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MR in Children with L-Carnitine Deficiency

J. E. Thompson, M. Smith, M. Castillo, M. Barrow, and S. K. Mukherji

PURPOSE: To describe the MR imaging findings in five children with proved L-carnitine deficiency.

METHODS: MR imaging studies (five without contrast, two with contrast) were obtained in five children (mean age, 9 years) who presented with stroke symptoms and who proved to have L-carnitine deficiency as established by serum levels. **RESULTS:** In three of five patients, infarctions were confined to arterial distributions; one patient had a hemorrhagic infarction in one frontoparietal region; and one patient had only nonspecific periventricular white matter T2 hyperintensities. Serum L-carnitine levels normalized after correction; sequelae included seizures in two patients, hemiparesis in one patient, normal outcome in one patient, and death in one patient.

CONCLUSION: L-Carnitine deficiency is a rare metabolic disorder leading to cerebral infarctions, as seen in our five patients, and should be considered in the differential diagnosis of children who have had a stroke, particularly when associated with hypoglycemia and myopathy.

Index terms: Brain, infarction; Brain, magnetic resonance; Children, diseases; Metabolic disorders

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Cerebral infarctions in children occur with an approximate frequency of 2.5 per 100 000 persons (1). Most common underlying causes of infarction are thrombi, emboli, vasculitis, trauma (dissections), hematologic disorders (including coagulopathies), metabolic disorders, and idiopathic sources. L-Carnitine deficiency is a rare metabolic disorder that is characterized mainly by myopathy, nonketotic hypoglycemia, cardiomyopathy, recurrent infections, hepatic dysfunction, and in some patients, particularly those with the systemic form of the disease, encephalopathy and coma, as in a Reye-like syndrome (2). One case of a patient with L-carnitine deficiency who presented with a cerebral infarction has been reported (1). We describe the magnetic resonance (MR) imaging findings in five patients with L-carnitine deficiency.

Subjects and Methods

Our study group consisted of five children, three girls and two boys, newborn to 15 years old (mean age, 9 years), who presented with stroke symptoms. All patients underwent MR imaging, which consisted of noncontrast sagittal and axial T1-weighted studies, 500/16/1 (repetition time/echo time/excitations), axial T2-weighted studies (2300/20,80/1), and, in two cases, contrast-enhanced axial and coronal T1-weighted studies (500/16/1). One patient also had three-dimensional time-of-flight MR angiography of the circle of Willis, and one patient had conventional catheter angiography. All MR studies were performed on a 1.5-T unit. The MR images were reviewed with special attention to presence, size, number, pattern of enhancement, and distribution of infarctions. The medical records of all five patients were also reviewed.

Serum L-carnitine levels (including total L-carnitine, free L-carnitine, and acylcarnitine) were obtained and quantified by gas chromatography-mass spectrometry methods. Normal levels for these metabolites are as follows: total plasma carnitine, 47 nmol/mL (deviation of 11); free carnitine, 38 nmol/mL (deviation of 11); and acylcarnitine, 95 nmol/mL (deviation of 5).

Results

MR images revealed infarctions in four of five patients. In a newborn (case 1), an area of increased T1 signal intensity was seen in the right perirolandic region confined to the gray matter and presumed to be a hemorrhagic infarction

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(Fig 1). T2-weighted images in this patient were unremarkable. In a different patient (case 2), who presented with right hemiparesis, MR images showed an area of increased T2 signal intensity involving the distribution of the left middle cerebral artery including the basal ganglia (Fig 2A and B). An MR angiogram in this patient was significant for stenoses in two branches of the ipsilateral middle cerebral artery



Fig 1. Case 1: axial T1-weighted (500/16/1) MR image shows increased signal intensity (arrow) in right perirolandic region, suggesting hemorrhagic infarction in cortex.

tery immediately after the trifurcation (Fig 2C). Another patient (case 3) had a right parietal infarct with surrounding edema; no enhancement was present after administration of contrast material (Fig 3). A conventional angiogram showed prominent vessels in the stroke region presumed to be caused by hyperemia. In case 4, MR T2-weighted images showed increased signal intensity in the right calcarine cortex (Fig 4). After contrast administration, no enhancement was present. In the last patient (case 5), MR images showed only nonspecific periventricular white matter T2 hyperintensities. The clinical information, MR findings, and outcomes in these patients are described in the Table. All patients had documented plasma L-carnitine deficiencies (see above). After carnitine supplementation, levels of all three metabolites in plasma returned to normal.

Discussion

The L-carnitine family is composed of short-, medium-, and long-chain acyl esters (3). L-Carnitine is synthesized by the liver and kidneys from dietary methionine and lysine or may be obtained directly from food. It is stored in striated muscles. Dietary L-carnitine is necessary to maintain adequate serum levels in all age

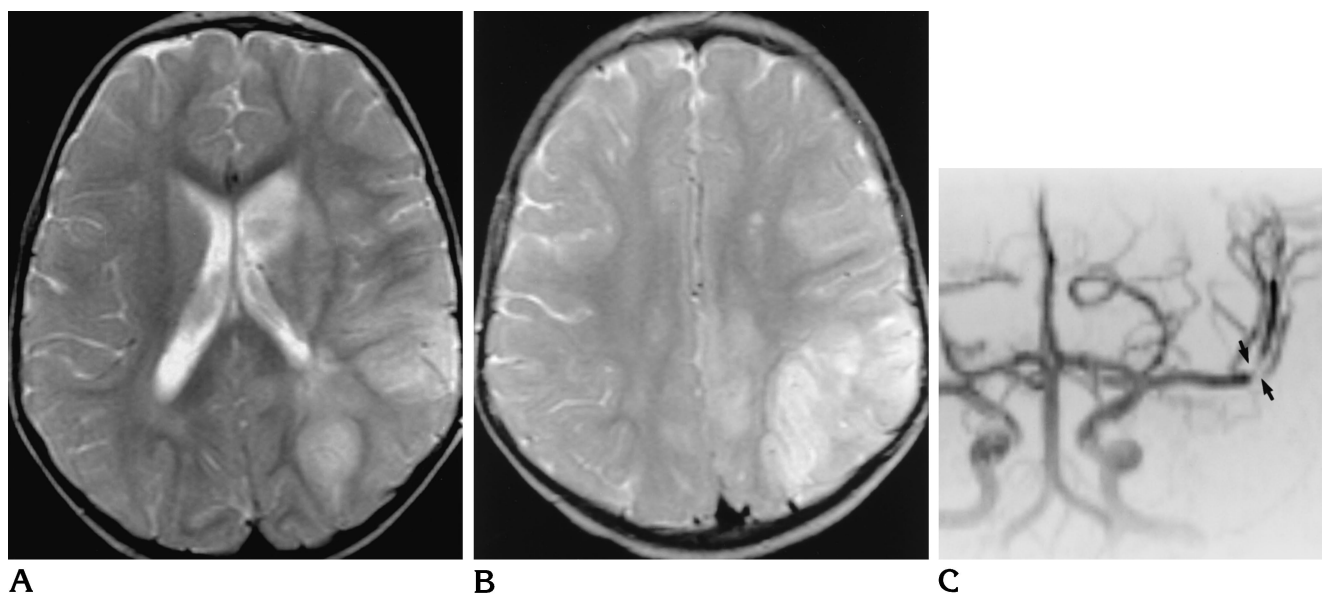


Fig 2. Case 2.

A, Axial T2-weighted (2300/80/1) MR image shows increased signal intensity and thickening (edema) of cortex in left temporooccipital region as well as in the head of the ipsilateral caudate nucleus.

B, Axial T2-weighted (2300/80/1) MR image shows that superior aspect of left-sided infarct has a typical wedge-shape configuration.

C, Frontal projection of time-of-flight three-dimensional MR angiogram shows focal stenoses (arrows) at branches of left middle cerebral artery at trifurcation.

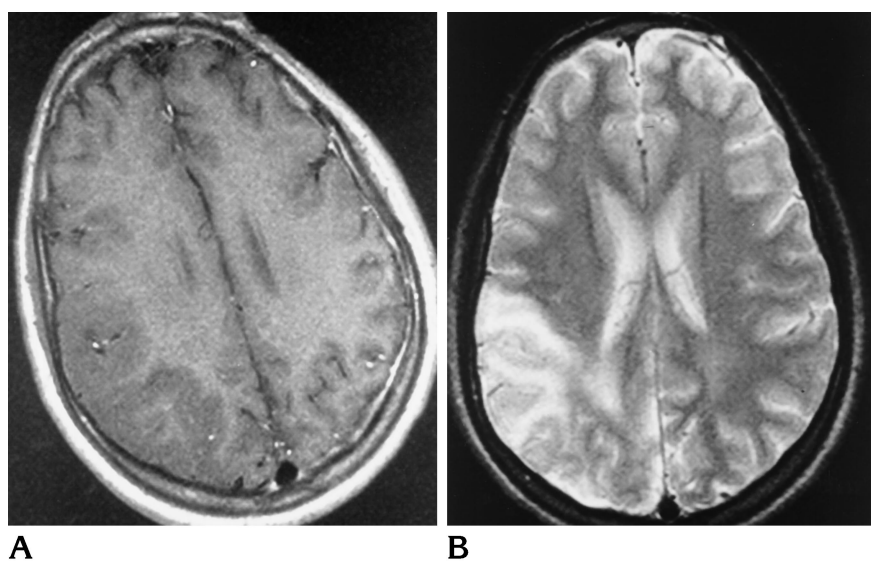


Fig 3. Case 3.

A, Axial postcontrast T1-weighted (500/16/1) MR image shows swollen right parietal cortex in wedge-shape configuration, typical of infarction.

B, Axial T2-weighted (2300/80/1) MR image at level slightly lower than in A shows typical right parietal hyperintense infarction.

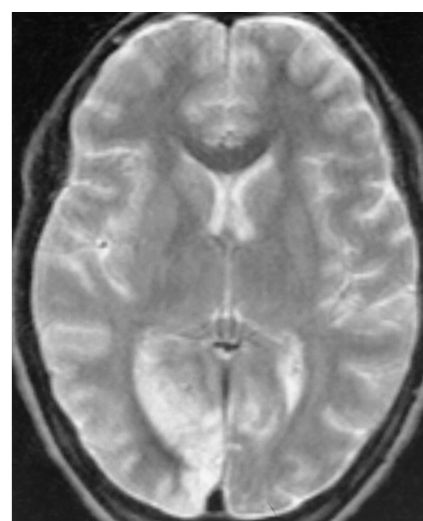


Fig 4. Case 4: axial T2-weighted (2300/80/1) MR image shows increased signal intensity in right occipital lobe involving calcarine cortex, compatible with infarction.

Clinical and imaging features of patients with L-carnitine deficiency

Patient	Sex/Age	Symptoms	MR Findings	Clinical Outcome
1	M /20 d	Loss of consciousness/hypoglycemia*/cardiomyopathy	R perirolandic hemorrhagic infarct	Normal
2	M /16 mo	Hemiplegia/cardiomyopathy	L middle cerebral artery infarct/middle cerebral artery stenoses (MR angiography)	Hemiparesis
3	M /14 y	Seizures/myopathy†	R parietal infarct	Seizures, dementia
4	F /15 y	Seizures/myopathy†	R occipital infarct	Seizures
5	F /10 mo	Failure to thrive/hypoglycemia*/myopathy†	Periventricular white matter high signal	Died

* Hypoglycemia was defined as glucose level below 1.2 mmol/L for case 1 and below 3.6 mmol/L for case 5.

† Myopathy was characterized by systemic weakness and hypotonia.

groups. L-Carnitine is an essential nutrient in children and in patients undergoing total parental nutrition (4). Its functions include the transport of long-chain fatty acids into the mitochondria for beta oxidation, which results in energy-providing compounds needed for metabolism. This is accomplished by modulating a rise in the acyl coenzyme A/coenzyme A (acyl-CoA/CoA) ratio, which relieves inhibition of intramitochondrial enzymes involving amino acid and glucose catabolism. L-Carnitine is also essential in the export of certain acyl-CoA groups and toxic intermediates from the mitochondria and peroxisomes as well as the regeneration of free CoA, which is essential in fatty acid oxidation (5). In the presence of L-carnitine deficiency,

accumulation of acyl-CoA derivatives disrupts the normal acyl-CoA/CoA ratio, resulting in inhibition of important enzymatic reactions (6). Additionally, an equilibrium between acyl-CoA and acylcarnitine prevents ketoacidosis. It is believed that L-carnitine may also play a role in the inhibition of erythrocyte aggregation (6). In summary, L-carnitine is involved in the oxidative use of fatty acids, ketone bodies, glucose, and various amino acids. The most important consequence of its deficiency is impaired energy metabolism.

L-Carnitine deficiency may be congenital or acquired (6). L-Carnitine and its metabolites are most commonly measured in plasma but may also be quantitated in bile and by skeletal mus-

cle biopsy. Congenital deficiency is of three types, which include myopathic, systemic, and organic aciduria. Acquired deficiency is commonly due to excessive loss or inadequate dietary intake of L-carnitine (particularly in patients with phenylketonuria) and may also be drug-induced (usually seen with valproic acid administration, which increases the excretion of L-carnitine) (6, 7). Treatment consists of dietary supplements and a high-carbohydrate/medium-chain triglyceride diet. Thiamine supplements may also be helpful. Despite therapy leading to normalization of L-carnitine levels, the eventual outcome of the disease is probably not significantly altered (8).

L-Carnitine deficiency may result in sudden infant death syndrome. Some patients present with a Reye-like syndrome, which includes nausea, vomiting, liver failure, mental status abnormalities, encephalopathy, and coma. This may be precipitated by intercurrent childhood illnesses, stress, and immunizations (2, 9). A cerebral infarction has been described in one case (1). Normally, fasting will induce hypoglycemia that initiates fatty acid oxidation and ketosis. In the presence of L-carnitine deficiency there is impaired mitochondrial enzymatic transport, impaired beta oxidation, and secondary accumulation of intraorganelle toxic metabolites that may produce the associated neurologic symptoms. Other metabolic disorders that may result in cerebral infarctions include MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), Leigh disease, organic acidemias, and diabetes mellitus, all of which are the result of either diminished or unavailable energy metabolism at the mitochondrial level. Hyponatremia may also induce cerebral infarctions in children (10, 11).

In our patients, the main symptom was stroke. This is unusual: we found only one reported patient with L-carnitine deficiency who presented with cerebral infarction (1). In our experience, five of 55 children with cerebral infarctions (excluding periventricular leukomalacia) seen at our institution during the last 4-year period had L-carnitine deficiency. We believe that this high percentage is due to the tertiary nature of our institution. Nevertheless, it is important to consider L-carnitine deficiency in the differential diagnosis of metabolic diseases and strokes in children, because it is a potentially treatable disease. MR imaging, we believe, is

the best method to document the presence of cerebral infarctions in children. MR images in our patients had only the typical findings associated with cerebral infarctions. No unique imaging features for L-carnitine deficiency were identified. In the literature, MR imaging findings that have been described for related deficiencies (3-ketothiolase) include increased T2 signal intensity in the posterolateral putamina. In two patients, delayed myelination was documented by MR imaging (12). In one child, MR images showed a cerebral infarction and atrophy (1).

In summary, L-carnitine deficiency is a rare metabolic abnormality that, in children, may manifest as hypoglycemia and cerebral infarctions. Because L-carnitine and related metabolites can be quantitated in plasma, it should be added to the list of metabolic disorders in children who present with stroke, particularly those associated with hypoglycemia and myopathy.

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