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Case report

Sirolimus therapy and follow-up in a patient with severe congenital hyperinsulinism following subtotal pancreatectomy

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What is already known on this topic?

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in neonates and infants. Sirolimus may be an effective treatment option in patients with CHI resistant to traditional medical therapy or failure of subtotal pancreatectomy, but experience is limited.

What this study adds?

This article further revealed the safety and efficacy of sirolimus in the very young patient with CHI, which can make us better understand the new treatment. The patient has a heterozygous ABCC8 mutation. It's also the first Chinese CHI patient with heterozygous ABCC8 mutation who used sirolimus.

Abstract

Congenital hyperinsulinism (CHI) is the most common cause of severe, persistent hypoglycemia in neonates and infants. Current available treatment is subtotal pancreatectomy if the patient does not respond to medical treatment but some of the patients still experience severe hypoglycemia after the surgery. Sirolimus, a mammalian target of rapamycin(mTOR) inhibitor recently has been reported to be effective in the treatment of insulinoma and CHI patients. Here we report a patient with CHI who had prolonged hypoglycemia after the subtotal pancreatectomy. The patient with a heterozygous mutation in ABCC8 was unresponsive to **optimal dose** of diazoxide (15 mg/kg/day) and octreotide (30μg/kg/day). The patient subsequently had subtotal pancreatectomy; however, the patient continued to have severe and persistent hypoglycemia. Sirolimus was commenced. Glycemic control had remarkable improvement without major adverse events, although he required a small dose of octreotide to maintain euglycemia. Sirolimus therapy was discontinued when the patient was 15 months old. The patient had been having a good glycemic control at the time of this report when he was three years and 8 months old. This report suggests that sirolimus may be an effective treatment option in patients with CHI resistant to traditional medical therapy or failure of subtotal pancreatectomy. However, the long-term safety needs to be studied in larger group of very young patients.

Keyword: congenital hyperinsulinism; hypoglycemia; mTOR; sirolimus; ABCC8

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Introduction

Congenital hyperinsulinism (CHI), the major cause of persistent hypoglycemia in neonates and infants, is characterized by inappropriate insulin secretion from pancreatic beta cells in the presence of low blood glucose levels [1]. Prompt and early management of these patients is very important for the neurological prognosis [1,2]. The incidence of CHI in the general population is estimated at 1/30,000–1/50,000 live births [3,4]. Two major histologic subtypes have been described: diffuse (60%–70% of patients) and focal (30%–40% of patients) [5]. Mutations in ABCC8 and KCNJ11 cause severe CHI that is unresponsive to medical treatment with diazoxide and octreotide [1]. The current treatment for patients is a subtotal pancreatectomy [5,6]. However, despite surgery, 40-59% of operated patients continue to experience severe and persistent hypoglycemia for months or even years [7], and nearly 100% will develop diabetes mellitus within 11 years after the surgery [8]. Therefore, medical therapeutic alternatives should be considered aimed at reducing insulin secretion thereby preventing neurologic consequences. Constitutive activation of the mTOR pathway has been postulated as a mechanism for hyperinsulinism and β-cell hyperplasia in diffuse CHI [9]. Recent advances have shown the effectiveness of sirolimus, mTOR inhibitor, in infants with severe diffuse CHI that had been unresponsive to medical therapy [10,11,12,13], one of which had undergone subtotal pancreatectomy [10]. During follow-up no major adverse events had been observed in the patients. We report a patient with CHI failed to achieve euglycemia after pancreatectomy. The patient was successfully treated with sirolimus without further surgical intervention.

Case report

The patient, a male infant, was born by cesarean **at** the 39th week of gestation to nonconsanguineous Chinese parents after an uneventful pregnancy. Birth weight was 3600 g. On the first day of his life, he was found to have severe hypoglycemia when he developed lethargy and seizures. He required high intravenous glucose infusion rate (GIR) (13mg/kg/minute) to maintain normal blood glucose level. As he had persistent and severe hypoglycemia, he was transferred to our hospital for further management **on postnatal day (PD) 13. During an hypos episode, the relevant inspection results are as follows**: glucose, 2.3 mmol/L; concomitant serum insulin, 13.52 (4.03-23.46)μIU/mL; C-peptide 4.25(0.3-3.73)ng/mL; Beta-hydroxybutyrate<0.1mmol/L. He had a normal TSH and free T4 levels; Screening of plasma and urine metabolic profiles were no specific. Genetic analysis subsequently confirmed a novel mutation c.1585_1587del in exon 10 of ABCC8 gene (Figure 1), which is predicted to result in 529 amino acid (Glu) deletion of encoded protein. His father has the same mutation, **but in normal phenotypes. The mutation is absent from a race-matched population and the protein length changes due to in-frame. According to ACMG (American college of Medical Genetics) criteria， the mutation is uncertain significance and should be further studied [14].** MRI scan of brain showed abnormalities on both sides of the parietal white matter. Subsequently maximal GIR was 16 mg/kg/min administered parenterally via a central venous catheter. Diazoxide therapy was commenced on **PD** 14 and was gradually increased to an **optimal** dose of 15 mg/kg/day with no response. On **PD** 20 Nifedipine was added to the therapeutic regimen, but it was discontinued after a week due to lack of response. Subcutaneous octreotide was initiated on **PD** 29. The octreotide dose was increased to a maximum dose (30μg/kg/day), but only a 20% reduction in total glucose requirements. On **PD** 55 a subtotal pancreatectomy was performed at Children's Hospital of Fudan University, Shanghai, China. **Histopathological results** confirmed diffuse hyperplasia of the islet cells (Figure 2). Subcutaneous octreotide was discontinued after the surgery, but the minimum GIR was 10 mg/kg/min. Octreotide subcutaneous injection was resumed with the dose of 30 μg/kg/day. Over the next few weeks, there was no reduction in his glucose requirement. The total volume of nasogastric and parenteral fluids reached 190 ml/kg/d and it was

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also very difficult to establish a central venous line.

In view of the multiple medical problems, further surgery was being contemplated. After reviewing the risks and benefits Sirolimus was proceed as an alternative treatment option. Sirolimus was initialed at 4.5 months of age with the dose of 0.5 mg/m^2/day. The dose was gradually increased to the goal of reaching a serum trough level of 5-15ng/dL. The serum trough level of sirolimus was measured every 5-7days. After **10 days** treatment with sirolimus, intravenous glucose infusion and subcutaneous octreotide were gradually tapered. Four weeks following initiation of sirolimus, stable blood glucose homeostasis was achieved without intravenous glucose infusion, and the octreotide dose was reduced from 30 μg/kg/day to 15 μg/kg/day. The patient was able to tolerate fasting for 4 h with blood glucose level > 60mg/dL prior to discharge **according to continuous glucose monitoring**. The patient was followed regularly for assessment of glycemic control and measurement of serum sirolimus levels. Sirolimus was discontinued at 15 months of age. **The maximum dose of sirolimus used was 3.2 mg/m^2/day.**

The patient has been having a good glycemic control when suspend sirolimus. When his appetite was bad, he still **needed** to use low dose of octreotide to control blood glucose. Complete blood count, serum lipid profile, renal function and liver function have been monitored regularly and no significant side effects were observed except mildly elevated triglyceride level at 2 years and 3 months old. The patient was followed up to 3 years and 6 months old until the article was written. The octreotide dose was 2ug/kg/day when his appetite was poor. **At the last visit, the patient was able to tolerate fasting for 6 h according to continuous glucose monitoring. The blood glucose was 95mg/dL and the insulin was 4.9μIU/mL.**

Discussion

The management of diffuse CHI that is unresponsive to diazoxide poses a major therapeutic challenge. While subtotal pancreatectomy remains the procedure of choice following failure of medical therapy, **the** surgery is not completely curative and **it still could be** associated with unsatisfactory glycemic control. The fluorine-18-dihydrophenylalanine (^{18}FDOPA) positron emission tomography was not performed in our patient before the surgery since it was not **available in children in China at the time**, but based on **the increased number** of islets and **enlarged volume** of partial regional islets in histopathology as well as the recurrent severe hypoglycemia after subtotal pancreatectomy the patient likely has a diffuse CHI. **The patient has a heterozygous mutation in ABCC8. Definitely, most dominant acting monoallelic KATP gene mutations cause mild diazoxide responsive CHI. But Saint-Martin C. et al. reported that some dominant ABCC8 mutations are responsible for a subset of diffuse diazoxide-unresponsive forms of CHI. The mechanism is unclear and need further studied [15]. After the pancreatectomy,** the total amount of nasogastric and parenteral fluids had reached the maximum, and it was also very difficult to establish a central venous line. Therefore, there was a need for an alternative **treatment** minimizing the requirement for repeat pancreatectomy, and the burden of demanding medical and nutritional intervention in our patient.

Sirolimus has been reported as a treatment option for unresponsive CHI [10,11,12,13]. No major adverse reactions were observed during follow-up period in these case reports, though a recent study in two large centers showed that mTOR inhibition achieved **euglycemia**, fasting tolerance and reduced medical therapy only in 30% patients and **more adverse** events were observed [16]. mTOR is a serine and threonine protein kinase that integrates signals from mitogens and the nutrients, glucose and amino acids, to regulate cellular growth and proliferation [17]. The mechanism of mTOR inhibitors in CHI has not been fully delineated. The hyperplasia of β-cell has been proposed to involve in **trans differentiation** of mature acinar and ductal elements of exocrine pancreas into insulin-secreting cells, which is possibly mediated by the constitutive activation of the mTOR pathway [18]. mTOR inhibition may also affect the number of insulin receptors that are present in pancreatic β-cells, which would reduce insulin production [19]. In cultures, sirolimus has been used to induce fulminant diabetes by promoting insulin resistance and reducing β-cell mass through apoptosis induction [20, 21]. Furthermore, long-term management with sirolimus was found to cause glucose intolerance by up-regulating hepatic gluconeogenesis [22]. The mechanism of mTOR inhibition is also postulated to reduce in islet cell proliferation [11,12]. This was recently confirmed by genomic datasets implicating the IGF-1/mTOR/Akt pathway with the pathophysiology of CHI [9] but another

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study shown that mTOR pathways are not downregulated in keeping with nonresponse to sirolimus and the observation that proliferation remains high after treatment with sirolimus [16].

The reported adverse effects of sirolimus treatment include stomatitis, fatigue, immunosuppression, increased risk of infections, renal function abnormalities, hyperlipidemia, and pneumonitis [21,23], which are reversible with dose reduction. Mild elevation of triglycerides **was** observed in our patient. Sirolimus appears to be well tolerated in children post renal transplant even when initiated with higher doses [6 mg/(m2 day)] and thereafter adjusted to achieve target trough levels in the range of 10–20 ng/mL [24]. These studies provide a reasonable safety profile of sirolimus, but the long-term safety remains unknown in younger children, particularly in neonates.

In conclusion, sirolimus was well-tolerated treatment in our patient with CHI who otherwise would have required second surgery, and no major adverse events were observed during the period of 10 months treatment. Sirolimus may be a feasible option for selected CHI patients with no contraindication, either before surgery or as an adjunctive therapy, although the mechanism and long-term adverse effects of such treatment require further study.

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Ethics

Ethics Committee Approval: The study was approved by the Institutional Review Board of Zhengzhou Children's Hospital.

Informed Consent: Informed consent was obtained from the parents of this patient.

Peer-review

Externally peer-reviewed

Authorship Contributions

Concept: Yun Yan, Haiyan Wei, Design: Haiyan Wei, Yongxing Chen, Data Collection or Processing: Qiong Chen, Xiaohong Wang, Haihua Yang, Yingxian Zhang, Xiaojing Liu, Analysis or Interpretation: Yongxing Chen, Yun Yan, Literature Search: Yongxing Chen, Yun Yan, Writing: Qiong Chen, Yongxing Chen, Yun Yan and Haiyan Wei.

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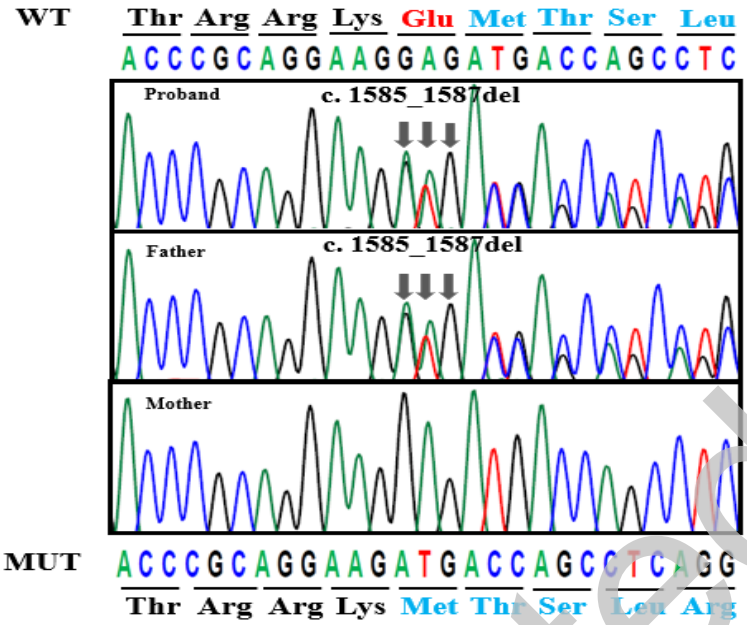

Figure1: Sanger sequencing of ABCC8 gene in the proband and his parents: the arrows showed the mutation site of the ABCC8 gene.

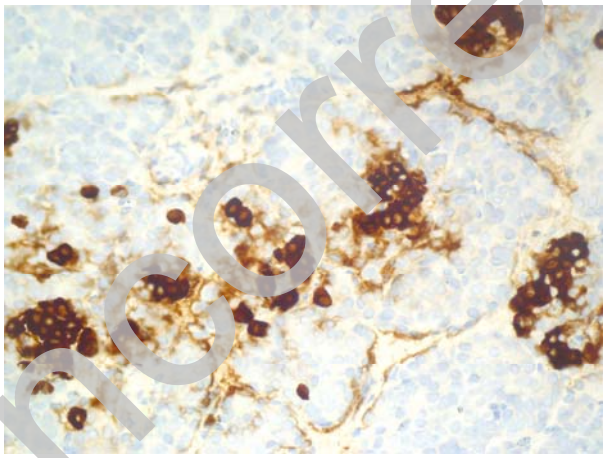

Figure 2: **Histopathological result** confirmed diffuse hyperplasia of the islet cells.

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