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Investigating glucose metabolism in children with Williams-Beuren syndrome: A case study on WBS and DKA

Ying Zhang¹, Shunli Tang¹, Yabin Chen¹, Hua Liu¹, Xinmin Qiu², Zhiren He^{3,*}¹ Department of Pediatrics, The First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, Guangzhou 510405, China² Research Laboratory, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510405, China³ Department of Nephrology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510405, China* **Corresponding author:** Zhiren He, he.zhiren@gzucm.edu.cn

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Abstract: Objective: More attention should be paid to glucose metabolism in children with Williams-Beuren syndrome (WBS). **Methods:** The clinical data of a child diagnosed with WBS due to diabetic ketoacidosis (DKA) were retrospectively analyzed, and the related literature was reviewed. **Results:** An 8-year-old boy presented with thickened upper lip, low palatal arch, strong heart sound, rumbling murmur in the apex area, a little pigmentation in the webbed margin of fingers and toes, and atypical elfin features. Blood gas analysis showed severe ketoacidosis with significantly elevated amylase, significantly increased amylase, elevated blood lipids, abnormal thyroid function, negative C-peptide, diabetic. Echocardiography showed supra-aortic stenosis and abnormal aortic valve. The large copy number variation of the nuclear genome revealed a heterozygous variation in the 7q11.23 region, with a 1.4 Mb deletion in the 7q11.23 region, and the related gene in the region was elastin gene. **Conclusion:** DKA was reported for the first time as the first symptom of WBS diabetes. The mechanism of concurrent DKA in WBS is not well understood.

Keywords: Williams-Beuren syndrome; diabetes mellitus; ketoacidosis

Williams-Beuren syndrome (WBS) is an autosomal dominant genetic disorder caused by deletion of a gene fragment in a specific region of chromosome 7 (7q11.23) [1]. The condition is characterized by distinctive facial features (commonly known as “elf-looking”: broad forehead, full eye circumference, low nose bridge, low cheekbones, almond-shaped eyes, oval ears with a star-shaped blue sclera, thick lip, slender chin, narrow face, wide mouth, long face, underdeveloped teeth, etc.), as well as intellectual impairment, cardiovascular disease, endocrine disorders, and growth retarding. The disease often affects multiple organ systems, with damage to the cardiovascular system being the most common. The endocrine problems of WBS are mainly manifested as hypercalcemia, hyperglycemia, thyroid dysfunction and precocious puberty. In June 2022, the First Affiliated Hospital of Guangzhou University of Chinese Medicine admitted a child with severe diabetic ketoacidosis (DKA), which was eventually diagnosed as WBS. The following is a summary of the treatment process of this child and a review of relevant literature.

1. Patient data

An 8-year-old boy presented with progressive dyspnea accompanied by fatigue after drinking a lot of carbonated beverages, and came to the doctor with the chief complaint of “dyspnea accompanied by fatigue for 1 day”. At the emergency

department, the child presented with confusion, shortness of breath at a rate of 55 beats per minute, heart rate up to 130 beats per minute, abnormally high blood glucose measurements, and blood pressure of 85/50 millimeters of mercury (mmHg). After rapid intravenous infusion of normal saline, the child was admitted to the hospital with “severe diabetic ketoacidosis.”

History review: The child was the second child, full term natural birth, no asphyxia at birth, the mother was healthy during pregnancy, and the parents were not married to close relatives. She had type 2 diabetes in her family and denied any other genetic history. The child was diagnosed with “autism” at the age of 2, and is now undergoing regular rehabilitation training, and has been able to make basic eye contact and simple responses.

Physical examination showed that the child was 131 cm tall, weighed 27 kg, and had a BMI of 15.73 kg/m². Long in the middle, thickened upper lip, low palatal arch, strong heart sound, audible and rumbling murmurs in the apex of the heart, no pathological murmurs found in the rest of the auscultation area, slight pigmentation at the edges of the fingers and toes.

Auxiliary test results: Blood gas analysis showed potential of hydrogen (pH) 6.835, blood glucose 33.7 mmol/l, lactic acid 2.12 mmol/l, total carbon dioxide (TCO₂) 2.8 mmol/l, standard base excess (SBE) −31.6 mmol/l, actual base excess (ABE) −30.8 mmol/l. β-hydroxybutyric acid 11.54 mmol/l; Lipase 642 U/L, amylase 1132 U/L, uric acid 862 umol/L; C-peptide 0.107 ng/ml; The thyroid function test results were thyroid stimulating hormone(TSH) 0.350 mIU/L, total triiodothyronine (TT3) 0.68 nmol/L, total thyroxine (TT4) < 6.4 nmol/L, free triiodothyronine (FT3) 3.05 pmol/L, free thyroxine (FT4) 3.64 pmol/L. Cortisol > 60 ug/dl, adrenocorticotrophic hormone (ACTH) 955.28 pg/ml; Total cholesterol 5.75 mmol/L, triglyceride 5.08 mmol/L; Diabetes autoantibodies: Negative; Bedside electrocardiogram: No abnormalities detected. Cardiac ultrasound findings: Ejection fraction (EF) 59%, congenital heart disease with supravalvular aortic stenosis (pressure gradient = 42 mmHg), anomalous Eustachian valve, and mild tricuspid regurgitation.

Treatment process: After admission, after 48 h of balanced fluid rehydration (keeping fluid tonicity at 1/2 strength and maintaining a drip rate of 105 mL/h) and continuous injection of low-dose insulin (0.1 U/kg/h), metabolic indexes such as amylase, blood lipids, thyroid function, cortisol and ACTH gradually returned to normal. After the condition stabilized, the treatment was changed to subcutaneous insulin injection (insulin aspartate + insulin glargine) with a dose of 1 IU/Kg/day. The changes of various blood laboratory test indicators are shown in **Table 1**.

Table 1. Changes in various indicators over time.

	Day 1 4 am	Day 1 8 am	Day 1 12 am	Day 1 6 pm	Day 1 10 pm	Day 2 9 am	Day 2 3 pm	Day 2 10 pm	Day 3 7 am	Day 4 7 am
BG (mmol/L)	20.6	12.8	11.4	11.9	6.1	7.0	10.2	12.1	15.3	
pH	6.970	7.163	7.223	7.288	7.414	7.37	7.405	7.475	7.436	
Bicarbonate (mmol/L)	3.1	6.0	11.2	14.4	15.2	19.3	21.1	20.9	20.2	
BOHB (mmol/L)	8.62	4.90	2.73	0.86	0.77	1.18	0.12	0.10	0.07	

Table 1. (Continued).

	Day 1 4 am	Day 1 8 am	Day 1 12 am	Day 1 6 pm	Day 1 10 pm	Day 2 9 am	Day 2 3 pm	Day 2 10 pm	Day 3 7 am	Day 4 7 am
K (mmol/L)	4.64	4.61	3.96	3.40	3.61	3.88	3.14	2.78	3.25	
Na (mmol/L)	124.7	125.0	123.9	125	125.6	129.1	128.9	129.7	129.1	
WBC ($\times 10^9/L$)	43.79		27.39							5.61
NEUT ($\times 10^9/L$)	33.76		22.27							2.61
PCT (ng/L)	14.14		22.98							1.19
AMY (U/L)	1132		2064						312	
TC (mmol/L)	5.75									3.01
TG (mmol/l)	5.08									1.31
HDL-C (mmol/l)	1.32									1.12
LDL-C (mmol/l)	2.41									1.37
TSH (mIU/L)	0.359									2.038
TT3 (nmol/L)	0.68									0.83
TT4 (nmol/L)	< 6.4									60.56
FT3 (pmol/L)	3.05									3.07
FT4 (pmol/L)	3.64									7.12

BG: Blood Glucose; pH: Potential of Hydrogen; BOHB: Beta-Hydroxybutyrate; AMY: Serum Amylase; K: Serum Potassium Ion; Na: Serum Sodium Ion; WBC: Blood White Blood Cell; NEUT: Blood Neutrophilic Granulocyte; PCT: Procalcitonin; TC: Total Cholesterol; TG: Triglyceride; HDLC: high density lipoprotein cholesterol; LDLC: low density lipoprotein cholesterol; TSH: thyroid stimulating hormone; TT3: free triiodothyronine; TT4: total thyroxine; FT3: free triiodothyronine; FT4: free thyroxine.

Genetic testing results: Full exon genetic testing was performed with the family’s consent. The results showed that there was about 1.4 Mb fragment deletion (see **Figure 1**) in the 7q11.23 region of the chromosome genome, involving several functional genes such as elastin gene (ELN) (see **Figure 2**). This deletion region was consistent with the recurrent copy number variation region of Williams-Beuren syndrome. Based on the patient’s history, symptoms, signs, and test results, WBS was diagnosed.

Chromosomal band	Variant type	Genes within the region	Related diseases	Variant source	Variant classification
7q11.23	Heterozygous deletion	ELN	Williams-Beuren syndrome	NA	Pathogenic variant

Result Interpretation: The CMA test results of the examinee indicate a deletion of approximately 1.4Mb in the chr7q11.23 region of the chromosome genome which includes several functional genes such as ELN. This copy number deletion region is consistent with the recurrent copy number variation region of 7q11.23 (Williams-Beuren Syndrome) (includes ELN), and this region is recorded in the ClinGen database as a definitive pathogenic region of haploinsufficiency.

Figure 1. Screenshot of the genetic disease gene detection report for the patient’s blood sample sent to Guangzhou KingMed Diagnostics for testing.

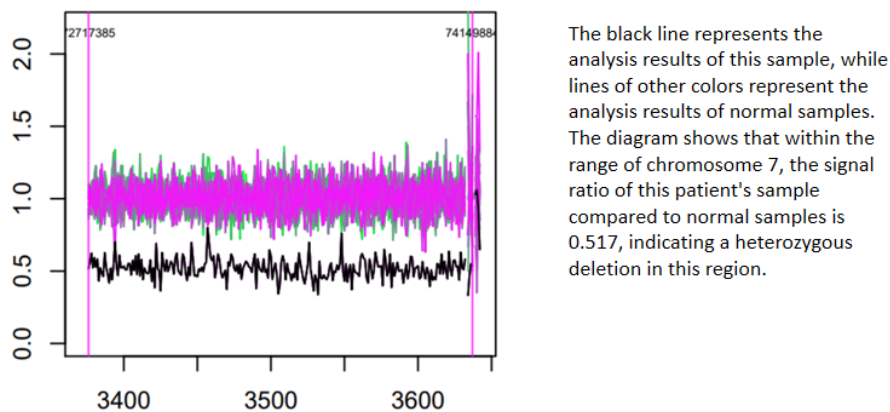


Figure 2. A segmental deletion on chromosome 7 in patients with Williams-Beuren syndrome (WBS).

Follow-up: After the diagnosis of diabetes, the child began to receive subcutaneous injection of insulin (insulin aspartate combined with insulin glargine). After one week of treatment, the blood sugar level of the child gradually decreased, and even hypoglycemia occurred during the treatment. Subsequently, we carefully adjusted the insulin dosage, and finally managed to control the blood sugar stability with only a small dose of insulin aspartate, and successfully discharged from the hospital. Blood glucose was self-monitored at home and returned to the hospital regularly for re-examination. The level of HBA1c was maintained between 6.5% and 7%, and the level of C-peptide fluctuated between 0.6–0.8 ng/ml. No abnormalities were found in thyroid function, cortisol, ACTH, pancreatic enzyme, blood lipid and blood calcium. After 2 years of follow-up, the patient was regularly treated with low-dose insulin aspartate and had no recurrence of DKA.

2. Discussion

WBS A rare genetic disorder of mental retardation characterized by dysfunction of multiple organ systems. The condition was first reported by Williams in New Zealand in 1961 and Beuren in Germany in 1962. WBS has a variety of clinical manifestations and can affect multiple body systems such as the cardiovascular system, nervous system and endocrine system. According to statistics, about 80% of children with WBS have cardiovascular malformation, of which suprapulvalvular stenosis is the most common, accounting for about 65%, followed by pulmonary stenosis and aortic coarctation, and these vascular stenosis conditions may gradually worsen with age. The child in this case was identified as suprapulvalvular stenosis, a major specific symptom of WBS, and is currently being regularly followed up by the Department of Cardiology without further intervention [2]. Children with WBS often experience varying degrees of growth retardation, motor or mental retardation, and abnormalities in behavioral and cognitive function. The child was diagnosed with autism at 2 years of age, but did not have the typical elven features (e.g., wide forehead, eyebrows, full eye circumference, wide eye distance, small eye cleft, star sclera, flat nose, forward nostril, long man, wide lips, round face, protruding ears, and small jaw), due to the fact that the child's facial features were only long for human appearance and wide lips. At that time, WBS was not considered and he only received mental rehabilitation training. Endocrine disorders of WBS include short

stature, early puberty or precocious puberty, hypercalcemia, hypothyroidism, dyslipidemia, bone metabolism disorders, impaired glucose tolerance and adult diabetes mellitus [3]. The patient was found to have elevated blood sugar due to severe diabetic DKA, and no abnormal conditions such as hypercalcemia and premature sexual development were found in the follow-up so far.

3. Review of relevant literature

In view of the early onset of severe DKA in this child, we conducted a review of relevant studies: microdeletions in the 7q11.23 chromosome region are the root cause of WBS. The high incidence of abnormal blood glucose in patients with WBS suggests the role of genetic factors, but the specific mechanism is not fully understood. Insufficient haploidy in key gene regions of WBS may increase the risk of developing diabetes. Because the clinical manifestations of WBS do not correspond directly to the genotype, but may involve complex intergene interactions, including the STX-1A gene encoding syntaxin-1A, a key protein for vesicle docking and insulin secretion [4,5]. And transcription factor MLX Interacting Protein Like (MLXIPL) encoding MAX Dimerization Protein (MLX) interacting protein-like or carbohydrate response element binding protein, which is involved in regulating insulin sensitivity related to glucose metabolism [6,7].

The gene report of the patient in this case indicates the deletion of ELN gene, which belongs to elastin coding, an extracellular matrix protein, and is mostly associated with the clinical phenotype of cardiovascular abnormalities in Williams syndrome. This patient had typical clinical manifestations of cardiovascular abnormalities, consistent with the clinical phenotype of ELN gene deletion. One animal study [8] showed that elastin deficiency ($Eln^{+/-}$) alone does not independently affect glucose metabolism or tissue lipid accumulation in mice. Apolipoprotein E (ApoE) deficiency alone ($ApoE^{-/-}$), in a model of hyperlipidemia and atherosclerosis, does not impair insulin sensitivity. However, mice with $Eln^{+/-}$ and $ApoE^{-/-}$ double mutations showed significant hyperglycemia, adipocyte hypertrophy, adipose tissue inflammation, and ectopic lipid accumulation in liver tissue. In addition, $Eln^{+/-}$ independent of body weight or diet showed significant impairment of insulin sensitivity in ApoE mutants through insulin tolerance tests, suggesting that elastin deficiency may lead to metabolic diseases in susceptible individuals by affecting metabolic pathways such as glucose metabolism, insulin secretion and insulin sensitivity. However, the follow-up whole exon gene test of this patient did not find significant ApoE gene or other gene mutations, large fragment deletion and other conditions. Therefore, the mechanism of diabetes and DKA in children with WBS remains unclear.

Seven studies have reported the oral glucose tolerance test (OGTT) results of WBS children and adults [8–14], and found that most WBS patients with diabetes do not have a typical family history of diabetes, low body mass index (BMI), and normal or mildly elevated HBA1c levels [9,11,12]. Despite the limitations of traditional diabetes diagnostic methods and risk assessment tools in early identification of impaired glucose tolerance or diabetes in patients with WBS, OGTT is still considered the preferred method for screening for diabetes in patients with

WBS. The researchers recommend that starting at puberty, fasting blood glucose testing should be performed first, and if abnormal fasting blood glucose is found, further OGTT testing should be performed. One study [15] performed OGTT testing on 28 adult WBS patients, 75% of whom showed abnormal glucose metabolism profiles that met diagnostic criteria for diabetes or prediabetes. In addition, to date, no positive islet autoimmune markers have been reported in patients with WBS, so routine islet autoantibody testing is not recommended in patients with WBS. However, islet autoantibody testing is still justified and necessary in children or adolescents with WBS who develop diabetes, and in adults with rapid deterioration of atypical blood glucose accompanied by ketosis. According to literature analysis, the pathogenesis of diabetes in patients with WBS may be more similar to that of type 2 diabetes.

For the diagnosis of diabetes or abnormal glucose tolerance in common children, current first-line treatment usually involves lifestyle changes, primarily weight loss through diet and exercise management. However, for the treatment of diabetes in children with WBS, there is a lack of long-term complication risk assessment and studies on specific drug formulations. Although metformin offers a multipotency and low-risk treatment option, it is unclear whether these children need medication, as well as the benefits and benefits of this form of treatment and whether it reduces the risk of diabetes-related complications.

Summarizing the existing literature, the onset of diabetes in WBS patients is mostly in adolescence or adulthood, and the incidence is less and the symptoms are mild in childhood. The cases of WBS diabetes in children with DKA as the first symptom have not been reported. Based on literature reports and United States of American National Institutes of Health (NIH) treatment recommendations, glucose tolerance testing after age 20 is recommended for patients with WBS. Our reported cases, although their pathogenesis is unclear, suggest that clinicians may need to pay earlier attention to glucose metabolism in children with WBS.

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Ethical approval: The studies were conducted in accordance with the Declaration of Helsinki, involving human participants were reviewed and approved by Ethics Committee of First Affiliated Hospital of Guangzhou University of Chinese Medicine. The ethics approval number is K-2024-064.

Conflict of interest: The authors declare no conflict of interest.

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