

## CASE REPORT

# Prenatal presentation of glutaric aciduria type II: A case report with radiologic, clinical, biochemical, molecular, and pathological phenotyping

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## Abstract

We know that glutaric aciduria type II is an inborn metabolism. This case report highlights that polycystic kidneys with hepatomegaly in prenatal ultrasound are suggestive of glutaric aciduria type II and it identifies a new variant as pathogenic.

## KEYWORDS

genetics, obstetrics and gynecology, prenatal diagnosis

## 1 | INTRODUCTION

Glutaric aciduria type II (GA2), or multiple acyl-CoA dehydrogenase deficiency (MADD), is an autosomal recessive disorder. It is caused by mutations in the *ETF A* (15q23-q25), *ETF B* (19q13.3-q13.4), and *ETFDH* (4q32-q35) genes, which encode the alpha and beta subunits of electron transfer flavoprotein (ETF) and ETF-coenzyme. These mutations affect mitochondrial function as well as fatty acid, amino acid, and choline metabolism.<sup>1</sup> Glutaric aciduria type II affects approximately 1/200 000 live births.<sup>2</sup> Its presentation is variable and has been categorized into three clinical types. Type

one is characterized by neonatal onset with congenital anomalies. Type two is also characterized by neonatal onset but lacks congenital anomalies. Type three is milder and of later onset.<sup>3</sup> The neonatal forms are most often lethal and typically present with respiratory distress, acidosis, and refractory hypoglycemia.<sup>4-6</sup> Congenital anomalies that can be seen include dysplastic kidneys with multiple cysts, facial dysmorphism, rocker-bottom feet, and abnormal external genitalia.<sup>7</sup> The literature on prenatal imaging of this pathology is scarce. In this report, we detail prenatal ultrasound features of a case of GA2, which was comprehensively phenotyped in the neonatal period. This comprehensive phenotyping allows the

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classification of a previously unreported variant of the *ETFA* gene as pathogenic.

## 2 | CASE

A 29-year-old nulliparous woman was referred to our multidisciplinary prenatal diagnosis unit at 21 weeks' gestation for fetal renal anomalies. The family history was notable for consanguinity. A detailed obstetrical ultrasound showed placenta praevia, large (40 mm CI:21–34mm) undifferentiated hyperechoic kidneys with multiple corticomedullary millimetric cysts and a large hyperechoic liver with unusual millimetric bile cystic structures (shown in Figure 1A–C). Fetal growth and amniotic fluid were normal. The patient declined amniocentesis. Given consanguinity and suspicion of autosomal recessive polycystic kidney disease, she underwent carrier testing for *PKHD1*, which was negative. At 25 weeks, a narrow fetal chest was noted, and oligohydramnios developed by 27 weeks. On the 29 weeks' ultrasound, an enlarged cavum vergae, augmented and unusually trabeculated subarachnoid space was noted in addition to the anomalies previously described (shown in Figure 1B). At 36 weeks, the patient underwent a cesarean delivery for placenta praevia.

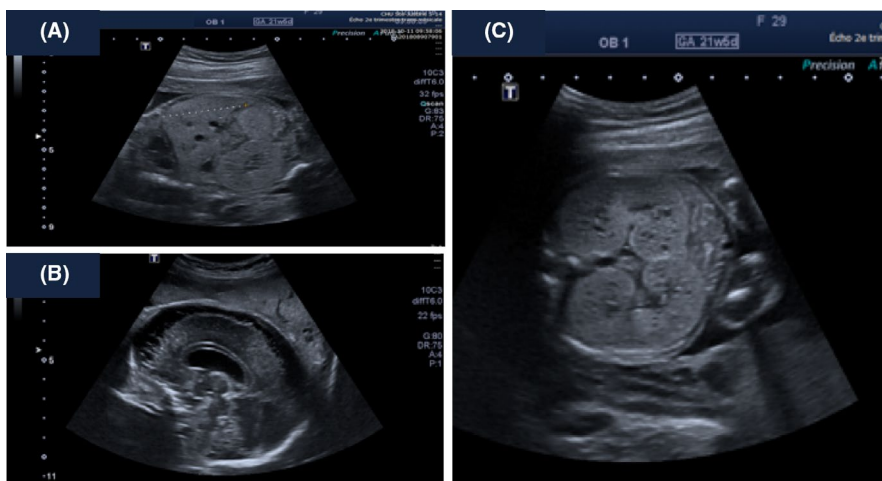
The male newborn, weighing 3050g with an APGAR of 7-7-7, was quickly transferred to the neonatal intensive care unit for respiratory distress and significant respiratory acidosis. Neonatal cerebral ultrasound was suggestive of gyration anomalies. Cardiac ultrasound demonstrated a large type 2 atrial septal defect with bidirectional shunting and a large aneurysm of the atrial septum. Prenatal renal findings were confirmed postnatally, with numerous microcystic lesions predominantly cortical and subcortical. He suffered from seizures, as well as pulmonary and intracranial hemorrhage. Metabolic abnormalities ensued upon improvement of respiratory acidosis. Over the next two days, there was persistent primary metabolic acidosis with hyperkalemia and

hyperlactatemia. There was no hypoglycemia. Supportive therapy with carnitine, riboflavin, and coenzyme Q10 was begun on the presumptive diagnosis of GA2. Urinary organic acid profile abnormalities included significant elevations of 2-OH-glutaric acid, highly suggestive of GA2. Acylcarnitine profile abnormalities corroborated this suspicion. Despite optimal management, the neonate died on the third day of life.

Autopsy findings supported the clinical diagnosis of GA2. Neuropathology yielded finding of diffuse polymicrogyria affecting the cortex and significant white matter disease, in a pattern characteristic of disorders of energy metabolism. There was generalized anasarca with features of Potter sequence. Renal histology was of nonobstructive tubular cystic dysplasia. Renal weight was twice the upper limit of normal. There was mild hepatomegaly due to microvesicular steatosis and passive congestion. There was cardiomegaly with left ventricular hypertrophy as well as left pulmonary isomerism.

The *ETFA*, *ETFB*, and *ETFDH* genes were studied by sequencing with copy number variant detection (average NGS coverage 120x). A homozygous, previously unreported variant in *ETFA* was identified, c.3G>A (p.Met1?). This variant was never previously reported in an affected patient. It was not reported in gnomAD, ExAC nor 1000 genomes. There was no functional data available. Location implied this variant lead to the loss of the translational methionine start site. The variant was predicted disease-causing in MutationTaster. Both parents were confirmed heterozygous carriers of the identified variant. The comprehensive phenotyping of this patient led to our classification of the previously unreported variant of the *ETFA* gene as pathogenic.

During the subsequent pregnancy, the patient underwent chorionic villus sampling for prenatal diagnosis based on this familial mutation. Biopsy result was negative for GA2. This subsequent pregnancy was uncomplicated and a healthy liveborn was delivered at term in our center with a normal neonatal course.



**FIGURE 1** A, 21 weeks' ultrasound showing enlarged liver with slightly heterogeneous and hyperechoic appearance. B, 29 weeks' ultrasound showing augmented and unusually trabeculated subarachnoid space. C, 21 weeks' ultrasound showing large undifferentiated hyperechoic kidneys with multiple corticomedullary millimetric cysts

### 3 | DISCUSSION

Although enlarged hyperechoic kidneys seen on prenatal ultrasound are often suspicious of polycystic kidney disease, rarer disorders such as GA2 can also be associated with this finding. Our case highlights the importance of including GA2 in the differential diagnosis of enlarged hyperechoic kidneys especially when there is associated hepatomegaly, which is typically found at birth in neonates affected by this inborn error of metabolism secondary to fatty infiltration.<sup>2,8</sup> The antenatal ultrasounds did not show cerebral anomalies suggestive of polymicrogyria. However, it is rarely seen on fetal ultrasound. In index cases, a fetal MRI could be proposed to screen for polymicrogyria. Indeed, as our complete phenotyping of this case suggests, polycystic kidneys, hepatomegaly, and polymicrogyria are highly suggestive of GA2.

Prenatal diagnosis of GA2 with molecular testing has been reported in families where mutations have been identified in an index case. Sequencing the three known GA2 genes in an index case carries the risk of finding variants of undetermined clinical significance. Our case also highlights the importance of reports, such as this one, which allow the reclassification of such variants as pathogenic based on comprehensive phenotyping. Alternatively, rare cases of metabolic corroboration have been reported, namely by enzymatic analysis of amniotic fluid or maternal urine.<sup>9,10</sup>

### 4 | CONCLUSION

To our knowledge, this is the first case describing the presence of both hyperechoic kidneys and hepatomegaly found during prenatal ultrasound in glutaric aciduria type II. Because neonatal phenotypes are lethal, prenatal genetic testing is key for informed decision-making about perinatal management.

#### ETHICS STATEMENT

This was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Parents have given their written informed consent.

#### ACKNOWLEDGEMENTS

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#### CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

#### AUTHOR CONTRIBUTIONS

LC collected the data and wrote the first draft. All authors helped revised the article up to the final draft.

#### DATA AVAILABILITY STATEMENT

Data will be available upon request.

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