

Slowly Progressive Type 1 Diabetes following Steroid-Sensitive Relapsing Nephrotic Syndrome in Childhood: A Case Report

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Established Facts

- In cases of idiopathic nephrotic syndrome (NS) and type 1 diabetes (T1D) coexistence, diabetes typically precedes or develops concurrently with NS, presenting acutely and requiring immediate insulin therapy.
- Slowly progressive type 1 diabetes mellitus (SPT1D) lacks acute hyperglycemic crises and canonical T1D symptoms, often leading to misdiagnosis as type 2 diabetes.

Novel Insights

- Hyperglycemia and glycosuria resulting from SPT1D can be recognized more broadly in patients with refractory NS undergoing steroid treatment.
- Anti-islet cell antibody testing, glucose monitoring, and insulin secretion evaluation should be considered in patients with steroid-induced glucose abnormalities.

Keywords

Nephrotic syndrome · Slowly progressive type 1 diabetes · Pediatric diabetes · Steroid therapy

Abstract

Introduction: In rare cases, idiopathic nephrotic syndrome (NS) and type 1 diabetes coexist, with diabetes typically preceding NS or presenting almost simultaneously with an acute onset requiring immediate insulin therapy. **Case Presentation:** We report a unique case of a 5.1-year-old male who developed idiopathic NS and experienced glycosuria during steroid treatments for

relapses, initially attributed to steroid-induced hyperglycemia. At age 10.2, he developed persistent glycosuria without steroid administration, and an oral glucose tolerance test confirmed diabetes. Despite positive anti-insulinoma-associated protein-2 antibodies, the patient maintained non-insulin-dependent glycemic control until, 13 months later, rapid-onset hyperglycemia necessitated insulin therapy, leading to a diagnosis of slowly progressive type 1 diabetes (SPT1D). **Conclusion:** This case represents the first reported instance of steroid-sensitive relapsing NS followed by SPT1D in childhood.

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Introduction

Slowly progressive type 1 diabetes mellitus (SPT1D) is a clinical subtype of type 1 diabetes (T1D) that is distinct from the acute-onset form. SPT1D is characterized by the absence of an absolute insulin requirement for survival or blood glucose regulation at the time of diagnosis, despite persistent detection of islet cell antibodies that attack and destroy pancreatic beta cells. SPT1D typically develops in adolescence, as beta-cell function gradually declines, eventually leading to insulin deficiency and manifesting as SPT1D over several months or years [1, 2]. This subtype of T1D is also predominantly observed in adults, where it is referred to as latent autoimmune diabetes in adults (LADA) [2–4]. SPT1D typically lacks the propensity for acute hyperglycemic crises and the hallmark symptoms of T1D seen in children, such as polyuria and polydipsia at diagnosis, and is sometimes associated with higher levels of insulin resistance. Therefore, patients affected by SPT1D are often misdiagnosed and incorrectly treated as having type 2 diabetes mellitus (T2D) [5]. SPT1D can also be encountered in children, although most diabetic children are diagnosed with the acute-onset form of T1D [6].

Idiopathic nephrotic syndrome (NS) is a prevalent non-diabetic chronic kidney disease (CKD) in children, with steroids being a primary treatment. Additionally, steroids are extensively used in the management of other inflammatory and autoimmune disorders. However, steroid therapy can induce various adverse effects, including steroid-induced abnormal glucose metabolism (AGM), which encompasses hyperglycemia, prediabetes (impaired glucose tolerance [IGT] and impaired fasting plasma glucose [IFG]), and diabetes, particularly when high doses are administered over prolonged periods [7, 8]. The primary mechanisms underlying AGM include increased hepatic gluconeogenesis, reduced insulin sensitivity, and inhibited glucose uptake in muscle and peripheral tissues [7]. Steroids may also exert complex effects on beta cell function [7]. Steroid-induced AGM typically improves with dose reduction and reverses when steroids are discontinued [8]. However, specific criteria or guidelines for screening patients, especially pediatric patients treated with steroids, for steroid-induced AGM are lacking. In addition, the development of SPT1D remains inadequately elucidated.

Herein, we report a unique case of a child with steroid-sensitive NS who subsequently developed SPT1D. This case represents the first documented instance of SPT1D emerging during idiopathic NS under the administration of steroids.

Case Presentation

A 5.1-year-old Japanese male was diagnosed with idiopathic NS. At presentation, he exhibited facial and peripheral edema, along with a 2 kg weight gain from his baseline of 16.5 kg (<50th percentile for age-group). He had no significant medical history, with no evidence of obesity. However, his maternal grandfather had a history of T2D and obesity. The patient initially responded well to standard prednisolone therapy, consisting of 60 mg/m²/day for 4 weeks, followed by 40 mg/m²/alternate days for an additional 4 weeks. Over the subsequent 5 years, he experienced six relapses of NS at ages 5.9, 6.7, 8.0, 8.7, 8.9, and 9.5 years. Each relapse was successfully managed with prednisolone following the International Study of Kidney Disease in Children protocol and complete remission was achieved.

During relapses, glycosuria was noted while on steroid therapy. However, this resolved upon tapering or discontinuing steroids. Despite the presence of glycosuria, the patient did not exhibit symptoms such as polydipsia, polyuria, or weight loss. His weight increased with age, remaining between the 50th and 75th percentiles for his age-group. His glycated hemoglobin (HbA1c) levels ranged from 5.5% to 6.2% (NGSP), with a single episode of hyperglycemia (12 mmol/L, 217 mg/dL) recorded at age 8.7 years during steroid therapy (Fig. 1). Ophthalmologic evaluation at the time revealed no abnormalities. Based on these findings, the patient was diagnosed with steroid-induced hyperglycemia.

At age 10.3 years, persistent glycosuria was observed despite discontinuation of steroids, with his weight remaining below the 75th percentile. An oral glucose tolerance test (OGTT) with a 75 g glucose load revealed mild impairment of early-phase insulin secretion, although basal insulin secretion remained normal (Fig. 2). Anti-insulinoma-associated protein-2 (IA-2) antibody levels were low positive (6.7 U/mL), while anti-glutamic acid decarboxylase antibody (GADA) levels were negative (0.9 U/mL). The patient displayed no clinical symptoms of diabetes and did not require insulin therapy. A diagnosis of T2D potentially related to previous steroid use was made, and treatment with an alpha-glucosidase inhibitor (miglitol) was initiated. His HbA1c (NGSP) levels remained stable between 5.7% and 6.4%, and random blood glucose levels ranged from 6.1 mmol/L (110 mg/dL) to 9.8 mmol/L (177 mg/dL; Fig. 1).

At age 11.4 years, 13 months after the OGTT, the patient developed symptoms of polyuria and polydipsia and experienced a weight loss of 3.4 kg from his baseline of 36.4 kg (<50th percentile) over 1 month. Laboratory

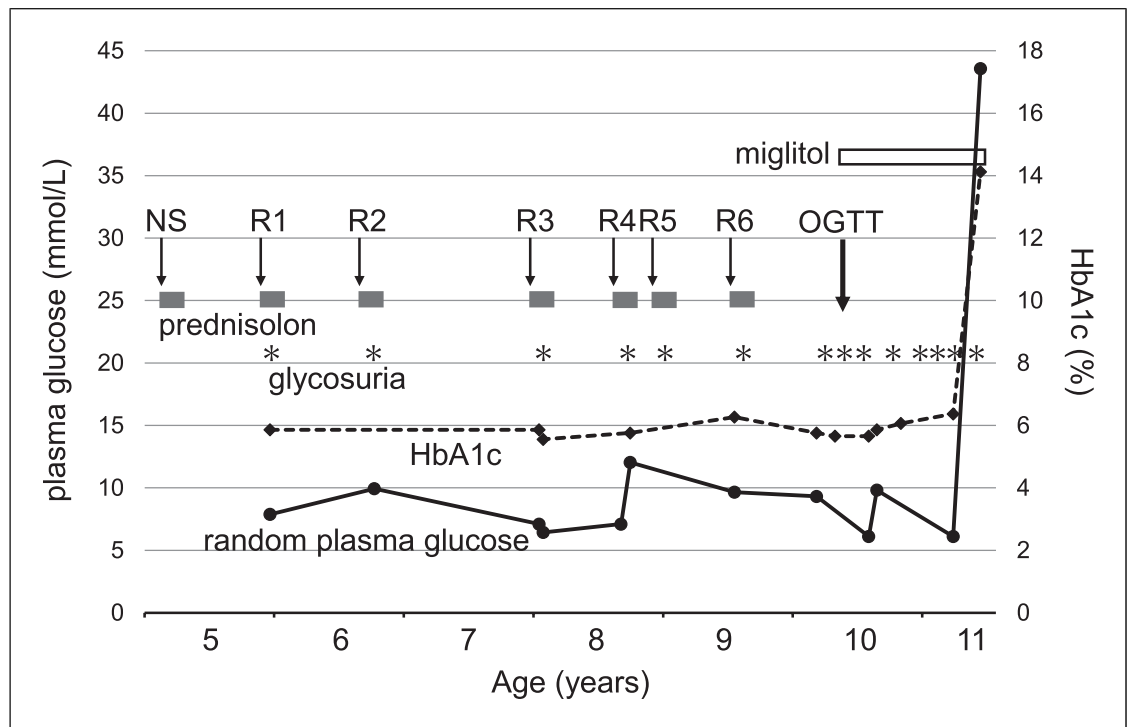


Fig. 1. Clinical course of the patient. NS, onset of nephrotic syndrome; R1, first relapse of nephrotic syndrome; R2, second relapse of nephrotic syndrome; R3, third relapse of nephrotic syndrome; R4, fourth relapse of nephrotic syndrome; R5, fifth relapse of nephrotic syndrome; R6, sixth relapse of nephrotic syndrome; OGTT, oral glucose tolerance test.

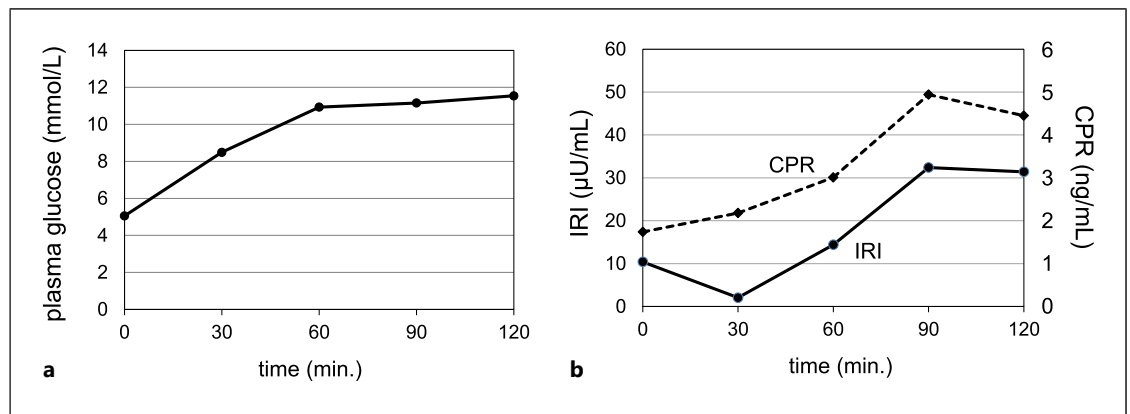


Fig. 2. A 75 g oral glucose tolerance test performed at the age of 10.3 years. **a** Changes in the plasma glucose level. **b** Changes in the plasma immunoreactive insulin (IRI) and C-peptide immunoreactivity (CPR) levels.

findings revealed severe hyperglycemia with a blood glucose level of 43.5 mmol/L (785 mg/dL) and an HbA1c of 14%. Further testing showed a pH of 7.277, a standard base excess of -10.1 mmol/L, an anion gap of 23.6 mmol/L, and ketonuria. The patient was diagnosed with diabetic ketoacidosis secondary to the development of SPT1D, necessitating

immediate initiation of insulin therapy. Although IA-2 antibody levels remained positive at a low titer (6.7 U/mL), GADA, anti-insulin antibody (IAA), and anti-islet cell antibody (ICA) levels were undetectable. Over the subsequent 3 years, IA-2 antibody levels became undetectable, but the patient continued to require insulin therapy.

Discussion and Conclusions

Our patient exemplifies the development of SPT1D following idiopathic NS in childhood. The diagnosis of SPT1D in our patient is supported by the initial absence of insulin dependency for glycemic control at the time of diagnosis via OGTT, subsequent progression to insulin dependence over 13 months, and sustained positivity for IA-2 antibodies – a marker indicative of islet cell autoimmunity. Traditional paradigms classify T2D as occurring in adults, often associated with obesity and progressive beta-cell insulin secretion deficiency, whereas T1D is generally characterized by autoimmune beta-cell destruction usually leading to absolute insulin deficiency, typically manifesting in childhood [9]. However, both T1D and T2D are heterogeneous disorders with diverse clinical presentations and progression patterns. SPT1D aligns with a form of slowly progressive autoimmune diabetes with a presentation similar to LADA. Despite ongoing debate about whether SPT1D should be classified as LADA or a stage of T1D, its clinical recognition is valuable for identifying and managing progressive autoimmune beta-cell destruction [9]. Early diagnosis and intervention may help delay or prevent progressive beta-cell failure in patients with SPT1D. The benefits of early insulin therapy for SPT1D/LADA have been well established [10], and evidence suggests that dipeptidyl peptidase-4 inhibitors may offer long-term efficacy during the non-insulin-dependent stage of SPT1D [11].

In pediatric patients with SPT1D, Klingensmith et al. [12] reported that 9.8% of children with clinical T2D were positive for autoantibodies and exhibited evidence of insulin deficiency due to islet cell autoimmunity. In Japan, pediatric cases of SPT1D may not be rare, as many instances of T1D are identified incidentally through school-based urine glucose screening programs, along with most cases of T2D, often presenting with only minimal to moderate symptoms and without ketosis [6]. In our patient, the initial manifestation of SPT1D was characterized by transient glycosuria during steroid treatment for NS relapse, without accompanying symptoms of hyperglycemia. Therefore, the condition was initially interpreted as steroid-induced hyperglycemia, and no diagnostic tests for diabetes were conducted until persistent glycosuria was observed.

Steroid-induced AGM, including diabetes, prediabetes, and hyperglycemia, are common complications associated with long-term and frequent use of steroids in the context of various inflammatory diseases, autoimmune disorders, non-diabetic CKDs, and organ transplantation [8]. These disorders can increase the risk of developing T2D, with some patients progressing to persistent AGM, including

diabetes. The American Diabetes Association (ADA) criteria are typically used to define these conditions in adults [9]. According to ADA guidelines, diabetes is diagnosed when 2-h plasma glucose levels exceed 11.1 mmol/L (200 mg/dL) during an OGTT or when fasting plasma glucose (FPG) exceeds 7.0 mmol/L (126 mg/dL). IGT is characterized by a 2-h plasma glucose level ranging from 7.8 mmol/L (140 mg/dL) to 11.0 mmol/L (199 mg/dL) during an OGTT. IFG is defined by an FPG between 5.6 mmol/L (100 mg/dL) and 6.9 mmol/L (125 mg/dL). However, specific guidelines for screening pediatric patients undergoing steroid treatment are currently unavailable.

Takahashi et al. [13] recently reported a high prevalence of medication-induced AGM in children with refractory NS, including 2 patients who exhibited reduced insulin secretion at follow-up evaluation despite negative islet cell antibody tests. However, there are no reports specifically describing the role of steroids in the development of T1D, particularly in cases of SPT1D. In our patient, blood glucose levels (both preprandial and postprandial) and HbA1c were only intermittently monitored during the administration of steroids. Islet cell autoantibodies (ICAs) were not tested before the diagnosis of diabetes by OGTT. Therefore, the precise onset of SPT1D in this case remains unclear.

In cases where T1D coexists with idiopathic NS, several reports – particularly in cases involving children – indicate an almost simultaneous onset of both conditions and the development of NS shortly after the diagnosis of T1D, with all diabetes cases presenting acutely. These reports exclusively described renal pathology attributable to diabetes and the management of relapsing NS with steroid treatment [14–16]. Therefore, causation in these cases remains unclear, although the association between T1D and idiopathic NS has been suspected for some time. Conversely, a few reports present cases where NS preceded the development of T1D. For instance, Goldman et al. [16] documented a patient who developed T1D 6 months after the onset of NS. This patient exhibited glycosuria and hyperglycemia within 2 weeks of NS onset, but the case was not specifically analyzed for SPT1D or ICAs. Other reported cases involved a rapid onset with overt symptoms of diabetes and ketoacidosis, characteristic of acute-onset T1D [17].

In conclusion, hyperglycemia and glycosuria resulting from SPT1D should be recognized more broadly in patients with CKD undergoing steroid treatment, including those with refractory NS. Consequently, we recommend that testing for ICAs, close monitoring of glucose levels, and thorough evaluation of insulin secretion should be considered in patients with steroid-induced AGM. This approach will ensure that intensive insulin treatment is both effective and safe for CKD patients with SPT1D. The CARE

Checklist was completed by the author of this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000545216>).

Statement of Ethics

Written informed consent for publication of the details of this medical case was obtained from the patient, who had reached adulthood before the initiation of this case report. Every precaution was taken to maintain the patient's anonymity. According to local and national guidelines, ethical approval was not required for this study.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Masashi Kitahara was responsible for patient care, conceptualized and designed the report, and wrote the manuscript. Kenji Kurata was involved in the medical management of the patient.

Data Availability Statement

Patient data were obtained from medical records in NHO Matsumoto Medical Center, Japan, and are not publicly accessible. Additional information is available from the corresponding author upon reasonable request.