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Is L-Carnitine an Effective Treatment to Improve the Quality of Life for Patients with Rett Syndrome?

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Is L-carnitine An Effective Treatment To Improve The Quality Of Life For Patients With Rett Syndrome?

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ABSTRACT

Objective: To determine "Is L-carnitine an effective treatment to improve the quality of life for patients with Rett Syndrome?"

Study Design: Review of all English language randomized controlled trials and cohort trials from 1999-2007.

Data Sources: Randomized, placebo-controlled, double-blind crossover trial, randomized controlled trial, and cohort trial comparing L-carnitine to placebo or control group were found using OVID MEDLINE, and Cochrane Databases

Outcomes Measured: The trials measured the effects of L-carnitine on physical well-being, motor skills, sleep efficiency, physical activity, and cardiac dysautonomia using the following assessment tools: The Rett Syndrome: Symptom Severity Index (RT:SSI), Patient Well-Being Index, SF-36 Health Survey, Hand Apraxia Scale, RS Motor Behavioral Assessment, 7 day-night sleep diary, TriTrac-R3D ergometers, electrocardiogram.

Results: Two studies demonstrated that the patient well being, behavior/social and orofacial/respiratory motor skills, sleep efficiency, sleep latency, proportion of total sleep that occurred during the day, energy level, communication skills, expressive language, and teeth grinding all improved with L-carnitine treatment. The third study demonstrated a reduction in the risk for cardiac arrhythmias in treatment with L-carnitine. Parents/caregivers of participants in the study reported minor side effects with treatment, but no major side effects were reported.

Conclusion: Based on the three trials, L-carnitine does improve the quality of life in patients with Rett Syndrome.

Key Words: Rett Syndrome, L-carnitine

Introduction

Rett Syndrome is a severe neurodevelopmental disorder that primarily affects females and is defined by progressive loss of intellectual functioning and fine and gross motor skills, deceleration of head growth, and the development of stereotypic hand movements occurring after a period of normal development.[1,2,3] The risk of sudden death is increased in Rett Syndrome patients due to the occurrence of lethal arrhythmias, which can be related to long QT intervals and/or low heart rate variability.[3]

Rett Syndrome is considered to be the second most common cause, after Down syndrome, of severe mental retardation in girls. Its worldwide prevalence rate ranges from 1:10,000 to 1:23,000 live female births.[1] Although the exact cost of medical care for patients with Rett Syndrome is unknown, the syndrome is extremely difficult to manage and for some health insurance policies it can be filed under a "pre-existing condition" which makes it nearly impossible to obtain coverage for these patients. Also, the number of healthcare visits per year for patients with Rett Syndrome varies depending on the severity of the disease and other existing medical conditions.

The etiology of Rett Syndrome is unknown; however, in 80% of cases there is a mutation of a methyl-CpG-binding protein 2 (MECP2).[3]

No treatments for Rett Syndrome as a whole currently exist; however, there are a variety of ways to minimize the effects of Rett Syndrome by treating specific symptoms. Current therapies include physical therapy, occupational therapy, speech-language therapists, anti-seizure medication, OTC medications for constipation and indigestion. Another proposed therapy that is being researched is treatment with L-carnitine. Evidence suggests that an underlying defect in

Rett Syndrome may lie within mitochondrial energy production, which can interfere with the active cellular carnitine uptake process.[1,2,3]

Objective

The objective of this systematic review is to determine whether or not "Is L-carnitine an effective treatment to improve the quality of life for patient with Rett Syndrome?" Previous studies have shown that a plasma carnitine deficiency exists in some patients with Rett Syndrome; therefore it is suggested that Rett Syndrome patients will have positive outcomes when treated with L-carnitine.

Methods

Randomized Controlled Trials were searched for those with a female patient population over the age of 2 with clinically diagnosed Rett Syndrome, as well as those whose treatment interventions include L-carnitine. In addition, only those articles that compared the treatment groups receiving L-carnitine to a placebo group or control group were considered. Under these criteria, one randomized, placebo-controlled, double-blind crossover trial, one cohort, and one randomized controlled trial were identified and included in this review.

A detailed search was completed by the author using the following search engines: OVID MEDLINE, Cochrane Database of Randomized Controlled Trials, and Cochrane Database of Systemic Reviews. The key words "Rett Syndrome" and "L-Carnitine" were used in combination to search for English articles and all of the resulting articles were published in peer-reviewed journals from 1999 to 2007. The articles were selected based on the importance of the outcomes to the patient (Patient Oriented Evidence That Matters, POEMS). Studies that were included were those that were randomized, controlled, and based on patient oriented outcome. Those that were excluded were studies in which the patients were neither female nor diagnosed

with Rett Syndrome. Table 1 includes the demographics of the included studies. Results were reported based on p-values, clinically importance (CI), relative risk reduction (RRR), absolute risk reduction (ARR), relative benefit increase (RBI), absolute benefit increase (ABI), and numbers needed to treat (NNT).

Outcomes Measured

The outcomes measured had to be POEMS, such as the positive effects of L-carnitine on physical well-being, motor skills, sleep efficiency, physical activity, and cardiac dysautonomia.[1,2,3] To help measure these outcomes several tools were used. The Rett Syndrome: Symptom Severity Index (RT:SSI), Patient Well-Being Index, and SF-36 Health Survey were used to measure the physical well being of participants. The hand apraxia scale and RS Motor Behavioral Assessment were used to measure motor skills. A 7 day-night sleep diary was kept to measure sleep efficiency. TriTrac-R3D ergometers were used to measure physical activity and cardiac dysautonomia was measured using an electrocardiogram. These tools were used by parents/caregivers to assess the outcomes of the trials. To compare treatment score differences the Wilcoxon matched-pair, signed-rank test was used.[1,2,3]

Table 1. Demographics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Ellaway, 1999	Randomized, placebo-controlled, double-blind crossover trial	39	4-35 yo	Females diagnosed with Rett Syndrome	None	4	Phase 1- Group 1 received L-carnitine and Group 2 received placebo both for an 8 week period followed by an 8 week wash-out period. Phase 2- Group 1 receive placebo and Group 2 received L-carnitine for an

							8 week period.
Ellaway, 2001	Cohort	21	7-41 yo	Females diagnosed with Rett Syndrome	None	0	Subjects assessed before treatment and after a 6 month treatment of L-carnitine with the Rett Syndrome
Guideri, 2005	Randomized Control Trial	22	2-21 yo	Females with Rett Syndrome whose diagnosis was confirmed by 2 child neuropsychiatrists	None	0	All participants initially treated with carbamazepine. Participants divided into 2 groups: one group received Acetyl-L-carnitine treatment for 6 months and the other group was the control group.

Results

Two randomized controlled trials and one cohort trial are presented in this review, analyzed with intention to treat and with study participants being clinically diagnosed with Rett Syndrome. Patients were seen in an outpatient setting in all trials and all participants were clinically diagnosed with Rett Syndrome.

In the first Ellaway study, participants received 100 mg/kg/day of L-carnitine three times a day and in the follow-up study the same dosage was given twice a day.[1,2] In the Guideri study participants received 50 mg/kg day.[3] A total of four participants in all studies experienced very loose bowel movements so their L-carnitine dosage was lowered to 75 mg/kg/day; however, constipation is often a problem with Rett Syndrome so patients benefited from the mild

laxative.[1,2] Four other families reported a fishy body or urine odor coming from their daughters.[1,2]

Thirty five female participants completed the initial Ellaway trial. The patient's ages ranged between 4 and 35 years, with a median of 9 years. At the end of the trial, the mean total plasma carnitine level was 43μmol/L with a range of 17 to 61μmol/L (normal, 35-65μmol/L). The mean increase in total plasma carnitine was 23μmol/L with a range of -5 to 68μmol/L. The mean free plasma carnitine level was 36μmol/L with a range of 15-54μmol/L (normal, 30-60μmol/L) and the mean increase in free plasma carnitine was 18μmol/L with a range of -4 to 54μmol/L. In all but three subjects the total and free plasma carnitine increased between pre- and post-treatment. The outcome of the treatment was measured using the Wilcoxon matched-pair, signed-rank tests. The p-values for the Parent/Caregiver assessment as well as a medical follow-up are given in Table 2.[1]

Table 2. Wilcoxon Matched-Pair, Signed-Rank Test Results

	P Value of Parents/Caregivers	**P Value of Medical follow-up**
Rett Syndrome Motor Behavior Assessment		
Behavioral/social	0.091	0.006
Orofacial/respiratory	0.087	0.018
Motor assessment/physical signs	0.537	0.284
Hand Apraxia Scale	0.228	0.058
Patient Well-Being Index	0.015	0.000

The change in status reported by parents and/or caregivers and at medical follow-up after completion of L-carnitine therapy compared to placebo can be seen in Table 3. In the parent/caregiver completed questionnaires the only significant improvement seen was in the

subjects' well-being when treated with L-carnitine relative to their status on the placebo. At medical follow-up, more subjects improved than worsened in the behavioral/social subscale of the Rett Syndrome Motor Behavioral questionnaire. Using the Well-Being Index and Hand Apraxia scale significantly more children improved than worsened or stayed the same on L-carnitine relative to the placebo.[1]

Table 3. Change in Status After Completion of L-carnitine Therapy Compared to Status on Placebo

	Improved		Same		Worse	
	Number	Percent (95%CI)	Number	Percent (95% CI)	Number	Percent (95% CI)
Parent /Caregiver						
Rett Syndrome Motor Behavioral Assessment						
Behavioral/social	11	35.5	15	48.4	5	16.1
Orofacial/respiratory	8	25.8	15	48.4	8	25.8
Motor assessment/physical signs	8	25.8	17	54.8	6	19.4
Hand Apraxia Scale	6	19.4	15	48.4	10	32.3
Patient Well-Being Index	17	54.8	9	29.0	5	16.1
Medical follow-up						
Rett Syndrome Motor Behavioral Assessment						
Behavioral/social	19	54.3	12	34.3	4	11.4
Orofacial/respiratory	15	42.9	13	37.1	7	20.0
Motor assessment/physical signs	19	54.3	8	22.9	8	22.9

Hand Apraxia Scale	28	80.0	1	2.9	6	17.1
Patient Well-Being Index	25	71.4	8	22.9	2	5.7

Treatment effects included relative benefit increase (RBI), absolute benefit increase (ABI), and numbers need to treat (NNT), whose calculation can be seen in Table 4. The RBI was found to be 1.86% and the ABI was 0.26%. The NNT was found to be 4.[1]

Table 4. Treatment effects of randomized, placebo-controlled, double-blind crossover trial

CER	EER	RBI	ABI	NNT
0.14%	0.4%	$\frac{0.4\% - 0.14\%}{0.14\%} = 1.86\%$	0.4% - 0.14%= 0.26%	1/ 0.2%= 3.85= 4

Twenty-one female participants completed the follow-up Ellaway study, with an additional 62 participants in a control group. The participants ranged in age from 7 to 41 years, with a mean age of 14.4 years. The mean total plasma carnitine concentration at the commencement of the trials was 35.2μmol/L, with a range of 16.0-54.0μmol/L. At baseline, ten subjects had low total plasma carnitine. In all cases the total carnitine concentrations increased between pre- and post treatment with L-carnitine. Table 5 shows the results of paired t-tests and Wilcoxon matched-pair, signed-ranks tests for the RS:SSI, hand apraxia scale and sleep diary data. Significant improvement in scores for the RS cases ($P<0.05$) was seen for sleep efficiency, sleep latency, and the proportion of total sleep that occurred during the day. Significant improvement was seen in communication skills, energy level, teeth grinding, and expressive speech for RS cases based on the RS:SSI ($P<0.05$). The SF-36 Health Survey and Hand Apraxia Scale for the cases or controls showed no significant changes.[2]

Table 5. Paired t-test and Wilcoxon matched-pair, signed-rank test results for outcome measures for cases and controls.

Outcome Measures	**RS cases**	**RS cases: low plasma carnitine**	**RS controls**
RS:SSI (N)	21	10	62
Communication Skills	0.004	0.971	0.726
Energy Level	0.001	0.689	0.500
Teeth Grinding	0.002	0.419	0.565
Expressive Speech	0.011	0.302	0.347
Hand Apraxia Scale (N)	21	10	62
	0.782	0.111	0.644
Sleep Diary Data (N)	21	10	60
Total sleep time	0.641	0.754	0.673
Sleep latency	0.026	0.602	0.054
Sleep efficiency	0.005	0.082	0.220
SF-36 Health Survey (N)	18	10	62
Physical functioning	0.269	0.659	0.060

Ten females participated in the Guideri trial, along with 12 control patients. The participants ranged in age from 2-21 years. Heart rate variability (HRV), corrected QT interval (QTc), and QTc dispersion (QTcD) were measured by means of a t-test. Three main spectral components were identified: very low-frequency (VLF) <0.04 Hz, low-frequency (LF) between 0.04-0.15 Hz, and high-frequency component (HF) between 0.15-0.4 Hz. Table 6 demonstrates the results of the trial group compared to the control group. No significant differences between the trial and control groups existed at basal condition. After 6-18 months, the control group had a significant reduction in total power spectrum of HRV ($p=0.04$) and the LF spectral variable

(p=0.05), but a significantly increased QTcD (p=0.01). In the treatment group, there was a significant increase in total power, VLF, and LF spectral variables but no significant reduction in QTcD occurred.[3]

Table 6. Comparison of spectral variables and QTc interval in control group and trial group at basal evaluation and after 6-18 months.

	R-R interval	Total Power ($msec^2$)	VLF ($msec^2$)	LF ($msec^2$)	HF ($msec^2$)	LF:HF	QTc (sec)	QTcD (sec)
Control Group (n=12)	*p*=0.06	*p*=0.04	*p* =0.6	*p* =0.05	*p* =0.3	*p*=0.5	*p* =0.9	*p*=0.01
Basal Evaluation	602 ± 121	1197± 483	332±47	470± 236	171±119	4±2.6	0.429± 0.02	0.03± 0.01
After 6-18 mo.	584±78	**830± 343**	373± 223	**286± 195**	129± 105	5± 5	0.430 ± 0.02	**0.05 ± 0.02**
Trial Group	*p* =0.6	*p* =0.01	*p* =0.01	*p* =0.009	*p* =0.1	*p*=0.8	*p* =0.6	*p* =0.64
Basal Evaluation	583±61	1004± 430	369± 235	369± 181	191± 116	2.3± 1.2	0.43± 0.04	0.039± 0.01
After 6-18 mo.	616± 61	**3094± 2108**	**1003± 697**	**963± 564**	796± 1042	2.2± 1.8	0.425± 0.03	0.036± 0.01

Treatment effects included the relative risk reduction (RRR), absolute risk reduction (ARR), and NNT, whose calculation can be seen in Table 7. The RRR was found to be -0.18% and the ARR was -0.1%. The NNT was found to be -10.[3]

Table 7. Treatment effects of randomized controlled trial

CER	EER	RRR	ARR	NNT
0.55%	0.45%	$\frac{0.45\% - 0.55\%}{0.55\%} = -0.18\%$	0.45%-0.55%= - 0.1%	1/-0.1%= -10

Discussion

The randomized controlled trials and cohort trial demonstrate that L-carnitine can be used to improve the quality of life in Rett Syndrome patients by improving symptoms and reducing the risk of sudden cardiac death.

In the initial Ellaway study, there was improvement in the patient's well-being according to parental and/or caregiver assessment but no other improvements were statistically significant.[1] The medical follow-up for this study showed significant improvement in the behavior/social and the orofacial/respiratory subscale of the Motor Behavioral Assessment and Hand Apraxia scale. Based on qualitative symptomatic data, 70% of parents reported subtle but important improvements in the quality of life of the subjects while on the L-carnitine phase of the trial. These improvements included improved eye contact and concentration span, lack of daytime somnolence, improved vocalization, increased mobility, and the perception that the girls were much happier. Limitations of this study included subjective assessment tools which were insensitive to minor improvements in patients and potential unblinding of parents/caregivers and investigators due to the change in bowel habits of the subjects..[1]

In the follow-up Ellaway study, Rett Syndrome patients treated with L-carnitine showed significant improvement over the 6 month period in sleep efficiency, sleep latency, proportion of total sleep that occurred during the day, energy level, communication skills, expressive language and teeth grinding.[2] In this follow-up study established tools and the RS:SSI were used as objective outcome measures to assess the effects of L-carnitine on participants. The RS:SSI is a more reliable and valid assessment tool when compared to those used to assess outcomes in the initial study.[2] One limitation of the study was that the individual improvements of the girls could

have had significant impact on the patients as well as their families, thus affecting the subjective outcomes.

The Guideri trial showed that L-carnitine had many effects on ECG parameters. There was a significant increase in HRV total power and a slight reduction in sympathetic over-activity (expressed by LF:HF ratio) which can correlate with a reduction of the risk of cardiac arrhythmias is females with Rett Syndrome.[3] A small sample size was studied for this trial which limits the overall validity of the study.

L-carnitine is currently sold as a nutritional supplement and is used primarily for heart-related conditions, such as angina.[3] It has also been shown to have the potential to prevent myocardial sympathetic nervous dysfunction in diabetic patients.[3]

Conclusion

Based on the three trials, L-carnitine does improve the quality of life in patients with Rett Syndrome. Since there were no baseline criteria for the severity of Rett Syndrome in participants, the effects of the L-carnitine were varied. Further studies need to be investigated in which L-carnitine is used for longer than a 6-month period in order to observe any long term effects of the medication and a baseline severity of Rett Syndrome needs to be established for participants. Also, researchers need to investigate a way to minimize subjective data in order to have the data be more statistically significant. Mortality rates and/or annual hospital visits should be included in future studies of the effect of L-carnitine on cardiac dysautonomia in order to demonstrate the effect of treatment on patient outcomes.

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