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Case Report

L-Carnitine as a treatment of lethargy in children with chronic neurologic handicaps

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We present five cases of children with severe neurologic handicaps whose management was complicated by excessive lethargy. Treatment with L-carnitine in a dosage range of 35–50 mg/kg/day resulted in a marked improvement in alertness and arousability. In four cases, when L-carnitine was discontinued for a month, they all promptly became lethargic. When L-carnitine was re-started, the lethargy resolved and the improvement has been maintained for up to 14 months. In three children who were tested, serum carnitine levels (total and free) were normal before starting L-carnitine treatment.

Key words: L-Carnitine; Lethargy

1. INTRODUCTION

Carnitine is essential in mitochondrial energy metabolism. It has two principal functions: (i) to transport long-chain fatty acids into the mitochondrion; (ii) to help regulate the intramitochondrial ratio of acetyl-coenzyme A (CoA) to free CoA (reviewed in [1]). Carnitine deficiency conditions may be primary, such as those associated with inborn errors of metabolism, or secondary, such as those associated with inadequate intake or those that are induced by medications. Clinical symptoms of carnitine deficiency may include: myopathy, cardiomyopathy and Reye syndrome-like encephalopathy. In a child with Rett syndrome, with normal total and free serum carnitine levels, L-carnitine treatment resulted in improved neurologic functioning, especially in improvement in her level of alertness [2]. We decided to treat four children who were developmentally disabled and who were excessively lethargic, with L-carnitine to see if their level of alertness could likewise be improved.

2. MATERIALS AND METHODS

2.1. Case 1

This is a 16-year-old female. At the age of 4 months, after receiving a DPT and oral polio immunization, she developed seizures and respiratory insufficiency. Her spinal fluid analysis revealed pleocytosis (30 lymphocytes per mm^3) with normal chemistries and negative cultures. She was treated with ampicillin, isoniazid and streptomycin. EEG tracings revealed hypsarrythymia. She eventually developed microcephaly, spastic quadriparesis and an ongoing seizure disorder which was controlled with valproic acid and carbamazepime. Psychologic evaluation revealed a Bayley Scale of Infant Development IQ of below 10 (profound mental retardation) and Vineland Adaptive Behavior Scales of between 0 and 1 months in communication, daily living skills and socialization. The medications that she was taking were 2,100 mg per day valproic acid, 450 mg per day carbamazepime, and 30 mg per day clorazepate di-potassium for spasticity. Her routine blood chemistries, thyroid function tests, liver function tests,

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venous ammonia level, serum lactate level, blood counts and anti-convulsant levels were all normal.

She was noted to be chronically very lethargic and difficult to arouse. Before starting L-carnitine treatment her total serum carnitine level was 73.9 μg/dl (normal 30–73) and free serum carnitine level was 62.4 μg/dl (normal 19–60; determinations were performed by the Mayo Clinic Laboratories). She was treated with 750 mg of L-carnitine twice a day (35 mg/kg/day). Within a month she was much more alert, more easily arousable and improved her school goals. She made significant improvements in responding to vocal stimulation, in tracking objects with her eyes and in responding to tactile stimulation. This improvement was maintained for 7 months. When the L-carnitine was discontinued, within a week she became much more sleepy and lethargic. Her school performance decreased. When the L-carnitine was re-started 1 month later, she again became more alert, responsive and improved in school. The improvement has been maintained for an additional 14 months. There have been no complications from the L-carnitine. In particular there was no change in seizure frequency.

2.2. Case 2

This is a 10-year-old male with a congenital encephalopathy which manifested itself as a severe seizure disorder starting at 2 days of age and marked cerebral atrophy on CT scans. Extensive metabolic evaluations have failed to reveal an etiology for this child's neurologic handicap. He has spastic quadriparesis. Psychologic evaluation revealed a Slosson IQ of 9 (profound mental retardation). Michigan Early Intervention Developmental Profile ranged from 8 months (cognition) to 16 months (toileting skills). The medication that he was taking was 1,125 mg per day valproic acid. His routine blood chemistries, thyroid function tests, liver function tests, venous ammonia level, serum lactate level, blood counts and anti-convulsant level were normal.

He was noted to be chronically lethargic and difficult to arouse despite adequate rest at night. Before starting L-carnitine his total serum carnitine was 38.9 μg/dl and free serum carnitine was 33.7 μg/dl (both results normal; determinations were performed by the Mayo Clinic Laboratories). He was treated with 650 mg of L-carnitine three times a day (50 mg/kg/day). Within a month he was much more alert, particularly during the evening hours. He also made much better eye contact. After 2 months the L-carnitine was discontinued. Within a week he became much more lethargic, would sleep through the evening dinner and lost eye contact. When the L-carnitine was re-started after 1 month, he became more alert, slept less in the evening and regained eye contact, an improvement which has been maintained for an additional 9 months. There have been no complications from the L-carnitine. In particular, there was no change in seizure frequency.

2.3. Case 3

This is a 21-year-old female who developed rubella encephalitis at 2 years and 9 months of age. She was comatose for 1 month. Subsequently she was non-verbal and developmentally delayed but was ambulatory and hyperactive. At the age of 8 years she developed a severe aspiration pneumonia with hypoxic-ischemic encephalopathy. This resulted in her becoming totally non-ambulatory from spastic quadriparesis and having seizures. Psychologic evaluation revealed her Bayley Scale of Infant Development IQ to be below 10 (profound mental retardation) and the Vineland Adaptive Behavior Scales were 0–4 months for communication, daily living skills and socializing. The medications that she was taking were 1,125 mg per day valproic acid and 10 mg per day diazepam for spasticity. Her routine blood chemistries, thyroid function tests, liver function tests, venous ammonia level, serum lactate level, blood counts and anti-convulsant levels were normal.

She was noted to be chronicaly very lethargic and frequently difficult to arouse. She was treated with 990 mg of L-carnitine twice a day (45 mg/kg/day). Within a month she was much more alert and easy to arouse. In school she significantly improved her ability to respond to spoken language. After 3 months the L-carnitine was discontinued. Within a week she became much more lethargic and very difficult to arouse. When the L-carnitine was re-started after 1 month, she became much more alert and responsive, an improvement which has been maintained for an additional 9 months. There have been no complications from the L-carnitine. In particular, there was no change in seizure frequency.

2.4. Case 4

This is a 12-year-old female with congenital cytomegalovirus (CMV) infection, periventricular calcifications, agenesis of the corpus callosum, obstructive hydrocephalus which required insertion of a ventriculoperitoneal shunt, and in the past a refractory seizure disorder. She is non-ambulatory with spastic quadriparesis and is blind with bilateral optic nerve atrophy. Psychologic evaluation revealed her Bayley Scale of Infant Development IQ to be less than 20 (profound mental retardation) and the Vineland Adaptive Behavior Scales of 0–1 month for communication, daily living skills and socialization. The medications that she was taking were 1,050 mg a day valproic acid and 36 mg a day phenobarbital. Her routine blood chemistries, thyroid function tests, liver function tests, venous ammo-

nia level, serum lactate level, blood counts and anti-convulsant levels were normal.

She was noted to be chronically very lethargic and difficult to arouse. She was started on 1 g of L-carnitine two times a day (50 mg/kg/day). Within a month she was much more alert, was easily arousable, was less irritable and significantly improved her school performance. She improved in her ability to roll from her side to her back and in being able to grasp objects in her left hand. After 3 months of treatment, the L-carnitine was discontinued. Within a week she became much more lethargic and hard to arouse. When the L-carnitine was re-started after 1 month she became much more alert and responsive, an improvement which has been maintained for an additional 9 months. There have been no complications from the L-carnitine. In particular, there was no change in seizure frequency.

2.5. Case 5

This is a 2-year- and 6-month-old female who was entirely healthy until 18 months of age when she suffered severe hypoxic-ischemic encephalopathy secondary to aspiration pneumonia. The hypoxic brain damage was associated with a burst supression pattern on EEG and difficult to control seizures. This resulted in her becoming totally non-ambulatory from spastic quadriparesis, becoming blind and suffering from seizures. Psychologic evaluation revealed her to be functioning in the profound range of mental retardation. The medications that she was taking were 200 mg per day phenytoin and 0.1 mg per day clonazepam. Her routine blood chemistries, thyroid function tests, liver function tests, venous ammonia level, serum lactate level, blood counts and anti-convulsant levels were normal.

She was noted to be chronically lethargic and sleepy. In school it was almost impossible to arouse her. She was sleeping nearly continuously day and night. Before starting L-carnitine her total serum carnitine was 44.8 μg/dl and free serum carnitine was 35.6 μg/dl (both results normal; determinations were performed by the Mayo Clinic Laboratories). She was treated with 400 mg of L-carnitine twice a day (50 mg/kg/day). Within a month she was much more alert, particularly in school. She was awake during the entire school day. She would turn her head in response to sounds. She would smile when approached and spoken to. She has even tried to vocalize to sounds that she has heard, something that she had never done previously. The improvement has been maintained for an additional 2 months. There have been no complications from the L-carnitine. In particular, there was no change in seizure frequency.

3. DISCUSSION

The five children in this report all have severe neurologic handicaps. They are all profoundly mentally retarded, have a seizure disorder and are non-ambulatory. The etiology of their handicap is diverse: one with post-immunization encephalopathy, one with rubella encephalitis, one with congenital CMV infection, one with an undiagnosed congenital encephalopathy, and one with a severe hypoxic-ischemic encephalopathy. All of them had a difficult management problem: excessive lethargy. In all cases this problem significantly improved with L-carnitine treatment in a dose range of 35–50 mg/kg/day. In all of the four cases where L-carnitine was discontinued for a month, the lethargy returned. With re-introduction of L-carnitine they again promptly became much more alert and arousable, an improvement that has been maintained for up to 14 months.

It is unlikely that the children in this report were nutritionally carnitine deficient because in all cases their diets included foods or formulas that contained L-carnitine. Furthermore, in the three cases where we determined serum carnitine levels, both the total and free carnitine concentrations were normal. This is in keeping with a report of a Rett syndrome patient who improved with L-carnitine [2] and who likewise had normal serum carnitine determinations. In a report of 51 children with serum carnitine deficiency [3], the primary clinical symptoms of carnitine deficiency were hypotonia in 40, failure to thrive in 33, and recurrent infections in 33, problems which were not present in our children. Serum levels may not be an accurate indication of bodily carnitine stores [1,4,5]. Tissue carnitine levels, as determined in muscle biopsies, are more reliable. However, in our patient population, due to legal restrictions, muscle biopsies could not be obtained.

Four of the five treated children were receiving valproic acid for seizure control. Valproic acid can produce lethargy when serum levels are high but that was not the case in our children. Valproic acid can also produce hyperammonemia, with or without elevated liver function tests [6–9], but in all of our cases the venous ammonia levels and results of liver function tests were normal. Valproic acid has been reported to induce coma within days in two patients who had unrecognized secondary carnitine deficiency before valproic acid administration [10]. Our patients had been on valproic acid for years without signs of hepatic dysfunction or a change in their encephalopathy. It is possible that the valproic acid had produced a secondary carnitine deficiency condition [1] and that their lethargy was secondary to carnitine deficiency. This is

unlikely, however, because in the two patients where we measured serum carnitine concentrations we obtained normal results. Serum carnitine concentrations should be low in valproic acid-treated children [11]. Valproic acid-induced carnitine deficiency has been reported to clinically produce hypotonia [5,12], hepatotoxicity and worsening seizures [12], and cardiomyopathy [13]. None of our patients had any of these clinical findings. Reversible, L-carnitine-responsive lethargy has not been reported as a complication of valproic acid treatment. Furthermore, one of our treated children who responded dramatically to L-carnitine was not taking valproic acid. The etiology by which L-carnitine improved these children's lethargy remains unknown.

The total resident population number in our facilities is 144. In this report we have identified five children with severe lethargy which was reversible with L-carnitine treatment. If one adds an additional case of Rett syndrome which likewise had L-carnitine responsive lethargy [2], the incidence of this finding in our population was 4.2%.

L-Carnitine can be of benefit in improving lethargy in severely neurologically handicapped children irrespective of the cause of the handicap.

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