

Case Report

The First Reported Case of Down Syndrome Co-existing with Glycogen Storage Disease

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Abstract Although the association of Down syndrome with many diseases, such as autoimmune disorders and congenital malformation, has been frequently reported, association with metabolic diseases has not been reported in the literature thus far. Here, we presented a patient with Down syndrome coexisting with glycogen storage disease who could not be extubated due to marked hypotonia to emphasize that a wide spectrum of clinical entities can accompany Down syndrome.

Key words Childhood; Down syndrome; Glycogen storage disease

Introduction

Down syndrome (DS) is a genetic disease associated with various other diseases, including cardiac anomalies, immune and autoimmune diseases such as digestive system disorders, hepatic diseases, Celiac disease, autoimmune chronic hepatitis, sclerosing cholangitis, thyroid diseases such as Hashimoto's thyroiditis and Graves' disease, and type 1 diabetes mellitus.^{1,2} Glycogen storage diseases (GSD) are a group of inherited metabolic disorders characterised by accumulation of abnormal glycogen in muscle, the liver, or both. More than 10 types of GSD, each caused by a specific enzyme defect, have been identified. Symptoms

include hypoglycaemia, lactic acidosis, muscle weakness, convulsions, growth retardation, and hepatomegaly.

Although autosomal recessive inheritance is observed, association with another genetic disease has not been reported.^{3,4} Similarly, association of Down syndrome with a metabolic disease has not been reported yet. This 2-month-old boy who had severe hypotonia causing extubation failure is the first case of Down syndrome coexisting with GSD.

Method and Findings

A 2-month-old boy with birth weight of 3330 g who was delivered by spontaneous vaginal delivery from a 42-year-old woman (third pregnancy) was transferred to the paediatric intensive care unit (PICU) from the neonatal intensive care unit. In the anamnesis, it was found that he was intubated due to respiratory distress developed immediately after birth and underwent mechanical ventilation. It was also found that he received surfactant therapy for respiratory distress and phototherapy for hyperbilirubinaemia.

On admission to the PICU, the patient had poor health status with marked hypotonia and mongoloid facial appearance. On auscultation, breathing sounds were

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attenuated in both lungs. The liver was palpable 3 cm below the ribs, and other system examinations were normal. In the blood biochemistry, the following values were obtained: blood urea nitrogen, 13 mg/dL; glucose, 46 mg/dL; creatinine, 0.9 mg/dL; Na, 136 mmol/L; K, 5.2 mmol/L; Cl, 101 mmol/L; AST, 803 U/L; ALT, 788 U/L; CK, 8847 U/L; CK-MB, 566; uric acid, 4.3 mg/dL; and LDH, 1889 U/L. Several weaning trials were performed with noninvasive mechanical ventilation; however, the patient could tolerate extubation for only short periods of time and was reattached to mechanical ventilation. The patient was not able to be weaned from the ventilator due to marked hypotonia and insufficient respiratory effort.

Genetic testing was reported as trisomy 21. Hepatomegaly, elevated muscle and liver enzymes, and hypoglycaemia episodes during follow-up suggested a GSD. In the biochemistry evaluation following 8 hours of fasting, the following results were found: fasting blood glucose, 43 mg/dL; total cholesterol, 139 mg/dL; triglyceride, 367 mg/dL; uric acid, 2.3 mg/dL; plasma lactate, 27.3 mg/dL, plasma pyruvate, 1.2 mg/dL, ammonia, 53 mmol/L; and negative urine ketone. Elevation in the muscle and liver enzymes persisted during follow-up. The myocardium was considered to be normal. Hypoglycaemic episodes during follow-up and hepatomegaly suggested a metabolic disease, and metabolic panel was studied in the patient. Blood amino acids, urinary amino acids, urinary organic acids, amino acid by tandem mass, and acylcarnitine analysis were normal. Cranial magnetic resonance imaging was also normal.

A GSD was considered for the patient; thus, a liver biopsy was performed that revealed the presence of glycogen with PAS positive staining of hepatocytes (Figures 1 & 2). This finding was reported to be compatible with GSD. Genetic testing for Pompe's disease was found to be normal. An echocardiography in month 6 of life revealed no cardiomyopathy. It was considered that presence of failure to thrive, hepatomegaly, elevated liver and muscle enzymes, hyperlipidemia, and lack of prolonged hypoglycaemic episodes were compatible with type IIIA GSD. Enzyme analyses for a differential diagnosis between type Ia and IIIa GSD were not performed. A genetic analysis for type I GSD was reported as negative.

During PICU follow-up, weaning trials were performed; however, the patient could tolerate extubation only for short periods of time. The patient became ventilator dependent and died due to septic shock on month 7 after admission.

Discussion

Here, we described an infant with DS who presented with severe hypotonia, hypoglycaemia, hepatomegaly, and elevated liver enzymes and who was diagnosed as GSD. Genetic testing confirmed trisomy 21, whereas a histopathological examination of the liver biopsy was reported to be compatible with GSD. This is the first report of a patient with an association of these two genetic entities.

Many diseases have been reported in association with Down syndrome, including autoimmune diseases and cardiac disorders.¹ However, the association of Down syndrome with metabolic disease or GSD has not been reported in the literature thus far.

GSDs are a group of inherited metabolic disorders characterised by the accumulation of abnormal glycogen in muscle, the liver, or both. More than 10 types of GSD, each caused by a specific enzyme defect, have been identified. Symptoms include hypoglycaemia, lactate acidosis, muscle weakness, convulsions, growth retardation, and hepatomegaly.⁴ In this patient, hypotonia, hypoglycaemia, abnormal hepatic function tests, and elevated muscle enzymes suggested a GSD involving muscle and liver tissue,

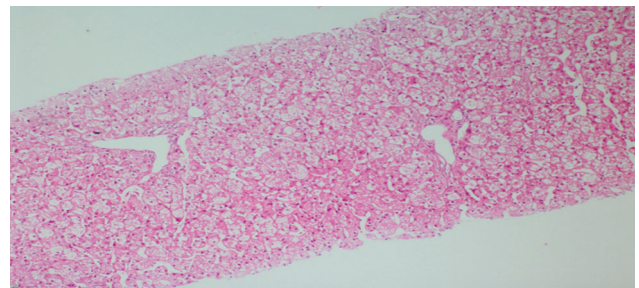


Figure 1 Disrupted relationship between portal and central veins and presence of hydropic degeneration in the liver biopsy.

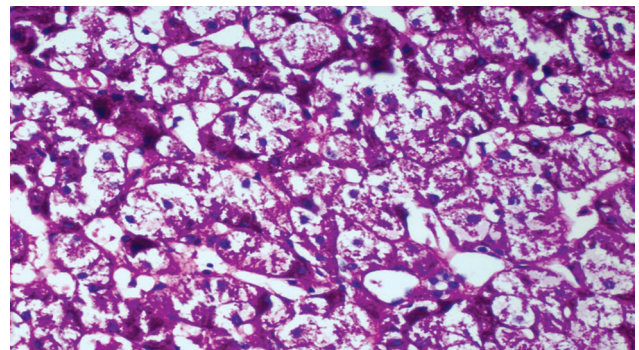


Figure 2 PAS positive accumulation in the liver biopsy.

which was confirmed by PAS positive staining in a liver biopsy. Although hypotonia causing extubation failure in our patient is a finding associated with DS, it is also seen in GSDs with muscular involvement. In particular, hypotonia is marked in type II GSD (Pompe's disease).³ No cardiomyopathy was detected in a baseline echocardiography. However, it was reported that cardiomyopathy may develop at a later stage of Pompe's disease; thus, the echocardiography was repeated in the patient, and genetic testing was ordered. The results of the echocardiography and genetic testing excluded Pompe's disease. In addition, the diagnosis of Pompe's disease was excluded due to the presence of hypoglycaemia attacks following fasting periods.

The presence of hepatomegaly, lactic acidosis, and elevated liver and muscle enzymes in addition to hypoglycaemic episodes and hypotonia, suggested type Ia GSD. The presence of hypoglycaemic episodes, lactic acidosis, and hyperlipidemia suggested type Ia GSD in the patient. However, a genetic analysis for type Ia GSD was found to be negative. Patients with type Ia GSD should regularly receive adequate amounts of exogenous glucose because they can rapidly develop severe hypoglycaemia, marked hypertriglyceridemia, hyperuricaemia, and elevated lactate levels.⁴ Mild hypoglycaemia after fasting in our patient excluded the diagnosis of type Ia GSD.

Mild hypoglycaemia after 8 hours of fasting suggested a type III GSD. In children with a type IIIa GSD, hypoglycaemia, hepatomegaly, slight hypotonia in infancy, and delayed growth are observed.⁵ Although phenotypic alterations in our patient were related to DS, midface hypoplasia with a depressed nasal bridge and a broad upturned nasal tip, indistinct philtral pillars, and bow-shaped lips with a thin vermilion border were described in patients with type IIIa GSD.⁶ Normal urine ketone during hypoglycaemia can also be seen in type III GSD, although it is rare. However, lactic acidosis seen after fasting period in our patient is not typically observed in type III GSD.⁷ An AGL gene and debrancher enzyme analysis for type III GSD was not performed due to technical limitations.

Severe hypotonia, muscular atrophy, and neuronal involvement can be seen in the congenital form of type IV GSD. The childhood form mainly progresses with myopathy and cardiomyopathy. However, hypoglycaemia can be seen only when hepatic cirrhosis is present in type IV GSD.⁸ Type

IV GSD was not considered in our patients due to a lack of cirrhosis findings in the liver biopsy and cardiomyopathy in the echocardiography.

However, we could not discriminate between type Ia and IIIa GSD in this patient because no enzyme analysis was performed.

Although it is known that many clinical conditions can accompany DS, its association with metabolic diseases has not been reported yet. This is the first case of DS coexisting with GSD in the literature. In our case, we think that GSD contributed to severe hypotonia, which caused extubation failure despite the lack of a pulmonary problem.

Declaration of Interest

None

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