Alpha ketoglutarate dehydrogenase deficiency: A Case Series and Literature Review.

Amal ELLEUCH[1], hassen ben khaled[1], faiza Safi[2], manel hsairi[1], Lamia Gargouri[1], and abdelmajid mahfoudh[1]

[1]University of Sfax Faculty of Medecine of Sfax
[2]Hedi Chaker Hospital

May 16, 2023

Introduction

Alpha-Ketoglutarate dehydrogenase (2-KGD) deficiency, a rare disorder of the Krebs cycle, was described for the first time as a progressive neurodegenerative disease with 2-ketoglutaric aciduria in two siblings of a Tunisian consanguineous family by Kohlschutter and colleagues (1982) [1]. Alpha-Ketoglutarate dehydrogenase is a multienzyme complex that catalyzes the oxidative decarboxylation of a-ketoglutarate to succinyl-coenzyme A in the tricarboxylic acid cycle. It is made up of three components:

- E1 a-ketoglutarate lipoamide oxidoreductase.
- E2 dihydrolipoamide succinyltransferase transfers the carboxyl group to the coenzyme A moiety.
- E3 dihydrolipoamide dehydrogenase transfers reducing oxygen from E2 to a flavoprotein and finally to nicotinamide-adenine dinucleotide.

Onset and clinical presentation of the reported cases of the (2-KGD) deficiency are heterogeneous, with mostly severe neurological impairment, including muscular hypotonia, developmental delay, extrapyramidal symptoms, ataxia, increased extensor tonus, and seizures. The age of onset varied between the neonatal period and 16 months. The oldest child reported died at the age of 10 years [1, 2, and 3].

Patient and observation

The patient was born in Tunisia to second cousins with no significant health problems. The pregnancy was easy. However, prenatal follow-up showed ectopic dilation of the congenital kidney. Despite these challenges, the baby was born naturally without any complications. His father's uncle, as well as the cousin of the mother, had epilepsy as children, and his aunt was deaf and mute.

Four months after birth, the patient was experiencing involuntary muscle spasms, uncontrollable muscle contractions of the neck, head, and trunk, and extended arms and legs that were not controlled. He was referred to the hospital to undergo further examination and treatment. A cranial magnetic resonance scan (CMRI) identified the presence of cortical atrophy but no brain malformations. A cerebrospinal CT scan showed bilateral supra - and infra-tentorial bursitis. Electroencephalogram (EEG) identified hypsarrhythmias, and psychomotor slowing was observed during this time. Treatment consisted of phenobarbital as well as vigabatrin to manage spasms.

At the age of five months, the baby began to experience epileptic seizures, which required 24 days at the Neuro-pediatric department to receive treatment with vigabatrin and topiramate, and B6 vitamin. At seven months old, the patient presented with status epilepticus and required hospitalization for one month.

At nine months old, the patient suffered seizures characterized by eyelid myoclonia, irregular facial move-

ments, lateral head tilt, eye deviation, an increased fever, and worsening general status. Initially, it was believed that myocarditis could be the diagnosis due to hepatomegaly, fever, and raised ESR; however, the Echocardiogram and troponin results were both normal. In the following days, the infant was diagnosed with an epileptic status that was resistant to treatment, with fever but without any signs of trauma, intoxication, infection, or poor compliance to treatment with pharmaceuticals. The infant was taken to a hospital and treated with intubation,ventilation, and sedation. The laboratory tests found no anomalies except for mildly elevated levels of ammonium. Eight days after admission, the patient experienced severe hyperammonemia, hypoglycemia, and metabolic acidosis. The analysis of organic acids in the urine showed increased excretion of 2-ketoglutaric and lactic acids and a slight increase of 2-ketoadipic acids. Unfortunately, the patient died from acute respiratory distress syndrome and heart failure.

Discussion:

This case report presented a male infant who developed involuntary muscle spasms, psychomotor retardation, cortical atrophy, and abnormal EEG patterns at four months. The patient later exhibited recurrent epileptic seizures and status epilepticus, eventually leading to his death at nine months of age due to acute respiratory distress syndrome and heart failure. The patient was diagnosed with alpha-ketoglutarate dehydrogenase deficiency, a rare metabolic disorder that affects the metabolism of amino acids and leads to impaired energy production in the brain.

This case's significance lies in the disease's rarity, and the challenges clinicians face in diagnosing and managing such patients. The symptoms of alpha-ketoglutarate dehydrogenase deficiency are nonspecific and can be confused with other neurological disorders. Therefore, it is crucial to consider this condition in the differential diagnosis of infants presenting with developmental delay, psychomotor retardation, and seizures, especially in those with a family history of consanguinity or metabolic disorders.

The existing literature on alpha-ketoglutarate dehydrogenase deficiency is limited, and most of the reported cases are from consanguineous families in Middle Eastern and North African countries. In a recent literature review, Almutairi et al. (2020) reported 18 cases of alpha-ketoglutarate dehydrogenase deficiency, with variable clinical presentations ranging from neonatal encephalopathy to infantile-onset epilepsy and psychomotor regression [4]. The authors highlighted the importance of early diagnosis and prompt treatment with a ketogenic diet and carnitine supplementation, which can improve clinical outcomes and prevent metabolic crises.

The current literature suggests that alpha-ketoglutarate dehydrogenase deficiency is a rare metabolic disorder that can present with a wide range of clinical features, including seizures, hypotonia, developmental delay, and lactic acidosis [5]. However, the diagnosis can be challenging due to the nonspecific nature of the clinical presentation and clinicians' need for more awareness of this condition.

In this case, the diagnosis was delayed, and the patient was treated for epilepsy for several months before making the correct diagnosis.

The management of alpha-ketoglutarate dehydrogenase deficiency involves a combination of dietary interventions and pharmacological therapies [6]. In this case, the patient was treated with a high-fat, low-carbohydrate diet and several antiepileptic drugs, including phenobarbital, vigabatrin, topiramate, and pyridoxine. However, despite these interventions, the patient continued to have recurrent seizures and ultimately died due to complications of the disease.

The findings of this case report are consistent with previous reports of the challenges in diagnosing and managing alpha-ketoglutarate dehydrogenase deficiency. Diagnosing this condition requires a high index of suspicion, and prompt diagnosis and management are essential to prevent long-term morbidity and mortality. The current literature suggests that early diagnosis and treatment with dietary interventions and pharmacological therapies can improve the long-term outcomes of patients with alpha-ketoglutarate dehydrogenase deficiency [7].

Conclusion:

this case report highlights the challenges in diagnosing and managing alpha-ketoglutarate dehydrogenase deficiency. It emphasizes the importance of considering metabolic disorders in the differential diagnosis of infantile seizures. The findings of this case report add to the existing literature on this rare condition and provide valuable insights into the diagnosis and management of this disorder. Further research is needed to improve the understanding of alpha-ketoglutarate dehydrogenase deficiency's pathophysiology and identify more effective diagnostic and therapeutic interventions for this condition.

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Acknowledgements:

I would like to thank the co-authors for their high expertise and valuable assistance throughout all aspects of our study and for their precious help in terms of writing the manuscript.

Declaration of interest statement:

The authors have no conflict of interests to declare.

Financial Disclosure: There is no financial support to disclose.

Availability of data and material: None.

Ethical/consent statement: Our study did not require an ethical board approval because this was a retrospective descriptive chart study and did not include clinical trials, informed consent was not required.