Case Report

Report of Prolonged Neonatal Hypoglycemia in Three Infants of Mothers With Variants in HNF1A

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A B S T R A C T

Background/Objective: Genetic variants in hepatic nuclear factor 1α (HNF1A) cause maturity-onset diabetes of the young (MODY). We sought to examine whether HNF1A MODY variants also cause neonatal hypoglycemia.

Case Report: We present 3 infants with variants in HNF1A shared with their mothers. The infants experienced neonatal hypoglycemia, 2 extending beyond 1 year and the third resolving by 28 days, and all were large for gestational age (birth weights of >99th percentile). In 2 cases, genetic testing for neonatal hypoglycemia revealed pathogenic variants in HNF1A; 1 mother was previously diagnosed with HNF1A MODY, and the other’s genetic testing and ultimate MODY diagnosis were prompted by her child’s hypoglycemia workup. In the third case, the infant’s persistent hypoglycemia prompted genetic testing, revealing an HNF1A variant of uncertain significance, which was then identified in the mother.

Discussion: Genetic variants causing HNF1A MODY have not been definitively linked to neonatal hypoglycemia or fetal overgrowth in utero. MODY caused by HNF1A is clinically similar to that caused by HNF4A, for which a causal relationship with neonatal hypoglycemia is more certain. Case reports have previously implicated variants in HNF1A in congenital hyperinsulinism; however, these cases have generally not been in families with MODY. The cases presented here suggest that HNF1A variants causing MODY may also cause neonatal hypoglycemia.

Conclusion: Although confounding factors make the assessment of neonatal hypoglycemia challenging, these cases offer potential support for single genetic variants in HNF1A causing both MODY and neonatal hypoglycemia, with associated fetal overgrowth in utero.

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Introduction

Mutations in hepatic nuclear factor-1α (HNF1A) are among the most common causes of maturity-onset diabetes of the young (MODY). Also known as “MODY 3,” HNF1A MODY is marked by glycosuria, progressive β-cell dysfunction, and sensitivity to sulfonylureas causing hypoglycemia. HNF1A MODY is clinically similar to...
A 22-year-old woman presented for diabetes care during pregnancy. She was diagnosed with HNF1A MODY based on genetic testing (report unavailable) when she was approximately 15 years old. She was initially diagnosed with type 1 diabetes (T1D) at the age of 8 years and started on basal-bolus insulin therapy. Owing to excellent glycemic control and minimal insulin requirements, her diagnosis was changed to type 2 diabetes (T2D) at approximately 9 years of age, and she transitioned to metformin monotherapy. Her strong family history of diabetes mellitus in her brother, mother, and maternal aunt prompted genetic testing at the age of approximately 15 years, leading to a clinical diagnosis of HNF1A MODY. She subsequently transitioned to sulfonylurea monotherapy, which she continued initially during the pregnancy, prior to transitioning to a basal-bolus insulin regimen at 5 weeks of gestation because of frequent hypoglycemia. Glycemic control during pregnancy remained within to slightly above the goal range (fasting glucose level, 60–110 mg/dL; 2-hour postprandial glucose level, 100–184 mg/dL; hemoglobin A1C [HbA1C] level, 27–33 mmol/mol [4.6%–5.2%]; postpartum HbA1C level, 29 mmol/mol [4.8%]), with a reported maximum glucose level of 189 mg/dL on continuous glucose monitoring (CGM) throughout the entire pregnancy. Nevertheless, ultrasonography demonstrated fetal overgrowth (estimated fetal weight [EFW] of >90th percentile at 29 weeks).

Child History
She delivered a girl via cesarean delivery at 38 weeks and 2 days of gestation with a birth weight of 4.38 kg (>99th percentile) and Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. The infant's initial point-of-care glucose level was 30 mg/dL at 1 hour of life, with a confirmatory serum glucose level of 34 mg/dL. She received a 10% dextrose bolus, followed by continuous infusion for 7 days (maximum glucose infusion rate of 8.7 mg/kg/min) and fortification of feeds (24 kcal/oz); critical hypoglycemia laboratory samples were not collected. Feeds were not defortified until day 25 of life, and the infant remained admitted for approximately 1 month because of concerns regarding hypoglycemia and feeding difficulties. Prior to discharge, a 6-hour safety fast resulted in glucose values ranging between 57 and 68 mg/dL.

At her first endocrine evaluation at the age of 6 weeks, the infant was formula feeding every 1 to 2 hours. Home blood glucose monitoring, including with CGM, revealed blood glucose values routinely of 50 to 60 mg/dL despite frequent feeding.
insulin-to-carbohydrate ratio of 1:8 and insulin sensitivity factor of 1:60 in the third trimester). Despite tight glycemic control (eg, mean ± standard deviation, glucose level of 102 ± 29 mg/dL on CGM in a 14-day period during the second trimester and 87-97 ± 22 mg/dL over a 28-day period during the third trimester; time above range <5% throughout the pregnancy), fetal monitoring revealed fetal overgrowth first noted at 30 weeks of gestation (EFW, 85th-90th percentile), with fetal abdominal circumference measurements in the 97th to 100th percentiles.

Child History

Labor was induced at 38 weeks of gestation and complicated by chorioamnionitis. She delivered a girl via cesarean delivery (for failure to progress) with a birth weight of 3.90 kg (>99th percentile) and Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The initial glucose level within the first hour of life was <20 mg/dL, improving to 34 mg/dL after administration of dextrose gel and formula and then to 49 mg/dL after repeat administration of dextrose gel. Critical hypoglycemia laboratory samples were not collected. Hypoglycemia recurred within several hours, and she required admission to the neonatal intensive care unit (NICU) for intravenous dextrose infusion (weaned on day of life 64). He was discharged home on day of life 76 after successfully undergoing an 8-hour safety fast while taking diazoxide 5 mg/kg/d.

After discharge, diazoxide was titrated to a maximum of 10.5 mg/kg/d at the age of 4 months in response to recurrent hypoglycemia documented at home. Genetic testing (University of Chicago 17-gene congenital hyperinsulinism panel, 2020) revealed a missense mutation in HNF1A (c.794A>G, p.Tyr265Cys). This variant has been classified as both VUS and likely pathogenic by the reporting laboratory; however, upon expert review by the Monogenic Diabetes Variant Curation Expert Panel in June 2021 using new gene-specific curation guidelines, it was classified as a VUS.

After delivering the infant, the mother transitioned to metformin monotherapy with an increase in the HbA1C level to 84 mmol/mol (9.8%). Glimepiride was added, with initial improvement in the HbA1C level to 48 mmol/mol (6.5%) but later an increase to 88 mmol/mol (10.2%) in the setting of weight gain and possible non-adherence. She was treated with metformin, glimepiride, and mixed insulins with an HbA1C level of 48 to 58 mmol/mol (6.5%-7.5%) for approximately 1 year before starting semaglutide. Initiation of semaglutide resulted in significant weight loss, improvements in hyperglycemia (HbA1C level, <7.0 mmol/mol [<6.0%]), and resolution of her insulin requirement. After her son’s mutation was discovered, she underwent genetic testing by the same laboratory and was found to have the same variant in HNF1A.

Discussion

In this manuscript, we report 3 mother-child dyads in which the mothers had pregestational diabetes and genetic testing revealing HNF1A variants (2 pathogenic and 1 VUS) and their children experienced prolonged neonatal hypoglycemia, supporting the potential connection between HNF1A MODY variants and neonatal hypoglycemia.

HNF1A MODY has an autosomal dominant mode of inheritance, with penetrance estimated from clinically selected cohorts of approximately 70% by the age of 25 years and 97% by the age of 50 years. Often patients are initially misdiagnosed with either T1D or T2D prior to receiving a genetic diagnosis; these patients may initially be treated with insulin until eventually receiving a genetic diagnosis of HNF1A MODY and transitioning to noninsulin agents, including sulfonylureas, to which many patients are exquisitely sensitive leading to hypoglycemia even at low doses. Sulfonylurea monotherapy may be sufficient to maintain glycemic control for years or decades, although patients may eventually progress to requiring insulin. A recent trial has also suggested that glucagon-like peptide 1 receptor agonists are an effective treatment option.

The cases reported here (with key features summarized in Table 1) contribute to a limited literature composed predominantly

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of case reports and small case series linking heterozygous mutations in HNF1A and neonatal hypoglycemia attributed to CHI.\textsuperscript{7,8,15} In fact, to our knowledge, there are only 6 unique cases reported in which an HNF1A variant currently classified as pathogenic or likely pathogenic in ClinVar has been associated with neonatal hypoglycemia or CHI (Table 2). Additionally, the fact that 2 of the mothers we report on have a definitive diagnosis of MODY (the third had a VUS in HNF1A) supports a more controversial relationship in which single variants may cause both HNF1A MODY and neonatal hypoglycemia, in contrast to the firmer connection between variants in HNF4A MODY and neonatal hypoglycemia.\textsuperscript{2}

It is important to note that several factors can contribute to neonatal hypoglycemia, including maternal hyperglycemia and perinatal stress, making it challenging to definitively determine that a given genetic variant is responsible. Nevertheless, such environmental factors are more likely to cause transient hypoglycemia than persistent hypoglycemia extending beyond 7 days.\textsuperscript{20} All infants described experienced prolonged hypoglycemia, with 2 cases extending beyond 1 year. Furthermore, although maternal glycemic control during pregnancy varied in each case, case 2 had particularly tight control with the CGM mean ± standard deviation glucose level: 87 to 102 ± 22 mg/dL throughout pregnancy. We also note that CHI was diagnosed and treated presumptively without confirmation with critical hypoglycemia laboratory samples; however, as described, there was documented hypoglycemia that resolved with diazoxide treatment.

The connection between variants in HNF1A and neonatal hypoglycemia has been controversial, as demonstrated by a large case series of kindreds with HNF1A MODY mutations, which did not identify an increased prevalence of neonatal hypoglycemia in infants who inherited the mutation (in contrast to kindreds with HNF4A MODY mutations).\textsuperscript{2} Yet, a number of case reports have described patients with HNF1A mutations and persistent hypoglycemia, generally by examining infants with unexplained CHI.\textsuperscript{7,15,16} Of these, 2 large case series of infants with confirmed CHI revealed multiple cases in which HNF1A variants were detected: in a series of 204 infants in a single U.S. institution, 7 were found to have variants in HNF1A,\textsuperscript{2} and in a series of 40 infants in the Czech Republic, 5 were found to have variants in HNF1A.\textsuperscript{19} Of note, some variants identified in these cases had not been curated using current standard of care guidelines,\textsuperscript{22} and some have since been classified as VUS or likely benign. Furthermore, the mild and less persistent hypoglycemia described in some case reports,\textsuperscript{19} as was observed in case 2, is more suggestive of transient neonatal hyperinsulinism than of CHI and makes it more difficult to distinguish HNF1A-associated hypoglycemia from hypoglycemia associated with maternal peripartum hyperglycemia. A similar spectrum of hypoglycemia severity has been described for HNF4A-associated hypoglycemic phenotypes.\textsuperscript{2} It is possible that the location or characteristics of the specific variant leading to different degrees of protein dysfunction or incomplete penetrance may lead to different phenotypes in childhood and adulthood.

As noted, the co-occurrence of childhood CHI and adult HNF1A MODY in families sharing the same genetic variant has not been extensively described. In the available literature, the family members of infants with HNF1A-associated CHI who shared the same genetic variants had variable phenotypes, including euglycemia,\textsuperscript{4,5,19} known MODY,\textsuperscript{7,9} gestational diabetes only,\textsuperscript{7,9} and diabetes not yet determined to be MODY.\textsuperscript{5,7,8,15} Of the 7 infants with CHI from 5 parents found to have HNF1A mutations in the first large case series described earlier, each had a parent with the same genetic variant, but only 2 of these had any known glycemic abnormality.\textsuperscript{5} In a second series, of 5 infants with CHI from 5 parents carrying the same variant, 4 of the parents had a known glycemic abnormality.\textsuperscript{5} CHI has also been described in an infant with a pathogenic HNF1A variant whose father had HNF1A MODY (p.Arg159Gln).\textsuperscript{7} We believe that our case 1 offers the strongest evidence in this case series for co-occurrence of persistent hypoglycemia (presumed CHI) and MODY due to the same genetic variants in HNF1A within a family.

Although examples of specific HNF1A mutations causing both neonatal hypoglycemia and MODY within a single individual at different stages of life are limited (eg, the mother in case 2 reported unprovoked, recurrent, and symptomatic childhood hypoglycemia, although objective data were not available), there is precedent for a single genetic variant causing both CHI in childhood and MODY in adulthood. This has been described for variants in both ABCC8\textsuperscript{23,24} and HNF4A.\textsuperscript{5,26}

It is paradoxical that 1 genetic variant could lead to both hyperinsulinism and defective insulin secretion. Although it is proposed that β-cell hyperresponsiveness leading to burnout, impaired incretin response,\textsuperscript{26} or changes in transcription factor function\textsuperscript{2}
may be the physiologic causes of these phenotypes, little data exist to support these hypotheses. Stem cell models of *HNF1A* deficiency in pancreatic islets demonstrate bias toward an alpha cell fate during differentiation and progressive impaired glucose-stimulated insulin response but no clear evidence of early hypersecretion.27 Murine models of *HNF4A* deficiency have suggested disparate effects of defective *HNF4A* at different times of life—promoting insulin secretion in the fetal and neonatal periods while preventing insulin secretion and leading to beta cell loss in adulthood2— it is possible that *HNF1A* may have a similar pattern.

# Table 2
Previous Reports of *HNF1A*-Associated Neonatal Hypoglycemia or Congenital Hyperinsulinism

| Publication citation | Variant(s) reported | ClinVar variant classification (for MODY)† | Duration of hypoglycemia (or age at which diazoxide was discontinued) | Presence of macrosomia or LGA birth weight | Report of MODY within the same individual, age at diagnosis |
|----------------------|---------------------|------------------------------------------|---------------------------------------------------------------|------------------------------------------|----------------------------------------------------------|
| Bruggaard et al,2 Endocr Abstr 2006 (abstract only) | c.476G>G; A. p.Arg159Gln | 1. Pathogenic | 1. 3 y | 1. Yes, 4378 g | 1. Unclear |
| Pearson et al,2,3 PLoS Med 2007 | 1. Mutation not reported | 1. Unknown | 1. <48 h | 1. Not reported | 1. Not reported |
| Stanescu et al,4,5 J Clin Endocrinol Metab 2012 | 1. c.94G>T; p.Glu32X | 1. Pathogenic | 1. 6 y | 1. Yes, 93rd percentile | 1. Not reported |
| 2. c.871G>T, p.Arg291Ser | 2. Likely benign | 2. 36–42 mo | 2. No, 7th percentile | 2. Not reported | 2. Not reported |
| Snider et al,21 J Clin Endocrinol Metab 2013 | 1. c.94G>T, p.Glu32X (previously included in the study by Stanescu et al,4, case 1) | 1. Pathogenic (duplicate) | 1. Not reported | 1. Not reported | 1. Not reported |
| 2. c.871G>T, p.Arg291Ser (previously included in the study by Stanescu et al,4, case 2) | 2. Pathogenic (duplicate) | 2. Not reported | 2. Not reported | 2. Not reported | 2. Not reported |
| 3. c.1541A>G, p.His514Arg | 3. VUS vs benign | 3. Not reported | 3. Not reported | 3. Not reported | 3. Not reported |
| Tung et al,22 Pediatr Diabetes 2018 | 1. c.94G>T, p.Glu32 (previously included in the studies by Stanescu et al,4 and Snider et al,21, case 1) | 1. Pathogenic (duplicate) | 1. 6.8 y | 1. Yes, 4167g, 92nd percentile | 1. Yes, 4750 g (+1.99 SD) |
| 2. c.871G>T, p.Arg291Ser (previously included in the studies by Stanescu et al,4 and Snider et al,21, case 2) | 2. Likely benign | 2. 3.5 y | 2. No, 7th percentile | 2. Yes, age 19 y |
| 3. c.872dupC, p.Pro291fs | 3. Pathogenic | 3. Continued on diazoxide at time of publication | 3. No, 71st percentile | 3. Yes, age 19 y |
| 4. c.654T>A, p.Tyr218 | 4. Not classified | 4. 7.3 y | 4. No reported | 4. Yes |
| 5. c.654T>A, p.Tyr218 | 5. Not classified | 5. Continued on diazoxide at time of publication | 5. No | 5. Yes |
| 6. c.872dupC, p.Pro291fs | 6. Pathogenic | 6. Continued on diazoxide at time of publication | 6. No, 84th percentile | 6. Yes, age 19 y |
| 7. c.872delC, p.Pro291fs | 7. Pathogenic | 7. Continued on diazoxide at time of publication | 7. Yes, 97th percentile | 7. Yes, age 19 y |
| 8. c.872dupC, p.Pro291fs | 8. Pathogenic | 8. “At least 1 attack of symptomatic hypoglycemia in childhood” at the age of 9 y in the setting of fasting; experienced tonic-clonic convulsions repeatedly in childhood without blood glucose check but semiquantitative estimations of urine ketone bodies were positive (grades 3–4) | 8. No, 44th percentile | 8. Yes |
| 9. c.815G>A, p.Arg272His | 9. Likely pathogenic | 9. VUS vs likely benign | 9. Yes, age 19 y | 9. Yes, age 19 y |

Abbreviations: LGA – large for gestational age; MODY – maturity-onset diabetes of the young; VUS – variant of uncertain significance.

Unique reports of cases with pathogenic or likely pathogenic variants are shown in bold

† Variant classification obtained from ClinVar database, June 29, 2022.22 All variant classifications were based on clinical laboratory submissions and/or expert panel review after the publication of the 2015 American College of Medical Genetics variant classification criteria.22
Still, the mechanism underlying these opposing phenotypes remains poorly understood.

Lastly, these cases suggest a possible association between variants in \textit{HNF1A} and fetal macrosomia. Infants of women with \textit{HNF1A} MODY, similar to infants of mothers with other forms of diabetes, are at risk of complications including fetal overgrowth and neonatal transitional hypoglycemia related to maternal glycemic control.\textsuperscript{15,29} Although imperfect glycemic control during pregnancy may lead to increased fetal growth,\textsuperscript{20} in our cases, each infant was strikingly large for gestational age (>99th percentile), despite one of the mothers reporting particularly tight glycemic control during pregnancy (case 2). Macrosomia independent of glycemic control is well described in infants with \textit{HNF4A}\textsuperscript{2,26}; however, at least 1 case series suggested that this is not the case for infants with variants in \textit{HNF1A}: this series found no difference in birth weight among infants with \textit{HNF1A} mutations and their unaffected family members, although notably only 1 infant in this series with an \textit{HNF1A} variant experienced hypoglycemia.\textsuperscript{2} In contrast to studies unselected for neonatal hypoglycemia, 2 case series in infants with hyperinsulinism found increased rates of large-for-gestational-age among infants with \textit{HNF1A} mutations. In the first, infants with \textit{HNF1A}-associated CHI weighed only 30 g less on average than those with \textit{HNF4A}-associated CHI.\textsuperscript{2} In the second, although infants with \textit{HNF1A} mutations had lower birth weight on average than infants with \textit{HNF4A} mutations (4100 ± 300 g, n = 2), their birth weights were 378 g heavier (3540 ± 884 g, n = 5), on average, than infants with hyperinsulinism without any mutations found (3162 ± 882 g, n 20); 60% of infants with \textit{HNF1A}-associated CHI in this series were large for gestational age.\textsuperscript{19} It should be noted, however, that both of these later case series included individuals with \textit{HNF1A} variants that would no longer be classified as likely pathogenic or pathogenic using the most recent guidelines (only 4 of 7 in the first series and only 1 of 5 in the second series).\textsuperscript{22} Still, the cases described in this report support that \textit{HNF1A} mutations associated with neonatal hypoglycemia may contribute to fetal macrosomia independent of maternal glycemic control.

This study is strengthened by a detailed description of the genotype and phenotype of both mothers and their infants. However, as a retrospective case series, it is limited both by missing or self-reported data in some cases and by its small sample size. Furthermore, the absence of a critical sample collected at the time of hypoglycemia prevents the confirmation of hyperinsulinemic physiology in each of these cases, although CHI is the leading cause of persistent hypoglycemia in infants and the natural history of their disease and response to treatment is consistent with CHI.\textsuperscript{21,31-34}

In summary, we report 3 cases of mother-infant dyads with mutations in \textit{HNF1A}. Although several factors can contribute to hypoglycemia and fetal macrosomia, these cases suggest that single mutations in \textit{HNF1A} can cause both neonatal hypoglycemia and MODY. Long-term follow-up of neonatal hypoglycemia cases is needed to confirm whether a single mutation can result in both hypoglycemic and hyperglycemic phenotypes in a single individual at different stages of life.

Disclosure

S.J.C. reports employment of a close family member by Johnson & Johnson. D.M.M. has received consulting fees from Amolyt Pharma for unrelated work. All other authors have no multiplicity of interest to disclose.

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Author Contributions

S.J.C., A.C.S., C.P., D.M.M., and M.S.U. contributed to the conception and design of the study, with C.P. identifying and contributing several cases. S.J.C., A.C.S., E.R., and K.S. contributed to data collection. S.J.C. drafted the manuscript, with critical revisions by all authors. All authors give approval of the manuscript to be submitted.

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