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The Effects of N-Acetyl-L-Leucine on the Symptoms in Patients with Spinocerebellar Ataxia: A Four-Case Experimental Study

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Abstract

Background & Objective: This study aimed to evaluate the effect of N-acetyl-L-leucine (NALL) supplementation on motor symptoms and quality of life (QOL) in patients with spinocerebellar ataxia (SCA). Due to the lack of effective treatments for this disorder and previous evidence suggesting potential neuroprotective effects of this compound, investigating its efficacy could be a crucial step toward improving clinical outcomes.

Methods: This study was a four-case experimental study with a cross-over design involving children with SCA. Patients were randomly assigned to one of two treatment sequences: the intervention-placebo sequence, or the placebo–intervention sequence. During the first phase, one group received NALL supplementation while the other received a placebo over four weeks. Following a four-week washout period, the treatment sequences were switched between the two groups. Patients were evaluated using standard measures including SARA, SCAFI, and the PedsQL QOL questionnaire at baseline and the end of each phase. A fasting blood sample was taken from all participants at each stage of the study. Additionally, adverse drug reactions were assessed after each intervention to monitor safety.

Results: Four girls with SCA, with an average age of 12.25±2.87 years, completed the study. The findings suggested improvements in the Total SARA Score, physical functioning as reported by the parents, and psychosocial health as reported by the child. The study showed that administering 2-4 grams of NALL per day over a four-week period to these patients did not result in any adverse effects.

Conclusion: Short-term NALL supplementation appeared safe and well tolerated in this small series. The trends towards improvement in certain measures, along with positive individual clinical responses, highlight the need for larger, longer-term, and more rigorously controlled trials.

Key Words: N-acetyl-L-leucine; Neurodegenerative disease; Motor symptoms; Quality of life; Spinocerebellar ataxia.

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1- INTRODUCTION

Spinocerebellar ataxias (SCAs) are heterogeneous progressive disorders that lead to premature death (1). The global prevalence of SCA is reported as 1-5 per 100,000. In Europe, the prevalence is 0.9 to 3 per 100,000. SCA3 is known as the most common type of SCAs, followed by SCA2, SCA6, and SCA7 (2). The primary clinical characteristic of these disorders is a loss of balance and motor coordination, often accompanied by slurred speech, with onset typically occurring in adulthood. Genetically, SCAs can be categorized into two groups: those caused by gene duplication expansions, and the less common group caused by non-recurrent mutations (3).

Most SCA mutations result in significant damage to cerebellar Purkinje neurons. Additionally, other parts of the nervous system, including the spinal cord, basal ganglia, and pontine nuclei in the brainstem, may also be affected (1). Instead of being caused by a single molecular mechanism, each type of SCA may involve multiple pathogenic pathways simultaneously, including: proteotoxicity/toxic gain-of-function, RNA toxicity, protein loss-of-function, mitochondrial dysfunction, ion channel dysfunction, transcriptional dysregulation, and glial cell dysfunction (4).

Currently, there is no known treatment for SCAs, so clinical care is mainly symptomatic. This includes medications that modulate cerebellar circuits and focuses on managing symptoms (1). New research includes antisense oligonucleotides, RNA interference, and stem cell therapies (5). Newer drugs, such as Troriluzole, which has recently entered a phase III trial, are also being evaluated (5). The available evidence suggests that N-acetyl-DL-leucine (NADLL, Tanganil) can improve cerebellar function and slow the progression of symptoms through neuroprotective and anti-inflammatory effects (6-9). It has shown potential beneficial effects in improving motor symptoms in pre-clinical and clinical studies (7-11). N-acetyl-L-leucine (NALL), also known as Levacetylleucine, is actually the L-enantiomer of the racemic mixture (NADLL) and has recently attracted attention for its neuromodulatory properties and potential for the treatment of ataxia disorders (10,12). However, this evidence is mainly limited to studies conducted abroad, and its efficacy has not yet been evaluated in the country.

Given the genetic, environmental, and epidemiological differences between populations, conducting such a study is necessary to accurately evaluate the effects of the drug in patients in our country. Additionally, the rarity of the disease and the lack of effective treatments double the importance of conducting innovative interventional research. This study could be the first step towards a scientific and documented study of this medicinal compound and pave the way for more extensive research and the design of targeted therapeutic interventions. While the racemic mixture, NADLL, has been used in some clinical trials, the current study specifically utilized the pure L-enantiomer, NALL, due to its specific pharmacological activity (12).

2- METHODS

2-1. Study Design and Population

The current study was a four-case experimental study (13) that was registered in the Iranian Registry of Clinical Trials (IRCT) system (ID= IRCT20210413050958N7; 26.05.2023). A pediatric neurologist at Ghaem Hospital introduced four patients with SCA to the research team. The study objectives were then explained to them.

The volunteer was randomly assigned to one of two treatment sequences and received the NALL or placebo for 4 weeks, and then transferred to the

alternative treatment after a 4-week washout period (Figure 1). A 4-week washout period is long enough to prevent the effects of NALL (14). The dosing algorithm of the supplement during the two 4-week periods was described in Table 1 (15, 16).

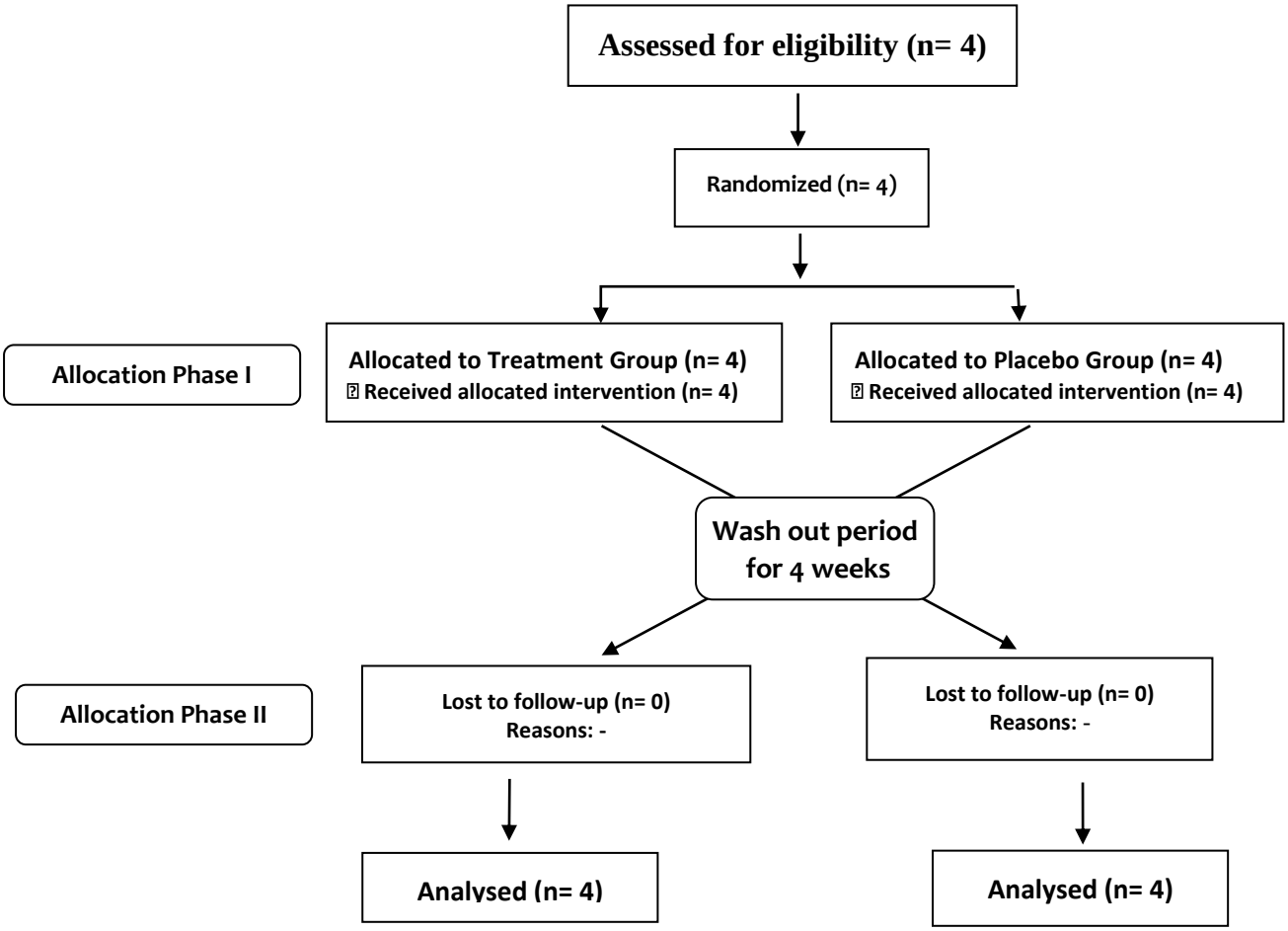


Figure-1: The study flowchart. Patients received their first intervention, then crossed over to the opposite intervention after a 4-week washout.

Table-1. Clinical dosing algorithm based on age and body weight criteria (15, 16).

Age/Weight Group	Daily Dose (gr)	Dosing Schedule (gr)		
		Morning	Afternoon	Evening
≥ 13 years old or 6-12 years old and weighed ≥ 35 kg	4	2	1	1
6- 12 years old and weighed 25 to <35 kg	3	1	1	1
6 to -12 years old and weighed 15 to <25 kg	2	1	-	1

Abbreviation gr: grams; **kg:** kilograms.

2-2. Outcome Measurement

Motor function was evaluated using the Scale for Assessment and Rating of Ataxia (SARA) and Spinocerebellar Ataxia Functional Index (SCAFI) scores as primary outcomes for each volunteer. The language validation for the primary outcome (SARA) has been formally addressed. We utilized the validated Persian version of the SARA scale, for which the reliability and validity have been rigorously established through a dedicated research study (17). To ensure consistency and eliminate inter-rater bias, a trained

medical student performed all assessments for every participant at each time point. He underwent specific training in the administration of the SARA and the SCAFI before the initiation of the study to ensure reliability.

Furthermore, quality of life (QOL) was assessed using the Persian version of the PedsQL questionnaire as secondary outcomes (18).

2-3. Inclusion and Exclusion Criteria

Inclusion criteria: Patients must meet all of the following criteria to be eligible for the study: 1- Definitive diagnosis of SCA, 2- Age over 6 years, 3- Presence of clinical symptoms of SCA, 4- If the patient is currently taking any medication, the dose must be stable, and no changes in treatment are allowed during the study, 5- not currently taking any of the following medications: NADLL, aminopyridines, riluzole, gabapentin, varenicline, chlorzoxazone, sulfasalazine, or rosuvastatin. 6- No history of chronic diarrhea, malignancy, insulin-dependent diabetes, or hypersensitivity to N-acetyl-leucine. 7- No significant visual or hearing impairment. 8- No arthritis or other musculoskeletal disorders.

Exclusion criteria: Patients meeting any of the following criteria were excluded from the study: 1-Unwillingness to continue participation in the study. 2- Compliance less than 90% with the study medication.

2-4. Drug Preparation

NALL powder was obtained from a commercial supplier (Shenzhen Ipure Biological Co., Ltd). Caplets containing NALL and placebo (500 mg) were provided in the School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran. Placebo Caplets were the same shape, weight, and color as the NALL ones.

2-5. Blinding, Randomization and Allocation Concealment

A staff member outside the research team blinded the medications. All volunteers, the implementation team, and the statistical analyst were blinded to the medications.

Participants were randomly assigned to one of two treatment sequences: 1- the intervention-placebo sequence (AB), or 2- the placebo–intervention sequence (BA). A restricted randomization method was used to achieve a perfect 2-2 balance. Four cards were prepared, two labeled “AB” and the others labeled “BA.” The cards were placed in opaque, sealed, and sequentially numbered envelopes and thoroughly shuffled to ensure concealment of the allocation sequence until the time of assignment. As each patient entered the study, one of the envelopes was drawn without replacement and assigned to that participant. This process continued until all four envelopes were drawn.

2-6. Safety Parameters

To evaluate probable adverse drug reactions (ADR), fasting blood samples were taken before and after both study phases. The complete blood count (CBC), serum concentrations of sodium, lactate dehydrogenase, potassium, creatinine, serum bilirubin level, aspartate aminotransferase, alanine aminotransferase, urea, and alkaline phosphatase were measured.

2-7. Statistical Analysis

Data were reported descriptively, with quantitative data expressed as mean and standard deviation (SD), and qualitative data reported as a ratio (percentage). For the data analysis, the effect size and 95% Confidence Interval (CI) of the means have been reported.

2-8. Ethics

The study protocol was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Mashhad University of Medical Sciences (MUMS) (ID= 4010696, IR.MUMS.MEDICAL.REC.1402.038). Written informed consent was obtained from the parent or legal guardian of every participant, together with age-appropriate assent from the participant, and the patients were enrolled in the study.

3-RESULT

A total of four female patients, aged 8 to 16 years, participated in the present study. Table 2 summarizes the baseline characteristics of the subjects. The results of the study showed that the mean age and weight of the patients were 12.25±2.87 years and 40±12.4 kg, respectively.

Table-2. Baseline characteristics of the study population.

Case	Gender	Age (years)	Weight (kg)	Height (cm)	Variant	Age at diagnosis	Physical /speech therapy history	Drug history	Drug received in the first study phase	Count adherence	Parental consanguinity
1	Girl	8	20	122	SCA5	7	Since the age of 5 years	omega 3, vitamin E	B	100%	Yes
2	Girl	16	52	162	SCAR20	12	Between the ages of 8 and 13 years	risperidone, variopeptyl, piracetam, calcium D, folic acid, clonidine, rahakin	A	100%	Yes
3	Girl	12	48	158	SCA7, ceroid lipofuscinosis, neuronal, 2	9	Physical therapy since the age of 8.5 years	propranolol, clonazepam, omega 3	A	100%	Yes
4	Girl	13	40	149	SCA6	3	Physical therapy from 15 months to 4 years; speech therapy between the ages of 5 and 7 years	None	B	75%	None

As summarized in Table 3, NALL was well tolerated by all patients during the study period, with no serious or unexpected adverse events reported. Safety parameters, including indices of liver and kidney function, remained within normal limits.

Table 4 shows the effects of NALL on Ataxia Moving Symptoms in patients with SCA. A slight improvement trend was observed in the NALL group compared to the placebo in the SARA subscales and its total score (Figure 2A).

Table 5 shows the results of the effect of NALL on the quality of life among patients with SCA. Two subscales of physical functioning, as reported by parents (Figure 2B), and psychological functioning, as reported by children themselves (Figure 2C), showed an improvement trend after taking NALL. However, NALL did not have a positive effect on other subscales, including emotional, social, and academic domains, as well as composite indicators of quality of life in both groups.

4- DISCUSSION

In this four-case experimental study, the effect of NALL supplementation on motor symptoms, quality of life, and safety parameters of children with SCA was investigated. Physical functioning from the parent's perspective and psychological functioning from the child's perspective showed a trend toward improvement in the NALL group.

Table-3. The effect of N-acetyl-L-Leucine on safety parameters in patients with spinocerebellar ataxia.

Variables	NALL-Placebo (AB)	Placebo- NALL (BA)	Cohen's d Effect Size	95% Confidence Interval of the Difference
WBC (103/ µ)	0.425±0.247	-0.212±0.053	3.56	-1.32 to 1.40
RBC (103/ µ)	-0.007±0.031	-0.058±0.001	2.27	-0.04 to 0.14
Hemoglobin (g/dl)	0.025±0.070	-0.262±0.017	5.57	0.06 to 0.50
Hematocrit (%)	-0.162±0.123	-0.575±0.318	1.70	-0.62 to 1.45
MCV (fL)	-0.217±0.293	-0.227±0.781	0.01	-2.52 to 2.54
MCH (Pg)	0.088± 0.302	-0.246±0.065	1.53	-0.16 to 0.73
MCHC (103/ µ)	0.177±0.251	-0.178±0.242	1.44	-0.46 to 1.87
Platelets (103/ µ)	3±3.535	-13.375±26.339	0.87	-64.48 to 97.23
RDW (%)	0.200	-0.062±0.176	14.84	-0.01 to 0.53
Lymphocytes (103/ µ)	-1.687±1.891	-0.562±1.396	-0.67	-8.02 to 6.02
BUN (mg/dl)	-0.625±2.298	-0.750±1.060	0.07	-7.57 to 7.82
Creatinine (mg/dl)	0.028±0.065	0.040±0.014	-0.23	-0.21 to 0.19
Sodium; Na (mEq/L)	0.250±0.353	-0.250±1.060	0.63	-2.90 to 3.90
Potasium; K (mEq/L)	0.050±0.035	-0.212±0.265	1.38	-0.55 to 1.07
LDH (U/L)	-30.750±28.284	-69.500±33.587	1.24	-94.84 to 172.34
SGOT(AST); (U/L)	-1.375±0.176	-0.625±0.883	-1.17	3.49 to 1.99
SGPT(ALT); (U/L)	1.875±1.237	-0.875±0.176	3.11	-1.05 to 6.55
Alkaline phosphatase; (U/L)	-19±43.840	-16±4.242	-1.01	-128.81 to 79.56
Bilirubin Total (mg/dl)	-0.042±0.081	0.037±0.017	-1.36	-0.33 to 0.17
Bilirubin Direct (mg/dl)	-0.005±0.003	0.032±0.045	-1.15	-0.17 to 0.10

Abbreviation : NALL: N-acetyl-L-Leucine, **WBC:** white blood cell, **RBC:** red blood cell, **MCV:** mean corpuscular volume, **MCH:** mean corpuscular hemoglobin, **MCHC:** mean corpuscular hemoglobin concentration, **RDW:** red cell distribution width, **BUN:** blood urea nitrogen, **LDH:** Lactate dehydrogenase

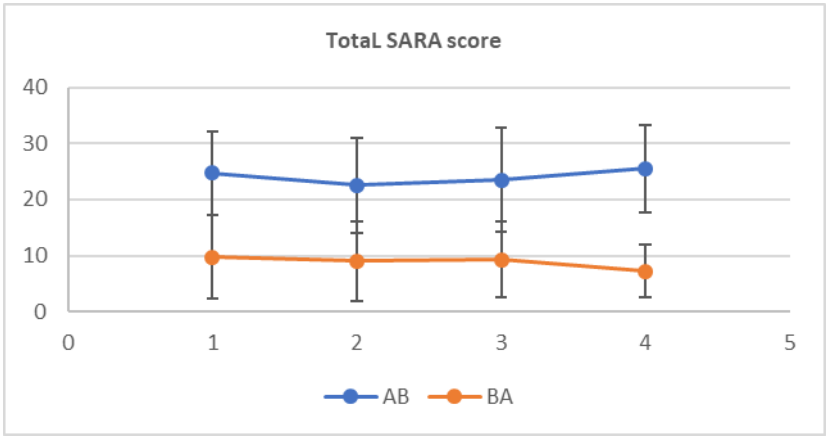
Table-4. The Effects of N-acetyl-L-Leucine on Ataxia Moving Symptoms in patients with spinocerebellar ataxia.

Variables	NALL-Placebo (AB)	Placebo-NALL (BA)	Cohen's d Effect Size	95% Confidence Interval of the Difference
Scale for the assessment and rating of ataxia (SARA)*				
Gait	3.25	1.75	1.34	-0.83 to 1.58
Stance	2	3	-1.00	-0.66 to 0.41
Sitting	3	2	1.00	-0.41 to 0.66
Speech-Disturbance	0±0.353	-0.125±0.176	0.447	-1.08 to 1.33
Finger-Chase	0.125±0.176	0	1.00	-0.41 to 0.66
Finger-to-Nose	0.187±0.088	0±0.176	1.34	-0.41 to 0.79
Fast-Alternating-Hand-Movements	0.250	0	-	-
Heel-to-Shin	-0.062±0.265	0.062±0.088	-0.632	-0.97 to 0.72
Total SARA Score	0.750±0.176	-0.437±0.618	2.61	-0.77 to 3.14
Spinocerebellar Ataxia Functional Index (SCAFI)				
SCAFI-9HPT dominant	0±11.313	-1±4.242	1.38	-1.31 to 2.56
SCAFI-8MWT	-2.125±7.247	-0.125±0.530	-0.389	-24.11 to 20.11

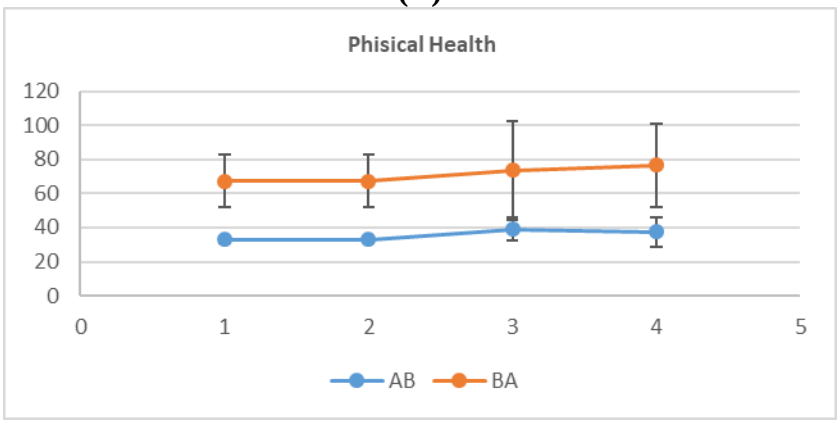
*** Note:** "+" means improvement in the sequence AB and "-"means improvement in the BA sequence.
Abbreviation: NALL: N-acetyl-L-Leucine, **9HPT:** 9-hole peg test; **8MWT:** 8 m walking time.

Table-5. Effects of N-acetyl-L-Leucine on Quality of Life in patients with spinocerebellar ataxia.

Variables	NALL-Placebo (AB)	Placebo-NALL (BA)	Cohen's d Effect Size	95% Confidence Interval of the Difference
Child self-report				
Physical Health	-4.69±2.20	4.68±2.21	2.23	-1.80 to 5.71
Emotional Functioning	-1.25±3.535	-4.375±4.419	1.56	-8.71 to 18.71
Social Functioning	1.875±0.883	0.625±4.419	0.186	-13.86 to 15.11
School Functioning	-0.625±0.883	-2.5±3.535	0.728	-9.21 to 12.96
Total Psychosocial Health	-0.208±0.295	-1.465±3.249	0.80	-8.16 to 11.92
Total Score	0.136±0.192	-1.358±3.459	1.054	-7.96 to 13.12
Quality of life index	0.195±0.166	-1.367±3.369	1.30	-8.63 to 16.17
Parent proxy-report				
Physical Health	0.781±1.104	2.343±2.211	-0.599	-9.58 to 7.24
Emotional Functioning	-1.25±1.767	0±1.767	1.38	-6.57 to 12.82
Social Functioning	1.875±4.419	0±1.767	0.137	-18.95 to 20.20
School Functioning	-3.125±2.651	-0.625±2.651	-0.943	-13.91 to 8.91
Total Psychosocial Health	-0.833±0.001	-0.208±0.295	1.41	-0.45 to 1.68
Total Score	-0.272±0.385	0.680±0.961	-0.156	-3.88 to 3.61
Quality of life index	-0.430±0.275	-1.758±3.866	1.09	-10.60 to 17.83



(A)



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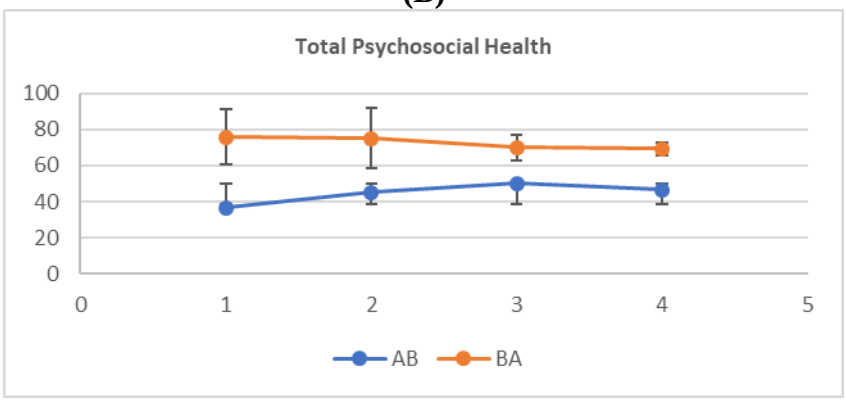

(C)

Figure -2: (A) The effects of N-acetyl-L-Leucine on Total SARA score in subjects with spinocerebellar ataxia; (B) The effects of N-acetyl-L-Leucine on Physical Health according to parent proxy-report in subjects with spinocerebellar ataxia; and (C) The effects of N-acetyl-L-Leucine on Total Psychosocial Health according to child self-report in subjects with spinocerebellar ataxia. AB: NALL-Placebo group, and BA: Placebo- NALL group, 1: Baseline-1, 2: Response-1, 3: Baseline-2, 4: Response-2.

These findings suggest that short-term NALL supplementation may produce mild biological or functional effects that require more detailed investigation in studies with larger sample sizes and longer durations. Our findings are in line with previous studies (6, 7, 16) that have shown NALL to be a safe drug with possible neuromodulatory or neuroprotective effects, although its definitive efficacy requires multicenter studies with larger sample sizes and longer follow-up.

Table 6 lists previous observational and experimental studies using acetyl leucine in subjects with ataxia. The available evidence for NALL and its more commonly used clinical counterpart, NADLL, comes mainly from small trials, open-label designs, and case series in patients with ataxia. A study in 18 patients with sporadic or hereditary cerebellar ataxia (12 sporadic and 6 hereditary), with a median age of 58 years, showed that a one-month treatment with 5 gr of NADLL daily was able to reduce the coefficient of variation of stride time in 14 patients. The SARA score also improved, with a median decrease from 13 to 11 points (19).

Table-6. Observational and experimental studies using Acetyl-Leucine in subjects with ataxia.

Reference	Year/Place	Design	Disease	Drug-Dose	Duration	Findings
(19)	2013-2014, Germany	Observational	18 patients with sporadic or hereditary cerebellar ataxia	Acetyl-DL-leucine, 5 gr/day	4 week	Reduction in CV of stride time and SARA from 13 to 11
(6)	2013, Germany	Case series	13 patients with cerebellar ataxia	Acetyl-DL-leucine, 5 gr/day	7 day	Reduction in SARA from 16.1±7.1 to 12.8±6.8, improvement in SCAFI subscales, increased quality of life
(14, 20)	2016–2017, Germany & Austria	Multi-center, Randomized double blinded cross over clinical trial	108 patients with hereditary or non-hereditary cerebellar ataxia	Acetyl-DL-leucine, 5 gr/day	6 week	There was no significant difference observed in SARA scores between the drug and placebo groups.
(7)	2023, Germany	Observational	22 patients with cerebellar ataxia	Acetyl-DL-leucine, 4-5 gr/day	4.7 month	Increased cortical activity and decreased cerebellar activity have been reported, with clinical improvement being correlated with metabolic changes.
(9)	2023	Case series	4 children with CACNA1A-related disorders	N-acetyl-DL-leucine, 1-5 g/day		There has been rapid and sustained improvement in SARA, SCAFI, and CGI-I.
(16)	2024, Iran	Randomized double blinded cross over clinical trial	16 children with ataxia telangiectasia	N-acetyl-L-leucine, 1-4 gr/day	6 week	No significant changes were observed in SARA and SCAFI scores, but there was an improvement in nausea and constipation.
(11)	2023, Iran	Case report	9-year-old child with ataxia telangiectasia	N-acetyl-DL-leucine, 4 gr/day	16 week	11-point improvement in SARA (48.9%) scores, and an improvement in quality of life
(10)	2023, Iran	Crossover case study	12-year-old child with multiple sulfatase deficiency	N-acetyl-L-leucine, 3 gr/day	4 week	Improvement of the ataxia symptoms, quality of life, and serum IL-6 level.
Current study	2025, Iran	Randomized double blinded cross over clinical trial	3 children diagnosed with SCA and 1 child with SCAR20	N-acetyl- L-leucine, 1-4 gr/day	4 week	No significant changes were observed in SARA and SCAFI scores.

Another study was conducted on 22 adult patients with cerebellar ataxia (mean age 61.9 years, 13 females and 9 males). The study aimed to investigate the therapeutic effect of NADLL and compensatory brain processes using [18F]-FDG-PET brain imaging. Patients underwent PET twice: before treatment and during drug administration (4–5 g/day, mean 4.7 months). This study showed that NADLL can enhance compensatory processes of brain networks in responding patients (7).

The multicenter, double-blind, randomized, crossover ALCAT study enrolled patients with cerebellar ataxia (mean age 54.8±14.4 years, 50.9% females). Their total SARA score at baseline was 13.33±5.57. Of these patients, 80 patients had hereditary ataxia (suspected or genetically confirmed), and 25 had non-hereditary or unknown ataxia. In this study, patients were randomly assigned to receive either NADLL (5 g/day after a 2-week dose titration) or placebo, or vice versa. Each treatment period lasted 6 weeks, with a 4-week washout period between the two periods. The results showed that there was no significant difference in the absolute change in SARA score between the two treatments. However, the drug was well tolerated, and no serious adverse events were reported (20).

In 2024, we reported the results of a randomized double-blinded, crossover clinical trial in which NALL supplementation for 6 weeks among 16 children with ataxia telangiectasia was found to be safe and improved symptoms of nausea and constipation (16). The intervention period in this study was longer compared to a previous case study involving the same drug (NADLL) (11) and the current study. The current study is the first conducted by our team in patients with SCA**.**

4-1. Study Strengths and Limitations

From a scientific and clinical perspective, the present study has several strengths. It is the first study on the effect of NALL in patients with SCA, utilizing a rigorous crossover design and valid measurement tools. Additionally, the focus on a pediatric population, which has received less attention in the global literature, adds to the significance of the study. However, limitations such as the small population size, genetic heterogeneity of the patients, and the presence of concomitant medications in some individuals emphasize the need for caution in generalizing the results. Moreover, the comorbidity of SCA7 with ceroid lipofuscinosis neuronal in case 3 further limits the interpretation of the findings.

5- CONCLUSION

Our preliminary findings suggest that NALL, with its good safety and high tolerability, may have a consistent beneficial effect on individual patients with SCA. These findings emphasize the importance of designing large-scale, multicenter, and long-term trials to determine the true place of this drug in the clinical management of ataxia patients.

6- ACKNOWLEDGMENT

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7- FUNDING

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8- CONFLICT OF INTERESTS

The authors report no actual or potential conflicts of interest.

9- AVAILABILITY OF DATA AND MATERIALS

Raw data will be shared upon a reasonable request from the corresponding author.

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