Atypical Presentation of 17q12 Recurrent Deletion Syndrome, Mistaken for Meckel-Gruber Syndrome: A Case Report

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Introduction

17q12 recurrent deletion syndrome (OMIM #614527) is a rare microdeletion syndrome characterized by multicystic dysplastic kidneys, maturity onset diabetes of the young type 5 (MODY5), and cognitive impairment. These deletions include *HNF1B* (OMIM #189907), which is believed to be responsible for appropriate nephron development. Occipital encephalocele and polydactyly have not been previously reported with this condition. Here we present a case of 17q12 recurrent deletion syndrome in a patient with dysplastic kidneys, cognitive impairment, occipital encephalocele, and preaxial polydactyly who was initially diagnosed with Meckel-Gruber Syndrome (MKS). MKS is often a neonatal lethal condition due to severely impaired renal function. The additional symptoms in the patient that are inconsistent with the official diagnosis of 17q12 recurrent deletion syndrome could be attributed to diabetic embryopathy, a condition in which maternal hyperglycemia and/or hyperketonemia has teratogenic effects to the fetus.[1]

Case Presentation

Neonatal History

- Male born at 36 weeks via cesarean section to 32-year-old G3P1011>2012 mother with intellectual disability whose pregnancy was complicated by uncontrolled diabetes
- Paternal history: Unknown
- Ultrasound at 18 weeks gestation: Revealed multiple fetal anomalies
- At birth: Bilateral thumb polydactyly, occipital encephalocele, and congenital renal dysplasia
  - Triad classically associated with Meckel-Gruber syndrome (MKS)[2]
  - Cryptorchidism present
  - MRI: Revealed mild colpocephaly

Additional Medical History

- Age 10 days: Encephalocele was resected and repaired
- Age 3 months: Right-sided frontal ventriculoperitoneal (VP) shunt placed
- Age 20 months: Additional digits were excised and reconstructed
- Age 28 months: Surpassed latest known MKS life expectancy[2]
- Age 6: First febrile seizure
- Age 7: Last reported seizure
- Age 10: Says 3 – 4-word phrases, is social, and has independent dining skills; not yet toilet trained

Molecular Studies

- At birth: Karyotype revealed clinically insignificant inv(9)
  - Clinical diagnosis of MKS was assigned due to triad of preaxial polydactyly, occipital encephalocele, and renal dysplasia
- Age 10:
  - MKS gene panel: Negative
  - Proband only exome sequencing:
    - Hemizygous variant of uncertain significance (VUS) in ATP7A
    - Heterozygous VUS in MAF
  - Chromosomal microarray analysis (CMA): 1.5 Mb deletion in 17q12

Discussion

- While renal dysplasia, intellectual disability, and global developmental delay are findings characteristic of 17q12 recurrent deletion syndrome, occipital encephalocele and polydactyly have not been reported previously; neither of which are typical features seen with *ATP7A* or *MAF* pathogenic variants.[3-5]
- Polydactyly and central nervous system anomalies have been associated with diabetic embryopathy, as seen in this case.
  - Hyperglycemia in pregnancy may cause epigenetic changes, such as altered *PAX3* expression and glycosylation of histone proteins, that can induce neural tube defects and other teratogenic effects.[1]
  - Preaxial polydactyly is usually on feet rather than hands, and encephalocele is not often encountered in diabetic embryopathy.[6-7]
- Patient does not currently present with endocrine problems, such as MODY5, liver abnormalities, or eye abnormalities but will be surveilled by relevant specialists.

Symptoms	MKS	17q12 DS	Patient
Renal dysplasia	+	+	+
Occipital encephalocele	+	-	+
Preaxial polydactyly	+	-	+
Neurodevelopmental Disorders	-	+	+
Mild dysmorphic features	-	+	-
Hyperparathyroidism	-	+	-
Maturity-onset diabetes of the young type 5	-	+	-
Genital abnormalities	-	+	+
Liver abnormalities	+	+	-
Eye abnormalities	-	+	-
Pancreas abnormalities	-	+	-
Structural brain findings	-	+	-
Prematurity	-	+	-

Figure 1: Comparison of common symptoms between Meckel-Gruber syndrome (MKS) and 17q12 recurrent deletion syndrome (17q12 DS). Renal dysplasia is seen in both syndromes. Occipital encephalocele and preaxial polydactyly are common in MKS, whereas 17q12 DS is highly variable. Children with MKS seldom survive long enough for some other features to evolve.

Conclusion

We report a case of 17q12 recurrent deletion syndrome in a patient born with congenital renal dysplasia, encephalocele, and polydactyly suggestive of MKS. Panel testing and exome sequencing revealed no variant in genes associated with MKS. CMA discovered a deletion in the long arm of chromosome 17q12.

The atypical findings of encephalocele and polydactyly in this patient suggest the need for additional genetic testing in suspected cases of MKS. The influence of maternal diabetes on gene expression in the fetus also warrants additional exploration. Finally, these findings suggest the need for expansion of 17q12 recurrent deletion syndrome phenotype to include occipital encephalocele and preaxial polydactyly.

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