



ISSN: 2230-9926

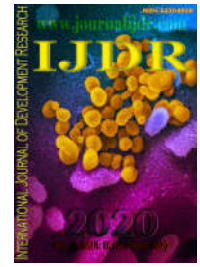
Available online at <http://www.journalijdr.com>

IJDR

International Journal of Development Research

Vol. 10, Issue, 11, pp. 42143-42147, November, 2020

<https://doi.org/10.37118/ijdr.20473.11.2020>



RESEARCH ARTICLE

OPEN ACCESS

EARLY WARNING SIGNS FOR AUTISM SPECTRUM DISORDER IN INFANTS

***¹Francisco Plácido Nogueira Arcanjo, ¹Andreza Moita Morais, ¹Paula Andréia Araújo Monteiro, ¹Izabella Vieira dos Anjos Sena, ²Jeferson de Sousa Justino, ³Luiza Fernanda Araújo Monteiro, ³Priscila Gonçalves Teixeira, ¹Cecília Costa Arcanjo and ¹Felipe Costa Arcanjo**

¹Universidade Federal do Ceará, Av. Comandante Maurocélcio Rocha Ponte, 100 – Derby, 62.042-280 – Sobral-Ceará, Brazil; ²Hospital Regional Norte, Av. John Sanford, 1505 - Dr. Jose Euclides Ferreira Gomes Junior, 62.030-340 – Sobral-Ceará, Brazil; ³Instituto Técnico Sobralense, Cel. Diogo Gomes, 857 - Centro, 62.010-150 - Sobral-Ceará, Brazil; ⁴Centro Universitário INTA, R. Cel. Antonio Rodrigues Magalhães, 359 - D. Expedito Lopes, 62.050-100 – Sobral-Ceará, Brazil

ARTICLE INFO

Article History:

Received 02nd August, 2020

Received in revised form

18th September, 2020

Accepted 09th October, 2020

Published online 30th November, 2020

Key Words:

Autism Spectrum Disorder;
Early Diagnosis; Infant Behavior; Review.

*Corresponding author:

Francisco Plácido Nogueira Arcanjo.

ABSTRACT

Autism spectrum disorder (ASD) is one of the most prevalent neurodevelopmental disorders in childhood, and early specialized treatment for ASD may contribute to significant gains in cognitive, social, and linguistic functioning. However, early diagnosis is challenging and there is frequently a delay between the first warning signs and diagnosis. The aim of this study was to identify the state of knowledge on the early warning signs for ASD in infants (0-23 months of age) from a review of the literature. The main early warning signs identified in this review were: less inclination to follow gaze; decline in eye fixation; less social communication skills; less receptive and expressive speech; less empathic concern; lack of interest in play; motor stereotypies; repetitive manipulation of objects; low rates of canonical babble; and low volubility.

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Citation: Francisco Plácido Nogueira Arcanjo, Andreza Moita Morais, Paula Andréia Araújo Monteiro et al., 2020. "Early warning signs for autism spectrum disorder in infants", *International Journal of Development Research*, 10, (11), 42143-42147.

INTRODUCTION

According to estimates by the World Health Organization and the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network, the prevalence of the autism spectrum disorder (ASD) has increased in recent years, estimating that 1 in every 68 children has ASD; moreover, ASD is about 4.5 times more frequent among boys (1 in 42) than among girls (1 in 189) (Christensen *et al*, 2016; World Health Organization, 2019). ASD originates in the first years of life; however, its trajectory is not uniform. Some children show symptoms soon after birth, however, in most cases, they are only consistently identified between 12 and 24 months of age (Johnson *et al*, 2007; Ozonoff *et al*, 2009; Tierney *et al*, 2012). Despite this evidence, the diagnosis of ASD occurs, on average, at four or five years of age (Mandell *et al*, 2005; Shaw *et al*, 2020). Some scholars have suggested that early and intensive intervention has the potential to prevent the complete manifestation of ASD, as it coincides with a period of

development in which the brain is highly plastic and malleable (Estes *et al*, 2015; Hodel, 2018; Herbrecht *et al*, 2020). In this sense, the search for early warning signs of ASD remains an area of intense scientific investigation. Given this premise, the objective of this study was to identify the state of knowledge on early signs of ASD in infants (0-23 months of age) from a review of the literature, believing that the earlier the diagnosis, the more effective treatment interventions will be.

FINDINGS

As far as this review could determine, there is a relatively small number of published studies on this theme. The main findings of which are summarized in this review and presented in Table 1 to simplify comparisons. Thorup *et al* (2016) conducted a study using eye tracking to assess eye movement during 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 & Klin (2013), 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) 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) 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) 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) 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 involved the successful implementation of monitoring the development of early markers for ASD disorders in a community-based setting (Barbaro & Dissanayake, 2013). The aim of this study was 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. In addition, such behaviors together with pretend play formed the best group of predictors for 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 (Kellogg *et al*, 2014). 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 (Roux *et al*, 2012). 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 were unclear, and positive predictive values for ASD were less than 10% for individual predictors and aggregate risk scores (Lemcke *et al*, 2013).

The First Year Inventory-Lite 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 (Ben-Sasson *et al*, 2014). Using the Checklist for Autism in Toddlers (CHAT), 8000 infants aged 18-36 months were screened, of which 367 children presented risk for ASD, and posteriorly 22 of them were diagnosed with ASD. In this sample, the prevalence of ASD was 27.5 per 10000 (Huang *et al*, 2014); 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 (Rowberry *et al*, 2015); 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 (Kihara & Nakamura, 2015).

Other predictors have served as an object of study, 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 (Elison *et al*, 2013); 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 (Patten *et al.*, 2014). More recently, Northrup *et al.* (2020), in a prospective study of toddlers at risk for ASD, evaluated how accurately and specifically composite measures of social engagement, pretend play, and empathic concern obtained at 22 months of age were able to predict the diagnosis of ASD at 36 months. The results of this study demonstrated a high degree of specificity and relatively moderate sensitivity; the presence of poor or delayed social development in the areas of social engagement, pretend play, and empathic concern are excellent markers for the future diagnosis of ASD; however, the absence of these cannot be used to discard a diagnosis.

fully manifested, thereby reducing or preventing symptoms from developing. In another review conducted by Sacrey *et al.* (2015), which 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, found that 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

Table 1. Studies reporting on the early warning signs for ASD in infants included in this review

First author	Year of publication	Notes on inclusion
Thorup	2016	Eye tracking was used to assess eye movement during interaction with 10-month-old infants with high familial risk for ASD
Jones	2013	Infants subsequently diagnosed with autism demonstrated decreased attention to the eyes of other people, from the age of 2 months.
Swain	2015	Significantly lower social communication skills at 12 months of age.
Gammer	2015	Behavioral markers on the Autism Observational Scale for Infants for infants were evidenced at 14 months of age.
Mammen	2015	Predictive associations between infant responses to tactile stimuli and infant autism spectrum, internalizing, and externalizing behavior.
Lazenby	2016	Less receptive and expressive speech scores in infants who were later diagnosed with ASD.
Barbaro	2013	Main markers: deficits in eye contact and pointing; and from 18 months of age, deficits in visual contact and pointing at objects.
Kellogg	2014	The MacArthur-Bates Communicative Development Inventories Words and Gestures and the Child Development Inventory were used to develop profiles of children.
Roux	2012	Developmental screening and autism by telephone with M-CHAT, 21.2% of the children presented high risk for ASD.
Lemcke	2013	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.
Ben-Sasson	2014	The First Year Inventory-Lite (FYI-L), a standardized questionnaire with 24 items for ASD screening at 12 months of age.
Huang	2014	Use of standardized questionnaire — CHAT to diagnose risk for ASD in infants.
Rowberry	2015	Lack of interest in play and communication and impaired vocal imitation.
Kihara	2015	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.
Elison	2013	Increased patterns of stereotyped motor mannerisms and repetitive manipulation of objects in infants later diagnosed with ASD.
Patten	2014	Lower rates of canonical babbling and low vocalization frequency compared to infants with typical development.
Northrup	2020	At 22 months of age, the presence of poor or delayed social development in the areas of social engagement, pretend play, and empathic concern are excellent markers for the future diagnosis of ASD.

Table 2. The main early warning signs of ASD

<ul style="list-style-type: none"> • Less inclination to follow gaze • Decline in eye fixation • Less social communication skills • Less receptive and expressive speech • Less empathic concern • Lack of interest in play • Motor stereotypies • Repetitive manipulation of objects • Low rates of canonical babble • Low volubility
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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 warning signs. From this review, we were able to identify several main early warning signs of ASD (Table 2). Dawson & Bernier (2013), in a review of progress in the early detection and treatment of ASD, 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

infants for ASD (siblings of children who had already been diagnosed) at 12 and 18 months of age, Sacrey *et al.* (2018) identified that parents of autistic children are more likely to perceive early signs in high-risk children than clinicians. Bhat *et al.* (2014) 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. Early diagnosis and increased recognition, as demonstrated in prevalence rates, have significant implications for diagnostic and therapeutic services. This review describes the early warning signs of ASD in infants, and the dissemination of such information may aid 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 to recognize the 'red flags' for ASD, in order to ensure further specific investigation.

Conclusions

With increasing interest in identifying methods to detect ASD, there has been progress in establishing early warning signs. Early intervention is associated with significant gains in the child's cognitive and adaptive functioning. However, much remains to be investigated to achieve the goal of diagnosing ASD in all children before the age of 2 years. The information presented in this review may facilitate the early identification of ASD, and in turn, possibly improve the effectiveness of ASD therapeutic interventions.

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