Low Lever Laser Therapy (LLLT) In Autism: Age Group Analysis

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Abstract

In our preceding studies our findings strongly illustrated that LLLT produced significant and clinically meaningful improvement of behaviors expressions of autism spectrum disorder (ADS) in children and adolescents, continuing to produce a progressive and meaningful improvement in symptoms for up to 6 months, following completion of the procedure administration protocol. In this paper, an analysis of subject findings by age group was performed for all 40 subjects who had received the active laser treatment (inclusive of subjects initially randomized to the active procedure group, and the cross-over initial placebo subject group). The four age groups evaluated were the following: 5 to 6 years, inclusive; 7 to 8 years, inclusive; 9 to 12 years, inclusive (pre-teen); 16 to 17 years, inclusive (teen). Our main results demonstrated that scales, subscales scores, and CGI-S Ratings, obviously showed a greater improvement in in younger age groups (5-6, 7-8, and 9-12 years old), compared to older participants (age 16-17); in general, the age group 5-6 years old demonstrated the greatest improvement after LLLT. These results suggest that LLLT interventions should be applied in autistic children as early as possible in lifespan, which requires new efforts for a very early diagnosis of ASD onset.

INTRODUCTION

Autism spectrum disorder (ASD) is complex neurodevelopmental disorder of multifactorial etiology, characterized clinically by language impairment, dysfunction in social engagement, language, stereotypical movements and behaviors, and various and varied cognitive deficits.(1-9)

We recently examined the efficacy of low level laser therapy (LLLT) to treat autistic children and adolescents. Twenty-one of the 40 participants received 5-minute active (test) procedure administrations across a four-week period, while the remaining 19 participants received fake (placebo) procedure administrations. The adjusted mean difference in the baseline to study endpoint change in the ABC Irritability Subscale score between test and placebo participants was 15.17 in favor of the test procedure group. In a second paper we presented the results of the 6 months follow up assessment, demonstrating that improvement in symptoms continued after 6 months following completion of the LLLT procedure for autistics.(5, 10)

Therefore, we suggested that our results demonstrated clinical improvement of the key evaluable behaviors characteristic of autism disorder in children and adolescents, in symptoms for up to 6 months after following treatment completion. We also argued that these ground-breaking results might be patho-physiologically supported with the fact that LLLT progressively rearrange anatomical, functional and effective connectivity, modifying those neuronal networks related to the complex symptoms in autistics. (5, 6, 10)

ASD is considered a highly heritable (11-17) disorder with estimates as high as 80-90%. Initial evidence for this came from early twin pair studies. Converging evidence over the past three decades has established that the typical trajectory of brain development is altered in children with ASD; the process starts prenatally and persists into adult life.(18) Although at birth, the brain size may be normal or even smaller as compared to a typically developing normal child's brain, there is accelerated growth starting around 6 months of age into toddlerhood; this is followed by slowing in brain growth by school age. Several authors have

concluded that etiopathogenesis of a disorder such as ASD has strong genetic origin relationship.(19-21)

Nonetheless, although we had noted some different results regarding to age, we had not performed an age group analysis.(5, 10). Therefore, we will analyze in this paper the LLLT improvement effect according to different age groups

METHODS

In our first publication, the participants initially consisted of 40 individuals, divided in two groups: the active procedure group which received the LLLT intervention (20 subjects), and a placebo group (20 subjects).(5)

In this paper, an analysis of subject findings by age group was performed for all 40 subjects who received the active laser treatment (inclusive of subjects initially randomized to the active procedure group and the cross-over initial placebo subject group).

The four age groups evaluated are the following:

- 5 to 6 years, inclusive
- 7 to 8 years, inclusive
- 9 to 12 years, inclusive (pre-teen)
- 16 to 17 years, inclusive (teen)

Inclusion and exclusion criteria have been previously described. (5, 10) Diagnosis was confirmed by the Autism Diagnostic Interview (ADI-R). Each participant demonstrated "irritable" behaviors such as tantrums, aggression, self-injurious behavior, or a combination of thereof.

The participant's Aberrant Behavior Checklist (ABC) irritability subscale score was >18; the Clinical Global Impressions Severity Scale (CGI-S) score was >4 (4 = moderately ill). The participants' therapeutic/intervention plan had been consistent/stable for 3 months. They abstained: from undertaking new treatments during the study time. Exclusion criteria were the following: history of a primary or concurrent diagnosis of another disorder, including neurological, use of a psychotropic drug, or any participation in a research study within 30 days prior to the commencement of that study.(5)

Test Procedures

Participants received 5-minute procedure administrations to the base of the brain and temporal areas with the Erchonia® EAL Laser across a four-week period: two procedures per week, each procedure three to four days apart at the investigator's test site.

Ethics

The study received an approval: from the Ethics Committee of the Institute for Neurology and Neurosurgery in Havana, Cuba, and was registered with the NIH (identifier: NCT03379662). Informed written consent was obtained from the parent or guardian of each participant, after a full explanation of the procedures to be undertaken. The informed consent forms, research protocol, and approvals are available for inspection in the Office of Research Integrity at the Institute of Neurology and Neurosurgery in Havana, Cuba.

Statistical analysis

Mean and standard deviation of the ABC Global and Subscale scores from baseline through 8 weeks' evaluation, and the change between. The change in CGI-S ratings from Baseline to 8 Weeks evaluation was calculated by age group.

RESULTS

In tables 1, 2, and 3, scales and subscales scores, and CGI-S Ratings clearly showed a superior improvement in younger age groups (5-6, 7-8, and 9-12), compared to older participants (age 16-17); in general, the age group 5-6 years old demonstrated the highest improvement after LLLT.

ABC Global and Subscale Scores

Table 1

ABC Global and Subscale Scores: Baseline to 8 Weeks: By Age Group. Mean and standard deviation of the ABC Global and Subscale scores from baseline through 8 weeks' evaluation, and the change between.

ABC Global Score		Baseline	4 Weeks	8 Weeks	Change: Baseline to 8 Weeks
5-6 years	Mean	98.45	54.18	33.91	**-64.20**
n=11	SD	28.46	20.45	54.91	25.62
7–8 years	Mean	121.40	73.60	57.20	**-64.20**
n=10	SD	19.91	32.92	39.55	26.02
9–12 years	Mean	110.63	69.83	53.19	**-57.44**
n=16	SD	18.73	27.34	29.36	21.66
16-17 years	Mean	106.67	92.00	80.33	**-26.33**
n=3	SD	22.03	42.14	49.94	33.50
Irritability & Agitation		Baseline	4 Weeks	8 Weeks	Change: Baseline to 8 Weeks
5-6 years	Mean	26.40	15.00	9.20	**-19.40**
n=11	SD	5.77	2.35	3.70	6.38
7–8 years	Mean	33.67	23.33	20.33	**-19.10**
n=10	SD	12.06	10.97	9.29	9.21
9–12 years	Mean	31.56	17.56	12.19	**-19.38**
n=16	SD	6.11	9.31	9.31	6.16
16-17 years	Mean	30.00	26.00	22.00	**-8.00**
n=3	SD	8.54	14.73	16.70	8.72
Lethargy & Social Withdrawal		Baseline	4 Weeks	8 Weeks	Change: Baseline to 8 Weeks
5-6 years	Mean	20.45	11.27	7.09	**-13.36**
n=11	SD	9.82	7.27	7.34	9.79
7–8 years	Mean	28.10	17.10	13.30	**-14.80**
n=10	SD	6.35	9.19	10.78	5.59
9–12 years	Mean	23.88	15.38	11.63	**-12.25**
n=16	SD	6.72	8.16	8.87	6.83
16-17 years	Mean	27.33	23.00	22.33	**-5.00**
n=3	SD	5.13	11.79	13.58	8.89
Stereotypic Behavior		Baseline	4 Weeks	8 Weeks	Change: Baseline to 8 Weeks
5-6 years	Mean	11.45	5.91	4.09	**-7.36**
n=11	SD	5.56	4.06	3.45	4.08
7–8 years	Mean	13.80	8.80	8.00	**-5.80**
n=10	SD	5.35	5.05	4.99	4.44
9–12 years	Mean	13.38	8.38	7.19	**-6.19**
n=16	SD	4.59	4.51	4.26	3.67
16-17 years	Mean	16.00	13.67	12.33	**-3.67**
n=3	SD	3.61	7.09	9.29	6.35
Hyperactivity & Noncompliance		Baseline	4 Weeks	8 Weeks	Change: Baseline to 8 Weeks
5-6 years	Mean	33.64	19.73	12.27	**-21.36**
n=11	SD	8.26	5.80	6.34	9.48
7–8 years	Mean	40.10	26.10	19.40	**-20.70**
n=10	SD	6.37	9.45	12.54	10.77
9–12 years	Mean	34.06	22.88	17.06	**-17.00**
n=16	SD	8.41	10.11	10.02	7.76
16-17 years	Mean	28.00	23.67	19.00	**-9.00**
n=3	SD	6.24	11.02	11.79	9.85
Inappropriate Speech		Baseline	4 Weeks	8 Weeks	Change: Baseline to 8 Weeks
5-6 years	Mean	5.91	4.00	2.64	**-3.27**
n=11	SD	3.11	2.05	1.91	2.33
7–8 years	Mean	6.80	4.50	3.00	**-3.80**
n=10	SD	4.39	2.72	2.54	3.88
9–12 years	Mean	7.75	5.69	4.50	**-3.25**
n=16	SD	3.38	3.03	2.85	2.62
16-17 years	Mean	5.33	5.67	4.67	**-0.67**
n=3	SD	2.52	3.06	2.52	0.58

CGI-S Ratings

The change in CGI-S ratings from baseline to 8 weeks'

evaluation was calculated by age group. Table 2 below shows the number of subjects by change in severity rating. CGI-S ratings improved substantially by 3 or 4 categories for 36% (4 out of 11) of subjects aged 5-6 year; 40% (4 out of 10) of subjects aged 7-8 years and only 12.5% (2 out of 16) of subjects aged 9-12 years.

Table 2

CGI-S Ratings Changes: Baseline to 8 Weeks: By Age Group

	0	-1	-2	-3	-4
5-6 years	-	1	6	3	1
7–8 years	-	5	1	2	2
9–12 years	1	2	11	2	-
16-17 years	2	-	-	1	-

CGI-I Ratings

Table 3 below shows CGI-I ratings at 8 Weeks evaluation by age group. A CGI-I rating of "1: Very Much Improved" was attained for 54.5% (4 out of 11) of subjects aged 5-6 year; 40% (4 out of 10) of subjects aged 7-8 years and only 25% (4 out of 16) of subjects aged 9-12 years.

Table 3

CGI-I Ratings at 8 Weeks: By Age Group

	1	2	3	4
5-6 years	6	4	1	-
7–8 years	4	4	2	-
9–12 years	4	11	-	1
16-17 years	1	-	2	-

DISCUSSION

Our main results demonstrated that scales, subscales scores, and CGI-S Ratings obviously show a greater improvement in in younger groups (5-6, 7-8, and 9-12 years old), compared to older participants (age 16-17); in general, the age group 5-6 years old showed he greatest improvement after LLLT.

We recently found brain connectivity abnormalities, both anatomical (AC) and functional (FC) in autistic children. (6-8) AC was assessed by the DW-MRI technique and FC by EEG coherence calculation, determining the relationship between AC and FC, with consideration of short-range and long-range brain networks. We found correlations among AC and FC measurements, and concluded that an impaired audiovisual interaction, due to AC and FC abnormalities are present in autistic children. Moreover, our data in individuals with ASD from ages 4-7 shows a disruption of long-range connections involving the superior longitudinal fasciculus (SLF) and uncinate fasciculus. SLF is associated with spatial working memory and the integration of the auditory and speech areas of the brain. The left SLF is important for information exchange between Broca's and Wernicke's areas. Thus, abnormal connectivity in SLF may underpin the neurobiological basis of language deficits in ASD. On the other hand, the uncinate fasciculus has traditionally been considered to be a part of the limbic system and is known for its involvement in human emotion processing, memory and language. We concluded that a dominant finding with respect to the anatomical connectivity in ASD is that there is a combined pattern of local over-connectivity and long distance under-connectivity.(7) Hence, the study of both brain anatomic and functional connectivity should be a powerful tool to assess ASD in present and future research.(6-8)

It is widely accepted that the brain develops by a dynamic interplay between the genetic factors and experience of the child. Although brain development starts in utero, infancy and toddlerhood are remarkable for peak synaptogenesis and generation of early neural circuitry; in concert with experiential/environmental factors, as well as genetically programmed pruning in childhood and adolescence, the connections and neural circuits are further sculpted. The brain attains 80% of its adult weight within the first 2 postnatal years: adult cerebral volume is attained by 5 years of age, with a significant reduction in gray matter (GM) after 12 years of age.(17, 18, 22-26)

ASD is a considered a greatly heritable disorder with estimates as high as 80-90%. Initial evidence for this came from early twin pair studies.(18) Subsequent studies found 60% of monozygotic (MZ) twins to be concordant for autism versus none for dizygotic (DZ) pairs; 92% of MZ twins were concordant for a broad spectrum of autism related cognitive and social abnormalities versus 10% for DZ twins. Concordance rate for siblings ranges from 3 to 14%. Therefore, it has been suggested that in ASD there is a developmental expression of a gene or set of genes. (18, 27-31)

The most severe deficit of both neuronal nucleus and cytoplasm volume with increase of age in autistic children appears to be a reflection of early developmental alterations that may have a major contribution to the autistic phenotype. The broad range of functions of the affected structures suggests that their developmental and age-associated abnormalities contribute not only to the diagnostic

procedures of autism but also to the wide-ranging spectrum of clinical alterations associated with autism. Lack of clinical improvement in autistic teenagers and adults indicates that the observed increase in neuron nucleus and cytoplasm volume, close to control level, does not normalize brain function.(18, 32)

Several authors have conjectured that for underlying these age-specific variations in anatomic abnormalities in autism, it should be related to age-specific changes in gene expression, molecular, synaptic, cellular and circuit abnormalities. A peak age for detecting and studying the earliest fundamental biological groundworks of autism is prenatal life and the first three postnatal years. Studies of brain from the older autistics may not find original anatomic and functional grounds to explain ASD behaviors.(19-21, 24)

ASD behavioral signs onset is usually categorized as happening in one of two ways: an early onset pattern, in which children demonstrate delays and deviances in social and communication development early in life, and a regressive pattern, in which children mostly normally develop for some period and then experience a substantial decline in formerly developed skills. It has long supposed that the majority of autistic children show an early onset pattern, although it has been recently suggested that a regressive pattern of onset is much more common than previously thought, and that can occur early in lifetime. Moreover, it has been argued that ASD symptoms emerge over the first two years of life, but several authors emphasize that for an early diagnosis needs to focus on very early-appearing social behaviors, such as social interest, shared affect, gaze to faces and eyes, and response to name, for an early ASD diagnosis in lifespan.(2, 19, 21, 24, 33-35)

In our previous studies our findings strongly illustrated that not only does application of the Erchonia® HLS Laser effect a sizable, statistically significant and clinically meaningful improvement in all of the key evaluable behaviors characteristic of autism disorder in children and adolescents, continuing to affect a progressive and meaningful improvement in symptoms for up to 6 months following completion of the procedure administration protocol, during which time no LLLT procedure administrations were applied to patients. (5, 10)

These results suggest that LLLT interventions should be applied in autistic children as early as possible in lifetime, which requires new efforts for a very early diagnosis of ASD onset. Therefore, we will develop future protocols including age groups of autistics as early as possible in lifetime.

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