L-Carnitine as a Treatment for Rett Syndrome

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ABSTRACT: A 17-year-old girl with Rett syndrome, who was taking no other medications, was treated with L-carnitine (50 mg/kg/day). Within 2 months of initiation of treatment, she became much more alert, developed good eye contact, started reaching for objects with both hands, and answered simple questions with one or two words. L-carnitine was discontinued and within 1 week she lapsed into her pretreatment condition of lethargy with no interest in her environment, not reaching for objects, poor eye contact, and not speaking. One week after L-carnitine was resumed, she again became alert, started reaching for objects, and saying one or two words. Her serum carnitine levels (free and total) were within normal limits before and after L-carnitine treatment, but were higher while she was taking L-carnitine. Her serum ammonia was within normal limits prior to starting L-carnitine. L-carnitine appears to be an effective treatment for this girl with advanced Rett syndrome.

RETT SYNDROME is a progressive neurologic disorder in girls first described by Rett in 1966.[1] There is no known effective treatment of this condition. Mitochondrial abnormalities have been described in Rett syndrome, including swollen and dumb-bell shaped mitochondria in muscle biopsy specimens[2,3] and large, swollen mitochondria with scant cristae in nerve biopsy specimens.[4] Carnitine has two principle functions: to transport long-chain fatty acids into the mitochondrion and to help regulate the intramitochondrial ratio of acyl-coenzyme A (CoA) to free CoA.[5] Mitochondrial carnitine deficiency impairs energy metabolism by restricting mitochondrial beta-oxidation of long-chain fatty acids and by permitting build up of acyl-CoA within the mitochondrion resulting in dysfunction in those tissues most dependent on mitochondrial energy metabolism: brain and muscle.[5] Because Rett syndrome has been associated with mitochondrial structural abnormalities that may indicate functional mitochondrial abnormalities and because L-carnitine is an effective treatment for selected cases of mitochondrial carnitine deficiency, we treated one Rett syndrome patient with L-carnitine.

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CASE REPORT

The pregnancy was without complications. The patient was born to a 21-year-old gravida 2, para 1 mother after a full-term pregnancy. Labor started spontaneously and she was born of a vaginal, vertex presentation with a birth weight of 7 lb and 11 oz. Her 1 minute Apgar score was 10. At birth her head circumference was 33 cm (50th percentile). There were no postnatal difficulties. The possibility of developmental delay was raised at 6 months of age, but she was able to walk independently at 14 months of age.

At 5 years of age she failed preschool and on informal testing was noted to have expressive and receptive language delay, poor visual skills, and an overall cognitive level of a 3-year-old. At 6 years of age her Stanford Binet IQ was 39. Between 6 and 7 years of age, her gait started to deteriorate and she became progressively more ataxic. At this time she also started to lose verbal abilities. At 8 years of age her head circumference was 48 cm (below the 2nd percentile) and she had a developmental age of 32 months. At 12 years of age she was admitted to Marklund Children's Home. At that time she was able to walk with assistance and speak in one- and two-word sentences. Over the following 2 years she lost all walking and speaking abilities. At 13 years of age, she required a gastrostomy tube due to progressive dysphagia. The tube has been used since then to provide supplemental feedings. When she was 15 years of age, her Slosson scale revealed a mental age of 1 year and 3 months and social-emotional development of 3 months. Her head circumference was 49 cm (4 standard deviations below the mean). When she was 17 years old, her head circumference remained 49 cm. Her weight was 33.3 kg (4 standard deviations below the mean) and height was 148 cm (below the 2nd percentile). On examination she had no dysmorphic features, organomegaly, or any signs of a neurocutaneous disorder. Neurologically she was nonverbal, did not respond to any verbal commands, and had hypertonia and hyperreflexia.

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When she was 8 years old, abnormal EEG findings included right frontal spike and wave discharges aggravated by photic stimulation. Although she never had clinical seizures, diphenylhydantoin and later valproic acid were tried without clinical benefit. At 10 years of age she had a repeat EEG that revealed diffuse slowing with bilateral sharp waves, more in the left temporal area. She had extensive examinations at 10 years of age. Head computed tomography scan revealed diffuse cerebral atrophy. Blood testing results were normal for thyroid functions, amino acids, ammonia, lysosomal enzymes, lactate, pyruvate, complete blood count, and routine chemistries. Urine analyses showed normal organic acids and mucopolysaccharides. Cerebrospinal fluid examination revealed no cells with normal glucose, protein, lactate and no oligoclonal banding. Ophthalmologic examination did not reveal any retinal or optic nerve abnormalities. There was no family history of any neurologic difficulties.

At the onset of treatment with L-carnitine, she was 17 years old and was taking only multiple vitamins and ferrous sulfate supplements. Before giving the patient L-carnitine, we sent frozen serum samples to the Mayo Clinic laboratories. Her serum ammonia was 79.2 μg/dL (normal 17 to 80), total serum carnitine was 39.7 nmol/mL (normal 30 to 73), and free serum carnitine was 36.8 nmol/mL (normal 19 to 60). She was treated with 500 mg of L-carnitine 3 times a day (50 mg/kg/day).

Within 2 months of starting L-carnitine, the patient showed significant improvement. She became much more alert, started to make good eye contact, and her appetite increased. She started to show much more interest in her environment and started to reach for objects with both hands. When a magazine was placed before her, she would look at the pictures and turn the pages, whereas before starting the L-carnitine she would consistently push the magazine off the table. She also became more attentive to sounds and enjoyed listening to music played through head phones, whereas before the L-carnitine she would always shake off the head phones.

Most dramatically she started to respond to verbal commands and to speak. Prior to L-carnitine there was no expressive vocabulary and no suggestion of receptive language skills. From pictures presented to her, she has been able to identify and say the following words without prompts: "ball," "brush," "comb," "locker." She would say "thank you" appropriately without visual or verbal prompts. When she has been in the bathroom and is asked where she is, she would answer "bathroom." She has been able to repeat words and match words to pictures with 75% accuracy. After 2 months of treatment, her total serum carnitine was 66.6 nmol/mL and free serum carnitine was 59.0 nmol/mL.

After 2 months of treatment, the L-carnitine was discontinued. Within a week she became lethargic and disinterested in her environment. She no longer reached for objects and did not respond verbally. Her appetite also decreased. At this time her total serum carnitine level was 35.1 nmol/mL and free serum carnitine was 29.9 nmol/mL.

L-carnitine was resumed and within a week she regained all of her previous improvements. She has remained clinically stable for 3 months.

DISCUSSION

Although the course of her illness was slightly later in onset and progression than is usual for Rett syndrome patients,[6] she does qualify for this diagnosis because of acquired microcephaly, progressive verbal and cognitive deterioration, progressive social withdrawal, progressive gait ataxia, and progressive loss of hand functions. She also had abnormal EEGs (without clinical seizures), progressive spasticity, and growth retardation. She did not meet any exclusion criteria.[6] Despite extensive investigations, no other cause of her neurologic deterioration has been identified.

Decreased serum levels of carnitine have been reported in Rett syndrome,[7,8] but in this case the levels were normal.

She had a very significant neurologic improvement on L-carnitine. She became more alert, developed eye contact, started reaching for objects with both hands, and, most dramatically, even regained receptive and expressive verbal abilities. Her appetite improved on L-carnitine, as has been noted in other Rett syndrome patients treated with L-carnitine (M. Philippart, oral communication, March 1992) but to the authors' knowledge there have been no previous reports of such a pronounced neurologic improvement in Rett syndrome with the use of L-carnitine. Perhaps the explanation is that we used a larger dose of L-carnitine (50 mg/kg/day) than that previously used (25 mg/kg/day; M. Philippart, oral communication, March 1992). When this medication was discontinued, the patient promptly deteriorated. With reintroduction of L-carnitine, she regained her improvements and has remained clinically stable.

Although muscle levels of carnitine were not measured, her serum levels of free and total carnitine were normal. She was not taking any medications that might have interfered with carnitine metabolism. It seems likely that L-carnitine was beneficial by stimulating or normalizing mitochondrial function. L-carnitine may be of clinical benefit to other children with Rett syndrome and may even be useful in preventing the deterioration seen in this condition.

References

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EDITOR'S NOTE: Cost to the pharmacist based on Average Wholesale Price listings in *Drug Topics Red Book 1993:* L-carnitine (Carnitor), $67.68 per 90 tab, 330 mg.