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LETTER TO EDITOR

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Primary carnitine deficiency presenting as intractable seizures

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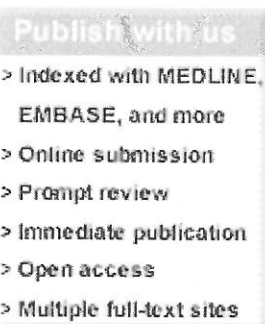
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Sir,



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Mitochondrial β -oxidation of fatty acids is an essential energy producing pathway during increased metabolic demands. Carnitine has an important role in the transfer of long-chain fatty acids into the mitochondria for beta-oxidation, especially in tissues like the liver, the skeletal muscles, and the cardiac muscles.

A 3-month old male infant was admitted with fever and abnormal body movements for one day. There was a history of two episodes of pneumonia since birth; and, 3-4 episodes of subtle seizures per day. His development was normal for his age. There was no history of seizures, consanguinity or neonatal/unexplained infantile deaths in the family. On examination, he had an altered sensorium with fever, tachypnea, tachycardia, seizures and an oxygen saturation of 62%. His vital and anthropometric parameters were normal. He had hypertonia with a decerebrate posturing, the tendon reflexes were brisk and the plantars were bilaterally extensor. He had a short systolic murmur in the left parasternal area, decreased air entry bilaterally in the lungs, and crepitations in the chest. Hepatomegaly was present. On investigation, his hemogram, electrolytes, calcium and cerebrospinal fluid evaluation, and kidney function tests were within normal limits. His blood culture was sterile and the screening tests for the presence of sepsis did not reveal any abnormality. He experienced hypoglycemic episodes, had metabolic acidosis, and had raised transaminases and an elevated creatinine phosphokinase (CPK). His echocardiography showed a left ventricular concentric hypertrophy with minimal pericardial effusion. His ultrasonography showed a hepatomegaly. The MRI of the brain revealed effacement of sulci in bilateral cerebral and cerebellar hemispheres with effacement of the cisterns and the presence of a transtentorial herniation. The patient was managed with mechanical ventilation, intravenous fluids, antibiotics and antiepileptic medication. His clinical and biochemical parameters improved but

seizures persisted. His investigations revealed a deficiency of free plasma carnitine (4.46 mM/l; 4% of the expected values) and acyl carnitine (3.85 mM/l; 4% of the expected values). The proportionate decrease in both these values was diagnostic of a primary carnitine deficiency. The patient was started on L- carnitine supplements at the rate of 100 mg/kg/day in divided doses, and frequent nasogastric feeds supplemented by medium chain triglycerides were added to the diet in sufficient quantities. The child was gradually weaned off from ventilatory support and his antiepileptics were tapered. He was discharged on oral carnitine and frequent feeds enriched with medium chain triglycerides. At follow-up, the patient is doing well with normalization of his clinical and biochemical parameters.

Mitochondrial β -oxidation of fatty acids is an essential energy-producing pathway during prolonged periods of starvation, reduced caloric intake and increased energy expenditure. In these situations, the body derives its major fuel by switching from carbohydrates to fats. The fatty acids are the important sources of energy for the skeletal and cardiac muscles. The end products of fatty acid oxidation are ketone bodies that are an important source of energy for the brain.

Genetic defects have been identified in nearly all the steps of fatty acid oxidation. Carnitine is a naturally occurring hydrophilic amino acid derivative produced endogenously in the kidneys and liver and derived from meat and dairy products in the diet. Its essential role is in the transfer of long-chain fatty acids into the mitochondria for beta-oxidation. The biological effects of carnitine deficiency are not evident until its level is reduced to less than 10-20% of the normal values.

Carnitine deficiency may be primary or secondary. In primary carnitine deficiency, there is deficiency in the plasma membrane carnitine transporter due to the SLC22A5 gene mutation [1] that encodes for carnitine plasma membrane transporter OCTN2. [2], [3] Regulation of the intra mitochondrial free coenzyme (Co) A is affected leading to the accumulation of acetyl-CoA esters in the mitochondria which affects the pathways of intermediary metabolism that require CoA (for example, the Krebs' cycle, pyruvate oxidation, amino acid metabolism, mitochondrial and peroxisomal beta oxidation). The three main areas of involvement include the cardiac muscles, the

central nervous system and the skeletal muscles.

[2] Secondary carnitine deficiency occurs in metabolic disorders (for example, fatty acid oxidation disorders, organic acidemias, conditions like renal tubulopathies and on administration of drugs like valproic acid).






Primary carnitine deficiency presents as a hypoketotic hypoglycemic encephalopathy, often associated with hepatomegaly, elevated liver transaminases, hyperammonemia, cardiomyopathy, pericardial effusion, muscle weakness, gastrointestinal dysmotility, with recurrent episodes of abdominal pain and diarrhea along with a hypochromic anemia and recurrent infections. [2] Secondary carnitine deficiency may have additional clinical manifestations of the primary pathology. Primary carnitine deficiency can be diagnosed by estimating the plasma carnitine levels. The carnitine level in plasma in this condition is usually less than 5% of normal and acylcarnitines are proportionately reduced. [4] An enzyme assay may be done for demonstrating an enzymatic defect. The molecular diagnosis provides information regarding the mutated gene responsible for the synthesis of the carnitine transporter that is defective in primary carnitine deficiency.

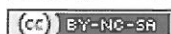
The treatment of primary carnitine deficiency includes stabilization of vital parameters, intravenous carnitine supplementation and subsequently, lifelong medical therapy with oral carnitine at the rate of 100 mg/kg/day. [5], [6] A carnitine rich diet and frequent meals are advised and situations of stress and a prolonged period of starvation are to be avoided. In secondary carnitine deficiency, the management of the primary metabolic defect essentially comprises of administering the dietary regimens recommended specifically for the management of this condition. [5]

Carnitine deficiency has a good long term outcome if diagnosed early and managed with adequate carnitine supplementation and a diet rich in carnitine.

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