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ORIGINAL ARTICLE

Autism spectrum disorder

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Abstract

Objective: there was an increase in autism spectrum disorder (ASD) prevalence over the past years in many countries. Brazilian data have reached an estimate of 500 thousand affected individuals in 2010. This paper's aim is to review the epidemiology, etiology, differential diagnosis, and treatment of ASD considering recent published advances from the scientific literature. **Methods:** review on the diagnosis and approach to autism in children based on the published papers over the past five years selected through keywords "autism" and "autistic spectrum" in databases PubMed and CAPES, as well as recent editions of pertinent scientific books. **Results:** ASD diagnosis is clinical and based on the clinical history obtained from the patient's family, child's clinical observation and physical examination, and video-recording made at home by parents or guardians during the first years of life. Its clinical picture varies throughout time, according to DSM-5 diagnostic criteria. The etiology is thought to have a genetic, neurobiologic, and neuropsychologic basis. ASD may be associated with a variety of known condition and genetic syndromes. **Conclusions:** the pediatrician is required to familiarize with red flags that lead one to suspect an ASD diagnosis, in order to coordinate an early intervention and multidisciplinary treatment for the patient, thus contributing to his/her development recovery, and to advocate in favor of affected children and adolescents needs.

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INTRODUCTION

Autism spectrum disorder (ASD) is one of the most prevalent childhood neurodevelopmental disorders. It is characterized by the involvement of two central areas: 1) deficits in social communication and social interaction, and 2) restricted and repetitive patterns of behavior, interests, or activities. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) in 2013,[1] the diagnoses of ASD encompasses autistic disorder (autism), Asperger's syndrome, childhood disintegrative disorder, and global developmental disorder not otherwise specified, which appeared as subtypes of global developmental disorder in the previous edition (DSM-4). Rett syndrome no longer belongs to the same diagnostic category, but is one of the genetic causes of ASD.

Social interaction occurs atypically; there is little response to others, especially with regard to visual contact, and approximation in an attempt to interact often occurs in an inappropriate or inadequate manner. In certain social situations, like during recess at school or in the cafeteria, it is a challenge to maintain reciprocity and there is difficulty in understanding and interpreting social rules.[2]

The hallmark of ASD is the deficit in non-verbal communication that ranges from a total lack of facial expression to inexistent integration of gestural communication (eye contact, smiling, pointing, nodding the head, blowing a kiss, shrugging shoulders) with verbal communication.[3,4] Receptive language is generally less compromised than expressive language in highly verbal children with ASD.[5]

Lack of playfulness or repetitive play is a typical characteristic of children with ASD. Friendship is a challenge, and when it occurs, it usually results from some specific shared interest.[3]

Unfortunately, children with ASD are vulnerable to provocation and bullying.[2] The ability to imagine or understand another person's point of view or form self-representations of reality is called theory of mind in the field of cognition. The cognitive characteristics of individuals with ASD are believed to result from the lack of theory of mind.[6]

There is a variety of symptoms and a spectrum of intensity in individuals with ASD.[7] One very common manifestation is motor coordination deficit, which primarily manifests as difficulties with fine motor coordination in using tools and learning complex motor skills.[8]

The pattern of restricted and repetitive behavior, interests, or activities can occur in several ways:

- common repetitive speech or repetition of questions asked to the individual (echolalia): may be immediate or after the child has heard a TV phrase or memorized some conversation.[2]
- stereotyped movements that occur whenever the child is excited or upset, such as shaking hands, clapping, running aimlessly, swaying the body, pedaling, grinding teeth, walking on tiptoes, assuming uncomfortable and strange postures, or repeating actions like opening and closing the door or turning the light on and off.[2]
- exaggerated or decreased response to pain or temperature.[2]
- intense interest in some surrounding stimuli such as lights, patterns, and movements.[2]
- extreme rigidity or rituals related to the smells, textures, and appearance of food are common and may cause excessive food restrictions.[2]

The onset of symptoms may occur in the first year of life, or development may be normal until 12–18 months of age, followed by regression in language and/or social skills, which occurs in up to 30% of cases. Most typically, development is impaired after 6 months of age, as a plateau or deceleration in development, accompanied by some loss of skills in social communication such as joint attention, affection, and shared use of language.[2]

EPIDEMIOLOGY

According to estimates by the Autism and Developmental Disabilities Monitoring study, the prevalence of ASD among 8-year-old children in the United States increased from 1:150 in 2000 to 1:88 in 2008 and 1:68 in 2012.[3] In Brazil in 2010, there were an estimated 500,000 patients with autism.[9] ASD is prevalent in all racial, ethnic, and socioeconomic groups.[10]

The chance that the sibling of an autistic child will also be affected is 20 times greater, with prevalence increasing from 0.5% to 10.1%. If there are already two siblings with the disorder, the chance of the third sibling also having ASD increases to 25%. The risk of ASD in a family member of a patient is significantly greater than that in the general population.[2] The ratio between boys and girls with ASD is 4:1.[2,9]

There is a high prevalence of intellectual disability in populations with autism, ranging from 30% to 50%. ASD can also be associated with a mental disorder, with prevalence reaching 70%. Furthermore, 40% of patients with autism have two or more comorbid mental disorders.[1]

The prevalence of epilepsy among patients with autism is higher among those with intellectual disabilities and in the second decade of life. The risk of epilepsy persists into adulthood.[11,12] The risk of ASD in children with epilepsy is higher when seizures manifest early and present as epileptic spasms.[11]

ETIOLOGY

Individuals with ASD can be divided into two main groups:

- Primary or essential type: There is no specific cause.
- Secondary or syndromic type: A cause is identified.[13]

The secondary forms are subdivided according to etiology:

- Genetic: caused by chromosomal anomalies such as Down or Turner syndrome, structural genomic defects (from alterations in specific base pairs—the so-called single nucleotide variants—to deletions or duplications of many base pairs, known as copy number variants), and genetic syndromes such as Rett or Angelman syndromes, tuberous sclerosis, and fragile X syndrome.[13,14]
- Environmental: may be caused by infections, fetal poisoning, and other possible factors such as *in utero* exposure to valproic acid, which interact with the genome through epigenetic mechanisms.[13]

The interaction between the genetic material and the environment is studied in epigenetics.[15] Epigenetics probably explains the variability in the expression of ASD symptoms because mutations and gene inversions are insufficient to completely identify the origin of this disorder.[15]

The dysfunction of the associative cerebral cortex in ASD stems from changes in connectivity between the cerebral hemispheres, with areas of little and great connectivity, which causes difficulty integrating information and coordinating the different neural systems.[16,17] One of the main factors that contribute to the manifestation and symptoms of neurological development disorders such as ASD and schizophrenia is the interruption of the delicate balance between excitatory and inhibitory signaling in the brain, particularly in the prefrontal cortex. Social behaviors require the coordinated involvement of several regions of the brain, and irregularities in any one of these regions could contribute to social behavior disorders.[18]

It is estimated that genetic changes are responsible for 10%–30% of ASD diagnoses, whereas other studies have stated that heritability can reach up to 90%, suggesting the involvement of genetic causes that have not yet been clarified.[14,19]

Various etiologic mechanisms for ASD are being discussed in addition to genetic susceptibility and epigenetics, such as autoimmune deregulation. The findings suggestive of this hypothesis include abnormal levels of cytokines and growth factors, as well as fetal and maternal antibodies found in the brain tissue. Other hypothetical mechanisms are increased oxidative stress, mitochondrial dysfunction, brain serotonin abnormalities, abnormal white matter connectivity, decrease in the number of Purkinje cerebellar cells, and neuronal migration defects.[20] Despite advances in the neurobiological pathophysiology of ASD, there is not yet a specific marker for diagnosis.[21]

Risk factors

Numerous risk factors may contribute to the onset of the disorder and can be classified as prenatal, perinatal, environmental, or mutational:

Prenatal risk factors

There is a possible association with influenza; exposure to pesticides and insecticides; exposure to drugs such as misoprostol, thalidomide, and selective serotonin reuptake inhibitors; exposure to cocaine; or folic acid deficiency.[20]

There is a likely association with maternal fever, autoimmune diseases, diabetes, pre-eclampsia, and exposure to high atmospheric pollution.[20]

There is a definitive association between ASD and cytomegalovirus or rubella infection during pregnancy, maternal inflammation and autoimmune activation, or exposure to valproic acid and high levels of ethanol during pregnancy.[20]

On the other hand, there is no association with some infections during pregnancy, such as herpes, Epstein–Barr virus, varicella-zoster virus, and parvovirus, maternal smoking, or vitamin D deficiency.[20]

Perinatal risk factors

Extreme prematurity is a high risk factor and is associated with perinatal complications such as pre-eclampsia, intracranial hemorrhage, cerebral edema, low Apgar scores, and seizures.[2,7]

Environmental risk factors

These factors include advanced parental age, especially of the mother. Advanced paternal age also independently elevates the risk because new mutations can occur.[2,7]

Mutational factors

Factors that can cause mutations of genes involved in ASD include contact with mercury, cadmium, nickel, and trichloroethylene, as well as ambient air pollution.[2]

COMORBIDITIES

The prevalence of psychiatric disorders such as attention deficit/hyperactivity disorder [ADHD], anxiety, depression, and bipolar disorder associated with ASD reaches 79% and is higher than that in the general population.[22]

Other prevalent comorbidities include intellectual disability, epilepsy, and sleep disorders. The modulation of intellectual disability on the severity of ASD and epilepsy symptoms is quite interesting.[11]

The greatest risk factors for epilepsy in patients with ASD are regressions in skills, female sex, and overall cognitive function. However, cognitive deficit exerts a greater influence.[11]

Furthermore, epilepsy and ASD are associated with multiple neurodevelopmental disorders, such as language and learning disorders, ADHD, cerebral palsy, anxiety, and mood disorders. Epilepsy and ASD share common pathophysiological mechanisms, which increases concomitant occurrence.[11]

The prevalence of sleep problems among children with typical development has increased in all age groups.

They are also quite common in neurodevelopmental disorders such as ASD, intellectual disability, and ADHD. Sleep disorders affect function and increase the burden and stress on families of children with ASD. They also aggravate the symptoms of central domains of ASD, such as social skills and communication deficits, higher rates of stereotyped behaviors, and greater commitment to dysfunctional routines.[23]

DIFFERENTIAL DIAGNOSIS

The following diagnoses should be considered in children suspected with ASD:

- Rett syndrome: This syndrome almost exclusively affects girls; there is a breakdown in social interaction, principally at the time of diagnosis, during the regressive phase between 1 and 4 years of age. After this period, most patients improve their social communication skills.[1]
- selective mutism: The child is mute in some environments, but there is no damage to social reciprocity or patterns of restrictive or repetitive behavior.[1]
- language disorders and social communication disorder (pragmatic): Non-verbal communication is usually normal in language-specific disorder[1,21] when there is impairment in social communication and social interactions; however, in the absence of restrictive or repetitive behaviors or interests, social communication disorder (pragmatic) should be diagnosed instead of ASD.[1]
- intellectual disability without ASD: This differentiation is difficult in very young children. This is the proper diagnosis when there is no apparent discrepancy between the level of social communication skills and other intellectual skills.[1]
- stereotypical movement disorder: The child presents only stereotypies, but when these cause self-harm and become a focus of treatment, ASD diagnosis may be appropriate.[1]
- ADHD: Attention abnormalities, such as exaggerated focus or easy distraction, are common in ASD, as well as hyperactivity.[1] Both diagnoses may be valid, but differentiation is based on a greater involvement of social communication skills in ASD.[24]
- Schizophrenia: Hallucination and delirium are defining characteristics of schizophrenia and not ASD. A prodromal state has been described in which there is social harm and atypical interests and beliefs, which could be confused with the social deficits observed in ASD.[1]

DIAGNOSTIC EVALUATION

Clinical investigation begins with complete anamnesis, paying special attention to the risk factors described above, and complete physical and neurological examination, with an emphasis on looking for dysmorphisms and signs of genetic syndromes that may be involved. Screening for hearing and visual impairments should be included.

The American College of Medical Genetics published updated guidelines in 2013 (Table 1) recommending chromosome microarray analysis, which can detect chromosomal deletions or duplications (i.e., variants in the number of copies, which are involved in up to 30% of cases). Boys should also undergo molecular testing for fragile X syndrome, whereas the *MECP2* gene involved in Rett syndrome should be sequenced in girls.[25]

Other evaluations such as neuroimaging examinations and metabolic tests should only be conducted when suggestive clinical findings are present.[2]

If development regresses, a prolonged (6–8 h) electroencephalogram (EEG) should be performed, ideally at night to register deep sleep and rule out a differential diagnosis of Landau–Kleffner syndrome, which progresses to aphasia and epileptiform activity with slow continuous wave peaks during most of delta wave sleep.[2]

Recent efforts have been focused on identifying an ASD biomarker using EEG. A computerized algorithm that analyzes overlapping frequencies in different brain regions was able to predict, at 3 months of age, the diagnosis of ASD in the second year of life, with a sensitivity of 95% in 99 infants, who had an older sibling previously diagnosed with ASD.[26] Additional studies are needed in larger samples to validate this diagnostic method.

When to consider autism spectrum disorder?

The pediatrician must remain alert to the warning signs of impaired social communication development in the first years of life:

1. Lack of vocalization at 6 months of age[2]
2. Lack of babbling syllables with consonants at 12 months of age[2]
3. Lack of communication using gestures at 12 months of age; for example, the child does not point to a desired object or look when another person points[2]
4. Speech does not include simple words, in addition to “mama” and “papa,” spoken spontaneously at 16 months of age[2]
5. Speech does not include two-word phrases at 24 months of age or three or more words at 36 months of age[2]
6. Regression or stagnation in development milestones starting with loss of verbal and non-verbal communication skills[2]

Table 1. Diagnostic criteria for autism spectrum disorder, according to DSM-5

A	A. Persistent deficits in social communication and social interaction in multiple contexts, as manifested by the following, currently or according to previous history (examples are only illustrative, not exhaustive; see text): 1) Deficits in social and emotional reciprocity, ranging from abnormal social approach and difficulty establishing normal conversation to reduced sharing of interests, emotions, or affection and difficulty starting or responding to social interactions. 2) Deficits in non-verbal communicative behaviors used for social interaction, ranging from poorly integrated verbal and non-verbal communication to abnormal eye contact and body language, deficits in the understanding and use of gestures, and total absence of facial expressions and non-verbal communication. 3) Deficits in developing, maintaining, and understanding relationships, ranging from difficulty adjusting to adapt to social contexts, difficulty sharing imaginative play, or making friends to lack of interest in peers. *Specify current severity: Severity is based on damage to social communication and restricted and repetitive patterns of behavior.
B	B. Restricted and repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or according to previous history (examples are merely illustrative, and not exhaustive; see text): 4) Motor movements, use of objects, or stereotyped or repetitive speech (e.g., simple motor stereotypes, lining up toys or rotating objects, echolalia, idiosyncratic phrases). 5) Insistence on the same things, inflexible adherence to routines or ritualized patterns of verbal or non-verbal behavior (e.g., extreme suffering from small changes, difficulties with transitions, rigid patterns of thought, greeting rituals, the need to take the same route or eat the same foods every day). 6) Fixed and highly restricted interests that are abnormal in intensity or focus (e.g., strong attachment to or concern with unusual objects and excessively limited or continuous interests). 7) Under- or overreacting to sensory stimuli or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, contrary reaction to specific sounds or textures, smelling or touching objects excessively, visual fascination with lights or movement). *Specify current severity: Severity is based on damage to social communication and restricted and repetitive patterns of behavior.
C	Symptoms should be present early in the period of development (but may not manifest fully until social demands exceed the limited capabilities or may be masked by strategies learned later in life).
D	Symptoms cause clinically significant damage in function in the social, professional, or other important areas of the individual's life at the present time.
E	These disturbances are not better explained by cognitive deficit or global developmental delay.

Source: Cordioli et al.[1]

When one or more warning signs are observed, the pediatrician can use a diagnostic triage instrument such as the M-CHAT scale (Modified Checklist for Autism in Toddlers), which can be applied between 16 and 30 months of age. There are two additional instruments that strengthen the diagnosis: the Autism Diagnostic Interview and Autism Diagnostic Observation Schedule (second edition).[9,16]

These screening tests should show the risk of neurological development disorders, including ASD; they may not provide a definitive diagnosis, but indicate a possible developmental disorder and allow the identification of babies and families who require early support.[27]

TREATMENT

Currently, there is no pharmacological treatment for the central symptoms of ASD, but there are ongoing studies that so far have generated limited evidence.[22]

Recent studies on the role of epigenetics in ASD represent a growing and promising area of research,[28] which seek to allow modification of pathological epigenetic processes.[9]

Because of the complex nature of ASD's etiology, one very beneficial treatment is the inclusion of the child in interdisciplinary rehabilitation teams composed of experts from various areas, for example, doctors, psychoeducational specialists, speech therapists, occupational therapists, psychologists, and behavioral therapists.[29] The interventions offer special education programs, promotion of language/communication skills and social interactions, parent training, and behavioral change techniques.[29]

The following are some examples of therapeutic programs designed for ASD:

Applied Behavior Analysis: This method uses evidence-based teaching techniques to encourage functional behaviors and reduce behavior that is harmful or would interfere with the learning process. It has proven useful in improving communication, social interaction, and vocational skills.[29]

Developmental, Individual differences, & Relationship-based model: Also called floortime or time therapy, parents and therapists follow the child's lead by playing while guiding the child to engage in increasingly complex interactions.[29]

TEACCH Autism Program: This program promotes engagement in activities, existence, independence, and education through strategies based on the child's strengths and learning difficulties.[29]

There has been no evidence yet on the use of pharmacological treatments in children, but in adults, there are data confirming the use of serotonergic agents, particularly for

repetitive behaviors. Fluoxetine seems to be the best tolerated in these studies, but there has been no direct comparison of fluoxetine with other agents.[22]

Studies with the antipsychotics risperidone and aripiprazole showed modest efficacy in managing repetitive behaviors (evidence level IIa), but these studies focused on individuals with high levels of irritability, and it is not clear whether the findings can be more widely applied to the ASD population. Side effects should be considered before initiating treatment; the most common are weight gain, hyperkinesia, agitation, and emotional lability.[22]

Preliminary studies on oxytocin showed a significant action in patients with social cognition deficits (evidence level Ib), but large-scale long-term randomized clinical trials are still needed.[22]

Therefore, for each comorbidity, although there is no medication for the central symptoms of ASD, pharmacological treatment can be attempted to improve specific behaviors, thus providing some benefit for central symptoms and assisting in interventions by the interdisciplinary team.

Important comorbidities of treatment are anxiety, stereotyped repetitive movements, symptoms of obsessive–compulsive disorder, impulsivity, depression, mood swings, agitation, hyperactivity, and aggressiveness.[2]

The classes of medications that can be used to treat these comorbidities include antiepileptics, atypical antipsychotics, stimulants of the central nervous system (CNS), antidepressants, and mood stabilizers.[2]

The premise that modulating inflammatory responses in the CNS could improve ASD symptoms has led to trials using stem cells, including infusion of autologous cord blood cells or mononuclear autologous bone marrow cells; results have been promising but are still incipient.[30,31] The use of immunomodulators such as steroids is another therapeutic proposal that requires more study. Results from a randomized, double-blind, placebo-controlled study were encouraging.[32]

Proposals for nutritional intervention, such as diets eliminating gluten and/or casein and supplementation with vitamins and omega-3, lack scientific grounds.[33]

PROGNOSIS

Clinical progress of the patient with ASD is mainly linked to factors that influence prognosis:

- Presence or absence of intellectual disabilities and language impairment; presence of functional language at 5 years of age is a sign of good prognosis.[1]
- Epilepsy, as a diagnosis of comorbidity, is associated with more severe intellectual disability and lower verbal capacity.[1]

Modern antiepileptic medications and surgical interventions in epilepsy are effective in reducing seizures, but the rate of neurodevelopment, even when the seizures have stopped, is highly variable.[11]

CONCLUSION

Recent developments in diagnostic criteria and instruments, the understanding of multifactorial etiology including genetic, environmental, and epigenetic factors, and new therapeutic resources have brought ASD to the forefront of public health problems worldwide. The increased prevalence of this disorder presents a future scenario in which all institutions must create conditions to accommodate affected individuals. Therefore, there is good reason to expand scientific studies on this topic, exploring the different causes, individual peculiarities, and modalities of treatment.

In this context of intense transformation, pediatricians are on the front line and must be prepared to recognize warning signs that lead to a suspected diagnosis, taking the role as a coordinator of therapeutic efforts and manager of the needs of affected children and adolescents.

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