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ORIGINAL ARTICLE

ROLE OF FOLINIC ACID IN IMPROVING THE ADAPTIVE SKILLS AND LANGUAGE IMPAIRMENT IN CHILDREN WITH AUTISM SPECTRUM DISORDER

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ABSTRACT

OBJECTIVES: To determine role of folinic acid in improving the adaptive skills and language impairment in autism spectrum disorder (ASD) among children aged 3-14 years.

METHODS: This open label randomized controlled trial was conducted at the Out-patient Department of Pediatric Neurology, The Children Hospital & The Institute of Child Health Multan, Pakistan from October-2020 to March-2021. A total of 44 (22 in each group) children of both genders, aged 3-14 years with diagnosis of ASD were included. Children receiving folinic acid (dose of 2mg/kg/day in two divide doses) and behavioral therapy were assigned to Group-A while Group-B received only behavioral therapy. Primary outcome measures were improvement of language and adaptive skills while secondary outcome measures were stereotype movements, verbal communication, hyperactivity, peer relationship and inattention were these parameters measured at baseline, 6-weeks and 12-weeks (final outcome) intervals.

RESULTS: Of 44 children, 34 (77.3%) were male and 10 (22.7%) female. Mean age was 4.28±1.57 years. At baseline, outcome measures scores in between both study groups had no statistically significant difference ($p>0.05$). Regarding final outcome, among children in Group-A, primary outcome measures as gross motor development age (51.41±16.29 months vs. 39.23±51.41 months, $p=0.002$), self-help (48.64±13.68 months vs. 37.45±6.82 months, $p=0.001$) and language (18.68±6.34 months vs. 15.15±5.22 months, $p=0.050$) scores improved significantly when compared to Group-B. Regarding secondary outcome, stereotype movements ($p=0.028$) improved significantly in Group-A in comparison to Group-B.

CONCLUSION: Folinic acid along with behavioral therapy helped improving language and adaptive skills in children with ASD when compared to behavioral therapy alone.

Clinical Trial Registry Number: NCT05013164

KEYWORDS: Leucovorin (MeSH); Folinic Acid (MeSH); Behavioral therapy (Non-MeSH); Language impairment (Non-MeSH); Autism Spectrum Disorder (MeSH); Speech (MeSH); Verbal Behavior (MeSH); Childhood Autism Rating Scale (MeSH); Autism Symptoms Questionnaire (MeSH).

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INTRODUCTION

Autism spectrum disorder (ASD) is known to be spectrum of developmental disorders described as deficits in the reciprocal social interaction, verbal and nonverbal communication with limited repetitive interest and activities.[1] Several interacting factors are associated with pathology involving maternal, environmental, nutritional and perhaps genetic risk factors although no specific genetic cause has been found yet. Local data lacks details about the exact incidence of ASD in Pakistan but worldwide incidence is estimated to be around 7.6/1000.[2-4]

Children with ASD are thought to have impairment of the transportation of the folate across the blood-brain barrier because of "folate receptor autoantibodies (FRAA) that are either blocked or bounded to the "folate receptor alpha (FRα)". This creates the condition known as "cerebral folate deficiency" where serum folate concentrations are normal but CSF folate concentrations are low.[5] Studies have found that supplementing children with ASD with a reduced form of folate folinic acid allows for bypass of the impaired folate transport mechanism into the CSF, leading to improved behavior and language development.[6] Recent data showed that folinic acid supplementation among children with non-syndrome ASD resulted in significant improvement in language and aberrant behavior.[7]

Early intervention by a team of healthcare specialists including a psychologist, a speech and language therapist, and an occupational or physical therapist have been found to result in improvement in the child's development of age-appropriate language, social, and behavior skills.[8] As some researchers have pointed out that folinic acid may improve behavior and language development among children with ASD, not much data is available analyzing efficacy of folinic acid in improving the adaptive skills along with language impairment in these children. The findings of this study might help us analyzing useful insight about the potential role of folinic acid among children with ASD. Objective of this study was to find out the role of folinic acid in improving the adaptive skills and language impairment in autism spectrum disorder (ASD) among children aged 3-14 years.

METHODS

This open label randomized controlled trial was conducted at Out-patient

TABLE I: PRIMARY AND SECONDARY OUTCOME MEASURES SCORES AT BASELINE (N=44)

Outcome measures		Baseline		P-value
		Group-A (n=22)	Group-B (n=22)	
Primary Outcome Measures	Gross Motors Development Age (months)	32.23±8.2	29.41±5.0	0.177
	Self Help (months)	30.73±13.8	25.14±6.9	0.097
	Language (months)	12.36±5.8	10.27±3.9	0.169
Secondary Outcome Measures	Stereotype movements	8 (6.8-8.3)	8 (7-8)	0.834
	Verbal Communication	3 (2-4)	2 (2-3)	0.412
	Hyperactivity	8 (7-8)	6 (6-8)	0.007
	Peer Relationship	2 (2-3.3)	2 (0-2.3)	0.015
	Inattention	8 (7-8)	7 (6-8)	0.120

Independent sample t-test used. Primary outcome measure scores represented as mean and standard deviation. Secondary outcome measure scores represented as median and interquartile range.

Department of Pediatric Neurology, The Children Hospital & The Institute of Child Health Multan, Pakistan from October 2020 to March 2021. The study was approved from Institutional Ethical Committee. Written informed consent was taken from parents/guardians. Initially 100 children were selected for this study. Inclusion criteria was children of both genders aged 3 to 14 years with diagnosis of autism spectrum disorder established by DSM-5 Criteria, Childhood Autism Rating Scale (CARS) scoring[7] and clinical examination along with documentation of Language Impairment. All children having autism with seizure disorder, autism with serious medical illness within last 6 months or those with autism with well-defined genetic syndrome were excluded. After filtering children as per inclusion and exclusion criteria, 44 were found to be aligned as per inclusion/exclusion criteria.

A pre-designed Performa was used to collect relevant predecided all information. A detailed general physical examination and neurological examination was done at baseline and follow up visits. Sealed opaque envelope system was used for randomization. These pre-written sealed envelopes were opened at the time start of treatment. A total of 22 children receiving folinic acid and behavioral therapy were assigned to Group-A and 22 of those receiving only behavioral therapy were assigned Group-B (Figure 1). Folinic Acid was given at the dose of 2mg/kg per day in two divide doses (maximum 50 mg per day) given for 12 weeks. Applied behavior analysis (ABA) therapy consisted of sessions spanning 20 to 40 hours per week done by behavioral therapist. Children were planned to have 3 to 4 hours per day session (5 to 6 days a week) with the behavioral therapist while separate sessions were also conducted with parents/caregivers. Aim of the ABA was to improve wanted behaviors and decrease unwanted behaviors along with training parents/caregivers about the handling of the child at home. These sessions were conducted throughout the study period among all study participants. Outcome measures were based on Autism Symptoms Questionnaire.[7] Primary outcome measures was language improvement and adaptive skills (gross motor development age, self-help) while secondary outcome measures were improvement in stereotype movements, verbal communication, hyperactivity, peer relationship, inattention and these measured at baseline, 6-weeks and 12-weeks (final outcome) intervals. Following side effects were noted fever, vomiting, rash over the body.

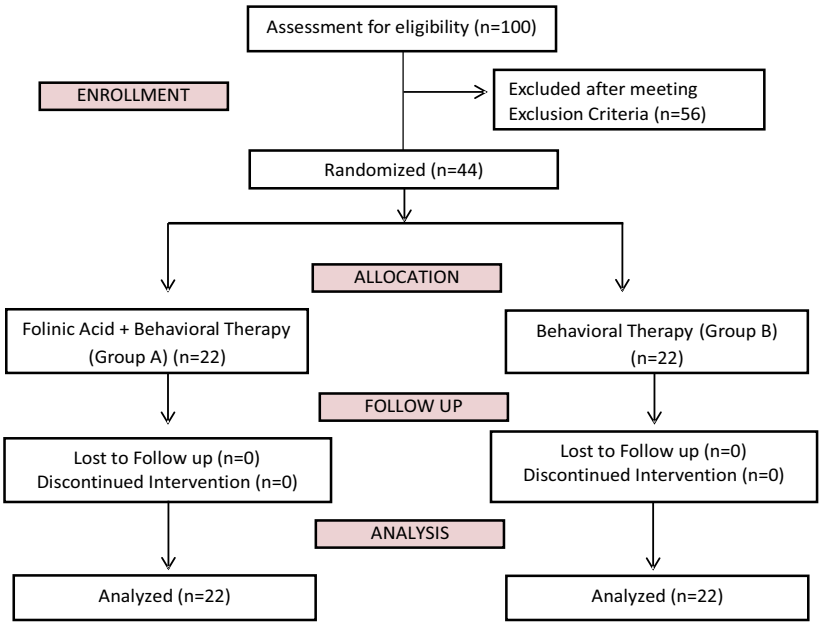

Figure 1: Methodology Flow Chart

Data was analyzed statistically by SPSS version 26.0. Gender was represented as frequency and percentage. Age and primary outcomes were described as mean and standard deviation. Independent sample t-test was used to measure level of statistical significance among both study groups. Chi square test was employed to compare qualitative variables like gender. Secondary outcome measure scores represented as median and interquartile range. Wilcoxin Signed Rank test used to note median differences between groups. P value < 0.05 was considered as significant.

RESULTS

Initially, 100 children were screened for this study but after matching children for age and gender and assessment according to inclusion and exclusion criteria, only 44 (22 in each group) were finally considered (Figure 1). Out of 44 children, there were 34 (77.3%) male and 10 (22.7%) female (p=0.869).

TABLE II: PRIMARY AND SECONDARY OUTCOME MEASURES SCORES AT 6-WEEKS AND FINAL OUTCOME (12 WEEKS) BETWEEN BOTH STUDY GROUPS (N=44)

Outcome measures		Outcome at 6-weeks		P-value	Final Outcome at 12-Weeks		P-value
		Group-A (n=22)	Group-B (n=22)		Group-A (n=22)	Group-B (n=22)	
Primary Outcome Measures	Gross Motors Development Age (months)	47.00±16.59	38.82±6.50	0.001	51.41±16.3	39.23±51.4	0.002
	Self Help (months)	44.59±13.33	31.95±7.66	<0.001	48.64±13.7	37.45±6.8	0.001
	Language (months)	15.82±5.8	12.86±3.97	0.055	18.68±6.3	15.15±5.2	0.050
Secondary Outcome Measures	Stereotype Movements	6 (5-7)	6 (6-7)	0.318	5 (4-6)	6 (5-6)	0.028
	Verbal Communication	3.5 (3-5)	3.5 (3-4)	0.509	4.5 (4-5)	4 (4-5)	0.252
	Hyperactivity	6 (5.8-7)	5 (5-6)	0.057	5 (4-6)	5 (5-6)	0.904
	Peer Relationship	4 (3-5)	3 (3-4)	0.033	5 (4.8-6)	3 (3-4)	0.073
	Inattention	6 (5-7)	5 (5-6)	0.449	5 (4-6)	5 (4-5)	0.710

Independent sample t-test used. Secondary outcome measure scores represented as median and interquartile range. Wilcoxin Signed Rank test used to note median differences between groups.

Overall, mean age was 4.28±1.57 years. In Group-A, mean age was 4.22±1.62 years versus 4.35±1.50 years in Group-B (p=0.784). Table I is showing outcome measures scores in between both study groups at baseline (p>0.05).

Table 2 is showing comparison of primary and secondary outcome measure between both study groups at 6 weeks and at final outcome (12-weeks). Primary outcome measure as gross motor development age improved significantly (47.00±16.59 months vs. 38.82±6.50 months, p=0.001) along with self-help (44.59±13.33 months vs. 31.95±7.66 months, p=<0.001) among children in Group-A in comparison to Group-B. With regards to secondary outcomes, peer relationship scores improved significantly in Group-A in comparison to Group-B (p=0.033). At 12 weeks, in terms of primary outcome among children in Group-A, gross motor development age (51.41±16.29 months vs. 39.23±51.41 months, p=0.002), self-help (48.64±13.68 months vs. 37.45±6.82 months, p=0.001) language (18.68±6.34 months vs. 15.15±5.22 months, p=0.050) scores improved significantly when compared to Group-B. Regarding secondary outcome, stereotype movements (p=0.028) scores were significantly improved in Group-A in in comparison to Group-B at 12 weeks.

DISCUSSION

Previously, researchers have found children with cerebral folate deficiency treated with folinic acid to result in normalization of CSF folate levels hence improving neurological symptoms significantly.[10,11] In the present study, folinic acid and behavioral therapy were found to result in improvement in final primary outcome measurement scores. Vargason T et al from United States comparing three clinical treatments for ASD found folinic acid to result in significant improvement in adaptive and behavioral skills.[12] A study done by Frye et al noted that irritability, lethargy, stereotyped behavior, hyperactivity and inappropriate speech improved in the folinic acid group as compared with the placebo group.[7] Stereotypic behavior and total score also significantly improved for the folinic acid group as compared with the placebo group. We also found that the effect of folinic acid is consistent with the therapeutic effect of early behavioral interventions[13,14] Local study has shown that integration of both occupational and speech therapy helped to bring improvement of social, learning and behavior skills required for rehabilitation of autistic children.[3]

Numerous pathways are hypothesized considering positive impact of folinic acid on the metabolism. Folinic acid is thought to normalize folate-dependent one-carbon metabolism[15] whereas contrary to folic acid, folinic acid enters the folate cycle without reduction by dihydro-folate reductase.[16] Folinic acid is also believed to cross the bloodbrain barrier utilizing the educed folate carrier in case Frα is blocked by FRAAs.[17] A well-tolerated medication targeting pathophysiological process as well as core symptoms linked with SD is required as FDA approved drugs for ASD currently affect lipid, cholesterol as well as glucose metabolism resulting in weight gain and increasing the chances the type-2 diabetes mellitus.[18,19]

This research has some limitations. Firstly, a relatively small sample size is perceived to impact baseline as well as final scores. Secondly, as this was a single center study, our findings cannot be generalized. Thirdly, we were unable to record severe adverse events among both study groups so safety of these treatment regimens needs further investigation.

CONCLUSION

Our small study observed that folinic acid along with behavioral therapy helped improving language and adaptive skills in children with ASD when compared to behavioral therapy alone. Further studies involving large sample size and multiple centers with longer duration are needed to further strengthen our beliefs about the role of folinic acid among children with autism spectrum disorder.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

RF: Conception and study design, analysis and interpretation of data, drafting the manuscript, critical review, approval of final version to be published

FS: Conception and study design, acquisition of data, drafting the manuscript, approval of final version to be published

AI, MW, AK & ME: Acquisition of data, drafting the manuscript, approval of final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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DATA SHARING STATEMENT

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