Journal of Pediatric Academy

Case Report

Year: 2022 Volume: 3 Issue: 3
Doi: 10.51271/jpea-2021-192

# Nephrotic syndrome in a patient with Glycogen Storage Disease Type IXb

*Author(s)*

Merve Yoldas Celik[1], Havva Yazıcı[1], Fehime Erdem[1], Ebru Canda[1], Banu Sarsık Kumbaracı[2], İpek Kaplan Bulut[3], Sema Kalkan Uçar[1], Süleyman Caner Kabasakal[3], Mahmut Çoker[1]

*Affiliation(s)*

[1]Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Metabolism and Nutrition, Izmir, Turkey
[2]Ege University Faculty of Medicine, Department of Pathology, Izmir, Turkey
[3]Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Nephrology, Izmir, Turkey

*Article Information*

**Article Type:** Case Report
**Article Group:** Pediatric Metabolism and Nutrition

**Received:** 12.08.2022
**Accepted:** 01.11.2022
**Available Online:** 23.12.2022

***Cite this article as:*** *Yoldas Celik M, Yazıcı H, Erdem F, et al. Nephrotic syndrome in a patient with Glycogen Storage Disease Type IXb. J Pediatr Acad 2022; 3: 132-134.*

## 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 various phosphorylase kinase subunits. Many isoforms of phosphorylase kinase subunit function fine-tune in 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.

**Correspondence:** Merve Yoldas Celik, Department of Pediatric Metabolism, Faculty of Medicine, Ege University, Izmir 35040, Turkey
**E-mail:** drmerveyoldas@yahoo.com

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 15$^{th}$ and weight at the 50$^{th}$ 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 mU/L, serum-free thyroxine (FT4): 0.7 ng/dL (normal range 0.96-1.77 ng/dL). Urinalysis showed a nephrotic proteinuria level (88 mg/m²/h and 1610 mg/24 hours) with no signs of hematuria. Renal ultrasonography was normal. Abdomen ultrasonography showed enlarged liver (140 mm) with grade 1 hepatic steatosis. Echocardiography was normal. Testing for active infections: Rhinovirus detected in the respiratory viral panel.

The patient nephrotic proteinuria, hypoalbuminemia, and edema were evaluated as nephrotic syndrome. Although the primary nephrotic syndrome was suspected in the patient without macroscopic hematuria and average complement level, the biopsy was performed due to the accompanying disease. Pathological findings included four global cases of sclerosis of approximately 50 glomeruli (**Figure 1**). Oral prednisolone treatment was initiated at 2 mg/kg daily. However, the patient experienced two attacks while on the steroid reduction scheme. The patient was evaluated as steroid-dependent nephrotic syndrome. Cyclosporine treatment was started in the patient (parents did not accept the recommended cyclophosphamide treatment according to our protocol). The patient followed in remission. The patient did not have hypoglycemia or hyperglycemia with steroid treatment. Levothyroxine was started due to hypothyroidism.

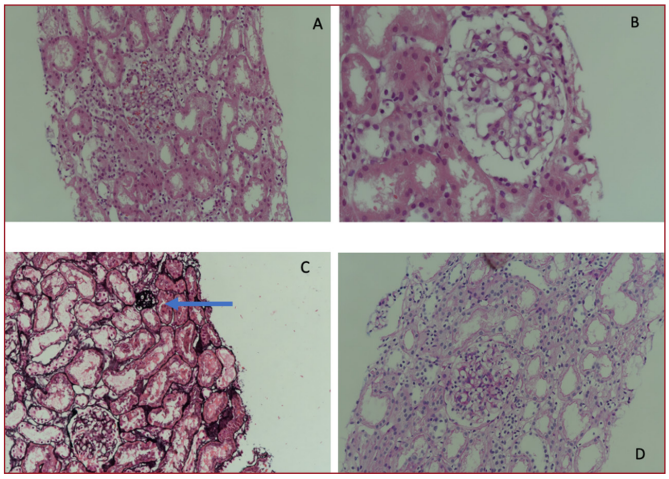


**Figure 1: A**, **B.** In light microscopic examination, the glomerulus is closely related to Bowman's capsule and distance narrowed. **C,** Global sclerotic glomeruli in Jones methenamine silver stain. **D,** Closely related appearance of tuft and capsule in PAS stain

## 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.[1] 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 patient[5], liver fibrosis was reported in another patient[6], 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.

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[7]; 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).[8]

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 rhinovirus 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.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Informed Consent:** Written informed consent was obtained from the parents of the patient.

## References

1. Wüllrich-Schmoll A, Kilimann MW. Structure of the human gene encoding the phosphorylase kinase beta subunit (PHKB). *Eur J Biochem.* 1996;238:374-380. *[CrossRef]*
2. Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet*. 2003;362:629-639. *[CrossRef]*
3. Okechuku GO, Shoemaker LR, Dambska M, Brown LM, Mathew J, Weinstein DA. Tight metabolic control plus ACE inhibitor therapy improves GSD I nephropathy. *J Inherit Metab Dis.* 2017;40:703-708. *[CrossRef]*
4. Kishnani PS, Goldstein J, Austin SL, et al. Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2019;21:772-789. *[CrossRef]*
5. Roscher A, Patel J, Hewson S, et al. The natural history of glycogen storage disease types VI and IX: Long-term outcome from the largest metabolic center in Canada. *Mol Genet Metab.* 2014;113:171-176. *[CrossRef]*
6. Burwinkel B, Maichele AJ, Aagenaes O, et al. Autosomal glycogenosis of liver and muscle due to phosphorylase kinase deficiency is caused by mutations in the phosphorylase kinase beta subunit (PHKB). *Hum Mol Genet.* 1997;6:1109-1115. *[CrossRef]*
7. Beauchamp NJ, Dalton A, Ramaswami U, et al. Glycogen storage disease type IX: High variability in clinical phenotype. *Mol Genet Metab.* 2007;92:88-99. *[CrossRef]*
8. Kishnani PS, Austin SL, Abdenur JE, et al. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. *Genet Med.* 2014;16:e1. *[CrossRef]*
9. MacDonald NE, Wolfish N, McLaine P, Phipps P, Rossier E. Role of respiratory viruses in exacerbations of primary nephrotic syndrome. *J Pediatr.* 1986;108:378-382. *[CrossRef]*
10. Melis D, Pivonello R, Parenti G, et al. Increased prevalence of thyroid autoimmunity and hypothyroidism in patients with glycogen storage disease type I. *J Pediatr.* 2007;150:300-305.e1. *[CrossRef]*