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Letter to the editor

Perioperative management of glucose and lactate homeostasis in paediatric glycogen storage disease type 1a coming for living donor liver transplant

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SUMMARY

Glycogen storage disease (GSD) is a rare inborn autosomal recessive inherited disorder of carbohydrate metabolism. There are multiple types of GSD, out of which GSD type I, III, IV, VI, and IX show liver involvement. Due to a deficiency of glucose-6-phosphatase enzyme in this disorder, glycogen stored in the liver cannot be metabolised, leading to poor tolerance to fasting and increased risk of hypoglycaemia and lactate acidosis. Inability to metabolise glycogen leads to progressive accumulation of glycogen in liver leading to hepatic adenoma (HA) and/or hepatocellular carcinoma (HCC). Liver transplantation (LT) has been proposed as the preferred therapy for these types of GSD, as it helps in correcting the primary hepatic enzyme defect, thereby improving the quality of life and reducing the risk of HCC. Herein we report our experience of perioperative management of paediatric GSD type 1a (Von Gierke's disease) patient undergoing living donor liver transplant (LDLT).

Introduction

Glycogen storage disease 1a is an autosomal recessive inborn disorder of carbohydrate metabolism caused by deficiency of glucose-6-phosphatase enzyme which plays an important role in glycogenolysis and gluconeogenesis [1]. Deficiency of this enzyme leads to impairment of glycogen metabolism and glycogen accumulation in liver, kidney and intestinal mucosa. The patients commonly present with growth retardation including delayed puberty and have doll-like facies. Metabolic derangements include hypoglycaemia leading to hypoglycaemic seizures, and raised triglycerides, uric acid and lactates. In addition, impaired platelet function and anaemia is seen along with hepatomegaly and renomegaly. Osteoporosis is a common feature too. A worrisome feature commonly noted is hepatic adenomas and/or HCC [2]. Overall incidence of the disease is ~1/100,000 but in Ashkenazi Jews the incidence is relatively high 1/20,000 [1]. Aim of conservative treatment is to maintain normoglycemia and normolactatemia to avoid long term complications. It includes dietary restrictions like avoiding fruits, dairy and foods containing sucrose and lactose [2]. Use of cornstarch is advised every 3–4 h to avoid hypoglycaemia. Most common indication for LT has been hepatic adenomas since the adenomas in GSD type 1 are known to progress to HCC. Besides hepatic adenomas [3] other indications for LT are growth failure and poor metabolic control [4].

Case details

A 13-year-old female child born of 2nd degree consanguineous marriage weighing 24.1 kg, height 117 cm, BMI of 17.6 kg/m^2 maintained on cornstarch diet, presented with history of recurrent hypoglycaemia, hyperlactatemia, metabolic acidosis, ketoacidosis and, hypertriglyceridemia. She had doll-like facies, was severely stunted with height being less than the third percentile and an absence of secondary sexual characteristics was noted.The patient had history of convulsions in the neonatal period for which she had received treatment. She also had hyperuricemia in the past, however no features suggestive of gouty arthritis were observed. Uric acid level was nearly normal as she was on tab allopurinol 100 mg twice daily. Abdominal examination revealed hepatomegaly, renomegaly and enlarged venous channels which was further corroborated by ultrasound scanning of abdomen. Bone densitometry revealed osteopenia. PET scan confirmed the presence of multiple bipolar hepatic adenomas (HA) none of which were larger than 5 × 5 cm. Alpha fetoprotein was normal (1.74 ng/ml), serum triglycerides were elevated to 2748 mg/dl. Preoperative cardiac workup included 2D echocardiogram and a 12-lead ECG. Both of these were normal and showed no structural or functional anomalies. Rest of the laboratory parameters were ~~also~~ within normal limits. Liver biopsy was done which was suggestive of glycogen storage disease. Clinical diagnosis of GSD type 1a was confirmed by the presence of G6PC gene mutation (pathogenic c.508C>T). Patient was advised to continue cornstarch, maintain adequate hydration, avoid long duration of fasting and avoid food items that contain sucrose and lactose. In order to bring down the triglycerides levels tab finofibrate 145 mg half tablet three times a day was started as hypertriglyceridemia is known to cause pancreatitis.

The donor was the child's mother, a 47-year-old ASA-I status female. All her laboratory and radiological parameters were normal making her a suitable candidate for live liver donation. The recipient's triglycerides showed a declining trend to 1461 mg/dL and she was admitted 48 h prior to surgery for optimisation. On the day of surgery the recipient was given oral cornstarch in the morning at 5am and kept nil by mouth after that. The patient was on overnight intravenous 10 % dextrose infusion at 70 ml/h, which was increased to 100 ml/h in view of fasting. Recipient was wheeled into the operation theatre only after transection of donor liver was started. This helped to curtail the duration of surgical stress which could be detrimental in view of this metabolic anomaly. Once

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inside the OT standard monitoring equipment was attached and patient was induced. Two arterial lines were inserted after induction; one in left radial and other one in right femoral artery. Intravascular access included a 5.5Fr central venous line, and a 7Fr hemodialysis catheter, both inserted in right internal jugular vein. Cardiac output monitoring was done throughout surgery using minimally invasive technique. ABG was done regularly throughout the surgery. 10 % dextrose infusion was continued at the rate of 100 ml/h throughout surgery. At the beginning of the surgery lactate was 2.6 mmol which gradually increased and reached its peak 10 min post-reperfusion at 12.1 mmol which came down to 10.9 mmol at end of surgery. Blood sugar level immediately after induction was 101 mg/dl and reached a peak value of 223 mg/dl 10 min post-reperfusion; Inj insulin 2 units bolus i.v. was given and by the end of surgery sugar levels had come down to 155 mg/dl. Estimated blood loss during surgery was 800 ml and she received 600 ml PRBC and 20 ml FFP during the intraoperative period. Patient was hemodynamically stable at the time of induction but post incision blood pressure (BP) started falling and inj noradrenaline 0.03 mcg/kg/min infusion was started which gradually increased to 0.1 mcg/kg/min by the end of dissection phase of surgery. During anhepatic phase further fall in BP was noted and inj phenylephrine 0.15 mcg/kg/min infusion was started. Reperfusion was managed with additional boluses of inj adrenaline. Requirement of vasopressors started decreasing post-reperfusion. Inj phenylephrine was gradually tapered off and patient was shifted to ICU with inj noradrenaline infusion at 0.15 mcg/kg/min. Patient received a left lobe graft weighing 450 g with a graft to recipient weight ratio (GRWR) of 1.89.

Patient was extubated on postoperative day (POD) 1, the lactates were ~~rapidly~~ declining and blood sugar values were in normal range. As per our institutional protocol considering the high risk of thrombosis in small paediatric arteries, we start heparin infusion in all paediatric LT recipients on POD 1 targeting an APTT level of 60–80 s. This is continued till POD 7 to ensure vascular patency, and the same was followed in this patient. Rest of the postoperative period was uneventful and patient was discharged from the hospital on POD 14.

Discussion

GSD type 1 is an inborn error of carbohydrate metabolism [1]. GSD type 1 patients are known to have multiple metabolic derangements like hypoglycaemia, hypertriglyceridemia, hyperuricemia, hyperlactatemia and Vitamin D deficiency. They also have bleeding diathesis and anaemia; in addition progressive accumulation of glycogen leads to hepatomegaly and renomegaly. Renal involvement is seen as proximal tubular dysfunction, glomerular dysfunction or renal failure. Polycystic ovaries are noted in female patients after 4 years of age [2], though this was not noted in our patient. Most common indication for LT in these patients is hepatic adenoma, HCC, growth failure and poor metabolic control [3,4]. Our patient suffered from all the metabolic derangements enumerated above leading to a poor quality of life. In addition, she had multiple hepatic adenomas. Literature reports 70–80 % incidence of adenomas by second decade of life and progression to HCC is noted despite good metabolic control [2]. Hence, in a patient with multiple adenomas LT should be considered [2–4].

Along with the routine challenges faced during paediatric LDLT like temperature control, fluid and electrolyte management; perioperative management of paediatric GSD coming for LDLT poses a distinct challenge of its own. As these patients need meticulous metabolic management in the perioperative period, importance of care by multidisciplinary team cannot be over-emphasised. In our case patient was admitted to hospital two days prior to surgery for pre-operative optimisation. As fasting for longer duration can lead to lactic acidosis, exogenous carbohydrate supply should be initiated, and it should be more than the estimated glucose requirement [5]. Our patient was receiving corn starch to prevent hypoglycaemia which was continued. Dose recommended for young children is 1.6 g/kg of cornstarch every 3–4 h and 1.7–2.5 g/kg every 4–5 h for older children, adolescents and adults [2]. In our patient 10 % dextrose intravenous infusion was started at 70 ml/h (3–4 ml/kg/h) [5] 24 h prior to LDLT with the target of keeping blood sugar >80 mg/dl. Intravenous fluids should be continued till oral feeding is restarted, ringer lactate should be avoided perioperatively.

One of the primary concern in Von Gierke's disease is hypoglycaemia and hyperlactatemia [2]. Glucose and lactate metabolism are closely interrelated. Apart from long duration of fasting leading to hyperlactatemia there are multiple factors during liver transplantation which can contribute to development of hyperlactatemia [6]. Surgery related stress and medications used during liver transplantation can lead to increase in endogenous lactate production due to increase in metabolic demand. Vasopressors are one of the frequently used medications during liver transplantation and these can lead to relative ischaemia and anaerobic metabolism. Adrenaline on the other hand is known to exert different metabolic effects on pancreatic islet cells, liver and muscle cells leading to increased lactate production. These metabolic responses are relatively less pronounced with noradrenaline or phenylepinephrine (a selective alpha1 agonist); hence these vasopressors were the preferred vasopressors in our case. These patients lack the ability to convert lactate into glucose by gluconeogenesis in the liver, kidney, and intestine due to this enzymatic defect; therefore, clearance of lactate in these patients is dependent upon a combination of renal clearance, metabolic clearance in the brain and respiratory compensation to maintain physiological pH. Finally in the context of liver transplantation blood loss during surgery can also lead to hyperlactatemia secondary to anaerobic metabolism; also clamping of portal vein and inferior vena cava during anhepatic phase will lead to raised lactates because of anaerobic metabolism.

Propofol should be avoided in view of hypertriglyceridemia, therefore we used inj thiopentone 5 mg/kg intravenous for induction. Though the exact aetiology of bleeding diathesis in Von Gierke's disease is unknown, multiple factors have been suggested in its development. These include platelet dysfunction, decreased platelet adhesiveness, and abnormal aggregation [2], dysfunctional von Willebrand factor and/or decreased von Willebrand factor antigen [7]. Majority of the patients with Von Gierke's disease will also have anaemia by the time they reach adulthood [2]. Anaemia in Von Gierke's disease is multifactorial [2], these factors include bleeding diathesis,restricted nature of diet, renal involvement, poor metabolic control, hepatic adenomas. These two hematological findings can complicate LDLT necessitating multiple blood products transfusion. Studies have shown that in patients with Von Gierke's disease good metabolic control achieved through infusions of glucose and total parenteral nutrition corrected the bleeding time and *in vitro* platelet function, suggesting that coagulation defects were secondary to metabolic abnormalities [2]. Deamino-8-D-arginine vasopressin and antifibrinolytics are used for treatment of platelet dysfunction/ von Willebrand disease but deamino-8-D-arginine vasopressin must be used cautiously in this group of patients as it carries a risk of fluid overload and hyponatremia when used along with intravenous dextrose administration [2]. Vitamin D deficiency is frequently found in these patients leading to osteopenia and fractures [8]. Organomegaly and osteopenia mandate extra care while positioning and padding which was diligently followed in our patient.

In patients with Von Gierke's disease kidney involvement is common and can manifest in the form of proximal tubular dysfunction, hypercalciuria, nephrolithiasis, or frank renal failure [2]. Citrate supplementation is usually used to prevent hypercalciuria. Potassium citrate is preferred over sodium citrate as higher sodium levels are linked with greater urinary calcium excretion and it can also result in systemic hypertension [2]. Thiazide diuretic is another treatment option available which enhances reabsorption of calcium and decreases calcium concentration in urine [2]. Our patient never had any history of proximal renal tubular acidosis or nephrolithiasis but had insignificant microalbuminuria. This microalbuminuria can progress to frank proteinuria.

Chronic proteinuria can lead to glomerular injury through induction of chemokines and inflammatory pathways [2]. In a recent study it was shown that renal failure was the most common complication with an incidence of 24 % in patients with GSD 1a undergoing LT and 21 % required dialysis [9] and these findings can further get complicated by postoperative immunosuppressives. In view of these findings throughout perioperative period multiple reno-protective measures were taken in the form of maintaining adequate hydration and urine output, during the surgery 0.5 g/kg of inj mannitol was given i.v. slowly over a period of 30–45 min before the clamping of inferior vena cava, inj N-acetyl cysteine infusion was used throughout surgery. With the help of these protective measures urine output was in the range of 2–3 ml/kg/h throughout surgery. In the postoperative period immunosuppression was started with minimal dose and serum creatinine was checked regularly. Patients pre-operative serum creatinine was 0.29 mg/dl, on POD 1 and 2 it was 0.19 and 0.15 mg/dl, respectively. After starting tab tacrolimus on POD 2 it gradually increased to 0.33 mg/dl on POD 12 then plateaued and at the time of discharge it was 0.29 mg/dl. 6months post LDLT her serum creatinine is 0.28 mg/dl.

Involvement of kidneys in GSD I, postoperative renotoxic immunosuppression and the finding that LT alone was unable to prevent the progression of glomerulosclerosis has led to the recommendation of combined liver-kidney transplant by a few researchers [4]. However, the increased risk associated with dual organ transplant and the use of tacrolimus which is comparatively less nephrotoxic makes combined liver-kidney transplantation an option only if kidneys are significantly compromised [4]. In our patient preoperative renal functions were within normal range hence we considered the option of LDLT.

In some patients pulmonary hypertension has also been reported [10]. Though the exact mechanism is not known several risk factors have been suggested in the pathogenesis of pulmonary arterial hypertension (PAH) and these include drugs, portal hypertension, HIV infection, genetic susceptibility, collagen vascular diseases, congenital systemic-pulmonary cardiac shunts and abnormal production of vasoconstrictive amines such as serotonin [10]. Since patients with PAH are either asymptomatic or have nonspecific symptoms diagnosis of PAH was delayed in patients with Von Gierke's disease and many patients have fatal outcomes within months. Therefore, a high level of suspicion is needed to diagnose PAH in Von Gierke's disease patients. Any patient complaining of chest pain or syncope should be immediately screened for PAH with trans-thoracic echocardiography. In patients suffering from Von Gierke's disease PAH occurs in the second or third decade of life, suggesting that long-term metabolic abnormalities may contribute to the latency of PAH [10]. Our patient never had these symptoms and 2D echocardiograpam showed no structural abnormality or pulmonary hypertension. 2D echocardiograph repeated during postoperative period also showed no signs of PAH.

Unlike GSD II and III heart is not the primary affected organ in GSD I. Systemic hypertension is the most common abnormality seen in GSD I patients and is usually seen in patients having renal disease [2]. Our patient did not have any clinical features of hypertension and preoperative ECG and 2D echocardiogram did not reveal any cardiac hypertrophy or other abnormalities.

Conclusion

GSD is known to involve multiple organs and causes multiple metabolic derangements. Liver transplant is a good therapeutic option for these patients as it provides an opportunity for catch up of growth and improved quality of life by better metabolic control. It also reduces the chances of hypoglycaemic incidents and HCC occurrence. The perioperative management of Von Gierke's disease coming for LDLT is quite challenging. A multidisciplinary team can greatly aid in achieving good metabolic control and avoiding catabolic stressors. In view of increased incidence of postoperative renal complications, care should be given to adequate management of perioperative hydration and postoperative immunosuppression.

CRediT authorship contribution statement

Annu Sarin Jolly: Conceptualization, Supervision. **Vidyadhar Metri:** Conceptualization, Data curation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sanjay K. Goja:** Conceptualization, Supervision. **Manoj K. Singh:** Conceptualization, Supervision, Writing – review & editing. **Varun Mahabaleshwar:** Conceptualization. **Sahana Shankar:** Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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