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Case Report

Metabolic Encephalopathy in the Emergency Department; 28 Year Old Female Patient With Diagnosis of Carbamoyl Phosphate Synthetase 1 Deficiency

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Abstract

Urea cycle disorders are commonly seen in the newborn and paediatric population, however presenting cases in adults are uncommon and are usually misdiagnosed before a correct diagnosis is elicited. Several enzymes are involved in the urea cycle, and a defect in any of them can lead to specific laboratory abnormalities and variable clinical presentations. Deficiency of the enzyme ornithine transcarbamylase (OTC) is the most common inherited urea cycle disorder; however, other less common enzyme deficits have been described. In adults, manifestations range from severe encephalopathy to subtle psychiatric manifestations. Prompt diagnosis and recognition are essential to a successful outcome. In this article, we present the case of a 28-year-old female admitted to an A&E department with encephalopathy of unknown aetiology resulting in a diagnosis of carbomoyl synthetase 1 deficiency as well as an unfortunate outcome.

Keywords: OTC deficiency, urea cycle disorders, metabolic encephalopathy

Karbamol Fosfat Sentetaz 1 Eksikliği Tanısı ile Acil Servise Başvuran 28 Yaşındaki Kadın Hasta

Özet

Üre döngü bozuklukları çoğunlukla yeni doğan ve çocuklarda görülmesine rağmen, ender olarak erişkinlerde de görülür ve doğru tanı alana dek genellikle farklı tanılar alır. Üre döngüsünde çeşitli enzimler yer alır ve herhangi birinin hasarı özgün laboratuvar anormallikleri ve farklı klinik tablolara neden olur. Ornitin transkarbamilaz eksikliği (OTC) en sık kalıtılan üre döngü bozukluğu olmasına rağmen, daha az görülen enzim bozuklukları da bildirilmiştir. Yetişkinlerde bulgular, ağır ensefalopati tablosundan hafif psikiyatrik bozukluklara dek uzanır. Hızlı tanı ve hastalığı tanıma başarılı sonuç için gereklidir. Bu makalede, acil servise nedeni belli olmayan ensefalopati tablosu ile başvuran ve incelemede karbomol sentetaz 1 eksikliği saptanan kötü prognozlu bir olgu sunulmaktadır.

Anahtar Kelimeler: OTC eksikliği, üre döngü bozuklukları, metabolik ensefalopati

INTRODUCTION

The term encephalopathy describes a general alteration in brain function manifesting as a disorder of attention anywhere within the continuum of a hyper-alert agitated state to a comatose state. In clinical practice, the diagnosis of encephalopathy is usually reserved for the diffuse brain dysfunction felt to be due to

a systemic, metabolic, or toxic derangement, rather than, for example, a multifocal structural process; Therefore the adjectives "metabolic" or "toxic-metabolic" are usually implied when the diagnosis of encephalopathy is made. Emergency physicians frequently evaluate patients with encephalopathies. In many cases, an aetiological diagnosis can be made through history, examination, laboratory studies, and imaging leading to a specic medical intervention and therefore a more rapid clinical resolution, helping prevent irreversible neurologic dysfunction. Physicians should approach each patient with encephalopathy with an especially high level of suspicion for those causes that may lead to incomplete neurologic recovery if not specically and expeditiously diagnosed and treated.

CASE PRESENTATION

In this case, a 28-year-old female presents to A&E with episodes of incoherent language and disconnection with the environment of unknown aetiology. The patient had been admitted to the observation ward in the same hospital 2 days previous following a similar episode lasting approximately 1 hour. Investigations, which had included blood tests, a CT head and lumbar puncture, had all been normal. During a 24-hour period of observation, she remained asymptomatic and was reviewed by a neurologist and the Mental Health Team. She was eventually discharged with a diagnosis of anxiety and depression. A collateral history from the family also highlighted the patient had been experiencing recurrent episodes of nausea and vomiting, insomnia, isolated episodes of incoherent language and disconnection with the environment over the last 2 months.

There was no previous personal or family history of cardiovascular, neurological or mental health problems. The management when discharged initially included escitalopram, mirtazapine, levonogestrel/etinilestradial and domperidone. Following discharge, the patient began to feel unsteady and dizzy in the morning and made an appointment with her primary care physician where on arrival she had an episode of collapse with loss of consciousness lasting approximately 2 minutes. On arousal, the patient was disoriented with a GCS of 13 (E4, V5, M5) and the patient was immediately transferred and admitted to hospital under the neurology team for further investigations. After 48 hours of admission the patient suddenly deteriorated, dropping her GCS to 6, (E1, V2, M3) requiring endotracheal intubation and mechanical ventilation. Immediate CT was performed (Figure 1) followed by a lumbar puncture and she was admitted to the Intensive care unit (ITU). In ITU, after making the protocol point of metabolic origin, high levels of blood ammonia were observed, 990 µmol/L(normal <50 µmol/L), which suggested the diagnosis of a urea cycle disorder whilst other blood tests, including blood cell count, liver tests, coagulation and cultures, were all negative. The CT was reported as showing a marked loss of differentiation of white and grey substance with effacement of sulci and frontal predominance suggesting generalized hypoxic ischemia. The MRI (Figure 2) was reported as showing cortical encephalopathy. Neurosurgical assessment was requested, however determined that decompression was not indicated. The patient was dialyzed to remove excess ammonia, but despite improvement in the levels of ammonia, the patient remained in deep coma with fixed dilated pupils. The evolution was torpid and the patient had a cardiorespiratory arrest and died the next morning. In retrospect, the patient"s family reported aversion to "usual" meat and frequent episodes of misconduct

which is suggestive of the presumptive diagnosis of a urea cycle disorder.

The pathological findings included severe cerebellar herniation of the cerebellar vermis with necrosis and diffuse cerebral oedema suggestive of hyperammonemic encephalopathy. Based on liver biopsy, genetic studies of ornithine transcarbamylase deficiency were negative. Whilst ornithine transcarbamylase deficiency is the most common, other rarer enzyme defects may be present, therefore samples were sent for genetic study at the University Children's Hospital in Zurich, Switzerland where DNA sequence analysis confirmed the diagnosis of carbamoyl phosphate synthetase 1 (CPS, chromosome 2q35), Exon 17: c.1910T>(val637Ala). Heterocygote Exon 32: c.3927+2T>A splicing Heterocygote. A sister and a brother of the deceased patient have been further investigated with molecular analysis demonstrating similar mutations, and are both currently under follow-up with a multidisciplinary unit. The results of the molecular investigations in the parents are still pending.

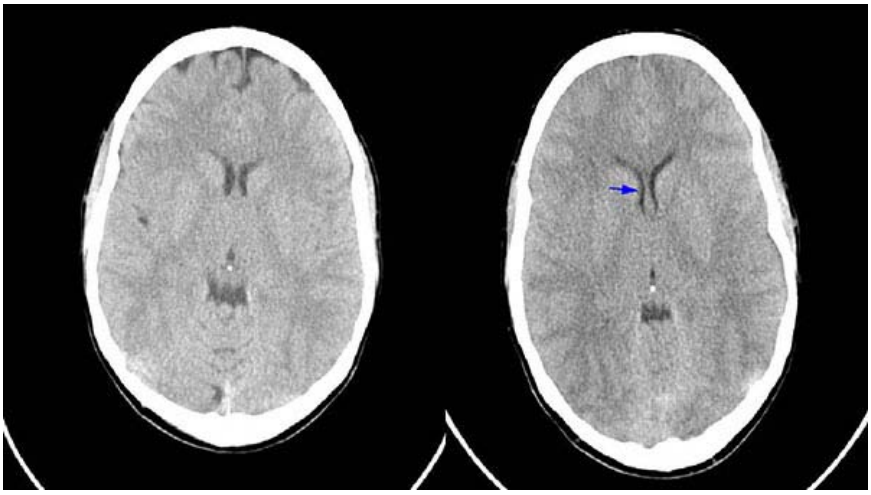

Figure 1; *Axial cranial CT without contrast at the level of the basal ganglia. Compared with a previous normal study 48 hours ago shows general effacement of sulci observed in both hemispheres secondary cerebral oedema and discrete ventricular compression. Note that the frontal horns of the ventricular system (blue arrow), shows a smaller caliber than the previous study.*

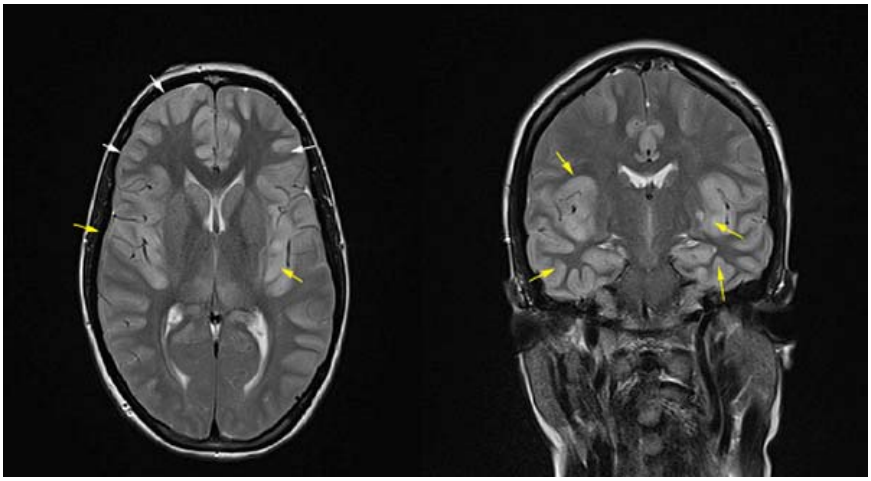

Figure 2; *Cranial MRI T2 sequence in the axial and coronal plane respectively. Thickening and increased signal intensity of the cerebral cortex predominantly in the frontal lobes (white arrows) and temporal lobes (yellow arrows), without significant involvement of the subcortical white matter. Widespread effacement of sulci in both cerebral hemispheres.*

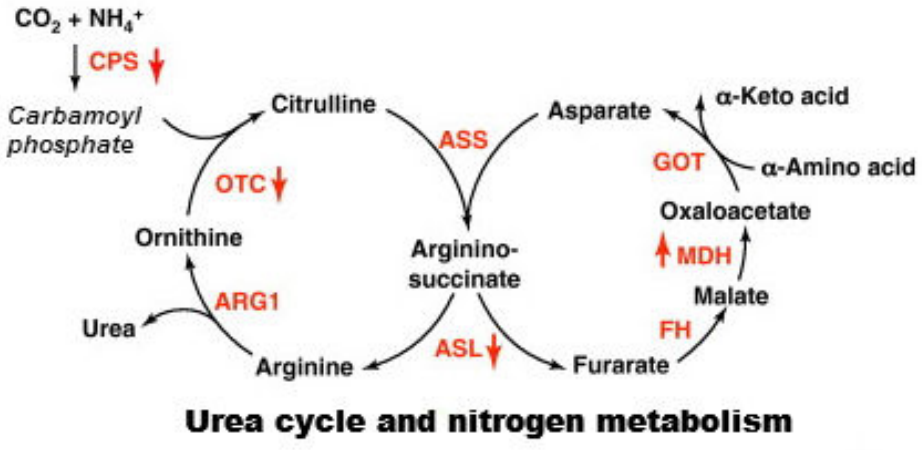

Figure 3; *Urea cycle and nitrogen metabolism CPS, Carbamoyl phosphate synthetase; OTC, Ornithine Transcarbamylase; ARG1 arginase 1; ASL Argininosuccinate Lyase; GOT oxaloacetate transaminase; MDH malate dehydrogenase; FH fumarate hydratase.*

DISCUSSION

The triad of hyperammonemia, encephalopathy, and respiratory alkalosis characterizes urea cycle disorders. Five disorders involving different defects in the biosynthesis of the enzymes of the urea cycle have been described: ornithine transcarbamylase deficiency, carbamyl phosphate synthetase deficiency, argininosuccinate synthetase deficiency, or citrullinemia, argininosuccinate lyase deficiency, and arginase deficiency (Figure 3). Carbamoyl phosphate synthetase 1 (CPS1) deficiency (CPS1D) is an inborn error of the urea cycle having autosomal (2q34) recessive inheritance that can cause hyperammonemia and neonatal death or mental retardation (14). The estimated frequency of CPSID is 1 in 150-200,000 births. The estimated frequency of urea cycle disorders collectively is 1 in 30,000. However, because urea cycle disorders like CPSID often go unrecognized, these disorders are under-diagnosed, making it difficult to determine the true frequency of urea cycle disorders in the general population.

The first report of CPS1 deficiency was by Hommes et al in 1969 (9), with other early-onset cases subsequently reported (7,14). Granot et al first reported the delayed form in 1986 in a 9 year old with hyperammonemic coma simulating Reye syndrome (8). Some individuals with carbamoyl phosphate synthetase (CPS) deficiency reach adulthood prior to diagnosis. Verbiest et al. described a 32-year-old woman who was first discovered to have CPS I deficiency when investigated after valproic acid-induced coma (15). Valproate sensitivity has been observed with ornithine transcarbamylase deficiency and citrullinemia, two other causes of hyperammonemia. Valproate can cause hyperammonaemia in patients with normal concentrations of urea cycle enzymes. VPA inhibits the activity of carbamoyl phosphate synthetase I, the first enzymatic reaction in the urea cycle, thereby hindering the excretion of ammonia and raising plasma ammonia levels. Valproate discontinuation is currently the mainstay of treatment for valproate encephalopathy, although more research is warranted to delineate the underlying risk factors for valproate encephalopathy and consolidate treatment modalities for this potentially life-threatening drug adverse effect (4). In the reported case, valproate was not included in her treatment. Wong et al described a 26-year-patient who presented with coma after childbirth and was found to have

CPS I deficiency (16). Ten hours after delivery of her only pregnancy, she became disoriented, agitated, and progressed within a few hours to coma and decerebrate posturing. She was declared dead 3 days after delivery at which time her EEG showed no cerebral electrical activity. The history reported by the authors indicated that she had been on a self-selected diet with little or no meat or dairy products and that she had occasionally complained of spells of confusion and disorientation and had been diagnosed as having complex partial seizures.

In a recent study Batshaw et al reported the results of an analysis of 614 patients with urea cycle disorders (UCDs) enrolled in the Urea Cycle Disorders Consortium's longitudinal study protocol (1). The most common disorder was ornithine transcarbamylase deficiency, accounting for more than half of the participants, mortality rate was 24% in neonatal onset cases and 11% in late onset cases. Carbamyl phosphate synthetase deficiency was found in 17 individuals (3%) with the risk of mortality (neonatal plus late onset) to be 42%. According to a study of urea cycle diseases in Finland, 3 cases of CPS deficiency had been reported by 2007(10). A study in Italy provided an overview of clinical findings with biochemical and molecular data concerning 13 Italian patients (6). The Spanish urea cycle disorders study group (5) included 104 patients from 98 different families, with the diagnosis: 67 OTC deficiency (64.4%), 22 ASS deficiency (type 1 citrullinemia) (21.1%), 10 ASL deficiency (argininosuccinic aciduria) (9.6%), 2 CPSID deficiency (1.92%), 2 ARG1 deficiency (1.92%) and 1 NAGS deficiency (0.96%).

In this case no evidence of liver disease was found, therefore the cause for hyperammonemia was suspected to have been caused by a metabolic disorder. The urea cycle is the only effective system that converts waste nitrogen from protein intake and the breakdown of endogenous protein into urea, which is excreted from the body (Figure 3). The mechanisms leading to the effects of ammonium exposure on the brain have remained poorly understood. In the last few years, new data has shown that ammonium exposure alters several amino acid pathways and neurotransmitter systems, cerebral energy, nitric oxide synthesis, axonal and dendritic growth, signal transduction pathways and water channels. The most important mechanism of how hyperammonemia damages the brain is brain oedema induced by disruption of the aquaporin system and brain electrolyte homeostasis. The central feature of hyperammonemia-induced encephalopathy is an increase in astrocytes, glutamine synthesis and swelling of astrocytes in response to the osmotic effect of glutamine accumulation, resulting in increased intracranial pressure (3). All these effects of ammonium on the CNS may eventually lead to energy deficit, oxidative stress and cell death.

Common symptoms include lack of appetite, vomiting, drowsiness, seizures, coma, anorexia, irritability, lethargy, disorientation and somnolence. Several triggers have been reported in adulthood, including valproic acid, postpartum stress, heart and lung transplant, short bowel and kidney disease, parenteral nutrition with high nitrogen intake and gastrointestinal bleeding. Routine laboratory studies are of no diagnostic help. A low BUN is suggestive of a urea cycle defect. The biochemical way to distinguish CPS from other UCDs, is the presence of low to absent citrulline on plasma amino acids with normal (not elevated) orotic acid in the urine. A diagnosis of CPSID involves a detailed patient/family history, identification of characteristic findings, and a variety of specialized tests. Specific blood tests may reveal excessive amounts of ammonia in the blood, which is the

main criterion for a diagnosis of urea cycle disorders including CPSID. However, high levels of ammonia in the blood may characterize other disorders such as the organic acidemias, congenital lactic acidosis, liver disease, and fatty acid oxidation disorders. Urea cycle disorders can be differentiated from these disorders through the examination of urine for elevated levels or abnormal organic acids. In urea cycle disorders, urinary organic acids are normal except for the presence of orotic acid in OTCD. Measurement of CPSID1 enzyme activity on cells obtained from a liver biopsy confirms the diagnosis. Individuals with CPSID will show absent or low enzyme activity. Molecular genetic testing for mutations in the CPSID1 enzyme is also available without the need for a liver biopsy for enzyme assay.

A recent study has demonstrated that in-patients with UCDs,the frequency of acute liver failure is a common complication, which may not always lead to severe symptoms and may therefore be underdiagnosed (12). In this case liver functions tests (LFTs) before admission were mildy elevated, however on arrival and during the course of the disease, no obvious abnormalities were observed.

The immediate therapeutic goal for patients with acute hyperammonemia is the rapid removal of ammonia to prevent irreversible cerebral damage. An emergency management protocol for UCDs and hyperammonemia is available from the British Inherited Metabolic Disease Group (2). Protein should be removed from the diet. Immediate initiation of IV alternate forms of waste nitrogen excretion (sodium benzoate and sodium phenylacetate) as well as arginine are essential to lower ammonia alongside an infusion of glucose to stop catabolism. In addition, if these agents are not readily available the patient should be transferred as an emergency to a hospital where they are available and where a clinician experienced in their administration is available. If this is not feasible, then hemodialysis should be initiated as quickly as possible in a patient confirmed to have an ammonia over 250. Once the acute hyperammonemic crisis is past, the long-term goals are the promotion of normal growth, development, and function and the prevention of recurrent attacks. The mainstays of treatment are dietary protein restriction, arginine or citrulline supplements, and oral alternative pathway therapy with sodium phenylbutyrate. Plasma glutamine seems to predict hyperammonemia and may be the best single guide to the effectiveness of treatment. Orthotopic liver transplantation should be considered for patients with more severe UCDs because of the poor prognosis.

In a recent cross-sectional observational report on a large cohort of patients with non-classical UCDs highlighted a high proportion of adult patients, clinically affected female OTC patients and cognitive impairment (13). There was often along delay in reaching the correct diagnosis, which may add to a relevant extent to the morbidity of this cohort similar to the reported case. There is a need for greater awareness that these disorders can present in a non-classical way and outside the neonatal period.

CONCLUSION

Urea cycle disorders are a rare but important cause of acute encephalopathy and can present for the first time in adulthood. Due to the rarity of these disorders, most physicians have relatively little experience with management. It is essential to be familiar and be aware of this condition as it is readily treatable, but can be fatal if undiagnosed and untreated. Determination of plasma ammonia levels should be included in a laboratory work-up in cases of acute psychiatric and neurological symptoms or unexplained coma in the emergency department. Early recognition and treatment with

medication, dietary protein restrictions, and/or liver transplant can improve long-term outcome and prompt specialty care including neurology/genetics should be considered.

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