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Assessment of the effect of auditory integration therapy on human forkhead box protein J1 and its impact on behavioral, social, and sensory symptoms in children with autism spectrum disorder

Laila Yousef AL-Ayadhi [1, 2], Abdulrahman Mohammed Alhowikan [1, 2], Nadra Elyass Elamin [1], Dost Muhammad Halepoto [1, *]

[1]*Autism Research and Treatment Center, Department of Physiology, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia*
[2]*Department of Physiology, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia*

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ABSTRACT

This study aimed to explore the effect of auditory integration therapy (AIT) on the forkhead box J1 protein and assessed its impact on behavioral, social, and sensory symptoms in children with autism. Behavioral, social, and sensory scores were calculated for each child using the childhood autism rating scale, social responsiveness scale, and short sensory profile before and after AIT. The plasma level of Foxj1 was [575 (351-2553) pg/mL] [median (interquartile range)] before AIT. This level did not change significantly ($p>0.05$) immediately [1143(336-4599)], after one month [1268 (275-4932)], or three months [1058 (184-3462)] AIT. However, results revealed that behavioral, social, and sensory rating scales were improved after AIT. Pearson correlation (r) values before and after AIT between severity variables were calculated. Unchanged plasma levels of Foxj1 after AIT supported the non-therapeutic effect of AIT on Foxj1 in autistic children. A significant change in behavioral, social, and sensory symptoms was noticed in autistic children. Additional research, on a large population, is necessary to assess AIT's impact on behavioral and social changes in children with an autism spectrum disorder.

1. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental behavioral disorder with an onset prior to 3 years of age. Autism is described by social interaction impairment, repetitive behavior, and sensory abnormalities (APA, 2000). Although the etiology and pathogenesis of ASD are not clear, increasing evidence suggested that it can be originated from a range of factors including autoimmunity (Al-Ayadhi and Mostafa, 2012).

In spite of the urgent medical necessity, at present, there is no known active complete therapy available for ASD. Several educational pieces of training, including habilitative therapies and behavioral strategies, have been applied to treat children with ASD, however, very limited interventions have been focused on essential systematic research (Scott and Chris, 2007). Timely treatment has revealed an improvement in the prognosis of ASD children (Rogers and Vismara, 2008), but the most useful method of treatment is still unclear (Paul, 2008).

On the basis of several principles, integration deformities and sensory processing may play key roles in impairments of cognition, behavior, and perception in autistic subjects. Among these sensory deformities, distortion of auditory perception may responsible for several particular signs of autism (Sokhadze et al., 2016). Disability in sensory processing has been revealed in forty-two to Eighty-eight percent of autistic children; though, an experimental study exploring the presence of sensory processing defects in children with ASD is uncommon. However, very limited study on the association between possible biomarkers and sensory processing dysfunction has been reported in subjects with ASD (El-Ansary et al., 2016). Data from a previous publication (Boddaert et al., 2004) indicated that about 50% of autistic children had serious hearing problems; furthermore, irrationally anxious action and poor oral communication were

* Corresponding Author.
Email Address: dr_m_halepota@yahoo.com (D. M. Halepoto)
https://doi.org/10.21833/ijaas.2023.01.011
Corresponding author's ORCID profile:
https://orcid.org/0000-0001-7705-8348

strongly associated with auditory irregularities. Moreover, different interventions were established to control the usual auditory sensitivity differences in subjects with ASD and generally called auditory integration therapies.

Auditory integrative training (AIT) was established as a method to develop unusual sound sensitivity in subjects with behavioral disorders including ASD (Sinha et al., 2011). Bérard (1993) advised that the irregular sensitivity to particular sound wave frequencies, irrespective of general listening capability, is linked with a variety of learning and behavior difficulties and that AIT would lead to "retraining" of the hearing process.

Several researchers have proposed that AIT plays a key role to improve typical behavior symptoms, restrictions in social interactions, and language disorders (Sokhadze et al., 2016; Al-Ayadhi et al., 2013; Zhang et al., 2009). Furthermore, important advances in autistic behavior and the severity of disease in relation to intelligence quotient (IQ) and verbal presentation have been reported after 3–12 months of intervention (Sokhadze et al., 2016; Zhang et al., 2009). Russo et al. (2010) assessed the effect of AIT on auditory processing and recognized biological modifications, including pitch tracking, and cortical and brainstem response timings, in autistic children. Li et al. (2018) observed the efficiency of AIT for Chinese children with and without ASD and suggested that AIT can decrease the Aberrant Behavior Checklist (ABC), and Autism Treatment Evaluation Checklist (ATEC) scores and increase the IQ score in ASD subjects. However, there is debate in the published research relating to the efficiency of AIT in decreasing auditory hypersensitivity. A literature review determined the effect of AIT or other sound therapy techniques on subjects with ASD (Sinha et al., 2006). According to the review, three trials demonstrated improvements in ABC scores after three months of AIT, and the remaining three studies showed no AIT effect in autistic subjects.

Extensive studies (Al-Ayadhi et al., 2018; 2019) have confirmed that AIT plays an important role in the biological and behavioral changes in ASD. However, research on the impact of AIT on biological markers in ASD is rare. Recently our group discussed the striking impact of AIT on Transforming Growth Factor-β1 (TGF-β1) (Al-Ayadhi et al., 2018) and Human Glial Cell Line–Derived Neurotrophic Factor (GDNF) (Al-Ayadhi et al., 2019). These studies suggested that an abnormal immune system may cause adverse neuroimmune interactions, autoimmunity, or abnormal immune responses, during brain development.

Forkhead box protein J1 (Foxj1) is a member of the forkhead family transcription factors (Larson et al., 2019) associated with an extensive range of biological processes including DNA repair, cell cycle regulation, neurogenesis, and apoptosis (Genin et al., 2014). Foxj1 is associated with the production of motile cilia which are the main elements of ependymal cell differentiation and function in the central nervous system (CNS) (Spassky et al., 2005).

Several studies have advised that Foxj1 also plays major roles (Coffer and Burgering, 2004) in lymphocyte progress and effector function, including regulation of CD4+T cell tolerance. Thus, in many immune cell lineages, and their down-regulation, Foxj1 probably involves in the pathogenesis of numerous immunological disorders, proposing that Foxj1 investigation will result in the advancement of innovative treatment markers in autoimmune diseases. Forkhead box protein J members are usually formed in the brain during embryonic development but during CNS development their role is not known (Pérez-Sánchez et al., 2000). Huang et al. (2013) explored the Foxj1 expression pattern in the rat brain and suggested that Foxj1 contributes to neurogenesis and neuronal production in the brain after cerebral ischemia.

Previously Foxj1 was identified as a unique transcription factor involved in autoimmunity (Lin et al., 2005). Srivatsan and Peng (2005) suggested that Foxj1 prevents spontaneous autoimmunity to some extent by antagonizing NF-κB activation. Microarray studies noticed the immunological importance of the Foxj1 gene and identified novel transcription factors in autoimmunity (Lin et al., 2004). Molecular characteristics and expression pattern Like the Foxo transcription factors, Foxj1 is expressed mainly in naïve T cells and is rapidly down-regulated upon activation, such as during IL-2 exposure and/or TCR ligation (Lin et al., 2004). Hence the genetics, molecular biology, and biochemistry of Foxj1 are not known.

Limited research has examined the role of Foxj1 in human diseases. Certainly, given the immunological phenotype of Foxj1 deficiency, and the relative Foxj1 deficiency detected in non-autoimmune versus autoimmune mice (Lin et al., 2004), irregularities in Foxj1 gene expression, metabolic pathway, and/or function may affect inflammatory conditions and/or another autoimmunity. Tuteja and Kaestner (2007) have established that the Foxj1 gene controls the action of IL-2 and IFN-γ, along with transcription factor NF-κB, liable for the generation of the expression of pro-inflammatory mediators. Coffer and Burgering (2004) suggested that the inhibition of T lymphocyte activation and development of autoimmune reaction resulting in Foxj1 mutations in mice is the development of systemic autoimmune inflammation.

There is no single study related to Foxj1 and ASD has been reported so far. However, one of the FOX family member Foxp1 variants has been identified in several subjects with intellectual disability (ID), sporadic ASD, moderate to severe speech delay, and global developmental delay (Palumbo et al., 2013). We hypothesized that Foxj1 could play a pathogenic role in the immune system in patients with ASD. These findings have directed us to search for biomarkers that may help us prior to the discovery of ASD. As the plasma levels of Foxj1 in ASD, subjects have never been measured earlier, the main aim of

the current study was to determine a possible role for Foxj1in children with ASD before and after AIT and also to evaluate the impact of AIT on behavior, social and sensory symptoms in children with ASD.

2. Material and methods

2.1. Study participants

Twenty-six ASD subjects (20 males and 6 females) 3.6 to 11.2 years of age (mean±SD=6.9±2.0 years), were recruited for this study from the Autism Research and Treatment Centre at the King Saud University, Kingdom of Saudi Arabia. All subjects were screened and assessed using the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (APA, 2013). Foxj1 plasma concentrations were measured by ELISA before and after AIT intervention (immediately, one and three months) for each child. Pre and post-autism severity were measured in all children by using CARS (Bashir et al., 2014), SRS (Constantino and Gruber, 2012) and SSP (Dunn, 1999) scales as described in our previous studies (Al-Ayadhi et al., 2018; 2019).

Children with neurological diseases (tuberous sclerosis, cerebral palsy), allergic signs, seizures, autoimmune diseases, or a concomitant infection and metabolic disorders (e.g., phenylketonuria), were excluded from the study. According to the guidelines of the Ethics Committee of the King Khalid Hospital, King Saud University written consent from the parents of each child was obtained. Children were not allowed to begin any new therapies or stop any current therapies, including medications and supplements during the study period. Ethical approval was obtained for the study by the Institutional Review Board of the College of Medicine, King Saud University.

2.2. Auditory integration training

Auditory integration training was carried out by following the available protocol (Bérard, 1993) and formerly reported by our group (Al-Ayadhi et al., 2013; 2018; 2019).

2.3. Blood sample collection

After overnight fasting blood sample (3 ml) was collected from each child in coded test tubes containing EDTA. The blood samples were centrifuged at 3,000 rpm to collect plasma, which was then stored in a freezer at −80°C until analysis. Foxj1 plasma concentrations were measured using a commercially available sandwich ELISA kit (Cusabio Biotech Co. Ltd., Wuhan, China). All samples were assayed in duplicate, and mean values were calculated. No significant cross-reactivity or interference was observed.

2.4. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS 21.0 for Windows; SPSS, Chicago, IL, USA). The parametric data were presented as mean and standard deviation (SD). Also, nonparametric data were presented as median and IQR levels. Paired t-test was used for the comparison of parametric data, while the Mann-Whitney U-test was used for the comparison of nonparametric data before and after AIT. The Pearson correlation coefficient 'r' was employed to determine correlations between severity variables (SRS, CARS, and SSP). The p values less than 0.05 were considered significant.

3. Results

The changes in Foxj1 levels [median (interquartile range=IQR)] and the mean scores ±SD of the three behavioral rating scales (CARS, SRS, and SSP) before and immediately, 1 and 3 months after AIT are summarized in Table 1. The median plasma Foxj1 level before AIT was found 575 pg/mL, this level did not change significantly (p=>0.05) immediately, 1, and 3 months after AIT. However, we found that the AIT had a significant effect in improving autism symptoms after intervention using behavioral rating scales (CARS, SRS, and SSP). Mean scores of behavioral rating scales (SRS, CARS, and SSP) after AIT is also presented in Fig. 1.

Results showed that scores of CARS, an indicator of autism severity, were decreased significantly by 19% and 15% after 1 month (p=<0.01) and 3 months (p=0.05) respectively after AIT compared to before AIT. The mean SRS score was significantly decreased (13%) after 3 months (p=<0.05) while a non-significant increase in SSP scores was observed 1 month and 3 months (p=>0.05) after AIT.

Table 1: Effect of AIT on Foxj1 protein and social behavioral scales (CARS, SRS, and SSP) in children with autism (n=26)

Variable	Before AIT	Immediately after AIT	1 month after AIT	3 months after AIT	p
Foxj1 (ng/mL) Median(IQR)	575 (351- 2553)	1143 (336- 4599)	1268 (275- 4932)	1058 (184- 3462)	> 0.05
CARS (mean ± SD)	37 ± 11		30 ± 6	31 ± 9.0	0.01*, 0.05**
SRS (mean ± SD)	180 ± 18		186 ± 20	156 ± 19	0.31* < 0.05**
SSP (mean ± SD)	146 ± 36		161 ± 22	149 ± 22	0.14* 0.73**

*= Before v/s 1 month, **= before v/s 3 months

Pre and post Pearson correlation (r) values between severity variables (CARS, SRS, and SSP) are shown in Table 2. Significant correlations between values of CARS scores and SRS scores before AIT (r=0.42, p=0.042) were observed. While there was a positive correlation between values of CARS scores and SRS scores after AIT (r=0.42), however, this correlation was not significant (p>0.05). Also, there was a non-significant positive correlation between CARS and SSP before AIT (r=0.155, p=0.54) and, negative correlations (-0.158 (p=0.46) 3 months after AIT. Furthermore, a significant correlation (p=<0.05) before AIT (r=0.91, p=<0.001) and a non-significant correlation (r=0.25, p=0.91) after AIT were found between SRS and SSP scores.

Table 2: Pearson correlation (r) values before and after AIT between severity variables (CARS, SRS, and SSP)

Variables	SRS before AIT	SRS after 3 months AIT	SSP before AIT	SSP After 3 months AIT
CARS before AIT	r = 0418 (p=0.042)*	-	r = 0.155 (p=0.54)	-
CARS after 3 months AIT	-	r=0.42 (p=0.84)	-	r= -158 value (p=0.46)
SRS before AIT	-	-	r=0.91 (p=<0.01)*	-
SRS after 3 months AIT	-	-	-	r=0.25 (p=0.91)

*=significant (<0.05)

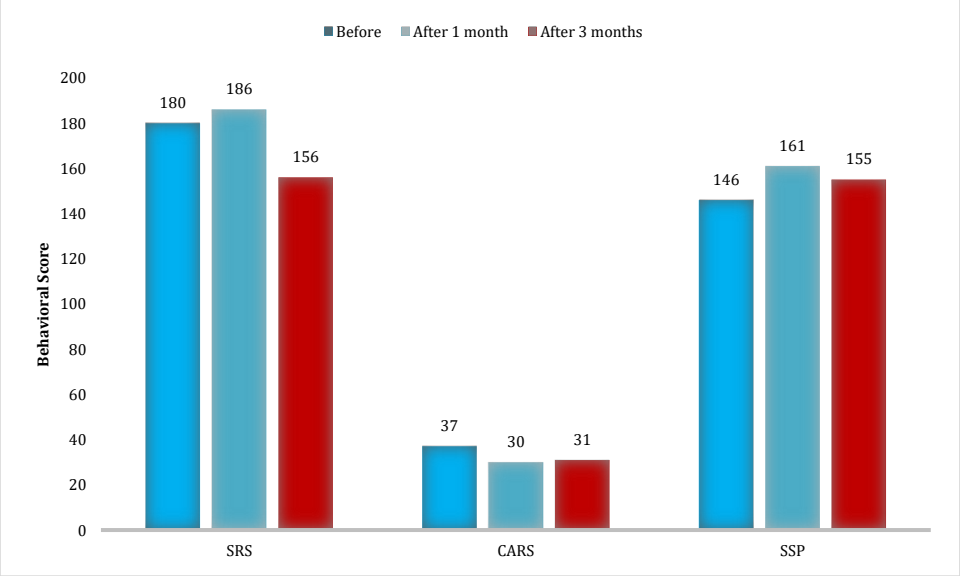

Fig. 1: Social responsiveness scale (SRS), childhood autism rating scale (CARS), and short sensory profile (SSP)

4. Discussion

The neurological origin of ASD is largely unknown, increasing evidence suggested that it can be instigated by a range of factors including autoimmunity (Al-Ayadhi and Mostafa, 2012; Cohly and Panja, 2005). However, the connection between neuro-inflammation and autoimmunity needs to be investigated. Autoimmunity to CNS was recognized by numerous research studies, confirming the existence of brain-specific auto-antibodies in some children with ASD (Mostafa and Al-Ayadhi, 2012), however, the cause behind the presence of brain autoantibodies in autistic children is not clear. It was hypothesized that an autoimmune reaction to neurons might be activated by some cross-reacting antigens in the environment resulting in the discharge of neuronal antigens. These neuronal antigens may result in the initiation of autoimmune reactions through the activation of the inflammatory cells in genetically vulnerable subjects (Al-Ayadhi et al., 2015).

Communication between language and speech systems is extremely impaired in ASD. Sensory dysfunction is the main outcome of ASD, including auditory stimulation, sensation, tactile smell, taste, and visual. Hypersensitivity to sensory stimuli is accepted as a disturbing factor in autism, especially hypersensitivity to auditory stimuli (Baranek, 2002). This results in communication problems which lead to social isolation and subsequently to complications in rehabilitation and learning (APA, 2013). Auditory integration training requires listening to music that has been computer reformed to eliminate frequencies to which an individual shows hypersensitivities and to decrease the probability of auditory configurations. This therapy has been suggested to recover irregular sound sensitivity in subjects with behavioral disorders, including ASD (Bérard, 1993).

There has been very limited research available on the link between sensory processing dysfunction and the biomarkers investigated in subjects with ASD (Baranek, 2002). Investigations of several biomarkers to confirm the characteristics of autism severity, like cognitive dysfunction and sensory defects, can provide us with valuable knowledge about the pathophysiology of ASD (El-Ansary et al., 2016). There are no potential biomarkers for ASD, immune abnormalities are often defined among

subjects with ASD (Bjørklund et al., 2016). Taking into consideration the essential role of Foxj1 in brain development (Spassky et al., 2005), it was our concern to explore the role of Foxj1 in the pathophysiology of ASD. Hence, this research was carried out to examine the possible impact of AIT on Foxj1 and explore the link between plasma Foxj1 levels and the severity of diseases related to behavioral, social, and sensory dysfunction in ASD children.

Some studies demonstrated a potential role for Foxj1 in the inhibition of autoimmune reactions (Lin et al., 2004) and reported that Foxj1 can prevent NF-κB signaling through the generation of IκB proteins. Previous research showed that Foxj1 might control inflammatory reactions and prevent autoimmunity by antagonizing the transcription of genes that encode pro-inflammatory cytokines (Coffer and Burgering, 2004). Nonetheless, much remains to be learned about the Foxj1 role in immunology. The mechanism by which it is regulated is largely unknown. Immunological functions of Foxj1 have been implicated in vitro but not so far tested in vivo. It was hypothesized that investigation of Foxj1 in ASD before and after AIT may likely offer important knowledge related to mechanisms of immune regulation, along with inflammation and/or immunosuppressant disorders. Furthermore, it will conclude unique and precise policies for the therapeutic modulation of ASD.

The current study is the first to explore the effect of AIT on plasma Foxj1 levels in autistic children. It was not possible to trace data in the literature regarding the Foxj1 levels in ASD as well as the effect of AIT on Fox family proteins, including Foxj1. Therefore, it was very interesting to investigate the effect of AIT on Foxj1 and also explore the role of Foxj1 in the deregulated processes associated with autoimmunity, and cognitive activity with behavioral changes in children with ASD.

Our results revealed that the Foxj1 plasma levels were not affected in the ASD after AIT, which supported the idea that Foxj1 may not implicate the pathological and physiological progression in ASD. However, more research is required to confirm these reports. However, results show a significant improvement in some aspects of ASD social, behavioral and sensory symptoms. This is confirmed by substantial variations in CARS, SRS, and SSP scores immediately, one, and three months following AIT intervention.

The mean value of CARS scores was significantly decreased by 19% and 15% after 1 month ($p=<0.01$) and 3 months ($p=<0.01$) respectively after AIT compared to pre-AIT intervention. Similarly, the mean SRS total score significantly decreased (13%) after 3 months ($p=<0.05$) while a non-significant 10% increase ($p=>0.05$) in SSP scores was observed 1 month after AIT indicated typical performance (Dunn, 1999). Thus a considerable decrease in autistic behavior after AIT shows that AIT may have significant therapeutic importance in autistic children. Similar results were achieved previously with improvement in SRS, SSP, and CARS scores in ASD children following the AIT intervention (Al-Ayadhi et al., 2013; 2018; 2019). The justification for the improvement may be the amelioration of compromised dopamine and serotonin systems, pro-apoptotic markers, and glutamate excitotoxicity that are involved in autism severity measures (Al-Ayadhi et al., 2019).

It is interesting that the correlation between SRS, SSP, and CARS scores is defined to highly contribute to the impairment in social interaction, sensory profile, and cognitive ability as three key scales of autism severity. The positive correlations observed between CARS, SRS, and SSP before and after AIT may support that there is a substantial decline in autistic behavior in children who exhibit improved behavioral scores. It was also assumed that establishing the association between AIT and the severity of ASD measured by the CARS, SRS, and SSP could increase efforts at early diagnosis, intervention, and prevention; hence, it may contribute to a decrease in the prevalence of autism.

There is conflict about the reports of AIT to decrease auditory hypersensitivity. In the previously reported review, three out of six studies revealed no impact of AIT compared with control conditions, however, the remaining three studies presented improvements in the AIT group after three months of therapy on the basis of ABC (Sinha et al., 2006). However, more recent studies found significant social and cognitive improvements after AIT in children with ASD (Al-Ayadhi et al., 2013; 2018; 2019). These studies proposed that AIT could clinically reduce an ASD core symptom about social reciprocity with the improvement of brain activity and functional coordination in children with ASD.

The present investigations may have a remarkable effect on upcoming biological and clinical trials of the therapeutic impacts of AIT on children with ASD. We suggested that the use of AIT intervention would lead to improvement in behavioral evaluation scores in children with ASD. However, these results should be treated with caution until more studies are conducted in a larger subject size, to decide whether the improvement in CARS, SRS, and SSP scores is a simple outcome of autism or has a pathogenic role in the disease.

One of the possible limitations of the current study is the small sample size; we measured Foxj1 plasma concentrations pre and post-AIT, which might not precisely reflect levels in the cerebrospinal fluid or in brain regions, whereas cytokines readily cross the blood-brain barrier, suggesting that plasma levels should correlate well with cerebrospinal fluid levels (Coccaro et al., 2015). However, a disrupted blood-brain barrier has been established in autism (Fiorentino et al., 2016). An additional possible limitation of the present study is that the exact mechanism of action of AIT remains to be clarified. Finally, a further potential limitation of the current study is the fact that the period of AIT used may not have been ideal. Moreover, it is also of interest to measure plasma levels of Foxj1 in children without

autism before and after AIT in order to determine the role of Foxj1 as a serological marker for children with ASD.

5. Conclusion

Our findings suggest that AIT did not affect Foxj1 levels but it could play an important role in the improvement of autistic behavior. Furthermore, other factors suggesting different signaling pathways associated with the pathology of autism are suggested. Generally, the results of our study support the therapeutic effect of AIT resulting in improvements in clinical ASD severity scores (CARS, SRS, and SSP). Furthermore, our results may offer important evidence to learn the cellular and molecular mechanisms underlying AIT intervention and offer a novel strategy for the treatment of ASD. More studies with larger sample sizes on human forkhead box protein family members including Foxj1 in subjects with ASD and healthy children (controls) are strongly suggested to evaluate the exact beneficial effect of AIT and to confirm the highest level of validity and reliability.

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Compliance with ethical standards

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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