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Case report

A female carrier of ornithine carbamoyltransferase deficiency masquerading as attention deficit-hyperactivity disorder

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Abstract

Many females who are heterozygous for ornithine carbamoyltransferase (OTC) deficiency are asymptomatic or intermittently symptomatic with great phenotypic variability. Therefore, the diagnosis of this condition is occasionally a challenge and is often delayed. A 12-year-old girl who was initially diagnosed as having attention deficit-hyperactivity disorder (ADHD) became comatose and developed right-sided hemiparesis during her psychiatric admission. Brain magnetic resonance imaging indicated diffuse but extensive swelling in the left hemisphere with multiple lesions suggestive of an old infarction. Repeated evaluations revealed hyperammonemia and orotic aciduria, and she was diagnosed as having an OTC deficiency. Genetic analysis revealed a heterozygous mutation of N47I in the X-linked OTC gene. Her mental status and hemiparesis improved after hyperammonemia treatment. Here, we report a rare case of a manifestating female carrier with severe symptoms of OTC deficiency masquerading as ADHD.

Keywords: Ornithine carbamoyltransferase deficiency; Stroke; Attention deficit-hyperactivity disorder; Female carrier

1. Introduction

Ornithine carbamoyltransferase (OTC) deficiency is a common X-linked urea-cycle disorder. Hemizygous males present with severe hyperammonemic encephalopathy, seizures, and death during the neonatal period [1]. The diagnosis of the disease is usually established early.

In contrast, heterozygous females display great phenotypic variability; most are asymptomatic or mildly symptomatic, presenting with only protein avoidance or intermittent vomiting, but a few others present with coma or even death [2]. This heterogeneity, transience, and various ages of onset in heterozygous females often delay the diagnosis or lead clinicians to an incorrect diagnosis. Additionally, normal laboratory findings during uneventful periods also hinder the determination of a correct diagnosis by physicians.

Here, we report the case of a girl who was diagnosed after 1 year of treatment in a psychiatric clinic as having heterozygous OTC deficiency, which initially presented

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as attention-deficit/hyperactivity disorder (ADHD) and behavioral problems.

2. Case report

A 12-year-old girl was admitted to a closed psychiatric ward for the evaluation of worsening behavioral problems. She was born to healthy non-consanguineous parents without any perinatal problems. Her neonatal period was uneventful with the exception of two isolated seizure events. Her developmental milestones were normal. There was no family history of seizure, mental retardation, psychiatric disorder, metabolic disorder, coma, or sudden death. With regard to diet, the patient strongly preferred beans and vegetables and avoided beef and chicken.

The patient experienced a traffic accident at 8 years of age and was admitted for the supportive management of a right tibial fracture and a left temporal bone fracture. Brain magnetic resonance images (MRI) did not reveal any abnormalities. Irritability, confusion, visual hallucinations, and right-arm weakness developed on the eighth day of admission, but her symptoms improved spontaneously without any special management and no further attacks were noted.

At 11 years of age, the patient was diagnosed with ADHD according to DSM-IV diagnostic criteria. She was hyperactive, inattentive, impulsive, and stubborn. Her intelligence quotient score was 84 by the Wechsler Intelligence Scale for Children-Revised, and she had difficulties in learning and establishing social interactions with her classmates. Her behavior did not improve despite 1-year treatment with psychosocial education, methylphenidate, and risperidone® therapy. At 12 years of age, she threatened her friends with a knife after an argument. She was immediately hospitalized at a psychiatric facility for further evaluation. During her stay, she exhibited agitation, episodic blank staring, ataxic gait, and abnormal behavior by entering the rooms of other patients day and night. On the seventh day of admission, mental alteration associated with fever was developed. Her Glasgow Coma Scale score was 7 (E1V2M4) and right sided hemiparesis occurred with times. Acute encephalitis was suspected and she was transferred to a department of pediatric neurology for evaluation and management.

On Laboratory examination, there was an elevated ammonia level (285 g/dL; reference range, <75 g/dL) with mild hyperbilirubinemia (1.7 mg/dL; reference range, 0.2–1.2 mg/dL). Initial plasma amino acid analysis on that day revealed no abnormalities with the exception of a slightly elevated glutamic acid level (80 mol/L; reference range, 14–78 mol/L). Other laboratory findings including liver enzyme, blood gas, lactic acid, and autoimmune antibody levels, cerebrospinal fluid examination, culture studies were all unremarkable. Brain MRI indicated diffuse but extensive swelling in the left cerebral cortex and localized cortical atrophy in the right occipital lobe (Fig. 1A). A follow-up MRI, performed 4 days later, indicated progressive swelling in the left hemisphere with a mass effect (Fig. 1B). MR spectroscopy showed elevated levels of the glutamine/glutamate complex (2.05–2.55 ppm and 3.68–3.85 ppm) and elevated levels of the lipid/lactate complex (0.8–1.5 ppm) (Fig. 1C). Electroencephalography revealed the presence of nearly continuous anteriorly dominant high-amplitude delta activity.

Based on the MR findings we repeated metabolic screening on the twenty-third day of admission, which revealed an elevated glutamine level (1,344 mol/L; reference range, 457–857 mol/L) and a decreased citrulline level (10 mol/L; reference range, 19–52 mol/L). Urine organic acid analysis revealed increased orotic acid excretion (218.84 mmol/mol Cr). Therefore, we suspected OTC deficiency and performed mutation analysis of the OTC gene; this revealed a heterozygous mutation of c.140A>T (p.Asn47Ile).

She was treated with lactulose, mannitol, sodium benzoate, and protein-restricted diet therapy. MR images obtained on the twenty-eighth day of admission showed improved cortical swelling of the left hemisphere and the appearance of a new T2 prolongation in the left caudate nucleus and putamen (Fig. 1D). Her mental status and the right-sided hemiparesis improved as her ammonia level normalized. She was discharged on the thirty-fourth day of admission. During follow up periods, she could walk on her own and speak a few words. Her impulsivity, agitation, aggressive behaviors, and wandering improved but did not completely disappear. Four months after discharge, she is clinically well and has experienced no further attacks of coma or hemiparesis.

3. Discussion

Heterozygous female carriers of OTC deficiency have been known to present with great phenotypic variability. Therefore, early diagnosis in these cases remains a challenge to pediatric neurologists, and the determination of a correct diagnosis is often delayed unless severe symptoms such as coma, stroke, or suspicious metabolic encephalopathy occur [3]. Here, we reported a girl who was initially diagnosed with ADHD but was later confirmed as having heterozygous OTC deficiency.

Various abnormal behaviors have been reported in patients with OTC deficiency. However, as behavioral problems are common in the general population, a correct diagnosis of OTC deficiency can be made only in cases of high suspicion of the disease, particularly when abnormal behaviors are the only manifesting symptoms. Most patients with OTC deficiency present with nonspecific psychiatric disturbances, and only a few were