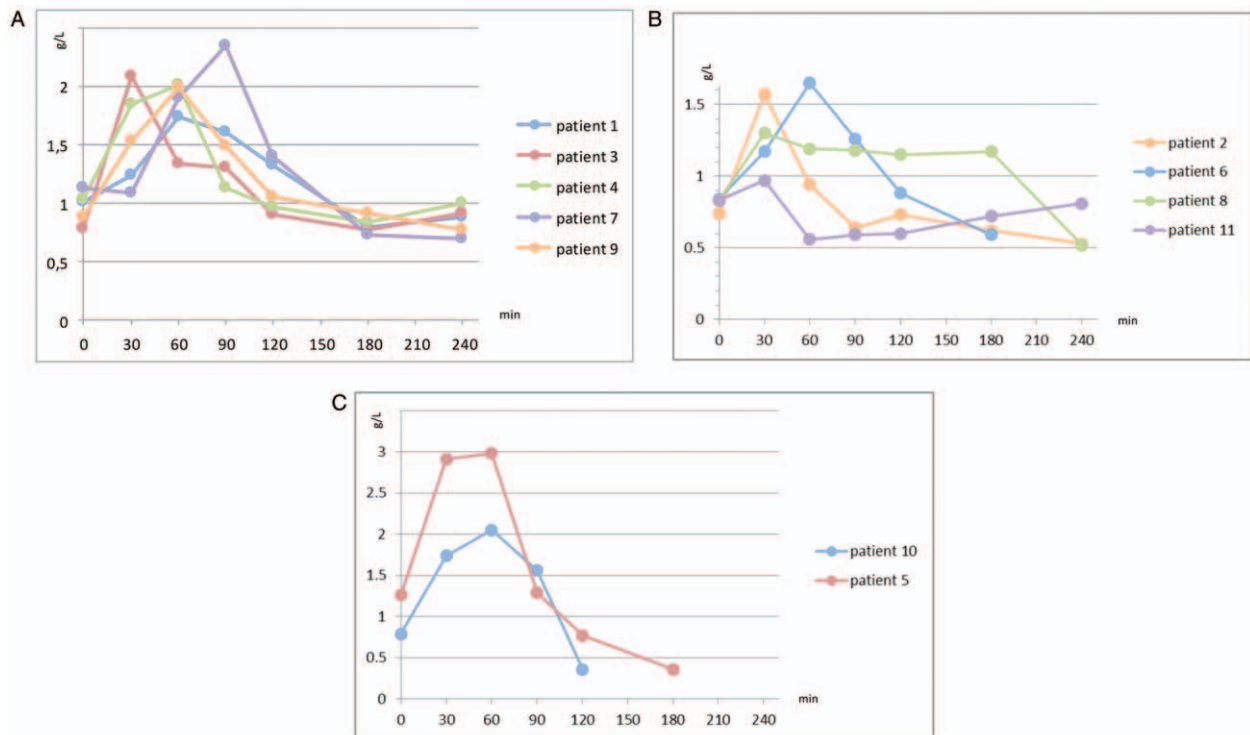


FIGURE 1. Glycaemic variation with time in the 11 patients of the study with abnormal oral glucose tolerance test (OGTT). x Axis: time after glucose ingestion (min), y axis: glycaemia (g/L). A, Glycaemic variation with time in the 5 patients with early DS. B, Glycaemic variation with time in the 4 patients with late DS. C, Glycaemic variation with time in the 2 patients with early/late DS.

respect to sex, prematurity, birth weight, associated malformation, enteral bolus nutrition, weight at time of OGTT, characteristics of the surgical repair, postoperative complication, or presence of early or late clinical signs (Table 1).

DISCUSSION

The results of the present study show that abnormal OGTT is frequently observed at the age of 3 months in infants operated at birth for type C OA, even in the absence of antireflux surgery. They also suggest that the above-mentioned case reports of DS in OA infants without prior fundoplication were not fortuitous and there is a need to consider DS as a complication of OA. As suggested by the recent European Society for Paediatric Gastroenterology Hepatology and Nutrition-North American Society for Pediatric Gastroenterology, Hepatology and Nutrition consensus on OA, DS can occur in these children and manifest as various and unspecific symptoms (feed refusal, nausea, retching, pallor, lethargy, diaphoresis, watery diarrhoea) (2).

No factor linked to the surgical repair (ie, type of anastomosis, tension in the anastomosis, difficult anastomosis) could be identified. DS could be related to accidental vagal trauma inherent to surgical repair or to intrinsic dysmotility (esophageal and/or gastric) associated with the underlying digestive malformation (14–17). Indeed, vagus nerve is suspected to be congenitally abnormal in its branching or course (14) that could increase the risk of surgical damage to the vagus (18). Accidental vagotomy causes rapid liquid emptying leading to an inflow of hyperosmolar nutrients in the small bowel that are responsible for a shift of fluid from intravascular compartment to the lumen and hypotension, tachycardia, or syncope. The hyperosmolarity causes distension of small bowel that is responsible for the digestive symptoms. Abnormalities of intrinsic motility involve both excitatory and inhibitory intramural nerves of the oesophagus. In fact, development of myenteric plexus of the oesophagus and stomach in OA is suspected to be abnormal (larger ganglia, thicker nerves fibres) (15), which can affect gastric function (18). Evidence of abnormal OGTT in isolated congenital TOF (where dysmotility similar to OA has been reported) (17) before surgical repair could help clarify the underlying mechanism. Further knowledge on the pathophysiology of gastric motor function abnormalities in OA could facilitate clinical management of DS. A comparative evaluation of gastric emptying in patients with OA with and without DS would be informative. Unfortunately, such assessments are not easily performed in children of this age due to lack of validated tests.

No clinical signs specific of abnormal OGTT could be identified in the present cohort in which some patients in both groups were symptomatic. In children, clinical signs of abnormal OGTT are mostly early and nonspecific (feeding difficulties, abdominal pain, irritability, nausea, crying) due to the osmotic movements of fluids from the intravascular compartment to the intestinal lumen or related to the late postprandial hypoglycaemia (19,20). All these symptoms are frequently encountered in OA, due to esophageal dysmotility, gastric emptying abnormalities, GORD, or anastomotic stricture, which makes DS difficult to suspect clinically. Although they are not specific for DS, it is of note that bloating and abdominal pain were frequently observed in the early postprandial period in our patients with OA, as were signs of hypotonia and agitation late after meal.

There is no available study evaluating the long-term history of OGTT abnormalities, irrespective of its underlying cause. Clinical reports suggest that abnormalities are likely to be transient, especially in patients with OA. It may be due to adaptive changes in the enteric nervous system leading to resolution (21,22). No systematic follow-up of OGTT abnormalities could be performed in

our series. A second OGTT performed 6 months after the first one in 3 patients of the OGTT+ group who no longer had any clinical signs of abnormal OGTT while treated with cornstarch, turned out to be normal. Based on these results, we suggest to treat every patient with abnormal OGTT and to check—off treatment—whether OGTT abnormalities persist between 6 months and 1 year of age.

Untreated DS may be harmful. Postprandial diarrhoea, abdominal pain, and bloating are associated with feeding disorders and poor quality of life of children/parents. Repeated hypoglycaemia can result in life-threatening complications as seizures and loss of consciousness, and lead to neurological damage in a developing brain (23,24). In addition, DS can be responsible long term for anorexia and/or growth failure that could not be tested in our population because of the lack of hindsight. All these complications highlight the need for early diagnosis, treatment, and follow-up of infant with DS and abnormal OGTT. This is particularly critical as the current study suggests that no specific symptoms can identify these patients.

We chose to look for abnormal OGTT at 3 months of age, where full oral feeding is usually achieved in a vast majority of patients with OA. This was indeed the case for most (90%) of our population. Earlier transient abnormalities, however, could have been missed.

To screen for these abnormalities, we chose to use OGTT, which is considered as the criterion standard of DS (25,26). Diagnostic criteria of DS are, however, not consensus based. Several authors consider that spontaneous postprandial hypoglycaemia alone is diagnostic of DS (25), whereas others advocate the need for performing OGTT in all cases (5,6). There are no established cutoff values for OGTT and we used the norms as proposed by Guthrie et al (12), which can be questionable. No previous research was achieved to define norms of OGTT in infants with dumping syndrome, and today, such a protocol would not be ethically acceptable. The discontinuous measurements of glycaemia are an inherent limitation of the OGTT. We artificially distinguished early and late DS to better correlate symptoms and glycaemia changes, but we cannot exclude that the discontinuous measures of glycaemia resulted in erroneous categorization of patients into those with early/late DS. The diagnosis of such abnormalities could benefit from the use of continuous glucose monitoring (27).

CONCLUSIONS

Our data show that patients with OA with no prior history of fundoplication are at risk for developing DS. As it can be responsible for serious short- and long-term consequences, and symptoms are nonspecific, we propose OGTT to be considered for infants with OA in the first few months of life. If DS is found, close monitoring and therapy with cornstarch may be considered for at least 6 months. Further data in a larger cohort of patients are needed to support these findings and provide more clear recommendations.

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