JCEM Case Reports, 2023, **1**, 1–3
https://doi.org/10.1210/jcemcr/luad089
Advance access publication 14 August 2023
Case Report

Siblings With *HNF4A* Congenital Hyperinsulinism From Possible Parental Gonadal Mosaicism

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Abstract

Congenital hyperinsulinism is the most common cause of persistent hypoglycemia in early infancy. Mutations in the gene for heterozygous hepatocyte nuclear transcription factor 4-alpha (*HNF4A*) account for approximately 5% of cases and are inherited in an autosomal dominant fashion or arise as de novo mutations. This case describes a unique presentation of parental gonadal, or germline, mosaicism as the suspected inheritance pattern for siblings with congenital hyperinsulinism caused by *HNF4A* mutations. Two siblings presented with hypoglycemia in the first hours of life and were subsequently confirmed to have hyperinsulinism. In each patient, glycemic control was achieved at relatively low doses of diazoxide. Both siblings tested positive for the same *HNF4A* mutation, whereas the parents tested negative for *HNF4A* mutations. Gonadal, or germline, mosaicism became the presumed leading diagnosis, given 2 unaffected parents with 2 children with congenital hyperinsulinism. The older sibling demonstrated additional clinical features of liver disease and renal Fanconi syndrome, both of which are associated with *HNF4A* mutations.

Genetic testing plays an important role in the diagnosis and management of congenital hyperinsulinism. *HNF4A* mutations may arise by a range of mechanisms, including gonadal, or germline, mosaicism. *HNF4A* mutations have phenotypic variance that may affect multiple organ systems at any age.

Key Words: germline mosaicism, hypoglycemia, *INSR*, diazoxide

Abbreviation: *HNF4A*, hepatocyte nuclear transcription factor 4-alpha.

Introduction

Congenital hyperinsulinism is a rare disorder, with an estimated incidence of 1 in 40 000 to 1 in 50 000, accounting for most cases of persistent hypoglycemia in early infancy [1]. Hypoglycemia from congenital hyperinsulinism can range from mild and asymptomatic to severe, causing neurologic impairment, seizures, or death. The physiologic response to hypoglycemia is inhibition of insulin secretion to prevent further hypoglycemia. Congenital hyperinsulinism is defined by inappropriately high levels of insulin or C-peptide in the setting of hypoglycemia. Neonatal hypoglycemia is defined as serum glucose less than 70 mg/dL (3.9 mmol/L). Congenital hyperinsulinism is initially treated with diazoxide, a medication that opens the ATP-sensitive plasma membrane potassium channel in pancreatic β cells and prevents insulin release [2].

Diagnostic evaluation of congenital hyperinsulinism can be difficult because only approximately half of the patients with this disorder have a genetic mutation identified [3]. Mutations in the gene for heterozygous hepatocyte nuclear transcription factor 4-alpha (*HNF4A*) are an autosomal dominant inherited cause of congenital hyperinsulinism, accounting for about 5% of all cases [4]. HNF4A mutations commonly arise as de novo mutations [4]. *HFN4A* acts as a transcription factor for genes affecting several organs, including pancreatic β cells. Mutations in *HNF4A* can cause varying effects on different organ systems, leading to a high degree of phenotypic variance. The most common clinical phenotype of *HNF4A* mutations includes congenital hyperinsulinism presenting in the first days of life, macrosomia, and monogenic diabetes, also known as maturity-onset diabetes of the young [5]. Monogenic diabetes, a nonautoimmune pancreatic β-cell failure disease, presents in adolescence or young adulthood [6]. An additional specific phenotype, Fanconi-Bickel syndrome, presents as congenital hyperinsulinism with a combination of renal Fanconi syndrome and hepatic glycogen storage disorder [7]. A case series by Hamilton et al identified a specific mutation in *HNF4A*, c.187C > T (p.Arg63TrP), termed *HNF4A R76W*, in association with this presentation of congenital hyperinsulinism and renal Fanconi syndrome. Overall, genetic testing is recommended in all cases of congenital hyperinsulinism because identification of specific genetic mutations can guide management.

Case Presentation

Patient 1

Patient 1 was a term female infant who presented with jitteriness at 1 hour of life. Point-of-care glucose was undetectable

Received: 25 January 2023. **Editorial Decision:** 28 June 2023. **Corrected and Typeset:** 14 August 2023

at that time. She required a glucose infusion rate of 25 mg/kg/min to maintain euglycemia. The diagnostic evaluation revealed an inappropriately high insulin level of 180.3 mIU/L (1252 pmol/L), whereas serum glucose was 59 mg/dL (3.3 mmol/L). Thus, a diagnosis of hyperinsulinism was made and genetic testing was performed.

Genetic testing revealed heterozygous *HNF4A* c.187C > T (p.Arg63TrP), also referred to as *HNF4A R76W*, and insulin receptor (*INSR*) c.3410T > C (p.Ile1137Thr) mutations. *HNF4A* was considered a pathogenic variant, given the known association with congenital hyperinsulinism. *INSR* was considered a variant of unknown significance because it had not been associated with congenital hyperinsulinism at the time of the testing. Both parents are healthy and did not have hyperinsulinism in infancy or diabetes mellitus as adults. Peripheral blood leukocyte genetic testing was negative for *HNF4A* mutation in both parents. Parents were not tested for *INSR* mutations. Thus, with negative parental genetic testing, patient 1 was considered to have a de novo mutation at that time.

Patient 2

Patient 2 is the younger sibling of patient 1, who was also born at term. Immediately after birth, her serum glucose was less than 4 mg/dL (0.2 mmol/L). She required multiple 10% dextrose fluid boluses escalating to a glucose infusion rate of 21 mg/kg/min to maintain euglycemia. In the diagnostic evaluation, serum glucose was measured at 40 mg/dL (2.2 mmol/L) with an inappropriately detectable insulin level of 44.9 mIU/L (312 pmol/L), which confirmed hyperinsulinism. The congenital hyperinsulinism which developed in patient 2 was unexpected, given the negative parental genetic testing.

Treatment

Patient 1

Diazoxide treatment was initiated at a dose of 10 mg/kg/d within the first few days of life, after the diagnosis of hyperinsulinism. She demonstrated robust diazoxide responsiveness and subsequently required decreasing her dose of diazoxide because of hyperglycemia. She was discharged home at 60 days of life with euglycemia maintained on 6.4 mg/kg/d of diazoxide. Diazoxide was discontinued after a slow wean at 26 months of age without recurrence of hypoglycemia.

Patient 2

Patient 2 was started on a lower dose of diazoxide after considering patient 1's robust response to diazoxide. Patient 2 was started on a diazoxide dose of 5 mg/kg/d and ultimately maintained euglycemia on a dose of 7 mg/kg/d of diazoxide. Patient 2 was discharged from the hospital on day of life 10. By 5 weeks of age, diazoxide was weaned to 2 mg/kg/d secondary to hyperglycemia. Genetic testing results were the same as for her sibling: heterozygous pathogenic *R76W* mutation in *HNF4A* [c.187C > T (p.Arg63TrP)] and *INSR* [c.3410T > C (p.Ile1137Thr)] variant of unknown significance.

Outcome and Follow-up

Patient 1 With Extrapancreatic Disease

In addition to hyperinsulinism, patient 1 developed renal and hepatic clinical manifestations, both of which are associated with *HNF4A* mutations [6]. She developed renal Fanconi syndrome causing hypophosphatemic rickets, renal tubular acidosis, and carnitine deficiency. Medical management includes calcitriol, levocarnitine, and potassium and sodium phosphate packets. Her stature has been short since birth with a height for age consistently less than the first percentile. She had also developed intermittent hepatomegaly that was associated with elevated transaminases. Diagnostic laboratory evaluation for hepatitis yielded no specific etiology. Ultrasound and magnetic resonance imaging of the liver have shown nonspecific echogenic liver lesions. The hepatitis and liver lesions have only been transiently present, and she has been asymptomatic; thus, no biopsies have been performed.

Patient 2 has been stable with euglycemia on low-dose diazoxide. She has not had other organ systems affected by her HNF4A mutation.

Discussion

Patient 1 was initially considered a de novo mutation; however, this became less likely when patient 2 presented with congenital hyperinsulinism as well. Both parents had peripheral blood testing, which was negative for the *HNF4A* mutation, but had children who are both positive for the mutation. There is a higher probability that 1 parent has gonadal, or germline, mosaicism than parents having 2 children with the same de novo mutations causing hyperinsulinism. Thus, a parental gonadal mutation is the most probable explanation for the genotype and phenotype seen in this family. Parents have declined gonadal/germline genetic testing because they do not plan to have more children at this time. The potential of nonpaternity was considered in this case. This was discussed with parents on multiple occasions, independently, but denied as a possibility. The phenotypic appearance of both patients is similar to the father, although this does not confirm paternity. The leading diagnosis is 1 of the parents having gonadal mosaicism of *HNF4A*.

Gonadal mosaicism, or germline mosaicism, is a unique genetic change in gamete cells, which may or may not be present in somatic cells throughout the body. A genetic mutation in a parent's gonadal, or germline, DNA would present as unaffected parents giving birth to children affected by an autosomal dominant condition [8]. There has been 1 prior case of gonadal mosaicism with *HNF4A* mutation in an individual who also demonstrated somatic mosaicism (26% of leukocytes with mutation). The individual and the partner were unaffected and gave birth to 2 girls with somatic *HNF4A* mutations. The first child presented in childhood with rickets, short stature, and renal Fanconi syndrome. The other child presented at birth with hypoglycemia and hyperinsulinism that were responsive to diazoxide [2].

HNF4A mutations are rare and thus the literature describing inheritance and phenotypic variance is limited. The inheritance patterns previously described have not been affected by the sex of the patient. Both of these patients were female infants, which has an unclear contribution at this time but may contribute to the literature regarding inheritance patterns. The patients in this case present 1 of the many phenotypes that have been specifically associated with the HNF4A R76W mutation. Whether patient 2 will also develop renal and hepatic disease secondary to the mutation remains to be seen.

Both patients, in this case, had *INSR* mutations [c.3410T > C (p.Ile1137Thr)], which were considered variants of unknown

significance. *INSR* encodes the transmembrane insulin receptor, and mutations have been associated with severe insulin resistance [9]. The clinical phenotype in patient 1 is specific to *HNF4A* mutation, but the possibility of *INSR* mutation contribution to neonatal hypoglycemia and hyperinsulinism should be considered.

Learning Points

- Genetic testing is recommended in all cases of congenital hyperinsulinism as identification of specific genetic mutations can guide management [3].
- Hepatocyte nuclear transcription factor 4-alpha (*HNF4A*) mutations may arise by a range of mechanisms, including gonadal, or germline, mosaicism.
- *HNF4A* mutations may demonstrate a robust response to diazoxide as well as an ability to wean off diazoxide in early childhood [2].
- Patients with *HNF4A* mutations should be monitored for other clinical manifestations of the mutation, including diabetes (maturity-onset diabetes of the young), renal Fanconi syndrome, and hepatic disease.

Contributors

T.E. and J.S. were involved in the diagnosis and management of patient 1. R.W., T.E., and J.S. were involved in the diagnosis and management of patient 2. R.W., T.E., and J.S. reviewed and approved the final draft.

Funding

The authors did not receive public or commercial funding for the submitted work.

Disclosures

The authors have no disclosures to declare for this case report.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patients' relatives or guardians.

Data Availability Statement

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

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