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Fumarase deficiency: a difficult diagnosis and a challenging treatment approach

Déficit de fumarasa: un difícil diagnóstico y abordaje terapéutico

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Resumen

Introducción: El déficit de fumarasa es una enfermedad rara del metabolismo, autosómica, que cursa con hipotonía, hiperlactacidemia y convulsiones. El diagnóstico basado en pruebas de laboratorio debe realizarse con precaución ya que la mayoría de enfermedades relacionadas con el metabolismo presentan la misma sintomatología: hipotonía, convulsiones y acidemia láctica y pirúvica.

Método: Analizar retrospectivamente el manejo farmacológico y nutricional de un neonato con síntomas relacionados con errores del metabolismo congénitos.

Resultados: La paciente de 3 meses de vida presentaba una mutación heterocigota en el gen de la fumarasa y síntomas relacionados con la alteración de la función enzima. La paciente presentaba hiperlactacidemia, aciduria orgánica y alteraciones analíticas de los aminoácidos. El primer diagnóstico supuesto fue un déficit de piruvato deshidrogenasa, por lo que se inició tratamiento nutricional con dieta cetogénica. Tras el alta de la paciente, volvió a ingresar por urgencias sufriendo una parada cardíaca y descompensación metabólica. El test genético reveló la presencia de una mutación heterocigota en el gen de la fumarasa. La sintomatología clínica pudo haber empeorado debido al difícil diagnóstico.

Conclusiones: El tratamiento farmacológico y nutricional del déficit de fumarasa es esencial para la buena evolución del paciente, pero es necesario que se realicen más estudios para entender con profundidad el mecanismo de los errores congénitos del metabolismo. Los equipos multidisciplinares permiten manejar la enfermedad desde distintos puntos de vista clínicos para un diagnóstico correcto y poder decidir el tratamiento adecuado con precisión.

Palabras clave: déficit de fumarasa; acidemia láctica; dieta cetogénica; enfermedad metabólica; aciduria orgánica.

Abstract

Introduction: Fumarase deficiency is a rare autosomal metabolic disease that curse with hypotonia, hyperlacticaemia and seizures. Diagnosis based in laboratory test might be done carefully, as most of metabolic diseases present similar symptomatology: hypotony, convulsions, lactic and pyruvic acidemia.

Method: The objective is to analyse the pharmacological and nutritional approach of a neonate who presented symptoms of metabolic congenital disorders.

Results: The patient is a three-month girl with heterozygote mutation in fumarase gene, who presented clinical manifestations of the altered enzyme function. She presented hyperlacticaemia, organic aciduria and alterations of amino acid levels. First diagnosis suspected was pyruvate dehydrogenase deficiency, so nutritional treatment with ketogenic diet was initiated. After medical discharge, she was hospitalized in emergency basis with cardiac arrest and metabolic decompensation. Genetic test revealed a heterozygote mutation in fumarase. Clinical symptomatology could have worsened because of the difficult diagnosis.

Conclusions: Nutritional and pharmacological treatment of fumarase deficiency is considered essential for the patient's evolution, but further researchers must be carried out to profoundly understand the mechanism underlying metabolic inborn errors. Multidisciplinary teams would manage the disease from the point of view of diverse clinician experts so the correct diagnosis and treatment would be decided with precision.

Keywords: fumarase deficiency; lactic acidosis; ketogenic diet; metabolic disease; organic aciduria.

Highlight

Fumarase deficiency is a rare autosomal metabolic disease with a difficult diagnose. Treatment based on drugs is well established but nutritional support remains unclear. Ketogenic diet has been used in children to treat seizures refractory to antiepileptic drugs, but it seems to be contraindicated in fumarase deficiency or other enzyme failure of the Krebs cycle. Multidisciplinary team approach is essential to make the right diagnosis and adjust the correct treatment.

This study adds clinical information about the disease as the literature about metabolic errors as fumarase deficiency is limited.

Introduction

Fumarate hydratase (FH) deficiency was first described in 1987 by Zinn et al, reporting the case of a male infant with mitochondrial encephalopathy and other symptoms as lethargy, seizures, hypotonia, lactic, pyruvic and fumaric acidemia[(1)]. Since then, less than 100 cases have been reported[(2)]. FH is involved in tricarboxylic acid cycle and cytosolic isoenzyme is involved in urea cycle. Fumarase also functions as a tumor suppressor. Heterozygote mutation is related with renal cell cancer and multiple cutaneous and uterine leiomyomatosis[(3)]. Clinical manifestations of fumarase deficiency complicate the diagnosis of the syndrome, as hypotony, convulsions, lactic and pyruvic acidemia are some of the symptoms underlying other metabolic disorders and respiratory chain alterations. Management and treatment involve pharmacological, nutritional and in most of the cases, respiratory and cardiovascular support. Nowadays, prognostic and clinical evolution of the syndrome is still unfavourable as genetic approach of the disease continues in experimental trials[(2)]. We discuss the case of a three-month girl with heterozygote mutation in fumarase gene, who presented clinical manifestations of the altered enzyme function.

Method

We performed a bibliographic revision in Pubmed about fumarase deficiency using the terms: fumarase deficiency OR fumarate hydratase deficiency. The objective is to analyse retrospectively the pharmacological and nutritional approach of a neonate who presented symptoms of metabolic congenital disorders. This clinical revision of the case made retrospectively has low ethical impact.

A patient new-born is hospitalized at Neonatology Unit presenting hypotony, sensory alterations with no response to stimulus, stare and mild tachypnea. No fever, no cyanosis, either abnormal movement were reported. Empiric antibiotic therapy was initiated. Parents were informed and authorized lumbar puncture.

Results

After two hours from admission, the patient presented tonic-clonic seizures with general hypotony after the episode. Gasometry showed metabolic acidosis was maintained through the day. The following test results were obtained: pH 7.14; pCO_2 45 mmHg; pO_2 25 mmHg; lactic acid 9 mmol/L; HCO_3 12.6 mmol/L; glucose 109 mg/dL; creatinine 0.23 mg/dL; negative PCR for viruses and bacteria; computed tomography (CT) normal; ammonium 59 µmol/L. Cerebral bioelectric activity resulted abnormal with focal slowing over the frontotemporal region. Organic aciduria (hyperlacticaemia without hyperammonaemia) and metabolopathy with seizure crisis was suspected, so treatment with cofactors was evaluated: Arginine 750 mg/day; riboflavin 100mg/day; carnitine 45 mg/8h; thiamine 100 mg/day; coenzyme Q105 mg/8h. After two days of hospitalization, parenteral nutrition with proteins 1g/kg/day; carbohydrates 4.5 mg/kg/min; lipids 0.5 g/kg/day was initiated as well as vitamin-therapy and levetiracetam 11 mg/kg/day. The fifth day, protein content in parenteral nutrition was 2.2 g/kg/day and results of ammonium, b-hydrobutiric in blood were normal, just pyruvic was elevated, possibly for com-

pensation of hyperlacticaemia. Cerebral activity continued to be abnormal and phenobarbital 4 mg/kg/b.d was added to pharmacotherapy. Through the days, test results showed lactic, pyruvic and alanine elevated in blood levels. Cephalorraquid liquid tests showed hypoglycorrhachia and an elevated levels of proteins and lactic acid. After 26 days of hospitalization, a muscular biopsy is programmed in suspicious of mitochondrial respiratory chain alterations, results obtained were normal. On the other hand, pyruvate dehydrogenase deficit was the first diagnostic option because of the clinical symptoms and analytic data. Nutritional treatment was re-evaluated and ketogenic diet was implemented considering risks and benefits. The highest level of lactate occurred when diet was exclusively composed by carbohydrates. Magnetic resonance image (MRI) showed lactate in periventricular substance and axonal symmetric degeneration in corticospinal tracts, manifestations of hypoxic ischemic insult.

Once she seemed stabilised, medical discharge was indicated. The patient continued with ketogenic diet and coenzymes and cofactors supply. After a month, the girl was hospitalized on an emergency basis with cardiac arrest. After 24 hours, she continued without neurological response to stimulus, mobility, either spontaneous respiration, manifesting hypotonic coma. Test results showed: troponine I, 235.7 pg/mL; ammonium, 201.2 µmol/L; hyperlacticaemia and metabolic acidosis with latter normalization of ammonium. Nutritional treatment was initiated with a low protein supply, combined with ketogenic diet. Phenobarbital 20mg/kg dosage was necessary for seizure activity. Forty-eight hours since cardiac arrest, she presented poor condition, needing an adaptative support ventilation. Genetic test revealed mutational change in fumarase gene.

Even though fumarase deficiency is an autosomal recessive metabolic disorder, this mutation is considered pathogenic. A urine metabolic screen found increased lactic acid, 3-methylmalonate, ethylmalonic and normal levels of fumaric acid, succinyl and alpha-ketoglutaric. Finally, clinicians agreed establishing sedation as the patient showed hypotonic coma and complications derived from metabolic decompensation.

Discussion

Fumarase deficiency is a rare autosomal recessive inborn error of the metabolism with clinical features common to other energy metabolism alterations and mitochondrial disorders. Our patient failed to thrive since birth and presented poor weight gain, hypotony, cerebral atrophy, seizures and acidosis. Lactic acidosis is reported in major of metabolic disorders and study of mitochondrial metabolism is required for diagnosis. Pyruvate dehydrogenase complex disorders are the principal cause of lactic acidosis in paediatrics[4]. The patient showed clinical symptoms related to pyruvate dehydrogenase deficiency so ketogenic diet was initiated. Efficacy of ketogenic diet in metabolic disorders is controversial, as it seems to be slightly effective[2].

Nutritional approach in fumarase deficiency has been quite described in literature[5]. An increase in glucose has demonstrated an increase in lactate, as occurred in our case, when the highest level of lactate was reported with a diet only based in carbohydrates[2]. Protein restriction diet seems to be ineffective as fumaric acid would still be high in urine collection[6]. After ketogenic diet, urine metabolic test showed increased metabolites of valine and leucine catabolism (3-methylmalonate, ethylmalonic), which are properly ketogenic amino acids. During catabolism of those amino acids, acetoacetate, acetyl-coA and propionyl-coA are produced and degraded by fatty acid metabolism[2].

Contrary to Smith and Robinson's results, fatty acid b-oxidation may not have diminished[7]. Ketone bodies produced in the liver during fatty acid metabolism apparently have neuroprotective actions in mitochondrial diseases[8]. Thus, ketogenic diet has been used in children to treat seizures refractory to antiepileptic drugs[8], but it seems to be contraindicated in fumarase deficiency or other enzyme failure of the Krebs cycle[2]. Laboratory tests revealed high levels of most amino acids. It has been demonstrated fumarase deficiency alter amino acid metabolism including isoleucine, proline, lysine, glycine, citrulline, alanine, tyrosine and aspartic acid. FH metabolize fumarate into malate which is transformed in oxaloacetate and it can be converted to aspartate[9]. Study of amino acid in blood test revealed low concentration of aspartate while pyruvic acid, lactate and alanine remained high.

Phenotype-genotype correlations in FH deficiency has not been reported. Fumaric aciduria is highly suggestive of FH deficiency but it might not be reliable[10,11]. In our case, normal levels of fumarate in urine were detected. Ottolenghi et al. described three patients with different residual enzyme activity and clinical presentations. The manifestations that they describe of one of those patients are similar to this case: mildly or normal levels of urinary fumarate with lactate levels elevated in blood and cerebral spinal fluid[11]. A case report described by Saini and Singhi either referred abnormal fumaric levels in urine[12].

Therapeutic strategies are limited, patients with metabolic disorders usually present multisystemic syndrome. Secondary complications are the main cause of death during infancy[13,14]. Controlled tracing by physicians and health care providers including nutritionist, pharmacist, clinical geneticist and laboratory analyst is required to manage FH deficiency[15, 16, 17].

Conclusions

Clinical course of fumarase deficiency is still unfavourable and management remains supportive. Laboratory test results might be considered cautiously in the assumption of a diagnosis. Treatment with cofactors may help stabilize enzyme activity, but further studies in metabolomics and gene therapy are required for inborn errors of metabolism. Due to lack of enough evidence about supportive therapy in FH deficiency we encourage other clinicians to share their findings. Multidisciplinary team approach is essential to make the right diagnosis and adjust the correct treatment by clinician experts in order to improve patient healthcare.

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