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Research Letter

Prenatal Diagnosis of a Case of Severe *DGUOK* Deficiency Did Not Affect the Postnatal Outcomes

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Mitochondrial diseases affect about 1 in 5,000 live births and have the highest incidence among all inherited metabolic disorders.[1] They can be caused by mutations in either mitochondrial DNA (mtDNA) (25% of cases) or nuclear DNA (75% of cases).[2,3]

Severe early onset of mitochondrial diseases typically results in death in the first year of life[4] and constitutes approximately 8.5% of the cases of mitochondrial diseases with childhood onset.[5]

Severe diseases are usually diagnosed antenatally after the death of a subject in a family and may be challenging for prenatal counseling.[5]

mtDNA depletion syndromes (MDS) (OMIM #251880) are a heterogeneous group of autosomal recessive diseases due to defects in mtDNA maintenance caused by pathogenic variants in nuclear genes that are involved in either mitochondrial nucleotide synthesis (*TK2*, *SUCLA2*, *SUCLG1*, *RRM2B*, *DGUOK*, *TYMP*, and *ABAT*) or mtDNA replication (*POLG*, *TWNK*, *TFAM*, and *RNASEH1*).[6,7] MDS are characterized by a reduction in mtDNA content leading to energy deficiency in affected tissues and organs.[7] They cause severe phenotypes and are usually classified as myopathic, encephalomyopathic, hepatocerebral, or neurogastrointestinal forms.[7]

Deoxyguanosine kinase (*DGUOK*) deficiency causes an MDS affecting mainly the liver and central nervous system and it accounts for about 15%–20% of all individuals diagnosed with MDS.[8] Mutations in *DGUOK* cause variable clinical patterns, ranging from a neonatal-onset multisystem disorder and an isolated hepatic disorder with infantile- or childhood-onset.[9,10] The majority of affected patients have a severe multisystem disease with hepatic involvement and neurologic manifestations that appear within a few weeks after birth. Liver failure is the most common cause of death in both multisystem disorders and isolated hepatic disorders.[6]

The diagnosis of *DGUOK* deficiency is confirmed by the identification of biallelic pathogenic variants in the *DGUOK* gene.[6]

Treatment is mostly symptomatic, as, currently, no disease-modifying therapy exists. Diet management of hepatic disease together with fat-soluble vitamins and essential fatty acids supplementation may be beneficial in patients with cholestasis.[6] Liver transplantation (LT) is an option only for patients with isolated hepatic disease. In patients with multi-organ disease LT provides no survival benefit.[11]

Prenatal testing for *DGUOK* deficiency caused by a previously identified pathogenic variant is possible. The clinical impact of prenatal diagnosis on prognosis in patients with *DGUOK* deficiency is not clear because no cases are reported in the literature. Here we describe a familial case in which prenatal diagnosis did not affect the postnatal outcomes.

The first patient, a female, was born at term after a pregnancy that was complicated by intra-uterine growth retardation. The parents were consanguineous. No prenatal malformations were detected. Her birth weight was 1,890 g (<3rd percentile). At 12 hours after birth, the patient developed recurrent hypoglycemia. Within the first day of life, she presented liver failure with persistent hypoglycemias (glucose 23–35 mg/dL), severe lactic acidosis (ph 7.18, HCO_3 10.3 mEq/L, BE -22, lactate 18 mmol/L), and coagulopathy not responsive to intravenous (IV) vitamin K (PT 4.09 INR). The patient required regular fresh frozen plasma transfusions and continuous glucose 10% infusion. She had normal transaminases, high ferritin (971 ng/mL), and α-fetoprotein levels (88,846 ng/mL). A mitochondrial disorder was suspected and the diagnosis was confirmed by next-generation sequencing (NGS) analysis testing a panel of hepatocerebral forms of MDS. The analysis revealed the presence of homozygous missense c.352C>T (p.Arg118Cys) mutation in the *DGUOK* gene.[4]

In the first month of life, her neurological status was characterized by mild hypotonia followed by a severe psychomotor delay that became progressively evident. Brain magnetic resonance imaging revealed no overt brain anomalies. However, magnetic resonance spectroscopy revealed a peak of lactate. At 2 months of age, the patient had constant striking oscillating eye movements.

Keywords: *DGUOK* deficiency; mtDNA depletion syndrome; Prenatal diagnosis; Postnatal outcomes; Case report.

Abbreviations: *DGUOK*, deoxyguanosine kinase; LT, liver transplantation; MDS, mtDNA depletion syndromes; mtDNA, mitochondrial DNA; NGS, next generation sequencing; UPD2, uniparental disomy of chromosome 2..

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Table 1. Useful information for counseling families with a prenatal diagnosis of *DGUOK*

Missense versus null variants	Two null variants have been typically related to severe multisystem phenotypes.[9] On the contrary, no clear genotype-phenotype correlations have been observed among patients harboring pathogenic missense variants in the *DGUOK* gene.[6] In particular, affected individuals with the same genotype can show a good response to liver transplantation or a very poor outcome.[6]
Family history	Affected sibs with the same *DGUOK* missense variants could exhibit different long-term outcomes, such as the life expectancy upon liver transplantation.[6] On the contrary, our affected sibs with missense variants showed very similar short-term outcomes.
Availability of Intensive Postnatal Care Program	In our case, immediate intensive postnatal care did not affect the short-term outcomes.
Availability of Perinatal Palliative Care Program	In our case, palliative care team activation improved the management of the patient by several points: (1) support in best interest choice and decision making; (2) planning in the location of care (hospital vs home); (3) multi-agency assessment of the family's goals of care and needs; (4) coordinated multi-agency care plans; (5) end of life care plan; (6) siblings and extended family support and bereavement care.

DGUOK, deoxyguanosine kinase.

At 3 months of age, she presented disconjugated and multidirectional eye movements and upbeating nystagmus.[12] Liver failure progressed despite supportive therapy. Given the overall clinical situation of the patient, LT was not considered as a treatment option. Upon this decision, the Pediatric Palliative Care protocol was activated. She died at 3 months of age because of end-stage hepatic failure.

The second patient was the first case's brother. Chorionic villus sampling performed at 13 weeks of gestation identified the same mutations of the deceased sister. Morphological ultrasound did not detect fetal malformations. The parents decided to continue the pregnancy. Palliative care team activation was antenatally required. The appearance of intra-uterine growth retardation and preeclampsia forced a preterm birth at 31 weeks of gestational age by cesarean section. The birth weight was 1,070 g (3^{rd}-10^{th} percentiles) and at birth, he required only airway management with nasal continuous positive airway pressure. Due to his prematurity, the patient continued respiratory support without oxygen supplementation until the 32^{nd} week of gestation.

According to the prenatal diagnosis of *DGUOK* mutation, we immediately started IV vitamin K supplementation and parenteral nutrition with a low supply of glucose (glucose rate 4.5 mg/Kg/min). Nonetheless, in the first few hours of life, he presented progressive lactic acidemia (ph 7.25, HCO_3 15.1 mEq/L, BE -12, lactate 10.2 mmol/L), hypoglycemias (glucose 28 mg/dL), and hepatic failure with coagulopathy refractory to IV vitamin K (PT 2.1 INR) and mild cholestasis (GGT 514 U/L). Diet modulation, supplementation with fat-soluble vitamins, and IV vitamin K continued in the following days. We also introduced enteral nutrition with medium-chain triglycerides oil supplementation, which gradually increased to achieve the suspension of parenteral support in the first month of life. Despite the supportive therapy, liver failure progressed and LT was excluded. Supplementation with fresh frozen plasma was interrupted. The patient died at 2 months of age due to end-stage liver failure.

After a prenatal genetic test, parents and families require accurate information and strong support. An appropriate exchange of information between the genetic counselor and the family is crucial for helping the parents to manage the stress following a prenatal diagnosis.[13] To reach this goal, it is usually necessary to adopt a multidisciplinary approach including obstetricians, neonatologists, pediatricians, psychologists, and others.[5]

A study evaluated the information needs of pregnant women following the prenatal diagnosis of fetal anomalies:[13] Two key points emerged. First, among the "Information needed for clarifying the diagnosed anomaly and making a decision", "the need for more information to gain control over the situation" came up as crucial. Then, among the "Information needed for preparing for the future" the need to know "the delivery and postnatal situation" and "future mortality and morbidity of the especial anomaly" were particularly relevant.[13]

Therefore, prenatal genetic counseling should provide rigorous information about the disorder, including whether the prenatal diagnosis can have a positive impact on the postnatal outcomes of the child.

In our case, prenatal diagnosis did not affect both the short and long-term postnatal outcomes. Moreover, prompt supplementation with IV vitamin K and parenteral nutrition with a low supply of glucose did not prevent hypoglycemias, severe hyperlactacidemia, and liver failure in the first 24 hours of life.

Both patients developed severe neurological disease in the first month of life. In both cases, LT was not considered as a treatment option.

The c.352C>T (p.Arg118Cys) mutation in the *DGUOK* gene (located in 2p13.1) was previously described in a case of maternal uniparental disomy of chromosome 2 (matUPD2). At two days of age, the patient presented with hypoglycemia. In the first month of life, the patient rapidly presented with feeding difficulties, hypotonia, growth retardation, liver enlargement, cholestasis, and jaundice. The authors highlighted that the identification of UPD2 facilitated the interaction between the genetic counselor and the parents, given that the recurrence risk for UPD2 is very low.[4]

The missense mutation identified in our patient constituted a significant challenge during prenatal counseling. In fact, no clear genotype-phenotype correlation exists among patients harboring pathogenic missense variants in the *DGUOK* gene.[6] The genotype and/or the family history may not be useful to predict outcomes in individuals with pathogenic missense variants.[6] In particular, very different long-term outcomes, such as the life expectancy upon liver transplantation, have been observed.[6] On the contrary, in our case, the short-term outcomes were very similar in both patients.

There are few data on the impact of antenatal diagnosis of *DGUOK* on the postnatal outcomes.[6,9] We summarized the main points in Table 1. It implies potential constraints regarding the accuracy and comprehensiveness of the information accessible to healthcare providers when guiding families about *DGUOK* deficiency.

In conclusion, the advent of NGS analysis has increased the diagnostic possibilities for mitochondrial diseases, concurrently with

the increasing need for prenatal diagnosis.

The management of antenatal counseling in the case of *DGUOK* deficiency is challenging because accurate data is still lacking. The availability of a Perinatal Palliative Care Program may support parents, siblings, and family to cope with the diagnosis and in planning for choices and decision-making.

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Conflict of interest

The authors have no conflicts of interests related to this publication.

Author contributions

Study concept and design (EM and RF); acquisition of data (CR); drafting of the manuscript (EM, CR, and MB); critical revision of the manuscript for important intellectual content (MS, MB, and FS); English editing (GP); and study supervision (MS and RF). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

The mother of the patient authorized the publication of this report via written consent.

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