

## Ethylmalonic Aciduria: Report of a new Case

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### Abstract

### Case Report

Ethylmalonic aciduria is an organic, genetic aciduria, of autosomal recessive inheritance, responsible for a major metabolic disorder, causing the vital prognosis. We illustrate through our work, the case of an infant of 9 months with sibling death as personal history. He was admitted to our department for neurological, digestive and cutaneous symptomatology (purpuric lesions and orthostatic acrocyanosis), evolving since the neonatal period with no improvement under symptomatic treatment. The metabolic assessment revealed a high serum concentration of lactate, acylcarnitine C5 and urinary excretion of ethylmalonic acid, suggesting the diagnosis of ethylmalonic aciduria. The evolution of our patient was fatal before the confirmation of the diagnostic through a genetic study.

**Keywords:** Ethylmalonic, genetic Aciduria, autosomal.

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## INTRODUCTION

Ethylmalonic aciduria is a fatal metabolic disease caused by mutations in ETHE1 gene [1, 2]. It is related to a dysfunction of the mitochondrial sulfide dioxygenase [3], which causes an abnormality of hydrogen sulfide (H<sub>2</sub>S) catabolism [4]. The accumulation of H<sub>2</sub>S in the blood and various tissues explains the main clinical manifestations of this deadly disease (encephalopathy, diarrhea and purpuric lesions). Our work aims to draw the attention of health professionals to this serious pathology, in front of the association of chronic diarrhea with neurological signs.

## CASE REPORT

JAD, 9-Month-Old Baby, 6<sup>th</sup> of a sibling of 6, born to a consanguinity of 2<sup>nd</sup> degree parents, was admitted to our department for hypotonia. The patient had three deaths among its siblings (2 brothers at the age of 8 months and 10 months and a sister at the age of 22 months) in a table of hypotonia and chronic diarrhea.

Its symptomatology goes back to day 15 of life by the appearance of liquid diarrhea in a context of apyrexia and hypotonia having required several consultations where the infant was put on symptomatic treatment but without any improvement!

The clinical examination on admission found a conscious, apyretic, eupneic, hemodynamically stable infant, a normal weight estimated at 9 kg, a normal size

estimated at 72 cm, a normal cranial perimeter at 45 cm, an axial hypotonic and peripheral, a delay in psychomotor acquisitions and osteotendinous reflexes which were lively. The rest of the clinical examination showed punctiform purpuric lesions in the upper and lower limbs, orthostatic acrocyanosis (Image 1) and hepatomegaly estimated at 9cm. Ophthalmologic examination and retinography were normal.



Image-1: Ethylmalonic aciduria: punctiform purpuric lesions of the upper limb

The biological assessment showed the absence of blood dyscrasia disorder (TP at 83%, platelets at 704000E / mm<sup>3</sup>), acidosis (RA = 13), normal hepatic assessment, normal creatinine Kinase at 38UI / L, and a high LDH at 542UI / L.

The metabolic balance showed a high lactatemia at 803 mg/L, an amonemia at 137  $\mu\text{g} / \text{dl}$ , a C5-carnitine level at 0.35  $\mu\text{mol/l}$  (0.07 to 0.33), and the presence of organic glutanic 2 OH methylsuccinic acids were also confirmed in case of our patient.

Brain MRI has objectified a widening of the deep arachnoid spaces, associated with anomalies of the supratentorial signal (image 2). We noted the presence of diffuse epileptic graphic element predominant in bilateral frontotemporal with the electroencephalogram. The genetic study for the ETHE1 gene is underway.

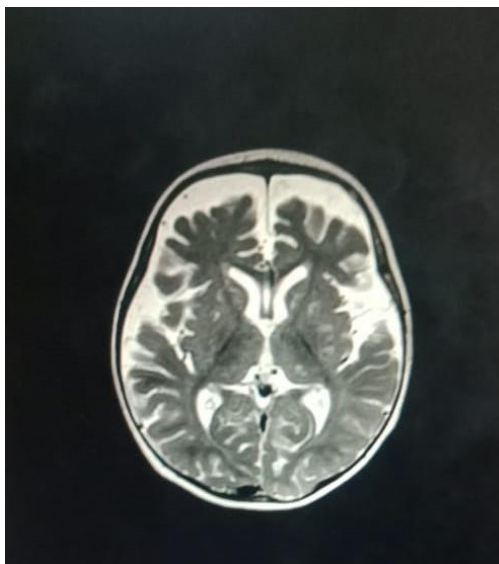
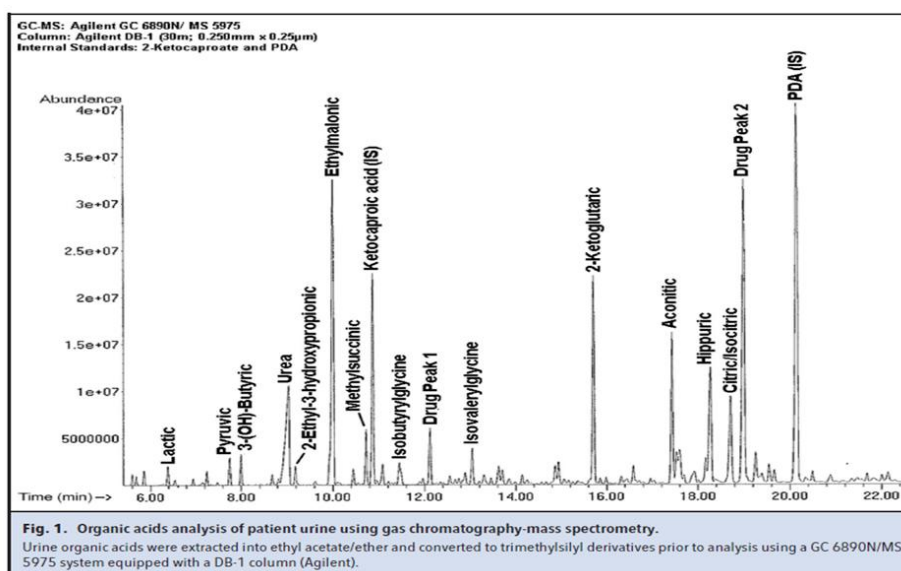


Image-2: Magnetic resonance imaging showing enlargement of the arachnoid spaces and signal anomalies

## DISCUSSION

Ethylmalonic encephalopathy is an autosomal recessive genetic disorder that affects several body systems, particularly the nervous system. It was first described in 1991 [1, 5]. It is an organic aciduria. Its main biochemical characteristic is the production of

ethylmalonic acid in the urine (299 mg / g creatinine (reference range 0.5-20.0)), accompanied by the production of lactic acid, 2-methylsuccinic acid, and branched-chain 4- and 5-carbon acylglycines, isobutyrylglycine, and isovalerylglycine (Fig. 1) [6].

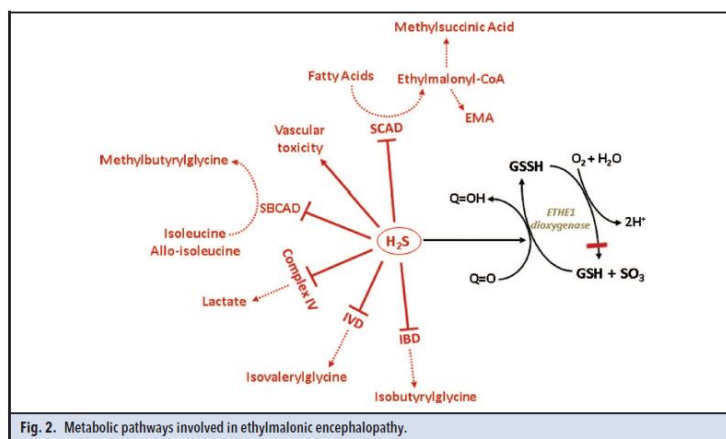


The elevation in serum lactic acid is explained by the disruption of the mitochondrial chain, caused by the inhibition of cytochrome C oxidase (CCO) in the muscles, the brain and the colonic mucosa. This terminal oxidase is also responsible for the inhibition of the activity of short-chain acyl-CoA dehydrogenase,

hence the serum C4-C5 acylcarnitines elevation and the high urinary excretion of ethylmalonic acid and acylglycines C4-C6 [3, 7]. In the case of our patient, we also observed a high serum concentration of lactate (803mg/L), acyl carnitine C5 (0.35 $\mu\text{mol} / \text{l}$ ) and urinary excretion of ethylmalonic acid.

Due to the similar biochemical results of ethylmalonic aciduria, the disorder is often misdiagnosed as short-chain acyl-CoA dehydrogenase deficiency, which is considered to be a benign entity [8].

Several studies [3] have shown that the toxicity of H<sub>2</sub>S due to a deficiency in mitochondrial sulfur dioxygenase [3] is responsible for all the disorders associated with this clinical entity (Figure 2) [6].



High plasma H<sub>2</sub>S levels cause damage to all vascular endothelial cells [3, 7, 9]. This explains the main clinical manifestations of this pathology, namely recurrent petechiae, orthostatic acrocyanosis, chronic diarrhea following haemorrhagic suffusions in the intestinal mucosa, hypotonia and severe psychomotor delay and regression with spastic tetraparesis relationship to necrotic brain damage [1, 2, 5, 9]. Our patient presented from the neonatal period a neurological symptomatology (hypotonia, delay of psychomotor acquisitions), chronic diarrhea, associated with recurrent petechiae and orthostatic acrocyanosis (image 1). The diagnosis is based on the genetic study, which identifies a mutation in the ETHE1 gene [1]. In our case, the genetic study is in progress.

Treatment is based on effective antibiotic therapy against the anaerobic bacterial flora of the large intestine, considered as the main source of hydrogen sulfide production in mammals [10]. N-acetyl cysteine ensures the permeability of glutathione precursor cells, which act as an intracellular buffer of hydrogen sulfide. The combination of these two therapeutic options improves the non-neurological symptoms [11]. Early liver transplantation [12] is a new therapeutic approach, very effective, preventing the fatal outcome (usually in the first two years of life) [13, 14]. This can only be done by installing a neonatal screening device, which can detect the early rise of acylcarnitine C4. In the case of our patient, the evolution was fatal at 9 months of life, even before the confirmation of diagnosis and the initiation of an effective treatment.

## CONCLUSION

Ethylmalonic aciduria is a rare and severe metabolic disorder. The diagnosis should be evoked before any encephalopathy associated with digestive

disorders and skin manifestations. The presence of a mutation in the ETHE1 gene confirms the diagnosis. Neonatal screening, which is based on the observation of an elevation of acylcarnitine C4 is essential, allows adequate early therapeutic management, in order to prevent the fatal development of this disease. This is thanks to the implementation of an effective therapy newly installed (liver transplantation).

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