Case Report

Early onset stage III diabetic nephropathy in a child with Prader-Willi syndrome treated with dulaglutide: a case report

Yonghua He[1#], Rongrong Xu[1,2,3#], Xueqing Ma[1], Jianhua Zhou[1], Liru Qiu[1]

[1]Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [2]Department of Pediatrics, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [3]Key Laboratory for Molecular Diagnosis of Hubei Province, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Contributions: (I) Conception and design: Y He, R Xu, L Qiu; (II) Administrative support: L Qiu, J Zhou; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: Y He, R Xu, X Ma, L Qiu; (V) Data analysis and interpretation: Y He, R Xu, X Ma, L Qiu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Liru Qiu, MD, PhD. Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan 430030, China. Email: liruqiutj@163.com.

Background: Prader-Willi syndrome (PWS) is a multisystem genetic disorder caused by chromosomal imprinting gene defects, with approximately 70% of cases resulting from paternal deletion of the chromosomal region 15. The main clinical features include severe infantile hypotonia, early-onset childhood obesity, hyperphagia, and underdeveloped external genitalia. As individuals with PWS age, they may exhibit irritability, social dysfunction, impaired gonadal development, and metabolic syndrome. Previous literature places the prevalence of type 2 diabetes mellitus (T2DM) in PWS at approximately 7–24%. Oxytocin is a neuropeptide secreted by the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus and regulates energy metabolism, which is involved in PWS. Due to age limitations, very few patients progress to diabetic nephropathy during childhood, and reports of typical diabetic nephropathy in PWS during childhood are extremely rare. Dulaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist which can be used in the treatment of T2DM.

Case Description: This article reports a case of a child with PWS complicated by stage III diabetic nephropathy, providing a retrospective analysis of the diagnosis and treatment process, as well as a review of domestic and international literature, to enhance understanding of this condition. And this article provides a treatment idea for PWS patients with diabetic nephropathy.

Conclusions: It is very important to enhance understanding of PWS. And we offer new diagnostic and possible therapeutic approaches for pediatric patients with diabetic nephropathy.

Keywords: Prader-Willi syndrome (PWS); diabetic nephropathy; pediatrics; case report

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Introduction

Prader-Willi syndrome (PWS) is a genetic disorder caused by imprinting gene defects. Approximately 70% of cases are attributed to paternal deletion of the chromosomal region 15q11-13, while around 25% result from maternal uniparental disomy imprinting defects (1). PWS manifests with a variety of clinical features, including hyperphagia (excessive appetite), hypotonia (low muscle tone), intellectual disability, pituitary hormone deficiencies, and metabolic syndrome. Nearly 98% of PWS patients are overweight or obese (2).

The mortality rate among individuals with PWS is approximately 3% per year, and it increases to around 7% per year for individuals over the age of 30. Obesity-related complications, including type 2 diabetes mellitus (T2DM), arterial hypertension, sleep apnea, respiratory insufficiency, and cardiovascular disease, are the primary risk factors for mortality in individuals with PWS (3,4). Previous literature places the prevalence of T2DM in PWS at approximately 7–24% (5). However, it is extremely rare for PWS patients to develop diabetic nephropathy during childhood. Dulaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. Its mechanisms of action are augmentation of hyperglycemia-induced insulin secretion, suppression of glucagon secretion, deceleration of gastric emptying to prevent large post-meal glycemic increments, and a reduction in calorie intake and body weight (6-8).

In this article, we report a case of a child with PWS complicated by stage III diabetic nephropathy. We describe the clinical presentation, diagnostic and treatment process, as well as the follow-up and prognosis of the patient. It plays an important role in the early diagnosis and treatment of diabetic nephropathy. We present this case in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-518/rc).

Case presentation

A 10-year and 9-month-old male was admitted to the hospital due to the discovery of "elevated blood glucose with abnormal urine test results" for over 3 years. The patient's weight was 68.3 kg (+3 standard deviation), height was 142 cm (–1 standard deviation), and body mass index (BMI) was 33.87 kg/m^2. The patient had fair skin, light hair color, red rashes scattered on the face and back, a few pustules on the abdomen, a chubby facial appearance, a slightly narrow forehead, uneven ear positions (left ear higher than right ear), thin lips, a small chin, normal muscle strength and tone in the limbs, and relatively small hands and feet. There was no edema in the lower extremities. The patient had thickened breasts with slightly prominent areola and normal areola pigmentation. Testicular volume was 1 mL bilaterally, penis length was 3 cm, and no pubic or axillary hair was observed.

The patient was the second born, delivered via full-term cesarean section. At birth, the patient was hospitalized due to "ABO hemolytic jaundice, ischemic-hypoxic encephalopathy, and feeding difficulties". At the age of 3 months, the patient was diagnosed with hypotonia and received intermittent rehabilitation therapy until the age of 2. At the age of 3, the patient underwent surgery for undescended testicles. Three years ago, during a physical examination, elevated blood glucose levels (around 12 mmol/L) and 1+ urinary protein were discovered. The patient controlled the diet for 2 years, but body weight increased to 66 kg. In a follow-up examination at another hospital, the patient's fasting blood glucose level was 17.87 mmol/L, triglycerides were 27.13 mmol/L, total cholesterol was 13.18 mmol/L, and urinary protein was 3+. The diagnosis was "type 2 diabetes, proteinuria, and hyperlipidemia". The patient was treated with insulin, benapril, and atorvastatin. After 10 months of treatment, the patient's fasting blood glucose level was 10.4 mmol/L, total cholesterol was 9.8 mmol/L, and urinary protein was 3+. He did not have autism spectrum disorder.

The parent's father had slightly elevated blood glucose levels (around 7.5 mmol/L). The mother and the patient's sister had no history of diabetes, and there was no family history of similar conditions.

Upon admission, the patient's temperature and blood pressure were in the normal range (*Figure 1*), his random blood glucose level was 13.6 mmol/L, fasting blood glucose level was 10.4 mmol/L, glycated hemoglobin (HbA1c) was 8.9%, insulin level was 16.7 uIU/mL, C-peptide level was 2.51 ng/mL. Other laboratory findings included albumin level of 37.0 g/L, creatinine level of 41 μmol/L, triglycerides level of 7.64 mmol/L, and total cholesterol level of 5.18 mmol/L. The urine analysis revealed 3+ glucose, urinary albumin/creatinine ratio of 3,612.6 μg/mg. Urine tests for β2-microglobulin, blood complement, anti-neutrophil cytoplasmic antibodies (ANCA), anti-glomerular

Highlight box

Key findings

- We offer new diagnostic and possible therapeutic approaches for pediatric patients with diabetic nephropathy.

What is known and what is new?

- Prader-Willi syndrome (PWS) is a multisystem genetic disorder caused by chromosomal imprinting gene defects, the prevalence of type 2 diabetes mellitus in PWS at approximately 7–24%.
- We report a case of a child with PWS complicated by stage III diabetic nephropathy, and provide a treatment idea for patients.

What is the implication, and what should change now?

- Only one case, and the patient used multiple drugs at the same time. More research and cases are still needed.

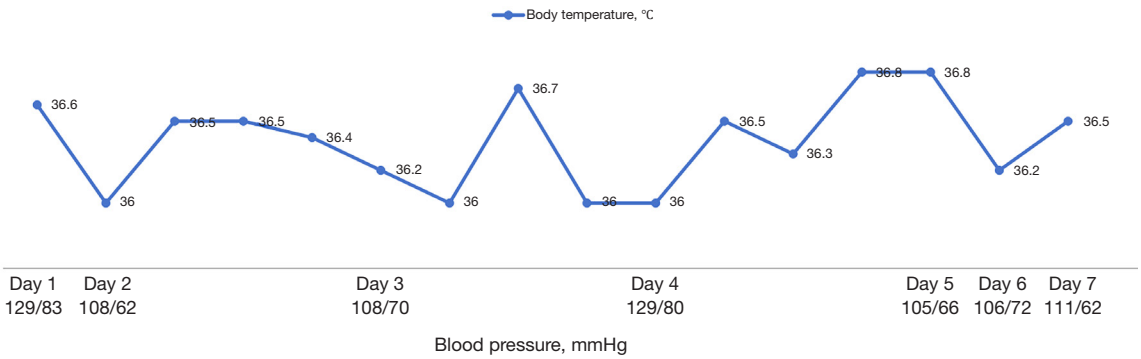

Figure 1 The patient's body temperature after admission.

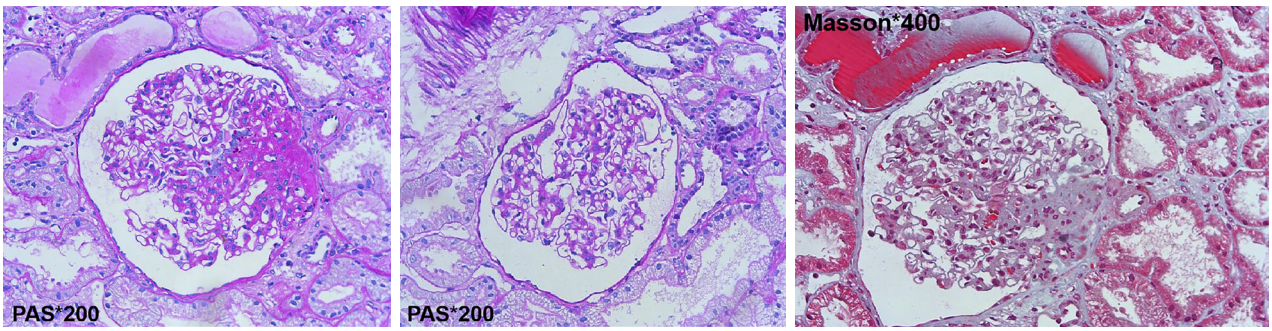

Figure 2 Renal biopsy. PAS, periodic acid-Schiff.

basement membrane antibodies (GBM), and a complete rheumatologic panel showed no abnormalities. His oxytocin was not measured. Renal biopsy showed obvious mesangial matrix proliferation, Kimmelstiel-Wilson (K-W) nodules and mild mesangial cell proliferation in most of the glomerular glomus. It indicated stage III diabetic nephropathy (*Figure 2*). Thrombosis and hyalinization were observed in small vessels in the renal interstitium. Genetic testing revealed a deletion of the SNRPN (NM_003097.5) gene fragment in the 15q11.2-q13 region. The average methylation level in the gene promoter region was 100%, indicating the loss of the paternal fragment (*Figure 3*, *Table 1*).

Based on the patient's clinical manifestations, laboratory findings, pathological features, and genetic testing results, the patient is diagnosed with "Prader-Willi syndrome, type 2 diabetes, diabetic nephropathy, hyperlipidemia, and obesity". The patient was treated with an angiotensin receptor blocker (ARB) and dulaglutide (0.75 mg/week). After 8 months of treatment, the patient's BMI, fasting blood glucose levels, and urinary protein levels showed improvement compared to before (BMI of 28 kg/m^2, fasting blood glucose levels of 6.9–7.3 mmol/L, urinary albumin/creatinine ratio of 258 μg/mg), and glycated hemoglobin levels returned to normal.

All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of Tongji Hospital (No. TJ-IRB20230702) and with the Helsinki Declaration (as revised in 2013). Informed consent was taken from the patient's guardians for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

PWS is caused by a defect or deletion in the imprinting of genes in the 15q11.2-q13 region of chromosome 15. The syndrome is characterized by distinctive facial features, hypotonia (low muscle tone), feeding difficulties in early infancy, hypogonadism (reduced sexual function), delayed neurodevelopment, and compulsive overeating leading to

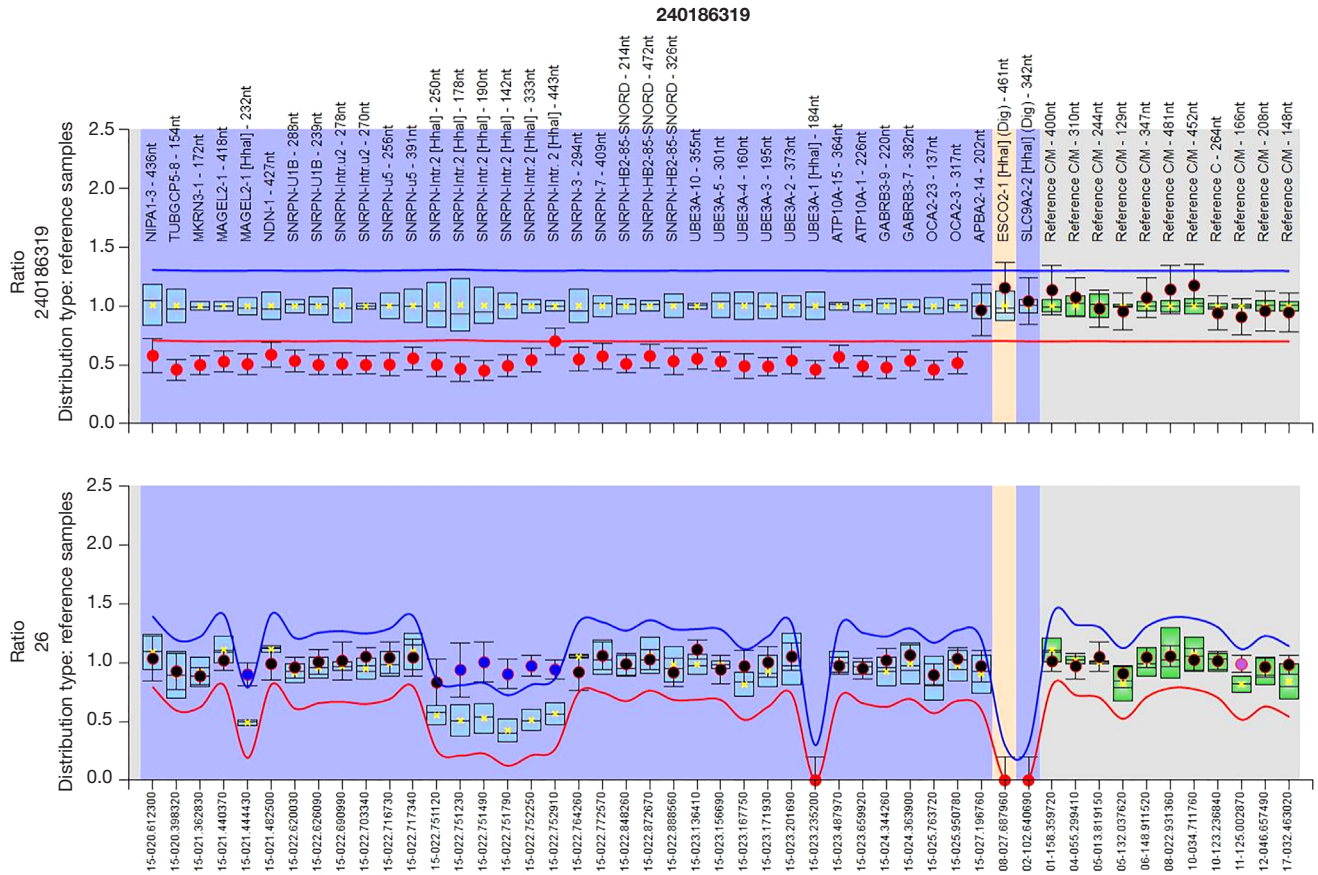

Figure 3 Detail map of the genetic testing. SNRPN (NM_003097.5) 15q11.2-q13 fragment deletion.

Table 1 PWS copy number and methylation detection

Reference sequence	Region	Locus 1	Locus 2	Conclusion
SNRPN (NM_003097.5)	15q11.2-q13	Deletion of CNV signal	The methylation level is approximately 100%	PWS

PWS, Prader-Willi syndrome; CNV, copy number variation.

morbid obesity (1,9). Individuals with PWS experience hyperphagia, lack of satiety, and low energy expenditure, leading to almost universal obesity in affected individuals. In this case, the patient's BMI value was significantly elevated, indicating obesity.

The average age of onset for diabetes in PWS patients is reported to be between 15.9 and 20.0 years (5,10). Adolescents with diabetes have a higher risk of renal failure and the need for dialysis compared to their non-diabetic peers of the same age (11-13). However, the progression to diabetic nephropathy usually takes time, and there are very few reports of children with PWS developing diabetic nephropathy.

Our patient had elevated blood glucose with abnormal urine test results for over 3 years, and his renal biopsy after admission indicated stage III diabetic nephropathy. After reviewing the literature, no reports of PWS progressing to diabetic nephropathy in childhood have been found. This highlights the rarity of early-onset diabetic nephropathy in PWS children and underscores the importance of reporting this case.

Dulaglutide, a GLP-1 receptor agonist, reduces ghrelin secretion, promotes insulin secretion, and increases the number and function of peripheral endothelial progenitor cells (EPCs) in T2DM patients (6,7). EPCs, under specific conditions, can enter the peripheral blood circulation

and differentiate into mature endothelial cells. They play a crucial role in promoting vascular formation and maintaining vascular homeostasis. The quantity and function of EPCs are highly correlated with cardiovascular risk factors and the development of atherosclerosis. Dulaglutide helps control blood glucose levels, decreases appetite, improves glucose metabolism, reduces inflammation, and maintains vascular homeostasis. Moreover, GLP-1 receptors are widely distributed, particularly in the renal glomeruli and proximal tubules, and have a direct regulatory effect on the kidneys. Therefore, GLP-1 receptor agonists provide renal protection while lowering blood glucose levels (14-17). The REWIND study showed that dulaglutide reduced the risk of composite renal endpoint events by 15% compared to placebo, and the risk of new-onset macroalbuminuria was significantly reduced by 23%. Adding a GLP-1 receptor agonist to insulin-based therapy not only achieves better glycemic control but also lowers the incidence of diabetic macroalbuminuria by reducing glomerular hyperfiltration in diabetes patients (18,19). The study has shown that dulaglutide has a good effect on the treatment of blood glucose control in youths with T2DM. Gastrointestinal symptoms were among the most common adverse events but were primarily mild and were most likely to occur soon after the initiation of therapy (20).

Regarding clinical trials for PWS patients, Salehi *et al.* conducted a six-month study in 2016 to investigate the effects of exenatide (a GLP-1 receptor agonist) treatment. The study involved ten obese adult PWS patients and found that exenatide did not significantly affect body weight, BMI, or truncal obesity. However, a significant decrease in appetite scores and dietary behaviors was observed (21,22). Currently, there are no reports or clinical trials regarding the use of dulaglutide for PWS treatment.

In this case, abnormal blood glucose and urinary protein were discovered in the patient at the age of 8, but renal biopsy was not performed initially. After insulin treatment, both blood glucose and urinary protein control remained poor. Subsequently, renal biopsy was performed, revealing stage III diabetic nephropathy. After initiating dulaglutide treatment, significant improvements in blood glucose and urinary protein were observed. This provides a new treatment perspective for PWS patients, especially those with concurrent kidney involvement. It is rare for patients to progress to diabetic nephropathy during childhood; however, in this case, the patient exhibited abnormal blood glucose and urinary protein at the age of 8, but further renal biopsy was not conducted to determine the extent of disease progression. For patients with issues in both blood glucose and urinary protein, it is advised to perform timely renal biopsy to facilitate early treatment, which holds great significance in improving patient prognosis.

All PWS patients experience some degree of hypogonadism, with cryptorchidism occurring in 66–100% of newborn males. Most studies report normal onset of puberty in males; however, puberty arrest often coincides with testicular failure. Testicular volume can develop up to 6–7 mL but remains small in adulthood (23-26). In this case, the patient exhibited typical facial features, short stature, obesity, hypogonadism, and metabolic syndrome. Genetic testing confirmed the diagnosis of PWS.

In conclusion, while focusing on controlling diabetes and urinary protein to prolong survival, we should also consider the patient's psychological well-being and long-term quality of life. It is recommended that renal biopsy should be performed promptly if urinary protein is detected. Once the diagnosis of diabetic nephropathy is confirmed, GLP-1 agonists may be an alternative treatment method. This approach aims to prevent obesity and improve the long-term prognosis and quality of life for patients.

Conclusions

The clinical features of PWS are complex and varied. And the renal biopsy should be performed promptly if urinary protein is detected in patients with PWS. In the paper, we provide a treatment idea for PWS patients with diabetic nephropathy, and GLP-1 agonists may be an alternative treatment method.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-518/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-518/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of Tongji Hospital (No. TJ-IRB20230702) and with the Helsinki Declaration (as revised in 2013). Informed consent was taken from the patient's guardians for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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