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The Effect of Nicotinamide Riboside on Serum Brain-Derived Neurotrophic Factor (BDNF) Levels, Clinical Symptoms, and Sleep Quality in Patients with Neurodevelopmental Disorders at the West Java Provincial Mental Hospital

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ABSTRACT

Neurodevelopmental disorders, including Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and mental retardation, are associated with neuroplasticity disorders, cognitive deficits, and behavioral dysregulation. Nicotinamide Riboside (NR), a precursor to NAD+, is thought to enhance neuroplasticity and modulate neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF). This study involved 48 children diagnosed with ASD, ADHD, or mental retardation according to DSM-5, who were recruited using consecutive sampling and randomly divided into an intervention group (NR 2 mg/kg body weight per day, n=24) and a control group (placebo, n=24) for 30 days. Serum was collected for BDNF measurement using the Quantikine™ ELISA Total BDNF kit, while clinical symptoms were assessed with the Aberrant Behavior Checklist – Irritability Subscale (ABC-I) and sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI). Data analysis was performed using descriptive statistics and logistic regression through Epi Info™ version 7 to assess the effect of the intervention on biological, behavioral, and sleep quality changes. Results showed that the intervention group had a significant increase in serum BDNF levels compared to the control group ($p<0.001$) and a higher likelihood of clinical improvement (odds ratio 5.5; 95% CI 1.03–29.45; $p=0.0465$), but no significant effect on sleep quality was found ($p=0.9643$). In conclusion, Nicotinamide Riboside supplementation in children with neurodevelopmental disorders is associated with increased serum BDNF levels and clinical improvement, suggesting potential biological and therapeutic relevance, while its effects on sleep quality remain unclear. Further research with larger samples and longer intervention durations is needed.

Keywords: Nicotinamide Riboside, Brain-Derived Neurotrophic Factor, Clinical Improvement, Sleep Quality, Neurodevelopmental Disorders

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INTRODUCTION

Neurodevelopmental disorders are a group of disorders that occur as a result of suboptimal brain development, thereby affecting an individual's cognitive, behavioral, and emotional functions. Disorders included in this group include Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and intellectual disabilities. Epidemiologically, neurodevelopmental disorders are estimated to affect around 5–7% of the child population, with ASD prevalence at around 1%. Data from visits to the child and adolescent mental health clinic at the West Java Provincial Mental Hospital in 2021 shows that neurodevelopmental disorders are the second most common diagnosis after psychotic disorders, with 662 cases.

The etiology of neurodevelopmental disorders is multifactorial and involves various factors, including biological and genetic factors, metabolic and toxic disorders, endocrine dysfunction, complications during pregnancy, stress and illness in the mother, malnutrition, and other environmental factors. The impact of these disorders is not only felt by the individuals who experience them, but also by their families and social environment, resulting in a long-term burden both clinically and psychosocially.

Various studies have shown that neurodevelopmental disorders are associated with energy metabolism disorders in the brain, increased oxidative stress, and mitochondrial dysfunction. One molecule that has received a lot of attention in recent years is nicotinamide adenine dinucleotide (NAD+), an important cofactor in cellular metabolism that plays a role in mitochondrial function, epigenetic regulation, and protection against oxidative stress. Decreased NAD+ levels have been associated with impaired nerve function and reduced neuroplasticity. Nicotinamide Riboside (NR) is a precursor to NAD+ that has been shown to increase intracellular NAD+ levels in various research models. Increased NAD+ levels are known to contribute to improved cognitive function, enhanced neuroplasticity, and protection against oxidative stress, which are important mechanisms in the pathophysiology of neurodevelopmental disorders. Preclinical studies show that NR supplementation can improve cognitive function and neurological deficits in various neurodegenerative conditions and neurodevelopmental disorders.

In addition, pharmacogenomic studies show that NAD+-based therapy can affect the expression of genes related to neurotrophic factors, including Brain-Derived Neurotrophic Factor (BDNF), which plays an important role in nerve development, synaptic plasticity, and cognitive function. However, to date, clinical studies specifically evaluating the effects of Nicotinamide Riboside in patients with neurodevelopmental disorders are still very limited, especially in Indonesia.

Therefore, this study aimed to evaluate the effect of Nicotinamide Riboside administration on patients with neurodevelopmental disorders at the West Java Provincial Mental Hospital on changes in BDNF levels, clinical condition improvement, and sleep quality, in an effort to understand the potential clinical and biological benefits of this intervention.

METHODS & MATERIALS

This study employed a non-probability sampling technique, specifically consecutive sampling, in which all eligible patients meeting the predefined diagnostic and clinical criteria were recruited sequentially during the study period until the required sample size was achieved. This approach ensured that participant selection was based on availability and eligibility, thereby reducing selection bias and improving the representativeness of the clinical population.

A total of 48 pediatric participants were recruited for this study. All participants continued to receive standard therapy for their respective neurodevelopmental disorders during the study period. These

therapies included pharmacological treatments such as stimulants (e.g., methylphenidate), antipsychotics (e.g., risperidone), or other medications as clinically indicated, as well as behavioral and educational interventions. To minimize variability, only patients with stable treatment regimens (no change in medication type or dosage within at least 4 weeks prior to enrollment) were included in the study. Thus, Nicotinamide Riboside was administered as an adjunctive (adjuvant) therapy to standard treatment.

The sample size was determined using the Slovin formula, based on the average number of pediatric neurodevelopmental disorder patients treated at the hospital over the preceding six months and adjusted according to the availability of laboratory reagents for serum BDNF analysis. Based on this calculation, 48 participants were considered sufficient to represent the study population. Participants were randomly assigned into two groups: an intervention group (n = 24) and a control group (n = 24 The intervention group received Nicotinamide Riboside at a dose of 2 mg/kg body weight per day for 30 days, while the control group received a placebo for the same duration. Randomization and double-blinding procedures were implemented to minimize selection and observer bias. Randomization was performed using a computer-generated random allocation sequence with a 1:1 ratio. Allocation concealment was ensured using sealed, opaque envelopes prepared by an independent researcher not involved in data collection or analysis. Both participants, caregivers, and outcome assessors were blinded to group allocation. Nicotinamide Riboside and placebo were prepared in identical forms in terms of appearance, taste, and packaging to maintain blinding. This study was not registered in a clinical trial registry, which is acknowledged as a limitation.

All participants were monitored throughout the 30-day intervention period under routine clinical supervision. Venous blood samples were collected before and after the intervention to assess changes in serum BDNF levels.

Instrument

This study used several instruments to assess biological and clinical aspects in participants with neurodevelopmental disorders:

Brain-Derived Neurotrophic Factor (BDNF)

- Used to assess biological changes related to nerve function and neuroplasticity.
- Sample used: participant blood serum.
- Reagent kit : Quantikine™ ELISA Total BDNF (R&D Systems, Inc., Minneapolis, USA), Cat: DBNT00, Lot: P480295, ED: March 3, 2027.
- Standard calibration range : 15.6 – 1000 pg/mL, with a detection limit of 0.997 pg/mL.
- Measurement results are expressed as decimal numbers (decimal point separator), with a 100X dilution factor; reported values have been multiplied by the dilution factor.
- Serum sample values from 36 healthy subjects: 9042–57830 pg/mL, with an average value of 35615 pg/mL (medical records not available).
- Conversion to NIBSC/WHO 1st Reference Reagent BDNF (96/534): NIBSC (96/534) approximate value (IU/mL) = 0.0006 × Quantikine Total BDNF value (pg/mL).
- Measurement instrument: Bio-Rad model 680 Microplate Reader (Bio-Rad Laboratories Inc., CA, USA) with Microplate Manager software ver 5.2.1.
- This kit is for research use only (not for diagnostic or therapeutic procedures).

Aberrant Behavior Checklist – Irritability Subscale (ABC-I)

- Used to assess maladaptive behavior, particularly irritability and aggressiveness.

- Completed by the participant's parents or guardians before and after the intervention.

Pittsburgh Sleep Quality Index (PSQI)

- Used to assess the participant's sleep quality.
- Completed by the participant's parent/guardian or by the participant themselves if they are old enough, before and after the intervention.

Procedure

The research procedure began with participant recruitment. Participants were recruited consecutively based on DSM-5 diagnostic criteria and clinical evaluation during the study period. A total of 48 child participants were then randomly divided into an intervention group (n=24) and a control group (n=24).

- The intervention group received 2 mg/kg body weight of nicotinamide riboside for 30 days.
- The control group received a placebo for the same period.

The intervention was conducted using a double-blind method to minimize bias. During the intervention, all participants were monitored routinely.

Variables were measured before and after the intervention:

- Serum was collected for BDNF analysis using the procedure described in the instrument.
- The ABC-I and PSQI were completed by parents/guardians or participants according to their ability.

The collected data were then analyzed using descriptive statistics and logistic regression to assess the effect of the intervention on biological, behavioral, and sleep quality changes.

Control of Confounding Variables

Several potential confounding variables were considered and controlled as follows:

- Medication stability: Only participants with stable pharmacological treatment were included.
- Sleep patterns: Sleep quality was assessed using PSQI to monitor baseline and post-intervention conditions.
- Physical activity and daily routine: Caregivers were instructed and periodically reminded to maintain consistent daily routines throughout the study period.
- Psychosocial stressors: Participants experiencing acute stress events (e.g., hospitalization or major family changes) were excluded.
- Metabolic conditions: Participants with known metabolic or chronic systemic diseases were excluded.

However, these variables were not objectively quantified and largely relied on caregiver reporting, which may introduce measurement bias. Therefore, residual confounding could not be completely eliminated, particularly given the relatively short duration of the study.

RESULTS

The data analysis techniques used in this study included descriptive statistical analysis and logistic regression analysis. Descriptive statistical analysis was used to describe the characteristics of the subjects and the distribution of the study variables. Logistic regression analysis was used to analyze the relationship and influence of independent variables on categorical dependent variables. The entire data processing and analysis process was carried out using Epi Info™ version 7 (Centers for Disease Control and Prevention/CDC), with the selection of analysis models tailored to the research objectives and data characteristics.

The characteristics of the research subjects are presented in Table 1. In general, the research subjects were predominantly aged 5–12 years, with a higher proportion of males than females. The distribution of diagnoses shows that Attention Deficit

Hyperactivity Disorder (ADHD) is the most common diagnosis, followed by Autism Spectrum Disorder (ASD) and intellectual disability, while a small proportion of subjects have a combination of diagnoses. This picture reflects the variety of neurodevelopmental disorders commonly found in the clinical population of children and adolescents in referral mental health services.

Table 1. Characteristics of Research Subjects

Variable	Frequensi	Persen (%)
Age (years)		
13-18 Years old	3	6.25%
5 – 12 Years Old	45	93.75%
Total	48	100.00%
Gender		
Male	39	81.25%
Female	9	18.75%
Total	48	100.00%
Diagnosis NDD		
ADHD	25	52.08%
Retradasi Mental	9	18.75%
ASD	13	27.08%
ADHD + ASD	1	2.08%
Total	48	100.00%

Descriptive statistical analysis was performed to describe the distribution of changes in serum Brain-Derived Neurotrophic Factor (BDNF) levels in the intervention and control groups. Changes in BDNF levels were classified into three categories: increased, decreased, and not applicable. To assess the relationship between the type of research group and changes in serum BDNF levels, a Chi-square statistical test was used, given that the variables analyzed were categorical. The results of the analysis showed a difference in the distribution of BDNF level changes between the intervention group and the control group, as presented in Table 2. The Chi-square test results showed a χ^2 value of 16.49 with a p-value of 0.0003. A p-value smaller than the significance threshold of 0.05 indicates that there is a statistically significant relationship between the research group and changes in serum BDNF levels. Thus, the observed difference in BDNF level changes between the intervention group and the control group did not occur by chance but reflects a significant relationship between the intervention and changes in BDNF levels.

Table 2. Distribution of BDNF Level Changes in the Intervention Group and Control Group

Group	BNDF Level			
	Increase	**Decrease**	**N/A**	**Total**
Intervention	14	9	1	24
Row%	58.33%	37,50%	4.17%	100,00%
Col%	93.33%	31.03%	25.00%	50,00%
Control	1	20	3	24
Row%	4.17%	83.33%	12.50%	100.00%
Col%	6.67%	68.97%	75.00%	50.00%
Total	15	29	4	48
Row%	31.25%	60.42%	8,33%	100.00%
Col%	100.00%	100.00%	100.00%	100.00%

Single Table Analysis

Chi – Squared	df	Probability
16.49391	2	0.0003

Table 3. Analysis Results The Effect of the Intervention Group on Changes in BDNF Levels

Term	Odds Ratio	95%	C.I.	Coefficient	S.E.	Z-Statistic	P-Value
Group	0.0311	0.0036	0.2695	-3.4691	1,1010	-3,1509	0,0016
Constant	*	*	*	3,1327	1,0202	3.0707	0.0021

Convergency : Converged
Iterations : 5
Final -2*Log-Likelihood : 40.9151
Cases Included : 48

Test	Statistic	D.F	P-Value
Skor	16,1162	1	0.0001
Likelihood Ratio	20,1455	1	0,0000

The results of the analysis in Table 3 show that there is a significant relationship between the intervention group and changes in BDNF levels. The odds ratio (OR) value of 0.0311 with a 95% confidence interval of 0.0036–0.2695 and a p-value of 0.0016 indicates that the difference between the groups is significantly related to changes in BDNF levels. The negative regression coefficient (β = –3.4691) indicates a difference in the direction of BDNF level changes between the intervention and control groups. This result indicates that BDNF level changes were more prevalent in the intervention group than in the control group. The logistic regression model showed good fit, marked by convergence after 5 iterations and a –2 Log Likelihood value of 40.9151. The overall model fit test also showed significant results based on the Score test (p = 0.0001) and the Likelihood Ratio test (p < 0.001), indicating that the model was generally able to explain the relationship between the treatment group and changes in BDNF levels.

Table 4. Analysis of the Effect of Nicotinamide Riboside on Sleep Quality

Term	Odds Ratio	95%	C.I.	Coefficient	S.E	Z-Statistic	P-Value
Group	398673,5868	0,000	>1.0E12	12,8959	288,1968	0,0447	0,9643
Constant	*	*	*	1,6094	0,5477	2,9384	0,0033

Convergence : Converged
Literations : 14
Final -2*Log-Likelihood : 21,6269
Cases Included : 48

Test	Statistic	D.F	P – Value
Score	10,2330	1	0,0014
Likelihood ratio	16,6181	1	0.0000

Based on the analysis results (Table 4), the treatment group variable had an odds ratio (OR) value of 398,673.59 with a very wide 95% confidence interval and a p-value of 0.9643, indicating that statistically there was no significant relationship between Nicotinamide Riboside administration and sleep quality in the study subjects.

The Z-statistic value of 0.0447 indicates that the contribution of the treatment group variable to the model is not significant. However, the model fit test showed statistically significant results, as indicated by the Score test (p = 0.0014) and Likelihood Ratio test (p < 0.001). The regression model reached convergence after 14 iterations with a –2 Log Likelihood value of 21.6269, involving 48 research subjects.

Based on the results of the analysis in Table 5, the treatment group variable showed a significant relationship with clinical improvement. The group that received Nicotinamide Riboside had an odds ratio (OR) value of 5.50 with a 95% confidence interval of 1.03–29.45 and a p-value of 0.0465. These results indicate that Nicotinamide Riboside administration is significantly associated with an increased

Tabel 5. Analysis of the Effect of Nicotinamide Riboside on Clinical Improvement

Term	Odds Ratio	95%	C.I.	Coefficient	S.E	Z-Statistic	P-Value
Group	5,5000	1,0271	29,4507	1,7047	0,8561	1,9912	0,0465
Constant	*	*	*	0,6931	0,4330	1,6008	0,1094

Convergence : Converged
Literations : 5
Final -2*Log-Likelihood : 44,3208
Cases Included : 48

Test	Statistic	D.F	P – Value
Score	5,9152	1	0,00150
Likelihood ratio	7,4189	1	0.0065

chance of clinical improvement. Practically, these results indicate that patients receiving Nicotinamide Riboside are approximately 5.5 times more likely to experience clinical improvement than patients in the control group. The logistic regression model showed good performance, marked by convergence after 5 iterations and a –2 Log Likelihood value of 44.3208, with a total of 48 subjects analyzed. The overall model fit test also showed significant results based on the Score test (p = 0.0150) and the Likelihood Ratio test (p = 0.0065). This indicates that the regression model used is valid and capable of explaining the relationship between Nicotinamide Riboside administration and clinical improvement.

LIMITATIONS

This study has several limitations. First, the relatively small sample size (n = 48) may limit the generalizability of the findings. Second, the use of a non-probability consecutive sampling method may further limit generalizability. Third, although efforts were made to control confounding variables, some factors such as dietary intake, physical activity, and environmental stressors were not objectively measured. Fourth, the relatively short duration of intervention (30 days) may not fully capture the long-term effects of Nicotinamide Riboside. Future studies with larger sample sizes, longer intervention durations, and stricter control of confounding variables are needed to validate these findings.

CONCLUSION

Based on the results of this study, the characteristics of the subjects show that patients with neurodevelopmental disorders who were the research population were predominantly children aged 5–12 years, male, with the most common diagnosis being Attention Deficit Hyperactivity Disorder (ADHD). These characteristics describe the clinical profile of patients with neurodevelopmental disorders commonly found in referral mental health services. The administration of Nicotinamide Riboside in the intervention group was associated with better changes in Brain-Derived Neurotrophic Factor (BDNF) levels compared to the control group. These changes indicate that Nicotinamide Riboside has an effect on biological responses related to nerve function and plasticity in patients with neurodevelopmental disorders. In addition to biological changes, Nicotinamide Riboside administration was also associated with clinical improvement in patients. Patients who received Nicotinamide Riboside showed a higher likelihood of clinical improvement compared to patients who did not receive the intervention. These findings are in line with the study's objective of assessing the impact of Nicotinamide Riboside on the clinical condition of patients. However, the effect of Nicotinamide Riboside on sleep quality has not shown a clear relationship in this study. This indicates that the effects of Nicotinamide Riboside are not uniform across all clinical aspects and may be influenced by factors other than the intervention provided. Overall,

this study shows that Nicotinamide Riboside was associated with improvements in biological and clinical parameters to patients with neurodevelopmental disorders. These results can serve as a basis for further research to evaluate the effectiveness of Nicotinamide Riboside more comprehensively with a larger sample size and longer intervention duration.

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CONFLICT OF INTEREST

The author declares that there are no conflicts of interest, either financial or non-financial, that could potentially influence the conduct of the research, data analysis, interpretation of results, or the preparation and publication of this manuscript. All scientific data presented in this study are used solely for academic purposes and the advancement of science, without any institutional or commercial interests that could have consequences in the future.

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