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Nephrotic syndrome co-existing with type 1 diabetes in a 12-year-old boy: Case report and literature review

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Abstract

Occurrence of early nephrotic syndrome in type 1 diabetes mellitus patients is extremely rare. Herein, we report the case of a 12-year-old boy who presented to our pediatric nephrology clinic with generalized edema. He had been diagnosed with type 1 diabetes mellitus at age 9 and had been treated with regular insulin. Examinations revealed normal kidney function, hypoalbuminemia, proteinuria (4+), hyperlipidemia, and low protein-to-creatinine ratio. The patient was diagnosed with idiopathic nephrotic syndrome and was empirically administered prednisolone for 12 weeks. Subsequently, prednisolone was tapered over 10–12 weeks. The patient showed good response to treatment. In conclusion, co-existence of nephrotic syndrome and type 1 diabetes mellitus may suggest an immunological basis; therefore, further studies are needed to investigate the relationship between these two conditions.

Keywords

Nephrotic syndrome, type 1 diabetes, edema, prednisolone

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Introduction

Nephrotic syndrome is a common childhood disease characterized by massive proteinuria, hypoalbuminemia, hyperlipidemia, and edema.[1,2] Notably, it exhibits a variety of patterns on histopathology analysis, such as minimal change disease (MCD), focal segmental glomerulonephritis, and membranoproliferative glomerulonephritis; MCD comprises the most common pattern in children.[3,4] Clinicians are often cautious when differentiating between nephrotic syndrome in a diabetic patient and diabetic nephropathy. Importantly, diabetic nephropathy is associated with long-term diabetes (>10 years) and a certain pattern of reduced renal function.[5] The occurrence of nephrotic syndrome and type 1 diabetes mellitus (T1DM) is extremely rare.[6] Herein, we report the case of a 12-year-old boy with T1DM who developed early-onset nephrotic syndrome.

Case

A 12-year-old Caucasian boy presented to the pediatric nephrology clinic with generalized edema that had originated periorbitally and then progressed to cover his entire body. He had been diagnosed with T1DM (1A) at the age of 9 and had been treated with insulin 1 U/kg/day, administered as short-acting insulin before each meal three times per day, combined with long-acting insulin glargine once per day. The patient reported a healthy diet and a habit of exercise. His HbA1C level was between 5% and 5.6% and he had not developed any diabetic complications, such as retinopathy and neuropathy. There was no family history of edema. His weight was 35 kg (25th percentile), height was 145 cm (25th percentile), and body mass index (BMI) was 16.6 kg/m^2 (25th percentile).

Laboratory investigations revealed normal kidney function, hypoalbuminemia, proteinuria (4+), hyperlipidemia, protein-to-creatinine ratio of 3.5, normal thyroid function, and negative celiac screen. The laboratory results are shown in Table 1. The patient was diagnosed with idiopathic

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Table 1. Laboratory test results of the patient.

Lab test	Results	Normal range	Last follow-up
Creatinine	40 µmol/L	30–50 µmol/L	42 µmol/L
Albumin	20 g/L	53–45 g/L	41 g/L
Cholesterol	7 mmol/L	<5.2 mmol/L	3.2 mmol/L
Protein-to-creatinine ratio	3.5 mg/mg	<0.2 mg/mg	
Thyroid function test	T4 15 pmol/L	T4 11–21 pmol/L	
	T3 4 pmol/L	T3 3–6 pmol/L	
	TSH 2 mU/L	TSH 0.5–5 mU/L	
Celiac screen test (tissue transglutaminase antibody)	1 U/mL (negative)	<4 U/mL	
C-peptide	112 pmol/L (low)	300–1300 pmol/L	
Anti-islet cell autoantibody	Positive	Negative	
Antibodies to glutamic acid decarboxylase	8 U/mL (elevated)	<0.7 U/mL	
Anti-insulin antibody	12 U/L	<1 U/L	
HLA	Not done	Not done	

T4: thyroxine; T3: triiodothyronine; TSH: thyroid-stimulating hormone; HLA: human leukocyte antigen.

nephrotic syndrome and treated empirically with prednisolone (60 mg/m^2 for 6 weeks, followed by 40 mg/m^2 for an additional 6 weeks) with "sliding scale" insulin therapy. Prednisolone was then tapered over 10–12 weeks. Blood glucose levels were strictly controlled. The patient's symptoms improved, and proteinuria disappeared within 12 days after initiating steroid treatment.

Discussion

The incidence of nephrotic syndrome in children in the United States and Europe is 1–7 per 100,000 children.[7–9] Patients with T1DM present with proteinuria (diabetic nephropathy) at a late stage,[10] approximately 12 years after the onset of diabetes.[11] A short period of T1DM and the absence of target organ damage (e.g. retinopathy)—as in our case—suggest the existence of a non-diabetic nephropathy and emphasize the importance of renal biopsy.[5] Early diabetic nephropathy is detected by an increased glomerular filtration rate, which is related to increased cell growth and expansion in the kidneys that may be induced by hyperglycemia. Microalbuminuria typically occurs 5 years after the onset of T1DM. Moreover, nephropathy with proteinuria (>300 mg/day) often develops 10–15 years after the onset of T1DM. End-stage renal failure develops in 50% of patients within 10 years of the onset of T1DM.[12]

Although the association between nephrotic syndrome and T1DM is rare, there is some evidence to support an immunological basis in multiple patients. The underlying etiology of this relationship is unknown. Notable examples include the following: a 3-year-old boy was simultaneously diagnosed with T1DM and nephrotic syndrome; he exhibited positivity for human leukocyte antigen (HLA) A24, DR4, and DR53 antigens.[13] Another report described the presence of DR4 in a 4-year-old boy with T1DM who developed nephrotic syndrome.[14] T1DM and steroid-sensitive nephrotic syndrome may share HLA loci that carry a genetic predisposition to both diseases.[6] Importantly, previous studies have revealed an HLA-related association among autoimmune diseases, including celiac disease, autoimmune thyroiditis, autoimmune hepatitis, and T1DM with nephrotic syndrome. A notable example was a 35-year-old man who was referred to the nephrology clinic for treatment of edema; he had an 18-year history of T1DM and a 6-year history of Hashimoto's thyroiditis. In that patient, a relationship was reported among T1DM, Hashimoto's thyroiditis, and MCD.[15] Furthermore, thyroiditis and diabetes-associated autoantibodies were present in a young girl with T1DM who developed icterus, which was caused by autoimmune hepatitis; HLA typing revealed DRB1*03 heterozygosity, associated with both autoimmune hepatitis and T1DM.[16]

To further highlight the association between nephrotic syndrome and T1DM, we note the case of a 19-year-old female with a 4-year history of T1DM, who had been treated with insulin and aspirin of 100 mg/day; she reported the occurrence of facial and bilateral limb edema for the prior 1 month. She reported no arthralgia and had a history of an uneventful pregnancy with a stillborn child, 8 months prior. Physical examination revealed pitting edema on the legs and face; urinalysis showed proteinuria of 5.3 g/24 h, and renal biopsy findings indicated MCD.[10]

In addition, Urizar et al. reported five cases of patients who were diagnosed with T1DM and developed manifestations of nephrotic syndrome, such as generalized edema, proteinuria, hypoproteinemia, and hypercholesterolemia. These cases were managed by administration of insulin, steroid, or both; the dose of insulin was increased to normalize hyperglycemia caused by steroid intake, as in our case.[17] Moreover, Robinson et al.[17] described a patient with uncontrolled diabetes during administration of steroid therapy; thus, the dose of insulin was increased. Regarding the outcome of nephrotic syndrome, our patient showed a dramatic response to treatment with complete remission. In contrast,

Table 2. Summary of prior reports of nephrotic syndrome associated with early-onset type 1 diabetes mellitus in pediatric patients.

References	Age at onset of diabetes (years)	Age at onset of nephrotic syndrome (years)	Proteinuria level (g/24 h)	Treatment	Outcome
Urizar et al.[17]	4	4 (1 week after DM1)	3.4	Insulin	Resolved completely
Urizar et al.[17]	8	8	7.2	Steroid	Resolved completely
Urizar et al.[17]	3	4	14	Steroid	Resolved completely
Urizar et al.[17]	5	5	17	Steroid	Recurrence
Urizar et al.[17]	2 months	10	7.3	Steroid	Recurrence
Robinson et al.[18]	3	3 (2 months after DM1)	–	Steroid	Resolved completely
Agras et al.[13]	3	3 (10 months after DM1)	–	Steroid	Relapsed
Otukesh and Torabi[6]	Infancy	5	–	Steroid	Recurrence
Rego Filho et al.[14]	3	3	0.529	Steroid–cyclophosphamide	Relapsed
Dizdar et al.[15]	17	35	3.7 g/day	Cyclophosphamide	Resolved completely
Moyses Neto et al.[10]	15	19	5.3 g/24 h	Steroid	Resolved completely

two prior patients exhibited relapse and recurrence.[6,13] A summary of the above cases is shown in Table 2.

Conclusion

Co-existence of nephrotic syndrome and T1DM may suggest an immunological basis for the relationship between these diseases; further studies are needed to explore the underlying etiology.

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Declaration of conflict of interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval

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