Relapsed 6q24-related transient neonatal diabetes mellitus successfully treated with sulfonylurea

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To the Editor: Neonatal diabetes mellitus (NDM) is defined as diabetes diagnosed within 6 months after birth and occurs in approximately one in every 90,000 to 160,000 live births, with an 80% yield due to a known genetic diagnosis. NDM can be classified as transient (TNDM), permanent (PNDM), or syndromic, in which TNDM accounts for approximately 45% of all cases of NDM. Overexpression of genes on chromosome 6q24 is the most common cause of TNDM (OMIM_601410), which accounts for approximately 70% of all cases and occurs by one of three mechanisms: (1) paternal uniparental disomy (41%), (2) duplication of paternal alleles (33%), or (3) hypomethylation of the maternal allele (26%).[1] TNDM can be characterized as small for gestational age and yield a "Diabetes-Remission-Relapse" natural history, where insulin is deemed to be the original treatment.[2] However, there is no standard treatment for relapsed patients. Hence, we report a Chinese male patient with a history of 6q24-related TNDM (hypomethylation of the maternal allele) who relapsed at 14 years old and was successfully treated with a low dose of glimepiride.

A 15-year-old male with a history of TNDM appeared to relapse at 14 years of age. He was born prematurely at 36^{+2} weeks because of a premature rupture of membranes to healthy Chinese parents; and his birth weight was 1700 g. He was admitted for symptoms of polyuria, polydipsia, and polyphagia on day 45. The laboratory data indicated that his fasting glucose was 30.6 mmol/L and his glycated hemoglobin A1c (HbA1c) was 12.4%, and he was initially treated by an intravenous insulin infusion at a dose of 0.02 to 0.05 U/kg per hour. The requirement for insulin gradually decreased in the following days and finally ceased at 3 months of age. Annual biochemical examinations showed no glucometabolic disorder (self-reported). His pre- and postnatal periods and developmental milestones were normal. However, his fasting glucose was 11.3 mmol/L and his HbA1c was 8.2% at 14 years old. We conducted a 2h-oral glucose tolerance test (2h-OGTT) with standard meal when his diabetes relapsed: glucose at 0 h was 6.64 mmol/L and at 2 h was 13.47 mmol/L; insulin at 0 h was 9.29 μU/mL and at 2 h was 36.2 μU/mL; and C-peptide at 0 h was 1.98 ng/mL and at 2 h was 5.82 ng/mL. At this time, his height was 176 cm and his weight was 52.5 kg. The patient tested negative for antibodies to type 1 diabetes (GAD, IAA, IA2) and displayed normal islet function. His detailed history and endocrinological testing did not demonstrate secondary diabetes. Whole exome sequencing revealed no mutations. Therefore, the patient was treated with Lantus (8 U/day) together with lifestyle modifications. His fasting and postprandial capillary glucose were 7 to 8 mmol/L and 10 to 11 mmol/L, respectively, on a home glucometer, with HbA1c ranges from 7.5% to 8.0%.

A methylation-specificmultiplex-ligation-dependent probe amplification (MS-MLPA) assay was performed with a SALSA MS-MLPA kit ME033 (MRC-Holland, Amsterdam, the Netherlands). The kit contains eight probes that are specific for sequences in or near the TNDM critical region of chromosome 6q24. Meanwhile, two blank control probes (*IGF2R* and *RB1*) are included in the kit. The threshold for chromosomal abnormalities was established as follows: the lower limit was 0.7 for deletion and the upper limit was 1.3 for duplication. Abnormal values are colored red and plotted outside the threshold line. Three probes in *PLAGL1* revealed a maternal peak reduction or paternal uniparental disomy (patUPD6) [Figure 1A]. Additionally, a global screening array (GSA) microchip (Illumina, Inc., Singapore) including 660,000 SNPs of the whole genome was used for possible paternal uniparental disomy detection. The results of the GSA analysis demonstrated no paternal uniparental disomy (patUPD6) in the region of chromosome 6q24 [Figure 1B]. In other words, the patient had hypomethy-

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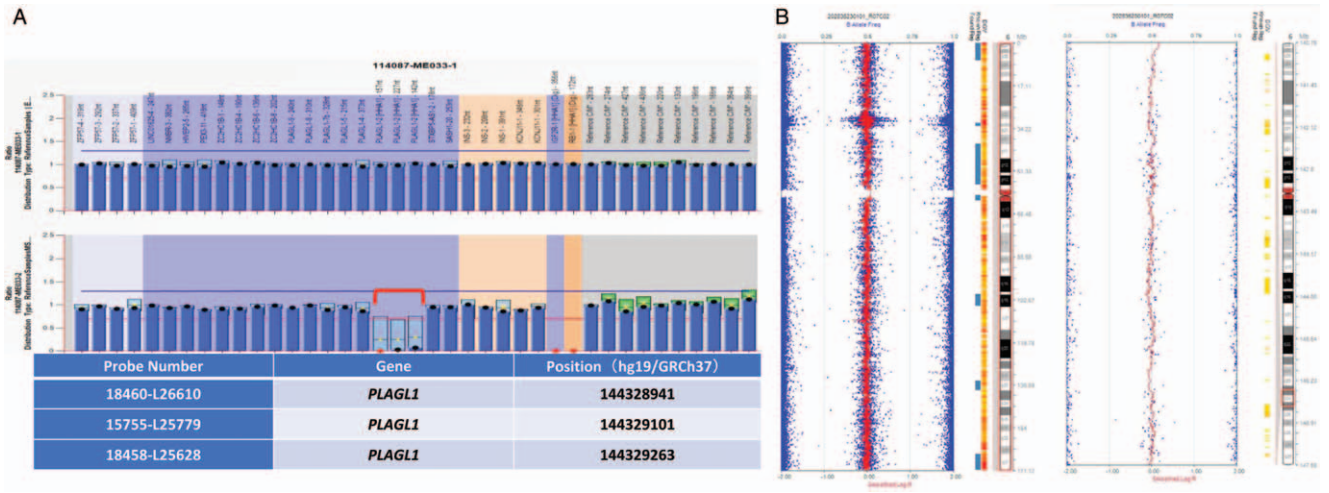

Probe Number	Gene	Position (hg19/GRCh37)
18460-L26610	*PLAGL1*	144328941
15755-L25779	*PLAGL1*	144329101
18458-L25628	*PLAGL1*	144329263

Figure 1: Results of the methylation-specificmultiplex-ligation-dependent probe amplification (MS MLPA) (A) and global screening array in the region of chromosome 6q24 (B). A MS-MLPA assay was performed with a SALSA MS-MLPA kit ME033. The kit contains eight probes specific for sequences in or near the TNDM critical region of chromosome 6q24. The threshold for chromosomal abnormalities was established as follows: the lower limit was 0.7 for deletions and the upper limit was 1.3 for duplications. Abnormal values are colored red and plotted outside the threshold line. There are three probes in *PLAGL1* that revealed a maternal peak reduction or paternal uniparental disomy (patUPD6) (A). A global screening array (GSA) microchip that includes 660k SNPs of the whole genome was used for possible paternal uniparental disomy detection. The results of GSA analysis demonstrated no paternal uniparental disomy (patUPD6) in the region of chromosome 6q24 (B).

lation of the maternal allele in the region of 6q24. After confirming the diagnosis and obtaining informed consent from the patient, he was treated with glimepiride once a day at a dose of 1 mg. His fasting and postprandial capillary glucose were 6–7 mmol/L and 8–10 mmol/L, respectively, on a home glucometer. After 3 months of treatment, his HbA1c levels dropped by approximately 1% and remained stable for over 6 months without hypoglycemia.

6q24-related TNDM is considered to be caused by overexpression of the paternal genes on chromosome 6q24. The region includes two genes, pleiomorphic adenoma gene-like 1 (*PLAGL1*, also known as *ZAC1*) and hydatidiform mole associated and imprinted (*HYMAI*). The specific mechanism of how *PLAGL1* causes 6q24-related TNDM remains uncertain. In rodents, overexpression of *Plagl1* destroys the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways in beta cells at birth. MAPK and PI3K are important for glucose-induced insulin secretion, and overexpression of *PLAGL1* is believed to cause a decrease in beta cell mass at birth. As for the treatment of 6q24-related TNDM, insulin is widely considered to be the first-line therapy for TNDM due to chromosome six abnormalities during the neonatal period.[2] Given that patients with 6q24-related TNDM have relatively healthy beta cell function at remission, sulfonylurea treatment has a biological rationale in patients with 6q24-related TNDM, as its potential mechanisms are: (1) patients with 6q24-related TNDM presumably have intact sulfonylurea receptors at the pancreatic ß-cell and (2) the beta cells of patients with 6q24-related TNDM have decreased sensitivity to glucose, so sulfonylurea helps to improve the release of insulin. The most common adverse effect of sulfonylurea is hypoglycemia, which can be avoided by a dose adjustment. Other side effects, such as diarrhea and weight gain, are relatively rare and less severe. In 2015, the first 6q24-related TNDM Chinese patient who received a successful sulfonylurea treatment was reported.[3] Consistent with our results, the patient demonstrated a low birth weight, early onset diabetes, high blood glucose and high HbA1c levels. Importantly, both patients were processed with low dose sulfonylurea and received successful glucose control with no side effects, remaining stable for a long period of time. Additionally, Garcin *et al*[4] described three cases and reviewed 11 patients with 6q24-related TNDM who were treated with low dose sulfonylurea. Thirteen of them were successfully treated with sulfonylurea, including five before remission and eight after relapse. However, sulfonylurea had no therapeutic effects in one remaining case. A recent study found that the antidiabetic agent-dipeptidyl peptidase-4 inhibitor provides a useful alternative for relapsed 6q24-related TNDM.[5]

In summary, the evidence of the efficacy and safety of sulfonylurea therapy in 6q24-related TNDM provided by this study supports that sulfonylurea is an essential treatment for TNDM after relapse. Further studies of sulfonylurea therapy in larger numbers of patients with 6q24-related TNDM are necessary.

Declaration of patient consent

The author certifies that they have obtained all appreciate patient consent forms. In the form, the patient's/patients' guardians have given their consent for their images and other clinical information to be reported in the journal. The patient's/patients' guardians understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

None.

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