MEGHDEL SYNDROME ASSOCIATED WITH SECONDARY 3-METHYLGLUTACONIC ACIDURIA: CASE REPORT OF EARLY NEONATAL DIAGNOSIS

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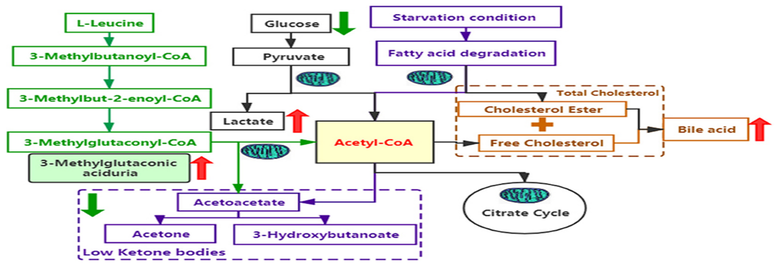
BACKGROUND

MEGDEL syndrome (acronym for 3-methylglutaconic aciduria type V with encephalopathy, sensorineural deafness, and liver disease) is a rare autosomal recessive mitochondrial disorder caused by mutations in the SERAC1 gene. It is characterized by a wide clinical spectrum including neurological, metabolic and hepatic alterations, often with early onset. Timely identification is crucial for multidisciplinary management and monitoring of target organs.



NEUROIMAGING

Moderately enlarged periencephalic CSF spaces in the bilateral temporo-fronto-insular regions. Bilateral and symmetrical areolae with altered signal, hyperintense on long-TR sequences and with restricted diffusion on DWI/ADC, are evident in correspondence with the pale globes and cerebral peduncles bilaterally (with likely involvement of the corticospinal tracts).

PATIENT AND METHODS

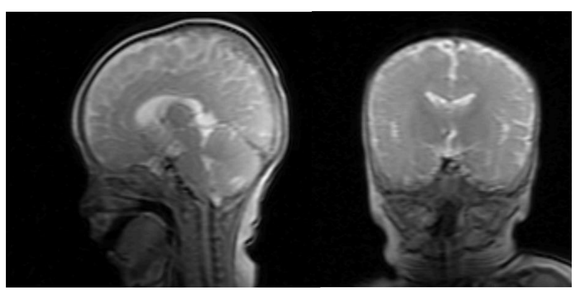
Female newborn, delivered at term (40+1 weeks) by emergency cesarean section for pathological cardiotocography, birth weight 2446 g (SGA).
Clinical features from the first hours of life included feeding difficulties, recurrent vomiting, metabolic acidosis, hypoglycemia, and apnea crises. Extensive metabolic and biochemical investigations were performed during two hospitalizations and subsequent multidisciplinary follow-up.

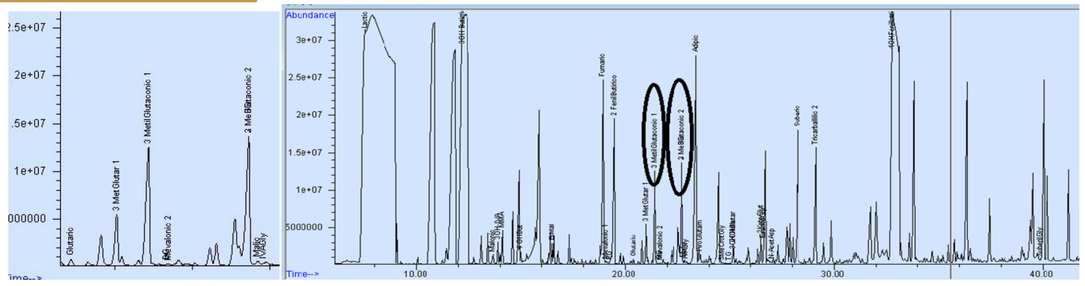
DISCUSSION

This case highlights the importance of careful neonatal clinical observation and early metabolic, endocrinological, and genetic assessment in the presence of signs suggestive of mitochondrial disease. Although neonatal diagnosis of MEGDEL does not alter the disease course, it enables early clinical management, monitoring of systemic complications, and targeted therapeutic support.

RESULTS

Urinary organic acid profiling revealed increased levels of adipic, suberic, pyruvic, lactic, and 3-methylglutaconic acids. Chronic cholestasis with persistent hepatic hyperechogenicity, hypoketotic hypoglycemia despite adequate nutrition, and vitamin K-responsive coagulopathy were observed. Elevated TSH (13.34 mU/L) required levothyroxine replacement therapy; ACTH was persistently elevated (up to 305 ng/L) with normal cortisol. ACTH stimulation test showed increased 17OH-progesterone (>16 ng/ml), suggestive of impaired steroidogenesis.
NGS identified the homozygous SERAC1 variant c.1822_1828+10delinsACCAACAGG, classified as pathogenic (class V), confirming an atypical, early-onset form of MEGDEL syndrome.
A VUS of the ATP7B gene (associated with Wilson's disease) in heterozygosity was also found.





Total ion chromatogram (TIC) of a patient's urinary organic acid profile with increased 3-methylglutaconic acid (cis and trans) observed in a urine specimen.

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