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BRIEF REPORT

Clinical correlates of low serum carnitine levels in hospitalized psychiatric patients

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Abstract

Objective. We sought to evaluate clinical correlates of low serum carnitine levels in hospitalized psychiatric patients. *Methods.* We retrospectively reviewed the charts of 40 psychiatric inpatients identified to have low serum carnitine levels. *Results.* Cognitive impairment was present in 38 (95%) cases, frequently accompanied by imbalance, agitation and extrapyramidal symptoms. Valproate therapy was encountered in 28 (70%) patients. The dosage of valproate negatively correlated with total and free carnitine levels ($P = 0.003$ and 0.0136). Polypharmacy also affected carnitine levels, indicating additional modulatory effects on carnitine metabolism. We encountered a disproportionately high prevalence of mental retardation and dementia in association with hypocarnitinemia. *Conclusion.* We hypothesize that in the context of mental illness hypocarnitinemia may be associated with metabolic encephalopathy and cognitive impairment. As carnitine deficiency is a potentially treatable condition further studies are warranted.

Key words: *Carnitine, psychiatry, valproic acid, dementia, encephalopathy*

Introduction

The amino acid derivative L-carnitine is an important regulator of lipid metabolism in humans, responsible for the transport of long-chain fatty acyl groups into the mitochondrial matrix, facilitating β-oxidation and energy production via the Kreb's cycle. An additional role of carnitine is the elimination of toxic acylcoenzyme-A metabolites from mitochondria, via formation and excretion of acylcarnitine esters (Angelini et al. 1992). Although it can be synthesized endogenously, most of the daily requirements of carnitine are obtained through diet (Evans and Fornasini 2003; Rebouche 2004).

Carnitine deficiency indicates conditions in which carnitine tissue and serum concentrations are below the requirements for normal metabolism, while carnitine insufficiency indicates a relative lack of carnitine in relation to increased metabolic demand, leading to carnitine depletion and secondary deficiency (Angelini et al. 1992; Guarnieri et al. 2003). An elevated serum acylcarnitine/free carnitine (AC/FC) ratio > 0.4 is by many authors considered an indicator of carnitine insufficiency and secondary deficiency (Angelini et al. 1992; Guarnieri et al. 2003; Lheureux et al. 2005).

Primary carnitine deficiency is an autosomal recessive disorder caused by a defect in the plasma membrane carnitine transporter (Longo et al. 2006). Secondary carnitine deficiency is related to inborn errors of metabolism, renal failure, hepatic disease or the chronic use of certain medications, most notably valproic acid (VPA) (Ohtani et al. 1982; Laub et al. 1986; Breningstall 1990; Pons and De Vivo 1995; Fouque et al. 2006; Longo et al. 2006).

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The principal clinical manifestations of carnitine deficiency include metabolic encephalopathy, myopathy and cardiomyopathy, which can be effectively treated by carnitine supplementation (Breningstall 1990; Pons and De Vivo 1995; Lheureux et al. 2005, Longo et al. 2006).

Although VPA, a widely used mood stabilizer, is known to lower serum carnitine levels (Moreno et al. 2005), the clinical implications of carnitine deficiency or insufficiency have not been studied in the psychiatric population. In our study, we explore the clinical correlates of low serum carnitine levels within a population of a psychiatric state hospital.

The aim of our study is to alert the reading audience to this previously under-studied metabolic disarrangement in a psychiatric setting.

Methods

This study was approved by the South Carolina Department of Mental Health Institutional Review Board. Of patients who were hospitalized at the Department of Mental Health hospitals (DMHH) in fiscal year (FY) 2006, we reviewed the inpatient charts of those who had been identified to have low serum carnitine levels in the process of their routine multidisciplinary treatment. The DMHH system consists of acute and chronic psychiatric hospitals serving a total of 5,870 individuals in FY 2006.

We reviewed pertinent charts for vital statistics, chief complaints, psychiatric and medical diagnoses, medication regimen, laboratory data, mental status exam, hospital notes and neurology consultations up to the point at which hypocarnitinemia was identified. We used descriptive statistics to summarize the clinical correlates of hypocarnitinemia.

We analyzed correlations of carnitine levels with variables previously cited to affect carnitine metabolism, such as age, gender and VPA therapy. To explore the relationship between hypocarnitinemia and cognitive status, we calculated correlations between carnitine levels and Mini Mental-State Exam (MMSE), orientation scores and ammonia levels, as well as diagnoses of dementia and mental retardation. We also analyzed correlations between carnitine levels and the most frequently prescribed medications.

A general linear model was used to evaluate the above noted correlations. A level of $\alpha = 0.05$ was used to determine covariate significance, while using backward elimination in construction of regression models. Once the significant covariates were identified, interaction terms were considered for each model. All interaction terms were eventually found to be insignificant and were excluded from the final models. Tests for model assumptions including linearity, normality, independence, and homogeneity of residuals were met for all models. SAS version 9.2 was used for conducting all statistical analyses.

In this small, exploratory study, as we are trying to identify model candidates for future studies, we did not utilize formal corrections for Type I error, given that such corrections for accumulated error may be too conservative at this initial stage.

Results

A total of 40 patients with low serum carnitine levels were identified within the reviewed period; 31 males (77.5%), nine females (22.5%), 19 Caucasian (47.5%) and 21 African American (52.5%), with a mean age of 51.8 (range 26–72) and a standard deviation (SD) of 12.8 years. All our patients were prescribed a balanced, calorie controlled diet, with a mean of 2375 kcal per day (range 1800–2800 kcal), individually adjusted by quarterly nutritionist evaluations, following the National Academy of Sciences guidelines (National Academy of Sciences 1996). The mean body mass index (BMI) of our patients was within the overweight range (Table I).

All subjects had total and free serum carnitine levels below the expected normal reference range, while the acylcarnitine serum levels were below normal range in 13 (32.5%) cases and within normal limits in the remainder of patients. The mean acylcarnitine/free carnitine (AC/FC) ratio was within normal limits (Table I).

Hyperammonemia was the most frequent additional laboratory abnormality (Table I). Venous ammonia levels were available in 27 patients, and

Table I. Pertinent laboratory and MMSE findings in our patients with hypocarnitinemia.

Test	*N*	Mean	SD	Reference	Units
Carnitine total	40	28.6	6.1	42–81	μmol/l
Carnitine free	40	24.0	5.9	35–67	μmol/l
Carnitine esters	40	4.6	2.3	3.8–19	μmol/l
AC/FC ratio	40	0.21	0.1	<0.25	N/A
Venous ammonia	27	47.8	24.4	9–30	μmol/l
Valproic acid level	28	73	26.1	50–100	μg/dl
MMSE	31	18.2	7.1	28–30	N/A
Creatinine	40	0.98	0.3	0.9–1.3	mg/dl
Blood urea nitrogen	40	15.1	5.4	6–20	mg/dl
AST	40	33.5	10.3	17–59	U/l
ALT	40	35.4	10.9	21–72	U/l
Albumin	40	4.02	0.4	3.2–4.8	gm/dl
Body mass index	40	28.8	6.3	18.5–25	N/A

AC/FC ratio, acylcarnitine/free carnitine ratio; ALT, alanine aminotransferase; AST, aspartat aminotransferase; MMSE, mini mental-state exam; *N*, number of cases tested; Reference, normal reference values; SD, standard deviation.

found elevated in 18 cases (66.7% of 27 measured, 45% of the 40 cases with low carnitine levels). Of the 18 hyperammonemic patients, 16 (88.9%) cases were associated with VPA therapy. Venous ammonia levels were significantly higher in the patients with reported violent outbursts, compared to patients without agitation, with respective mean values of 61 and 40 μmol/l, and with a Pearson's correlation coefficient of 0.411 and *P* value of 0.033. None of our patients had elevated hepatic enzymes, and their albumin status was within normal limits in all cases (Table I). All patients had normal creatinine and BUN values, with the exception of three cases with mildly elevated serum creatinine levels of 1.3, 1.6 and 2.1 mg/dl, respectively (Table I).

The most prevalent psychiatric diagnoses were chronic schizophrenia (17 total cases including nine paranoid and eight undifferentiated type) and dementia (16 total cases including four alcohol related, three unspecified, two post-traumatic, two Alzheimer's type and the remainder with sporadic aetiologies). Other frequent psychiatric diagnoses included schizoaffective disorder, bipolar disorder, alcohol dependence and mild to moderate mental retardation. The most predominant medical conditions included hypertension, hyperlipidemia, epilepsy, diabetes mellitus and hypothyroidism (Table II).

Documented psychiatric findings were consistent with chronic psychiatric illness in each individual patient, although nonspecific symptoms such as disorientation and loosening of association prevailed. Additional frequent symptoms included auditory hallucinations, agitation, depressed mood and delusions (Table III).

The most frequent finding on neurological exam was impaired cognition, noted in 38 (95%) patients (Table III). In 31 of these patients the age and education adjusted MMSE was impaired, with a mean score of 18.2 (Table I) (Folstein et al. 1975; Crum et al. 1993). Seven patients were profoundly cognitively impaired and unable to complete the MMSE. In two patients formal cognitive testing was not documented. Additional frequent neurological findings included impaired ambulation (11 cases of ataxia, six of shuffling gait, seven wheel chair confined for years) and extrapyramidal symptoms (Table III). Documented vital signs were normal in all patients.

The most frequently prescribed medication was VPA, with a mean dose of 1661 mg/day (SD 705.0). Other frequently prescribed medications included benztropine, olanzapine, clonazepam and levothyroxine (Table IV). The mean number of daily prescribed medications per patient was 7.1 (SD 3.3).

Linear regression analysis revealed a positive association between age and acylcarnitine levels. Female gender correlated with lower free carnitine levels, and with higher acylcarnitine levels and AC/FC ratios. The number of medications prescribed per patient negatively correlated with free carnitine, and positively with acylcarnitine levels and AC/FC ratios. The dosage of VPA negatively correlated with total and free carnitine levels. The levothyroxine dose negatively correlated with free carnitine, and positively with acylcarnitine levels and AC/FC ratios, while the olanzapine dose positively correlated with acylcarnitine levels (Table V). Mild mental retardation was associated with lower total and free carnitine levels,

Table II. Most frequent diagnoses in our 40 patients with hypocarnitinemia.

	N	%
Axis I diagnoses		
Schizophrenia	17	42.5%
Dementia	16	40%
Schizoaffective D/O	7	17.5%
Bipolar D/O	6	15%
ETOH dependence/abuse	6	15%
Axis II diagnoses		
Mild to moderate MR	8	20%
Personality D/O NOS	2	5%
Axis III diagnoses		
Hypertension	16	40%
Hyperlipidemia	13	32.5%
Epilepsy	10	25%
Hypothyroidism	8	20%
Diabetes mellitus	8	20%
Chronic renal failure	5	12.5%

%, percentage of total; D/O, disorder; ETOH, alcohol; MR, mental retardation; *N*, number of cases; NOS, not otherwise specified.

Table III. Most frequent psychiatric and neurological findings in our 40 patients with hypocarnitinemia.

	N	%
Psychiatric findings		
Disorientation	31	77.5%
Loosening of associations	17	42.5%
Hallucinations	16	40%
Violent outbursts	10	25%
Delusions	9	22.5%
Labile affect	9	22.5%
Flat affect	8	20%
Depressed mood	7	17.5%
Neurological findings		
Impaired cognition	38	95%
Impaired gait/ambulation	24	60%
Tremor	12	30%
Dysarthria	10	25%
Orofacial dyskinesias	7	17.5%
Rigidity	5	12.5%

%, percentage of total; *N*, number of cases with listed finding.

Table IV. Most frequently prescribed medications in our 40 patients with hypocarnitinemia.

			Therapy duration (months)
Medication	*N*	%	Mean (SD)
Valproic acid	28	70%	13.4 (14.6)
Benztropine	16	40%	14.6 (15.7)
Clonazepam	11	27.5%	8.4 (10.4)
Levothyroxine	10	25%	21.4 (21.0)
Olanzapine	10	25%	7.9 (8.8)

%, percentage of total cases with hypocarnitinemia; *N*, number of cases; SD, standard deviation.

while the diagnosis of dementia positively correlated with acylcarnitine levels. Each patient's orientation to calendar year, city and hospital (cumulatively scored 0–3) positively correlated with MMSE scores, with a *P* value of <0.007. Orientation scores also positively correlated with free carnitine levels, and negatively with AC/FC ratios (Table V).

Discussion

General considerations

Although carnitine deficiency may result from malnutrition, this was not a likely cause in our patients, as they had individualized and standardized nutritional supervision during their hospitalization. Most of our patients were overweight and their albumin status was within normal limits in all cases. Chronic renal or hepatic disease may also contribute to secondary carnitine deficiency. However, none of our patients had abnormalities of hepatic enzymes, and almost all had normal renal function. Therefore, we believe that carnitine deficiency in most of our patients resulted from additional metabolic modifiers.

The reduction of carnitine levels in our patients was less profound than would be expected with homozygous primary carnitine deficiency (Longo et al. 2006). Therefore, general etiological considerations could include a heterozygous carrier state for primary carnitine deficiency, secondary deficiency, malabsorption, impaired synthesis, or other conditions affecting carnitine bioavailability, resulting in moderate hypocarnitinemia (Angelini et al. 1992; Scaglia et al. 1998; Guarnieri et al. 2003). In addition, even in a healthy population, functional polymorphisms in the carnitine transporter gene may lead to significant alterations in carnitine metabolism (Urban et al. 2006).

Age and gender influence carnitine metabolism and serum levels (Takiyama and Matsumoto 1998). In our patients, age positively correlated with acylcarnitine levels, while female gender was associated with significantly lower free carnitine levels, but higher acylcarnitine levels and AC/FC ratios (Table V). These findings suggest a relative susceptibility of our patients toward carnitine insufficiency and secondary deficiency with advancing age, particularly in females.

The number of daily medications prescribed to each of our subjects negatively correlated with free carnitine levels and positively correlated with acylcarnitine levels and AC/FC ratios, suggesting a negative effect of polypharmacy on carnitine bioavailability, with a shift toward carnitine insufficiency and secondary depletion. The respective dosages of valproate, olanzapine and levothyroxine statistically correlated with different subsets of carnitine levels, suggesting additional modulatory mechanisms in this clinical context (Table V).

Several biochemical mechanisms have been recognized to promote carnitine depletion with VPA therapy (Camiña et al. 1991; Tein and Xie 1994; Lheureux et al. 2005). In our subjects, we found a

Table V. Statistically significant correlates of hypocarnitinemia in our patients (*N*=40).

	Total carnitine		Free carnitine		Acylcarnitine		AC/FC ratio	
Pearson correlation	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age	0.20	0.209	0.05	0.782	**0.42**	**0.007**	0.28	0.082
Female gender	−0.27	0.088	**−0.43**	**0.006**	**0.38**	**0.015**	**0.52**	**0.001**
N/O medications	−0.22	0.161	**−0.36**	**0.021**	**0.34**	**0.032**	**0.42**	**0.007**
Valproic acid dose	**−0.54**	**0.003**	**−0.46**	**0.014**	−0.27	0.167	−0.08	0.688
Levothyroxine dose	−0.36	0.310	**−0.66**	**0.038**	**0.83**	**0.003**	**0.89**	**0.001**
Olanzapine dose	0.15	0.677	−0.10	0.784	**0.69**	**0.026**	0.63	0.050
Mild MR	**−0.37**	**0.018**	**−0.32**	**0.045**	−0.17	0.305	−0.17	0.305
Dementia	0.21	0.199	0.09	0.578	**0.32**	**0.046**	0.23	0.159
Orientation score*	0.25	0.125	**0.35**	**0.029**	−0.24	0.137	**−0.34**	**0.035**

AC/FC, acylcarnitine/free carnitine; **bold print**, statistically significant correlation; MR, mental retardation; N/O, number of; *P*, Pearson's correlation *P* value; *r*, Pearson product-moment correlation coefficient; *orientation to time; place and situation cumulatively scored 0–3 in each patient.

negative statistical correlation between VPA dose and total and free carnitine serum levels, which may suggest a negative effect of valproate on carnitine bioavailability and metabolism. However, we also identified 12 (30%) patients with hypocarnitinemia who were not on VPA therapy, indicating that in our patients VPA was not sole contributor to hypocarnitinemia.

While prior studies have reported a strong interdependence of thyroid hormone and carnitine metabolism (Mynatt et al. 1994; Galland et al. 2002; Sinclair et al. 2005), olanzapine has not been referenced in association with carnitine metabolism. In our study olanzapine dosage correlated positively with acylcarnitine levels, suggesting a possible shift of carnitine metabolism toward its detoxifying role.

Behavioral correlates of hypocarnitinemia

Although in animal models carnitine is known to have a modulatory effect on dopamine output in the meso-limbic cortex, the relationship between carnitine metabolism and mental illness in humans has not been investigated (Tolu et al. 2002).

When compared to DMHH diagnostic data for FY 2006, schizophrenia and other inherent mental disorders were relatively more prevalent in our patient group, while alcohol dependence and personality disorders were less prevalent (Figure 1). Such redistribution may have resulted from a selection bias in our patient group, but also raises the question whether there is a relationship between carnitine metabolism and certain mental disorders.

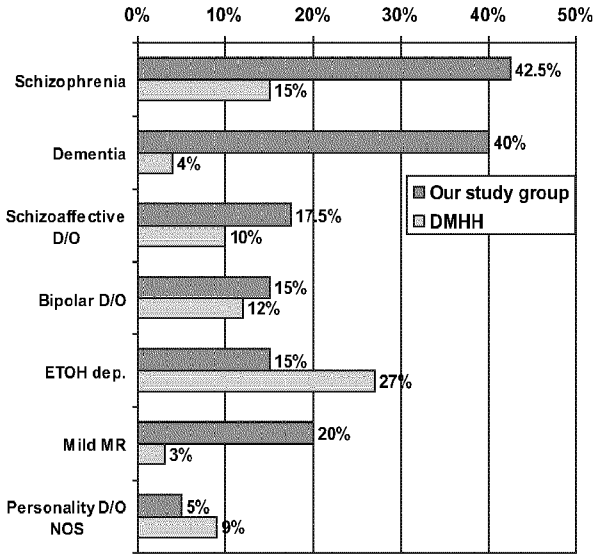

Figure 1. Respective prevalence of selected psychiatric diagnoses within our study group (N=40) and within the total DMHH population in FY 2006 (N=5870). DMHH, Department of Mental Health Hospitals; D/O, disorder; ETOH dep., alcohol dependence; MR, mental retardation; N, number of individuals; NOS, not otherwise specified.

The importance of carnitine in the central nervous system is evidenced by a wide array of disorders associated with its dysregulation. Abnormalities of carnitine metabolism have been found in pediatric patients suffering from developmental delay, mental retardation and autism (Breningstall 1990; Pons and De Vivo 1995; Filipek et al. 2004). In addition, various authors have reported the beneficial effects of carnitine supplementation in a variety of neurological disorders including chronic fatigue, age-associated cognitive decline, Down syndrome, Alzheimer's disease, ammonia-related neurotoxicity and hepatic encephalopathy (Montgomery et al. 2003; Pistone et al. 2003; Pueschel 2006; Malaguarnera et al. 2007, 2088a,b). In animal models carnitine has shown protective properties against the processes that promote neurodegeneration and dementia (Binienda et al. 2005; Abdul and Butterfield 2007). However, the association of hypocarnitinemia and cognitive impairment in the context of chronic mental illness has not been previously recognized nor studied.

All our subjects, when tested, had some degree of cognitive impairment. Patients with mild mental retardation and patients with dementia were, respectively, 7 to 10 times more prevalent in our study population, as compared to DMHH prevalence data for FY 2006 (Figure 1). The diagnosis of mild mental retardation correlated with lower total and free carnitine levels, while the diagnosis of dementia positively correlated with higher acylcarnitine levels (Table V). These findings raise the question whether there is a relationship between carnitine metabolism and cognitive impairment in our patients.

Although we did not find a significant correlation between MMSE scores and carnitine levels in our patients, we did find a positive correlation between each patient's orientation scores and free carnitine levels, and a negative correlation with AC/FC ratios (Table V), which may tentatively indicate a possible relationship between basic cognitive status and carnitine metabolism.

Carnitine deficiency may result in hypoketotic-hypoglycemic, hyperammonemic or mitochondrial encephalopathy, presenting with intermittent mental status changes, precipitated by fasting, stress, infection or catabolism (Hsu et al. 1995; Longo et al. 2006). It is plausible that vulnerable psychiatric patients may be susceptible to metabolic encephalopathy. However, in the psychiatric population a superposition of metabolic encephalopathy may be difficult to differentiate from the exacerbation of mental illness, dementia or delirium (Dealberto 2007). In our patients, symptoms of cognitive impairment, imbalance and agitation are suggestive of a toxic-metabolic encephalopathy (Brenner 1985).

Normal vital signs and absence of autonomic dysregulation would argue against the diagnosis of delirium. Based on our observations, we cannot extrapolate a single mechanism by which carnitine deficiency could lead to the given clinical picture, although the development of hyperammonemia seems a plausible factor in 45% of our patients.

Valproate-related hyperammonemic encephalopathy, with normal liver function, is a recognized phenomenon in psychiatric practice, and carnitine deficiency is known to facilitate VPA induced hyperammonemia by inhibiting urea cycle enzymes (Ohtani et al. 1982; Sztajnkrycer 2002). In our patients with hypocarnitinemia, violent behaviour statistically correlated with higher ammonia levels. However, in this study we could not demonstrate direct correlations among the MMSE, ammonia and carnitine levels.

The presence of an encephalopathic clinical picture without documented hyperammonemia in 55% of our patients, suggests additional pathophysiological mechanisms. Due to the retrospective nature of our study, we did not have data such as serum pyruvate and lactate levels, serum ketone bodies or acylcarnitine profiles that could provide more insight into any additional metabolic effects of hypocarnitinemia.

Limitations of the study

Serum carnitine levels are rarely, if ever, monitored in psychiatric practice, which resulted in the small sample size in our study. Consequently, some of the calculated statistical measures are subject to type I and II error, as they may gain or lose significance if the sample size were increased. This study did not include a representative random sample of psychiatric patients, but a selected subgroup of patients predetermined by low serum carnitine levels, which precludes extrapolation of the findings to the general psychiatric population. Important additional limitations include retrospective, cross-sectional study design and lack of control groups.

Some tests included in our observations were not available in all of our patients which further limits our findings. The lack of sufficient statistical power, inter-rater variability of MMSE scores, serum handling issues and natural fluctuations of the carnitine and ammonia serum levels may have additionally affected our results. We did not find any statistical associations among VPA, ammonia and carnitine serum levels or MMSE findings, which may be due to the retrospective design of our study, as such tests were usually completed at different points in time, days to weeks apart.

Conclusion

In this study we cannot make inferences with respect to a causal relationship between carnitine deficiency and the above noted correlates, nor can we project our findings to the general psychiatric population. Notwithstanding the inherent limitations, our findings raise a valid question whether in a vulnerable psychiatric population hypocarnitinemia may be associated with metabolic encephalopathy and cognitive impairment. Additional questions that would require further elaboration include a possible role of carnitine metabolism in modulation of mental illness, as well as the possible effects of hyperammonemia on cognitive impairment and violent behavior. Future studies of carnitine metabolism in the context of mental illness are warranted, particularly as carnitine deficiency is a potentially treatable disorder.

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None.

Statement of interest

None to declare.

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