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Case Report

Relapsing 6q24-related transient neonatal diabetes mellitus with insulin resistance: A case report

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Abstract. The overexpression of imprinted genes on chromosome 6q24 causes 6q24-related transient neonatal diabetes mellitus (6q24-TNDM). Most cases of 6q24-TNDM show transient diabetes mellitus (DM) during the neonatal period, followed by relapse after puberty. These two courses of DM are both characterized by insulin insufficiency. However, there has been no previously reported case of 6q24-TNDM with insulin resistance at relapse. We report the case of a 10-yr-old Japanese girl with relapsing 6q24-TNDM. In the neonatal period, she had hyperglycemia and was treated with insulin injection until 2 mo of age. After several years of remission of DM, her HbA1c level increased to 7.4% at 10 yr of age. Homeostasis model assessment of insulin resistance (HOMA-IR) score was high at 6.2. After starting metformin therapy, her glycemic control improved along with normalization of HOMA-IR score. Using microsatellite marker analysis on the 6q24 region and array comparative genome hybridization, we diagnosed her with 6q24-TNDM due to paternally inherited duplication of 6q24. These data indicate that patients with 6q24-TNDM can develop relapsing DM with insulin resistance.

Key words: 6q24-related transient neonatal diabetes mellitus, insulin resistance, metformin

Introduction

6q24-related transient neonatal diabetes mellitus (6q24-TNDM) is a rare form of diabetes mellitus (DM) caused by the overexpression of two imprinted genes on chromosome 6q24: *PLAGL1* and *HYMAI*. The mechanisms of overexpression of the paternal allele include duplication of the paternal allele (33%), paternal uniparental disomy (41%), and hypomethylation of the maternal allele (26%) (1). In most cases, hyperglycemia due to insulin insufficiency typically commences during the neonatal period and resolves by 18 months. Relapsing DM after puberty is characterized by insulin insufficiency without obesity and has been described in a significant fraction of patients (1). Busiah K *et al*. reported that DM relapsed in 82% of patients within 20 yr of remission (2). Here, we report a case of a patient with 6q24-TNDM who had insulin resistance at relapse. To our knowledge, there have been no such report in the literature.

Case Report

A Japanese girl was born after 38 wk of an uneventful pregnancy to healthy parents. Her birth length and weight were 41.9 cm (–3.36 SD) and 1,765 g (–3.63 SD), respectively. On the 11th day of life, hyperglycemia (590 mg/dL) was detected without symptom. She was diagnosed with neonatal DM, and continuous intravenous insulin infusion was started, followed by multiple daily insulin injections with a combination of insulins glargine and lispro. Her insulin

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requirement gradually decreased, and the treatment was ceased at 2 mo of age. At that time, an oral glucose tolerance test (OGTT) still indicated DM with impaired insulin secretion (**Fig. 1A**). By 4 mo of age, she underwent catch-up growth of her length (58.5 cm, –1.77 SD) and weight (6.06 kg, –0.5 SD), and OGTT revealed normal glucose tolerance with improved insulin secretion (**Fig. 1B**).

After genetic counseling, we obtained informed consent from her parents and performed genetic tests. Microsatellite markers on 6q24 region were analyzed using an autosequencer (ABI PRISM 310, Applied Biosystems, Foster City, CA, USA) and GeneScan software, as described previously (3). Microsatellite markers on the 6q24 region showed that peak heights were distinctly greater in paternally inherited markers than maternally inherited markers; however, those inherited paternally had higher molecular weight with lower amplification efficiency than those inherited maternally. This suggested that the patient had 6q24-TNDM due to paternally inherited duplication of 6q24.

During remission, she was followed-up annually using glycated hemoglobin (HbA1c) levels and urinalysis. She underwent breast enlargement from 8 yr of age and experienced menarche at 10 yr and 8 mo of age. At 10 yr and 10 mo of age, glucosuria was detected for the first time since early infancy, and HbA1c level increased from 6.2% to 7.4% over a 6-mo interval. Her height, weight, and body mass index were 148.3 cm (0.81 SD), 35.7 kg (0.05 SD), and 16.3 (–0.31 SD, 29.3th percentile), respectively. Autoantibodies against glutamic acid decarboxylase, islet antigen type 2, or insulin were negative. Fasting glucose and insulin levels revealed that the homeostasis model assessment of insulin resistance (HOMA-IR) score was 6.2 [reference range in non-obese pubertal girls, ≤ 2.6 (4)]. OGTT indicated DM with elevated insulin levels (**Fig. 1C**). She did not have any endocrine abnormalities leading to insulin resistance, and her serum GH, cortisol, free triiodothyronine, free thyroxin, thyrotropin, leptin, and adiponectin levels were 1.51 ng/m, 8.07 μg/dL, 3.38 pg/mL, 1.21 ng/dL, 0.959 μIU/mL, 8.2 ng/mL (reference range, 2.5–21.8 ng/mL), and 9.7 μg/mL (reference range, > 4.0 μg/mL), respectively. Her serum triglyceride, total cholesterol, LDL-cholesterol, and HDL-cholesterol levels were 80 mg/dL, 175 mg/dL, 96 mg/dL, and 80 mg/dL, respectively. Abdominal ultrasound and computed tomography did not detect fatty liver or visceral fat accumulation. Continuous glucose monitoring (CGM) detected hyperglycemia throughout the day (**Fig. 2A**). Although HOMA-IR is correlated with insulin resistance which is assessed by glucose clamp test only in case of fasting glucose level at 140 mg/dL or less, we considered her HOMA-IR score was enough high to indicate insulin resistance. We diagnosed her with relapsing 6q24-TNDM with insulin resistance and started metformin therapy at 250 mg twice daily. We did not prescribe any lifestyle

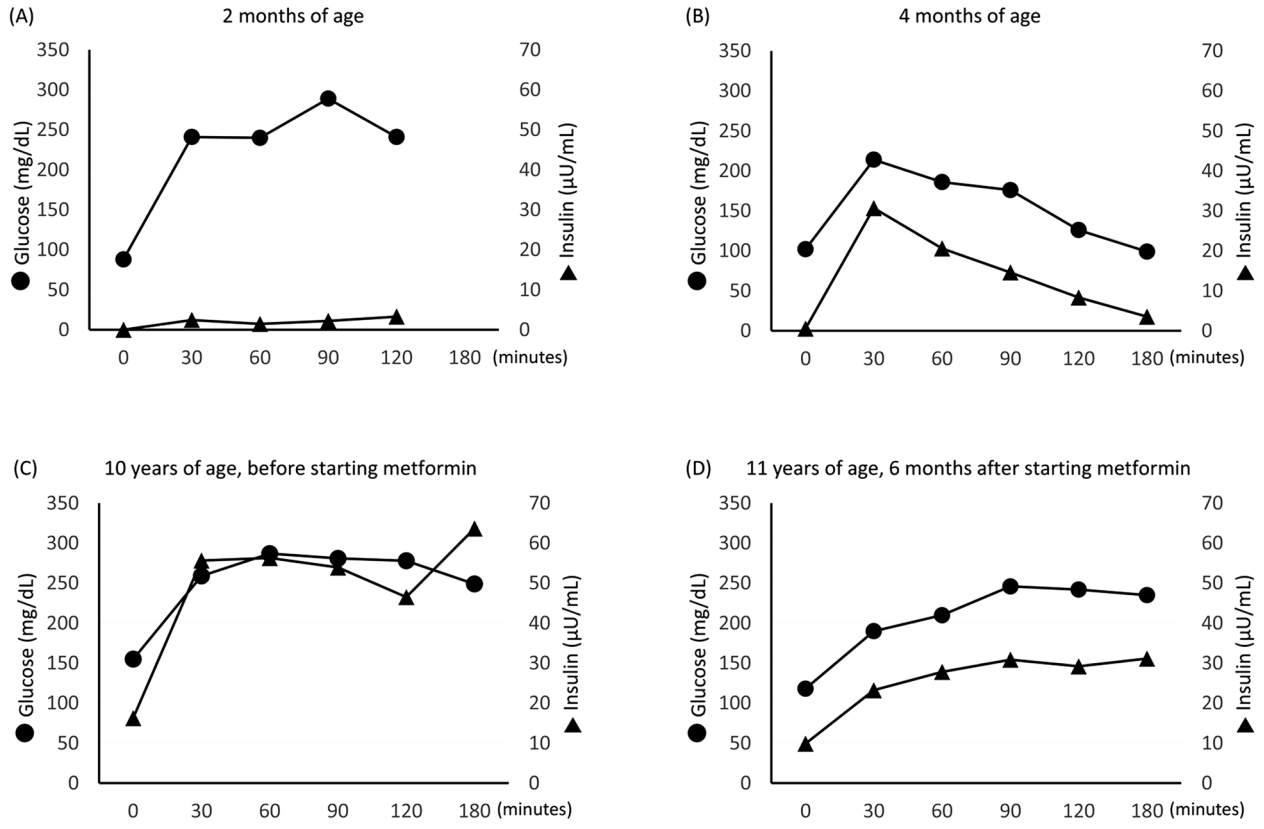

Fig. 1. Oral glucose tolerance tests at 2 mo of age (A), at 4 mo of age (B), at the time of recurrence (C), and 6 mo after the initiation of metformin treatment (D). Circles and triangles indicate glucose and insulin, respectively.

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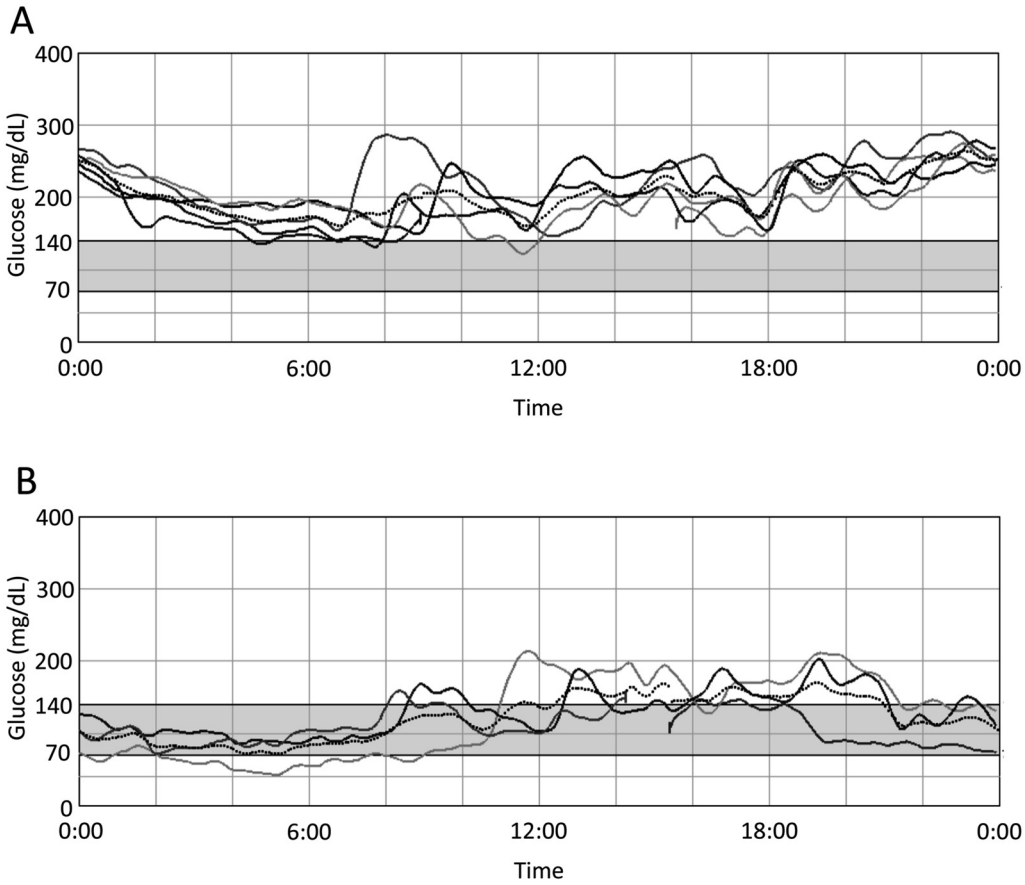

Fig. 2. Continuous glucose monitoring before metformin treatment (A) and 10 mo after the initiation of metformin treatment (B).

modification because she maintained an adequate calorie intake of 1,800 kcal/d and moderate physical activity. The dose of metformin was increased to 750 mg twice daily by 6 mo. Her HbA1c levels dropped by 0.5–1.0% and remained below 7.0% for more than 12 mo (**Fig. 3**). CGM showed a significant reduction in time above the range of glucose level (**Fig. 2B**). During this period, HOMA-IR scores dropped to 1.6, and OGTT showed relatively improved glycemic control and slightly reduced insulin levels despite the pattern of DM (**Fig. 1D**).

Because of the atypical phenotype, we performed further genetic tests. An array comparative genomic hybridization revealed a 1.5-Mb duplication spanning *PLAGL1* and *HYMAI*. Next-generation sequencing-based mutation screening of major causative genes of glucose metabolism disorders (*ABCC8, APPL1, BLK, GCG, GCGR, GCK, GIPR, GLUD1, HNF1A, HNF1B, HNF4A, INS, INSR, KCNJ11*, and *KLF11*) did not detect any pathogenic variants. Based on these findings, we confirmed the diagnosis of 6q24-TNDM due to paternally inherited duplication of 6q24.

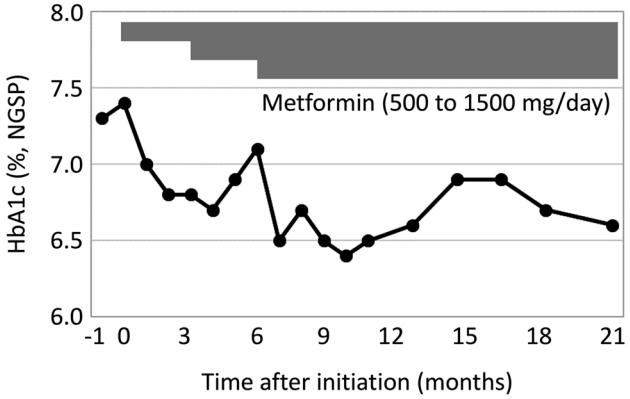

Fig. 3. HbA1c levels after the initiation of metformin treatment. The solid bar at the top indicates the duration and dosage of treatment.

Discussion

We report the first case of relapsing 6q24-TNDM with predominant insulin resistance. Many patients with 6q24-TNDM are born small for gestational age (SGA) and develop relapsing DM after puberty. The size and location of duplication in our patient was similar to that reported in previous cases and cannot explain this unique condition. It is well-known that SGA and puberty are risk factors for increasing insulin resistance. Ballerini MG *et al*. reported that HOMA-IR scores were higher in pubertal children than in the prepubertal group (4). Blusková Z *et al*. reported that non-obese SGA children had higher levels of HOMA-IR than non-obese children

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born appropriate for gestational age (5). Darendeliler F *et al*. reported that HOMA-IR scores were significantly higher in term SGA children than in preterm SGA children (6). Kerkhof GF *et al*. reported that rapid weight gain during the first 3 months of life is a risk factor for insulin resistance in children born SGA (7). These reports suggest that the etiology of insulin resistance in our patient can be partially explained by puberty and rapid catch-up growth after severe SGA birth at term, although an unknown genetic cause of insulin resistance is not excluded. Docherty LE *et al*. reported that the mean (± SD) birth weights and gestational weeks of patients with 6q24-TNDM were 2,001 (± 417) g and 37.8 (± 2.7) weeks, respectively (8). Temple IK *et al*. reported that some patients with 6q24-TNDM experience rapid growth catch-up in the first months of life (9). Although our patient may possess an unidentified genetic factor associated with insulin resistance, at least some patients with 6q24-TNDM are potentially at risk for developing insulin resistance during puberty due to SGA.

Metformin therapy for relapsing DM improved insulin sensitivity and led to adequate glycemic control in this patient. The rarity of 6q24-TNDM precludes the establishment of standard therapy for relapsing 6q24-TNDM. Patients with relapsing 6q24-TNDM may require life-style modification, sulphonylurea, or insulin injections depending on their severity of DM (1). Yorifuji T *et al*. reported that treatment targeting GLP1 pathway was useful in a patient with relapsing 6q24-TNDM because the pathway is not affected (10). However, it is unclear whether this treatment is useful for other patients with relapsing 6q24-TNDM, especially those with insulin resistance. Considering the high HOMA-IR score and preserved insulin secretion, we treated this patient with metformin only. Her glycemic control successfully improved. These results suggest that metformin could be a treatment option for 6q24-TNDM with insulin resistance. However, the question remains whether the combination therapy of metformin and insulin secretagogue is useful. Further cases are necessary to establish an effective treatment for relapsing 6q24-TNDM with insulin resistance.

In conclusion, we report a novel observation of relapsing DM with insulin resistance in a patient with 6q24-TNDM. Our report expands the clinical features of 6q24-TNDM and raises the possibility that patients with 6q24-TNDM can develop relapsing DM due to insulin resistance. Therefore, assessment of insulin resistance is recommended in patients with relapsing 6q24-TNDM.

Conflict of interests: The authors disclose no financial conflicts of interest.

Acknowledgments

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