Turkish Archives of Pediatrics

REVIEW
DOI: 10.5152/TurkArchPediatr.2023.23194

Autism Spectrum Disorder in 2023: A Challenge Still Open

Annio Posar[1,2], Paola Visconti[1]

[1]IRCCS Istituto delle Scienze Neurologiche di Bologna, UOSI Disturbi dello Spettro Autistico, Bologna, Italy
[2]Department of Biomedical and Neuromotor Sciences, Bologna University, Bologna, Italy

ABSTRACT

In this paper, we provide an update on autism spectrum disorder (ASD), including epidemiology, etiopathogenesis, clinical presentation, instrumental investigations, early signs, onset patterns, neuropsychological hypotheses, treatments, and long-term outcome. The prevalence of this condition has increased enormously over the last few decades. This increase prompted a search for possible environmental factors whose effects would add up to a genetic predisposition leading to the development of autism. But the genetic and environmental variables involved are extremely numerous, and conclusive data regarding the etiopathogenesis are still far away. Assuming that a well-defined etiology is still found today only in a minority of cases, numerous pathogenetic mechanisms have been hypothesized. Among these, we mention oxidative stress, mitochondrial dysfunction, alteration of the intestinal microbiota, immune dysregulation, and neuroinflammation. These pathogenetic mechanisms could alter epigenetic status and gene expression, finally leading to ASD. Inherent in the term spectrum is the great clinical heterogeneity of this condition, mainly due to the frequent comorbidity that characterizes it. The earlier the diagnosis is made and the earlier psychoeducational treatment begins, the better the prognosis. In this sense, the role of pediatricians can be decisive in making children with signs suggestive of autism undergo a specialist diagnostic course. The development of increasingly advanced cognitive-behavioral educational techniques has considerably improved the prognosis of affected individuals, even though only a small minority of them come off the autistic spectrum. Pharmacological therapies are used to treat comorbidities. During childhood, the most important prognostic factor for long-term outcome seems to be intellectual functioning.

Keywords: Autism spectrum disorder, neurobiology, clinical presentation, neuropsychology, treatment, long-term outcome

INTRODUCTION

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), autism spectrum disorder (ASD) is an early-onset, mostly lifelong condition characterized by persisting deficits in social-communication skills (including social-emotional reciprocity, nonverbal communication, and developing/maintaining relationships) and restricted, repetitive behaviors (including stereotypies, insistence on sameness, highly restricted and fixated interests, and sensory abnormalities). Symptoms are present early in development and cause significant impairments in social and occupational functioning. ASD symptoms are not better explained by intellectual disability or global developmental delay, and this is a very important concept in order to avoid confusing these conditions. However, ASD often co-occurs with intellectual disability; comorbid diagnoses of ASD and intellectual disability are possible only when social communication skills are lower than expected in relation to the general developmental level. According to DSM-5, 3 levels of severity of ASD have been established: level 1 (requiring support), level 2 (requiring substantial support), and level 3 (requiring very substantial support).[1] The choice made in the DSM-5 to cancel the subdivision

Corresponding author:
Annio Posar
✉ annio.posar@unibo.it
Received: August 22, 2023
Accepted: September 5, 2023
Publication Date: October 13, 2023

Cite this article as: Posar A, Visconti P. Autism spectrum disorder in 2023: A challenge still open. *Turk Arch Pediatr.* 2023. [epub ahead of print]

into the 5 diagnostic categories established by the DSM-IV (autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified),[2] unifying everything under the term ASD,[1] has not been without criticism, and it is hoped that it will be corrected in the next edition of the DSM.[3] Despite various attempts to find a biological marker, today, the diagnosis of ASD is still based solely on clinical criteria.[1]

From a historical perspective, the first reports of children with autism have been till today attributed by most authors to Leo Kanner (1943)[4] and Hans Asperger (1944),[5] but in reality, the first to describe this condition in a scientific journal was a woman, Grunya Efimovna Sukhareva, who in 1926 reported 6 boys with autism (which today would be defined "high functioning"), providing a lot of clinical details, including sensory abnormalities,[6,7] which acquired their proper weight only in the DSM-5's description of ASD.[1]

As concerns ASD etiopathogenesis, while in the past the psychogenetic theories prevailed, today we know that ASD is a condition with a neurobiological basis. The etiology is multifactorial and is characterized by an interaction between genetic and environmental factors.[8]

In this narrative review, we aim to provide an update about this condition, considering epidemiology, etiopathogenesis, clinical presentation, instrumental investigations, early signs and onset patterns, neuropsychological hypotheses, treatments, and long-term outcome.

EPIDEMIOLOGY AND ETIOPATHOGENESIS OF AUTISM SPECTRUM DISORDER

According to the most recent epidemiological studies carried out in the United States, ASD recurs in 1 in 36 children at age 8, and it is about 4 times more frequent among males than females.[9] The prevalence of this condition has increased enormously over the last few decades; This increase would be to some extent apparent as there is now greater awareness of this condition, but it would be largely real.[10] This last aspect prompted a search for possible environmental factors whose effects would add up to a genetic predisposition leading to the development of autism.[8] Indeed, early exposure, in particular during pregnancy and in the first year of extrauterine life, to air pollutants (especially particulate matter with an aerodynamic diameter $\leq$2.5 μm)[11] or to agricultural pesticides[12] is associated with a higher risk for ASD.

But the genetic and environmental variables involved are extremely numerous, and conclusive data regarding the etiopathogenesis of ASD are still far away. Assuming that a well-defined etiology is still found today only in a minority of cases with ASD, numerous pathogenetic mechanisms have been hypothesized and supported by interesting data. Among these mechanisms, we mention oxidative stress,[13,14] mitochondrial dysfunction,[15] alteration of the gut microbiota (see the wide variety of microorganisms colonizing the human gastrointestinal tract),[16] immune dysregulation,[17] and neuroinflammation.[14] Note that these mechanisms are not mutually exclusive but could act in synergy with each other, leading to the development of ASD.[8] In reality, the true meaning of the alterations to these mechanisms has yet to be understood. Let us take the example of the gut microbiota: are the alterations found in subjects with ASD the cause of the disorder or its consequence, taking into account the food selectivity they often display and their propensity to bring inedible objects to their mouths?[18]

A key to understanding how these pathogenetic mechanisms could act is given by the concept of epigenetics. Epigenetics is a crucial gene regulation system based on chemical changes in DNA and histone proteins without altering the sequence of DNA. The abovementioned pathogenic mechanisms could alter epigenetic status and gene expression, finally leading to ASD. Also, some environmental factors, including heavy metals (e.g., lead) and endocrine disrupting chemicals (e.g., pesticides), could directly or indirectly modify the epigenetic status.[19,20]

However, the fact that, according to the most recent studies, the prevalence of ASD in males is confirmed (male-to-female ratio = 3.8)[9] suggests that, in the etiopathogenesis of the disorder, genetics still outweighs acquired factors.

We dedicate a last mention to the so-called syndromic autism. It describes the minority of individuals with ASD who present comorbid features and/or a putative genetic etiology. This concept has been deeply criticized, also because it has no single definition, and is probably destined to fall into disuse.[21] We have preferred not to use it in this review.

HETEROGENEITY OF AUTISM SPECTRUM DISORDER CLINICAL PRESENTATION

Inherent in the term "spectrum" is the great clinical heterogeneity of this condition. The range of possible impairments in ASD goes from severe disability with almost complete absence of personal autonomy to a so-called high-functioning condition in which the individual can have normal or even higher-than-normal intellectual functioning and can play a role of responsibility in the social context.[3] The considerable heterogeneity of the ASD clinical picture is mainly due to the frequent comorbidity that characterizes it. Intellectual disability, attention-deficit/hyperactivity disorder (ADHD), insomnia, mood disorders, and epilepsy are just some of the possible neuropsychiatric comorbidities. Also, medical comorbidities, in particular gastroenterological ones (including celiac disease), can complicate the clinical picture of individuals with ASD.[3,22]

Another element of clinical heterogeneity is given by the possible presence of sensory abnormalities that are very often found in subjects with ASD, especially in the first years of life, leading to a distortion of the perception of reality and representing the possible key to understanding many of their atypical behaviors (e.g., attraction to artificial lights, annoyance for crowded environments, food selectivity) and also of the so-called challenging behaviors (e.g., auto- or hetero-aggressiveness, throwing things, tantrums).[23] An impairment of multimodal integration (i.e., the ability to integrate information coming from different sensory channels: visual, auditory, somatosensory, etc.) has also been implicated.[23] In this regard, functional magnetic resonance imaging studies have highlighted elements that suggest an alteration of brain long-range connectivity in individuals with ASD,[24] which could lead precisely to an impairment of this integration capacity.

INSTRUMENTAL INVESTIGATIONS IN INDIVIDUALS WITH AUTISM SPECTRUM DISORDER

From the point of view of the etiological diagnosis, nowadays it seems essential to carry out the following investigations: hearing evaluation through behavioral audiometry or, if not possible, through an auditory brainstem response (ABR) test; genetic tests (array-based comparative genomic hybridization, or array CGH; in males, molecular search for fragile X syndrome; and in some cases, next generation sequencing); electroencephalogram possibly also during sleep, even in the absence of overt clinical seizures, in particular to rule out electroclinical conditions such as continuous spikes and waves during slow sleep (CSWS), which are potentially treatable with a drug therapy.[25] Common neuroimaging techniques, and in particular brain magnetic resonance imaging, are usually normal or at most show nonspecific findings;[26] therefore, they should be performed only in some cases, including: a clinical history characterized by marked and persisting neurocognitive deterioration; the presence of clear neurological signs (macrocrania or microcrania, cerebral palsy, dystonia, etc.); a genetic condition that notoriously predisposes to a brain malformation; epileptic seizures; an electroencephalogram showing relevant alterations such as focal paroxysmal abnormalities or asymmetries of the electrogenesis. At the conclusion of the etiological workup, genetic counseling is recommendable, even though instrumental investigations have not shown any significant results, aiming also at calculating the risk of recurrence of ASD (or other neurodevelopmental disorders) in the family.

EARLY SIGNS AND ONSET PATTERNS OF AUTISM SPECTRUM DISORDER

A reasonable diagnostic suspicion of ASD can usually be placed around 18 months of age, while a definitive diagnosis of ASD can commonly be made within 3 years of age. There are several tools for early screening of ASD; one of the most used is still today the Modified Checklist for Autism in Toddlers (M-CHAT).[27] To make the final diagnosis of ASD as objective as possible, standardized assessment tools are used today, such as the Autism Diagnostic Observation Schedule—Second Edition (ADOS-2),[28] and Autism Diagnostic Interview—Revised (ADI-R).[29] In this context, the time factor is very important.[27] The earlier the diagnosis is made and the earlier psychoeducational treatment begins, the better the prognosis.[30] In this sense, the role of pediatricians can be decisive in making children with signs suggestive of ASD undertake a specialist diagnostic course. Nowadays, several ASD screening tests for pediatricians are available, none of which, however, is without setbacks; they represent useful tools but should not be considered the only source of information in order to decide whether to start a diagnostic workup in a center specialized in neurodevelopmental disorders. For this purpose, it is very important to pay attention to all possible warning signs reported by parents as well as to directly observe the behavior of the child.[27] In infants, even before a possible speech delay becomes evident, the most indicative signs of ASD are strictly related to social-communication skills as follows: looking at the faces of others; orienting to name; presence of joint attention (i.e., the ability to share focus with others on 1 object); affect sharing; and imitation.[31] When some of these behaviors are lacking, a specific assessment is mandatory. Further, let us not forget that the core signs of autism are not infrequently preceded by signs of impaired motor development,[32] such as motor delay, mostly slight,[33] hypotonia,[34] walking on tiptoes, and/or clumsiness.[1] Therefore, the presence of an early motor impairment, even if mild, should be included among the first signs that could lead to a timely ASD diagnosis.[32]

Several different ASD onset patterns have been reported. The most frequent are the "early-onset" pattern, characterized by social-communication deficits developing in the first year or so, and the "regressive autism", characterized by an onset of autistic signs in the second year, mostly at 16–20 months, associated with a loss of social-communication skills. Another onset pattern is characterized by mixed features: first delay and later loss of social communication skills. There is also an onset pattern named "developmental plateau", characterized first by normal social development and/or non-specific abnormalities (involving also feeding or sleep), and later by a lack of new acquisitions on the socio-communicative level.[31]

NEUROPSYCHOLOGICAL HYPOTHESES ABOUT AUTISM SPECTRUM DISORDER

From a neuropsychological point of view, 3 main hypotheses have been developed to explain cognitive dysfunction in individuals with ASD.[35] First, failure of theory of mind refers to the inability to interpret the behaviors of others based on their feelings and beliefs and to identify their intentions and emotions, leading to social communication impairments.[36,37] Second, there is the hypothesis of a deficit of executive functions, which are a series of cognitive processes including attention, working memory, inhibitory control, planning, and cognitive flexibility that are crucial for adaptive behavior and social cognition skills.[38,39] Third, weak central coherence theory refers to the propension of individuals with ASD to use an information processing style that is excessively detail-oriented,[40,41] leading to an impairment of social interactions for which an adequate integration of diverse elements such as voice, mimicry, gestures, and environmental context is necessary.[41] This theory partly overlaps with what was mentioned above regarding the multimodal integration deficit and underlines once again the fact that, although visuospatial skills and attention to detail represent strengths in these subjects, when they have to integrate this type of stimuli with other types of stimuli, they may encounter great difficulty.[35]

These 3 theories are not mutually exclusive. Each of them is able to explain a part of the autistic symptomatology, but none is able to give a complete explanation.[35]

TREATMENTS FOR AUTISM AND LONGTERM OUTCOME

The development of increasingly advanced cognitive-behavioral educational techniques, of which the best known belong to applied behavior analysis (ABA) therapy, has considerably improved the prognosis of affected individuals. Applied behavior analysis utilizes the principles of psychological learning theory in order to modify the behaviors usually present in subjects with ASD. In the 1970s, Ole Ivar Lovaas

developed a method that was based on Burrhus Frederic Skinner's operant conditioning theory, with the aim of changing behaviors and improving social interactions in children with ASD. During the past 60 years, ABA has changed considerably, evolving into many treatment practices, with the aim of dealing with the problems of individuals with ASD in all functioning domains, such as cognition, social skills, language, daily living skills, and challenging behaviors.[42] Today, only a small minority of these subjects come off the autistic spectrum, but almost all can improve considerably by increasing their level of autonomy.[43] After the diagnosis, psychoeducational and often emotional support are very important for parents. Several other interventions are used extensively around the world for children with ASD, although the evidence for their effectiveness does not match that of ABA. Occupational therapy interventions, in particular those using new technologies such as the computer, have shown positive effects on activities of daily living and social skills.[44] In the contest of occupational therapy, sensory integration interventions, in particular when using the principles proposed by Anna Jean Ayres (e.g., tailoring challenges to assure that they are slightly beyond the current performance level of the child), showed positive effects on participation in daily-life activities and routines.[45] Floortime, a relationship-based therapy, has shown that it can improve communication, emotional functioning, and daily living skills in children with ASD.[46]

A pharmacological therapy for the core symptoms of autism does not exist. However, pharmacological therapies are used to treat comorbidities: for example, melatonin or (if not effective) niaprazine for sleep disorders, antiseizure drugs for epilepsy (the choice of drugs depends mainly on the type of epilepsy and possible behavioral undesirable effects), and methylphenidate for ADHD. In addition, drug therapy is used to treat challenging behaviors when cognitive-behavioral interventions have not produced adequate results. In these situations, atypical neuroleptics (e.g., risperidone and aripiprazole) are currently the most commonly often used drugs. Indeed, based on a recent systematic review and meta-analysis of antipsychotic medications in autism, there is some evidence for favorable effects of risperidone and aripiprazole on irritability and agitation in children with ASD.[47] However, we wish to underline that the use of pharmacotherapy should be resorted to only when there is a real need and, if possible, for limited periods of time.

Based on the hypothesis that children with ASD have increased levels of systemic heavy metals interfering with their neurodevelopment and leading to autism, in many of these patients, chelation therapy has been attempted using an agent that binds to the excess heavy metal, causing its excretion. Yet, clinical trials of this therapy in ASD are lacking. Based on literature data, in ASD there is no evidence for the effectiveness of chelation therapy, which is associated with very severe and potentially lethal side effects such as cardiac arrhythmias and hypocalcaemia.[48]

Interesting findings are emerging regarding diet therapy. One recent systematic review and meta-analysis suggests that diet therapies (including ketogenic diets, gluten-free diets, and gluten-free and casein-free diets), may have favorable effects even on ASD core symptoms. However, more high-quality clinical trials are needed.[49]

During childhood, the most important prognostic factor for long-term outcome seems to be intellectual functioning: the higher the intelligence quotient, the better the long-term evolution. But also, the presence of verbal language (although atypical) within 5-6 years of life appears to be a favorable prognostic factor.[43] Unfortunately, approximately 25%-30% of affected individuals develop very little to no verbal skills; they are called "minimally verbal" and usually show a poor long-term outcome. The severe deficit of communication skills (verbal and nonverbal) is very often the basis of the aforementioned challenging behaviors. Also for this reason, providing early non-speaker individuals with alternative means of communication, such as augmentative and alternative communication, is of paramount importance.[50]

CONCLUSIONS

For professionals who deal with ASD, it is a frustrating situation to witness the growth in the prevalence of this condition without knowing exactly the reasons and consequently without having the most suitable tools to counter it, despite all the knowledge about the neurobiology of ASD that has accumulated over the last years. Today, however, it seems clear that genetic factors alone are unable to explain this phenomenon that some have called the "autism epidemic." Therefore, in recent years, growing attention has been paid to the environmental factors that can trigger the mechanisms leading to the development of ASD. For these factors, actions of prevention could be very useful, but they require potentially unpopular political decisions whose possible effectiveness could be evaluated only in the long term. Unfortunately, nowadays we still know too little about environmental factors to undertake fully effective prevention actions.

From the research perspective, perhaps to better understand why a child develops an ASD, it would be interesting to study not only what is possibly missing in him/her (e.g., chromosomal deletion detected by the array CGH) or what malfunctions (e.g., focal paroxysmal abnormalities on the electroencephalogram), but also the existing possible protective factors, for example, in the genetic heritage of typically developing individuals and which would be missing in subjects with ASD. This research approach could provide very useful information in the future, but it would clearly be very complicated to put into practice.

The increasing prevalence of ASD clearly has a very negative impact on the public health service, due to the large human and material resources that must be employed to address the problem on the diagnostic and therapeutic sides. However, it should be clear that what we do for today's autistic children will inevitably affect tomorrow's autistic adults. Spending many resources on treatments for individuals with ASD in their developmental age in order to give them as much personal autonomy as possible, for example in terms of communication skills, is an investment for the future as it reduces the risk of challenging behaviors arising in adolescence or adulthood, which in turn involve the prolonged use of large resources.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept, Design, Writing, Literature Search – A.P.; Concept, Supervision, Critical Review – P.V.

Acknowledgment: The authors would like to thank Cecilia Baroncini for help in editing the text.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed (DSM-5). Arlington, VA: American Psychiatric Publishing; 2013.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed (DSM-IV). Washington, DC: American Psychiatric Association; 1994.
3. Posar A, Visconti P. Autism spectrum disorder and the diagnostic and statistical manual of mental disorders - Fifth Edition (DSM-5): the experience of 10 years. *Turk Arch Pediatr*. [In press].
4. Kanner L. Autistic disturbances of affective contact. *Nerv Child*. 1943;2:217-250.
5. Asperger H. "Autistic psychopathy" in childhood. *Arch Psychiatr Nervenkr*. 1944;117:76-136.
6. Ssucharewa GE, Wolff S. The first account of the syndrome Asperger described? Translation of a paper entitled "Die schizoiden Psychopathien im Kindesalter" by Dr. G.E. Ssucharewa; scientific assistant, which appeared in 1926 in the Monatsschrift für Psychiatrie und Neurologie 60:235-261. *Eur Child Adolesc Psychiatry*. 1996;5(3):119-132. [CrossRef]
7. Posar A, Visconti P. Tribute to Grunya Efimovna Sukhareva, the woman who first described infantile autism. *J Pediatr Neurosci*. 2017;12(3):300-301. [CrossRef]
8. Posar A, Visconti P. Autism in 2016: the need for answers. *J Pediatr (Rio J)*. 2017;93(2):111-119. [CrossRef]
9. Maenner MJ, Warren Z, Williams AR, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years - Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2020. *MMWR Surveill Summ*. 2023;72(2):1-14. [CrossRef]
10. Nevison CD. A comparison of temporal trends in United States autism prevalence to trends in suspected environmental factors. *Environ Health*. 2014;13:73. [CrossRef]
11. Liu H, Ding L, Qu G, et al. Particulate matter exposure during pregnancy and infancy and risks of autism spectrum disorder in children: a systematic review and meta-analysis. *Sci Total Environ*. 2023;855:158830. [CrossRef]
12. Bertoletti ACC, Peres KK, Faccioli LS, et al. Early exposure to agricultural pesticides and the occurrence of autism spectrum disorder: a systematic review. *Rev Paul Pediatr*. 2022;41:e2021360. [CrossRef]
13. Ghezzo A, Visconti P, Abruzzo PM, et al. Oxidative stress and erythrocyte membrane alterations in children with autism: correlation with clinical features. *PLoS One*. 2013;8(6):e66418. [CrossRef]
14. Usui N, Kobayashi H, Shimada S. Neuroinflammation and oxidative stress in the pathogenesis of autism spectrum disorder. *Int J Mol Sci*. 2023;24(6):5487. [CrossRef]
15. Caporali L, Fiorini C, Palombo F, et al. Dissecting the multifaceted contribution of the mitochondrial genome to autism spectrum disorder. *Front Genet*. 2022;13:953762. [CrossRef]
16. Korteniemi J, Karlsson L, Aatsinki A. Systematic review: autism spectrum disorder and the gut microbiota. *Acta Psychiatr Scand*. 2023;148(3):242-254. [CrossRef]
17. Robinson-Agramonte MLA, Noris García E, Fraga Guerra J, et al. Immune dysregulation in autism spectrum disorder: what do we know about it? *Int J Mol Sci*. 2022;23(6):3033. [CrossRef]
18. Yap CX, Henders AK, Alvares GA, et al. Autism-related dietary preferences mediate autism-gut microbiome associations. *Cell*. 2021;184(24):5916-5931.e17. [CrossRef]
19. Hill DS, Cabrera R, Wallis Schultz D, et al. Autism-like behavior and epigenetic changes associated with autism as consequences of in utero exposure to environmental pollutants in a mouse model. *Behav Neurol*. 2015;2015:426263. [CrossRef]
20. Kubota T, Mochizuki K. Epigenetic effect of environmental factors on autism spectrum disorders. *Int J Environ Res Public Health*. 2016;13(5):504. [CrossRef].
21. Vorstman JAS, Scherer SW. Contemplating syndromic autism. *Genet Med*. 2023;25(10):100919. [CrossRef]
22. Bougeard C, Picarel-Blanchot F, Schmid R, Campbell R, Buitelaar J. Prevalence of autism spectrum disorder and co-morbidities in children and adolescents: a systematic literature review. *Front Psychiatry*. 2021;12:744709. [CrossRef]
23. Posar A, Visconti P. Sensory abnormalities in children with autism spectrum disorder. *J Pediatr (Rio J)*. 2018;94(4):342-350. [CrossRef]
24. Minshew NJ, Williams DL. The new neurobiology of autism: cortex, connectivity, and neuronal organization. *Arch Neurol*. 2007;64(7):945-950. [CrossRef]
25. Posar A, Visconti P. Some considerations about the association between autism spectrum disorder and epilepsy. *Turk Pediatr Ars*. 2020;55(3):331-332. [CrossRef]
26. Rochat MJ, Distefano G, Maffei M, et al. Brain magnetic resonance findings in 117 children with autism spectrum disorder under 5 years old. *Brain Sci*. 2020;10(10):741. [CrossRef]
27. Posar A, Visconti P. Is it autism? Some suggestions for pediatricians. *Turk Pediatr Ars*. 2020;55(3):229-235. [CrossRef]
28. Lord C, Rutter M, DiLavore P, Risi S, Gotham K, Bishop S. *Autism Diagnostic Observation schedule-2nd Edition (ADOS-2)*. Los Angeles, CA: Western Psychological Corporation; 2012.
29. Lord C, Rutter M, Le Couteur A. Autism diagnostic interview-revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord*. 1994;24(5):659-685.
30. Bradshaw J, Steiner AM, Gengoux G, Koegel LK. Feasibility and effectiveness of very early intervention for infants at-risk for autism spectrum disorder: a systematic review. *J Autism Dev Disord*. 2015;45(3):778-794. [CrossRef]
31. Ozonoff S, Heung K, Byrd R, Hansen R, Hertz-Picciotto I. The onset of autism: patterns of symptom emergence in the first years of life. *Autism Res*. 2008;1(6):320-328. [CrossRef]
32. Posar A, Visconti P. Early motor impairment in children with autism spectrum disorder. *Turk Arch Pediatr*. 2021;56(6):646-647. [CrossRef]
33. Ozonoff S, Young GS, Goldring S, et al. Gross motor development, movement abnormalities, and early identification of autism. *J Autism Dev Disord*. 2008;38(4):644-656. [CrossRef]
34. Flanagan JE, Landa R, Bhat A, Bauman M. Head lag in infants at risk for autism: a preliminary study. *Am J Occup Ther*. 2012;66(5):577-585. [CrossRef]
35. Posar A, Visconti P. What underlies autism spectrum disorder? *Turk Arch Pediatr*. 2022;57(4):467-468. [CrossRef]
36. Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a "theory of mind"? *Cognition*. 1985;21(1):37-46. [CrossRef]
37. Andreou M, Skrimpa V. Theory of mind deficits and neurophysiological operations in autism spectrum disorders: a review. *Brain Sci*. 2020;10(6):393. [CrossRef]
38. Hill EL. Evaluating the theory of executive dysfunction in autism. *Dev Rev*. 2004;24(2):189-233. [CrossRef]
39. Pasqualotto A, Mazzoni N, Bentenuto A, Mulè A, Benso F, Venuti P. Effects of cognitive training programs on executive function in children and adolescents with autism spectrum disorder: a systematic review. *Brain Sci*. 2021;11(10):1280. [CrossRef]

40. Happé F, Frith U. The weak coherence account: detail-focused cognitive style in autism spectrum disorders. *J Autism Dev Disord*. 2006;36(1):5-25. [CrossRef]
41. Herringshaw AJ, Kumar SL, Rody KN, Kana RK. Neural correlates of social perception in children with autism: local versus global preferences. *Neuroscience*. 2018;395:49-59. [CrossRef]
42. Gitimoghaddam M, Chichkine N, McArthur L, Sangha SS, Symington V. Applied behavior analysis in children and youth with autism spectrum disorders: a scoping review. *Perspect Behav Sci*. 2022;45(3):521-557. [CrossRef]
43. Posar A, Visconti P. Long-term outcome of autism spectrum disorder. *Turk Pediatr Ars*. 2019;54(4):207-212. [CrossRef]
44. Domínguez-Lucio S, Compañ-Gabucio LM, Torres-Collado L, de la Hera MG. Occupational therapy interventions using new technologies in children and adolescents with autism spectrum disorder: a scoping review. *J Autism Dev Disord*. 2023;53(1):332-358. [CrossRef]
45. Schoen SA, Lane SJ, Mailloux Z, et al. A systematic review of Ayres sensory integration intervention for children with autism. *Autism Res*. 2019;12(1):6-19. [CrossRef]
46. Divya KY, Begum F, John SE, Francis F, dirs. DIR/Floor Time in Engaging Autism: a Systematic Review. *Iran J Nurs Midwif Res*. 2023;28(2):132-138. [CrossRef]
47. Deb S, Roy M, Limbu B, et al. Randomised controlled trials of antipsychotics for people with autism spectrum disorder: a systematic review and a meta-analysis. *Psychol Med*. 2023:1-9. [CrossRef]
48. Lagan NC, Balfe J. Question 2: does heavy metal chelation therapy improve the symptoms of autism spectrum disorder. *Arch Dis Child*. 2018;103(9):910-911. [CrossRef]
49. Yu Y, Huang J, Chen X, et al. Efficacy and safety of diet therapies in children with autism spectrum disorder: a systematic literature review and meta-analysis. *Front Neurol*. 2022;13:844117. [CrossRef]
50. Posar A, Visconti P. Update about "minimally verbal" children with autism spectrum disorder. *Rev Paul Pediatr*. 2021;40:e2020158. [CrossRef]