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Case Report

Wieacker–Wolff syndrome with hyperinsulinemic hypoglycemia successfully treated using diazoxide: A case report

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Highlights

- Wieacker–Wolff syndrome may complicate hyperinsulinemic hypoglycemia.
- Diazoxide may successfully treat this complication.
- A novel missense variant, c.557T>G, p.(Met186Arg), was identified in *ZC4H2*.

Abstract. Wieacker–Wolff syndrome (WRWF) is an X-linked genetic disorder characterized by neuromusculoskeletal abnormalities caused by loss-of-function variants of the *ZC4H2* gene. Here, we report the case of a male infant with WRWF manifesting as multiple joint contractures and congenital anomalies at birth. He underwent gastrostomy to treat the gastroesophageal reflux disease, which caused mixed apnea and transient bradycardia. The patient subsequently developed hyperinsulinemic hypoglycemia (HH) and was diagnosed with dumping syndrome. Although he underwent multiple treatments, including alpha-glucosidase inhibitors (α-GI) administration, he continued to exhibit HH with seizures and loss of consciousness. Whole-exome sequencing revealed a novel missense variant of *ZC4H2* [NM_018684.4: c.557T>G, p.(Met186Arg)] at Xq11.2 in both the patient and his mother. Based on these results and clinical symptoms, the patient was diagnosed with WRWF. Although WRWF is not considered a major cause of HH, we regarded it as a related complication based on previous reports. Diazoxide treatment was initiated, and the hypoglycemic attacks resolved almost entirely without any notable side effects after 18 mo. To the best of our knowledge, this is the first report of WRWF-associated HH treated with low-dose diazoxide and α-GI. Therefore, diazoxide is recommended for the treatment of WRWF-associated HH.

Key words: Wieacker–Wolff syndrome, *ZC4H2*, hyperinsulinemic hypoglycemia, diazoxide, alpha-glucosidase inhibitors

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Introduction

Wieacker–Wolff syndrome (WRWF) is an X-linked inherited arthrogryposis multiplex congenital disorder characterized by intellectual disability, motor developmental delay, poor growth, muscle weakness, and skeletal abnormalities. Patients with WRWF typically have multiple congenital joint contractures at birth due to muscle weakness beginning *in utero* (1–3). In 1985, Wieacker and Wolf reported six male patients with similar manifestations in a family spanning three generations (3). Using next-generation sequencing, Hirata *et al*. identified that *ZC4H2*, a zinc-finger gene, affects patients with WRWF (4).

A previous study showed that loss-of-function variants of *ZC4H2* can downregulate aberrant oxidative phosphorylation pathways and reduce neural stem cell proliferation (5). Functional analysis in zebrafish has revealed that the ZC4H2 protein is widely expressed in the nervous system, including the forebrain, midbrain, hindbrain, and spinal cord, and that anomalies in the muscle projections of motor neurons are present in individuals lacking functional *zc4h2* genes (4). To date, WRWF has been reported in seven families and one male sibling (1, 4, 6–9); however, its prevalence remains unknown.

In addition to neurological symptoms, patients with WRWF develop complex hypoglycemia caused by hyperinsulinemia or central adrenal insufficiency (8). However, literature discussing the treatment progress for this type of hypoglycemia has not been reported. Here, we report the first case of diazoxide use in a patient with WRWF complicated by hyperinsulinemic hypoglycemia (HH).

Case Presentation

The patient was a male infant born at 40 wk of gestation via emergency cesarean section because of arrested labor, with birth weight and height of 3620 (+1.3 standard deviation [SD]) and 49.5 cm (–0.2 SD), respectively. No abnormalities were observed during pregnancy. At birth, the infant was referred to our hospital because of respiratory disturbances and multiple joint contractures. Laryngomalacia, esophageal hiatal hernia, bilateral ptosis, external rectus muscle defect in the right eye, impaired ocular motility, inguinal hernia, cryptorchidism, multiple joint contractures, knee dislocation, and bilateral hip dislocation were identified as congenital anomalies (**Fig. 1**). Congenital anomaly syndrome was suspected; however, his karyotype was 46, XY, and no pathogenic variants were detected on the chromosomal microarray.

At 7 mo of age, the patient frequently experienced mixed apnea and transient bradycardia. At 8 mo of age, he underwent gastrostomy and fundoplication to treat

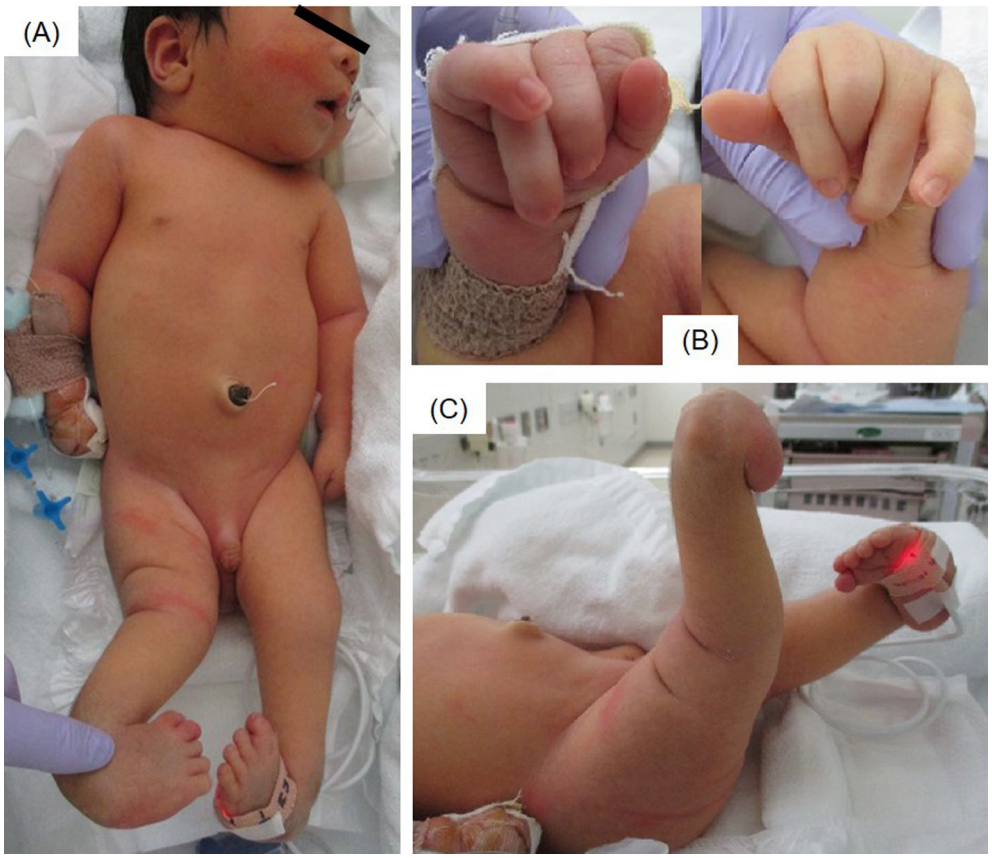

Fig. 1. Clinical features of the patient at 10 d of age. (A) Full-length photograph. (B) Bending and overlapping of the fingers. (C) Knee hyperextension and clubfoot.

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gastroesophageal reflux disease, which was presumed to have triggered these attacks. The patient subsequently developed HH following tube feeding and was diagnosed with dumping syndrome. Multiple tube-feeding methods were employed.

At the age of 2 yr, he underwent a TRH loading test and a GH-releasing peptide-2 test due to hypoglycemia and short stature. Based on the results (**Table 1**), GH deficiency (GHD) was suspected, and adrenal insufficiency was ruled out. The diagnostic criteria for GHD were not clearly met; however, owing to evidence of hypoglycemia, central hypothyroidism, and short stature, treatment was administered based on the guidelines for GHD. Although thyroid-stimulating hormone (TSH) responsiveness to TRH was observed, levothyroxine supplementation was initiated based on persistently low TSH (0.24–0.33 μIU/mL) and free T_4 (0.43–0.72 ng/dL) levels. The patient was diagnosed with central hypothyroidism. The patient's HH associated with dumping syndrome worsened; thus, alpha-glucosidase inhibitors (α-GI), voglibose 0.2 mg/d (three times daily, before each meal), and cornstarch 0.5 g/kg/dose mixed with a small amount of water (twice daily, before breakfast and sleep) were administered. He also underwent nutritional adjustment, but continued to have HH with seizures and loss of consciousness. No convulsions or epileptic seizures were observed in the absence of hypoglycemia. The patient's growth curve and treatment course are shown in **Fig. 2**.

At 4 yr of age, the patient and his mother underwent whole-exome sequencing. When the patient reached 6 yr of age, he and his mother were identified as harboring novel missense variants in the *ZC4H2* gene [NM_018684.4: c.557T>G, p.(Met186Arg)] at Xq11.2 (**Fig. 3**). The patient was hemizygous for this variant, whereas his mother was heterozygous. Based on the American College of Medical Genetics guidelines, the variant was classified as "likely pathogenic" (10). Based on the genetic results and patient's phenotype, WRWF was diagnosed. His mother had mild symptoms, such as congenital clubfoot, right eyelid ptosis, and right facial nerve palsy. Therefore, she was diagnosed with a milder form of WRWF. However, no abnormalities were detected on blood tests previously.

We considered HH to be associated with WRWF because it continued to be detected in the patient's blood evaluation (**Table 2**). Therefore, 50 mg of diazoxide (3 mg/kg/d) was initiated to treat the patient's HH once he reached 7 yr of age. After diazoxide initiation, continuous glucose monitoring (CGM) showed no hypoglycemia; thus, α-GI and cornstarch were discontinued. However, CGM showed hyperglycemia immediately after tube feeding, followed by subsequent hypoglycemia, which could be considered a recurrence of the dumping syndrome. Therefore, α-GI administration was resumed. The patient's blood glucose levels stabilized thereafter (**Fig. 4**). After 18 mo of diazoxide treatment, no side effects, including hypertrichosis, fluid retention, or other cardiovascular signs or symptoms, were observed (11, 12).

Table 1. Results of loading tests

TRH, GHRP2 at 2 yr old		Baseline	Peak
TSH	(μIU/mL)	0.83	6.74
GH	(ng/mL)	2.1	4.8
ACTH	(pg/mL)	17.1	33.9
Cortisol	(μg/dL)	12.3	16.6
GHRP2 at 3 yr old		**Baseline**	**Peak**
GH	(ng/mL)	1.57	2.97
ACTH	(pg/mL)	8.77	65.5
Cortisol	(μg/dL)	9.4	18.5

TRH, thyrotropin-releasing hormone; GHRP2, GH-releasing peptide-2.

Discussion

The patient in the present case was identified as having a novel hemizygous missense variant [c.557T>G, p.(Met186Arg)] in the *ZC4H2* gene. On the basis of this variant and the patient's phenotype, the patient was diagnosed with WRWF. This report describes the case of a mother and son with the same missense variant; it was considered a case of WRWF in the child and mild WRWF in the mother, rather than female-restricted WRWF (WRWFFR). This is because WRWFFR is thought to manifest as a complete loss-of-function variant, and affected males typically do not survive until birth (1, 5, 6). To the best of our knowledge, this is the first report of the use of diazoxide to treat HH associated with WRWF. In the present case, the addition of a small dose of diazoxide stabilized the patient's refractory glycemic control without causing any side effects.

The prevalence of hypoglycemia with *ZC4H2* pathogenic variants ranges from 21.7% to 41.2% in boys, and from 0% to 7.7% in girls (6, 7). In cases with *ZC4H2* pathogenic variants, attention should be paid to seizures associated with severe hypoglycemia (8). The six cases in which the detailed course has been reported (including our current case) of pathogenic *ZC4H2* variants associated with hypoglycemia are summarized in **Table 3** (1, 7, 8). Three of the six cases, including ours, had concomitant HH (7). In one case report, a 1-yr-old child was diagnosed with central adrenal insufficiency and severe recurrent hypoglycemia (8). The causes of the remaining two cases were not specified (1). One documented that a 7-yr-old boy died during sleep, although no association with hypoglycemia was shown (1). Although WRWF is not typically associated with HH, we considered HH as a complication of WRWF in our case based on a review of these previous reports. However, the decision to treat our patient with diazoxide was delayed because he had been treated for dumping syndrome before the age of 1 yr.

In an experiment using *Xenopus*, most frogs modified with *ZC4H2* substitution variants were unable to stabilize mothers against decapentaplegic homolog (SMAD) *in vivo*. Loss of ZC4H2 has been suggested to

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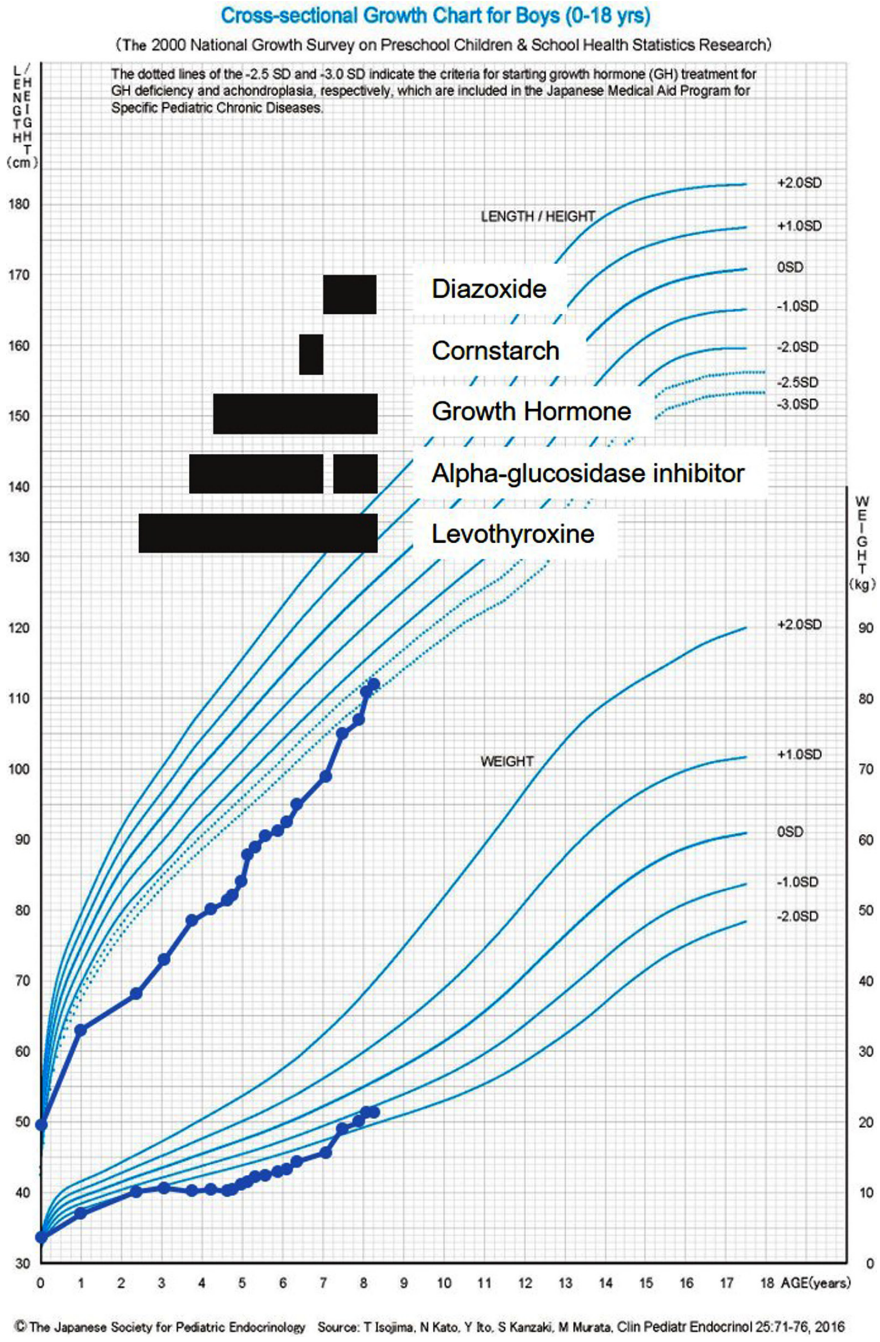

Fig. 2. Growth chart and medical treatment course of the patient. The black bars indicate the duration of each treatment. Height and weight improved after diazoxide was initiated.

affect bone morphogenetic protein (BMP) signaling by regulating the SMAD protein family (13). SMAD is a signaling factor that works together with transforming growth factor-β, which has demonstrated involvement in β-cell dysfunction by suppressing insulin transcription (14). Similarly, enhanced BMP signaling is also thought to cause β-cell dysfunction by suppressing β-cell proliferation and insulin secretion (15). These findings suggest that ZC4H2 dysfunction results in impaired insulin secretion, particularly hypersecretion. For these reasons, diazoxide, acting directly on β-cells, may be useful for treating HH associated with WRWF.

As previously mentioned, this case of WRWF was complicated by dumping syndrome. In recent years, several cases of improved glucose metabolism in children with dumping syndrome after the introduction of diazoxide have been reported (16–18). Nonetheless, diazoxide is associated with side effects such as hypertrichosis, fluid retention, and pulmonary hypertension, which require close monitoring. However, in the present case, the minimum dose of diazoxide was used, enabled by concurrent α-GI administration. The combination of low-dose diazoxide and α-GI may be a better treatment option for patients who have difficulty controlling HH due to dumping syndrome.

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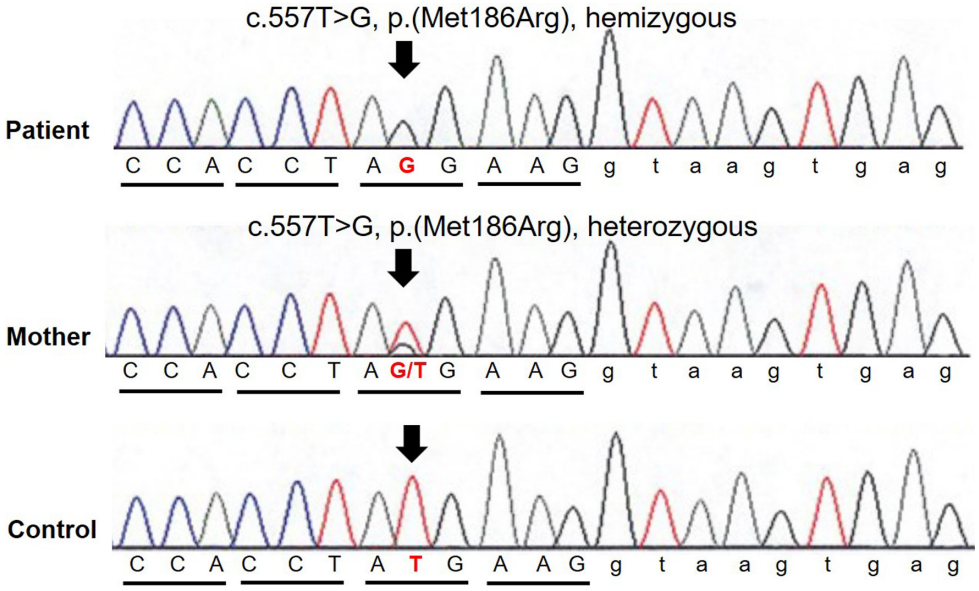

Fig. 3. Sanger sequencing of ZC4H2 at Xq11.2 identified a novel missense variant c.557T>G, p.(Met186Arg) in both the patient and his mother. The patient was hemizygous for this variant, whereas his mother was heterozygous.

Table 2. Laboratory data on admission at 7 yr old (2 hours after meal)

			Reference range
Plasma glucose	(mg/dL)	17	
HbA_{1c}	(%)	5.6	
Insulin	(μIU/mL)	20.2	
ACTH	(pg/mL)	33.9	
Cortisol	(μg/dL)	17.4	
TSH	(μIU/mL)	0.91	0.44–4.1
Free T_3	(pg/mL)	3.2	2.40–4.68
Free T_4	(ng/dL)	1.57	1.03–2.00
IGF-1	(ng/mL)	104	63–247*
Anti-insulin antibody	(U/mL)	< 0.4	< 0.4

*Reference range for males in the patient age group.
HbA1c, hemoglobin A1c.

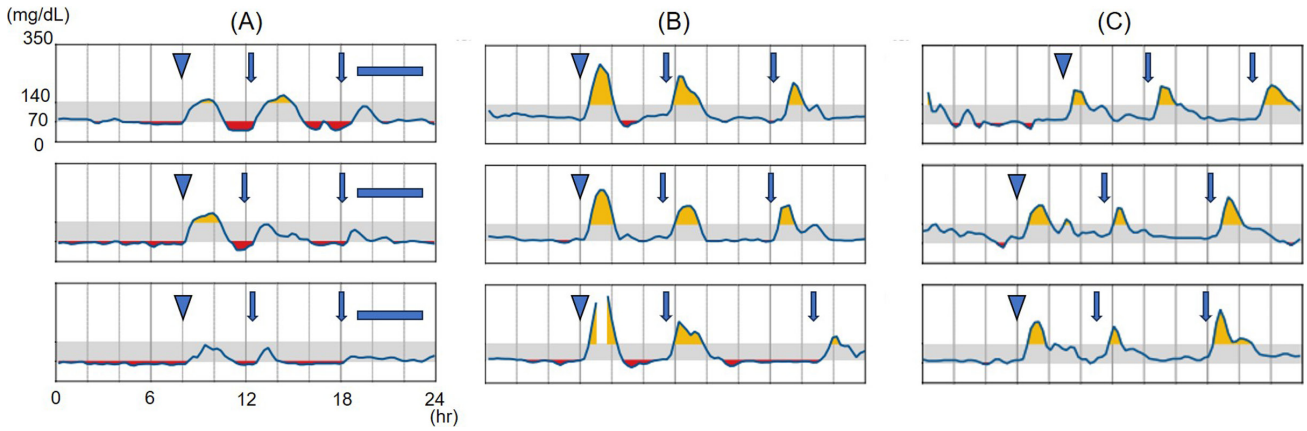

Fig. 4. Results of continuous glucose monitoring using the FreeStyle Libre Pro. Each rectangle represents one day. The gray areas indicate glucose levels in the range of 70–140 mg/dL. Arrowheads indicate infusion feeding, solid arrows indicate oral feeding, and blue squares indicate continuous infusion feeding. Alpha-glucosidase inhibitors (α-GI) were administered before each meal, and diazoxide was administered before breakfast and dinner. (A) Before diazoxide initiation, both basal and postprandial levels were low. (B) After diazoxide initiation and discontinuation of cornstarch and α-GI treatment, basal values improved but postprandial hyperglycemia and subsequent hypoglycemia persisted. (C) After restarting α-GI, both basal and postprandial levels were within the acceptable range.

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Table 3. Our case and previously reported variants, along with detailed hypoglycemia symptoms

	The diagnosis age of hypoglycemia	Sex	Variants	Symptoms presumed to be possibly related to hypoglycemia	Number of times described with hypoglycemic attack	Presence of GERD	Presence of dumping syndrome	Causes of hypoglycemia	Reference
1	8 mo	Male	p.(Met186Arg)	Recurrent apneic attacks and bradycardia. Seizures with hypoglycemia. Frequent episodes of hyperinsulinemic hypoglycemia.	Frequent recurrence	+	+	Hyperinsulinemia	This study
2	2 yr	Male	p.(Met186Ile)	Recurrent apneic attacks. Seizures with hypoglycemia.	1	+	N/A	N/A	Wongkittichote *et al.* (1); Patient 1
3	1 yr and 4 mo	Male	IVS2+5G>A	Seizures with hypoglycemia. Died at 7 yr old during sleep.	1	+	N/A	N/A	Wongkittichote *et al.* (1); Patient 4
4	3 yr	Male	p.(Lys209Asn)	Breath-holding spells. Seizures with hypoglycemia. Frequent episodes of postprandial hypoglycemia. OGTT showed hyperinsulinemic hypoglycemia.	1 In addition, OGTT induced	N/A	+	Hyperinsulinemia	Kondo *et al.* (7); Patient 1
5	8 yr	Male	p.(Lys209Asn)	Did not show clinical features. OGTT showed late-onset subclinical hyperinsulinemic hypoglycemia.	0 Only induced by OGTT	N/A	N/A	Hyperinsulinemia	Kondo *et al.* (7); Patient 2
6	1 yr	Male	p.(Arg198Gln)	Seizures with hypoglycemia and low plasmatic cortisol levels.	Frequent recurrence	N/A	N/A	Central adrenal insufficiency	Piccolo *et al.* (8)

GERD, gastroesophageal reflux disease; OGTT, oral glucose tolerance test; N/A, not applicable.

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Conclusion

We report a case of WRWF with HH that was successfully treated using low-dose diazoxide and α-GI, and identified a novel missense variant in the *ZC4H2* gene. Considering that HH can significantly impair the patients' quality of life, treating it effectively is important. The fact that diazoxide was effective in treating HH in this case suggests that the *ZC4H2* variant is associated with β-cell dysfunction. WRWF is a congenital abnormality syndrome that may be associated with HH and responds well to diazoxide treatment.

Conflict of interests: The authors declare no conflicts of interest.

Acknowledgments

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