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Autism Spectrum Disorders in Iran

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1. Introduction

Autism Spectrum Disorders (ASDs), which consist of Autistic Disorder, Asperger Syndrome and PDD Not Otherwise Specified (PDD-NOS), are subsets of Pervasive Developmental Disorders (PDD) (1, 2). Obviously, ASDs are characterized by abnormalities in social interaction and communication, as well as repetitive and stereotyped behaviors (3). Although various studies have been conducted in ASDs etiology across the world, it seems that they are still unknown in developing and developed countries. In fact, ASDs have been introduced as multifactorial disorders; from ascendancy of genetic to environmental factors are involved in causing them (4-7).

Although there are substantial biological bases for ASDs, no perspicuous symptoms exist for their diagnostic conditions. Therefore, behavioral criteria are mainly utilized to identify individuals with ASDs. Some assessment instruments are Autism Diagnostic Interview-Revised (ADI- R), Autism Diagnostic Observation Schedule (ADOS), Childhood Autism Rating Scale (CARS), Diagnostic Interview for Social and Communicative Disorders (DISCO), Developmental, Dimensional and Diagnostic Interview (3di), Autism Spectrum Disorders-Diagnostic for Children (ASD-DC), Autism Spectrum Disorders-Comorbidity for Children (ASD-CC) and Autism Spectrum Disorders-Behavior Problem for Children (ASD-BPC) (8-15). There is universal agreement in diagnostic criteria of ASDs; however, the cultural differences influence their diagnosis (16).

With regards to obscure etiology of ASDs, they have not been specifically treated up to now. Nevertheless, several treatments have been performed to improve ASDs including behavioral, medical, biological, sensory- motor and relationship development interventions (17-21).

Whereas cultural factors play an essential role in prevalence, diagnosis and treatment of ASDs, cross-cultural studies should be performed (22-24). Hence, some scientific researches have been conducted on ASDs in Iran. Several preliminary investigations have been done to evaluate ASDs prevalence and some risk factors and effective variables have also been studied in the field of etiology. Diagnostic evaluation of ASDs, especially based on EEG, and several pharmacological and behavioral interventions for ASDs treatment have been performed in Iran. In parental studies, mental health, stress levels and personality characteristics were investigated in parents of children with ASDs, with focus on mothers.

A systematic literature review was performed to identify the ASDs studies in Iran. Accordingly, PubMed, ISI web of Science, and four Iranian databases, including IranPsych, IranMedex, Irandoc and Scientific Information Database (SID) were searched to find Iranian studies in ASDs using combination of two groups of terms. The first group included the following terms: Autism Spectrum Disorders, Autism, Autistic disorder, PDD Not Otherwise Specified and Asperger, combined with OR; and the second group consisted of Iran or its major cities. The name of famous Iranian researchers in ASDs field and their curriculum vitae were also searched to find scientific studies on ASDs in Iran. Case reports were excluded. The results of 39 investigations including the original, review, editorial material and proceedings articles and available dissertations were separately assigned to prevalence, etiology, diagnosis and treatment divisions.

2. ASDs prevalence

Less attention has been paid to studying ASDs -especially about their epidemiology- in developing countries. In fact, most studies about ASDs prevalence have been done in the United States and Europe (25). Overall, recent scientific researches indicated more rates of ASDs. The study of ASDs prevalence in primary school children estimated the rate of 157 per 10,000 children in the United Kingdom (26). The only investigation on adults with ASDs evaluated the prevalence of these disorders to be 98 per 10,000 in England (27). Another study on 8 year-old children with ASDs estimated an average rate of 90 per 10,000 participants in the United States (28). In a comprehensive review article, the prevalence rate was around 20 per 10,000 for Autistic disorder, 30 per 10,000 for PDD-NOS, and 2 per 100,000 for Asperger syndrome (29). However, the rates of Asperger syndrome were estimated to be 36 out of 10,000 and 48 per 10,000 children in Sweden (30, 31). There were various results about ASDs prevalence across the world. Accordingly, diversity among prevalence estimations could be related to the age of participants, diagnostic criteria, and geographical locations.. In addition, less prevalence of ASDs can be explained by the less available services and lack of awareness about ASDs in developing countries (32).

While no advanced study have been conducted on the prevalence of ASDs in Iran (33), Ghanizadeh`s preliminary investigation on school children (2008) indicated the rate of 19 per 1000 for probable autistic disorder ,and 5 per 1000 for probable Asperger syndrome, which seem more than reported estimations of ASDs prevalence across the world (34). Also, Nejatisafa (2003) performed the first preliminary study to investigate the frequency of ASDs in university students ; while the scores were significantly higher for men than women, the results showed the frequency of 120 out of 1000 adult participants (35).

Another study showed the highest prevalence rate of ASDs for autistic disorder, then Asperger syndrome and PDD-NOS. It also indicated that boys were 4 times more likely than girls to have autistic and Asperger disorders (36). The prevalence rates of autistic students have been displayed 0.366% among exceptional students (37).

3. Etiology of ASDs

ASDs have multiple etiologies; genetic polymorphisms, epigenetics, convergent molecular abnormalities, mutations, chromosomal aberrations, disorders in mirror neuron system and

central coherence, brain structure anomalies, cytogenetic abnormalities, and single-gene defects, toxic exposures, teratogens, measles-mumps-rubella vaccines, some prenatal, obstetric and neonatal factors and etc have been specified as the contributing factors in the etiologies of ASDs in the different researches across the world (7, 38-44).

The relationships between ASDs and some effective factors have been investigated in Iran. In a recent study, the theory of mind development was significantly affected by gender and IQ. so low functioning autistic children had the poorest performance in the theory of mind development compared to high functioning autistic children and normal group (45). In one study, IQ variable was an important factor to determine visual memory of meaningless shapes in children with ASDs. While a significant difference was observed in visual memory of meaningless shapes between children with ASDs and normal group by entering the IQ effect, the results were contradictory as the association was inversed by removing IQ. However, IQ variable was not correlated to face memory in children with ASDs. Overall, there was no significant difference in face memory between children with ASDs and normal group in this study (46).

In a clinical study, no significant correlation was observed between gender and age, diagnosis and severity of the symptoms in children with ASDs (47).

Sasanfar (2010) investigated the parental age and education level as risk factors and indicated that higher paternal age, but not maternal age, and higher education level increased the risk of autism. However, it seems that parents with high education usually seek the diagnostic and therapeutic services more than less educated parents (48).

In another Iranian study, no correlation was observed between autism and Celiac diseases in autistic children compared to age and sex matched normal group (49).

Since brain stem has a critical role in processing hearing inputs, its hearing function has been investigated by an auditory brain stem response tool in children with slight and severe autism compared to normal group. This research demonstrates brain stem abnormality in severe autistic children which may result in intensifying autism symptoms (50).

Social interaction and stereotyped behaviors were investigated between autistic and trainable mentally retarded children. The results showed higher mean scores of qualitative damage to social interaction and stereotyped behaviors in autistic children compared to trainable mentally retarded children (51).

4. Diagnosis of ASDs by EEG

Several studies have been administered to diagnose abnormalities using quantitative electroencephalography (qEEG) analysis in children with ASDs compared with normal children. Considering that the relaxed eye-opened condition in alpha band was the best condition to discriminate between children with ASDs and normal group, the ASDs had significant lower spectrogram criteria values (p<0.01) at Fp1, Fp2, F3 and T5 electrodes and lower values (p<0.05) at T3, P3 and O1 electrodes. Accordingly, spectrogram criteria had displayed more abnormalities in the left brain hemisphere and prefrontal lobe in children with ASDs compared to normal children (52).

Moreover, Magnitude Squared Coherence values at 171 pairs of EEG electrodes in the relaxed eye-opened condition illustrated more abnormalities in the connectivity of temporal lobes with other lobes in gamma frequency band in children with ASDs (54).
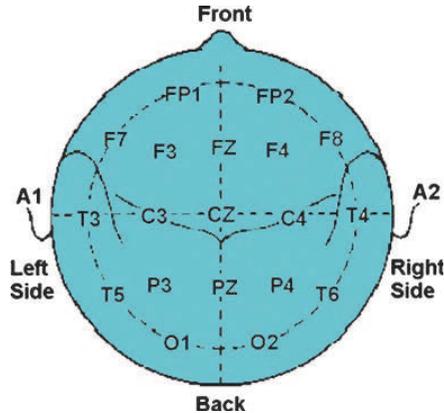
(From: Niedermeyer E, Lopes da Silva F. Electroencephalography: Basic principles, clinical applications, and related fields, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2005, p 140) (53)

Fig. 1. International EEG electrodes placement system

Electrodes	ASD children (Mean±SD)	Control children (Mean±SD)	p
Fp1*	0.238±0.156	0.381±0.131	0.018
Fp2	0.256±0.165	0.357±0.157	0.122
F7*	0.245±0.131	0.376±0.146	0.021
F3**	0.197±0.076	0.442±0.103	0.000
Fz	0.237±0.106	0.309±0.175	0.192
F4	0.270±0.174	0.309±0.137	0.529
F8	0.300±0.198	0.337±0.118	0.583
T3**	0.254±0.136	0.405±0.130	0.007
C3*	0.251±0.156	0.401±0.121	0.013
Cz*	0.267±0.146	0.407±0.173	0.030
C4	0.291±0.182	0.310±0.190	0.796
T4	0.313±0.175	0.391±0.219	0.308
T5*	0.238±0.156	0.396±0.150	0.014
P3	0.300±0.154	0.411±0.133	0.063
Pz	0.310±0.196	0.395±0.147	0.231
P4	0.340±0.194	0.407±0.179	0.373
T6	0.319±0.170	0.388±0.123	0.258
O1	0.304±0.169	0.381±0.151	0.234
O2	0.308±0.161	0.293±0.163	0.821

** $p < 0.01$ and * $p < 0.05$

(From: Sheikhani A, Behnam H, Mohammadi MR, Noroozian M, Mohammadi M. Detection of Abnormalities for Diagnosing of Children with Autism Disorders Using of Quantitative Electroencephalography Analysis. J Med Syst 2010) (54)

Table 1. The spectrogram criteria values of the EEG for the children with autism spectrum disorder (ASD) and control children for all electrodes in alpha band (8–13 Hz)

Notably, one research presented the gamma frequency band as the best discriminant in children with Asperger compared to normal group. Children with Asperger disorder had significant lower spectrogram criteria values (p<0.01) at Fp1 electrode and lower values (p<0.05) at Fp2 and T6 electrodes. Coherence values at 171 pairs of EEG electrodes displayed the connectivity at (T4, P4), (T4, Cz), (T4, C4) electrode pairs and (T4, O1) had significant differences (p<0.01) in the two groups in the gamma band. Accordingly, the prefrontal and right temporal lobes had more abnormalities based on using spectrogram, and coherence values showed more abnormalities in the connectivity of right temporal lobe with the other lobes in the gamma frequency band in children with Asperger Syndrome (55).
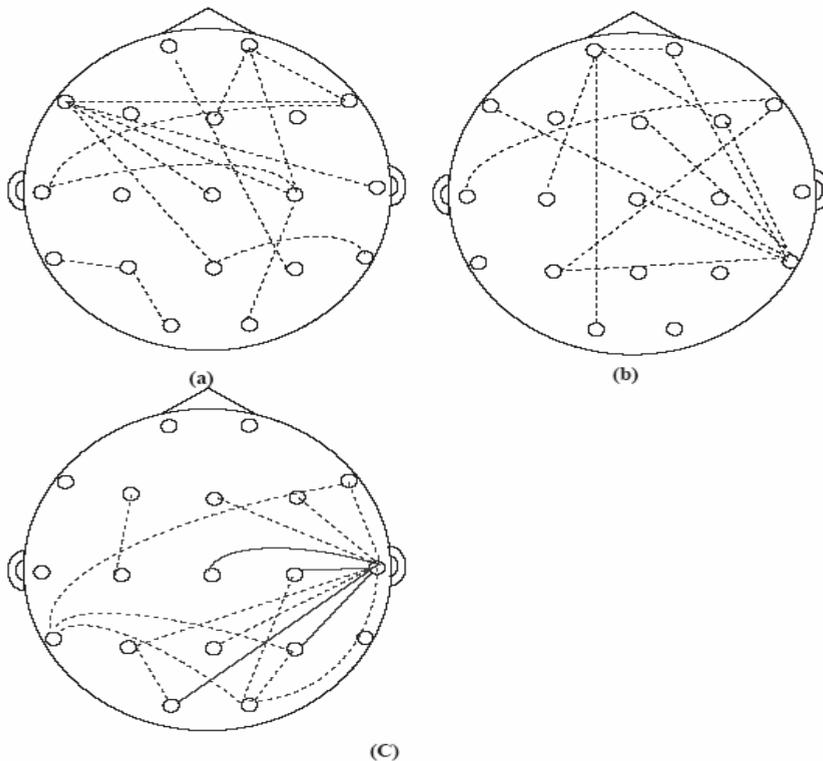
(From: Noroozian M, Sheikhani A, Behnam H, Mohammadi MR. Abnormalities of Quantitative Electroencephalography in Children with Asperger Disorder Using Spectrogram and Coherence Values. Iran J Psychiatry 2008; p 68) (55)

Fig. 2. Results of connectivity in 171 pairs of electrodes that had significant differences in frequency bands, Significantly differences with p<0.05 in two groups control subjects and Asperger disorder shown with dot lines and with p<0.01 shown with solid lines, a) alpha, b) beta and c) gamma frequency band.

In another study, a chaos theory was used to introduce a neural network model for EEG-based assessment of ASD ,and it appraised a precision of 90% (56).

5. Pharmacological therapy of ASDs

Although there is no strong evidence of dopamine involvement in autism, neuroleptics have been used for a long time to decrease aggressive behaviors, stereotypic behaviors, and impulsivity. Low-potency neuroleptics were soon abandoned due to their cognitive and sedative side effects. Among high-potency neuroleptics, haloperidol has been studied the most. Several controlled studies showed benefits over placebo among young children treated with dosages in the range of 1 to 2 mg daily to improve attention and to reduce hyperactivity, anger outbursts, and stereotypes (57, 58). However, problematic side effects in the form of acute dystonic reactions, withdrawal dyskinesias, and tardive dyskinesias were noted. Typical neuroleptics have been replaced with atypical antipsychotics that combine dopamine (D2) and serotonin (5-HT2) receptor antagonist actions (57-60). Following several open-label studies suggesting the efficacy of risperidone, a 12-week, double-blind, placebo-controlled trial was conducted with 31 adults (mean age 28 years) with autism and PDD NOS. Significantly, at a mean dosage of 2.9 mg daily, more responders (57% *vs.* 0%) were found in the risperidone than in the placebo group, and improvements were noted for irritability, anxiety or nervousness, aggression, repetitive behaviors, and depression. There were no improvements on objective measurements of social behavior and language, suggesting that the drug targets nonspecific behavioral problems associated with autism (61, 62). The drug was well tolerated. More recently, a multicentric, 8-week, double- blind, placebo-controlled trial of risperidone (dosage range 0.5 to 3.5 mg daily) was completed on 101 children with autism aged 5 to 17 years (mean age 8.8 years) presenting with clinical levels of tantrums, aggression, and self-injurious behavior. Significant benefits of the active medication were observed for the 2 primary outcome measures of reduced irritability scores (57% *vs.* 14%) and a rating of "much improved" or "very much improved" on a Clinical Global Improvement (CGI) scale (69% *vs.* 12%). Side effects such as fatigue, drowsiness, increased appetite, and drooling were more common in the risperidone group, as was a significantly higher weight gain (2.7 *vs.* 0.8 kgs). Promising open label studies have been conducted with olanzapine, quetiapine, clozapine, and ziprasidone. Several randomized studies are also under way. Atypical neuroleptics, therefore, appear to be promising agents in treating those behavioral symptoms which often occur among autism patients. Yet, despite their good tolerance, these drugs are associated with some undesirable adverse effects, such as tachycardia in young children taking risperidone and sedation for all atypicals, the most serious of which is substantial weight gain. There are no long-term studies of the drugs' efficacy and tolerability (60-64).

Several pharmacological interventions for children with ASDs have been performed in Iran. Akhondzadeh et al. (2010) administered a 10-week double-blind placebo-controlled trial to access the effects of pentoxifylline added to risperidone in comparison with placebo plus risperidone in the treatment of autistic disorder. The dose of risperidone was assayed up to 3 mg/day, and pentoxifylline was assayed 600 mg/day. The Aberrant Behavior Checklist-Community Rating Scale indicated lower scores for Irritability, Lethargy/Social Withdrawal, Stereotyped Behavior, Hyperactivity/Noncompliance and Inappropriate Speech in autistic children who used pentoxifylline plus risperidone as compared to the other group (65). In another study, Akhondzadeh examined the efficacy of piracetam added to risperidone in autistic disorder in a 10-week study. The dose of risperidone was assayed up to 2 mg/day for children between 10 and 40 kg and 3 mg/day for children weighting above 40 kg. The dose of piracetam was assayed up to 800 mg/day. The scores comparison

of the Aberrant Behavior Checklist-Community Rating Scale between the autistic children who had received piracetam plus risperidone and the group who had received placebo plus risperidone in the baseline and week 10 revealed that a combination of atypical antipsychotic medications and a glutamate agent such as piracetam may increase synergistic effects in the treatment of autism (66). In addition, combination of topiramate with risperidone demonstrated reduced scores for irritability, stereotypic behavior and hyperactivity/noncompliance in comparison with using placebo plus risperidone in autistic children. In this 8-week, double-blind, placebo-controlled study, the dose of risperidone was assayed up to 2 mg/day for children between 10 and 40 kg and 3 mg/day for children weighting above 40 kg. The dose of topiramate was assayed up to 200 mg/day for children weighting above 40 kg, and 100 mg/day for children weighting less than 30 kg (67). In another double-blind placebo-controlled trial, cyproheptadine as a 5-HT2 antagonist plus haloperidol was evaluated in the treatment of autistic disorder. The results suggested that the combination of cyproheptadine with a conventional antipsychotic may be more effective than conventional antipsychotic alone for autistic children (68). In comparison of celecoxib added to risperidone with risperidone plus placebo, significant differences were observed between the two groups and the results showed reduced scores for Irritability, Lethargy and Stereotyped behavior in autistic children who used celecoxib plus risperidone (69). Ghanizadeh (2011) hypothesized that Glycine site on the N-methyl-D: -aspartic acid (NMDA) glutamate receptor can be tested as a new strategy for the treatment of autism (70). He also introduced neurotensin as a novel approach to treat autism (71).

6. Behavioral and social therapies of ASDs

There are various intervention approaches for training children with ASDs. For instance, Applied Behavioral Analysis (ABA), Eclectic-Developmental (ED), Training and Education of Autistic and other Communication Handicapped Children (TEACCH), Picture Exchange Communication System (PECS), Learning Experiences and Alternative Program for Preschoolers and Their Parents (LEAP), and Early Intensive Behavioral Intervention (EIBI). Several studies indicated that these behavioral and social interventions can improve non-verbal IQ, expressive IQ, receptive language, adaptive behavior, verbal cognitive abilities, socialization, communication adaptive skills, reciprocal social interaction, intellectual and educational gains in children with ASDs   (72-80).
Applied Behavioral Analysis is a science that utilizes operant conditioning principles to increase desirable behaviors and decrease problematic behaviors; accordingly, reinforcement and punishment can be used to train individuals with ASDs. In ABA approach, firstly the baseline levels of target behaviors in individuals with ASDs should be operationally defined and measured; assessment instruments such as Vineland Adaptive Behavior Scale, AAIDD Adaptive Behavior Scale- School: Second Edition (ABS-S: 2) and Developmental Behavior Checklist (DBC) can be used to evaluate children abilities in different domains. Then, ABA intervention method is performed to alter target behaviors and finally, the rate of changing behavior can be revealed in the repeated measurement (81-85)
In Iran, home based lovaas approach was performed for treating autism, and the results showed that it was effective to improve social interaction, speech and language, play and behavior skills in autistic children (86). Furthermore, the effect of Applied Behavior Analysis (ABA) intervention method was demonstrated on autistic children who had acquired significant improvements in suitable behaviors (87). In another research, three therapeutic

interventions (drug, education and combined therapy) were administered to autistic children. The results showed that while risperidone therapy positively affected stereotyped behavior and hyperactivity, education (according to Lovaas approach) improved social communication and language development of autistic children (88). The effectiveness of parent-child interaction therapy was investigated in four young children with high functioning autism, and the result showed a decrease in their behavioral problems (89). In another study, social stories as a social skills training was evaluated in autistic children, and the results indicated that this intervention was effective to decrease autistic behavior and improve social development in autistic children (90).

7. Mental health of ASDs mothers

Since it seems that parents of children with ASDs experience some stresses such as stigma, blame and insufficient social support in developing countries (91, 92), several studies have been conducted to investigate parental problems, especially in mothers, in Iran. A scientific research indicated a significant difference in parenting stress and coping strategies (emotion focused and problem-focused) variables between mothers with autistic children and mothers who had normal children ; also a significant correlation was observed between stress levels and emotion-focused coping strategies in mothers with autistic children (93). Another study investigated personality characteristics and attachment style in mothers with autistic children in comparison with mothers who had normal children. This study showed a significant difference in Neuroticism versus Emotional stability, not other characteristics. Also no significant difference was observed in the attachment style between the two groups. Based on the results, while mothers with autistic children could be in the Neurotic group, mothers with normal children were almost in the emotionally stable group (94). The correlation between personality characteristics and coping strategies was studied in parents who had children with ASDs; the study indicated no significant difference in coping strategies between fathers and mothers of children with ASDs. However, original thinking, sociability and vigor characteristics were significantly different between them (95). In another study, parental stress was compared in mothers of autistic children with mothers who had normal children, and the results indicated higher scores of parental stress for mothers of autistic children (96). The results of another investigation showed that 27.5% of the mothers with autistic children had mental disorders, and a significant correlation was observed between insufficient coping strategies and mental health (97).

Some interventions were performed to reduce mental problems in mothers with autistic children. A preliminary investigation showed that the symptoms of stress, depression, and anxiety of mothers with autistic children were relatively reduced by guided imagery via music (98). In another study, the group counseling was administered to a group of mothers with autistic children and the results indicated significant differences in the family performance and marital satisfaction scores in mothers who had received group counseling compared to control group (99).

8. Summary

The first preliminary study to investigate the frequency of ASDs in university students was conducted by Nejatisafa (2003); while the scores were significantly higher for men than women, the results showed the frequency of 120 out of 1000 adult participants (35).

In school children, the rate of 19 per 1000 for autistic disorder and 5 per 1000 for Asperger syndrome seem more than the reported ASDs prevalence in developed countries. In this clinical study, no significant correlation was observed between gender and age, diagnosis and severity of the symptoms in ASDs children. The research indicated the brain stem abnormality in severe autistic children which may result in intensifying the autism symptoms. Social interaction and stereotyped behaviors were investigated between autistic and MR children. The results showed higher mean scores of qualitative damage to social interaction and stereotyped behaviors in autistic children compared to MR children. We diagnosed ASDs children using qEEG in comparison with normal children. Considering that the relaxed eye-opened condition in alpha band was the best condition to discriminate between children with ASDs and normal group, the ASDs had significant lower spectrogram criteria values ($p<0.01$) at Fp1, Fp2, F3 and T5 electrodes and lower values ($p<0.05$) at T3, P3 and O1 electrodes. Spectrogram criteria had displayed more abnormalities in the left brain hemisphere and prefrontal lobe in children with ASDs. Magnitude Squared Coherence values at 171 pairs of EEG electrodes in the relaxed eye-opened condition illustrated more abnormalities in the connectivity of temporal lobes with other lobes in gamma frequency band in children with ASDs. It should be noted that one study pointed the gamma frequency band as the best discriminant in children with Asperger compared to the normal group. Asperger children had significant lower spectrogram criteria values ($p<0.01$) at Fp1 electrode, and lower values ($p<0.05$) at Fp2 and T6 electrodes. Coherence values at 171 pairs of EEG electrodes displayed the connectivity at (T4, P4), (T4, Cz), (T4, C4) electrode pairs and (T4, O1) had significant differences ($p<0.01$) in the two groups in the gamma band. The prefrontal and right temporal lobes had more abnormalities based on using spectrogram, and coherence values showed more abnormalities in the connectivity of right temporal lobe with the other lobes in the gamma frequency band in Asperger children.

In pharmacotherapy, typical antipsychotics have been replaced with atypicals that combine dopamine and serotonin receptor antagonist. The effects of pentoxifylline added to risperidone in comparison with placebo plus risperidone in the treatment of autistic disorder. The Aberrant Behavior Checklist Community Rating Scale indicated lower scores for irritability, lethargy, social withdrawal, stereotyped behavior, hyperactivity, noncompliance and inappropriate speech in autistic children who used pentoxifylline plus risperidone. Autistic children who received piracetam plus risperidone might have experienced synergistic effects of medications. Topiramate with risperidone demonstrated reduced scores for irritability, stereotypic behavior, hyperactivity and noncompliance in comparison with using placebo plus risperidone in autistic children. Combination of celecoxib with risperidone in comparison with risperidone plus placebo, caused significant differences between the two groups and the results showed reduced scores for irritability, lethargy and stereotyped behaviors in autistic children.

In Iran, home based lovaas approach was performed for the treatment of ASDs, and the results showed that it was effective in improving the social relationships, speech and language, play and behavior skills in PDD children. The effect of ABA intervention was demonstrated in autistic children who had acquired significant improvements in behaviors. The results of another investigation showed that 27.5% of the mothers with autistic children had mental disorders, and a significant correlation was observed between insufficient coping strategies and mental health.

It seems that Autism Spectrum Disorders are unknown in developing and developed countries and parents who have children with ASDs suffer from lack of social support. Although several studies have been conducted on ASDs in Iran, still they are not sufficient, especially in ASDs epidemiology and etiology. Because of the essential role of cultural factors in better understanding and improvement of ASDs, more comprehensive researches in prevalence, etiology, diagnosis and treatment of ASDs should be performed in many countries including Iran.

9. Acknowledgment

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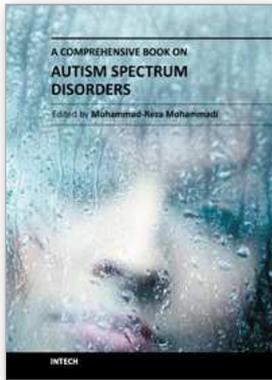
The aim of the book is to serve for clinical, practical, basic and scholarly practices. In twentyfive chapters it covers the most important topics related to Autism Spectrum Disorders in the efficient way and aims to be useful for health professionals in training or clinicians seeking an update. Different people with autism can have very different symptoms. Autism is considered to be a "spectrum" disorder, a group of disorders with similar features. Some people may experience merely mild disturbances, while the others have very serious symptoms. This book is aimed to be used as a textbook for child and adolescent psychiatry fellowship training and will serve as a reference for practicing psychologists, child and adolescent psychiatrists, general psychiatrists, pediatricians, child neurologists, nurses, social workers and family physicians. A free access to the full-text electronic version of the book via Intech reading platform at http://www.intechweb.org is a great bonus.

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