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Duplication 6q24: More Than Just Diabetes

Rachel H. Gore,[1] Maria Eleni Nikita,[1] Paula G. Newton,[1] Rebecca G. Carter,[1] Jeanine Reyes-Bautista,[1] and Carol L. Greene[1]

[1]*Department of Pediatrics, University of Maryland School of Medicine, Baltimore, Maryland 21201*

ORCiD number: 0000-0002-8253-5441 (R. H. Gore).

Chromosome 6q24-related transient neonatal diabetes mellitus is characterized by intrauterine growth restriction and low birth weight, with neonatal hyperglycemia resolving by 18 months and an increased risk for type 2 diabetes in adulthood. Molecularly, it is caused by overexpression of the 6q24 imprinted chromosomal region due to a duplication, uniparental disomy, or abnormal methylation. Conventional testing for this condition analyzes methylation patterns at the 6q24 locus but does not evaluate for the presence of other surrounding chromosomal abnormalities. We report a female with a history of neonatal hyperglycemia due to a paternally inherited duplication at chromosomal location 6q24. She subsequently presented to the pediatric genetics clinic at 15 months of age with developmental delay and abnormal balance. Microarray analysis identified a larger 14 Mb chromosomal duplication from 6q24 to 6q25.2, consistent with a diagnosis of duplication 6q syndrome. This case highlights the clinical importance of pursuing further genetic evaluation in patients diagnosed with chromosome 6q24-related neonatal hyperglycemia via targeted methylation-specific multiplex ligation-dependent probe amplification analysis identifying a duplication in this region. Early identification and intervention can improve developmental outcomes for patients with larger chromosome 6q duplications.

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Chromosome 6q24-related transient neonatal diabetes mellitus (TNDM) has an estimated prevalence of 1 in 400 000 and is the most common cause of diabetes restricted to the neonatal period [1]. The clinical course is characterized by low birth weight and hyperglycemia that requires insulin within the first week of life. Other features include macroglossia, umbilical hernia, and less frequently anomalies of the heart or renal tract [2]. In most patients, hyperglycemia resolves naturally before 18 months of age, though there is an increased risk for recurrence of diabetes in early adulthood.

Molecular abnormalities of the 6q24 chromosomal region have been shown to account for 70% of TNDM cases [3]. Testing of this region is used to anticipate whether diabetes will be transient or permanent. Finding an abnormality of 6q24 suggests the likelihood of transient diabetes as opposed to permanent diabetes, seen with pathogenic variants in the *KCNJ11* and *ABCC8* genes [4]. Additionally, identification of the underlying etiology is also important for management decisions [5]. Chromosome 6q24 is an imprinted region, and expression of the maternally inherited chromosome is normally silenced due to methylation. Chromosome 6q24-related TNDM is caused by overexpression of the genes at this region due to a paternally inherited duplication, paternal uniparental disomy, or hypomethylation of the maternal chromosome [1].

Abbreviation: TNDM, transient neonatal diabetes mellitus.

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1. Case Report

The female patient was born via cesarean section at 37 weeks' gestation to a G2/P1101 mother after a pregnancy complicated by intrauterine growth restriction and oligohydramnios. At birth, she was small for gestational age (1.82 kg, <1st percentile; 45 cm, 1st percentile) with microcephaly (head circumference of 29.5 cm, <1st percentile). She initially failed her newborn hearing screen but later passed a subsequent auditory brainstem response at 3 months of age. A small patent ductus arteriosus and patent foramen ovale were identified at birth and later resolved without intervention. An easily reducible umbilical hernia was detected and has not required surgical repair.

The patient initially presented with hyperglycemia at 10 hours of life on a 3-hourly feeding schedule. Her blood glucose ranged from 200 to 400 mg/dL with no ketosis or acidosis. Insulin treatment was initiated as a continuous infusion over the first 24 hours of life until blood glucose normalized. A trial off insulin infusion at day of life 3 resulted in recurrence of hyperglycemia. Intravenous insulin was restarted at 0.02 to 0.1 u/kg/hr. Laboratory evaluation while taking insulin at day of life 11 revealed a c-peptide of 0.5 ng/mL (normal range: 1.1-4.4 ng/mL) and insulin of 2.0 uIU/mL (normal range: 2.6-24.9 uIU/mL) when the blood glucose was 241 mg/dL. Renal and liver functions were normal. Due to great blood glucose variability and inability to convert to subcutaneous insulin at sufficiently low dose, the decision was made to proceed with a trial of sulfonylurea prior to the establishment of the genetic diagnosis [6]. At 4 weeks of age, the starting dose of sulfonylurea was 0.2 mg/kg/day titrated to 1 mg/kg/day while the insulin infusion was decreased. Within 5 days of starting sulfonylurea, she achieved good glycemic control without insulin. She had repeat c-peptide at 5 weeks of age that was 1.1 ng/mL (normal range 1.1-4.4 ng/mL) when blood glucose was 187 mg/dL. Due to hyperglycemia, the sulfonylurea was weaned and discontinued by 7 weeks of life. Her hemoglobin A_{1c} was 5.2%. She remained euglycemic thereafter. Her hemoglobin A_{1c} 5 months after discontinuation of the sulfonylurea was 4.9%

Evaluation for neonatal hyperglycemia included sequencing of the *KCNJ11* gene and sequencing with deletion/duplication analysis of the *ABCC8* gene, which were negative for a pathogenic variant. Methylation analysis of 6q24 identified a paternally inherited duplication at 6q24 consistent with a diagnosis of chromosome 6q24-related TNDM. Microarray was offered but not pursued by the family initially.

The patient re-presented to the genetics clinic at age 15 months with new concerns for developmental delay. Her diabetes had resolved, her height and weight were both above the 98th percentile, and her head circumference had normalized. She sat unsupported between 7 and 8 months; babbling was delayed, though single words were on time. At age 15 months, she was not walking independently, and when supported, the gait and balance were abnormal. She had overriding toes with the right third toe curling under the second.

Microarray was completed, identifying a 14 Mb gain of 6q24.1q25.2. This duplication includes approximately 73 genes and was classified as pathogenic by the testing lab due to known dosage pathogenicity of this region in association with a well-documented phenotype. The patient was referred for a formal developmental assessment and to developmental services.

2. Discussion

The chromosomal microarray findings in conjunction with the patient's presenting symptoms are consistent with a diagnosis of duplication 6q syndrome. This syndrome has been documented since the 1970s and is characterized by severe intellectual disability, short stature, joint contractures, feeding difficulties, and microcephaly. A distinct facial phenotype includes hypertelorism, down-slanting palpebral fissures, short neck, and tented upper lip [7]. Most reported cases of "classic" 6q duplication syndrome have a proximal breakpoint between 6q21 and 6q26 and include the 6q27 terminal band. Chromosome 6q

duplications are most commonly accompanied by a deletion of another chromosome due to a parental balanced translocation, which could potentially impact phenotype [8].

A milder presentation has been reported in patients with interstitial duplications similar in size to that of our patient. A 14-year-old female patient with a 15Mb duplication of 6q24.1-q25.3, and without a deletion, was reported to have syndrome-associated dysmorphisms, but growth parameters were normal and intellectual disability was classified as mild to moderate [9]. Another patient with a 6q23.2-q25.5 duplication was reported at age 2 months to have a history of intrauterine growth restriction and joint contractures but with normal growth and an overall milder presentation than observed in those with a terminal duplication. She also had a patent ductus arteriosus and an atrial septal defect, which have been associated with 6q duplication syndrome [8]. These cases illustrate the variable presentation of duplication 6q syndrome.

As molecular testing evolves, expanded approaches to genetic evaluation for TNDM have been proposed. A recent study tested 1020 patients with neonatal diabetes using a multigene approach that included 6q24 methylation studies as well as sequencing of all known genes associated with neonatal diabetes. Their findings indicate that a genetic cause was identified in 80% of participants with this testing strategy, allowing for a more accurate prediction of clinical course, anticipation of other complications, and the use of targeted therapy [10].

Previous studies have emphasized the importance of genetic evaluation of patients presenting with neonatal diabetes as a diagnostic tool that can guide therapy. To our knowledge, there is not yet data on the prevalence of larger duplications in the context of 6q24 TNDM. Finding a duplication of chromosome 6q24 should prompt concern for the possibility of a larger chromosomal abnormality. Understanding the specific mechanism causing chromosome 6q24-related TNDM also informs estimates of recurrence risk. Duplications can be inherited from a parent and passed on to siblings or offspring of an affected patient, while cases caused by paternal uniparental disomy or methylation are most likely de novo with a low chance for recurrence. Our case highlights the importance of further genetic evaluation following the identification of chromosome 6q24 to allow for earlier diagnosis and initiation of developmental interventions.

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Additional Information

Correspondence: Rachel H. Gore, ScM, CGC, 737 W. Lombard Street, Baltimore, MD 21201. E-mail: rgore@som.umaryland.edu.

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