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FULL COMMUNICATION

Alpha-Lipoic Acid Shows Promise to Improve Migraine in Patients with Insulin Resistance: A 6-Month Exploratory Study

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ABSTRACT Alpha-lipoic acid (ALA) is known to lower insulin resistance (IR), which is common among migraineurs. To assess the effect of ALA on headache in migraineurs with IR, we performed an exploratory study on a cohort of patients with migraine, followed at our Headache Center. The 32 patients took ALA 400 mg b.i.d. for 6 months in addition to their on-going treatment. The percentage of patients with a reduction of at least 50% of the attacks was 0.53 (confidence interval [95% CI] 0.36–0.70) at 2 months, 0.56 (0.39–0.73) at 4 months, and 0.69 (0.53–0.85) at 6 months. The incidence rate ratio of attacks at 6 months versus baseline was 0.48 (0.43–0.53, $P < .001$), corresponding to a mean (95% CI) number of attacks of 5 (4–6) versus 11 (10–12). The number of days of treatment in the previous month was 7.7 (6.8–8.7) at baseline, 5.4 (4.6–6.2) at 2 months, 5.3 (4.5–6.1) at 4 months, and 4.3 (3.6–5.0) at 6 months. Baseline and 120-min glucose and insulin and quantitative insulin sensitivity check index (QUICKI) and the Stumvoll index did not change at 6 months versus baseline. This exploratory study shows that the administration of ALA may be associated with a reduction in the number of attacks and the days of treatment in migraineurs with IR. A randomized controlled trial is needed to test this possibility.

KEYWORDS: • ***alpha-lipoic acid*** • ***cohort study*** • ***glucose*** • ***insulin resistance*** • ***insulin sensitivity*** • ***migraine*** • ***oral glucose tolerance testing***

INTRODUCTION

MOST MIGRAINEURS HAVE altered glycemic and insulinemic responses[1–4] associated with dysregulation of nitric oxide metabolism.[5–9] We have previously reported that a low-carbohydrate diet, coupled with metformin, has the potential to improve the headache of migraineurs with insulin resistance (IR)(Cavestro C., personal communication).

Alpha-lipoic acid (ALA), a cofactor of pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase, has neuroprotective and anti-inflammatory effects and lowers IR.[10–15] We hypothesized that ALA could reduce migraine attacks by lowering IR.

Although the best dietary strategy for handling hyperinsulinemic euglycemic dysfunction is unclear,[16] metformin is often used to treat hyperinsulinemia whether hyperglycemia is present or not.[17] Some patients, however, do not tolerate metformin and/or are not able to follow the diet.

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In the present study, we proposed to migraineurs, with IR who had had no benefit from diet and/or metformin, to add ALA to their on-going treatment. The aim was to explore the hypothesis that ALA can decrease migraine attacks by lowering IR.

MATERIALS AND METHODS

Study design

We performed an open-label cohort study on 32 consecutive patients followed at the Headache Center of the San Lazzaro Hospital (Alba, Italy), between December 1, 2013 and December 30, 2014. The inclusion criteria were as follows: (1) age ≥18 years; (2) migraine diagnosed following international criteria[18]; (3) IR; and (4) lack of reduction of at least 50% of migraine attacks after treatment with diet and/or metformin or inability to follow such a treatment. The exclusion criteria were as follows: (1) untreated thyroid disease; (2) untreated hyperprolactinemia; (3) polycystic ovary syndrome; (4) use of estrogens and/or progesterone; and (5) pregnancy. Thyroid-stimulating hormone (TSH), free levothyroxine (FT4), and prolactin were measured at both the

first and last visit. The study was authorized by the Local Authority (General Protocol Number 1790033, November 28, 2013), and all patients gave their written consent to participate to the study. The participants agreed that no promise or inducement to enter into the study had been offered or made.

Clinical assessment

At the baseline visit (0 months), the following information was collected: (1) age, (2) sex, (3) type of migraine (with or without aura), (4) on-going disease, and (5) on-going treatment. At each visit (0, 2, 4, and 6 months), the following additional information was collected: (1) time elapsed from the enrolment, (2) number of days with headache in the previous month, (3) number of days of headache treatment in the previous month, and (4) weight and height with calculation of body mass index (BMI).[19] BMI was classified following the NIH guidelines.[20]

Laboratory assessment

At the baseline (0 months) and last (6 months) visit, the patients underwent a measurement of TSH, FT4, and prolactin. At the same visits, an oral glucose tolerance test (OGTT) was performed with 1.75 g of glucose per kg of weight (up to 75 g).[21] Glucose was measured using an immunoenzymatic method (Roche Diagnostics, Germany) and insulin with an immunofluorometric assay (Tosoh Bioscience, Japan). IR was operationally defined as any value of OGTT insulin >99th internal percentile, that is, ≥10 μU/mL at 0 min and ≥55 μU/mL at 30, 60, or 120 min according to our internal laboratory. The quantitative insulin sensitivity check index (QUICKI)[22] and the Stumvoll index[23,24] were calculated as surrogate markers of insulin sensitivity.

Treatment

All patients took ALA 400 mg b.i.d. (Tiobec, Laborest, Italy) for 6 months in addition to their on-going treatment.

Outcomes

The primary outcome was the percentage of patients with a reduction of at least 50% of the number of attacks. Because this outcome is expressed as a change versus the baseline, only the 2-, 4-, and 6-month follow-up visits were considered for the analysis. This outcome was chosen because it is the criterion currently used to determine the efficacy of headache treatment.[18] We, however, analyzed also the change in the number of attacks during the study using all the visits (0-, 2-, 4-, and 6-month visits). The coprimary outcome was the change in the number of days of treatment in the previous month. Such analysis was performed using all visits (0, 2, 4, and 6 months). The secondary outcomes were the changes of QUICKI and the Stumvoll index at 6 versus 0 months. We also analyzed the changes in insulin at 0 min, insulin at 120 min, glucose at 0 min, glucose at 120 min, and BMI at 6 versus 0 months. The secondary outcomes were chosen based on our hypothesis that ALA may reduce migraine attacks by increasing insulin sensitivity.

Table 1. Baseline Measurements of the Subjects

	Without aura (N = 26)	*With aura (N = 6)*	*All (N = 32)*
Age (years)	44 (39–50)	44 (29–63)	44 (32–52)
Sex, *n* (%)			
Female	24 (92)	3 (50)	27 (84)
Male	2 (8)	3 (50)	5 (16)
Number of attacks per month	8 (4–20)	2 (0–3)	8 (4–20)
Number of days of treatment per month	6 (2–10)	2 (0–3)	4 (2–8)
BMI (kg/m^2)	24.7 (21.1–30.1)	26.0 (22.6–27.5)	25.2 (21.3–29.2)
BMI class (NIH), *n* (%)			
Underweight	2 (8)	1 (17)	3 (9)
Normal	12 (46)	1 (17)	13 (41)
Overweight	5 (19)	3 (50)	8 (25)
Obesity class 1	6 (23)	1 (17)	7 (22)
Obesity class 2	1 (4)	0 (0)	1 (3)
Glucose at 0 min (mg/dL)	100 (93–103)	89 (85–111)	100 (92–104)
Glucose at 30 min (mg/dL)	153 (137–167)	146 (126–152)	151 (137–166)
Glucose at 60 min (mg/dL)	139 (111–164)	114 (78–173)	126 (102–173)
Glucose at 120 min (mg/dL)	109 (80–120)	78 (70–81)	98 (75–118)
Insulin at 0 min (μU/mL)	12 (8–15)	20 (7–22)	12 (7–18)
Insulin at 30 min (μU/mL)	99 (66–150)	120 (98–161)	107 (71–159)
Insulin at 60 min (μU/mL)	103 (84–154)	124 (82–231)	103 (82–160)
Insulin at 120 min (μU/mL)	64 (37–107)	58 (17–94)	64 (35–107)
QUICKI (dimensionless)	2.13 (2.08–2.18)	2.09 (1.89–2.16)	2.13 (2.06–2.16)
Stumvoll index (μmol·kg^{-1}·min^{-1}·pmol·L^{-1})	0.08 (0.06–0.09)	0.08 (0.06–0.12)	0.08 (0.06–0.10)

Values are medians and interquartile ranges.

BMI, body mass index; NIH, National Institutes of Health Classification; QUICKI, quantitative insulin sensitivity check index.

Statistical analysis

All continuous variables besides QUICKI were not normally distributed as detected by using kernel density plots and the Shapiro–Wilk test and all are reported as median and interquartile range. Discrete variables are reported as numbers and percentages. We used generalized estimating equations (GEE) to quantify the time-related changes of the outcomes of interest 25. The GEE used a binomial family and a log link for the binary outcome (reduction of attacks ≥50% compared with baseline, 0 = no; 1 = yes), a Poisson family and log link for the count outcomes (number of attacks and number of days under headache treatment), and a Gaussian family and an identity link for the continuous outcomes (BMI, glucose at 0 min, glucose at 120 min, insulin at 0 min, insulin at 120 min, QUICKI, and Stumvoll index). The predictor variable of all the GEE, that is, time, was modeled as discrete (0 = baseline; 1 = 2 months; 2 = 4 months; 3 = 6 months). Three time points (2, 4, and 6) were used for the binary outcome; four time points (0, 2, 4, and 6) for the count outcome; and two time points (0 and 6 months) for the continuous outcomes (see also Outcomes section). The GEE correlation matrix was set to exchangeable in all cases. GEE can handle data missing completely at random (MCAR). An analysis of residuals was performed to evaluate model fitting as described in detail elsewhere.[25] Statistical analysis was performed using Stata 14.2 (Stata Corporation, College Station, TX, USA).

RESULTS

The baseline measurements of the 32 migraineurs consecutively enrolled into the study are given in Table 1. Twenty-seven (84%) of them were women and 26 (81%) had migraine without aura.

Table 2 lists concomitant diseases and Table 3 the pharmacological treatment at the baseline visit.

Before the enrolment (from 6 months to 5 years), all patients had been prescribed a low-carbohydrate diet with frequent meals. The proportion of patients (16, corresponding to 50%) compliant to such a diet was unsatisfactory. No patient regularly performed physical activity before or during the study.

The percentage of patients with a reduction of at least 50% of the attacks was 0.53 (confidence interval [95% CI] 0.36–0.70) at 2 months, 0.56 (0.39–0.63) at 4 months and 0.69 (0.53–0.85) at 6 months (Fig. 1A and Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/jmf).

The incidence rate ratio of attacks at 6 versus 0 months was 0.48 (95% CI 0.43–0.53, $P < .001$) corresponding to a mean (95% CI) number of attacks of 5 (95% CI 4–6) versus 11 (95% CI 10–12) (Supplementary Table S2).

The number of days of treatment in the previous month was 7.7 (95% CI 6.8–8.7) at baseline, 5.4 (4.6–6.2) at 2 months, 5.3 (4.5–6.1) at 4 months, and 4.3 (3.6–5.0) at 6 months (Fig. 1B and Supplementary Table S3).

The values of glucose and insulin at 0 and 30 min were missing in two patients and those at 60 and 120 min were missing in two patients. All patients completed the study but six did not repeat the OGTT at the end of the study. Such missing data were handled by GEE under the MCAR assumption. The values of BMI, glucose at 0 min, glucose at 120 min, insulin at 0 min, insulin at 120 min, QUICKI, and the Stumvoll index are given in Table 4. No statistically significant or clinically relevant change was observed in any of these variables.

Table 2. List of Diseases Other Than Insulin Resistance

Diseases	*No. of patients*
Vascular	
Hypertension	5
Patent foramen ovale	10
Myocardial infarction	1
Vein thrombosis	2
Lacunar encephalopathy	4
Hematologic	
Hyperhomocysteinemia	1
Antiphospholipid carrier	2
Protein S deficit	1
Chronic anemia	1
Immune-rheumatologic	
Connective tissue disorders	2
Psoriasis	6
Fibromialgia	1
Arthritis	1
Sarcoidosis	1
Allergy	3
Digestive	
Gastrointestinal diseases	10
Liver disorders	5
Endocrine	
Thyroid disorders	7
Hyperparatiroidis	2
Pituitary microadenoma	1
Polycystic ovarian syndrome	2
Neurologic	
Anxiety-depression	13
Epilepsy	1
Previous cerebral neoplasm	2
Arnod–Chiari syndrome	1
Peripheral neuropathy	1
Restless leg syndrome	1
Myotonic dystrophy	1
Other	
Neck–back disorders	14
Cheratocono	2
Asthma	1
Hypercholesterolemia	2
Hypertrigliceridemia	1
Kidney disorders	5
Previous neoplasm	1
Hypergammaglobulinemia	1
Hyper-IgE syndrome	1

DISCUSSION

We performed an exploratory study to evaluate whether ALA has the potential to reduce the frequency of headache

Table 3. List of Pharmacological Treatments the Patients Were Taking at the Baseline

Drug	*No. of patients on therapy*
Endocrine-metabolic	
Metformin	8
Acarbose	1
Cabergoline	1
Levotiroxine	7
Desogestrel	2
Estradiol valerate+dienogest	1
Ethinylestradiol+desogestrel	1
Antiplatelet drugs	
Acetyl salicylic acid	19
Clopidogrel	2
Antihypertensive	
Sartans	4
Angiotensin-converting enzyme inhibitors	1
Sartan plus hydrochlorothiazide	1
Beta-blockers	2
Neurologic	
Paroxetine	3
Citalopram	2
Sertraline	1
Duloxetine	1
Amisulpride	1
Amitriptiline	2
Mirtazapine	1
Pregabalin	1
Gabapentin	2
Levetiracetam	1
Topiramate	1
Benzodiazepines	3
Supplementations	
Folic acid	5
Vitamin B complex	1
Vitamin C	6
Vitamin D	9
Iron	1
Ca, Mg, K	3
Others	
Pantoprazole	2
Esomeprazole	1
Ranitidine	1
Atorvastatin	1
Etoricoxib	1
Idroxiclorochine	1

attacks in migraineurs with IR. We found a significant reduction in the number of attacks and days of treatment in migraineurs who had not responded to diet and metformin.

However, contrary to our expectations, such effects were not accompanied by changes in QUICKI, Stumvoll index, glucose and insulin. Hence, these preliminary findings do not support the idea that ALA may reduce migraine attacks by modulating glucose homeostasis. However, another potential mechanism by which ALA might reduce migraine attacks is its antioxidant effect. Indeed, migraine has been linked to oxidative stress,[5–9] and ALA is a potent antioxidant.[7,9,12–17]

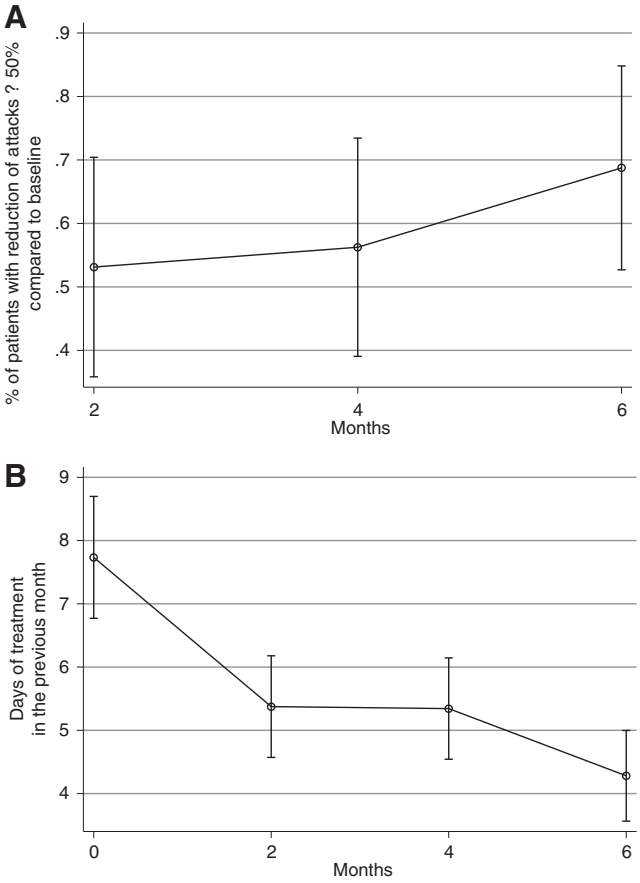

FIG. 1. Percentage of patients with reduction of attacks ≥50% compared with baseline **(A)** and days of treatment for migraine in the previous month **(B)** during the study. The effect sizes in **(A)** are obtained from the model given in Supplementary Table S1 and those in **(B)** from the model given in Supplementary Table S3.

This study has several limitations. First, it is an exploratory cohort study lacking a control group. Only a randomized controlled trial (RCT), with an adequate control group, would be able to adequately test the hypothesis that ALA can reduce the number of migraine attacks. We believe that the evidence provided by the present cohort study

Table 4. Secondary Outcomes at the Baseline Visit and 6-Month Follow-Up

	Baseline	*6-month*
BMI (kg/m^2)	25.5 (23.8–27.2)	25.0 (23.3–26.7)
Glucose at 0 min (mg/dL)	98 (95–101)	98 (94–101)
Glucose at 120 min (mg/dL)	104 (93–115)	101 (89–113)
Insulin at 0 min (μU/mL)	14 (11–16)	12 (10–15)
Insulin at 120 min (μU/mL)	76 (57–95)	69 (49–90)
QUICKI (dimensionless)	2.12 (2.07–2.16)	2.12 (2.07–2.17)
Stumvoll index ($\mu mol \cdot kg^{-1} \cdot min^{-1} \cdot pmol \cdot L^{-1}$)	0.08 (0.07–0.09)	0.08 (0.07–0.09)

Values are means and 95% confidence intervals estimated from generalized estimating equations with Gaussian family and identity link and discrete time as predictor. Missing data were handled under the missing completely at random assumption. No between-time difference is statistically significant.

justifies the design and conduct of such experimental study. Second, due to the low number of migraineurs with aura, we could not evaluate the differential effect of ALA in such patients. It is, however, of some interest that aura disappeared in four out six patients.

In conclusion, the present exploratory study shows that the administration of ALA is associated with a reduction in the number of attacks and days of treatment in migraineurs with IR. Based on such promising observational data, an RCT would be welcome to evaluate the effectiveness of ALA as a treatment for headache in migraineurs with IR.

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AUTHORS' CONTRIBUTIONS

C.C. designed and co-coordinated the study and drafted the article. G.B. performed statistical analysis and revised the article. F.M. performed laboratory tests. S.M. performed data collection. E.R. revised the article. M.C.F. co-coordinated the study.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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