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Case Report

A synonymous *KCNJ11* variant leading to MODY13: A case report and literature review

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ABSTRACT

Background: Maturity-onset diabetes of the young, type 13 (MODY13) is a specific subclass of monogenic diabetes mellitus that does not exhibit the typical clinical manifestations of diabetes, necessitating the use of genetic testing for accurate diagnosis. With the progression of monogenic diabetes and MODY, the number of reported MODY13 cases has reached a minimum of 22. Nevertheless, there remains a dearth of information regarding patients diagnosed with MODY13 presenting synonymous variants.

Case presentation: This study presents a description of the clinical and genetic features of a 9-year-old male patient diagnosed with MODY13. A noteworthy finding in this case was the occurrence of a "separation phenomenon" between C-peptide and insulin during the standard meal test. Whole exome sequencing (WES) identified a KCNJ11 c.843C > T (p.L281=) mutation in exon 1, which contradicted the previously reported phenotype. Following the onset of ketosis, the patient underwent insulin therapy for a duration of one month, during which the insulin dosage was gradually modified based on blood glucose levels. In order to maintain normoglycemia, he adhered to a diabetic dietary regimen and participated in 1–2 h of moderate exercise daily.

Conclusion: The study implies that patient with *KCNJ11* variant shows a "separation phenomenon" between C-peptide and insulin in standard meal test. Our report also enriched the genotype and phenotype spectrums of MODY13 and highlighted the importance of genetic testing in patients without characteristic clinical symptoms of diabetes.

1. Background

Maturity-onset diabetes of the young (MODY) is a group of autosomal dominant non-ketotic diabetes mellitus, characterized by young-onset (6 months to 25 years), autoimmune-antibody-negative, and non-insulin-dependent [1,2]. Maturity-onset diabetes of the young, type 13 (MODY13, OMIM #616329) is one of the MODY subtypes with extremely few cases reported to date [3–8]. The KCNJ11(Potassium Channel, Inwardly Rectifying, Subfamily J, Member 11) subunit (Kir6.2) plays a role in the regulation of cellular metabolism and insulin secretion [9–15]. In 2012, by whole exome sequencing (WES) of MODY-X type families, Bonnefond et al. [6] first reported *KCNJ11*-related MODY, named MODY13.

Upon searching various databases, including Pubmed, Medline, and Embase, it was revealed that there are currently 22 MODY13 patients reported, among whom 6 are Chinese. This condition presents a challenge in terms of clinical recognition, as it can only be conclusively diagnosed through genetic testing [16]. *KCNJ11* has been found to have over 180 reported variants, one of which is the c.843C > T (p.L281=) variant that has been identified in a Chinese patient diagnosed with congenital hyperinsulinism [17]. There is no patient diagnosed with MODY13 carrying a synonymous heterozygous variant in *KCNJ11* reported till now.

Herein, we describe a case of MODY13 in a Chinese child with

Abbreviations: MODY13, Maturity-onset diabetes of the young, type 13; WES, whole exome sequencing; KCNJ11, Potassium Channel, Inwardly Rectifying, Subfamily J, Member 11; KATP, ATP-dependent K+ channel protein; SUR1, regulatory sulfonylurea receptor 1; TNDM3, Diabetes Mellitus, Transient Neonatal, 3; PNDM2, Diabetes Mellitus, Permanent Neonatal, 2; HHF2, Hyperinsulinemic Hypoglycemia, Familial, 2; DEND syndrome,, developmental delay, epilepsy, and neonatal diabetes mellitus; ADHD, attention-deficit/hyperactivity disorder.

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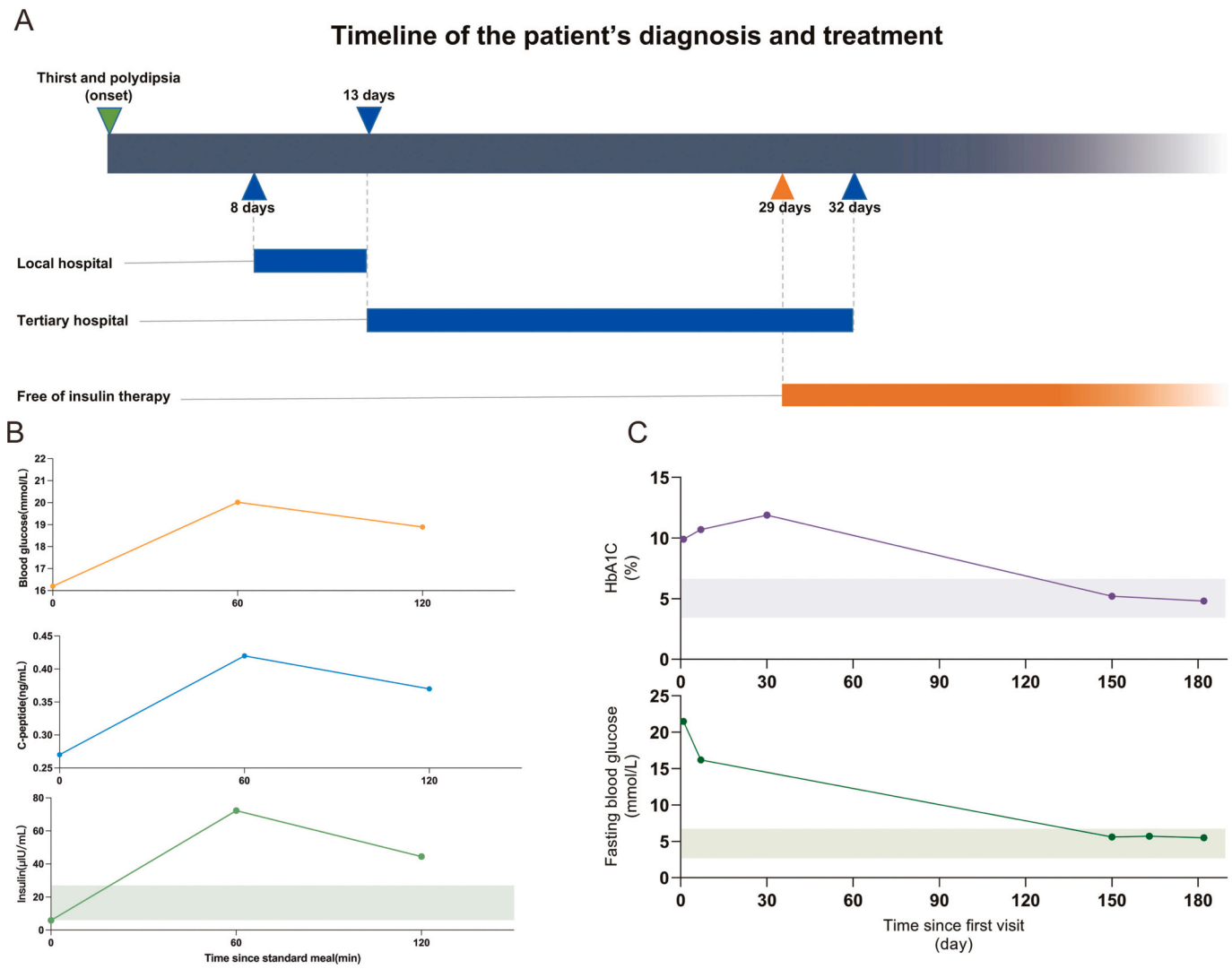

Fig. 1. A: Timeline of the patient's diagnosis and treatment. B: A two hours standard meal test showed a "separation phenomenon" between C-peptide and insulin in the standard meal test of the proband. At 1 h and 2 h, C-peptide was normal low while insulin was above twice normal values. C: The variation of fasting blood glucose and HbA1C in the patient.

KCNJ11 c.843C > T(p.L281=) variant who showed "separation phenomenon" between C-peptide and insulin in standard meal tests (normal low values of C-peptide while above twice normal values of insulin) and provide a comprehensive review of MODY13 to enhance the understanding of diagnosis and management.

2. Case presentation

The patient, a 9-year-old boy, G1P1, was born at 39th weeks with birth weight of 4 kg and his mother had a normal pregnancy without maternal diabetes or hypoglycemia. He presented to the local hospital with a two-week history of dry mouth and polydipsia and increased blood glucose levels (above 22 mmol/L) for eight days. He dropped 9 kg in a month. The patient's fasting blood glucose level was 21.5 mmol/L (3.9–6.2 mmol/L), urine ketones were present at a level of 3+, glycated hemoglobin was 9.9% (4–6%), and blood gas analysis revealed metabolic acidosis. 5 days in local hospital, the patient was diagnosed with metabolic acidosis. After ketoacidosis is corrected, the patient treated with a diabetes diet and insulin therapy, with fasting blood glucose ranging from 9.2 to 14.2mmo1/L, 2-h postprandial blood glucose ranging from 9.6 to 28.6mmo1/L. He was released once his health had stabilized (Fig. 1A). At the time of discharge, the insulin treatment plan is 8 IU menthol insulin intramuscularly before each meal and 6 IU glargine insulin before bedtime on the 8th day of onset (total insulin 30 IU/day, 0.625 IU/kg).

At the tertiary hospital, the patient sought advanced medical treatment after presenting with fasting glucose of 16.20 mmol/L (3.9–6.2 mmol/L) and glycated hemoglobin of 10.7% (4–6%). And the standard meal test demonstrated that his fasting blood glucose was 16.20 mmol/L, C-peptide was 0.27 ng/mL (1.1–5.0 ng/mL) and insulin was 5.9 IU/mL (6.0–27 IU/mL); postprandial 1 h blood glucose was 20.02 mmol/L, C-peptide was 0.42 ng/mL (1.1–5.0 ng/mL), and insulin was 72.3 IU/mL (6.0–27 IU/mL); postprandial 2 h blood glucose was 18.89 mmol/L, C-peptide was 0.37 ng/mL (1.1–5.0 ng/mL), and insulin was 44.5 IU/mL (6.0–27 IU/mL). In the standard meal test, there was a "separation phenomenon" between C-peptide and insulin (Fig. 1B). At 1 h and 2 h, C-peptide was normal low while insulin was above twice normal values. He was given an insulin pump regimen with fixed pre-meal dosing (1-2 IU/meal) at 13th day of onset. With titration based on blood glucose levels, the insulin pump was halted at 29th day of onset due to hypoglycemia (with blood glucose 3-4 mmol/L). After a four-month break from insulin, the patient returned to our hospital's outpatient clinic. His fasting blood glucose levels were 5–6 mmol/L, and postprandial glucose levels were 5–9 mmol/L (Fig. 1C). With diabetes diet management and

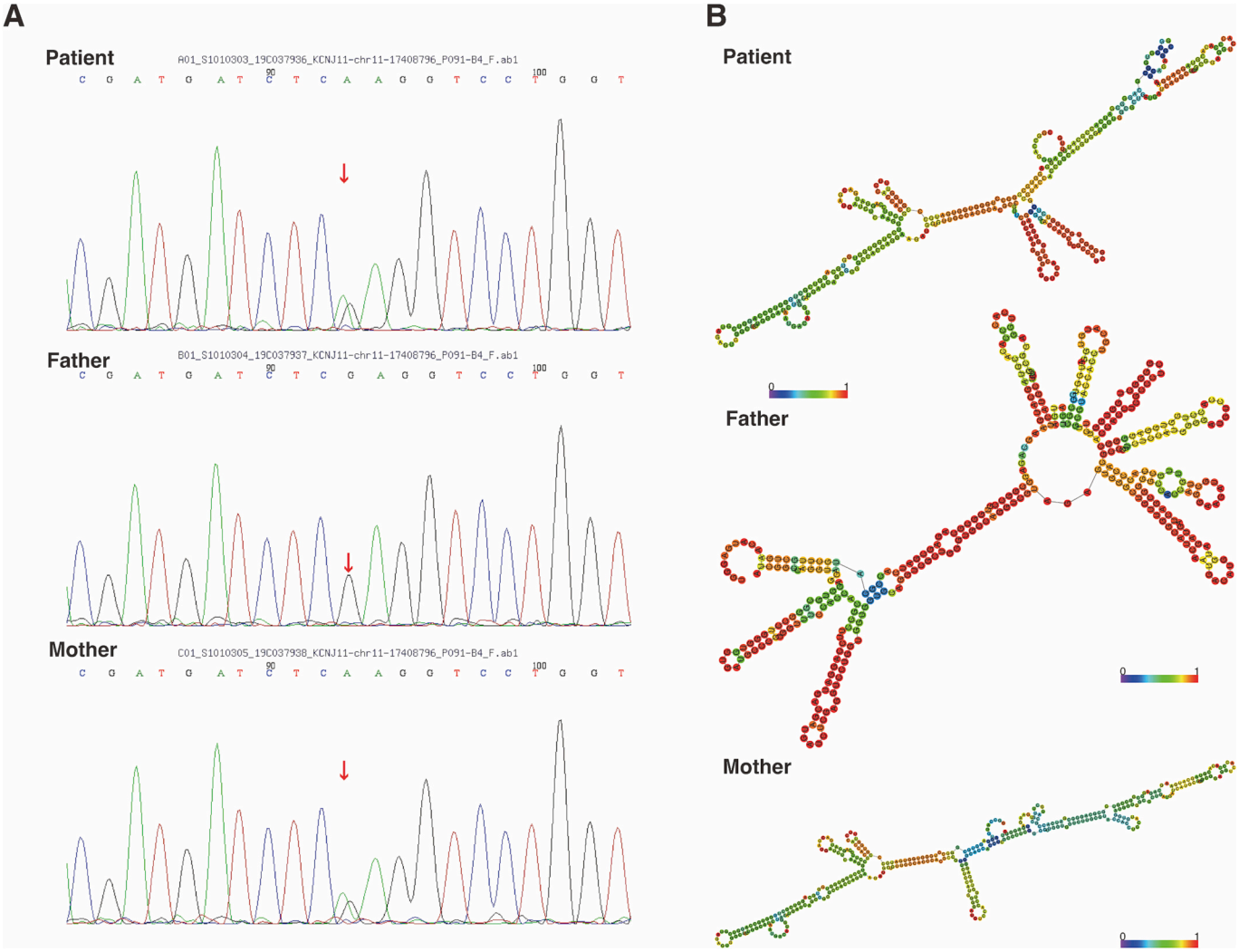

Fig. 2. A: Results of WES (Whole exon sequencing): WES revealed a heterozygous variant c.843C > T(p.L281=) in exon 1 of the KCNJ11, found in his mother, whereas his father had the wild type. B: Structure prediction of KCNJ11 by RNAfold (http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi): The patient and his mother who carries c.843C > T have morphologically comparable RNA structure of KCNJ11 which is completely separated from his mother.

regular moderate intensity aerobic exercise (60 min walks after dinner every day), his blood glucose remained at normal levels under continuous glucose monitoring.

There was no history of diabetes or obesity in the patient's family. On three separate occasions, the patient tested negative for anti-islet cell antibody IgG, anti-insulin antibody IgG, anti-glutamic acid decarboxylase antibody IgG, and anti-IA2. The blood count, stool routine test, thyroid function, and blood biochemical analysis were all normal. There were no abnormalities seen on an electrocardiogram or ultrasound examination of the liver, bile, pancreas, spleen, carotid artery, arteries, and veins of both lower limbs. A physical examination revealed no positive signs.

WES revealed a heterozygous variant c.843C > T(p.L281=) in exon 1 of *KCNJ11* (Fig. 2A), confirming a diagnosis of MODY13 in the patient, likely pathogenic in Clinvar. And the result of protein prediction software, such as REVEL, SIFT, PolyPhen_2, Mutation Taster, and GERP+, is unknown, respectively. The variant frequency of the population is 0.00036 (gnomAD v.2.1.1). Sanger validation of the variant gene showed the heterozygous variant c.843C > T(p.L281=) in the KCNJ11 was found in his mother, whereas his father had the wild type. Furthermore, none of the other MODY-related genetic abnormalities were detected [18]. The RNA structure of the patient and his parents is predicted by RNAfold (http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi) and reveals that c.843C > T(p.L281=) results in a significant change in RNA structure of *KCNJ11* (Fig. 2B).

3. Discussion and conclusions

The study reported the clinical and genetic characteristics in a Chinese patient with c.834C > T (p.L281=) in exon1 in *KCNJ11* diagnosed with MODY13. He is a 9-year-old boy with no diabetes family history, who had presented with dry mouth and polydipsia for two weeks, along with elevated blood glucose levels and weight loss. WES revealed that this child carries a synonymous heterozygous c.843C > T (p.L281=) in exon 1 of *KCNJ11*, derived from his mother, resulting in a significant change in the RNA structure of *KCNJ11*, and the pathogenicity of this variant is unknown.

Synonymous mutations play a key role in the regulation of gene expression and can be pathogenic in certain conditions. In 2020, Walsh [19] et al. found that codon-synonymous synapses can affect RNA structure, influence protein folding, and alter the function of molecular chaperones in the dynamic protein homeostasis network, resulting in pathogenicity. The same loci of variation may also exhibit diverse phenotypes due to multiple factors. In 2015, Victoria [20] et al. screened >1400 mutations in *Caenorhabditis elegans*, and it was found that 20% of the mutation types resulted in phenotypic severity that varied between

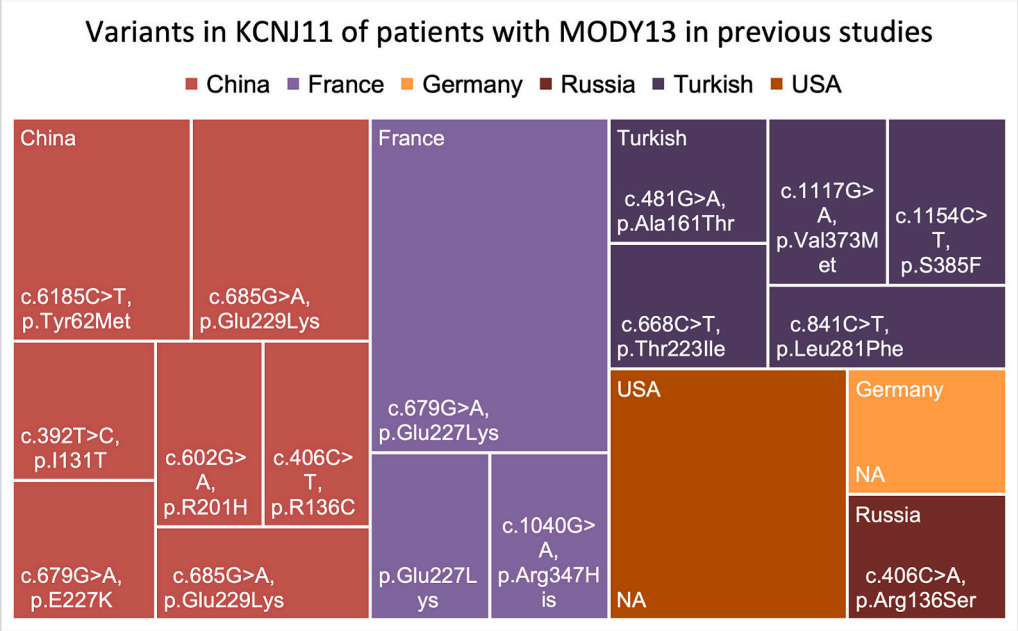

Fig. 3. Variants in KCNJ11 of patients with MODY13 in previous studies: 12 mutant loci in the KCNJ11 gene were reported, all of which are missense variants.

nematodes, and even some nematodes expressed opposite phenotypes, which are presumed genetic-background-related. c.843C > T(p.L281=) in *KCNJ11* was first reported by Fan et al. [17] in a Chinese patient diagnosed with congenital hyperinsulinism. They revealed that c.843C > T(p.L281=) reduces exonic splicing enhancers (ESEs), by exonic splicing enhancer finder (http://exon.cshl.edu/ESE/). The current study predicts the RNA structure of the family and reveals that c.843C > T(p.L281=) results in a significant change in the RNA structure of *KCNJ11* (Fig. 2B). Nevertheless, the remaining experiments are required to explore the role of this variant in the pathogenesis of CHI and MODY13.

Kir6.2, encoded by *KCNJ11,* forms the KATP with the SUR1 subunit of the sulfonylurea receptor in pancreatic β-cells, regulating cellular metabolism and insulin secretion [9–12]. Mutations in KCNJ11 are pathogenic in TNDM3 (Diabetes Mellitus, Transient Neonatal, 3, OMIM#610582), PNDM2 (Diabetes Mellitus, Permanent Neonatal, 2, OMIM#618856), HHF2 (Hyperinsulinemic Hypoglycemia, Familial, 2, OMIM#601820), type 2 diabetes, and MODY13 [9,12–15].

In 2012, Bonnefond et al. [6] first identified the MODY associated with KCNJ11, denoted MODY13. Since then, 12 KCNJ11 mutant loci of MODY13 have been identified, all of which are missense variants (Fig. 3). The child in this study carries a c.843C > T (p.L281=) synonymous variant in the KCNJ11 gene, which is the first reported case of a synonymous variant of MODY13.

MODY makes up about 2–5% of the diabetes population and is the most prevalent monogenic diabetes [21]. The ADAPP recommends that individuals with atypical diabetes and more than one family member with non-type 1 or type 2 diabetes should be considered for a diagnosis of MODY, [22]. Although diagnostic studies of monogenic diabetes and MODY have advanced in recent years, there are at least 22 cumulative cases of MODY13 patients reported, 6 of whom are Chinese.

MODY13 presents a diverse clinical phenotype. BMI ranged from 15.2 to 25.8 kg/m2. The age of onset ranged from 9 to 28 years, with more than half being between 12 and 14 years old. 4 patients presented with diabetic ketosis, feeling thirst, polyhydramnios, and polyuria. 2 patients were diagnosed with MODY13 due to gestational diabetes mellitus during the obstetric examination. Diabetes family history is described in 60% of the patients' families. Aside from blood glucose and genetic characteristics, there were no significant differences between MODY13 patients' sex, ethnicity, blood pressure, C-peptide, FT4, or insulin-related antibodies versus *KCNJ11*-associated neonatal diabetes mellitus [16,23–25]. In our study, the "separation phenomenon" between C-peptide and insulin in standard meal tests is first described, which we hypothesized to be in relation to patients harboring the homozygous mutation that had been reported in a CHI patient.

The treatment strategy for MODY13 can be conducted in two phases: the diabetic ketosis phase and the chronic phase. In the ketosis phase, insulin should be used individually according to the patient's blood glucose. In our study, the patient was treated with 8 IU menthol insulin intramuscularly before each meal and 6 IU glargine insulin before bedtime on the 8th day of onset (total insulin 30 IU/day, 0.625 IU/kg). He was given an insulin pump regimen with fixed pre-meal dosing (1-2 IU/meal) at 13th day of onset. With titration based on blood glucose levels, the dose of insulin was decreased gradually (minim 1-2 IU/day), and the insulin was halted at 29th day of onset due to hypoglycemia (with blood glucose 3-4 mmol/L).

In the chronic phase, therapeutic options include a diabetic diet, physical activity, and oral hypoglycemic medicines. Oral hypoglycemic medications for MODY13 include sulfonylureas (e.g. glimepiride), metformin, and acarbose. The average dose of glimepiride is 0.11 (0.07–0.39) mg/kg/day. The average dose of glimepiride for patients with a diagnosis of potassium channel variation <6 months is 0.07 (0.07–0.16) mg/kg/day, and for patients >6 months is 0.10 (0.04–0.19) mg/kg/day [8]. Glimepiride significantly lowers HbA1C in MODY13 patients compared to other medications (including insulin, metformin, and acarbose [26]). The patient in this study maintained satisfactory blood glucose levels following a diabetic diet and regular moderate intensity aerobic activity (walking for 60 min every day) [27], without oral medication or insulin (Fig. 2).

The prognosis of MODY13 patients varies widely. 25% of MODY13 patients can achieve blood glucose standards without medication and insulin. Neurological symptoms are observed in approximately 20% of patients due to Kir6.2 protein alterations, manifesting as DEND syndrome (developmental delay, epilepsy, and neonatal diabetes mellitus), ADHD (attention-deficit/hyperactivity disorder), autism, or selective mutism [28] [29]. In this study, no neurological symptoms were found.

4. Conclusion

KCNJ11 c.843C > T (p.L281=) variant is associated with MODY13. In hyperglycemic patients without classic characteristic diabetes

symptoms, genetic testing can help diagnose MODY13 in people who can manage their diabetes with lifestyle changes alone.

Ethics

Written informed consent for the publication of his clinical details was obtained from the parent of the patient. A copy of the consent form is available for review by the Editor of this journal.

Authors' contributions

CC wrote the manuscript, described the clinical case, and performed the research in the medical literature. YR collected the clinical case images and analyzed the patients' genetic data. YM reviewed the manuscript. All the authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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CRediT authorship contribution statement

Congli Chen: Conceptualization, Investigation, Writing – original draft. **Yurong Piao:** Data curation, Formal analysis, Methodology. **Yanmei Sang:** Funding acquisition, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

Data will be made available on request.

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