Case Report

Glycogen storage disorder Type IXa and congenital hypothyroidism: A novel association

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ABSTRACT

Glycogen storage disease (GSD) is a disorder of glycogen metabolism and GSDs are classified according to the enzyme deficiency and the affected tissue. Previously, an association of thyroid autoimmunity and hypothyroidism in patients with GSD has been reported. Here, we are presenting a rare association of congenital hypothyroidism with GSD IXa in a child who presented with progressive abdominal distension and hepatomegaly. GSD was suspected clinically and was confirmed by whole-exome sequencing.

Key words: Glycogen storage disease Type IX, Glycogen storage disorder, Hypothyroidism

Glycogen storage disease (GSD) is a disorder of glycogen metabolism, resulting from deficiencies of various enzymes or transport proteins of the glycogen metabolism pathway, which cause excessive accumulation of glycogen in tissues. GSDs are classified according to the enzyme deficiency and the affected tissue. Increased prevalence of thyroid autoimmunity and hypothyroidism in patients with GSD has been reported previously in the literature [1]. However, association between congenital hypothyroidism (CH) and GSD has not been previously reported. Here, we present a child who was known to have CH and was diagnosed to have GSD IXa, when he presented at 1½ years of age with progressive abdominal distension. On evaluation, he was found to have hepatomegaly; therefore, GSD was suspected clinically, which was confirmed by whole-exome sequencing.

CASE PRESENTATION

A boy aged 1½ years, born at term, of a non-consanguineous marriage, presented with history of motor developmental delay and progressive abdominal distension. Symptoms suggestive of hypoglycemic episodes were not found. Mother was diagnosed with glucose intolerance, pregnancy-induced hypertension, and hypothyroidism during pregnancy, and baby was delivered by emergency caesarean section.

He was diagnosed with CH at 15 days of life when he presented with lethargy and jaundice. His thyroid-stimulating hormone (TSH) was 150 mIU/ml (1.7–9.1) and T4 was 0.7 mcg/dl (5.4–17). Neck ultrasound demonstrated absent thyroid gland in the eutopic location (Fig. 1a) and technetium scan showed no tracer uptake (Fig. 1b). He was started on thyroxine at 12mcg/kg/d and euthyroid state was achieved by 8 weeks. Liver function tests (LFT) showed elevated liver enzymes aspartate aminotransferase (SGOT)-120 IU/L (16–67), alanine aminotransferase (SGPT)-85IU/L (16–63), and gamma-glutamyl transpeptidase (GGT)-376IU/L (23–174) with high unconjugated bilirubin 15.94 mg/dl (4–8) levels. The abnormal liver functions were thought to be secondary to hypothyroidism and no further investigations were done.

At 1½ years of age, he presented to the pediatric gastroenterology outpatient department with increasing abdominal distension and motor development delay. His fine motor and social milestone were appropriate for the age. His gross motor development quotient was 66%.

On examination, his abdomen was uniformly distended and liver was palpable 5 cm below the right costal margin. He had no jaundice or splenomegaly. His neurologic examination was normal except for mild generalized hypotonia. His length was 77 cm (3rd centile; Z score of – 2), weight was 9.7 kg (15th centile; Z score – 1), and weight for height Z score was between 0 and 1, and head circumference 47 cm (Z score 0).

Liver ultrasound revealed hepatomegaly with subtle-altered echogenicity. LFT's showed moderately elevated SGOT 738 mg/dl; SGPT 834 mg/dl; and GGT 283 mg/dl, with normal albumin levels. Triglycerides were found to be elevated 164 mg/dl (90–110). Creatinine phosphokinase (CPK) – 52 IU/L (31–152), lactate – 2 mmol/L (<2), and uric acid – 3.5 mg/dl (1.7–5.0) levels were normal. Amino acids and acylcarnitines in blood by tandem

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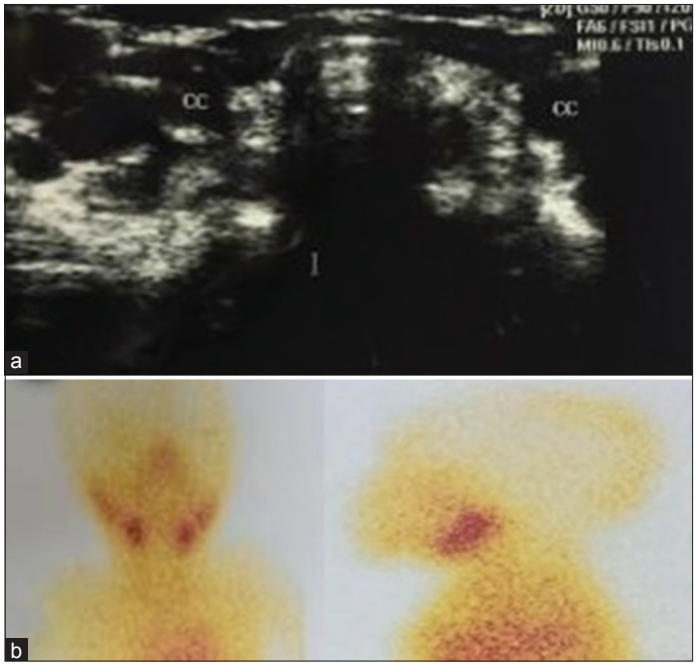

Figure 1: (a) Ultrasound of the neck demonstrating absent thyroid gland in the eutopic location and (b) technetium scan showing no tracer uptake in the region of the thyroid

mass spectrometer were normal and urine organic acid estimation by gas chromatography/mass spectrometry was normal. Based on the above clinical and biochemical profile, possibility of GSD was considered. Proband DNA was analyzed by next-generation sequencing (NGS) for a panel of genes, with particular attention to genes causing GSDs. The results of NGS showed hemizygous missense variation in exon 9 of PHKA2 gene, confirming the diagnosis of GSD Type IXa.

Management included frequent meals high in protein along with corn starch (CS) supplementation. CS dose was titrated by checking mid-night and early morning blood glucose levels. The blood glucose was targeted between 70 and 100 mg/dL. The blood glucose levels were monitored at home by parents using a glucometer. With the above management, his growth improved, and hepatomegaly started regressing. He also caught up with developmental milestones. He has been maintained on 6 mcg/kg/d of thyronorm and is euthyroid as of last follow-up at the age of 2 years with a TSH of 0.4 mIU/L and fT4 of 1.5 ng/ml

DISCUSSION

GSD-IX is a group of disorders characterized by a deficiency of the enzyme phosphorylase kinase comprising four subtypes; GSD-IXa, IXb, IXc, and IXd. GSD-IXa and GSD-IXc are caused by the deficiency of phosphorylase kinase in the liver. Both share the common clinical features, except that GSD-IXc tends to be severe with rapid progression to cirrhosis. GSD-IXb is secondary to phosphorylase kinase deficiency in the liver and muscle. GSD-IXd is characterized by phosphorylase kinase deficiency of the muscle (liver is not affected) [2].

GSD-IXa is estimated to occur in 1 in 100,000 (25% of all GSD cases) [3]. Signs and symptoms begin in early childhood. Children present with hepatomegaly, short stature, growth retardation, raised transaminases, elevated triglycerides, and occasional ketotic hypoglycemia during periods of fasting. These children usually show improvement in signs and symptoms with age. Development catch-up can be seen and adults reach normal height.

Our patient had raised transaminases at 2 weeks of age when he was admitted with neonatal jaundice. The raised transaminases were attributed to hypothyroidism and no further evaluation was done. Combination of indirect hyperbilirubinemia and raised hepatic transaminases has been reported in children with CH [4]. He had hepatomegaly and elevated triglycerides, but he never had symptomatic hypoglycemia. His CPK levels and echocardiogram were normal, indicating that there was no muscle involvement.

Occasional reports suggesting an increased risk of thyroiditis in GSD-1b patients have been published. Increased autoimmunity in GSD-1b patients has been suggested as a factor for such association [1]. Recent research suggests that increased autoimmunity risk in GSD-1b is secondary to reduced glycolysis in T-cells resulting in impaired regulatory T-cell function [5]. Glycolysis has a major role in the induction and suppressive function of human and mouse T regulatory cells [6]. Glycolysis controls the induction of human regulatory T-cells by modulating the expression of FOXP3 exon 2 splicing variants [7].

In our patient, CH was clearly related to the "agenesis" of thyroid gland. No such association between GSD-IXa and thyroid agenesis has been published so far in the literature to the best of our knowledge. Since our patient had CH associated with GSD, we hypothesize that there may be an embryological link between the two conditions. Both CH and GSD can have a significant impact on developmental milestones. Thyroid hormone requirement may be relatively higher in the presence of significant transaminase elevation with relatively more protein-bound T4 and less available free T4.

Our patient presented only with liver enlargement and elevated transaminase levels. Similar presentation has been described previously [3]. Hypoglycemia may not be an overt symptom in children with GSD-IXa, as gluconeogenesis and fatty acid oxidation pathways are intact. Our patient did not manifest hypoglycemia anytime. This has been observed in previous case reports too [8]. Due to the mild clinical symptoms, the diagnosis of GSD-IX can be easily missed. The average age of diagnosis of GSD-IX is around 6 years [9]. Physicians need to have a high degree of clinical suspension for the same. It is always prudent to evaluate raised transaminase levels further till we get an answer. With the wider availability of NGS panels, the diagnosis of GSD's has become easier.

CONCLUSION

We reported an association between CH and GSD-IXa for the 1st time and we suggest an embryological link between the two conditions. The diagnosis of GSD-IXa can be easily missed; therefore, one needs to have a high index of clinical suspicion. Thyroid hormone requirement may be relatively higher in the

presence of significant transaminase elevation with relatively more protein-bound T4 and less available free T4.

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