Docosahexaenoic Acid Is a Beneficial Replacement Treatment for Spinocerebellar Ataxia 38

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Objective: Spinocerebellar ataxia 38 (SCA38) is caused by mutations in the ELOVL5 gene, which encodes an elongase involved in the synthesis of polyunsaturated fatty acids, including docosahexaenoic acid (DHA). As a consequence, DHA is significantly reduced in the serum of SCA38 subjects. In the present study, we evaluated the safety of DHA supplementation, its efficacy for clinical symptoms, and changes of brain functional imaging in SCA38 patients.

Methods: We enrolled 10 SCA38 patients, and carried out a double-blind randomized placebo-controlled study for 16 weeks, followed by an open-label study with overall 40-week DHA treatment. At baseline and at follow-up visit, patients underwent standardized clinical assessment, brain 18-fluorodeoxyglucose positron emission tomography, electroneurography, and ELOVL5 expression analysis.

Results: After 16 weeks, we showed a significant pre–post clinical improvement in the DHA group versus placebo, using the Scale for the Assessment and Rating of Ataxia (SARA; mean difference [MD] = 51 2.70, 95% confidence interval [CI] = 51 0.13 to 51 5.27, p = 0.042). At 40-week treatment, clinical improvement was found significant by both SARA (MD = 51 2.2, 95% CI = 51 0.93 to 51 3.46, p = 0.008) and International Cooperative Ataxia Rating Scale (MD = 51 3.8, 95% CI = 51 1.39 to 51 6.41, p = 0.02) scores; clinical data were corroborated by significant improvement of cerebellar hypometabolism (statistical parametric mapping analyses, false discovery rate corrected). We also showed a decreased expression of ELOVL5 in patients' blood at 40 weeks as compared to baseline. No side effect was recorded.

Interpretation: DHA supplementation is a safe and effective treatment for SCA38, showing an improvement of clinical symptoms and cerebellar hypometabolism.

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Spinocerebellar ataxias (SCAs) are a group of autosomal dominant neurological disorders with a prevalence of 5.5 in 100,000.1 SCAs are phenotypically characterized by gait and limb ataxia, incoordination of eye movements, and speech disturbances. Cerebellar hypometabolism is well documented and considered a main diagnostic marker.2,3 More than 40 SCA subtypes have been reported, and 34 genes have been identified so far. Three main categories are defined on the basis of the mutation type,4 namely those due to CAG-coding polyglutamine repeat expansion, noncoding repeat expansions, and conventional mutations (http://neuromuscular.wustl.edu/ataxia/domatax.html).

We recently identified SCA38 (Mendelian Inheritance in Man 611805) as caused by mutations in the ELOVL5 gene.5 The disease onset is in the fourth decade of life, characterized by slowly progressive gait ataxia and associated in most of the cases with pes cavus and hypoesthesia. The disease progresses with limb ataxia, dysarthria, dysphagia, ophthalmoparesis, and, in the later stages, sensory loss. Brain imaging documented cerebellar hypometabolism with sparing of cerebral cortex.6

ELOVL5 encodes an elongase enzyme involved in the synthesis of very long-chain fatty acids with a high and specific expression in Purkinje cells.7 Its main products are the 22-carbon docosahexaenoic acid (DHA) and eicosapentaenoic acid of the omega-3 polyunsaturated fatty acid class. ELOVL5 mutations likely cause both an altered function of the enzyme and a possible gain of function. As a consequence, SCA38 patients have a reduction of serum DHA, and increased ELOVL5 gene expression and protein levels induced by transcriptional feedback loop regulation.5

In the present work, we performed a clinical trial on 10 SCA38 patients, and we demonstrated that oral DHA supplementation is a safe and effective treatment, exerting clinical efficacy and influencing cerebellar metabolism.

Patients and Methods

Subjects

Ten subjects affected by SCA38 were evaluated at the Center for Ageing Brain and Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Italy. Genetic test confirmed the c.689G>T (p.Gly230Val) variant.5 Patients had already been included in a previous work on clinical features of SCA38.6 Written informed consent was obtained from all patients.

In the Table, patients’ demographic and clinical features are reported. Mean age was 48.7 ± 10.8 years, and the mean age at onset was 38.4 ± 6.8 years; 6 patients were females, 4 males.

The study was approved by the ethics committee of Brescia Hospital, Italy (NP1821) and conformed to the Declaration of Helsinki principles.

Study Drug

The study drug was a algal oil derived-DHA (Sofedus, Milan, Italy) administered as sachets dosed at 600mg/day. Algal DHA contains approximately 75% of DHA by weight and does not contain eicosapentaenoic acid. The DHA dose was established considering a meta-analysis on several reported trials.7 The intake of 600mg/day of DHA was the highest dose employed in the majority of the studies without side effects. DHA and placebo sachets were indistinguishable and produced by the same company.

Study Design

The study design is shown in Figure 1. We performed a 2-phase trial: (1) a randomized double-blind placebo-controlled phase of 16 weeks and (2) an open-label phase of 40-week DHA supplementation. White bar = placebo treatment; gray bars = DHA treatment. Black blocks indicate the time points of clinical assessment (brain 18-fluorodeoxyglucose positron emission tomography [FDG-PET], electromyography/electroneurography [ENG], and blood sampling [blood]). w = weeks.

![FIGURE 1: Study design. We conducted a 2-phase trial consisting of a randomized double-blind placebo-controlled phase of 16 weeks, and an open-label phase of 40-week docosahexaenoic acid (DHA) supplementation. White bar = placebo treatment; gray bars = DHA treatment. Black blocks indicate the time points of clinical assessment (brain 18-fluorodeoxyglucose positron emission tomography [FDG-PET], electromyography/electroneurography [ENG], and blood sampling [blood]). w = weeks.](image-url)
[FDG] positron emission tomography [PET] scan, electromyography [EMG]/electroneurography [ENG], and blood sampling for biological analyses.

**INCLUSION CRITERIA.** Inclusion criteria were: (1) symptomatic p.Gly230Val mutation carriers, (2) age > 18 years old, and (3) ambulant (SARA score at baseline < 23).

**EXCLUSION CRITERIA.** Exclusion criteria were: (1) reported poor compliance with drug regimen, (2) uncontrolled diabetes (exclusion criterion to perform FDG-PET scan), (3) serum creatinine levels > 2.0mg/dl, (3) alcohol abuse (equivalent to > 12g/day) over the 30 days prior to screening, and (4) evidence of drug abuse within 6 months prior to screening.

**BLINDNESS.** To ensure blindness in the clinical assessment scoring, at each time point (T0, T1, and T2) neurological examination was video-recorded and analyzed blind by A.A., who was unaware of both time point and treatment (DHA or placebo), as the videos were presented randomly. Brain FDG-PET analyses were carried out by Statistical Parametric Mapping (SPM), which is fully automated, unbiased, and operator-independent software. Biological analyses were conducted by E.D.G., N.M., and D.C. without knowledge of time point and treatment intervention.

**OUTCOME MEASURES.** As primary efficacy measure, we evaluated the significant mean change from enrollment/baseline to endpoint on the clinical scales (SARA and ICARS). Secondary efficacy measures included change from baseline to endpoint on brain FDG-PET imaging and on DHA and ELOVL5 levels in blood.

**SAFETY ASSESSMENTS.** Safety assessments were conducted at screening and at each visit. Adverse events were elicited by questioning the patient throughout the study and through direct observation by the clinical team.

**Clinical Assessment, Instrumental Evaluation, and Molecular Analyses**

At each time point, videotapes of the SARA (range = 0–40) and the ICARS (range = 0–100) were employed to evaluate cerebellar deficits. Intra-assay variability of SARA and ICARS scores was evaluated between 2 independent neurologists (A.A. and M.M., SARA and ICARS alpha-Cronbach = 0.983 and 0.995, respectively).

Brain PET image-processing procedures were carried out using MATLAB (http://it.mathworks.com/products/matlab/; MathWorks, Sherborn, MA) and SPM (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) software. Details on image preprocessing are given elsewhere.10 Cerebellar metabolism changes were evaluated by nonparametric permutation test (10,000-permutation Statistical NonParametric Mapping; T0 vs T1 and baseline vs T2), and the threshold was set at \( p < 0.05 \), false discovery rate (FDR) cluster level corrected.11

EMG and ENG were performed according to standard procedures.

Blood sampling was performed at fast, between 8 and 9 AM. Each patient had undergone a poor-DHA diet, as recommended by an expert dietician, for 2 weeks before each blood sampling, to avoid possible confounders on blood analyses. We measured serum DHA levels and ELOVL5 expression, as previously published.5

**Statistical Analysis**

Comparison of clinical characteristics between groups (placebo vs DHA treatment) was carried out using Mann–Whitney test or chi-square test, as appropriate. To assess the effect of DHA treatment on clinical scores over time, in the double-blind phase we used 2-way mixed analysis of variance (ANOVA) with TIME (T0 vs T1) as within-subject factor and TREATMENT (placebo vs DHA) as between-subjects factor; in the open-label phase, we applied 1-way mixed ANOVA with TIME (baseline vs T2) as within-subject factor. Mauchly test was used to test for assumption of sphericity, whereas Greenhouse–Geisser epsilon determination was used to correct in case of sphericity violation.

Correlation between functional scores and demographic or clinical characteristics was assessed using Spearman rank-order correlations. Statistical analyses were performed using SPSS version 21 (SPSS, Chicago, IL).

**Results**

**Randomized Double-Blind Placebo-Controlled Phase**

No significant differences in demographic characteristics or SARA and ICARS scores between patients who received DHA or placebo were found. Clinical evaluation by SARA scores of the DHA versus placebo groups after 16 weeks (T0 vs T1) showed a statistically significant TIME × TREATMENT interaction (T0 vs T1, mean ± standard error, DHA group: 10.8 ± 1.0 vs 7.8 ± 0.9; placebo group: 9.7 ± 3.2 vs 9.4 ± 4.0; \( F_{1,8} = 5.88, p = 0.042 \); Fig 2A).

The pre–post effect (T0 vs T1) of the DHA group exhibited a non-null mean difference (MD) in SARA scores (MD = +3.00, 95% confidence interval [CI] = +1.46 to +4.65) as compared to the placebo group (MD = +0.30, 95% CI = −1.25 to +1.84). Accordingly, the TIME × TREATMENT mean difference was non-null (3.00 to 0.30 = +2.70, 95% CI = +0.13 to +5.27).

On ICARS scores, there was also an improvement, but not statistically significant TIME × TREATMENT interaction (T0 vs T1, DHA group: 22.0 ± 3.3 vs 17.0 ± 2.5; placebo group: 20.6 ± 8.1 vs 21.0 ± 9.2; \( F_{1,8} = 4.25, p = 0.073 \); see Fig 2A). The coverage interval of the TIME × TREATMENT mean difference included the null value (5.00 − [−0.40] = +5.40, 95% CI = −0.64 to +11.40), although the DHA group had a non-null pre–post effect (MD = +5.00, 95% CI = +1.37
18.63) as compared to the placebo group (MD = 0.4, 95% CI = 4.03 to + 3.23).

In both DHA and placebo groups, no significant differences of cerebellar metabolism at the preestablished threshold between T0 and T1 (T0 < T1) were reported. EMG/ENG parameters were unchanged in both groups. Serum DHA levels and ELOVL5 expression did not show any significant TIME × TREATMENT interaction.

Open-Label Phase

Each subject underwent DHA treatment (600mg/day) in the open-label phase for 40 weeks, and the differences between baseline and 40-week follow-up (T2) were evaluated. We found a significant improvement in clinical symptoms, with significantly reduced SARA scores at T2 compared to baseline (baseline: 10.1 ± 1.9, T2: 7.9 ± 1.7; MD = +2.2, 95% CI = +0.93 to + 3.46; F1,9 = 11.4, p = 0.008; see Fig 2B). The same pre–post effect was shown for ICARS scores (baseline: 21.5 ± 4.6, T2: 17.9 ± 4.2; MD = +3.8, 95% CI = +1.39 to + 6.41; F1,9 = 7.96, p = 0.020; see Fig 2B).

A significant difference in cerebellar metabolism between baseline and T2 was observed, with an increase in cerebellar metabolism at T2 as compared to baseline in the left posterior cerebellar lobe (x, y, z = 32, −79, −23; T = 8.56; p = 0.03, cluster size = 558) and in the right posterior cerebellar lobe (x, y, z = 22, −84, −17; T = 7.74; p = 0.03, cluster size = 475; Fig 3). No significant differences in the opposite contrast (baseline > T2) were found at the preestablished threshold.

On EMG/ENG, motor and sensory conduction velocities did not worsen during 40-week DHA treatment.

No differences in serum DHA levels before and after 40-week treatment were found. We showed a slight but significant reduction of ELOVL5 expression in blood comparing T2 with baseline (reduction to 88% from baseline, 95% CI = 74% to 94%; F1,9 = 5.48, p = 0.044).

There was no significant correlation between the change in SARA and ICARS scores (T2 minus baseline scores) and age, gender, age at disease onset, duration of disease, SARA and ICARS scores at baseline, change of ELOVL5 expression, and change of cerebellar metabolism as measured by brain FDG-PET (Spearman rank-order correlation, all p > 0.05).

Safety Assessment

No side effects or adverse events were reported during DHA supplementation in either the double-blind or the open-label phase.

Discussion

No effective treatment is currently available for most hereditary ataxias, and management remains supportive and symptomatic.12,13 The rationale of this study stemmed from the observation that SCA38 is characterized by an increased amount of ELOVL5 protein with a mislocalization of the aberrant form in the Golgi apparatus and by a decrease of its final products, in particular DHA, in patients’ serum.5

Because ELOVL5 is strictly regulated by the amount of arachidonic acid and DHA via a transcriptional feedback loop,14 we reasoned that the administration of DHA might have exerted a double goal: compensating the decrease of very long chain fatty acids
and lowering \(ELOVL5\) aberrant protein.\(^5\) The endogenous synthesis of DHA within the brain is low compared with its uptake from dietary and/or liver sources.\(^{15,16}\) DHA is a well-known dietary supplement, well tolerated at high dosage and with the ability to cross the blood–brain barrier by passive and active transport.\(^{17–19}\)

In recent years, polyunsaturated fatty acids like DHA have gained much attention due to promising results in a number of neurodegenerative conditions.\(^{20,21}\) Moreover, polyunsaturated fatty acids are required for the normal development of the central nervous system and their deficiency can impair cerebral function in mice.\(^{22}\)

### TABLE. Demographic and Clinical Characteristics of Enrolled Patients according to Treatment Group

| Variable                      | DHA Group | Placebo Group | SCA38 Overall Group, \(n = 10^a\) |
|-------------------------------|-----------|---------------|-----------------------------------|
| Gender                        | M M F F F | F M M F F     | 40% M                             |
| Age at onset, yr              | 38 46 35 38 36 | 50 44 34 37 26 | 38.4 ± 6.8                      |
| Age at evaluation, yr         | 46 49 51 49 39 | 73 47 40 58 35 | 48.7 ± 10.8                     |
| SARA score, \(T_0\)           | 13.5 9.0 13.0 10.0 8.5 | 17.5 5.0 6.0 17.5 2.5 | 10.2 ± 5.1                     |
| ICARS score, \(T_0\)          | 32.0 18.0 28.0 17.0 15.0 | 36.0 6.0 13.0 44.0 4.0 | 21.3 ± 13.2                     |
| First symptom                 | Gait ataxia Gait ataxia Gait ataxia Gait ataxia | Gait ataxia Gait ataxia Gait ataxia | —                               |

\(^a\)Mean ± standard deviations, otherwise specified.

DHA = docosahexaenoic acid; F = female; ICARS = International Cooperative Ataxia Rating Scale; M = male; SARA = Scale for the Assessment and Rating of Ataxia; SCA38 = spinocerebellar ataxia 38; \(T_0\) = time at enrollment.
In this study, we showed that DHA supplementation ameliorates clinical symptoms and cerebellar metabolism in SCA38 patients. Our data are in agreement with the hypothesis that DHA intake, acting directly on ELOVL5 expression, reduces mutant ELOVL5 cellular levels, as indicated by a decrease of ELOVL5 expression in patients’ blood after 40-week DHA treatment. Furthermore, a general neuroprotective effect of DHA may occur, by promoting brain cell survival and repair through neurotrophic, antiapoptotic, and anti-inflammatory signaling. As expected, DHA administration was safe and no side effect was reported.

The rationale of our study was similar to that described for X-linked adrenoleukodystrophy and Lorenzo oil treatment, the administration of which was able to normalize very long chain fatty acids in plasma and to provide a clinical benefit.

We conducted the present phase II study in 2 stages. We had already demonstrated a clinical improvement in the double-blind randomized placebo-controlled phase, although the low number of subjects (5 DHA vs 5 placebo) and the short-term follow-up prevented us from reporting significant changes of cerebellar metabolism and ELOVL5 expression. In the open-label phase presented here, in which we considered the 10 patients longitudinally, we reported significant clinical improvement, especially of posture and gait, along with a marked increase in cerebellar hypometabolism and restored ELOVL5 expression.

We acknowledge that the small number of patients and the lack of one of primary efficacy measure outcome (ie, ICARS) in the double-blind placebo-controlled phase are limitations of the study. Moreover, we did not find any significant change of serum DHA levels before and after treatment, and this might give rise to concerns regarding the robustness of the effect. Larger phase III studies addressing long-term efficacy and administration in still asymptomatic subjects with ELOVL5 mutations are warranted to prove DHA supplementation to be an effective therapy for SCA38. All patients included in this study carry the same mutation in ELOVL5. Therefore, only the effect of DHA on this single mutation has been assessed in this trial and generalization to all SCA38 patients is not possible, requiring further studies.

Possible benefits of DHA supplementation in other SCAs with reduced brain fatty acids and phospholipids, such as SCA1 and Friedreich ataxia, also need to be considered. Based on this observation, we may speculate that supplementation with DHA, the main component of brain phospholipids, might be beneficial in the early stage of such diseases.

The treatment is a relatively inexpensive (approximately $500 per patient per year), well tolerated, and easy to administer as a dietary intervention. We propose that this evidence-based strategy started early in life might delay disease onset and slow the progression of symptoms in SCA38. Thanks to replacement treatment, a delayed dependency in these patients may sensibly reduce direct and indirect costs on national health systems.

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Author Contributions
E.D.G., A.B., and B.B. contributed to the concept and study design. All authors contributed to data acquisition and analysis. M.M., A.A., A.B, and B.B. drafted the manuscript and figures, and all authors approved the final version.

Potential Conflicts of Interest
Nothing to report.

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