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HYPERARGININEMIA: A RARE DIAGNOSIS IN ADULTHOOD

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ABSTRACT

Background: Hyperargininemia is a rare inherited metabolic disorder of the urea cycle with an autosomal recessive transmission. It occurs due to a deficiency of the enzyme arginase I and causes progressive neurological damage. Very few cases are diagnosed in adulthood, with the majority being diagnosed before the age of 4. Currently, this condition is diagnosed by a mass spectrometry technique in neonatal screening, which has been implemented in Portugal since 2007; births before that were not screened for this entity.

Case description: We present a case of a 23-year-old woman referred to the internal medicine and neurology departments with a history of two hospital admissions for rhabdomyolysis at the age of 18, consanguineous parents, learning difficulties and multiple falls since the age of 8. In addition, the patient also had behavioural changes so she had psychological counselling at school, but lacked family support. Neurological examination showed mild proximal paraparesis, and spastic and paraparetic gait. The aetiological study revealed a pathological variant in homozygosity *ARG1* and increased blood levels of arginine. Therefore, the diagnosis of hyperargininemia was confirmed.

Conclusions: Compared to other urea cycle disorders, hyperargininemia is the rarest one. It is important to recognise the characteristic clinical features and diagnose it early because a favourable outcome can be achieved with appropriate treatment. This case shows a delayed diagnosis of hyperargininemia and highlights the importance of the internist's role in diagnosing rare diseases.

KEYWORDS

Metabolic disorder, hyperargininemia, rare diseases, urea cycle

LEARNING POINTS

- Hyperargininemia is a rare hereditary metabolic disease of the urea cycle and the rarest of the disorders affecting this cycle.
- The diagnosis is almost always made within the first four years of life and very few are diagnosed in adulthood.
- Early diagnosis is essential to reduce the progression of neurological damage, through appropriate treatment.

INTRODUCTION

Hyperargininemia is a rare inherited metabolic disorder of the urea cycle with an autosomal recessive transmission, and an incidence of 1 in 1,000,000 live births[1]. In the urea cycle, represented in *Figure 1*, multiple consecutive enzimatic reactions take place to convert waste nitrogen into urea.

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Blood analysis	Results	Reference value
Haemoglobin (g/dl)	12.8	13.7–17.3
White blood cell count (10^3/µl)	8.3	4.8–10.8
Platelets (10^3/µl)	339	144.0–440.0
Sedimentation velocity (mm)	30	<20
Creatinine (mg/dl)	0.72	0.70–1.20
Blood urea nitrogen (mg/dl)	14.9	16.6–48.5
Sodium (mmol/l)	136.0	136.0–145.0
Potassium (mmol/l)	4.8	3.50–5.10
Glutamic-pyruvic transaminase (GPT) (U/l)	80.9	< 33.0
Glutamic-oxaloacetic transaminase (GOT) (U/l)	142.0	< 32.0
Alkaline phosphatase (U/l)	90.0	35.0–104.0
Gamma-glutamyl transferase(U/l)	12.0	5.0–36.0
Total bilirubin (mg/dl)	0.68	< 1.20
Lactate dehydrogenase (U/L)	531	< 250.0
C-reactive protein (mg/dl)	5.1	< 5.0
Creatine kinase (U/l)	5957.0	< 170.0
Aldolase (U/l)	42.9	0.0–7.0

Table 1. Analytical results.

Disorders affecting all of the enzymes of this cycle have already been described[2]. Hyperargininemia is the rarest urea cycle disorder and occurs due to a deficiency of arginase, which is an enzyme responsible for converting arginine into urea and ornithine[3]. This entity is caused by heterogeneous mutations in the *ARG1* gene. Unlike the other urea cycle disorders that are associated with hyperammonemic encephalopathy in the neonatal period, this condition typically presents later in childhood, usually between 2 and 4 years of age, with slowly progressive neurological features such as muscle spasticity, ataxia, hyperreflexia and seizures[4]. If untreated, this disease progresses with gradual development regression. In Portugal, this entity has been diagnosed since 2007 using the mass spectrometry technique in neonatal screening, which allows the diagnosis of various metabolic diseases. All births before that were not screened for this entity.

We present a clinical case that shows a delayed diagnosis of hyperargininemia in adulthood associated with a rare feature, the presence of myopathy.

CASE DESCRIPTION

A 23-year-old woman with no previous personal history of known diseases was referred to the internal medicine and neurology departments. She had high values of creatine kinase (CK) above 5000 U/l of six years' duration, and two hospital admissions to the Internal Medicine Service for rhabdomyolysis at the age of 18. During the collection of the medical history, it was discovered that the parents were first-degree cousins. Until the age of 8, the patient was apparently a normal child without any complaints, then she began to fall several times and had difficulty climbing stairs. It was also noted that the patient had learning difficulties, had only completed the 7th grade, and had always received support from special education. Lastly, the patient received psychological support at school for her behavioural changes – easy irritability and hyperreactivity – and was even referred by a psychologist, but the family always missed most of the psychologist's appointments and downplayed the situation. At the internal medicine and neurology consultations the patient was oriented, afebrile and had a blood pressure of 104/68 mmHg. Neurological examination showed mild proximal paraparesis, osteotendinous hyperreflexia in both lower limbs, bilateral extensor plantar reflex, and spastic and paraparetic gait. Laboratory results showed aspartate aminotransferase 97.7 U/l, alanine aminotransferase 97.7 U/l and CK 5229.0 U/l. The remaining analytic results are presented in *Table 1*. The patient underwent a cranioencephalic computerised tomography scan, cranioencephalic magnetic resonance imaging and complete spinal magnetic resonance imaging, which showed no alterations. An electromyography was performed and showed a myopathic pattern. A muscle biopsy was carried out and findings were compatible with non-specific myopathic alterations. Laboratory tests for lysosomal storage diseases were all negative. Therefore, the genetic test for recessive spastic paraparesis linked to the X chromosome was requested, and was positive for a pathological variant in homozygosity denominated *ARGI* (NM_001244438 1) – c.782C>T (p(Th1261Ile)). Blood levels of amino acids were tested and showed a significant increased arginine of 533 µmol/l (reference value: 20–140) and a decreased ornithine

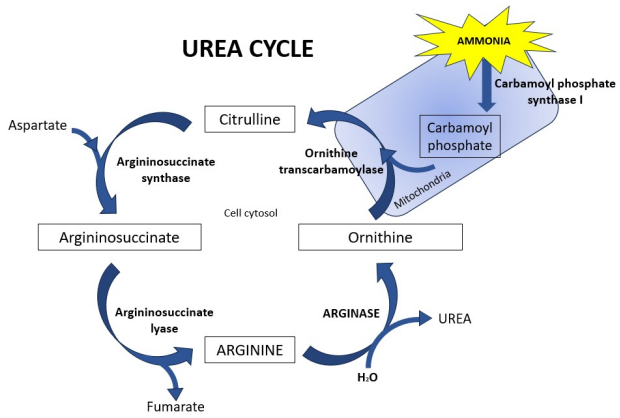

Figure 1. Graphic representation of urea cycle.

value of 23 µmol/l (reference value: 42–90). In that context, the diagnosis of hyperargininemia was made, and the patient was referred for a nutrition and metabolic diseases consultation.

DISCUSSION

Compared to other urea cycle disorders, hyperargininemia is the rarest one[1]. It is an entity poorly understood, leading very often to underdiagnosis. The vast majority of cases are diagnosed in childhood before the age of 4; very few are diagnosed in adulthood. The few reported cases of diagnosis in adulthood are sometimes associated with rare manifestations such as myopathy. A protein-restricted diet, supplementation of crucial amino acids and the use of other routes to eliminate nitrogen waste are the cornerstones of hyperargininemia treatment, and stop the progressive neurological deterioration[1,5]. Therefore, it is crucial to recognise the characteristic signs and symptoms of this metabolic disorder to diagnose it early, because a favourable outcome can be achieved with appropriate treatment.

In this case, a 23-year-old patient had already shown abnormal clinical signs since she was 8 years old – motor difficulties, learning difficulties and changes in behaviour. Despite some support from school psychology, she lacked the necessary family support. It was only in adulthood that she was referred to the appropriate consultations – so the diagnosis could have been made earlier if the appropriate measures had been taken and if family support had been provided. In general, the number of diagnoses of metabolic diseases in adults has risen sharply in recent years due to better knowledge of these pathologies and the evolution of diagnostic techniques in medicine[6]. This type of disease can therefore present itself to any doctor, especially an internal medicine doctor who diagnoses and treats a wide range of pathologies involving all organs and systems.

In this way, we aim to demonstrate a rare diagnosis and highlight the importance of the internal medicine doctor in diagnosing rare diseases, in a well-performed anamnesis and objective examination. This type of entity should also be considered in the presence of neurological signs and symptoms, parental consanguinity and delayed psychological development.

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