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Early Identification of Autism Spectrum Disorders

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ABSTRACT

Background: According to estimates by the World Health Organization and the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network, the prevalence of Autistic Spectrum Disorder (ASD) has increased significantly in recent decades, reaching today approximately 1 in every 68 children. **Objective:** To identify the state of knowledge regarding markers, predictors, and early diagnosis of ASD (0-23 months of age). **Methods:** A search was conducted for articles published in the PubMed Central: PMC scientific literature database, using the "*autism spectrum disorder*" and "*early diagnosis*" search algorithms. The following inclusion criteria were observed: articles describing predictors and early markers, and methods of diagnosis of ASD in infants. **Results:** A total of 65 documents were considered eligible and submitted to the full-text review, of which 42 met the inclusion criteria: 16 with predictors, 9 with early markers, and 16 with diagnostic tests for ASD. **Conclusions:** There is still a need to strengthen the evidence for the clinical practice of ASD diagnosis by 2 years of age. The findings of this study regarding predictors, early markers, and diagnostic tests are intended to facilitate the detection and early intervention in these patients by health professionals.

INTRODUCTION:

The word autism is derived from Greek autos (αὐτός, meaning self) and was introduced by the Swiss psychiatrist Paul EugenBleuler, who also claims responsibility for the first use of the term when in 1908, he defined the symptoms of schizophrenia.[1]

Years later, this word took on a modern sense through Hans Asperger, an Austrian pediatrician, who in 1938 adopted Bleuler's terminology "autistic psychopaths" while delivering a lecture on child psychology in Germany.[2]

Next, Kanner (1943)[3] reported the basic set of guidelines for the diagnosis of autism; while Asperger (1944)[4] discussed a pattern of behavior and skills, which he called "autistic psychopathy". The characteristics of such pattern involve: "lack of empathy, little capacity for socialization, unilateral conversation, intense absorption in a special interest and awkward movements".

Despite the reported findings, the autistic disorder received little attention, and only in 1981 did psychiatrist Lorna Wing present the term "Asperger syndrome", a subgroup of autism through a clinical report, now written in the English language. The approach in question discusses and classifies the syndrome encompassing autism in early childhood in a broader set of conditions that has impairments in the development of social interaction, communication, and imagination in common.[5]Of fundamental importance for the promotion of reviews, the term "autistic disorder" became, in 1981, a descriptor in the MeSH database (Medical Subject Headings).

The term "autism spectrum disorder" (ASD) came about more recently and it is defined as the general term used for a group of complex disorders of brain development, known as Global Developmental Disorders (GDD).[6-8] ASD is a developmental disorder that begins in childhood and its diagnosis depends on evidence of involvement in social communication and social interactions, in addition to persistent restricted and repetitive patterns of behaviors or interests.[9]

The subject heading "Autistic Disorder" was renamed "Autism Spectrum Disorder" in 2016, in the MeSH database, which covers conditions previously known as early childhood autism, childhood autism, Kanner Autism, high functioning autism, atypical autism, a global developmental disorder of no further specification, childhood disintegrative disorder and

Asperger's disorder, encompassed in the major groups of neurodevelopmental disorders in the book 'The *Diagnostic* and *Statistical Manual* of *Mental Disorders, 5th Edition* (*DSM–5*)'.[10]

According to estimates by the World Health Organization and the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network, the prevalence of ASD has increased in recent years, estimating that 1 in every 68 children has ASD; in addition, ASD is about 4.5 times more common among boys (1 in 42) than among girls (1 in 189).[6,11]

In more recent studies reporting on ASD, it is possible to perceive a quite different understanding of what has been seen previously. Based on the dramatic increase in cases in recent decades, a situation never before existing in history,[12] and with the change of descriptor; we find the need for a scientific update on the state of knowledge regarding ASD as well as the methods of early diagnosis.

Few studies are found using this new terminology, and diagnostic protocols still require refinements to improve treatments. Given this premise, the objective of this study was to identify the state of knowledge about predictors, early markers, and diagnostic tests of ASD in infants (0-23 months of age) from a review of the literature, believing that the earlier it is possible to diagnose the disorder, the more effective treatment interventions will be.

MATERIALS AND METHODS:

METHODS:

Study type

This study is a review of the literature which aims to identify studies that present information regarding predictors, early markers, and methods of diagnosis of ASD in infants.

Literature review technique

To carry out this review, the same steps of primary research were followed:

- Identification of the theme, to establish the objective of the study;
- Literature search, focusing specifically on the main theme of the study;

- Assessment of studies, applying inclusion and exclusion criteria;
- Analysis of data extracted from primary sources; and
- Elaboration and presentation of the synthesis with the construction of techniques and other related factors.

The literature search was performed in articles published in the database of the scientific literature of PubMed Central: PMC; this database was chosen considering its interest in exploring the construction of this knowledge throughout the world.

Search algorithms

The review was conducted using the search algorithms "autism spectrum disorder" and "early diagnosis". The publication dates were conditioned for the last 5 years (January 2013 to January 2018), because the study seeks the current state of knowledge about predictors and early markers, as well as methods of diagnosis of ASD in infants (0-23 months of age).

Inclusion and exclusion criteria

The following criteria were observed after reading the titles and abstracts, based on the relevance and consistency of the content: articles describing the theme of the study, as well as predictors, early markers, and methods of diagnosis of ASD in infants. Exclusion criteria were articles that did not directly address the theme of the study, articles on diagnosis in other age groups, and reviews of the literature. After the initial search, the reference lists of the selected articles were manually reviewed. Three reviewers (J.H.R.A., F.P.N.A., and M.D. dos S.) independently assessed the articles, seeking to examine eligibility through meetings to confirm the choice of studies. All possible disagreements between reviewers were resolved through dialogue, which determined the conformity of opinions.

Evaluation of the methodological quality of included studies

PRISMA guidelines on systematic reviews highlight the importance of differentiating quality and risk from bias and maintaining focus on evaluation and reporting of the latter when undertaking a systematic review.[13] However, in the review conducted here, the objective

consisted only in the identification and consolidation of early markers, diagnostic tests, and predictors of ASD. Therefore, the main objective of the analysis of the studies was not to accurately assess their quality or risk of bias.

Data extraction and management

Data extraction was made by three reviewers (J.H.R.A., F.P.N.A., and M.D. dos S.), independently, through frequent meetings, seeking to ensure that all appropriate data were collected. For the organization of the article data, tables containing the following items were elaborated: authors, title, year, type of study, information and/or details about predictors, early markers, and diagnostic tests of ASD, as well as the justification for inclusion in this review.

RESULTS AND DISCUSSION:

Using the search algorithms, a total of 193 unique documents were found, which were analyzed and selected for relevance (Figure 1). Of these, 65 documents were considered potentially relevant and submitted to full-text revision; 41 of them fulfilled inclusion criteria (16 with predictors (Table 1), 9 with early markers (Table 2), and 17 with diagnostic tests (Table 3) for ASD (One study was used in both the predictor and early marker categories).

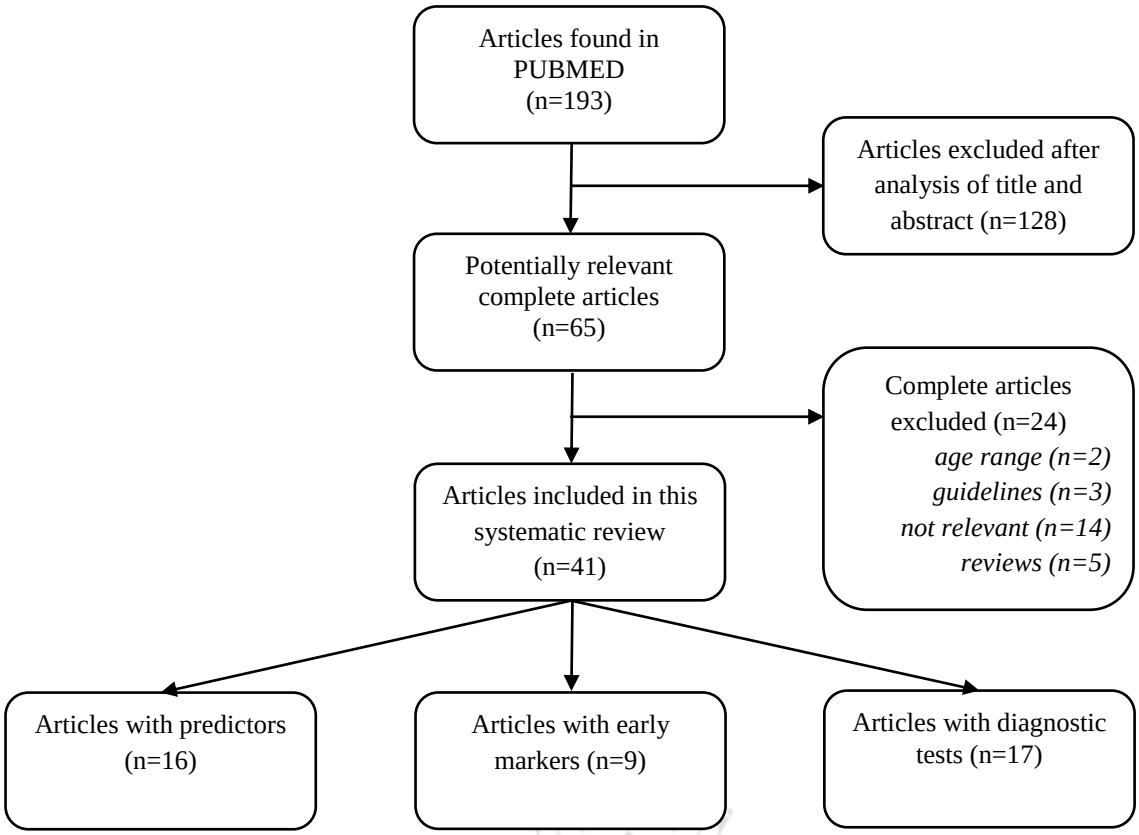

Figure No. 1: Flowchart of the review on the early diagnosis of ASD

Predictors of ASD

In table 1, the different predictors of ASD in infants found in literary publications in the last five years are presented. Thorup et al (2016)[14] conducted a study using eye-tracking to assess eye movement during an interaction, with a group of 10-month-old infants with high familial risk for ASD and another group with no familial risk. The children watched a researcher manipulate a puppet. Two situations served as a basis for comparison: in the first, the researcher moved his eyes and head towards the puppet (eyes and head condition), and in the second he used only eye movement (eyes only condition). Infants in the high-risk group were more likely to follow the researcher's gaze in the eyes and head condition than in the eyes-only condition. No differences were observed in the low-risk group.

In a prospective longitudinal study, conducted by Jones and Klin (2013),[15] researchers followed a group of infants from birth to 3 years of age using eye-tracking technology to measure how

infants observe and respond to visual stimuli. It was observed that infants later diagnosed with autism showed deficiency in attention to the eyes of other people from 2 months of age, a pattern not found in infants who did not develop ASD.

Swain et al (2015)[16] assessed in a retrospective study whether early communication skills can be detected at 12 months of age using the Communication and Symbolic Behavior Scales - Developmental Profile. It was identified that the children in the ASD group presented significantly lower social communication skills than the group with typical development. Gammer et al (2015)[17] in a prospective study using the Autism Observational Scale for Infants with two groups at 7 and 14 months of age, one at high familial risk and the other of low-risk controls. Scale scores at 14 months (but not at 7 months) were moderately correlated to later scores on the autism diagnostic timeline, suggesting the continuity of atypical autistic behavior, but only after the second year of life.

Mammen et al (2015)[18] dealt with the predictive associations between infant responses to tactile stimuli and infant autism spectrum, internalizing, and externalizing behavior. In the study, parents of adopted children painted the hands and feet of their nine-month-old children and pressed them to paper to form flowers. The researchers collected observational data on the negative reactions of infants (the expression of unpleasant feelings or emotions and avoidance behaviors). Since touch is essential in early social interactions, it has been perceived that avoiding physical contact during childhood may be a way of predicting impaired social development, which serves as the primary indicator for ASD.

Lazenby et al (2016)[19] observed language differences at 12 months of age in a prospective study with 346 children; these observations pointed to lower receptive and expressive language scores in infants who were subsequently diagnosed with ASD. The Social Attention and Communication Study[20] involved the successful implementation of monitoring the development of early markers for ASD disorders in a community-based setting. This study aimed to determine the most discriminatory and predictive markers of autism spectrum disorders used in the Social Attention and Communication Study at 12, 18, and 24 months of age to distinguish ASD more accurately in children. The recurrent key markers of autistic disorder and ASD, used at all ages, were deficiency in eye contact as well as in the act of pointing, from 18 months on deficits in social communication and the act of pointing at objects became important markers. Also, such

behaviors together with pretend play formed the best group of predictors for the best estimate diagnostic classification for autism/autism spectrum disorder at 24 months. Another study analyzed initial evaluation data (from 9 months on) with three deaf or hearing-impaired children and subsequently diagnosed with ASD, using the MacArthur-Bates Communicative Development Inventories; one of the children did not have the skills or language expected at the ages of 9 and 14 months, another child lost skills and language after 17 months, while the third presented results, mostly within/above the average range until 3 years of age.[21]

Other studies were conducted using questionnaires, the first conducted a developmental and autism screening by telephone, with 2845 children examined for developmental delays, using the Parents' Evaluation of Developmental Status (PEDS) instrument, and/or the Modified Checklist for Autism in Toddlers (M-CHAT) instrument. Among the 1605 children selected with M-CHAT, 21.2% were at high risk for ASD.[22] In another study, postpartum interviews were used as a research tool, comprised of more than 200 questions directed to 76,441 mothers, on the development of motor, cognitive, linguistic, and social skills, including vision and hearing skills of their children at 6 and 18 months. At 6 months, few associations were found between early signs of ASD or intellectual disability; however, at 18 months, there was efficiency in language, social, and motor skills, with a suspected vision and hearing problem. Even so, the signs that distinguished ASD from intellectual disability was unclear, and positive predictive values for ASD were less than 10% for individual predictors and aggregate risk scores.[23]

The First Year Inventory-Lite[24] consisted of a standardized questionnaire with 24 items for ASD screening at 12 months of age, followed by the Autism Observation Scale for Infants and the Mullen Scales of Early Learning, compared to controls, risk infants scored significantly higher on the observation scale, lower composite scores on the Mullen scale, and a higher baseline rate for a developmental assessment. Using the Checklist for Autism in Toddlers (CHAT), 8000 infants aged 18-36 months were screened, of which 367 children presented a risk for ASD, and posteriorly 22 of them were diagnosed with ASD. In this sample, the prevalence of ASD was 27.5 per 10000;[25] the same inventory was used in another study that examined whether a parent's report on socio-communicative and repetitive behavior at 12 months may be useful in identifying the disorder in younger siblings; the results showed that lack of interest in play, together with impaired vocal imitation and communication, correctly classified most cases of

ASD, with high specificity;[26] another study evaluated the characteristics of standard development in 6-month and 18-month-old post-term infants with extremely low birth weight, later diagnosed with ASD, using the Kyoto Scale of Psychological Development. According to the scale, the results were significantly lower for children with ASD than in infants with typical development, at 24- and 36-month assessments.[27]

Other predictors have served as an object of studies, such as the observation of patterns of stereotyped motor mannerisms and repetitive manipulation of objects, which pointed out that the group at high risk for ASD had significantly more stereotyped motor mannerisms and repetitive object manipulation, suggesting that the assessment of repetitive behavior during childhood may enhance early identification strategies;[28] a similar study analyzed the status of canonical babbling (repeated syllables made up of a consonant and a vowel) and vocalization frequency with retrospective video in children aged 9-12 and 15-18 months, most infants subsequently diagnosed with ASD produced low rates of canonical babbling and low vocalization frequency compared to those with typical development.[29]

Table No. 1: List of included articles regarding predictors for ASD

ID	Article	Notes on inclusion
14	Thorup E, Nyström P, Gredebäck G, Bölte S, Falck-Ytter T; EASE Team. Altered gaze following during live interaction in infants at risk for autism: an eye tracking study. Mol Autism. 2016;7:12. doi:10.1186/s13229-016-0069-9	Eye-tracking was used to assess eye movement during interaction with 10-month-old infants with high familial risk for ASD
15	Jones W, Klin A. Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. Nature. 2013;504(7480):427-431. doi:10.1038/nature12715	Infants subsequently diagnosed with autism demonstrated decreased attention to the eyes of other people, from the age of 2 months.
16	Swain NR, Eadie PA, Prior MR, Reilly S. Assessing early communication skills at 12 months: a	Significantly lower social communication skills at 12

	retrospective study of Autism Spectrum Disorder. Int J Lang Commun Disord. 2015;50(4):488-498. doi:10.1111/1460-6984.12150	months of age.
17	Gammer I, Bedford R, Elsabbagh M, et al. Behavioural markers for autism in infancy: scores on the Autism Observational Scale for Infants in a prospective study of at-risk siblings. Infant Behav Dev. 2015;38:107-115. doi:10.1016/j.infbeh.2014.12.017	Behavioral markers on the Autism Observational Scale for Infants were evidenced at 14 months of age.
18	Mammen MA, Moore GA, Scaramella LV, et al. Infant avoidance during a tactile task predicts autism spectrum behaviors in toddlerhood. Infant Ment Health J. 2015;36(6):575-587. doi:10.1002/imhj.21539	Predictive associations between infant responses to tactile stimuli and infant autism spectrum, internalizing and externalizing behavior.
19	Lazenby DC, Sideridis GD, Huntington N, et al. Language Differences at 12 Months in Infants Who Develop Autism Spectrum Disorder. J Autism DevDisord. 2016;46(3):899-909. doi:10.1007/s10803-015-2632-1	Less receptive and expressive speech scores in infants who were later diagnosed with ASD.
20	Barbaro J, Dissanayake C. Early markers of autism spectrum disorders in infants and toddlers prospectively identified in the Social Attention and Communication Study. Autism. 2013;17(1):64-86. doi:10.1177/1362361312442597	Main markers: deficits in eye contact and pointing; and from 18 months of age, deficits in visual contact and pointing at objects.
21	Kellogg EC, Thrasher A, Yoshinaga-Itano C. Early predictors of autism in young children who are deaf or hard of hearing: three longitudinal case studies. Semin Speech Lang. 2014;35(4):276-287. doi:10.1055/s-0034-1389100	The MacArthur-Bates Communicative Development Inventories Words and Gestures and the Child Development Inventory were used to develop profiles of children.

22	Roux AM, Herrera P, Wold CM, Dunkle MC, Glascoe FP, Shattuck PT. Developmental and autism screening through 2-1-1: reaching underserved families. Am J Prev Med. 2012;43(6 Suppl 5): S457-S463. doi:10.1016/j.amepre.2012.08.011	Developmental screening and autism by telephone with M-CHAT, 21.2% of the children presented high risk for ASD.
23	Lemcke S, Juul S, Parner ET, Lauritsen MB, Thorsen P. Early signs of autism in toddlers: a follow-up study in the Danish National Birth Cohort. J Autism DevDisord. 2013;43(10):2366-2375. doi:10.1007/s10803-013-1785-z	Postpartum interviews with more than 200 questions on the development of motor, cognitive, language, and social skills, including vision and hearing skills, at 6 and 18 months.
24	Ben-Sasson A, Habib S, Tirosh E. Feasibility and validity of early screening for identifying infants with poor social-communication development in a well-baby clinic system. J PediatrNurs. 2014;29(3):238-247. doi:10.1016/j.pedn.2013.11.001	The First Year Inventory-Lite (FYI-L), a standardized questionnaire with 24 items for ASD screening at 12 months of age.
25	Huang JP, Cui SS, Han Y, Irva HP, Qi LH, Zhang X. Prevalence and early signs of autism spectrum disorder (ASD) among 18-36 month-old children of Tianjin in China. Biomed Environ Sci. 2014;27(6):453-461. doi:10.3967/bes2014.008	Use of standardized questionnaire - CHAT to diagnose risk for ASD in infants.
26	Rowberry J, Macari S, Chen G, et al. Screening for autism spectrum disorders in 12-month-old high-risk siblings by parental report. J Autism DevDisord. 2015;45(1):221-229. doi:10.1007/s10803-014-2211-x	Lack of interest in playand communication and impaired vocal imitation.

27	Kihara H, Nakamura T. Early standard development assessment characteristics in very low birth weight infants later classified with autism spectrum disorder. Early Hum Dev. 2015;91(6):357-359. doi:10.1016/j.earlhumdev.2015.03.012	Using the Kyoto Scale of Psychological Development, results were significantly lower in children with ASD than infants with typical development, at 24- and 36-month assessments.
28	Elison JT, Paterson SJ, Wolff JJ, et al. White matter microstructure and atypical visual orienting in 7-month-olds at risk for autism. Am J Psychiatry. 2013;170(8):899-908. doi:10.1176/appi.ajp.2012.12091150	Increased patterns of stereotyped motor mannerisms and repetitive manipulation of objects in infants later diagnosed with ASD.
29	Patten E, Belardi K, Baranek GT, Watson LR, Labban JD, Oller DK. Vocal patterns in infants with autism spectrum disorder: canonical babbling status and vocalization frequency [published correction appears in J Autism DevDisord. 2014 Oct;44(10):2429]. J Autism DevDisord. 2014;44(10):2413-2428. doi:10.1007/s10803-014-2047-4	Lower rates of canonical babbling and low vocalization frequency compared to infants with typical development.

Bibliographic information of articles included in this review. For ease of reference, these are also included in the references.

Early markers for ASD

Some studies performed during the first years of life in children subsequently diagnosed with ASD indicate that these children have some abnormalities that may serve as early markers (Table 2). Zerbo et al (2014)[30] studied levels of cytokine and chemokine in newborn blood specimens, researchers found elevated levels of the chemokine MCP-1 (monocyte chemotactic protein) and decreased levels of chemokine RANTES (regulated under activation, expressed, and secreted by normal T cells) in the blood of neonates subsequently diagnosed with ASD. In another

retrospective study, Mizejewski et al (2013),[31] using blood samples in an immunoassay, determined that a statistically selected panel of 15 markers successfully discriminated newborns at risk for ASD.

Hazlett et al (2017)[32] report that post-natal cephalic hyper expansion of very early cortical surface areas may play an important role in the development of autism; and that understanding the mechanisms underlying the hyper expansion of surface area in the first year in human infants, could probably provide important information about the downstream pathogenesis of autism. Samango-Sprouse et al (2015)[33] analyzed head circumference and head tilt reflex in 9-month-old infants, seeking to identify risk for ASD. As a result, they found that abrupt acceleration of the circumference and absence of head tilt reflex were used to identify infants at risk of developing ASD. The results of this study provided a good positive predictive value (0.93) for the identification of ASD, before 12 months.

Righi et al (2015)[34] calculated the intra-hemispheric linear coherence between the anterior and posterior sites as a measure of neural functional connectivity derived from electroencephalography while infants were hearing speech sounds and found that children at risk for ASD, at 12 months of age, had reduced functional connectivity compared to low-risk children. Based on the observation of ASD-induced abnormalities in white matter tracts and brain connectivity that appeared within 24 months after birth, Jin et al (2015)[35] proposed a novel multi-kernel support vector machine classification framework according to the characteristics of white matter connectivity networks, which were generated through multiscale regions of interest and multiple diffusion statistics, such as fractional anisotropy, mean diffusivity and mean fiber length, for identification of 6-month-old children at high risk for ASD, reaching an accuracy of 76%. In a study conducted by Wolff et al (2017),[36] with a group of 217 children at high familial risk for ASD, specific cortical, cerebellar, and striatal white matter pathways were defined and measured at 6, 12 and 24 months. The results of the study suggest that the restricted and repetitive behaviors that contribute to the diagnosis of ASD at 2 years of age were associated with the structural properties of callosal and cerebellar white matter pathways during the first months of life.

In an eye-tracking screening study with 334 children aged 10-49 months, Pierce et al (2016)[37] identified that a visual preference for geometric repetition may be an early developmental

biomarker for a subtype of ASD with more serious symptoms. Elison et al (2013)[28] sought to determine whether specific patterns of oculomotor functioning and visual orientation characterize 7-month-old children, who later met the criteria for ASD and to identify the neural correlates of these behaviors. The authors concluded that the flexible and efficient orientation to point out information in the environment is fundamental for the subsequent cognitive and social development; furthermore, atypical visual orientation may represent an early prodromal characteristic of ASD.

Table No. 2: List of included articles regarding early markers for ASD

ID	Article	Notes on inclusion
30	Zerbo O, Yoshida C, Grether JK, et al. Neonatal cytokines and chemokines and risk of Autism Spectrum Disorder: the Early Markers for Autism (EMA) study: a case-control study. J Neuroinflammation. 2014;11:113. doi:10.1186/1742-2094-11-113	Elevated levels of the chemokine MCP-1 and decreased levels of chemokine RANTES in the blood of neonates.
31	Mizejewski GJ, Lindau-Shepard B, Pass KA. Newborn screening for autism: in search of candidate biomarkers. Biomark Med. 2013;7(2):247-260. doi:10.2217/bmm.12.108	A statistically selected panel of 15 markers successfully discriminated newborns at risk for ASD.
32	Hazlett HC, Gu H, Munsell BC, et al. Early brain development in infants at high risk for autism spectrum disorder. Nature. 2017;542(7641):348-351. doi:10.1038/nature21369	Early post-natal cephalic hyper expansion of cortical surface areas.
33	Samango-Sprouse CA, Stapleton EJ, Aliabadi F, et al. Identification of infants at risk for autism spectrum disorder and developmental language delay prior to 12 months. Autism. 2015;19(3):327-337. doi:10.1177/1362361314521329	Abrupt acceleration of the circumference and absence of head tilt reflex was used to identify infants at risk of developing ASD, positive predictive value = 0.93.
34	Righi G, Tierney AL, Tager-Flusberg H, Nelson CA. Functional connectivity in the first year of life in infants at	Reduced neural functional connectivity during speech

	risk for autism spectrum disorder: an EEG study. PLoS One. 2014;9(8):e105176. doi:10.1371/journal.pone.0105176	processing at 12 months of age.
35	Jin Y, Wee CY, Shi F, et al. Identification of infants at high-risk for autism spectrum disorder using multiparametermultiscale white matter connectivity networks. Hum Brain Mapp. 2015;36(12):4880-4896. doi:10.1002/hbm.22957	A novel multikernel support vector machine classification framework according to the characteristics of white matter connectivity networks, for identification of 6-month-old children at high risk for ASD, with an accuracy of 76%.
36	Wolff JJ, Swanson MR, Elison JT, et al. Neural circuitry at age 6 months associated with later repetitive behavior and sensory responsiveness in autism. Mol Autism. 2017;8:8. doi:10.1186/s13229-017-0126-z	Restricted and repetitive behaviors that contribute to the diagnosis of ASD at 2 years of age are associated with the structural properties of callosal and cerebellar white matter pathways during the first months of life.
37	Pierce K, Marinero S, Hazin R, McKenna B, Barnes CC, Malige A. Eye Tracking Reveals Abnormal Visual Preference for Geometric Images as an Early Biomarker of an Autism Spectrum Disorder Subtype Associated With Increased Symptom Severity. Biol Psychiatry. 2016;79(8):657-666. doi:10.1016/j.biopsych.2015.03.032	Visual preference for geometric repetition may be an early developmental biomarker for a subtype of ASD with more serious symptoms.
28	Elison JT, Paterson SJ, Wolff JJ, et al. White matter microstructure and atypical visual orienting in 7-month-olds at risk for autism. Am J Psychiatry. 2013;170(8):899-908. doi:10.1176/appi.ajp.2012.12091150	Specific patterns of oculomotor functioning and visual orientation characterize 7-month-old children that later met the criteria for ASD.

Bibliographic information of articles included in this review. For ease of reference, these are also included in the references.

Diagnostic tests for ASD

Diagnostic tests for ASD used in infants are cited in Table 3, which provides information on the use of the Modified Checklist for Autism in Toddlers (M-CHAT) alone, [38-47] and in combination with follow-up interview (M-CHAT / F).[38,45-47] M-CHAT is a checklist designed to detect risks of ASD in infants, a child has a positive diagnosis for the disorder when he or she fails in 3 of the 23 items, or in 2 of the 6 critical items. In the follow-up interview, the parents of children with a positive diagnosis are interviewed by a primary care pediatrician to confirm the results of the M-CHAT.

Different studies used the diagnostic criteria of DSM-5;[48-49] presented results that indicated good sensitivity and specificity for the DSM-5 criteria in the diagnosis of ASD in infants.

Grodberg et al (2016)[50] evaluated the use of the autism mental status exam, an eight-item brief observation tool designed by health professionals, in 45 children aged 18 months to 5 years, with suspected ASD or difficulties in social interaction and verbal communication; the findings indicated an optimized sensitivity of 94% and a specificity of 100% in the studied group.

Hedley et al (2015)[51] observed the effectiveness of the ADEC (Autism Detection in Early Childhood) tool to identify ASD in children aged 12-36 months with clinical reference in the USA; the tool that was developed in Australia is an interactive behavior-based tracking tool. The ADEC returned good sensitivity (0.93-0.94), but a lower specificity (0.62-0.64) for the diagnosis of ASD.

Miller et al (2017)[52] developed a response to name task, which was tested in children of 6, 9, 12, 15, 18, and 24 months of age. The task mentioned is to call the child's name in clear voice and normal volume up to 2 times while he or she is playing with toys and sitting on a parent's lap, at least 60 cm away (not facing) from the examiner. At 9 months of age the children with the disorder responded less to the stimulus of the call, situation persisting at 24 months. In this study, sensitivity/specificity to identify ASD based on at least 1 failure between 12 and 24 months was estimated to be 0.70.

Zander et al (2015)[53] analyzed the diagnostic validity of the revised autism diagnostic interview and the autism diagnostic observation program in a clinical sample of children aged 18 to 47 months. The autism diagnostic interviews (revised) provided excellent specificity (91-96%), but low sensitivity (44-52%), the application of adjusted cutoff points (lower than recommended based on receiver operating characteristics) resulted in a better balance between sensitivity (77-82%) and specificity (60-62%); the findings of the autism diagnostic observation program were compatible with previous studies with high sensitivity (94-100%) and low specificity (52-76%) when using the autism spectrum limit, but a more balanced sensitivity (81-94%) and specificity (81-83%) when using the cut-off point for autism.

More recently, Olliac et al (2017)[54] presented the PREAUT (*Program of Recherches et d'Etudessurl'AUTisme*) grid that was developed through the observation of family home movies of babies who were later diagnosed with autism, the baby's ability to spontaneously engage in synchronous and cheerful interactions; the grid is scored by a pediatrician during a visit to the baby and his or her mother (or other caregiver). Applied at 4 months of age the grade showed a sensitivity of 16.0-20.6%, specificity of 99.6%, positive predictive value of 25.4-26.3%; and at 9 months of age a sensitivity of 30.5-41.2%, specificity of 99.3-99.4%, and positive predictive value of 20.2-36.4%).

Table No. 3: List of included articles regarding diagnostic tests for ASD

ID	Article	Notes on inclusion
38	Sturner R, Howard B, Bergmann P, et al. Autism Screening With Online Decision Support by Primary Care Pediatricians Aided by M-CHAT/F. Pediatrics. 2016;138(3):e20153036. doi:10.1542/peds.2015-3036	Modified Checklist for Autism in Toddlers (M-CHAT) with follow-up interview (M-CHAT / F).
39	Wiggins LD, Piazza V, Robins DL. Comparison of a broad-based screen versus disorder-specific screen in detecting young	Comparison between two screening tests: autism spectrum disorder diagnosis and outcome of

	children with an autism spectrum disorder. Autism. 2014;18(2):76-84. doi:10.1177/1362361312466962	the Modified Checklist for Autism in Toddlers (M-CHAT) and Parents Evaluation of Developmental Status.
40	Kamio Y, Haraguchi H, Stickley A, Ogino K, Ishitobi M, Takahashi H. Brief Report: Best Discriminators for Identifying Children with Autism Spectrum Disorder at an 18-Month Health Check-Up in Japan. J Autism DevDisord. 2015;45(12):4147-4153. doi:10.1007/s10803-015-2527-1	Modified Checklist for Autism in Toddlers (M-CHAT-JV) (Japanese version).
41	Gabrielsen TP, Farley M, Speer L, Villalobos M, Baker CN, Miller J. Identifying autism in a brief observation. Pediatrics. 2015;135(2):e330-e338. doi:10.1542/peds.2014-1428	Comparison of brief clinical observations and Modified Checklist for Autism in Toddlers (M-CHAT) (Brief observation: 62% sensitivity, 82% specificity, 61% positive predictive value, and 81% negative predictive value).
42	Stenberg N, Bresnahan M, Gunnes N, et al. Identifying children with autism spectrum disorder at 18 months in a general population sample. Pediatric Perinatal Epidemiology. 2014;28(3):255-262. doi:10.1111/ppe.12114	Modified Checklist for Autism in Toddlers (M-CHAT) at 18 months of age. The M-CHAT 6 key items: sensitivity of 20.8%, specificity of 97.9% and positive predictive value of 3.3%; M-CHAT with a criterion of 23 items: sensitivity of 34.1%, specificity of 92.7% and positive predictive value of 1.5%.

43	Rotholz DA, Kinsman AM, Lacy KK, Charles J. Improving Early Identification and Intervention for Children at Risk for Autism Spectrum Disorder. Pediatrics. 2017;139(2):e20161061. doi:10.1542/peds.2016-1061	Modified Checklist for Autism in Toddlers (M-CHAT), and the Screening Tool for Autism in Toddlers & Young Children (STAT).
44	Gray PH, Edwards DM, O'Callaghan MJ, Gibbons K. Screening for autism spectrum disorder in very preterm infants during early childhood. Early Hum Dev. 2015;91(4):271-276. doi:10.1016/j.earlhumdev.2015.02.007	Checklist for Autism in Toddlers (M-CHAT).
45	Campbell K, Carpenter KLH, Espinosa S, et al. Use of a Digital Modified Checklist for Autism in Toddlers - Revised with Follow-up to Improve Quality of Screening for Autism. J Pediatr. 2017;183:133-139.e1. doi:10.1016/j.jpeds.2017.01.021	Modified Checklist for Autism in Toddlers-Revised with follow-up interview (M-CHAT-R / F).
46	Weitlauf AS, Vehorn AC, Stone WL, Fein D, Warren ZE. Using the M-CHAT-R/F to Identify Developmental Concerns in a High-Risk 18-Month-Old Sibling Sample. J Development Behavior Pediatric. 2015;36(7):497-502. doi:10.1097/DBP.0000000000000194	Modified Checklist for Autism in Toddlers-Revised with follow-up interview (M-CHAT-R / F) (sensitivity of 78.26%, specificity of 72.22%, positive predictive value of 78.26%, and negative predictive value of 72.22%).
47	Robins DL, Casagrande K, Barton M, Chen CM, Dumont-Mathieu T, Fein D. Validation of the modified checklist for Autism in toddlers, revised with follow-up (M-CHAT-R/F). Pediatrics. 2014;133(1):37-45.	Modified Checklist for Autism in Toddlers-Revised with follow-up interview (M-CHAT-R / F).

	doi:10.1542/peds.2013-1813	
48	Christiansz JA, Gray KM, Taffe J, Tonge BJ. Autism Spectrum Disorder in the DSM-5: Diagnostic Sensitivity and Specificity in Early Childhood. J Autism DevDisord. 2016;46(6):2054-2063. doi:10.1007/s10803-016-2734-4	DSM-5 diagnostic Criteria in children up to 5 years of age (sensitivity of 84% and specificity of 54%).
49	Barton ML, Robins DL, Jashar D, Brennan L, Fein D. Sensitivity and specificity of proposed DSM-5 criteria for autism spectrum disorder in toddlers. J Autism DevDisord. 2013;43(5):1184-1195. doi:10.1007/s10803-013-1817-8	Sensitivity and specificity of criteria proposed by DSM-5 (sensitivity of 93% and specificity of 74%).
50	Grodberg D, Siper P, Jamison J, Buxbaum JD, Kolevzon A. A Simplified Diagnostic Observational Assessment of Autism Spectrum Disorder in Early Childhood. Autism Res. 2016;9(4):443-449. doi:10.1002/aur.1539	Autism mental state examination in children aged 18 months to 5 years, with suspicion of ASD or difficulties in social interaction and verbal communication (sensitivity of 94% and specificity of 100% in the group studied).
51	Hedley D, Nevill RE, Monroy-Moreno Y, et al. Efficacy of the ADEC in Identifying Autism Spectrum Disorder in Clinically Referred Toddlers in the US. J Autism DevDisord. 2015;45(8):2337-2348. doi:10.1007/s10803-015-2398-5	The Autism Detection in Early Childhood – ADEC instrument (sensitivity of 93% and specificity of 63%).
52	Miller M, Iosif AM, Hill M, Young GS, Schwichtenberg AJ, Ozonoff S. Response to	Lower performance in response to name task is infants developing

	Name in Infants Developing Autism Spectrum Disorder: A Prospective Study. J Pediatr. 2017;183:141-146.e1. doi:10.1016/j.jpeds.2016.12.071	ASD (sensitivity and specificity estimated at 70%).
53	Zander E, Sturm H, Bölte S. The added value of the combined use of the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule: diagnostic validity in a clinical Swedish sample of toddlers and young preschoolers. Autism. 2015;19(2):187-199. doi:10.1177/1362361313516199	The combined use of the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule (sensitivity of 77-80% and specificity of 87-90%).
54	Olliac B, Crespin G, Laznik MC, et al. Infant and dyadic assessment in early community-based screening for autism spectrum disorder with the PREAUT grid. PLoS One. 2017;12(12):e0188831. doi:10.1371/journal.pone.0188831	The PREAUT grid is based on dyadic assessment through interaction and shared emotion (at 4 months of age: sensitivity of 16.0-20.6%, specificity of 99.6%, positive predictive value of 25.4-26.3%; at 9 months of age: sensitivity of 30.5-41.2%, specificity of 99.3-99.4%, positive predictive value of 20.2-36.4%).

Bibliographic information of articles included in this review. For ease of reference, these are also included in the references.

DISCUSSION:

ASD is a developmental disorder, characterized by persistent and significant deficits in social interaction, communication and behaviors, and restrictive and repetitive activities when such symptoms cannot be explained by any other condition. Few studies have examined knowledge

on early markers, predictors, and diagnostic tests for ASD using this new terminology, thus diagnostic protocols need to be refined to improve treatments.

In this review, different markers, predictors, and diagnostic tests of ASD were identified; the main ones are identified below:

- Early markers:
  - serum biomarkers;
  - cerebral biomarkers;
  - visual preference for geometric repetition;
  - cephalic hyperexpansion;
  - absence of head tilt reflex;
  - high expression levels of the MCP-1 chemokine;
  - a decrease in the RANTES chemokine; and
  - Reduced functional brain connectivity.
- Predictors:
  - less inclination to follow gaze;
  - decline in eye fixation;
  - less social communication skills;
  - less receptive and expressive speech;
  - lack of interest in play;
  - motor stereotypies;
  - repetitive manipulation of objects;
  - low rates of canonical babble; and

- low volubility.

- Diagnostic Tests:

- M-CHAT;

- M-CHAT / F;

- DSM-5 diagnostic criteria;

- Autism mental state examination;

- ADEC;

- Response to name task;

- Autism Diagnostic Interview - Revised;

- the autism diagnostic observation program; and

- The PREAUT grid.

Dawson and Bernier (2013),[55] in a review of progress in the early detection and treatment of autism spectrum disorder, report that changes in early behaviors as well as structural brain alterations in infants aged 6 to 12 months, may be used to detect autism before the syndrome is fully manifested, thereby reducing or preventing symptoms from developing.

Another review conducted by Sacrey et al (2015)[56] reports recent findings on early detection and/or diagnosis of ASD, as well as clinical trials of early interventions for children at risk and/or diagnosed with ASD. According to the findings, the "prodromal characteristics" (motor and sensory abnormalities) appear in the first year of life, before the abnormalities in the social communication and the repetitive behaviors that appear in the second year of life. However, the authors reported that further research is required to reach the goal of diagnosis and early intervention for all children with ASD.

In a cohort that verified agreement between parents and clinicians in observing early behavioral signs in high-risk infants for ASD (siblings of children who had already been diagnosed) at 12

and 18 months of age, Sacrey et al (2018)[57] identified that parents of autistic children are more likely to perceive early signs in high-risk children than clinicians.

Bhat et al (2014)[58] in a review, sought cause factors, early diagnosis, and ASD therapies; the authors report that although autism is a neurodevelopmental disorder that cannot be cured there are measures that can minimize the disabilities of this condition. According to the review, changes in X chromosome structure, due to environmental factors, variations in neural connectivity and different parts of the brain, converge to autistic symptoms and these symptoms of atypical behavior occur after 18-24 months, but the identification of phenotypic, behavioral and neurophysiological risk indexes, with the help of neuroimaging techniques, can determine the first signs of the disorder.

According to Allely et al (2014)[59] in a study that explored the differences in various regions of the brain in individuals with ASD or who later receive the diagnosis of ASD, it was concluded that studies conducted in these different areas revealed the existence of atypicalities in the first year of life, long before an ASD diagnosis is considered reliable.

Universal screening for ASD has been recommended by the American Academy of Pediatrics[60] since 2007, and in 2015, Zwaigenbaumet al[61] performed a review on screening evidence for ASD based on peer-reviewed articles. The authors concluded that screening in children aged 18-24 months may assist in early detection, according to the current recommendations from the American Academy of Pediatrics, they emphasized that there is a growing interest in possible biological measures that could be used before (or immediately after) birth, to assess risk for ASD; these markers include metabolites, amino acids, hormones, and immune factors, individually or in combination.

This review is the first to describe early markers, predictors, and diagnostic methods for ASD in infants after the emergence of the new term “autism spectrum disorder” in 2016. Early diagnosis and increased recognition, as demonstrated in prevalence rates, have significant implications for diagnostic and therapeutic services. Primary health care professionals, including general practitioners, social workers, nurses, nursing technicians, community health workers, public health agents and psychologists, as well as day-care teachers, need to be made aware through

training that enables them to recognize the early signs of a possible ASD, in order to ensure more specific investigation.

CONCLUSION:

With increasing interest in identifying early methods to detect ASD, there has been progressed in establishing early markers, predictors, and diagnostic tests. However, much remains to be investigated to achieve the goal of diagnosing ASD in all children before the age of 2 years; also, the findings of these studies need to be translated into clinical practice to assess risk and severity, providing information that may lead to appropriate specific therapeutic interventions from the respective health systems. This review may facilitate the early identification of ASD, and in turn, may possibly improve early ASD therapeutic interventions.

Declaration of conflicts of interest

The authors declare no conflicts of interest.

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