Nephrotic syndrome in a patient with Glycogen Storage Disease Type IXb

Abstract
Glycogen storage disorder (GSD) IXb is characterized by liver and muscle involvement. We present a GSD IXb patient with an incidental union of nephrotic syndrome. A 4 year-old-patient was diagnosed with GSD IXb at 13 months of age with mildly elevated transaminases and hepatomegaly. During the follow-up period, there was no hypoglycemia. Development and growth were normal. In the last month, the onset of generalized edema was reported. Urinalysis showed a high protein level. He had low serum albumin, high serum triglycerides cholesterol. Complement levels were normal. The patient was diagnosed as minimal change disease with a renal biopsy. He was treated with oral prednisone. Minimal Change Disease is the most common cause of idiopathic nephrotic syndrome cases in children, and the first step for therapy is the usage of corticosteroids. This is the first report of nephrotic syndrome associated with GSD IXb disease.

Keywords: Glycogen Storage Disease, Nephrotic syndrome, proteinuria

Introduction
Phosphorylase kinase is a vital regulator enzyme regarding glycogen metabolism. Glycogen storage disease (GSD) type IX occurs due to an inherited deficiency in phosphorylase kinase. Two types of phosphorylase kinase deficiency are defined. The liver-specific form is characterized by early childhood onset hepatomegaly, growth restriction, fasting ketosis, and hypoglycemia. Symptoms of the muscle-specific form are exercise intolerance, myalgia, muscle cramps, myoglobinuria, and progressive muscle weakness. This variation is because of mutations affecting different cell types. The multiple subtypes of GSD IX are classified: GSD IXa, GSD IXb (gene PKHB), GSD IXc, and GSD IXd. The gene encoding the autosomal recessive β subunit, PHKB (OMIM *172490), is expressed in all tissues. PHKB mutations could be responsible for conditions of phosphorylase kinase deficiency where multiple tissues, especially muscle and liver, are affected.1 The diagnosis should be considered in children with unexplained hepatomegaly accompanied by ketotic hypoglycemia. Diagnosis is best provided by mutation analysis using a DNA panel. Asymptomatic patients may not need treatment. Growth failure and symptomatic hypoglycemia could avoid with uncooked cornstarch and frequent meals.
Nephrotic syndrome is a significant chronic disease in childhood and the common primary etiology in steroid-sensitive nephrotic syndrome (SSNS). Rare genetic disorders, drugs, and infections are among the secondary causes of isolated nephrotic syndrome.2

Case Report
A 4-year-old male patient was diagnosed with GSD IXb with mild transaminase elevation and hepatomegaly at 13 months. Parents were first-degree cousins. A GSD gene panel detected homozygosity for c.305+1 G>A mutation in the PHKB gene. In the segregation analysis, both parents were carriers for the heterozygous of the c.305+1 G>A variant. During the follow-up period, there was no hypoglycemia. Lipid levels and uric acid were normal. Development and growth were normal (body height at the 15th and weight at the 50th percentile). The patient had treated with uncooked cornstarch. He was admitted to the emergency with generalized edema. His symptoms had started two days before. It was not accompanied by fever or a history of recent illnesses. His blood pressure and vital signs were normal. Renal function tests were normal; urea 29 mg/dL (normal range:10-50), creatinine <0.27 mg/dL (normal range:0.3-1.0). Blood testing showed; AST:149 U/L (N<35), ALT:107 U/L (N<45), low serum albumin of 10 g/L (normal range 3.5-5.2), high serum triglycerides of 199 mg/dL (normal range <100) and high serum cholesterol of 304 mg/dL(reference 200). Complement levels resulted in C3:144 mg/ dL (normal range 90-180) C4:22 mg/ dL (normal range 10-40), were normal. Electrolytes were normal. The laboratory tests were suggestive of hypothyroidism (thyroid-stimulating hormone (TSH): 24 mU/L(normal range 0.7-5.97 24 U/L (N<35), ALT:107 U/L (N<45), were normal. The patient did not have hypoglycemia or hyperglycemia to our protocol). The patient followed in remission. The recommendation cyclophosphamide treatment according to-case basis.

Discussion
Although renal tubular dysfunction, glomerulopathy, FSGS, proteinuria, renal failure, and nephrocalcinosis have been reported in other GSDs, they were not reported in GSD IXb.3 There are no cases in the literature with nephrotic syndrome associated with GSD IXb disease. GSD IXb is a metabolic disease with liver and muscle involvement. Renal involvement has not been reported. PHKB gene results in GSD type IXb, and mutations affect muscle and liver. However, PHKB is expressed in all tissues.4 Less than 20 patients reported clinical symptoms, with less severe to severe hepatic involvement.4 Patients typically present with hepatomegaly. Hypoglycemia can be mild. In the literature, adenoma-like mass was described in one patient6, liver fibrosis was reported in another patient, and one patient had interventricular septal hypertrophy.5 In our patient, renal involvement presenting with steroid-sensitive nephrotic syndrome was observed. Due to sclerosis of glomeruli in renal biopsy, FSGS can be evaluated as early-stage findings in the patient. However, this disease was assessed as an independent accompanying condition rather than an involvement.

Figure 1: A, B. In light microscopic examination, the glomerulus is closely related to Bowman’s capsule and distance narrowed. C, Global sclerotic glomeruli in Jones methenamine silver stain. D, Closely related appearance of tuft and capsule in PAS stain

The (c.305+1 G>A) variant has not been reported in the literature or ClinVar database and is classified as likely pathogenic in ACMG guidelines; it has an adverse change due to its location in the intronic region. The association with GSD type IXb and nephrotic syndrome may be a coincidental association or an involvement of the disease. Other forms of GSD associated with renal manifestations are Fanconi-Bickel syndrome (GSD XI) and GSD I, which present renal tubular dysfunction (proteinuria, phosphaturia, glucosuria, generalized aminoaciduria).6 The association between viral infections and glomerulopathy is known. Rhinoviruses belong to the Enterovirus genus in the Picornaviridae family. The literature stated that enteroviruses could cause nephrotic syndrome, but no cases caused by rhinoviruses were reported on a case-by-case basis.9 Although the increased prevalence of hypothyroidism in GSD Ib is known, hypothyroidism has not been reported in GSD type IX or other forms of GSD.10 It is thought our patient developed hypothyroidism due to urinary loss of thyroid hormones.
Conclusion

We reported the association between GSD IXb and nephrotic syndrome for the first time in the literature. However, this coexistence was evaluated as a comorbid condition rather than a disease involvement. Future studies will guide the clinical course of the GSD XIb with new cases to be reported.

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References