Volume 10, Supplement Number 2, November 1995

Journal of Child Neurology

An Interdisciplinary Forum for Child Neurology, Developmental Neurobiology, Pediatric Neuroscience, and Developmental and Behavioral Pediatrics

L-Carnitine

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Publication of this supplement was made possible by a grant from Sigma-Tau Pharmaceuticals, Inc.

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ISSN 0883-0738

Original Article

Carnitine Deficiency in Epilepsy: Risk Factors and Treatment

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ABSTRACT

Numerous studies have shown that plasma carnitine levels are significantly lower in patients taking valproate than in controls. Free carnitine deficiency is not uncommon in these patients and also occurs in newborns with seizures and in patients taking other anticonvulsant drugs. Carnitine deficiency in epilepsy results from a variety of etiologic factors including underlying metabolic diseases, nutritional inadequacy, and specific drug effects. The relationship between carnitine deficiency and valproate-induced hepatotoxicity is unclear. Carnitine treatment does not always prevent the emergence of serious hepatotoxicity, but it does alleviate valproate-induced hyperammonemia. These studies suggest that specific risk factors for carnitine deficiency can be identified. Preliminary data suggest that carnitine treatment may benefit high-risk, symptomatic patients and those with free carnitine deficiency. Carnitine treatment is not likely to benefit low-risk, asymptomatic patients and those with normal carnitine levels. (*J Child Neurol* 1995;10(Suppl):2S32–2S39).

Controversy persists about the role of carnitine in epilepsy, despite research on the subject that accelerated from the initial reports in 1982 to the present time and now includes many published studies. Clinicians still need answers to the questions of when to measure carnitine levels and when to provide treatment with carnitine. The purpose of this review is to summarize available information as it relates to these clinical questions. In particular, this review will seek to identify risk factors that might help clinicians to anticipate carnitine deficiency and to predict the response to treatment.

CARNITINE LEVELS

Table 1 summarizes data from some of the articles that investigated the occurrence of carnitine deficiency in patients with epilepsy. In general, mean plasma levels of total carnitine and free carnitine were lower in patients taking valproate than in controls. These differences were statistically significant in most studies[2–12,14–17] but not in a few others.[13,18] Two studies that examined carnitine levels longitudinally in patients before and after starting valproate showed that levels were significantly lower after taking valproate.[10,12] When examined separately, carnitine levels were lower in patients taking valproate plus other anticonvulsant drugs than in patients taking valproate alone.[3,6–9] In several studies, carnitine levels in patients taking valproate alone did not differ significantly from those of controls.[7,13,14] Most studies showing significantly lower carnitine levels in valproate-treated patients have investigated children. One study showed that carnitine levels in valproate-treated younger children (1 to 10 years old) were significantly lower compared to older children (10 to 18 years old).[19] Free carnitine deficiency was found in 13 of 18 newborn infants with seizures.[20] Significantly lower carnitine levels have also been reported in valproate-treated adults.[6,7]

Significantly lower carnitine levels have been reported in patients not taking valproate who were taking other anticonvulsant drugs, such as carbamazepine, phenytoin, or phenobarbital.[6,8] Other studies have found no difference, however.[7,13,14]

Several questions arise regarding the significance of these data. One is the validity of plasma carnitine levels as a measure of total body carnitine status. In some valproate-treated patients with normal plasma carnitine levels, muscle carnitine levels were significantly lower than in controls not treated with valproate.[21] These data (though unconfirmed) are not surprising, because 90% of total body carnitine is in muscle tissue, and the concentration of carnitine in muscle is as much as 10 times higher than in blood.[22] If blood carnitine levels fall late in the course of total body carnitine depletion, then it would make sense that muscle carnitine levels might be low while blood levels were still normal. Later in the course,

Received May 2, 1995. Received revised June 30, 1995. Accepted for publication July 5, 1995.

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Table 1. Carnitine Levels With Valproate Therapy*

	Subjects Taking VPA					*Controls*				
Source	*Description*	*n*	*TC*	*FC*	*AC*	*Description*	*n*	*TC*	*FC*	*AC*
Ohtani et al[2]	Age 3–21 yr	14	32.6†‡	28.6‡	—	Epilepsy, other drugs	11	48.6	43.0	—
						Healthy	27	49.0	44.2	—
Laub et al[3]	VPA alone; age 3–21 yr	14	46.4	34.7	11.7	Epilepsy, other drugs	21	47.0	39.9	7.0
	VPA plus other drugs	7	36.4	28.9	7.5	Healthy	21	49.5	41.2	8.0
Morita et al[4]	Age 1–30 yr	12	33.4‡	21.5‡	12.0	*Epilepsy, other drugs*	13	43.6	31.5	12.0
						Healthy	32	60.3	51.7	9.7
Melegh et al[5]	Children	11	24.3‡	16.8‡	—	*Healthy*	11	34.9	26.5	—
Rodriguez-Segade et al[6]	Age 17–65 yr	34	36.9	26.4	10.5	Epilepsy, other drugs	149	48.1	41.2	6.9
						Healthy	49	53.3	47.1	6.2
Beghi et al[7]	VPA alone; age 1–39 yr	54	49.4	36.2	13.1	Epilepsy, other drugs	51	46.9	37.0	10.1
	VPA plus other drugs	55	44.2	33.0	11.2	Epilepsy, no drugs	53	50.8	41.4	9.2
Hug et al[8]	VPA alone	53	35.6‡	27.0‡	8.6‡	Phenobarbital	119	32.7‡	24.6‡	8.1‡
	VPA plus other drugs	18	30.1‡	23.2‡	6.9‡	*Healthy*	32	57.8	42.5	15.3
Opala et al[9]	VPA alone	43	40.8	29.9‡	10.9	Epilepsy, other drugs	43	48.1	36.7	8.9
	VPA plus other drugs	91	29.3‡	21.4‡	8.0	*Healthy*	89	44.2	36.8	8.9
Riva et al[10]	Taking VPA for 45 days	22	50.0‡	35.0‡	15.0‡	*Same patients before VPA*	22	60.0	49.0	11.0
Toksoy et al[11]	Children	24	—	33.5‡	—	*Healthy age/sex matched*	24	—	50.8	—
Zelnik et al[12]	Taking VPA	14	—	29.1‡	—	*Same patients before VPA*	14	—	37.6	—
Murphy et al[13]	Under age 10 yr	13	39.6	—	—	Not stated	—	50.0	—	—

VPA = valproate; TC = total carnitine; FC = free carnitine; AC = acylcarnitine.
*Adapted from Coulter.[1]
†All carnitine values are mean levels in μmol/L.
‡Value is significantly different ($P < .05$) from respective value of the control group shown in italics in the same study.

blood levels might also fall. This argument predicts that when blood carnitine levels are low, muscle carnitine levels should also be low. Thus, total body carnitine depletion would be expected when blood levels are significantly low and might also occur even when blood levels are normal.[21] This argument is fairly speculative and needs to be confirmed.

Another question arises regarding the relevance of data showing significant differences in group means between valproate-treated patients and controls, as shown in Table 1. How many patients actually had plasma carnitine deficiency, defined as a free carnitine level more than two standard deviations below the mean for the controls? Using this definition, plasma carnitine deficiency was found in 4% to 76% of patients taking valproate[2,6–8,13,16] and in 8% to 36% of patients taking other anticonvulsant drugs.[6,8] The reasons for this wide variation in prevalence of plasma carnitine deficiency are unclear but presumably reflect the composition of the study group. Plasma carnitine deficiency appears to be more common in young patients with multiple disabilities[2,5,16] than in relatively healthy adults.[7] Studies that specifically examined the correlation of plasma carnitine deficiency with clinical symptoms found no relationship.[2,7,13,16]

In summary, plasma carnitine levels are decreased in many patients with epilepsy. They are lowest in patients taking valproate plus other anticonvulsant drugs but may also be decreased in patients taking valproate alone and in patients not taking valproate but taking other anticonvulsants, such as phenobarbital, phenytoin, or carbamazepine. Actual carnitine deficiency (free carnitine level more than two standard deviations below the mean) is also fairly common. Low carnitine levels in the blood probably reflect low levels in muscle tissue, but plasma levels may be normal even when tissue levels are low. The published studies suggest that risk factors for carnitine deficiency include young age, multiple disabilities, and presence of valproate plus other anticonvulsant drugs (valproate polypharmacy).

ETIOLOGY

The etiology of carnitine deficiency in patients with epilepsy may be related to nutritional factors, inborn errors of metabolism, or the effects of drugs and other diseases. In some patients, it may reflect the combined effect of several factors.

Carnitine deficiency has been reported in patients with seizures who have a variety of underlying metabolic disorders. These include defects in fatty acid metabolism,[23–27] mitochondrial disorders such as mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) or Leigh disease,[28–32] glutaric aciduria type 2[32] and other organic acidurias,[33] carnitine palmitoyltransferase deficiency,[34,35] and urea cycle disorders. Indeed, a patient with one of these inborn errors of metabolism may decompensate or become comatose when given a drug such as valproate that alters carnitine metabolism.[23,24,36]

Dietary carnitine is found in highest concentration in products derived from red meat and milk, so patients whose diets are deficient in these products may be at risk for nutritional carnitine deficiency. Most intravenous hyperalimentation solutions do not contain carnitine, so patients on total parenteral nutrition for long periods of time are also at risk for nutritional carnitine deficiency. Indeed, carnitine levels were lowest in premature infants with seizures who were on intravenous hyperalimentation.[20] Products used in tube feedings may or may not include carnitine, so clinicians need to check the label of whatever product is being used in order to prevent nutri-

tional carnitine deficiency in patients who rely on these products for most or all of their nutrition. Institutionalized and severely handicapped patients with multiple disabilities, whose dietary intake of carnitine may be deficient for any or all of these reasons, may be particularly likely to have carnitine deficiency. One study found that serum carnitine levels in these patients were significantly correlated with arm circumference, a measure of lean body mass reflecting nutritional status.[4] The etiology of carnitine deficiency in these patients may be multifactorial, including nutritional factors, underlying inborn metabolic errors causing multiple disabilities, and anticonvulsant drug therapy including valproate.

Valproate is a fatty acid and so would be expected to have effects on fatty acid metabolism. The weight gain sometimes associated with valproate therapy has been attributed to inhibition of fatty acid metabolism.[37] In developing mice, administration of valproate interfered with fatty acid oxidation and decreased levels of free coenzyme A in the liver,[38] an effect that was largely prevented by coadministration of carnitine and pantothenic acid.[39,40] Evidence of impaired fatty acid metabolism was also found in humans treated with valproate.[41,42] These metabolic effects were reversed by carnitine treatment in one study[42] but not in another.[41]

As a fatty acid, valproate combines with carnitine to form a valproylcarnitine ester.[43] This and other acylcarnitines are excreted in the urine. Total urinary excretion of acylcarnitines was increased in valproate-treated patients with elevated ammonia levels.[44,45] Acylcarnitine excretion was also increased in relatively asymptomatic patients in one study[10] but not in other studies.[5,46] This increased urinary excretion of acylcarnitine might also interfere with renal reabsorption of free carnitine.[44] In mice, valproate increased urinary excretion of acylcarnitine, whereas other anticonvulsant drugs (phenobarbital, phenytoin, and carbamazepine) increased urinary excretion of free carnitine.[47] These results suggest that the etiology of carnitine deficiency in valproate-treated patients might be related in part to increased renal excretion of carnitine. A similar mechanism might also account for the cases of carnitine deficiency observed in patients treated with other anticonvulsant drugs.

A previous review noted the absence of studies investigating the effects of valproate on carnitine absorption, transport, biosynthesis, and tissue uptake.[1] Tein et al subsequently studied the effect of valproate on carnitine uptake in cultured human skin fibroblasts. They found that valproate induced a reversible, dose-dependent reduction of carnitine uptake by as much as 50%[48,49] and noted that this effect might also account for the observation by others of reduced renal reabsorption of free carnitine. This valproate-induced impairment of tissue carnitine uptake could be an important mechanism causing carnitine deficiency in patients treated with valproate.

In summary, these published studies regarding the etiology of carnitine deficiency suggest that additional risk factors include nutritional inadequacy, reliance on tube feedings or intravenous hyperalimentation, and the presence of an underlying inborn error of metabolism.

VALPROATE-RELATED HEPATOTOXICITY

Several clinical patterns of hepatotoxicity exist in patients treated with valproate[50] and have been associated with carnitine deficiency. Transient elevation of transaminase levels often occurs when patients are first started on valproate. This is usually asymptomatic and typically reverses whether the dose is decreased or not.[51-53] Although this phenomenon has not been associated directly with carnitine deficiency, a possible relationship was suggested by in vitro studies of isolated rat hepatocytes. Valproate exposure induced leakage of transaminases into the culture medium, an effect that could be prevented by cotreatment with carnitine.[54]

A much more serious pattern of hepatic failure occurs rarely but may be irreversible and fatal. More than 100 patients have died from valproate-induced hepatic failure.[55] The risk varies from one in 500 for very young children to one in 120,000 for adults on monotherapy.[53,56] Although the principal risk factors are young age, presence of concomitant neurologic disabilities, therapy with multiple anticonvulsant drugs, and the recent addition (in the past 6 months) of valproate therapy,[53] these risk factors may be absent in as many as one third of fatal cases.[55] Symptoms and signs include anorexia, nausea, vomiting, lethargy, edema, fever, coma, and seizures.[50] Magnetic resonance imaging may show diffuse high signal intensity on T_2-weighted images.[57]

The role of carnitine deficiency in valproate-induced severe hepatotoxicity is unclear. Carnitine deficiency was found in several cases of valproate-induced hepatotoxicity[19] and in some cases of a Reye syndrome–like illness associated with valproate therapy[13,44,58] but not in another case.[3] Carnitine levels may be normal before the onset of hepatic failure, and pretreatment with carnitine may not prevent the onset of symptoms.[59,60] When symptoms developed, treatment with up to 100 mg/kg daily of L-carnitine in several cases did not reverse the symptoms or prevent death.[3,60,61] No controlled clinical trials have been reported of carnitine pretreatment to prevent valproate-associated hepatotoxicity or of acute high-dose carnitine therapy for patients with symptoms of valproate-induced hepatic failure, however. Thus, the absence of reported cases in which carnitine therapy was successful does not necessarily mean this therapy is useless, and further studies are needed. Until controlled studies demonstrate that a defined protocol for carnitine treatment does in fact protect against valproate-induced hepatotoxicity, clinicians should not rely on carnitine treatment to prevent this complication.

Anecdotal evidence suggests that unsuspected underlying inborn errors of metabolism may be a significant risk factor for valproate-induced coma or hepatic failure. Disorders of fatty acid oxidation[23,24] and urea cycle disorders[62] have been reported in patients who survived these

complications of valproate therapy. The author is aware of several unreported sibships in which one sibling died of valproate-induced hepatic failure before another sibling was found to have an inborn error of metabolism. These metabolic disorders may be associated with carnitine deficiency or insufficiency.[63] Preexisting metabolic disease may not account for all cases of valproate-induced hepatic failure, but it appears prudent to avoid giving valproate to patients who may have an inborn metabolic error. This means that in patients whose etiology of seizures is unknown, screening for metabolic disease should precede therapy with valproate.[64] This screening includes measurement of urinary organic acids, blood gases, and blood levels of lactate, pyruvate, carnitine, and ammonia.

Not all cases of valproate-associated hepatotoxicity are fatal, but no consistent differences have been found between those who survive and those who do not.[50] A protocol that included valproate monotherapy and carnitine supplementation was effective in preventing recurrence of hepatotoxicity and controlling seizures in several patients who had survived a previous hepatotoxic episode while on valproate polypharmacy and who had no evidence of underlying metabolic disease.[65] These patients were treated before the newer anticonvulsants such as felbamate or lamotrigine became available, however. This protocol must be considered high risk and warranted only when no reasonable alternatives exist for patients with serious refractory seizures.

The author is not aware of any studies that have examined carnitine levels in patients with other adverse effects of valproate such as pancreatitis or thrombocytopenia. Also, apparently no studies have examined carnitine levels in patients with adverse effects of other anticonvulsant drugs.

VALPROATE-RELATED HYPERAMMONEMIA

Hyperammonemia is a common occurrence in valproate-treated patients who do not have any evidence of hepatic failure. The initial reports emphasized the correlation of hyperammonemia with symptoms of lethargy and hypotonia.[66,67] Similar symptoms were noted in several subsequent reports of valproate-related hyperammonemia[68–71] but not in other studies.[2,7,15,72,73] Ammonia levels were not reported in two patients who developed asterixis on valproate.[74] Although hyperammonemia without hepatic failure is almost always reversible, one unreported case with a fatal outcome is known to the author. As a result of these studies, the clinical significance of hyperammonemia is controversial, and some authors consider it to be of little significance.[50,73] Hyperammonemia is surely not good, but it is unclear whether it is bad or always warrants a change in therapy. For example, the author does not change therapy if the patient is asymptomatic and the ammonia level is less than twice the normal level.

The mechanism of valproate-related hyperammonemia appears to be related to inhibition of carbamoyl phosphate synthesis and urea formation,[72,75] as well as to increased renal ammonia production.[76,77] It appears to be more common in patients on multiple anticonvulsant drugs including valproate than in patients on valproate alone.[1,78] Hyperammonemia was correlated with carnitine deficiency in some studies[3,14,15] but not in others.[3,7,15,17,46] Animal studies showed that carnitine treatment prevented or reversed valproate-related hyperammonemia.[79–84] Carnitine treatment also reversed hyperammonemia in several human studies.[2,15]

These data suggest that a reasonable clinical approach is to measure ammonia levels in patients taking valproate who develop symptoms of altered consciousness, hypotonia, asterixis, or ataxia. If the ammonia level is increased and alternative anticonvulsant therapy is available, valproate should probably be discontinued. If the ammonia level is increased and continued valproate therapy is indicated, withdrawal of other anticonvulsant drugs (valproate monotherapy) could be attempted first. If hyperammonemia persists, treatment with carnitine could then be provided.

CARNITINE TREATMENT

Carnitine treatment does not appear to be indicated for every patient taking valproate, so a risk-screening strategy seems warranted to identify patients most likely to benefit from treatment with carnitine.[85] Table 2 identifies risk factors that might be expected to predict carnitine deficiency, based on the data reviewed above. Young children (less than 10 years old) appear to have a greater risk than older children and adults. Patients with mental retardation who have multiple neurologic disabilities, such as cerebral palsy, microcephaly, or blindness, and who are nonambulatory are more likely to have carnitine deficiency than are patients with mental retardation who are robust and healthy. Patients who are malnourished or underweight or whose diets are low in carnitine-containing products, including those on intravenous hyperalimentation or on tube feedings not supplemented with carnitine, are at risk for nutritional carnitine deficiency. Numerous studies have shown that carnitine levels are lowest in patients taking multiple anticonvulsant drugs including valproate, so these patients are at risk for carnitine deficiency. The risk appears to be less in those on valproate monotherapy or on other anticonvulsant drugs,

Table 2. Risk Factors for Carnitine Deficiency

Young age (less than 10 years old)
Multiple neurologic disabilities (mental retardation, cerebral palsy, blindness, microcephaly)
Nonambulatory status
Underweight (decreased weight for height)
Diet low in meat and dairy products
On tube feeding or intravenous hyperalimentation
Taking multiple anticonvulsant drugs including valproate
Hyperammonemia
Hypoglycemia
Metabolic acidosis

but carnitine deficiency can occur in these patients as well. Hyperammonemia was correlated with carnitine deficiency in several studies. Hyperammonemia, hypoglycemia, and metabolic acidosis are risk factors for carnitine deficiency because they may indicate the presence of an underlying inborn error of metabolism.

When the risk factors shown in Table 2 were assessed in 38 children with epilepsy who had plasma carnitine levels measured, there was a significant inverse correlation between the number of risk factors present and the carnitine level. Carnitine levels were lowest in those with the greatest number of risk factors present. All children with less than two risk factors had normal carnitine levels, whereas all children with five or more risk factors had carnitine deficiency.[86]

Table 3 shows the effects of carnitine treatment on symptoms and signs in children with two or more of the risk factors shown in Table 2.[86] Clinical improvement was noted in more than 50% of children with symptoms of apathy, lethargy, listlessness, anorexia, constipation, nausea, and vomiting. Improvement was also noted in some children with symptoms of weakness and hypotonia, and some children had fewer seizures. Carnitine levels were not measured in all children before treatment, so correlation of the clinical response with preexisting carnitine status was not possible. This was an unblinded, uncontrolled study using varying doses of carnitine, and the response was measured clinically, so the results should be interpreted with caution. They do provide some preliminary support for further controlled trials of carnitine therapy in patients at risk for carnitine deficiency. The risk factors shown in Table 2 could be used to identify appropriate candidates for such trials.

Kelley noted the paucity of good scientific data on the effects of carnitine therapy in patients with epilepsy and called for more carefully controlled clinical trials to examine the benefits of this therapy.[87] Only one such study has been reported so far. This study examined the effects of carnitine therapy in 47 children with epilepsy. Seventeen were taking valproate alone, five were taking valproate plus other anticonvulsant drugs, and 15 were taking carbamazepine alone. All had normal carnitine levels, all were asymptomatic, and their baseline well-being was rated by their parents as above average on a scale devised by the investigators. Using a double-blind, placebo-controlled crossover design, the investigators showed no significant improvement in well-being when the children were taking carnitine.[88] These results underscore the importance of a risk factor approach to identifying patients for carnitine treatment; the subjects in this trial were asymptomatic and would not be considered at risk for carnitine deficiency or expected to benefit from carnitine therapy. Although the number of subjects in this study was small, the results provide no support for carnitine treatment of asymptomatic children taking valproate. The results also suggest that carnitine treatment is not likely to benefit patients with normal carnitine levels or patients with minimal risk of carnitine deficiency. Given the design of the study, however, these results should not be misinterpreted to predict that carnitine treatment would be equally ineffective in symptomatic patients and in patients who are at risk for carnitine deficiency. More controlled clinical trials of carnitine treatment are needed that explicitly target these substantially different populations.

Table 3. Results of Carnitine Therapy in 20 Children With Epilepsy Who Had Two or More Risk Factors for Carnitine Deficiency

Symptom or Sign Examined	*Present Before Treatment, no.*	*Improved After Treatment, no. (%)**
Muscle weakness	13	2 (15)
Muscle pain or tenderness	0	— (—)
Hypotonia	7	2 (29)
Incoordination	12	2 (17)
Frequent seizures	16	5 (31)
Lethargy	11	7 (64)
Listlessness	11	6 (55)
Apathy	13	7 (54)
Poor concentration	7	1 (14)
Headaches	0	— (—)
Loss of appetite	8	7 (88)
Nausea or vomiting	6	5 (83)
Constipation	4	3 (75)

*One child was worse because of irritability and agitation.

Most studies have reported that carnitine treatment had no effect on blood levels of valproate,[15,89] but one study reported a decrease in the valproate half-life after carnitine treatment.[90] Carnitine is usually well tolerated but occasional adverse effects include a "fishy" body odor, nausea, and diarrhea. Indeed, some parents elect to continue carnitine treatment for their children primarily because of the apparent improvement in gut motility and reduction in constipation. The benefits and adverse effects of very large doses of carnitine in patients with metabolic disease remain controversial.[87]

CONCLUSIONS

The purpose of this review was to summarize the available data in order to help clinicians answer the questions of when to measure carnitine levels and when to provide treatment with carnitine. Two conclusions are immediately available: carnitine deficiency is not uncommon in patients with epilepsy, and some patients appear to benefit from carnitine treatment. Faced with a particular patient, however, clinicians need to know whether that patient is likely to have carnitine deficiency and whether that patient is likely to benefit from carnitine treatment.

The data reviewed suggest that it may be possible to identify risk factors for carnitine deficiency in patients with epilepsy. These risk factors include young age, inadequate nutrition, multiple neurologic disabilities, therapy with multiple anticonvulsant drugs including valproate, hyperammonemia, and evidence of an underlying inborn error of metabolism (Table 2). Thus, measurement of carnitine levels is not necessary in all patients. When these risk factors are absent, carnitine deficiency appears to be unlikely, and measurement of carnitine levels is generally unnecessary. When several of these risk factors are pre-

sent, the likelihood of carnitine deficiency is increased and measurement of carnitine levels is worth considering. Mildly reduced carnitine levels that are still within the normal range may be of no clinical significance, but careful attention is warranted when plasma carnitine deficiency is present (free carnitine level more than two standard deviations below the mean for healthy controls). Muscle carnitine deficiency may exist even when blood carnitine levels are normal, but muscle biopsy for measurement of carnitine levels is ordinarily not indicated in patients with epilepsy.

Carnitine treatment will probably be ineffective and is not indicated if the patient is asymptomatic, has few or none of the risk factors listed in Table 2, or has carnitine levels in the normal range. Carnitine treatment is worth considering if the patient has free carnitine deficiency, hyperammonemia, or symptoms of apathy, lethargy, listlessness, anorexia, constipation, nausea, vomiting, weakness, or hypotonia. The patient's clinical response to carnitine therapy should be monitored carefully, and carnitine may be discontinued if there is no evidence of improvement. Routine administration of carnitine to young children taking valproate in order to prevent hepatic failure does not appear to be warranted, because there is no evidence that it is protective and hepatic failure has occurred in children taking carnitine. Acute administration of carnitine to patients with valproate-induced hepatic failure is generally recommended, however.

Clearly, more studies are needed to investigate the role of carnitine deficiency and its treatment in patients with epilepsy. These studies should be well designed and should include carefully controlled clinical trials in appropriately selected patients.

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