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Review Article

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Primary Carnitine Deficiency and Autism Spectrum Disorder is there a Relationship?

José Guevara-Campos[1*] and José Guevara-González[2]

[1]*Felipe Guevara Rojas, Hospital, Pediatrics Service. El Tigre-Anzoátegui- Venezuela.6050.*

[2]*Miguel Pérez Carreño Hospital, Neuropediatrics Service, Caracas Venezuela 1020.*

[*]Corresponding author

José Guevara-Campos, Felipe Guevara Rojas, Hospital, Pediatrics Service. El Tigre-Anzoátegui- Venezuela.

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Abstract

Carnitine plays essential role in energy metabolism .Systemic primary carnitine deficiency is a genetic disorder caused by decreased or absent organic cation transporter type 2 (OCTN2) carnitine transporter activity, resulting in low serum carnitine levels and decreased carnitine accumulation inside cells. The decrease carnitine results in impaired fatty acid oxidation.

Primary carnitine deficiency presents a hypoketotic, hypoglycemia and hepatic encephalopathy. Recently, primary carnitine deficiency has been associated with neurodevelopmental disorders including autism spectrum disorders. A seven year-old schoolgirl with intellectual deficit, autistic features and primary carnitine deficiency has been reported. A significant decrease in carnitine levels has been shown in patients with autism and this has been related to the existence of a mitochondrial disease and more severe autism.

The early identification of patients with low levels of carnitine or primary carnitine deficiency, with the different methods of measuring free carnitine, including tandem mass spectrometry could help to identify these patients early and achieve an early treatment and better neurological prognosis, because autism spectrum disorders may be preventable in this subgroup.

We hope that this paper is useful to neurologists and pediatricians, and may give them more reason to suspect a diagnosis of PCD and autism.

Keywords: Carnitine, Primary Autism, Encephalopathy, Mitochondrial, Disease Metabolism

Carnitine is a hydrophilic quaternary amine that plays an essential role in energy metabolism. The function of carnitine is the transfer of long chain fatty acids to mitochondria for subsequent B oxidation, especially in tissues like the liver, skeletal muscles, and cardiac muscles (1).When fatty acids cannot be used, glucose is consumed without regeneration via gluconeogenesis, resulting in hypoglycemia [1, 2].

The Systemic carnitine deficiency is rare disease, with a frequency of 1:40,000 to 120,000 newborns. Is an autosomal recessive disorder, encoded by the SLC22A5 gene on chromosome 5q31 [2].

Primary carnitine deficiency classically presents a hypoketotic, hypoglycemia, and hepatic encephalopathy, or later in life with skeletal and cardiac myopathy or sudden death from cardiac arrhythmia usually triggered by fasting or catabolic state [3, 4].

Patients with autism spectrum disorders (ASD) present deficits in social interactions and communication, they also show limited and stereotypical patterns of behaviors and interests. The pathophysiological bases of ASD have not been defined yet.

The causes of these disorders are still poorly understood, but growing evidence suggests that autism is a multifactorial disease influenced by genetic and environmental factors. ASD is associated with several genetic disorders and several studies have uncovered a range of metabolic abnormalities associated with non-syndrome cases of ASD. One of these, the alterations of carnitine and its derivatives [5].

ASD traits are also found in patients affected by several genetic diseases such as Rett syndrome or Angelman syndrome [6].

Metabolic disorders accompanied by altered carnitine biosynthesis have recently been linked to neuropmental disorders, such autism spectrum disorders (ASD)

Recently described a case of ASD girl with primary carnitine deficiency accompanied by intellectual disability, muscle weakness, and repeated episodes of hypoglycemia, autistic features and developmental delay [2].

The links between l-carnitine and autism rely on three major observations: 1.the alteration of mitochondrial function occurring in patients with ASD, 2.The relationships between L-carnitine levels and the severity of autism and, 3.Geneticc aspects of autism associated with L-carnitine metabolism [6].

Filipek et al.,Mostafa et al., and Frye el al., reported a decrease in L-carnitine levels in ASD patients. They described a decrease of almost 50% in L-carnitine levels in ASD children [7- 9].

Children with ASD exhibited an elevation in short-chain and long-chain, but not medium chain, acylcarnitines. This defect in L-carnitine levels is associated with mitochondrial dysfunction [6, 9]. Carnitine binds acyl residues and help in their elimination. This mechanism is essential in binding/removing abnormal organic acids in several organic acidemias and explain the secondary carnitine deficiency that can result from them [3].

Celestino-Sopea et al. identified a deletion of exon 2 of the TMLHE (Trimethyl lysine hydroxylase epsilon), this gene encode the first enzyme in the biosynthesis of carnitine which is located in mitochondria [10].

The high-affinity OCTN2 (SLC22A5 gene) carnitine transporter plays a key role in a carnitine homeostasis [4, 10]. It is highly expressed in the heart, muscle and kidney and operate a sodium-dependent transport of carnitine and a sodium-independent organic cation transport. A defect in the OCTN2 carnitine transporter cause primary carnitine deficiency and results in urinary carnitine wasting, low serum carnitine levels (0-8 μM, normal 25-50 μM) and decreased intracellular carnitine accumulation [2,3,11].

Another potential mechanism involving the role of carnitine in the onset of autism has been propose, it implies a defect in the transport of L-carnitine into the cells. The amino acid transporter SLC7A5, also able to transport carnitine [6, 12].

Patients with primary carnitine deficiency lose most, 10-95% of the filtered carnitine in urine, explaining their mildly reduced plasma carnitine levels [13].

The decreased carnitine results in impaired fatty acid oxidation. Abolished or reduced carnitine transporter activity impairs the proper use of fatty acids as an energy source during periods of fasting or stress [1-6]. If carnitine supplements are not promptly started, patients with primary carnitine deficiency can present with an acute metabolic decompensating early in life [13].

The metabolic presentation is more frequent before two years of age. These children stop eating and become irritable following an upper respiratory tract infection or an acute illness .Subsequently, become lethargic and minimally responsive [4, 14]. If children are not promptly with intravenous glucose, they progress to coma and death.

Approximately half of patients typically present in later childhood around the age of 4 years, with dilated cardiomyopathy, hypotonia, muscle weakness, and elevated CK .Cardiomyopathy in individuals with primary carnitine deficiency, can be progressive and results in death before a diagnosis is established or treatment initiated [15].

Measurements of plasma carnitine levels of children with primary carnitine deficiency will show extremely reduced plasma free carnitine levels (< 5μM).The diagnosis de PCD may be suspected when low plasma carnitine concentration is identified via newborn screening using tandem mass spectrometry [15].

Introducing mass spectrometry, a novel and highly sophisticated technique, mass spectrometry allowed the measurements of free carnitine along with the specific and sensitive determination of different carnitine esters [16].

Carnitine levels in unaffected newborns should normalize within two weeks after birth, therefore, if the initial newborn screen is suggestive of carnitine deficiency, a repeat plasma carnitine analysis should be performed. If the carnitine levels normalize without carnitine supplementation, then there is no additional need to screen the infant for carnitine deficiency [15, 17].

Further confirmation of the diagnosis, however relies a molecular genetic testing of the SLC22A5 gene. Sequence analysis is clinically available and can detect at least one mutation in approximately 70% de affected children [15].However, there is no correlation between genotype and clinical presentation [3].

If molecular and array comparative genomic hybridization (aCGH) fail to detect mutations or large deletions of the gene, then a kin biopsy may be considered to asses carnitine transport in cultured fibroblasts [3,10,15].

Metabolic studies performed enter ASD suggested the involvement of acquired mitochondrial disease in the pathogenesis of subgroup of autism, therefore the observed unique acylcarnitine profiles can be potential biomarkers reflecting the acquired mitochondrial disease in ASD [18].
Patients with Primary Carnitine Deficiency respond to carnitine supplementation, a doses of 100-200 mg/kg /day. The dose of carnitine should be divided in at least 3 daily administrations. The long-term prognosis is favorable as long as children and adults remain carnitine supplements [4, 15].

Malaguarnera and Cauli, suggests that carnitine administration showed some beneficial effects in core symptoms of ASD in patients with non-syndrome forms of autism [5].

Conclusion

Carnitine is essential for mitochondrial fatty acid oxidation. Mutations impairing the function of the OCTN2 transporter result in carnitine deficiency that can present early in life with hypoketotic hypoglycemia, or later in life with cardiomyopathy and arrhythmia. The association of disorders of carnitine biosynthesis with autism raise the possibility that carnitine could have some functions during critical periods of brain development.

Mass spectrometric measurements facilitated the accurate and precise determination of not only free carnitine but also individual acylcarnitines. Allowing the identification of children of risks for developmental of autism.

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