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Case Report

Compound Heterozygous *SLC22A5* Pathogenic Variants Presenting with ADHD and Silent Hyperammonemia in a Lebanese Child

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Abstract

With the continuous change in teaching methods and the increased exposure to screens, ADHD as well as multiple forms of learning disabilities are becoming very common, and are dealt with as a psychosocial disorder. The search for an underlying organic cause should always be considered specially when dealing with patients from highly consanguineous societies. In this paper we present the case of a patient presenting with a severe case of ADHD with a silent hyperammonemia, caused by novel compound heterozygous variants in the *SLC22A5* gene and responding to treatment by oral L-Carnitine supplementation.

Keywords: *SCL22A5, Carnitine Deficiency, ADHD, Learning Disability, Treatable, Silent Hyperammonemia*

Introduction

Pathogenic variants in the *SLC22A5* gene, encoding the OCTN2 carnitine transporter, lead to Primary Carnitine Deficiency (PCD). The typical clinical presentation of PCD includes metabolic decompensation in infants, hypoketotic hypoglycemia, skeletal and cardiac myopathy in adults, and possible sudden death from cardiac arrythmia.

The variable severity is mainly due to the effective state of the protein; missense or in-frame deletions carry the possibility of generating proteins that retain residual transport activity, while nonsense or null mutations produce the most severe presentations [1]. Variants in the *SLC22A5* gene would affect negatively the mitochondrial function as well as that of the urea cycle. The urea cycle's function, responsible for detoxifying ammonia levels, would be impaired and thus cause the hyperammonemia [2]. These major biochemical disturbances contribute the most to the clinical presentation of the patients, especially in the acute phase, where the patient would present with hyperammonemia, variably elevated liver function tests, and hypoglycemia with minimal to absent ketonuria.

Here we report on a Lebanese male child who presented with an attention deficit and hyperactivity disorder (ADHD) associated with a silent hyperammonemia without hypoglycemia. specific compound heterozygous variant in the *SLC22A5* gene.

Case Presentation

We report the case of a 5-year-old boy who presented to an outpatient clinic, with poor concentration, and learning difficulties. The patient was referred by his school, as a part of a regular neurological assessment performed on every child with confirmed ADHD. The patient had undergone a TOVA test that showed an Attention Comparison Score (ACS) of -3.66. A follow up with psychomotor therapists and speech therapist, with weekly sessions since 6 months did not contribute to any improvement of the patient's symptoms.

The patient was born to non-consanguineous parents, at term via normal vaginal delivery, with no perinatal complications. His birth weight and growth parameters were within normal limits. He attends a regular class but demonstrates poor writing skills, difficulty maintaining focus, and an inability to perform dual tasks since the 2 years.

The family history was unremarkable for metabolic or neurodevelopmental disorders. The parents mention that the child spends prolonged periods in front of screens and was described as a slow learner with poor counting ability since he started going to school, although generally intelligent and perceptive. Parents also noted limited social interaction and reduced eye contact.

On presentation, the child was at the 10^{th} percentile for height and weight. The physical examination showed a normal physical and neurological exam, the child was awake alert, interacting normally, with a slight slowing in response to orders. He had no dysmorphic features or focal neurological deficits. The child had normal motor and fine motor skills, the child had a normal speech for his age, was already able to write his name in detached letters in English, and was able to reproduce the shape of name in Arabic without individual letter recognition, he had a slow response to average questions.

The patient's paraclinical work up showed a mild anemia with a hematocrit at 28.1%, a lactate level at 0.57 mmol/L, pyruvate: 21 µmol/L, homocysteine: 17 µmol/L, normal CPK and liver function enzymes levels, and an Ammonia (NH_3) at 200 µmol/L.

The patient still always presented a normal awareness and a normal neurological exam. A treatment with oral sodium benzoate at 100 mg/kg/day was started. An ammonia level after 48 hours showed an increase to 300 µmol/L, despite a normal neurological examination. The chromatography of amino acids in blood and the chromatography of organic acids in urine were within normal ranges for age. And abdominal ultrasound and a hepatic MRI showed no anomalies. A cardiac ultrasound was performed and showed no anomalies as well.

An oral carnitine supplementation of 100 mg/kg/day was started while a whole exome sequencing was performed. 48 hours after the initiation of carnitine supplementation ammonia levels decreased to 70 µmol/L.

Subsequent whole-exome sequencing (WES) confirmed a diagnosis of Primary Carnitine Deficiency, identifying novel compound heterozygous pathogenic variants in the *SLC22A5* gene (NM_003060.3): c.505C>T (p.Arg169Trp); c.760C>T (p.Arg254Ter), consistent with a carnitine transporter (OCTN2) deficiency.

Six months after the initiation of the treatment, the patient's neurological examination remains within normal limits, the child is noted to be more active and responsive, and a clear improvement of the learning capacities and performance in all learning subjects at school, a clear decrease in the hyperactivity in class is noted and an improvement of the attention capacities during school hours and during daily life tasks is confirmed by the parents and the teachers and the therapists.

Discussion

ADHD is always regarded as a psychiatric disorder, and dealt with from the behavioral and rehabilitation angle, and very few specialists look for an underlying organic disorder unless a clear clinical sign is present. This management is regarded as appropriate unless the patient comes from a highly consanguineous society, where inborn errors of metabolism are individually rare but collectively common and can lead to multiple psychiatric presentations.[3]

Lebanon still exhibits, to this day, a high rate of consanguinity, especially in urban areas, predisposing the population to a number of inherited metabolic diseases [4,5].

Genetic variants are often considered and studied with the assumption that even the same variant can have different presentations both molecularly and clinically. This is emphasized in cases when a compound heterozygote mutation of the same gene presents atypically for both mutations.

Here, we present the case of a 5-year-old male child with silent hyperammonemia, developmental delay, severe anemia, and reduced verbal communication, which led to whole exome sequencing confirming a compound heterozygote in the SLC22A5, diagnostic of primary systemic carnitine deficiency (PSCD). To our knowledge, this is the first confirmed case in Lebanon with this compound heterozygote mutation.

Primary systemic carnitine deficiency is an autosomal recessive disorder of fatty acid oxidation, resulting in impaired ability to oxidize long-chain fatty acids. Primary carnitine deficiency is caused by a defect in the OCTN2 carnitine transporter encoded by the *SLC22A5* gene [1]. Carnitine is accumulated by cells and retained by the kidneys using OCTN2, a high-affinity organic cation transporter specific for carnitine [6].

In our case, the pathogenic variants 505C>T and 760C>T were both previously reported as disease-causing [7]. The missense variant 505C>T affects an amino acid leading to loss of affinity for substrates, while the 760C>T nonsense mutation leads to a stop codon, resulting in a nonfunctional protein. This dual presence explains the compound heterozygosity in our case.

Clinically, the patient presented with hyperammonemia (200–300 μmol/L) and psychomotor delay, with no signs of cardiomyopathy or muscle-related weakness. The clinical condition of the patient suggests a slowly accustomed condition to very high levels of ammonia, which in other patients would lead to a severe neurological distress. The only noted clinical sign was a hyperactivity and attention deficit disorder. Treatment with 100 mg/kg/day of L-Carnitine allowed to revert the Ammonia levels to normal (70 μmol/L), and the patient showed improved energy, focus, and concentration [8].

OCTN2 deficiency results in renal loss and systemic depletion of carnitine tissue stores [9,10]. The impairment of β-oxidation leads to the accumulation of long-chain fatty acids and an increase in nitrogen load due to protein degradation, resulting in hyperammonemia as observed in our patient [11].

The decrease in ammonia levels and absence of irreversible organ damage in this case demonstrate the importance of early and accurate diagnosis. Prophylactic carnitine, under several trusted recommendations, is an effective treatment capable of preventing metabolic crises and neurodevelopmental complications if started at the right time, whereas delayed treatment can lead to permanent encephalopathy or sudden cardiac death. Therefore, newborn screening should not only focus on the most common metabolic diseases but also include a broader range, especially in high-consanguinity communities, where *SLC22A5* variants may be underreported.

A similar therapeutic result was noted in the Hong Kong series [12], which studied six children with *SLC22A5* variants, including the same p.Arg254Ter mutation, presenting with cardiomyopathy and metabolic decompensation as predominant symptoms. With carnitine supplementation, the six patients returned to normal cardiac function. However, in comparison to the case presented in Lebanon, the phenotype was less severe, mainly involving neurological symptoms and biochemical alterations. The neurological symptoms, mainly the disturb neurodevelopment can be attributed to the mutation by itself as well as to the mitochondrial dysfunction in the brain cells due to the carnitine deficiency.[13]

This phenotypic difference may be due to compound heterozygosity (nonsense + missense) rather than homozygosity for a truncating allele, which could allow residual transporter activity sufficient to protect myocardial tissue. Alternatively, it may reflect the modifying influence of nutritional, environmental, or ethnic variables on the pattern of SLC22A5 expression. Nonetheless, both groups emphasize the important observation that early detection and carnitine treatment are lifesaving and fully corrective.

The phenotypical variability contributing to a lesser effect or rather a tolerance of the slowly rising hyperammonemia levels can explain the limitation of the clinical presentation in our patient to the ADHD symptoms. The primary systemic carnitine deficiency can also contribute to a dysregulation of the beta oxidation cycle leading to elevations in polyunsaturated long-chain fatty acids, saturated very-long-chain fatty acids, and lipofuscin deposits in the prefrontal cortex, which can also contribute to the decline in attention and higher cognitive functions.[14]

Conclusion

SLC22A5 encodes a plasma membrane carnitine transporter crucial for intracellular carnitine homeostasis and mitochondrial β-oxidation. Pathogenic variants lead to a systemic but reversible energy deficiency at the biochemical and neurological levels varying between severe encephalopathy to a mere learning disability.

Even though learning disabilities especially ADHD are widely considered as psychosocial disorders, the search for underlying organic causes is advised, even if major neurological or metabolic symptoms are absent. The risk of the occurrence of these diseases increases exponentially in closed or highly consanguineous societies, especially that the genotype-phenotype correlation is very variable, leading sometimes to a tolerance of substrate intoxication like the severe hyperammonemia in the case of our patient. The symptoms can sometimes be easily reversible with the appropriate management depending on the affected gene.

Conflict of Interest

None of the authors has a conflict of interest with the material presented in this paper.

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