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Signs and symptoms of Autism Spectrum Disorder and early diagnosis as a benefit in the prognosis of pediatric patients: A systematic review

Sinais e sintomas do Transtorno do Espectro Autista e o diagnóstico precoce como benefício no prognóstico do paciente pediátrico: Uma revisão sistemática

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ABSTRACT
Objective: To analyze the scientific production on autism spectrum disorder (ASD), seeking to relate the importance of describing the signs and symptoms that permeate ASD with the early diagnosis of pediatric patients and their better prognosis. Methodology: Systematic review, using the Pubmed and VHL database, with the descriptors: autism, diagnosis, signs and symptoms, prognosis, from 2019 to 2023. A total of 381 articles were identified and, after applying the inclusion and exclusion criteria, 21 studies were selected for analysis. Results: Due to its heterogeneous nature, ASD presents with a wide variety of clinical symptoms and environmental and genetic risk factors. Among the signs and symptoms could be listed: delays in expressive language, communication, deficits in social interaction, and restricted and repetitive behaviors added to interests or activities that cause clinical harm. Within the material analyzed, the studies highlighted the possibility of an early diagnosis based on specific questionnaires, eye monitoring, MRI patterns and behavioral patterns; in addition to the risk factors most related to ASD. Conclusion: Early recognition of the signs and symptoms that permeate autism spectrum disorder is essential to ensure a better long-term prognosis for these autistic children.

Keywords: Autism, Clinical diagnosis, Developmental disorder, Prognosis.

1 INTRODUCTION

Autism Spectrum Disorder (ASD) has become very relevant as a public health problem due to the significant increase in its prevalence in the last four decades. It is estimated that 1 in 68 children has ASD, and it is four times more frequent in males. (HERVAS A.; ROMARIS, P., 2019); MEDEIROS M.E.C. et al., 2019) The prevalence rate has reached more than 1% worldwide, prompting governments, health providers, and schools to develop programs and policies to address it. (STYLES, M. et al., 2020) This incidence number appears to be consistent globally and across ethnic and socioeconomic groups. (HERVAS A.; ROMARIS, P.,2019) It is questioned in the recent literature whether the prevalence of autism between the 1970s and 1990s was underdiagnosed or whether there was a true increase in individuals with ASD. Several factors have been attributed to the increase in clinical diagnosis, such as: the expansion of diagnostic criteria, the increase in efficiency over time in identification methods, and changes in diagnostic practices. (STYLES M. et al., 2020) (CARY. et al., 2021) Added to this, there was a genuine increase in the disorder due to the combination of genetic and environmental components. (CARY. et al., 2021)

Studies looking at the prevalence of ASD are vital to help healthcare providers plan their services. (STYLES M. et al., 2020) Diagnosing Autism Spectrum Disorder is a laborious and

multidisciplinary task, as there are no genetic tests or standard biological markers that detect it. (MEDEIROS M.E.C. et al., 2019) Currently, diagnosis is clinical based on the severity of a heterogeneous list of social, communicative, and behavioral deficits; however, there is no standardized universal assessment. (STYLES M. et al., 2020)

The most common proposed causes for ASD are physiological and metabolic disorders, involving immunity, oxidative stress, and mitochondrial dysfunction. However, caution needs to be taken when relating causality to prevalence due to the heterogeneous nature of the diagnostic criteria, as a variety of clinical symptoms and environmental and genetic risk factors are widely recognized among individuals with ASD, but none of the susceptible genes or environmental risk factors appear to be shared by all individuals within the spectrum. (STYLES M. et al., 2020); (YANG. et al., 2021)

Clinical and histological observations suggest that ASD is generated in utero. Thus, increased incidence has been related to maternal viral or microbial infection, febrile episodes, immune system activation, medications taken during pregnancy, vitamin D deficiency, or exposure to environmental hazards. Post-mortem analysis of the brains of children with ASD reveals an abnormal excess of neurons in the prefrontal cortex, indicative of origin in utero. The incidence of ASD also increases with cesarean delivery, obstetric complications, and preterm birth. (CARY. et al., 2021)

Autism spectrum behaviors arise during a highly dynamic period of postnatal brain growth, marked by cortical expansion, myelination and maturation of fibers and functional organization of neural circuits. Studies among infants and siblings that have incorporated large-scale neuroimaging have provided great insight into brain development in ASD, revealing that atypical brain phenotypes emerge during childhood, with altered developmental trajectories preceding the consolidation of symptoms that begins in the second year of life. This body of work has improved our understanding of the course of early ASD development and has recently demonstrated the possibility of using presymptomatic MRI in infants to predict diagnostic outcomes in early childhood, a breakthrough with important implications for clinical practice. (GIRALT, J.B.; PIVEN J. et al., 2020)

People with autism spectrum disorders have neurodevelopmental disorders that affect social communication, presenting stereotyped behavior patterns, a tendency to inflexibility, and sensory changes. These behaviors arise during a highly dynamic period of postnatal brain growth, marked by cortical expansion, myelination and maturation of fibers, and functional organization of neural circuits. (GIRALT, J.B.; PIVEN, J. et al., 2020)

ASD usually manifests with a wide range of comorbidities, including morphological and physiological conditions, immunological and psychiatric changes such as anxiety, depression, attention-deficit/hyperactivity disorder and epilepsy, among others. (STYLES M. et al., 2020) The autism spectrum is marked by being a heterogeneous disorder that, in a way, contributes to hindering early diagnosis. (SILVA. et al., 2021) Thus, most children are diagnosed at a later age when it becomes evident that the demands of the environment exceed the child's regulatory response capacity. This reinforces the importance of having reliable screening instruments adapted to the local culture, which can be applied to all children in routine health examinations in primary sector care. (HERVAS A.; ROMARIS P., 2019)

Therefore, ASD is a well-known and widespread neurobehavioral condition nowadays, however, it is a pathology that lacks satisfactory screening tools, thus contributing to a late diagnosis and delay in therapeutic advances due to the loss of the opportunity for reconstructive actions in the period of greater brain plasticity. (ALMANDIL N.B. et al., 2019) As a result, it is important to emphasize the good description of the signs, symptoms, and the benefits of starting the diagnosis as soon as possible, in order to provide timely and facilitating intervention. (WEI H. et al., 2022) (POSAR A.; VISCONTI P., 2020)

The general objective of the present study is to analyze the scientific production on autism spectrum disorder, seeking to relate the importance of describing the signs and symptoms that permeate ASD with the early diagnosis of pediatric patients and, consequently, obtaining a better clinical prognosis.

2 METHODS

This is a systematic review that seeks to understand the clinical aspects of autism spectrum disorder in order to ensure an early diagnosis of this disease, as well as to demonstrate the diagnostic and screening methods available for early identification of autism and its relationship with prognosis. For the development of this research, a guiding question was elaborated through the PVO strategy (population, variable and objective): "What is the importance of understanding the clinical aspects of autism spectrum disorder and what are the possible methods that can be used to ensure an early diagnosis and its benefits?".

The searches were carried out through searches in the PubMed Central (PMC) and Virtual Health Library (VHL) databases. Four descriptors were used in combination with the Boolean term "AND": Autism, Diagnosis, Signs And Symptoms, Prognosis. The search strategy used in the PMC database was: ((Autism) AND (Diagnosis)) AND (Prognosis) and in the VHL it was:

(((Autism) AND (Diagnosis)) AND (Signs And Symptoms)) AND (Prognosis). From this search, 381 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2023 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, made available in the form of an abstract, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After the association of the descriptors used in the researched databases, a total of 381 articles were found. Of these, 375 articles belonged to the PubMed database and 6 articles to the Virtual Health Library. After applying the inclusion and exclusion criteria, 21 articles were selected from the PubMed database and 0 articles from the Virtual Health Library, and a total of 21 studies were used to compose the collection.

3 DISCUSSION

Although the etiologies remain unclear, it is important to study the cause of ASD, as the results have the potential to inform the diagnosis, treatment, management, and prognosis of ASD, help predict or anticipate possible comorbid medical conditions, and increase adherence to intervention and rehabilitation regimens. In addition, the parents of these children often support the etiological research of ASD, as it helps with family planning and reduces anxiety, associated with their speculations about the cause of their children's pathology. (CHEN. et al., 2021)

Autism Spectrum Disorder is one of the most common and challenging neurodevelopmental disorders in children. (STYLES M. et al., 2020) Characterized by persistent deficits in communication and social interaction and restricted and repetitive behaviors, in addition to patterns of interests or activities that cause significant clinical impairment in several areas of functioning, which may be accompanied by a tendency to inflexibility and sensory alterations. (HERVAS A.; ROMARIS, P., 2019); (CARY. et al., 2021) Clinical expression varies greatly depending on the severity of symptoms and the individual's level of development. (WARS S. et al., 2021)

Symptoms begin in early childhood and last throughout life. Signs suggestive of ASD may be subtle and appear gradually due to compensatory mechanisms in childhood that cease to function effectively with greater social demands throughout life. Thus, most children are diagnosed after the age of four, when it becomes evident that the demands of the environment exceed the child's ability to respond. (MEDEIROS M.E.C. et al., 2019); (HERVAS A. ROMARIS

P., 2019) The onset of ASD symptoms or behaviors can occur in two ways: early or regressive. In early onset, symptoms of ASD (e.g., deficits or delay in social and speech development) occur in the first year of life. Children with regressive onset initially have age-appropriate development. However, in the second or third year of life, they begin to present symptoms or behaviors of ASD accompanied by loss of previously established social, communicative and/or motor skills. (CHEN. et al., 2021)

Expressive language delays are among the signs of ASD that are amplified over time with generalized delays and atypicality in other domains. Over time, they have highly variable language profiles such that some develop fluent language and others never acquire phrasal speech, while some have sentence speech delay and recover the delay later in childhood. Linguistic regression is characterized as a loss of previously acquired words or a stagnation of language development and there is some evidence that this alteration is specific to ASD. Results confirm that its occurrence does not necessarily foreshadow long-term developmental problems. (PICKLES. et al., 2022)

ASD usually presents with a wide range of comorbidities, including morphological conditions such as macrocephaly, physiological conditions such as gastrointestinal changes, and psychiatric conditions such as anxiety. In children and adolescents with ASD, rates of psychiatric comorbidity are approximately 70–75%. Psychiatric comorbidities increase the possibility of impaired quality of life in adulthood. Some studies have shown that Anxiety Disorder, Oppositional Defiant Disorder, and Attention Deficit Hyperactivity Disorder are among the most common psychiatric comorbidities in children and adolescents within the spectrum. (WARS S. et al., 2021) There are also some who have other medical comorbidities, such as: global developmental delay, cerebral palsy, epilepsy and genetic syndromes. (BURNS. et al., 2023) In addition, individuals with other neurodevelopmental disorders often have complex patterns of impairment in the motor, cognitive, and neurobehavioral domains, and may present characteristics that meet the criteria for an ASD diagnosis, highlighting the possibility of simultaneous or possibly confounding disorders. (BLESSON, A.; COHEN, J.S., 2020)

Some of these individual characteristics have been shown to moderate treatment response or significantly amplify the effects of a particular intervention, so that some children with ASD show more promising outcomes than others. (KLINGER L.G. et al., 2021) This heterogeneity has been a major obstacle to the development of effective treatments. Therefore, it is crucial to identify clinical subgroups and find significant biomarkers. (YANG. et al., 2021)

As a way to promote the early detection of ASD, the American Academy of Pediatrics (AAP) recommends the use of a universal screening protocol designed for all children in the age

group of 18 to 24 months of age, thus contributing to the reduction of the time between clinical suspicion and diagnosis. The suggested screening method is called the Modified Checklist for Autism in Children (M-CHAT) and offers an accessible and low-cost screening, however, scientific articles indicate that this method may be less reliable in rural regions, low socioeconomic status and low levels of education. (ACHENIE. et al. 2019)

The M-CHAT presented was revised in order to reduce false-positive results, contributing to the improvement in clinical utility and in order to optimize the screening time. A new version entitled M-CHAT-R/F (R/F: Reviewed with Follow-up) has been drafted, where a follow-up interview has been added during this process. (ACHENIE. et al. 2019) In addition, other advantages of M-CHAT-R/F over M-CHAT is the simplified score that this latest version presents, as well as the application age that is now 16 and 30 months old. (MEDEIROS M.E.C. et al., 2019)

After screening with M-CHAT, children classified as at low risk for ASD do not need to undergo further evaluation unless they have another reason for investigation. However, parents of children who are defined as medium risk receive Structured Follow-up (M-CHAT-R/F), which is based on additional interview questions that act to confirm the risk, while children who meet the high-risk criteria are referred for diagnostic evaluation and early intervention with a specialist. (ACHENIE. et al. 2019)

As an alternative to conventional screening, the study prepared by ACHENIE. et al. (2019) highlight the presence of an automated machine learning method, with the aim of overcoming technical barriers to ASD screening. The research was conducted using a feed-forward artificial neural network (fANN) that evaluated the M-CHAT-R files belonging to 14,995 children. The sample was divided into subgroups by race, sex, and maternal schooling in order to examine the differences between these subgroups. An additional contribution to the screening method, which was elucidated through this study, was the possibility of adapting the questionnaire to several subgroups, allowing the result to be directed by adapting the algorithm to a certain individual context. (ACHENIE. et al. 2019)

Currently, the diagnosis of ASD is made through the criteria established by the DMS-V, which classifies patients with autism into two categories, based on social communication deficits and the restrictive and repetitive pattern. Each of these categories receives a score ranging from 1 to 3 points depending on the severity, with a rating of 1 being the lowest and indicates the presence of mild and subtle symptoms, referring to the presence of mild and subtle symptoms, referring to the fact that it is a child who needs support, while a rating of 3 means that the symptoms presented are severe and that the child needs a lot of substantial support. (STYLES M. et al., 2020)

It is important to emphasize that the diagnosis in very young children is difficult, because in addition to being a stage marked by child development, there is an instability of signs and symptoms in this age group. However, there is a need to carry out studies aimed at providing greater support for the diagnosis of children in this age group; Therefore, it is recommended that a team work together with professionals from Child Psychiatry and Neuropediatrics/Pediatrics. This model of action improves diagnostic accuracy and enables earlier therapeutic intervention. (SILVA. et al., 2021)

The current scientific literature reliably demonstrates that the early diagnosis of ASD improves the long-term prognosis, the justification is based on the fact that the early detection of the pathology contributes to the formation of an individualized and timely treatment, ensuring better development of social and linguistic skills. (MEDEIROS M.E.C. et al., 2019) Thus, ASD is responsible for generating a significant social and economic impact for its patients and family environment, generating stress and conflicts, so it is essential to ensure support and structure for affected individuals and their families. (BAGHDLI. et al., 2019)

The study conducted by VACAS. et al. (2021) focus on the investigation of social care in patients with suspected ASD. Most social care studies use eye tracking as a research methodology, a technology capable of evaluating eye behavior, reliably recording the attention of the individual submitted to this screening. Thus, most of these studies have shown that the patient presents an impairment in the attention directed to social images to the detriment of the attention focused on non-social stimuli. Therefore, the pattern of atypical attention focused on social events suggests, from the first year of life of the autistic child, the timely and early identification of the disorder.

Premature babies have a higher risk of developing neurological sequelae resulting from prematurity, among them, autism is an important complication, therefore, a longitudinal and multidisciplinary follow-up of this pediatric population is necessary. The prevalence of ASD in extremely preterm infants is 8%, compared with 0.6% of full-term infants. The follow-up of these patients through the evaluation of developmental milestones is useful as a screening, due to the fact that it is a simple and valuable tool that contributes significantly to the early diagnosis of autism, since these patients may present an inappropriate development for their age, presenting a high predictive value in the ninth month of life compared to the twenty-fourth month. (TACZALA. et al., 2021)

Brain imaging of children with a previous diagnosis of autism showed lower levels of attention to plain language, a playful style of speech characterized by exaggerated intonation contours, simple grammar, high pitch, and slow pacing, also known as *parentae* or baby-directed

speech. It has long been known that children with autism spectrum disorder exhibit unusual and sometimes absent responses to auditory information in their environment. For example, children may not respond when their name is called or have a poor understanding of the meaning of words. At the neural level, studies often report a significant reduction in functional brain activity or a delay in response time to speech sounds. (PIERCE. et al., 2023)

According to the study described by PIERCE. et al. (2023), 70% of children with ASD preferred to listen to computer-generated sounds rather than manhês. Given the experience-dependent mechanisms that support learning during the first few years of life, babies who don't pay attention to plain speech, or human speech in general, would likely have more impaired language ability. However, reduced response to meek-talking is not commonly reported among children with non-ASD delays, suggesting possible specificity for ASD and usefulness as a diagnostic marker. There is less neuronal activation in the speech processing regions in these children compared to the children who presented a greater and more directed attention to speech in the morning, in addition, it was evidenced that if a child was less than 30% fixated on the morning, the probability of being diagnosed with ASD was 94%. Therefore, it is concluded that the identification of children who have considerable low levels of attention to soft speech is extremely beneficial to guide the screening, diagnosis and prognosis of ASD.

4 CONCLUSION

ASD is a disorder characterized by deficits in social interaction and communication, in addition to the presence of behaviors with restrictive and repetitive patterns that cause significant clinical impairment in the development of multiple areas of functioning. The clinical presentation of autism begins in early childhood, however, the signs are subtle in this age group, leading to a late diagnosis of ASD. Scientific studies have contributed to demonstrating ways to obtain an early diagnosis of ASD are capable of significantly improving the long-term prognosis of children with the disorder.

REFERENCES

ACHENIE, Luke EK et al. Uma estratégia de aprendizado de máquina para triagem de autismo em crianças pequenas. Revista de pediatria do desenvolvimento e comportamento: JDBP , v. 5, pág. 369, 2019.

ALMANDIL, Noor B. et al. Environmental and genetic factors in autism spectrum disorders: special emphasis on data from Arabian studies. International journal of environmental research and public health, v. 16, n. 4, p. 658, 2019.

BAGHDADLI, Amaria et al. Investigando a história natural e os fatores prognósticos do TEA em crianças: o estudo longitudinal multicêntrico de crianças com TEA - o protocolo de estudo ELENA. BMJ aberto , v. 6, pág. e026286, 2019.

BLESSON, Alyssa; COHEN, Julie S. Aconselhamento genético em transtornos do neurodesenvolvimento. Perspectivas de Cold Spring Harbor em Medicina , v. 4, 2020.

BURNS, Jessy et al. Comorbidities Affecting Children with Autism Spectrum Disorder: A Retrospective Chart Review. Children, v. 10, n. 8, p. 1414, 2023.

CALDEIRA DA SILVA, P. et al. Transtorno do espectro do autismo na primeira infância: o modelo do Centro de Estudos do Bebé e da Criança para Diagnóstico e Intervenção Terapêutica. Acta Médica Portuguesa , v. 10, pág. 657-663, 2021.

CALY, Hugues et al. A análise de aprendizado de máquina de dados de gravidez permite a identificação precoce de uma subpopulação de recém-nascidos com TEA. Relatórios científicos , v. 11, n. 1, pág. 6877, 2021.

CHEN, Wei-Ju et al. Percepções da etiologia do transtorno do espectro do autismo (TEA) entre pais de crianças com TEA. Revista Internacional de Pesquisa Ambiental e Saúde Pública , v. 13, pág. 6774, 2021.

COELHO-MEDEIROS, María Elisa et al. M-CHAT-R/F Validation as a screening tool for early detection in children with autism spectrum disorder. Revista chilena de pediatria, v. 90, n. 5, p. 492-499, 2019.

ESTILOS, Meghan et al. Fatores de risco, diagnóstico, prognóstico e tratamento do autismo. Fronteiras em Biociências , v. 25, n. 9, pág. 1682-1717, 2020.

GIRAULT, Jéssica B.; PIVEN, José. O neurodesenvolvimento do autismo desde a infância até a primeira infância. Clínicas de Neuroimagem , v. 30, n. 1, pág. 97-114, 2020.

GUERRERA, Silvia et al. Anxiety in Autism Spectrum Disorder: Clinical characteristics and the role of the family. Brain Sciences, v. 12, n. 12, p. 1597, 2022.

HERVAS, Amaia; ROMARÍS, Patrícia. Adaptación funcional y trastornos del espectro autista. Medicina (Buenos Aires), v. 79, n. 1, p. 10-15, 2019.

KLINGER, Laura Grofer; COOK, Michal L.; DUDLEY, Katerina M. Preditores e moderadores da eficácia do tratamento em crianças e adolescentes com transtorno do espectro do autismo. Revista de Psicologia Clínica da Criança e do Adolescente , v. 4, pág. 517-524, 2021.

PICKLES, Andrew et al. Preditores de regressão da linguagem e sua associação com o posterior desenvolvimento da comunicação em crianças com autismo. Revista de Psicologia Infantil e Psiquiatria , v. 63, n. 11, pág. 1243-1251, 2022.

PIERCE, Karen et al. Nível de atenção à fala manhesa como um marcador precoce do transtorno do espectro do autismo. Rede JAMA aberta , v. 2, pág. e2255125-e2255125, 2023.

POSAR, Ânio; VISCONTI, Paola. É autismo? Algumas sugestões para pediatras. Arquivos Turcos de Pediatria/Türk Pediatri Arşivi , v. 3, pág. 229, 2020.

TACZAŁA, Jolanta et al. The predictive value of 'red flags' as milestones of psychomotor development of premature babies–preliminary study. Annals of Agricultural and Environmental Medicine, v. 28, n. 1, p. 183, 2021.

VACAS, Julia et al. Visual preference for social vs. non-social images in young children with autism spectrum disorders. An eye tracking study. Plos one, v. 16, n. 6, p. e0252795, 2021.

WEI, Hua et al. Awareness and knowledge of autism spectrum disorder in Western China: Promoting early identification and intervention. Frontiers in Psychiatry, v. 13, p. 970611, 2022.

YANG, Ting et al. Projeto multicêntrico de autismo pré-escolar da China (CMPAP): design e metodologias para identificar características de sintomas clínicos e biomarcadores de transtornos do espectro do autismo. Fronteiras em Psiquiatria , v. 11, p. 613519, 2021