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Case Report

Treatment by haemodialysis in a case of adult-onset (type II) citrullinaemia in a Chinese patient with pulmonary tuberculosis

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Introduction

A 52-year-old male, with a history of delayed childhood development and recent pulmonary tuberculosis, presented to a regional hospital for acute onset of confusion 2 weeks after the start of antituberculous medications. The clinical course was later complicated by repeated episodes of seizure. Initial assessment showed that his Glasgow coma scale was 13/15. He had generalized brisk reflexes and bilateral up-going plantar response. His initial laboratory tests were unremarkable, apart from mildly raised alanine transaminase (ALT) and alkaline phosphatase (ALP) (both two times the upper limit of normal) and raised international normalized ratio (INR) (1.4). CAT scans of brain and lumbar puncture were unremarkable, while electroencephalogram showed evidence of encephalopathy. Serum ammonia was detected to be markedly raised. Liver biopsy and metabolic screening were performed. Citrulline was raised in urine and in blood. A diagnosis of type II (adult onset) citrullinaemia with hyperammonaemic encephalopathy precipitated by a hypercatabolic state due to pulmonary tuberculosis and liver derangement caused by the antituberculous medications was made. He was treated successfully by haemodialysis, with improvement of confusion and lowering of ammonia. The management of type II (adult onset) citrullinaemia is discussed.

Case

A 52-year-old male, with a history of delayed childhood development and an operated pleomorphic adenoma of the right parotid gland 4 years ago, presented with left pleural effusion. He was afebrile and his vital signs were stable. He had no jaundice or stigmata of chronic liver disease. His Glasgow coma scale was 13/15. He had no neck stiffness. Cranial nerves were intact. Limb tone and power were unremarkable. There were bilateral brisk tendon reflexes and bilateral up-going plantar responses. The rest of the physical examination was unremarkable, apart from a small amount of left pleural effusion. Bilirubin was 24 μmol/l, ALP 333 IU/l (normal: <200 IU/l) and ALT 94 IU/l (normal: <40 IU/l). INR was 1.4. Complete blood count, serum urea, creatinine, glucose and blood gases were normal. Human immunodeficiency virus antibody was negative. Chest X-ray showed mild left pleural effusion. Electrocardiogram and urgent CAT scan of the brain were normal. For the following days, he developed repeated episodes of confusion in the middle of the night that recovered during the daytime. Repeated physical examinations and CAT scan of the brain were unremarkable. Electroencephalogram showed sharp waves over both frontal areas in a background of generalized slow wave activities. The findings were in keeping with non-convulsive seizure with post-ictal drowsiness. Phenytoin was started.

The episodic confusion, however, did not improve after treatment with phenytoin for the following 8 days. Serial liver function tests remained deranged (ALT: 134 IU/l; ALP: 250 IU/l; bilirubin: 40 μmol/l). Lumbar puncture showed normal study with no organism grown. Ultrasonogram of the hepatobiliary system showed hepatomegaly compatible with drug-induced

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hepatitis. Repeated electroencephalogram showed diffuse slow wave activities. Magnetic resonance imaging (MRI) of the brain was unremarkable. For better control of the epilepsy, phenytoin was switched to valproate and later carbamazepine. Antituberculous medications were stopped for possible drug-induced hepatitis, with subsequent recovery of liver function tests, which remained stable on re-challenge with antituberculous drugs. Clonazepam was introduced on day 20 for poorly controlled seizure, despite several anti-epileptics. On day 36 the patient developed an episode of severe pneumonia with respiratory failure, upper gastrointestinal bleeding and hypovolaemic shock, from which he recovered. His INR remained prolonged, despite normal ALT, platelet and activated partial thrombin time. Ammonia level was then found to be elevated. Trans-jugular liver biopsy revealed microvesicular steatosis and focal glycogenosis in the nuclei of hepatocytes. There was no evidence of hepatitis or active necrosis. Plasma and urine amino acid analysis was performed with a pre-column, pre-derivatization method on a reversed phase high-performance liquid chromatography column with fluorimetric detection. Amino acid analysis revealed raised blood citrulline (247 μmol/l; normal: 5–95 μmol/l) and urine citrulline levels (145 μmol/mmol creatinine; normal: 1–6 μmol/mmol creatinine). Urine arginine was mildly elevated (28 μmol/mmol creatinine; normal: 1–10 μmol/mmol creatinine). Urine orotic acid was normal (normal: 0.4–1.2 μmol/mmol) as measured using a modified colorimetric method. A diagnosis of adult-onset (type II) citrullinaemia was made.

Protein restriction was started. As early and efficient treatment for hyperammonaemic encephalopathy was desirable, haemodialysis was started promptly to reduce ammonia levels. Marked improvement was obtained in conscious level and seizure control, while ammonia was intermittently removed by haemodialysis. Figure 1 shows the relationship between conscious level, seizure attacks and time of haemodialysis. He was stabilized and finally discharged with oral sodium benzoate 500 mg four times a day.

In summary, this is a case of adult-onset (type II) citrullinaemia, probably precipitated by a hypercatabolic state related to pulmonary tuberculosis (which increases the substrate of urea cycle) and by antituberculous drugs-induced hepatitis (which reduced the removal of urea cycle metabolites). He presented with episodic confusion, raised INR and hyperammonaemic encephalopathy. Diagnosis was made by raised plasma and urine citrulline level. Treatment of the hyperammonaemic encephalopathy was successful with haemodialysis, which was an efficient modality to remove small molecules like ammonia.

Discussion

Citrullinaemia is a rare inborn disorder of metabolism of the urea cycle (Figure 2), characterized by deficiency in argininosuccinate synthetase (ASS) and/or its activity, resulting in increased serum ammonia, citrulline and glutamine levels with normal acid–base balance. Classical citrullinaemia is an autosomal recessive disease caused by a genetic deficiency of ASS. There are three types of citrullinaemia. Classic neonatal or infantile form is classified under type I (abnormal ASS kinetics) or...
type III (undetectable or extremely low ASS level). Most adult-onset form is due to type II (decreased ASS activity in liver while having normal level of ASS and activity in other tissue) [1]. Cerebral manifestation is a distinctive feature of citrullinaemia and is due to neuron compression from adjacent swollen astrocytes, which is caused by glutamine influx and its metabolism in astrocytes [2].

The diagnostic clue is the raised ammonia, which should be checked in all patients with encephalopathy, even with normal liver function. Raised plasma citrulline level is diagnostic and is >1000 μM in most neonatal cases. In this case, citrulline level (247 μM) was not as high as expected in other classical neonatal cases, as only hepatic ASS is typically deficient while renal ASS is still available. Unlike neonatal cases, urine orotic acid was not raised in the present case, as in some reported cases in the literature [1]. ASS activity in liver biopsy could help diagnosis in difficult cases. Neurological symptoms were reported to correlate with cerebrospinal fluid ammonia levels [3]. This might explain the time lag of clinical response to plasma ammonia level in the present case. The tendency of nocturnal surges of plasma ammonia and citrulline [4] might have contributed to nocturnal confusion in the present case. The relationship between glutamine and neurological symptoms was not established in the present case, but would be interesting given the role of glutamine in astrocyte swelling [2]. MRI of the brain was unremarkable in the present case, but may show some lesion in the T2-weighted image which is reversible after successful liver transplant [5].

In this case, increased protein catabolism with concurrent pulmonary tuberculosis and decreased availability of ASS from drug-induced hepatitis in an already ASS-deficient liver might be the precipitating factors. To our knowledge, this is the first reported case of adult-onset (type II) citrullinemia associated with pulmonary tuberculosis, which is endemic in our locality. Clinicians should be aware of the possibility of hyperammonaemic encephalopathy and urea cycle disorder in cases of unexplained encephalopathy in patients with hypercatabolism.

The goal of treatment is to provide a diet rich in arginine and energy while maintaining nutritional status and preventing hyperammonaemia and hyperglutaminemia. Initial treatment may include arginine supplement, sodium benzoate [6] and/or sodium phenylacetate (or phenylbutyrate). Arginine (3 mmol/kg/day) can be supplemented if it is deficient, as in classical neonatal onset citrullinaemia. The arginine level was reported to be normal in the adult-onset case as the preserved ASS enzyme in the kidney might be adequate to provide the daily requirement [7]. Benzoate eliminates nitrogen by conjugating with glycine to form hippurate, which is rapidly excreted via the kidney. Phenylbutyrate serves to excrete nitrogen by liver conjugation with glutamine, which is rapidly excreted in urine. Arginine, benzoate and phenylbutyrate can be given as a cocktail with total parenteral nutrition (TPN) with D10 (and intralipid). In the present case, oral benzoate was given to the patient.

Haemodialysis can be used to remove ammonia rapidly in the case of failed treatment with arginine, benzoate and phenylacetate infusion via TPN. Haemodialysis is 10 times more efficient than either peritoneal dialysis or continuous veno-venous haemodialfiltration in ammonia removal and is a better choice in cases of encephalopathy. In this case, regular haemodialysis reduced seizure episodes, improved conscious level and reduced the ammonia level. Liver transplantation has been reported to lead to complete neurological and biochemical recovery of an adult patient with type II citrullinemia [5,8].

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Conflict of interest statement. None declared.

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