Fanconi-Bickel syndrome in an infant with cytomegalovirus infection: A case report and review of the literature

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BACKGROUND
Fanconi–Bickel syndrome (FBS) is a rare autosomal recessive disorder caused by mutation of the SLC2A2 gene, which encodes glucose transporter protein 2 (GLUT2).

CASE SUMMARY
We report a 7-mo-old girl with cytomegalovirus infection presenting hepatomegaly, jaundice, liver transaminase elevation, fasting hypoglycemia, hyperglycosuria, proteinuria, hypophosphatemia, rickets, and growth retardation. After prescription of ganciclovir, the levels of bilirubin and alanine aminotransferase decreased to normal, while she still had aggravating hepatomegaly and severe hyperglycosuria. Then, whole exome sequencing was conducted and revealed a homozygous c.416delC mutation in exon 4 of SLC2A2 inherited from her parents, which was predicted to change alanine 139 to valine (p.A139Vfs*3), indicating a diagnosis of FBS. During the follow-up, the entire laboratory test returned to normal with extra supplement of vitamin D and corn starch. Her weight increased to normal range at 3 years old without hepatomegaly. However, she still had short stature. Although there was heterogeneity between phenotype and genotype, Chinese children had typical clinical manifestations. No hot spot mutation or association between severity and mutations was found, but nonsense and missense mutations were more common. Data of long-term follow-up were rare, leading to insufficient assessment of the prognosis in Chinese children.

CONCLUSION
FBS is a rare genetic metabolic disease causing impaired glucose liver homeostasis and proximal renal tubular dysfunction. Results of urine and blood testing
suggested abnormal glucose metabolism could be the clues for FBS in neonates and infants. Genetic sequencing is indispensable for diagnosis. Since the diversity of disease severity, early identification and long-term follow-up could help improve patients’ quality of life and decrease mortality.

**Key Words:** Fanconi–Bickel syndrome; Glucose transporter protein 2; Case report; Children; Chinese

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**INTRODUCTION**

Fanconi–Bickel syndrome (FBS), also known as glycogen storage disease type XI (OMIM227810), is a rare, autosomal recessive disorder first described by Fanconi and Bickel in 1949[1]. FBS is caused by mutations in the _SLC2A2_ gene, which encodes glucose transporter protein 2 (GLUT2). GLUT2 is a member of the facilitative glucose transporter family and is expressed in liver cells, renal tubular epithelial cells, pancreatic β cells, and the intestinal mucosal epithelium. Mutations that alter the structure or structural dynamics of GLUT2 impair glucose transportation, leading to hepato-renal glycogen accumulation[2]. Generally, impaired glucose liver homeostasis and proximal renal tubular dysfunction are mainly present in FBS children. Clinical manifestations of FBS include hepatomegaly, glucose intolerance, fasting hypoglycemia, hyperglycosuria, proteinuria, hypophosphatemia, rickets, and growth retardation. To date, there have been more than 40 different _SLC2A2_ mutations reported in FBS patients across the world[3-13]. Due to the rarity of FBS, some patients may be misdiagnosed, especially if symptoms overlap those of other diseases. Here, we report a rare case of an infant with cytomegalovirus (CMV) infection that was identified with a mutation of the _SLC2A2_ gene and diagnosed with FBS.

**CASE PRESENTATION**

**Chief complaints**

A 7 mo-old girl presented obvious abdominal distension for more than 2 mo.

**History of present illness**

Two months ago, her parents found that this female infant presented aggravating abdominal distension and jaundice. She had normal milk ingestion and the color of the stool was normal. She failed to gain weight after 5 mo of age, while the motor development was normal referring to the age.

**Personal and family history**

The infant was born at full term and appeared healthy at birth, weighing 3.2 kg. She was fed a combination of breast milk and cow milk formula. Her brother was healthy with no symptoms. No family history of relevant diseases was reported.
Physical examination
The patient was found to have moderate jaundice and hepatomegaly with the liver palpable 5 cm below the costal margin (Figure 1). Her weight was 5.0 kg (< -2SD) and height was 54 cm (< -3SD) at examination.

Laboratory examinations
Laboratory tests showed elevated serum liver transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γ-GT), and alpha-fetoprotein, moderate hyperbilirubinemia (direct bilirubin 68%), fasting hypoglycemia (2.01 mmol/L), and hypophosphatemia. A routine urine test revealed proteinuria (+) and hyperglycosuria (++ to ++++), with a 24 h urinary protein excretion of 0.415 g. CMV infection was identified by CMV-IgM (> 140 U/mL) and positive urine and serum CMV-DNA (1.2 × 10⁵ copies/mL). Other laboratory tests were normal, including microbiology and ceruloplasmin. Hearing test was normal.

Imaging examinations
Contrast-enhanced computed tomography confirmed the presence of hepatomegaly and decreased liver density. There was no evidence of morphological abnormality in the kidney or other organs.

MULTIDISCIPLINARY EXPERT CONSULTATION
The infant was initially diagnosed with CMV infection and given a 2-wk course of ganciclovir, combined with a diet of milk without lactose and high in medium-chain triglycerides. Two weeks later, bilirubin and ALT levels decreased to normal. However, the patient still had aggravating hepatomegaly and severe hyperglycosuria. Sine congenital or hereditary liver diseases were suspected, whole exome sequencing was conducted.

FINAL DIAGNOSIS
Whole exome sequencing revealed a homozygous c.416delC mutation in exon 4 of SLC2A2, which was predicted to change alanine 139 to valine (p.A139Vfs*3), indicating a diagnosis of FBS. Both parents were also found to be heterozygous for the same mutation.

TREATMENT
The infant was supplied with corn starch besides the formula and extra vitamin D.

OUTCOME AND FOLLOW-UP
During the follow-up, all the laboratory test results maintained normal after one year of standard treatment. Her weight had increased to 12 kg (Z score: -2 to -1) and her liver was no longer enlarged. However, she still had short stature, with a height of 83 cm (Z score: < -2).

DISCUSSION
In this study, we report the case of an infant with CMV infection diagnosed with FBS. We made the diagnosis of CMV infection by elevated CMV specific IgM, and CMV-DNA in serum and urine by PCR. However, since we tested for CMV after 21 d and the hearing test was normal, we regarded that the virus was acquired postnatally. Initially, we attributed the signs and symptoms to the CMV infection as sequelae, and used ganciclovir. Although the levels of bilirubin and alanine aminotransferase decreased to normal after antiviral treatment, she still had aggravating hepatomegaly and severe hyperglycosuria. Perinatally, CMV infection acquired from infected mother...
is a common situation in Chinese infants (CMV maternal seroprevalence is 96.2%)\(^{[13]}\), while FBS is a rare metabolic disease worldwide. We proposed that hereditary metabolic diseases such as FBS ought to be considered in cases where initial therapy to treat CMV infection did not completely alleviate symptoms, or where there were other symptoms that could not be explained by CMV infection entirely.

In our case, proteinuria and hyperglycosuria were found in this 7-mo-old infant. Although there were some overlap symptoms with GSD-I like hepatomegaly and hypoglycemia, the previous cases reported by Riva S and Bahillo-Curieses MP suggested that FBS might be taken into consideration if infants present with polyuria, glycosuria, and hyperglycemia\(^{[14,15]}\). Therefore, the results of urine and blood testing suggesting abnormal glucose metabolism could be the clues for FBS in neonates and infants.

The most straightforward and accurate method to diagnose FBS is the sequencing of \(\text{SLC2A2}\) gene. Santer \textit{et al.}\(^{[14]}\) reported 33 different \(\text{SLC2A2}\) mutations (9 missense, 7 nonsense, 10 frameshift, and 7 splice-site) detected in 49 FBS patients. The prevalence of \(\text{SLC2A2}\) mutations is relatively low in most populations, and no mutation hot spots have been reported\(^{[14]}\). A liver biopsy also provides additional information for understanding this rare disease, but it is not definitive proof of FBS. Therefore, biopsies are typically performed only for unusual cases of FBS involving severe acute acidosis\(^{[17]}\) or hepatocellular carcinoma\(^{[18]}\).

Various \(\text{SLC2A2}\) mutations identified including missense, nonsense, insertions, deletions, splice site, and frame-shift indels have been reported in cases around the world. Previous studies reported that FBS patients with a homozygous p.R310X mutation had failure to thrive and a doll-like face and/or hepatomegaly\(^{[19]}\). However, diverse clinical presentations and progressions were observed even in patients with same mutation\(^{[11]}\). The association between phenotype and phenotype heterogeneity was controversial. Therefore, the disease severity was considered to be affected primarily by patient growth pattern, maximal electrolyte replacement, and skeletal and renal complications. Recently, Enogieru \textit{et al.}\(^{[21]}\) conducted a comprehensive analysis including functional assays and structural analysis of 17 mutations to characterize the pathogenesis of \(\text{SLC2A2}\) variants in FBS. They found that GLUT2 variants could affect substrate-binding, steric hindrance, or overall transporter structure. However, only half of the mutant transporters expressed on the plasma membrane had no function, while the majority of \(\text{SLC2A2}\) missense mutations were associated with normal glucose uptake.

Generally, the majority of FBS patients with mild symptoms have a good prognosis after treatment with standard therapy of supplementation with electrolytes, vitamin D, and corn starch. Poor clinical outcomes and complications including bone fractures, hepatocellular carcinoma, liver failure, and death were reported rarely in patients with delayed diagnosis and treatment\(^{[18,22,23]}\). Although patients exhibited catch-up growth with nutrition supported, some case series reported that there was still some impact on linear growth\(^{[24]}\). Recently, a study suggested the intensive nutritional intervention including nocturnal enteral nutrition and uncooked cornstarch was able to rescue...
growth failure with final growth parameters into the normal range\(^{25}\). Follow-up compliance and hospitalization also play a role in FBS prognosis. One study reported that a female FBS patient who was followed for at least 20 years became pregnant at 31 years of age and delivered a healthy boy, despite having reduced adult height, osteopenia, and other clinical problems\(^{26}\). This demonstrates the importance of long-term follow-up to deepen our understanding of this rare metabolic disorder and improve quality of life in affected children and their families. Little is known about epidemiological features of FBS children in China. The first two pediatric FBS cases were reported in 2011\(^7\). To date, there have been nine cases of FBS associated with various SLC2A2 mutations reported in China, including our case\(^{27-31}\) (Table 1). Seven patients were female, and one was male, suggesting that FBS might be more prevalent in females in China. The onset age of diagnosis ranged from 1-18 mo, with no adolescent cases. The majority of reported patients showed typical clinical features of FBS including hepatomegaly (100%), hypophosphatemic rickets (100%), failure to thrive, fasting hypoglycemia, postprandial hyperglycemia (100%), glucosuria (100%), and proteinuria (100%). All the cases were diagnosed through gene sequencing analysis. Except that one case was confirmed to have de novo mutation, all other patients inherited the FBS mutation from parents. No Chinese families with multiple familial FBS cases have been reported. All Chinese FBS patients had similar clinical manifestations, and there was no association found between clinical severity and mutations. Although no hot spot mutation was found, nonsense and missense mutations were more common than other types of mutations. Long-term follow-up data were rare in China, leading to insufficient assessment of the prognosis in Chinese children. Although symptoms were improved with appropriate treatment, one case was reported to be dead due to severe diarrhea and surgery, which may have been associated with a severe acid-base disturbance\(^{28}\).

**CONCLUSION**

In conclusion, FBS is a rare genetic metabolic disease causing impaired glucose liver homeostasis and proximal renal tubular dysfunction. Results of urine and blood testing suggesting abnormal glucose metabolism could be the clues for FBS in neonates and infants. Genetic sequencing is indispensable for diagnosis. Since the diversity of disease severity, early identification and long-term follow-up could help improve patients’ quality of life and decrease mortality.
Table 1 Fanconi-Bickel syndrome cases in China with different glucose transporter protein 2 mutations

| Patient | Age (mo) | Gender | Mutation | Amino acid change | Mutation in mother | Mutation in father | Mutation type |
|---------|----------|--------|----------|-------------------|--------------------|--------------------|--------------|
| 1[62]  | 12       | Female | c.1068+5G>C | Not stated | C.1068 + 5G>C | Unknown | Splice-site |
| 2[62]  | 9        | Female | c.1194T>A | p.Tyr398X | Unknown | Unknown | Missense |
| 3[62]  | 17       | Female | c.380C>A | p.Ala127Asp | None | c.380C>A | Missense |
| 4[62]  | Not stated | Not stated | c.970dupT | p.324Tyrfxf392 | None | None | Repeat (de novo) |
| 5[62]  | 12       | Female | c.682C>T | p.Arg228X | c.682C > T | None | Missense |
| 6[62]  | 11       | Male  | c.1194T>A | p.Tyr398X | None | c.1194T>A | Missense |
| 7[62]  | 1        | Female | c.609T>A | p.Ser203Arg | c.609T > A | c.609T>A | Missense |
| 8      | 6        | Female | c.416delC | p.A139Vfs*3 | c.416delC | c.416delC | Frameshift |
| 9      | 18       | Female | c.1134,1137del | p.V378fs | c.1134,1137del | - | Frameshift |

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