



A Case of Late-onset Hyperinsulinemic Hypoglycemia: HNF4A Mutation

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¹University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Clinic of Pediatric Endocrinology, İzmir, Turkey

²University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Genetic Diagnostic Center, İzmir, Turkey

ABSTRACT

Hyperinsulinemic hypoglycemia is a rare disease affecting infants and children. The frequency of HNF4A mutation is the third most common type following ABCC8 and KCNJ11 mutations. HNF4A inactivating mutations may cause hyperinsulinemic hypoglycemia generally in the neonatal period by impairing insulin production and the secretion in pancreatic β cells. Herein, we present a case of an 8-month-old girl with hyperinsulinemic hypoglycemia who had normal birth weight. In this case, hypoglycemia became prominent after acute gastroenteritis and long-term glucose infusion was administered to overcome hypoglycemia. On follow up, diazoxide treatment up to 12 mg/kg/day was required to achieve normal glucose levels. In the molecular genetic analysis, a heterozygous mutation was found in the *HNF4A* gene (c.266G> A, p.R89Q), which was previously described in a case with MODY (maturity-onset diabetes of the young) type 1. During two weeks of hospitalization, while the glucose infusion rate was tapered, oral feeding was increased. Diazoxide treatment continued after discharge and was gradually stopped when she was at the age of 14 months. Afterwards, no hypoglycemia was observed. *HNF4A* gene mutation should be kept in mind even if there is no macrosomia or family history of diabetes in patients presenting with hypoglycemia and requiring diazoxide therapy.

Keywords: Hyperinsulinemic hypoglycemia, *HNF4A* gene, diazoxide therapy

Introduction

Hyperinsulinemic hypoglycemia (HH) is a rare group of diseases that usually occur in infants and children. The incidence varies between 1/50,000 and 1/2,500 (1). Various prenatal, natal and postnatal factors can lead to this disease. Infants of diabetic mothers, macrosomia, perinatal stress (asphyxia, maternal toxemia, prematurity, IUGR), overgrowth syndromes (especially Beckwith-Wiedemann syndrome), blood transfusion/ exchange and misplaced umbilical venous catheters are associated with increased risk of HH (2). Other than these perinatal factors mentioned

above, several genetic defects, which are mostly inherited autosomal recessive or dominant, have been identified as causes of hyperinsulinemia. Mutations in the ABCC8 (ATP-binding cassette, sub-family C, member 8), KCNJ11 (potassium inwardly rectifying channel, subfamily J), member 11), GLUD1 (glutamate dehydrogenase), GCK (glucokinase) or HADH (hydroxyacyl-CoA dehydrogenase) are the most frequent causes leading to HH in infancy (3).

In addition, it has been shown that heterozygous inactivating mutations in the gene HNF4A (hepatocyte nuclear factor 4- α), leading to maturity onset diabetes of the young (MODY) type 1 in adolescence and adulthood,

Address for Correspondence

Gülçin Arslan MD, University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Clinic of Pediatric Endocrinology, İzmir, Turkey Phone: +90 555 811 95 77 E-mail: gulcinak_005@hotmail.com ORCID: orcid.org/0000-0003-4506-2654

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may also cause HH in infants and children (4-6). *HNF4A* plays a role in insulin production and secretion by interacting with various transcription factors in pancreatic β -cells. It is not yet clear how *HNF4A* gene mutations cause hyperinsulinism in newborns. It is thought that it may be due to an abnormal expression of one or more target genes involved in insulin production and secretion in islet cells (3,7). The frequency of *HNF4A* mutation in HH cases is reported to be approximately 5% (8). Additionally, in some studies, it has been reported that *HNF4A* mutation was found to be the third most common cause after *ABCC8/KCNJ11* mutations in patients with diazoxide-responsive HH (8,9). The clinical findings in cases with HH due to *HNF4A* mutation frequently occur in the first week of life and are usually transient (8,9). Moreover, in previous studies, it was reported that most cases with HH are macrosomic. In addition, in some of the cases, the disease can be controlled with glucose infusion alone; however, some patients may require diazoxide treatment.

In this report, unlike the cases that were reported to date, we present a case of an 8-month-old girl with normal birth weight who had HH due to *HNF4A* mutation requiring diazoxide therapy.

Case Report

An 8-month-old girl was brought to the emergency department with afebrile convulsion. It was learned that she had had vomiting and diarrhea for two days and her feeding had deteriorated. She was born with a weight of 3,130 g after an uneventful pregnancy and she did not have any health problems in the first eight months. Her parents have no consanguinity and there was no family history of diabetes or hypoglycemia. Physical examination revealed a weight of 7.5 kg (25-50 p), height of 68 cm (25-50 p), body temperature of 36.2 °C, heart rate of 122/min, blood pressure of 92/60 mmHg and capillary blood glucose of 37 mg/dL. Her convulsion was due to hypoglycemia. Initially, she was unconscious and mildly dehydrated. The cardiovascular, respiratory, and gastrointestinal system examinations were normal. No findings regarding syndromic features were observed. On laboratory examination, venous blood glucose was 20 mg/dL and complete blood count, renal function tests, and ions were normal as shown in Table 1. Serum levels of lactate and ammonia were normal and urine ketone was negative. After receiving critical blood samples, 2 mg/kg of 10% dextrose was given intravenously. Consequently, the blood glucose increased to the normal range, and then 6 mg/kg/min of glucose infusion was continued. Even after the symptoms of diarrhea and vomiting improved and oral

feed started, hypoglycemia (<50 mg/dL) persisted. Later on, in order to overcome hypoglycemia, the intravenous glucose infusion rate was increased step by step to 8-10 mg/kg/min. In order to rule out any neurological defect causing convulsion, EEG and cranial MRI of the patient were taken and both were reported as normal. While the increase in serum levels of cortisol and growth hormone were found to be normal during hypoglycemia, serum insulin was found to be relatively high (Table I). An increase of more than 30 mg/dL in blood glucose was detected after the administration of 1 mg of glucagon at the time of hypoglycemia, which is suggestive of HH. Glucose infusion was increased up to 12 mg/kg/min, but the clinical condition did not improve and normoglycemia was not achieved. Therefore, 5 mg/kg/day diazoxide was started and gradually increased to 12 mg/kg/day. Subsequently, clinical improvement was achieved and the glucose infusion rate was tapered and stopped. Then, she was discharged with continued diazoxide treatment. On the outpatient follow-up, the dose of diazoxide was reduced and stopped at 14 months of age. No further hypoglycemia was observed during the treatment or post-treatment periods.

In the genetic analysis, while no mutation was found in *ABCC8/KCNJ11*; a heterozygous missense mutation in the *HNF4A* gene (c.266G> A, p.R89Q) was seen. Her parents had no symptoms suggestive of diabetes, and their basal laboratory values (insulin, fasting glucose, HbA1c) were

Table I. Laboratory features of the patient at the time of hypoglycemia

Parameter	Value	Normal range
Glucose (mg/dL)	20	60-100
Blood urea nitrogen (mg/dL)	10.1	5.1-12
Creatinine (mg/dL)	0.4	0.2-0.5
Sodium (mmol/L)	141	136-145
Potassium (mmol/L)	3.9	3.7-5.5
Hemoglobin (gr/dL)	11.9	12-16
Leukocyte (cells/mm ³)	6,100	5,000 - 15,000
Platelets (cells/mm ³)	305,000	150,000 - 450,000
C-reactive protein (mg/dL)	0.02	<0.5
Serum insulin (μ U/mL)	4.4	2.6-24.9
C-peptide (ng/mL)	0.825	0.9-7.1
Growth hormone (ng/mL)	8.8	<8
Cortisol (μ g/dL)	18.9	3.7-19.4
Ammonia (μ g/dL)	73	27-115
Lactate (mmol/L)	14	4.5-19.8

normal. However, since they did not accept, genetic analysis could not be performed. Informed consent was obtained from the parents of the patient for this study.

Discussion

Herein, we present an 8-month-old girl with HH due to heterozygous missense mutation in the *HNF4A* gene (c.266G> A, p.R89Q) that was previously reported to be pathogenic in a patient with MODY (10). The clinical features of hypoglycemia in patients with a *HNF4A* gene mutation have a wide clinical spectrum ranging from a mild clinic, which was improved by feeding regulation alone, to severe hypoglycemia that requires diazoxide therapy for many years. It is not yet clear how *HNF4A* gene mutations cause HH. However, *HNF4A* is known to play a key role in the interaction of some transcriptional factors in islet cells (11,12). In addition, it has been shown that *HNF4A* is associated with PPAR α (peroxisome proliferator-activated receptor alpha), a transcription factor that controls the gene expression of some enzymes involved in β -oxidation of fatty acids (13).

No genotype-phenotype relationship was shown in patients with HH due to *HNF4A* mutations. However, it is suggested that macrosomia and HH are more frequent especially in mutations in the promoter region (P2) of the gene (5). The mutation in our case (c.266G> A, p.R89Q) is located in the second exon outside the P2 region. In addition, there are numerous mutations outside this region that have been shown to cause HH (4). Finally, further studies are needed to demonstrate this relationship.

HH that was caused by *HNF4A* gene mutations was first described by Pearson et al. (4). In the same retrospective study of families with *HNF4A* mutation-associated diabetes, it was reported that HH due to a heterozygous *HNF4A* mutation was seen in 8 out of 54 infants. Flanagan et al. (8) detected a genetic mutation in 59 of 220 diazoxide-responsive HH cases and that 11 (5%) were *HNF4A* mutations, 4 of these were de novo. In a study conducted by Kapoor et al. (9), *HNF4A* mutation was detected in 7 out of 41 patients with diazoxide-responsive HH.

HH cases with a *HNF4A* mutation are usually born with macrosomia (4). In a retrospective study by Pearson et al. (4), 56% of cases were reported to be macrosomic (790 gr more than controls). In another study, it was reported that the mean birth weight of patients with a *HNF4A* mutation was 751 gr more than those of healthy controls (6). In the study by Flanagan et al. (8), 9 of 11 patients were found to be macrosomic. In addition, in some case reports, macrosomic

cases with a *HNF4A* mutation have also been reported (5,14). In contrast, our case had a normal birth weight of 3,130 g, suggesting clinical variability.

HH due to *HNF4A* mutations usually present in the neonatal period (5,8,9). In the study by Flanagan et al. (8) all patients with *HNF4A* mutations presented with hypoglycemia in the first week of life (median age 1 day, range 1-7 days). In a study conducted by Pearson et al. (4), hypoglycemia was observed in the neonatal period in all cases with HH due to *HNF4A* mutation. In another study, it was reported that patients with *HNF4A* mutations presented with hypoglycemia earlier than those with *ABCC8/KCNJ11* mutations in the neonatal period (9). At the same time, apart from the neonatal period, HH due to *HNF4A* mutation that presented in childhood (at the age of 2.5 years) were also reported, suggesting that phenotypes in *HNF4A* may be heterogeneous with variable age of onset (15). In line with this, in our patient who had a missense mutation in the second exon of *HNF4A*, HH was detected in a late period (at the age of 8 months) with no previous symptoms or hospital admissions regarding hypoglycemia. Moreover, hypoglycemia was not reported in another patient with the same mutation as our patient and that case only presented with diabetes at the age of 25 years, which is suggestive that even in cases with the same mutation, different clinical presentations may occur (10). Moreover, besides the impact of a *HNF4A* mutation, gastroenteritis in our patient may also have precipitated the development of the clinical manifestations of hypoglycemia.

HH in patients with *HNF4A* mutations is usually transient (4,5). Some cases require short-term glucose infusion to normalize glucose levels, and others need diazoxide treatment. In the study by Kapoor et al. (5), 3 infants with severe HH were treated with diazoxide over periods ranging from 8 to 18 months and moreover, one of these cases was treated up to the age of 32 months. In our case, who was admitted with hypoglycemia at the age of 8 months, we used diazoxide treatment for 6 months and following discontinuation of the drug, euglycemic state was achieved.

HNF4A mutations, which may lead to hypoglycemia in the neonatal period, can also cause MODY type 1 in adolescents and adults. Therefore, a history of diabetes in a family member is of great importance in cases with HH, as it allows us to consider *HNF4A* mutations in the differential diagnosis (1,5). However, in HH cases without any family history of diabetes, the possibility of a mutation in *HNF4A* should not be excluded as it may be caused by de novo

mutations (7,14). In one study, only 4 of the 11 cases with a *HNF4A* mutation had a family history of diabetes, and the remaining did not have a family history of diabetes (8). Our patient did not have a family history of diabetes and genetic analysis of her parents revealed no mutation in the *HNF4A*, suggesting de novo mutation should be considered.

It is known that cases with a *HNF4A* mutation developed MODY type 1 in the later period (usually in adolescence or adulthood) after the regression of hypoglycemia (14). Five out of 54 patients with a *HNF4A* mutation were reported to have developed diabetes during adolescence (8). The age of onset of diabetes is variable in these patients. This has been shown to be related to the type and position of the mutations (15). It has been suggested that *HNF4A* mutations affecting exons 9 and 10 are associated with a later onset of diabetes compared to those with mutations in exons 2-8 (15). However, the case who had the same mutation as our patient presented with diabetes at the age of 25 years old, which is inconsistent with previous study results. We can speculate that there is no clear relation between genotype and phenotype. These findings point to the fact that in patients with *HNF4A* mutations, there is variability in the time of emergence of diabetes as well as the onset of hypoglycemia. Therefore, we should carefully follow-up those patients with HH, who have missense mutation in the 2nd exon of the *HNF4A*, in terms of developing diabetes in later life.

Conclusion

In conclusion, hyperinsulinism should be considered in infants who present with hypoglycemia even after the neonatal period. Clinical features of HH caused by *HNF4A* mutations can be varied in terms of age of onset, longevity and severity of hypoglycemia. Moreover, *HNF4A* gene mutation should be kept in mind in patients presenting with hypoglycemia and requiring diazoxide therapy even if there is no macrosomia or family history. Additionally, it should be kept in mind that HH cases with *HNF4A* mutations have a risk of developing diabetes in later in life and, therefore, these cases should be followed at regular intervals.

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.A., B.Özkan., Design: G.A., S.A., Data Collection or Processing: S.A, T.R.Ö., Ö.K., Ö.Kö., Analysis or

Interpretation: Ö.K., B.Ö., Ö.N., Literature Search: G.A., S.A., Writing: G.A., S.A.

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