Letter to the Editor

Mitochondrial DNA depletion syndrome in a newborn with Jaundice Caused by DGUOK mutation and complete uniparental disomy of chromosome 2

To the Editor,

Jaundice is one of the most common clinical signs in newborns. However, determining its etiology sometimes poses a challenge. Herein, we report a case of a newborn with hypoglycemia along with severe hepatic injury and specifically intractable jaundice.

A newborn male with jaundice was admitted to the neonatal intensive care unit in our hospital on the 18th day after birth. The patient, Han Chinese, was the first child of his parents and was delivered by cesarean section because of two loops of the umbilical cord around his neck at the gestational age of 39 weeks. The child was born with a normal birth weight of 2600 g. The cesarean was performed successfully without amniotic fluid pollution and aspiration, fetal asphyxia, or placental abnormality. His mother had taken no particular medication during pregnancy. The child’s physical examination revealed that his sclera and skin had visible yellowish discoloration. His biochemical blood tests showed elevated alanine aminotransferase (26 IU/L), aspartate aminotransferase (52 IU/L), total bilirubin (10.16 mg/dL), direct bilirubin (6.98 mg/dL), and alpha-fetoprotein (54,327 ng/mL, the age-matched upper limit of normal <7 ng/mL). His laboratory examination revealed coagulopathy (partial thromboplastin time 106.10 s) and severe hypoglycemia (glucose level 0.8 mmoL/L, the age-matched lower limit of normal >3.3 mmoL/L). Although no image of the gallbladder or the intestine was seen, a weak image of the liver was observed on dynamic hepatobiliary imaging over 24 h, indicating severe liver damage. His ultrasonography showed normal liver morphology and no other congenital malformations of the hepatobiliary system. There was no sign of infection with hepadnavirus and other pathogens. The patient’s condition was not improved after adequate symptomatic treatments. After 6 months, the patient died from liver failure, and possibly from spontaneous intracranial hemorrhage. The patient’s unexplained congenital liver injury and refractory jaundice prompted us to explore the cause.

The development of molecular genetics has enabled the widespread use of next-generation sequencing in the diagnosis of unexplained congenital diseases. DNA sequencing of our patient revealed a homozygous mutation of the DGUOK gene (c. 679G > A) on chromosome 2, resulting in an amino acid change from glutamic acid to lysine (E227K). The mutation is pathogenic since it can cause mitochondrial DNA depletion syndrome (MDS). MDS is associated with hepatocerebral and myopathic damage, and may only manifest as dysfunction of a single organ, such as the liver.

In our case, the patient’s father was healthy and was heterozygous for the mutation, whereas his mother did not carry the mutation (Fig. 1A). This contradiction to Mendelian inheritance encouraged us to study the underlying molecular genetics. There are 4 possible mechanisms to explain this phenomenon: heterozygous deletion of the DGUOK gene, (non)parent–child relationship, uniparental disomy (UPD) of chromosome 2, and an extremely low probability of a de novo mutation. Finally, a single nucleotide polymorphism microarray (Affymetrix Cytoscan...
750 k) was performed to confirm the complete UPD of chromosome 2 (Fig. 1B). UPD refers to the situation in which both homologous chromosomes have originated from only one parent, resulting in an aberrant dosage of the imprinting genes and homozygosity of a recessive mutation.2 There was no imprinting gene located on chromosome 2 and both maternal and paternal UPD2 have been reported in individuals with normal phenotypes.3,4 Considering that there had been no abnormal features, except MDS, we speculated that the homozygous mutation of \textit{DGUOK} caused by UPD2 was the cause of the disease in this patient. Moreover, to the best of our knowledge, this is the fifth reported case of complete paternal UPD of chromosome 2.3

Conclusions

The possibility of MDS or other hereditary diseases should be considered in children with intractable jaundice and liver function impairment. The diagnostic scenario also highlights the importance of applying molecular genetic tests to the diagnosis of agnogenic diseases.

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Declaration of Competing Interest

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References


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