



Submitted on: 04/08/2024

Approved on: 05/06/2024

CASE REPORT

Citrullinemia type I as a differential diagnosis of seizures in infants - case report

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Keywords:

Citrullinemia.
Hyperammonemia.
Metabolism,
Inborn Errors.
Urea Cycle
Disorders, Inborn

Abstract

Objective: To report the case of an infant diagnosed with type I citrullinemia, a rare inborn error of metabolism resulting from an enzymatic defect in the urea cycle, a differential diagnosis of seizures in infants. In addition, the literature is reviewed on the topic. **Case report:** Six-week-old infant presenting tonic-clonic seizures associated with hyperammonemia. It was identified heterozygous pathogenic variants in the ASS1 gene in the molecular testing, characteristic of type I citrullinemia. After dietary adjustment and initiation of nitrogen chelators, there was clinical and laboratory control, with adequate development and growth for sex and age. **Discussion:** The neuropsychomotor development in patients with type I citrullinemia is related to the maintenance of adequate levels of plasmatic ammonia. Therefore, early diagnosis is imperative, preferably through screening tests, before the development of symptoms due to hyperammonemia, to initiate specialized treatment the earliest possible and, consequently, aim for a better prognosis.

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INTRODUCTION

Seizures are common clinical manifestations in pediatric emergencies. The first year of an infant's life is crucial for neurological development, with increasing and progressive synaptogenesis and myelination. Therefore, any pathogenic event that occurs during this period of life can result in significant brain damage. Such events can often begin in a subtle and nonspecific manner at a younger age, which requires a high degree of clinical suspicion¹.

Among the metabolic causes that trigger seizures in infants, a portion of patients have inborn errors of metabolism (IEM) of the intermediate type that culminate in acute or chronic intoxication. These clinical conditions are individually rare and initially present with nonspecific symptoms, which leads to delayed diagnosis and, consequently, treatment, and can cause irreparable damage to the child's central nervous system. On the other hand, it is known that early diagnosis and intervention in patients with IEM can result in favorable clinical outcomes. Currently, several metabolic screening tests include IEM screening, but they are not yet widely available to the general population. Therefore, efforts in initial recognition, early diagnosis, and immediate management should be encouraged among the community of physicians who work in the initial evaluation of infants to improve the prognosis of these children^{2,3}.

CASE DESCRIPTION

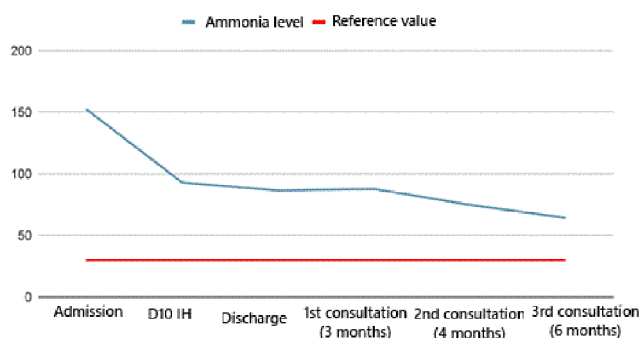
In April 2023, a 6-week-old white male infant was admitted to the IPPMG emergency room with a report of a tonic-clonic seizure associated with central cyanosis and sphincter release, lasting ten minutes, without fever. The child's mother reported a history of five hypertonia crises with cyanosis that began at 4 weeks of age, lasting less than 1 minute, which reversed spontaneously, and were evaluated in an emergency care unit near the home, with no further etiological investigation to date. Gestational history indicating hypertensive mother during the second trimester of pregnancy, had ten previous pregnancies, with seven living children from different fathers and two last pregnancies with the same father, which culminated in spontaneous abortion in the first trimester. There was no history of consanguinity or history of metabolic diseases in the family. The child was born by vaginal delivery at term, good vitality at birth, without complications in the neonatal period. Neonatal metabolic screening did not show alterations in the evaluation of hemoglobinopathies, congenital hypothyroidism, phenylketonuria, congenital adrenal hyperplasia, biotinidase deficiency, congenital toxoplasmosis and cystic fibrosis. Upon admission to the

emergency room, the infant was drowsy, afebrile, isophotoreactive pupils, without other alterations. Laboratory tests included: normal blood count, blood glucose 86 mg/dL, normal liver and kidney function, venous blood gas analysis with normal lactate assessment, absence of hydroelectrolytic disorders and elevated serum ammonia (152 mmol/L; reference value <30 mmol/L). The initial impression was of a seizure in the infant associated with hyperammonemia, and hospital admission was indicated for investigation.

During hospitalization, the infant underwent electroencephalogram during sleep with a pattern within the normal range for the age group, normal transfontanelar and abdominal ultrasound, normal thyroid hormone assessment (TSH and T4), normal fundoscopy and cerebrospinal fluid examination with normal cellularity, biochemistry and lactate. An evaluation was performed by the Nutrology department due to suspected metabolic etiology of the seizures, with an indication for initial screening for inborn errors of metabolism. The initial investigation included laboratory evaluation with normal metabolic screening (liver and kidney function, blood gas analysis with anion gap assessment, electrolytes), qualitative assessment of aminoaciduria in a frozen urine sample with a positive result and TANDEM profile on filter paper for quantitative analysis of amino acids and acylcarnitines, which showed a slight increase in the amino acid citrulline (result: 49.8 umol/L; reference value 6-40 umol/L). On the tenth day of hospitalization, the patient presented a tonic-clonic seizure episode without cyanosis, lasting two minutes, with laboratory tests in the immediate post-ictal period indicating sustained hyperammonemia (93 mmol/L). These results increased the etiological suspicion of a metabolic cause, so a dietary adjustment was made with a reduction in protein intake (1.18 g/kg/day), the ammonia chelator sodium benzoate 10% 100 mg/kg/day and L-carnitine 10% 100 mg/kg/day were started, and a genetic panel was collected with molecular analysis by next-generation sequencing to investigate potentially pathogenic variants present in genes listed for urea cycle disorders and treatable diseases. The result demonstrated the presence of the pathogenic variant chr9:130,458,483 G>A, promoting the replacement of the amino acid arginine at position 86 by histidine (p.Arg86His) in heterozygosis in the ASS1 gene (argininosuccinate synthase 1), which has previously been associated with citrullinemia type 1⁴.

After molecular diagnosis and control of the crises, the child was discharged from the hospital for outpatient follow-up, with serial collection of laboratory tests. He continued to use 10% sodium benzoate and L-carnitine, protein restriction in the diet with the use of a fractionated polymeric formula five times a day with three measures for

Evolution of ammonia



Graph 1. Evolution of laboratory results of serum ammonia comparing tests on admission, on the tenth day of hospitalization (D10 IH), hospital discharge and on the three subsequent outpatient visits, at three, four and six months of life, respectively.

100 mL of filtered water, added with 5 g of maltodextrin and 3 mL of olive oil in each meal, aiming for an intake of 115 kcal/kg/day. The patient evolved with maintenance of hyperammonemia in periodic examinations (Graph 1), without seizure spells, followed by a gradual increase in sodium benzoate 10% up to 240 mg/kg/day and L-carnitine up to 150 mg/kg/day, starting with L-arginine 100 mg/kg/day, associated with protein restriction of 0.8-1 g/kg/day. At six months of age, there was improvement in the control of ammonia levels (62.3 $\mu\text{mol/L}$) and a new quantitative analysis by amino acid chromatography with normal results. The child maintained adequate neuropsychomotor development according to the Denver scale, satisfactory weight gain and neurological examination remained normal for age during clinical follow-up until six months of age.

DISCUSSION

Citrullinemia type I (CTLN1) is an inborn error of metabolism of autosomal recessive inheritance caused by the mutation in the ASS1 gene, located on chromosome 9q34.1, with a prevalence of 1 in every 57,000 live births, being the second most common disease of the urea cycle⁴. It results from the deficiency of the third enzyme of the cycle, argininosuccinate synthase, distributed in several tissues, primarily in the liver, which catalyzes the formation of argininosuccinate from citrulline and aspartate^{4,5}. The urea cycle consists of a series of enzymatic reactions that culminate in the conversion of ammonia, a toxic metabolite that is released during the process of protein catabolism, into urea, the main nitrogenous waste, which is water-soluble, excreted in the urine and slightly toxic to the body⁶. When argininosuccinate synthase levels are deficient, citrulline and aspartate cannot be converted to argininosuccinate, which results in hyperammonemia and hypercitrullinemia,

accompanied by arginine deficiency (figure 1)⁵. Ammonia is known to be toxic to the brain, especially in early stages of neonatal neurodevelopment, and its plasma concentration varies according to the specific enzyme deficit and its residual plasma activity, the individual's protein intake and the rate of endogenous catabolism, which may be affected in situations of metabolic stress, such as infections^{4,6}.

CTLN1 presents clinically with increasing and progressive lethargy, somnolence, vomiting, hypotonia, seizures, and coma due to hyperammonemia^{4,5}. Diagnosis can be made through neonatal screening tests with quantitative analysis of citrulline on filter paper. In symptomatic individuals without screening tests, the diagnosis is established through hyperammonemia, increased plasma citrulline, and evaluation of pathogenic alleles in the ASS1 gene in molecular genetic tests⁴. Post-diagnosis assessment and follow-up include consultations with nutritionists, neurologists and dietitians, with serial assessment of plasma ammonia levels, blood gas analysis, plasma amino acids and electrolytes.

Nutritional and drug treatment involves maintaining low plasma ammonia levels by restricting dietary protein, according to age and sex, and their respective metabolic needs. Serum ammonia levels should be monitored and nitrogen binders, such as sodium benzoate, should be used, in addition to arginine and L-carnitine supplementation^{4,5}.

The clinical prognosis and the possibility of neurological sequelae appear to be related to the level of hyperammonemia during the first symptomatic episode, with 64% of infants with serum levels < 180 mmol/L presenting typical neurodevelopment and only 8% in cases of plasma ammonia > 360 mmol/L ^{4,7}. The risks of neurodevelopmental deficits can then be determined based on the plasma ammonia level and the duration of the encephalopathy episode.

Therefore, it appears that type 1 citrullinemia is an inborn error of intermediary metabolism with a broad and often nonspecific clinical picture, especially in infants, and may present with initially mild symptoms, such as hypotonia and drowsiness, to aggravating repercussions such as seizures and coma. There should be a high degree of clinical suspicion for subtle symptomatic events the younger the age and the more immature the synaptogenesis of the central nervous system. The variable short- and long-term prognosis is related to the level of hyperammonemia and the duration of the encephalopathy. Therefore, as it is a time-sensitive disease, early diagnosis is imperative, preferably before the development of symptoms, as in neonatal screening tests. Therefore, the need for clinical suspicion of IEM in acute neurological conditions in infants is evident in order to achieve a timely diagnosis and specialized treatment with the aim of achieving neuropsychomotor development within what is expected for the age.

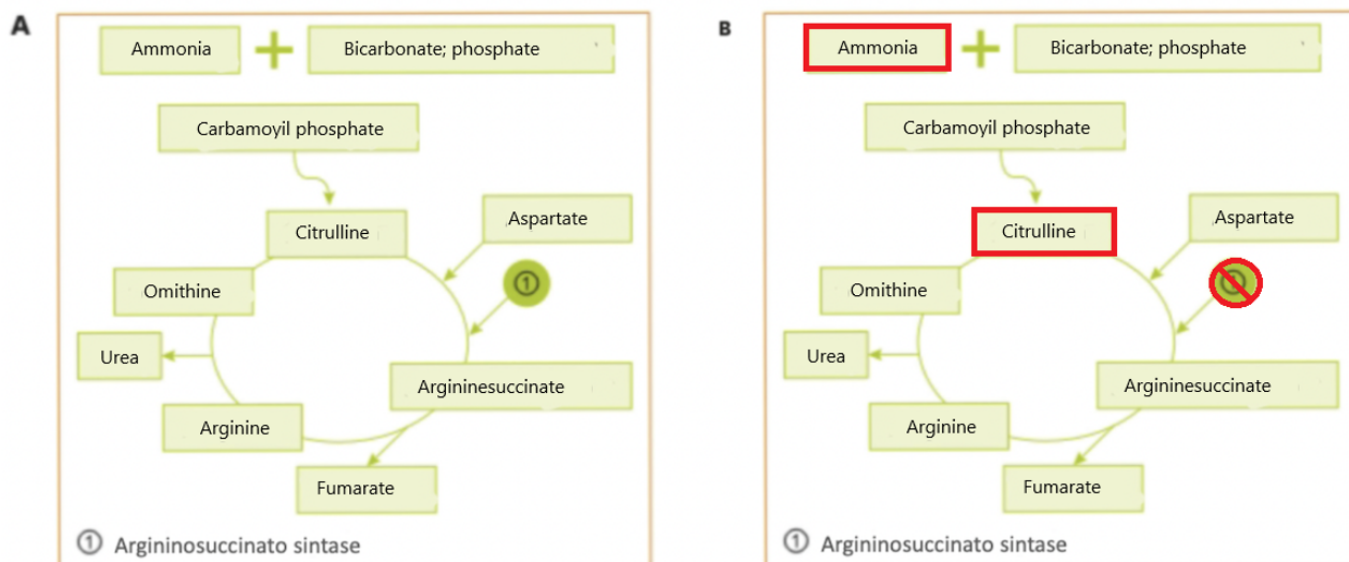


Figure 1. Normal urea cycle (A). Altered metabolism in Citrullinemia type I with suppression of the enzyme argininosuccinate synthase and elevation of ammonia and citrulline (B). Translated and adapted from Kang H, Kim M, Lee JH, 2021⁵.

REFERENCES

1. Baker PR. Recognizing and managing a metabolic crisis. *Pediatric Clinics of North America*. 2023 Oct;70(5):979–93. doi:10.1016/j.pcl.2023.05.009
2. Pavone P, Corsello G, Ruggieri M, Marino S, Marino S, Falsaperla R. Benign and severe early-life seizures: A round in the first year of life. *Italian Journal of Pediatrics*. 2018 May 15;44(1). doi:10.1186/s13052-018-0491-z
3. Leonard, J.V. Urea Cycle Disorders. In: Fernandes, J., Saudubray, JM., Van den Berghe, G., Tada, K., Buist, N.R.M. (eds) *Inborn Metabolic Diseases*. Berlin: Springer, 1995. p 167-176.
4. Quinonez SC, Lee KN. Citrullinemia Type I. 2004 Jul 7 [Updated 2022 Aug 18]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Disponível em: <https://www.ncbi.nlm.nih.gov/books/NBK1458/>
5. Kang H, Kim M, Lee JH. Nutritional management in a patient with citrullinemia type 1. *Clinical Nutrition Research*. 2021;10(3):268. doi:10.7762/cnr.2021.10.3.268
6. Rocha JC, Sequeira S, Cabral A, Almeida MF. Consenso para o tratamento nutricional das Doenças do Ciclo da Ureia. *Acta Pediatr Port* 2009;40(2):83-93. Disponível em: https://www.spdm.org.pt/media/1117/acta-pediatr-port-2009_40_83_consenso_tratamento_doen%C3%A7as_ciclo_ureia.pdf
7. Ziogas IA, Wu WK, Matsuoka LK, Pai AK, Hafberg ET, Gillis LA, et al. Liver transplantation in children with urea cycle disorders: The importance of minimizing waiting time. *Liver Transplantation*. 2021 Aug 1;27(12):1799–810. doi:10.1002/lt.26186