RESEARCH ARTICLE

Long-Term Nicotinamide Riboside Use Improves Coordination and Eye Movements in Ataxia Telangiectasia

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ABSTRACT: Background: Supplementation of nicotinamide riboside (NR) ameliorates neuropathology in animal models of ataxia telangiectasia (A-T). In humans, short-term NR supplementation showed benefits in neurological outcome.

Objectives: The study aimed to investigate the safety and benefits of long-term NR supplementation in individuals with A-T.

Methods: A single-arm, open-label clinical trial was performed in individuals with A-T, receiving NR over a period of 2 years. Biomarkers and clinical examinations were used to assess safety parameters. Standardized and validated neuromotor tests were used to monitor changes in neurological symptoms. Using generalized mixed models, test results were compared to expected disease progression based on historical data.

Results: NAD^+ concentrations increased rapidly in peripheral blood and stabilized at a higher level than baseline. NR supplementation was well tolerated for most participants. The total scores in the neuromotor test panels, as evaluated at the 18-month time point, improved for all but one participant, primarily driven by improvements in coordination subscores and eye movements. A comparison with historical data revealed that the progression of certain neuromotor symptoms was slower than anticipated.

Conclusions: Long-term use of NR appears to be safe and well tolerated, and it improves motor coordination and eye movements in patients with A-T of all ages. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: ataxia telangiectasia; nicotinamide riboside; niagen

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Introduction

Ataxia telangiectasia (A-T) is a rare progressive multisystemic, life-shortening disorder caused by pathogenic variants in *ATM* (*Ataxia Telangiectasia Mutated*) located on chromosome 11q22.3.[1] Symptoms include neurodegeneration, immunodeficiency, premature aging, and cancer predisposition.[2-4] *ATM* encodes the ATM kinase, a serine/threonine kinase[5] required for DNA damage response[6] and oxidative stress signaling.[7] Individuals with loss-of-function variants have classical A-T phenotypes, whereas those with residual kinase activity may have milder phenotypes known as variant A-T.[8]

The neurological manifestations of classical A-T typically begin with cerebellar ataxia, whereas other neuromotor symptoms, such as oculomotor apraxia, develop later.[4,9] Neurological features, such as ataxia, dystonia, bradykinesia, and involuntary movements, have a severe impact on motor function. Most people with A-T lose their ability to walk independently and require a wheelchair by the age of 10.[4]

The mechanisms underlying cerebellar degeneration and neurodegeneration are not fully understood but are believed to be related to failure to repair and appropriately respond to DNA damage.[10] We previously showed that chronic activation of PARP1, in an alternative DNA damage response pathway, led to depletion of intracellular stores of NAD^+ in *ATM* knockout cells and animals.[11] As NAD^+ is a critical cofactor for many cellular enzymes, including those involved in mitochondrial biogenesis and maintenance,[12] NAD^+-depletion has wide-ranging consequences for cellular functioning. Importantly, we found that restoring cellular NAD^+ levels with NAD^+ precursors, like nicotinamide riboside (NR), extended life and attenuated neuromuscular function loss in animal models of A-T.[11]

A 4-month open-label clinical trial of NR supplementation suggested that it may benefit individuals with A-T[13], but further research into long-term safety and the impact on neurological symptoms over time is required. In this study, we looked at the effect of NR supplementation on neuromotor function in individuals with A-T in a 2-year single-arm, open-label clinical trial.

Methods

Study Design

A single-arm, open-label observational intervention trial coordinated with regular clinical follow-up was approved by the Regional Committee of Ethics in Norway (REK 2019/417) and registered at ClinicalTrials.gov (NCT04870866) (Fig. 1A). The study was conducted after obtaining written informed consent from all participants.

The ChromaDex External Research Program (CERP) provided nicotinamide riboside (NR, Niagen). All study participants received standardized doses: the initial dose was 2 × 75 mg/day (Fig. 1A). After 2 weeks, participants returned for blood sample collection and an interview. If no adverse events occurred, the dosage was increased to 2 × 150 mg/day. After 2 months, sampling and interview were repeated, and if no adverse events occurred, the dose was increased to the final dose of 2 × 250 mg/day. After 3 months, a telephone interview was performed to assess potential adverse events of the final dose.

Inclusion and Exclusion Criteria

Individuals with A-T in Norway receiving regular clinical follow-up were invited to participate in the study based on two criteria: (1) a molecularly confirmed A-T diagnosis and (2) age above 3 years to obtain a reliable assessment of neuromotor function. Exclusion was based on the following criteria: (1) participation in another clinical trial, (2) signs of liver failure or kidney disease, (3) other medical conditions/symptoms/signs that could increase the risk for side effects. Vitamin supplements were discontinued 2 months before inclusion.

Outcomes

The primary outcome was changes in NAD+ levels in whole blood. Secondary outcomes included changes in biochemical markers and neuromotor function (Fig. 1A and Supplementary Table S1). The formal end point of the study was 24 months. Due to difficulties in arranging follow-ups for this patient group during the COVID pandemic, some data points could not be measured.

Safety

Clinical examinations and interviews were performed to monitor side effects. Liver and kidney toxicity as well as metabolic health was monitored by blood-based biomarkers (Supplementary Table S1).

Clinical Assessment

Clinical effect of the supplementation was assessed through blood-based biomarkers, physical examination, interviews with the patients and the parents/guardians, and neurological examinations (as detailed later).

The physical examinations included evaluation of general health status, concomitant diseases and well-being, as well as measurement of weight and body length.

Neuromotor Evaluation

Neurological and motor function (further called neuromotor function) were assessed every 6 months.

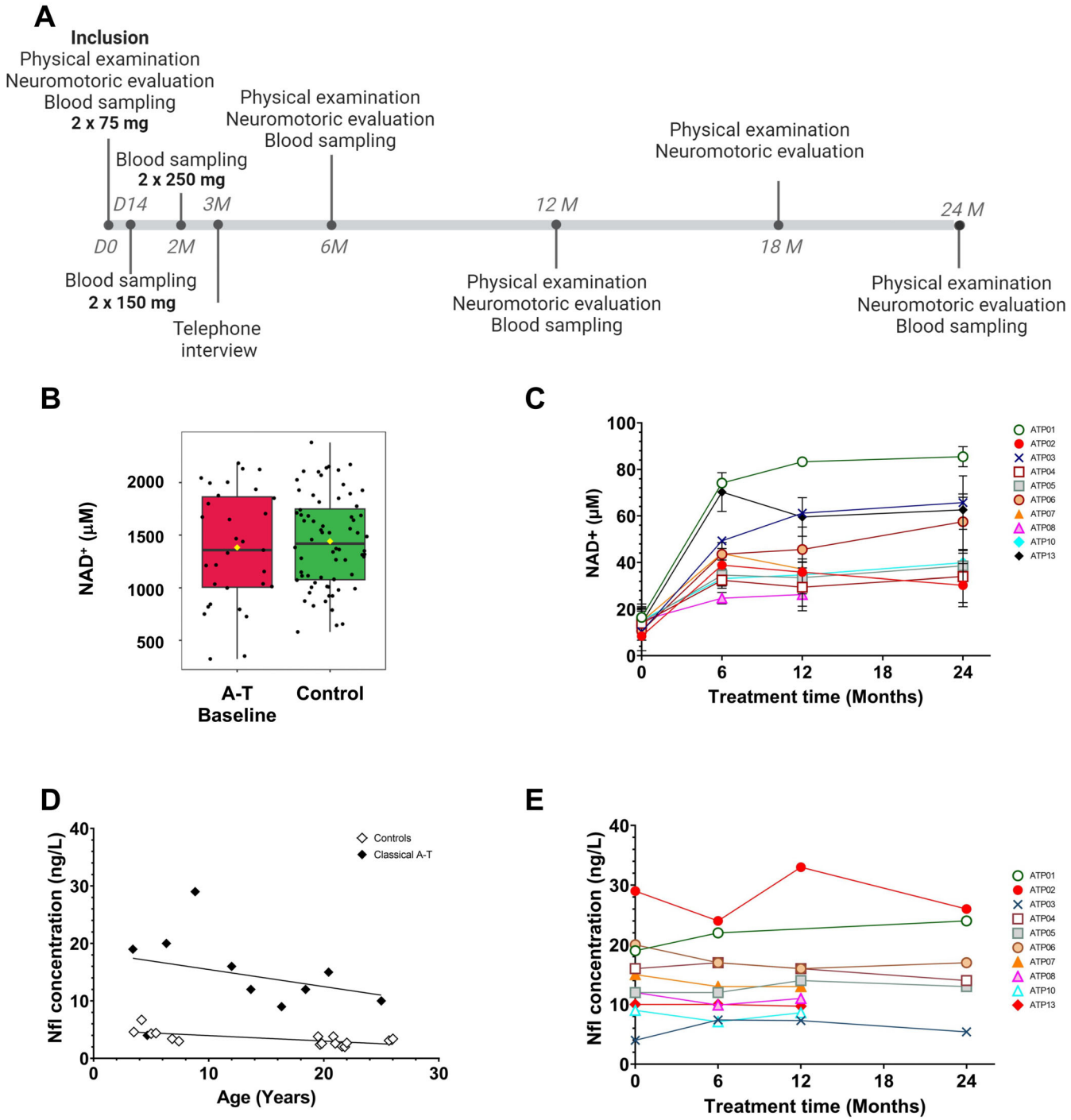

FIG. 1. Overview of the study and participants: (**A**) Schematic representation of study design. The timing of activities (physical examination, neuromotoric evaluation, and blood sampling) is indicated. (**B**) Normalized NAD^+ concentration (µM) in snap frozen whole blood measured using liquid chromatography mass spectrometry (LC–MS) in study participants at baseline and age-matched healthy controls (red and green bars, respectively), t-test FDR 2.0539e-32. (**C**) Whole blood NAD^+ concentrations measured using LC–MS in individual participants over the course of the study. (**D**) Baseline Neurofilament light values for participants and age-matched healthy controls. (**E**) Nfl concentrations during treatment. [Color figure can be viewed at wileyonlinelibrary.com]

All sessions were video recorded. The following scales were used:

1. The A-T Neurological Examination Toolkit (A-T NEST) was developed specifically for monitoring the progression of A-T.[14-16] Test domains were communication, eye movements, ataxia, movement disorder, power, and neuropathy. Score ranges from 0 to 101. A higher score reflects better function. The supplementary part was not used.

2. International Cooperative Ataxia Rating Scale (ICARS) test domains are: posture and gait, kinetic functions, speech, and oculomotor function.[17] A lower score reflects better function. Score ranges from 0 to 100. ICARS is validated for A-T.[14]
3. Scale for the Assessment and Rating of Ataxia (SARA) consists of eight items: gait, stance, sitting, speech, finger chase, nose-finger test, fast alternating hand movements, and heel-shin slide. A lower score reflects better function. Score ranges from 0 to 40. SARA has been validated for assessing early onset ataxias.[18-20]
4. Gait Scale (GS) where a higher score reflects better function, which ranges from 0 to 10.[21]

The four scales ICARS, SARA, A-T NEST, and GS were integrated in one test battery. Ataxia is a prominent symptom in A-T. Other neurological features such as dystonia, bradykinesia, and involuntary movements also have an impact on stability, movement control, timing, and pace of movement. These features are addressed in the following domains: movement disorder (A-T NEST), kinetic function (ICARS), and as separate test items (SARA). Most of the test items are conducted on the upper extremities. We refer to these test items as coordination.

Results

Eligible individuals defined by our inclusion criteria and receiving regular follow-up were invited to participate in the study (Table 1). Fourteen patients were invited, and 13 patients were enrolled. Of 13 enrolled, 2 were later excluded (at 2 weeks and 3 months) due to nutritional problems and pneumonia; additionally, one individual decided to withdraw after 12 months due to lose stools. Among the 13 enrolled, 10 completed 18 months of NR supplementation (Table 1). Among the 10 participants the mean age at baseline was 13Y 2 M (range 3Y 4 M–25Y 8 M); 7 children and 3 adults; 4 males and 6 females (Table 1). Four of the 10 participants received weekly subcutaneous immunoglobulins (Table 1).

NR Increases NAD^+ in Full Blood

In ATM-defective animals and cells restoring NAD^+ levels with NR attenuated neurodegeneration.[11] Consistent with the findings in animal models, where PARP1 overactivation is postulated to lead to NAD+ depletion (Supplementary Fig. S1A), NAM levels were higher in the A-T patients at baseline compared to age-matched controls (Supplementary Fig. S1B). The baseline NAD^+ levels in the study participants (13.4 μM ± 2.6) were similar to those in age-matched healthy controls (14.4 μM ± 2.5) (Fig. 1B). Average NAD+ levels rose quickly and stabilized in the treatment group (Fig. 1B). Following NAD^+ concentrations individually showed stabilization between two- and sixfold over baseline levels (Fig. 1C). Thus, NR supplementation gave higher blood NAD+ levels in all study participants with the fold-change mirroring the dose per kilogram.

Safety of Long-Term NR-Supplementation

No severe adverse events were observed during the 24-month study period. Thus, NR was generally well tolerated. Loose stools (one participant) and transient mild stomach discomfort were reported (one participant). One participant reported normalized bowel movements with less constipation. No other side effects were reported.

During the 2-year treatment period, no clinically significant changes in biomarkers related to liver or kidney function were seen. The liver-derived plasma protein AFP is one of the most commonly used biomarkers of A-T progression.[21] With correction for the changed laboratory method, the AFP levels remained stable for most participants over 2 years of NR supplementation (Supplemental Fig. S2A). Although other liver function markers such as ALT and AST showed increased baseline levels as expected in A-T, the levels remained stable over the intervention period (Supplementary Fig. S2B,E). Metabolic health, measured as LDL, HDL, and HbA1c, remained stable in all participants throughout the study treatment (Supplemental Fig. S2C,D,G). Marker of kidney health, serum potassium, was normal during the treatment period (Supplementary Fig. S2F). Taken together, NR supplementation did not cause notable side effects nor significant elevation of biomarkers of dysregulated liver, kidney, or blood sugar during the 2-year treatment period.

Notably, long-term NR supplementation caused no consistent changes in any hematological or immunological parameters. Thrombocytopenia was not observed. Leukocyte counts and lymphocyte subsets (CD4+, CD8+, CD19+, and CD14+) did not change. When the four individuals who received immunoglobulins were excluded from the evaluation (Supplementary Table S2), no changes in total immunoglobulin levels nor immunoglobulin subclasses were observed. In one patient (ATP03), we observed lower AFP levels and no immunodeficiency, consistent with previous reports of variant A-T.[22]

Elevation of Nfl in A-T

Nfl has been proposed as a marker for axonal/neuronal degeneration in several diseases, and in classical A-T, Nfl levels at least twice as high as in healthy controls are reported.[23,24] We found plasma Nfl concentrations in participants with A-T to be higher than in age-matched controls (Fig. 1D). The elevation of Nfl

TABLE 1 *Characteristics of the study patients*

Patient ID	Sex	Age at baseline	Ig (Y/N)	*ATM* variant[a] and predicted protein effect		AFP (kU/L) baseline
				Allele 1	Allele 2	
ATP01	F	3Y 4 M	N	c.5932G > T, p.Glu1978*	c.9126delC, p.Asn3044Ilefs*31	125
ATP02	F	8Y 9 M	N	**c.3245_3247delATCinsTGAT, p.His1082Leufs*14**	6679C > T, p.Arg2227Cys	251
ATP03	F	4Y 7 M	N	**c.3245_3247delATCinsTGAT, p.His1082Leufs*14**	8030A > G, p.Tyr2677Cys	30
ATP04[b]	M	13Y	Y	c.7671_7674delGTTT, p.Phe2558Leufs*5	8833_8834delCT	282
ATP05[b]	M	14Y 8 M	Y	c.7671_7674delGTTT, p.Phe2558Leufs*5	8833_8834delCT	322
ATP06	M	6Y 4 M	N	**c.3245_3247delATCinsTGAT, p.His1082Leufs*14**	5712dupA, p.Ser1905Ilefs*25	220[c]
ATP07[b,d]	F	20Y 6 M	Y	c.5932G > T, p.Glu1978*	c.2880delC, p.Leu961Cysfs*10	387
ATP08[b,d]	F	18Y 4 M	Y	c.5932G > T, p.Glu1978*	c.2880delC, p.Leu961Cysfs*10	405
ATP09[e]	M	25Y 5 M	N	**c.3245_3247delATCinsTGAT, p.His1082Leufs*14**	**c.3245_3247delATCinsTGAT, p.His1082Leufs*14**	563
ATP10	F	16Y 4 M	N	c.5932G > T, p.Glu1978*	c.7630-2A > C, Splice defect	541
ATP11[e]	F	16Y 3 M	Y	**c.3245_3247delATCinsTGAT, p.His1082Leufs*14**	c.4588G > T, p.Glu1530*	744
ATP13	M	25Y 8 M	N	**c.3245_3247delATCinsTGAT, p.His1082Leufs*14**	c.4111delG, p.Asp1371Ilefs*15	297
ATP15[f]	M	33Y 5 M	N	c.3576G > A, p.Lys1192*fs16	c.6047A > G, p.Asp2016Gly	278

[a]The highlighted genetic variant is the Norwegian founder mutation (Rendal mutation).[36] The ATM (*Ataxia Telangiectasia Mutated*) variants are annotated according to the reference sequence NM_00051.3.
[b]Siblings.
[c]AFP measurement done after 2 months of intervention.
[d]Dropout after 18 months.
[e]Dropout due to medical reasons.
[f]Dropout after 12 months.

was more pronounced in the younger participants, with lower values in older participants. Some of the oldest participants had values lower than 10 ng/L, which is within the normal reference interval.[25] One patient clustered with the controls (Fig. 1D). There was no change in Nfl levels in the participants during the treatment (Fig. 1E).

Long-Term NR Supplementation Improves Coordination and Eye Movement

Due to drop-out among the participants and difficulties to arrange follow-ups due to the COVID pandemic, results were primarily evaluated at 18 months. Improvement in neuromotor scores was observed in all ages, including individuals in the age group (6–9 years) that experiences the most rapid neuromotor decline, and surprisingly also in the oldest participants (Fig. 2 and Table 2). Comparing average A-T NEST total score from inclusion and after 18 months of NR supplementation, the average score increased by 4.7 ($P = 0.036$). All but one participant improved over the study period. The average ICARS total scores fell from 62.8 at baseline to 54.4 at 18 months, but the difference did not reach significance due to variability as one participant scored higher at the 18-month visit. The SARA total scores after 18 months were reduced by an average of 1.5 ($P = 0.048$). No change was observed in GS (Table 2 and Supplementary Fig. S3). The overall changes in the total scores were driven by improvements in the coordination subscores.

Oculomotor function improved in most participants using the A-T NEST score, but not in ICARS Oculomotor. Neither of these changes in scores were significant (Table 2). The SARA coordination subscore was reduced with 1.6 points from 8.4 at baseline to 6.6 at 18 months ($P < 0.001$). ICARS coordination score was reduced by 3.3 points ($P = 0.014$) at 18 months (Table 2). Only one participant had a higher ICARS score after 18 months. In the A-T NEST movement

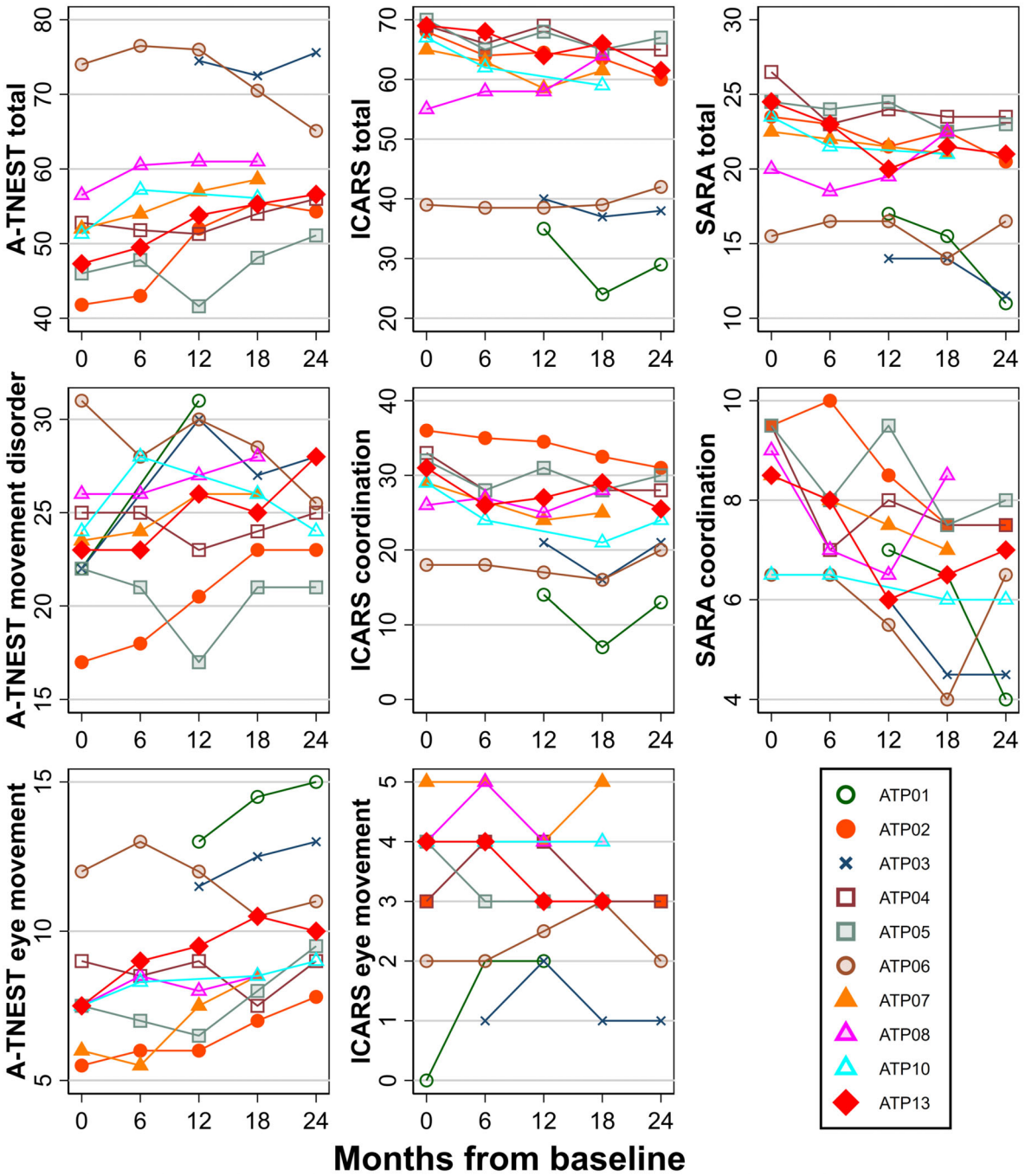

FIG. 2. Neuromotoric assessment. Neuromotor function was evaluated at baseline and every 6 months. Total test scores in (**A**) the A-T Neurological Examination Toolkit (A-T NEST), (**B**) International Cooperative Ataxia Rating Scale (ICARS), (**C**) Scale for the Assessment and Rating of Ataxia (SARA) scales and subdomains, (**D**) A-T NEST movement disorder, (**E**) ICARS coordination, (**F**) SARA coordination, (**G**) A-T NEST eye movement, and (**H**) ICARS eye movement. [Color figure can be viewed at wileyonlinelibrary.com]

disorders subscore, only one participant scored lower after 18 months, with a reduction of 1.7 ($P = 0.111$).

When compared to historical controls, GLMM effect analyses for NR supplementation at 24 months (Fig. 3 and Supplementary Table S3) showed improved within-group marginal mean scores for all neuromotor outcomes in the intervention group, whereas marginal means in controls remained relatively unchanged from baseline to 24 months (eg, from total score 44.71 to 44.96 and eye coordination from 6.58 to 6.37). A-T NEST total score tended to improve with an increased score by 6.02 (95% CI: −0.41 to 12.45, $P = 0.066$) in the intervention group than controls, albeit not significant. A-T NEST eye coordination did significantly improve by 1.51 (95% CI: 0.51 to 2.50, $P = 0.003$) in the intervention group compared to controls. Looking

TABLE 2 *Neuromotoric data from the study participants*

Average scores (SD)	Duration of study (months)						
	0	6	12	18	24	Difference 0–18	*P*-value
A-T NEST total	52.7 (9.7)	55.0 (10.3)	58.4 (11.8)	59.1 (7.9)	59.8 (9.0)	4.7 (5.1)	***0.036***
SARA Total	22.6 (3.4)	21.2 (2.7)	19.8 (3.7)	19.8 (3.8)	17.7 (5.6)	−1.5 (1.8)	***0.048***
ICARS total	62.8 (10.8)	60.6 (9.4)	55.1 (13.5)	54.4 (15.2)	51.8 (15.1)	−2.4 (5.1)	0.230
Gait Scale	3.2 (2.5)	3.2 (2.4)	3.3 (2.3)	3.2 (2.6)	3.9 (2.5)	0 (0.6)	1.000
A-T NEST eye movement	7.8 (2.0)	8.5 (2.3)	9.3 (2.8)	9.6 (2.4)	10.9 (2.3)	0.8 (1.6)	0.205
ICARS oculomotor	3.2 (1.5)	3.4 (1.4)	3.2 (0.9)	3.2 (1.1)	2.9 (1.2)	−0.1 (0.6)	0.598
A-T NEST movement disorders	23.6 (3.6)	24.1 (3.4)	25.6 (4.7)	25.4 (2.4)	24.9 (2.6)	1.7 (2.8)	0.111
SARA coordination	8.4 (1.3)	7.6 (1.2)	7.2 (1.3)	6.6 (1.4)	6.4 (1.5)	−1.6 (0.7)	***<0.001***
ICARS coordination	29.3 (5.4)	26.6 (4.7)	25.0 (6.8)	23.1 (7.9)	24.1 (6.0)	−3.3 (2.9)	***0.014***

Abbreviations: A-T NEST, the A-T Neurological Examination Toolkit; SARA, Scale for the Assessment and Rating of Ataxia; ICARS, International Cooperative Ataxia Rating Scale.

at individual trajectories, all but one intervention group participant improved over the study period for both A-T NEST scores (Fig. 2).

Significant improvements were found for the SARA total score by −2.32 (95% CI: −4.01 to −0.63, $P = 0.007$) and coordination score by −2.21 (95% CI: −3.15 to −1.27, $P < 0.001$) in the intervention group compared to expected scores among historical controls (Fig. 3; Supplementary Tables S3 and S4).

Estimation of ICARS marginal mean scores was not possible for time points 6, 12, and 24 months in historical controls due to no data, with just one patient with data at an 18-month interval (Supplementary Table S3). Looking only at the intervention group, model-estimated means at 24 months showed improved ICARS total scores by −3.67 (95% CI −5.84 to −1.50), coordination by −3.21 (95% CI −4.55 to −1.88), and oculomotor scores by −0.19 (95% CI −0.77 to 0.39) when adjusted for baseline values (Fig. 3; Supplementary Tables S3 and S4). Two individuals of the intervention group had a higher ICARS total and coordination scores after 18 and 24 months (Fig. 2E). The intervention had a negligible effect on the GS of 0.16 (95% CI: −0.23 to 0.54, $P = 0.418$) at 24 months comparing intervention and control groups (Supplementary Tables S3 and S4).

In summary, when compared to historical controls, long-term NR supplementation seems to improve coordination and eye movement.

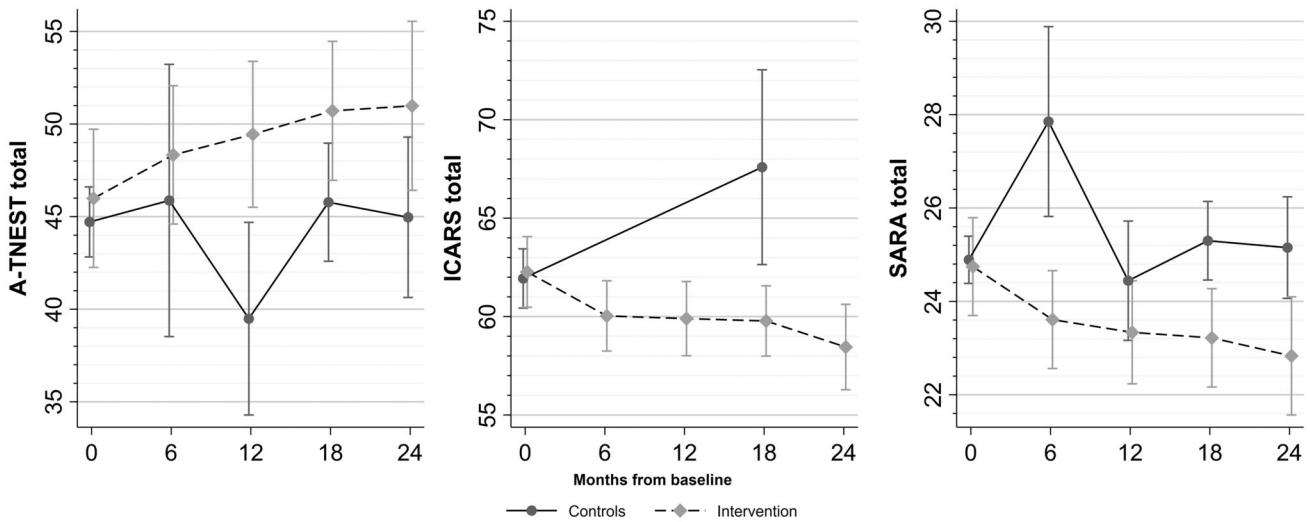

FIG. 3. Effect of nicotinamide riboside (NR) supplementation on total scores across all time points with estimated means and 95% confidence interval (CI). Predicted marginal means and 95% CI from generalized linear mixed models for the A-T Neurological Examination Toolkit (A-T NEST), International Cooperative Ataxia Rating Scale (ICARS), and Scale for the Assessment and Rating of Ataxia (SARA) total scores with random intercept and random slope, adjusting for study arm-time interactions, baseline levels of the outcome respective to each analysis, age, and gender.

Discussion

We present results from the longest-running dietary supplementation study with NR in A-T. We discovered that NR was bioavailable and safe, and it alleviated key clinical symptoms of A-T as evidenced by enhanced motor coordination and improved eye movements in all age groups of individuals with A-T.

The rationale of the study is that ATM defects lead to overactivation of PARP1.[11] A definite quantification of NAD+ levels in the target tissue neurons was not possible. Higher whole blood NAM levels in A-T patients than in age-matched controls are consistent with PARP1 being overactivated. It has been reported that CD38, the main consumer of NAD^+ in blood, regulates NMN levels.[26] Reduced NMN-levels in A-T patients might be an indication of increased CD38 activity (Supplementary Fig. S1C). Although whole blood NAD^+ measurements cannot be used as a marker of tissue NAD^+,[27] it served as a good marker of compliance as all participants had increased and stable NAD+ levels throughout the study.

With the exception that we found no changes in immunoglobulin levels, our study is consistent with previously published data, which also found NR to be efficacious and safe for short-term use in A-T.[13] In our study, the dose ranged from 10 to 37 mg/kg per day, with a median of 13 mg/kg per day. Except for two of the youngest, the effective dose used was lower than the 25 mg/kg per day used in the previous 4-month study.[13] The younger participants, who received a higher dose relative to body weight, remained stable despite being in the age where decline is most rapid. Positive effects were also seen for older participants receiving lower doses relative to body weight. The question of different dosage requirements depending on age, and the optimal dosage balancing effect and side effects,[28,29] should be addressed in a future, larger study.

We observed a comparable improvement in neuromotor function as measured by SARA and A-T NEST total scores, as well as a comparable but less pronounced change in ICARS scores, partly due to a lack of historical data. The comparable representation of the data by the four measures strengthens the validity of our findings. The ataxia subdomains walking, sitting, and standing did not improve.

Testing neuromotor function over time is difficult in A-T due to the strong influence of age on average scores. Due to age-related motor function, it is difficult to test and score all test items for children younger than 6 years. Thus, not all domains could be scored for the two youngest participants in this study. As part of the maturation process, neuromotor skills strengthen in toddlers, whereas children between the ages of 6 and 9 exhibit progressive neuromotor decline. Adolescents and young adults exhibit a less rapid neuromotor decline or even stabilization of certain neuromotor characteristics.[4] Due to variations in the natural development of neuromotor skills and a shortened attention span, it can be difficult to obtain scores that accurately reflect the neuromotor function of young children. The four scales were incorporated into a single test battery to eliminate the need for repetitive testing of similar characteristics. ICARS has been validated for A-T by others,[14] and satisfactory scale concordance has been observed between SARA and A-T NEST in adults with A-T.[30]

We found that neuromotor benefits were observed in participants regardless of *ATM* genotype. And surprisingly, we found improvement in motor coordination also in older individuals, who had similar benefits of the supplementation. The overall consistency between our study and that of Veenhuis et al[13] and a case report where a young individual received NR from the age of 3,5 years[31] supports the finding that NR supplementation has clear benefits for individuals with A-T across all ages.

The improvements on multiple motoric scales were not paralleled by a decrease in Nfl concentrations. Nfl levels in classical A-T have been found to be at least twice as high as in healthy controls,[24,32] whereas Nfl levels in variant A-T are typically closer to those of healthy controls.[24] The participant (ATP03) that clustered with the controls (Fig. 1D) was compound heterozygous for a missense variant previously identified in an Italian family with variant A-T, and the missense variant was functionally tested and found to be deleterious in transfected cells.[33,34] Thus, our findings add to the contradictory literature[23,24] regarding the relationship between neuromotor decline and Nfl levels, indicating the need for additional research to ascertain the clinical utility of Nfl in monitoring neuronal health in A-T.

A-T is an ultra-rare pediatric disorder, and placebo controlled randomized trials are difficult to conduct and raise ethical dilemmas. Incorporation of natural history controls in the clinical trial seeks to ameliorate the lack of randomized control groups. Historical controls have been used in clinical trials for rare diseases since the 1970s but have since then been a topic for discussion due to the risk of bias and confounding[35] and the lack of standard practice statistical analyses. Although half of the patient population in Norway participated in this study, the sample size was still small as we disallowed historical data from the study participants in the control group. Fluctuations from lower sample sizes at single time points, especially for historical controls, were within our expectations. This applies especially for example to A-TNEST total score at 12 months and SARA total score at 6 months. We,

however, consider the general trends indicative of ameliorated disease progression.

Conclusion

Our study suggests that NR supplementation is an easy, safe, and non-invasive intervention that seems to improve some areas of neuromotoric function in patients with A-T. Positive changes in the patients, both individually and as a group, were observed over a period of 1.5–2 years. As disease progression can be predicted to occur over this period, our data suggest that disease progression may be attenuated, but this must be corroborated in a larger study.

Author Contributions

Rebecca Presterud recruited and followed participants and controls, coordinated the study, obtained blood samples from patients and controls, analyzed blood samples, performed clinical assessments, analyzed data and wrote and edited the manuscript. Wei Hai Deng developed and performed the statistical analyses and wrote and edited the manuscript. Anna Berit Wennerström performed experiments, analyzed experiments, wrote and edited the manuscript, coordinated laboratory analyses and biobanking. Trudy Burgers performed the majority of, and scored all, neuromotor testing, collected the historical neuromotor data, analyzed data, and wrote and edited the manuscript. Kirsten Mattson and Agnes Solberg performed clinical interviews with the individuals with AT and their chaperones and assisted in coordinating the study. Bharat Gajera and Anni I. Nieminen performed targeted metabolite analyses and wrote the manuscript for these parts. Evandro Fei Fang provided the preclinical evidence that the study was founded on and edited the manuscript. Asbjørg Stray Pedersen, clinical principal investigator and responsible for recruitment, enrollment, and exclusion of participants, performed the medical examinations, was responsible for the study participants' health throughout the study, performed the *ATM* resequencing, requested and evaluated the blood sample tests, designed and supervised the study, analyzed data, and wrote and edited the manuscript. Hilde Loge Nilsen provided the preclinical evidence that the study was founded on, obtained funding, designed the study, obtained ethical approval, supervised the study, analyzed data, and wrote and edited manuscript.

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Conflicts of Interest

H.N. has a CRADA arrangement with ChromaDex (USA), which also supplied nicotinamide riboside for this clinical study. E.F.F. has an MTA with LMITO Therapeutics Inc. (South Korea), a CRADA arrangement with ChromaDex (USA), and a commercialization agreement with Molecule AG/VITADAO, and is a consultant to Aladdin Healthcare Technologies (UK and Germany), the Vancouver Dementia Prevention Centre (Canada), Intellectual Labs (Norway), MindRank AI (China), and NYo3 (China).

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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R.B.: data acquisition, analyses, drafting, editing, revising; W.H.D.: analyses, editing, revising; A.B.W.: data acquisition, analyses, drafting, editing, revising; T.B.: data acquisition, analyses, drafting, editing, revising; B.G.: data acquisition; K.M.: data acquisition; A.S.: data acquisition; E.F.F.: editing; A.I.N.: data analyses, drafting; A.S.P.: conception, design, data acquisition, analyses, drafting, editing, revising; H.N.: conception, design, funding acquisition, analyses, drafting, editing, revising.