Case Report

A Report of Two Families with Sarcosinaemia in Hong Kong and Revisiting the Pathogenetic Potential of Hypersarcosinaemia

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Abstract

Introduction: Sarcosinaemia is a rare metabolic disorder which has not been reported in Asia. Clinical Picture: The urine samples of 2 patients were screened as a routine metabolic screening offered for patients with mental retardation in our hospital. We used gas chromatography-mass spectrometry (GC-MS) which is capable of detecting abnormal pattern in amino acids and organic acids. Plasma sarcosine level was further quantified by GC-MS. The same methods were used in the investigations of asymptomatic family members. Urine examination by GC-MS revealed excessive amount of sarcosine in urine (normally undetectable) and their plasma sarcosine levels were raised. The 2 differential diagnoses of presence of sarcosine in urine – glutaric aciduria type II and folate deficiency – were ruled out by the absence of abnormal organic acids in the initial urine screen and by normal serum folate level respectively. Screening of the 2 families identified excessive sarcosine in urine in 2 siblings, one from each family. However, these 2 siblings of indexed patients thus identified have no neurological or developmental problem. Conclusion: Our finding was consistent with the notion that sarcosinaemia is a benign condition picked up coincidentally during screening for mental retardation.

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Key words: Gas chromatography-mass spectrometry, Hypersacosinaemia, Sarcosine, Sarcosine dehydrogenase

Introduction

Sarcosinaemia (OMIN 268900) is an autosomal recessive condition due to the deficiency of sarcosine dehydrogenase (E.C. 1.5.99.1). It is a rare condition with an estimated incidence of 1 in 350,000 in a newborn screening programme.[1] Sarcosinaemia is usually identified by metabolic screening in the investigation for mental retardation. To our knowledge, there has been no report of this condition in the Asian population in the English literature. We report a Chinese family and an Indian family with this condition identified in our hospital in Hong Kong.

Laboratory Methods

In our hospital, broad-spectrum metabolic screening is done by examining urine samples of patients with mental retardation. Gas chromatography-mass spectrometry (GC-MS) (Agilent Model 5890/5972, USA) is used. This method allows simultaneous qualitative analyses of amino acids including sarcosine, organic acids, sugars, sugar alcohols, sugar acids and nucleic acid bases.[2] It is capable of screening a great variety of inborn error of metabolism and is different from conventional GC-MS organic acidaemia screening procedures, which are not well-suited to detect metabolic disorders except organic acidurias.[2] When sarcosine was detected in urine samples of our indexed patients, plasma sarcosine levels were further measured by GC-MS. Urine screening was then performed for the siblings and the parents of the indexed patients using the same method. We measured plasma sarcosine levels of these family members when urine was positive for sarcosine.

Case Reports

A 9-year-old Chinese girl who is a known patient with mental retardation and autistic features presented with convulsion. Physical examination revealed no dysmorphic features or abnormal neurological signs. She is the third

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child of a non-consanguineous marriage. Initial urine screen by GC-MS found excessive amount of sarcosine without detection of abnormal organic acid; follow-up test of plasma sarcosine level by GC-MS was 262 μmol/L (normally undetectable). Folate deficiency was ruled out by a normal serum folate level. Hence, sarcosinaemia was diagnosed in this girl. The urine samples of her 2 older siblings and parents were also screened by GC-MS. The urine of an older brother tested positive for sarcosine. His plasma sarcosine level was 196 μmol/L. However, he is mentally normal and has no abnormal neurological signs. There are no behavioural problems either. He is studying in a primary school and has achieved good academic results.

The second patient, a 5-year-old Indian girl, was referred to our hospital for investigation of mental retardation. Our assessment showed that she had a mental age of 2 years. There were no dysmorphic features or autistic features. Magnetic resonance imaging (MRI) of the brain showed features compatible with Dandy Walker variant. She also had prominent left renal pelvis and bilateral vesico-ureteric reflux. The parents are not consanguineous. Urine examination of this patient by GC-MS revealed excessive amount of sarcosine without detection of abnormal organic acid. Plasma sarcosine level was 133 μmol/L. Her folate level was normal, which ruled out folate deficiency. Urine screening of the family members by GC-MS revealed that one of her 2 younger sisters also had sarcosine in urine. However, the younger sibling has no neurological or developmental problems. The parents declined test for plasma sarcosine level of this asymptomatic sibling.

Discussion

Sarcosinaemia is an autosomal recessive condition due to the deficiency of sarcosine dehydrogenase, which is a liver mitochondrial matrix flavoenzyme catalysing the conversion of sarcosine (N-methyglycine) to glycine. The gene for sarcosine dehydrogenase has been mapped to the locus 9q33-q34.[3]

Besides sarcosinaemia, 2 other diseases – folate deficiency and glutaric aciduria type II – could also lead to hypersarcosinaemia and have to be ruled out before the diagnosis of sarcosinaemia is made. In our indexed patients, we ruled out folate deficiency and glutaric aciduria type II as the patients had normal serum folate levels and the absence of abnormal organic acids, which is associated with glutaric aciduria type II. As sarcosine dehydrogenase is expressed only in liver, confirmation of diagnosis could only be made by liver biopsy, but this is not routinely performed in most laboratories.[4]

This condition was first reported in 2 siblings with mild mental retardation in 1966.[5] Over the years, asymptomatic individuals were also identified. Similar to our case report of the 2 Asian families, some of these asymptomatic subjects were siblings of indexed patients and were identified by family screening subsequent to the diagnosis of indexed patients.[4] Some other asymptomatic subjects with sarcosinaemia were picked up by the newborn screening programme.[1,6] Follow-up of these subjects for 20 years showed that they remained free of neurological symptoms. It is becoming clear that the diagnosis of sarcosinaemia in patients with neurological deficits is the result of bias of ascertainment: the discovery of sarcosinaemia in children being investigated for abnormalities.[4] Hence, sarcosinaemia is believed to be a benign metabolic state.[4] This notion is further supported by the mouse model of sarcosinaemia.[7] Mice with this condition are entirely asymptomatic.

However, there should be a word of caution. Subtle neurological abnormalities were reported in some "asymptomatic" individuals with sarcosinaemia: speech delay, hyperactivity, learning and emotional disorders.[4] It was reported that a girl with sarcosinaemia, who was normal initially, started to have progressive neurological regression from the age of 5.[8] At the molecular level, sarcosine is capable of augmenting the currents of N-methyl-D-aspartate (NMDA) receptors.[9] It has been postulated that enhanced neuronal cell death in the immature brain could occur through the mechanism of NMDA-mediated excitotoxicity resulting from repetitive or prolonged pain in premature infants.[10] NMDA receptors are also involved in the pathogenesis of a cognitive problem, schizophrenia[11] and attention-deficit disorders.[12] Therefore, we should have an open mind as to the pathogenetic potential of hypersarcosinaemia.

In conclusion, this is the first case report of sarcosinaemia in Asia in the English literature and the identification of sarcosinaemia in 2 normal siblings of 2 indexed patients with mental retardation is consistent with the notion that sarcosinaemia is a benign condition.

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