The warning signs of autism spectrum disorder: a systematic review

Os sinais de alerta para o transtorno do espectro autista: uma revisão sistemática

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ABSTRACT

Autism Spectrum Disorder (ASD) combines a group of delays in neurocognitive development, which become more expressed before the age of three years old. Determining ASD characteristics in children for reliable diagnosis requires acknowledgement of the warning signs, which may manifest as restricted/repetitive patterns of behavior, interests in peculiar activities, and deficits in communication and social interaction. The aim of this study is to analyze and identify the most common warning signs in children with ASD in early childhood. A systematic review was conducted following PRISMA Statement directions with an online search in the following databases: SCOPUS, MEDLINE, Lilacs, Web of Science, ScienceDirect and SCIELO. The study motivation question used to guide the selected descriptors followed
PICo strategy. The eligibility criteria considered full text articles published between 2017 and 2022, in Portuguese or English language. After applying the inclusion and exclusion criteria, 43 articles were included in the review and submitted to a full reading analysis and data extraction. Finally, the analysis of the results possibilities the understanding of the main warning signs of ASD in children aged 0 to 6 years and with this it may help in the detection and possible early diagnosis by health professionals.

**Keywords:** Autism Spectrum Disorder, early diagnosis, ASD characteristics in children, warning signs.

**RESUMO**

O Transtorno do Espectro Autista (TEA) reúne um grupo de atrasos no desenvolvimento neurocognitivo, que se manifestam mais antes dos três anos de idade. A determinação das características do TEA em crianças para um diagnóstico confiável requer o reconhecimento dos sinais de alerta, que podem se manifestar como padrões de comportamento restritos/repetitivos, interesses em atividades peculiares e déficits na comunicação e interação social. O objetivo deste estudo é analisar e identificar os sinais de alerta mais comuns em crianças com TEA na primeira infância. Foi realizada uma revisão sistemática seguindo as instruções do PRISMA Statement com uma pesquisa online nas seguintes bases de dados: SCOPUS, MEDLINE, Lilacs, Web of Science, ScienceDirect e SCIELO. A questão de motivação do estudo utilizada para guiar os descritores selecionados seguiu a estratégia PICo. Os critérios de elegibilidade consideraram artigos em texto completo publicados entre 2017 e 2022, nos idiomas português ou inglês. Após a aplicação dos critérios de inclusão e exclusão, 43 artigos foram incluídos na revisão e submetidos à análise de leitura na íntegra e extração de dados. Por fim, a análise dos resultados possibilita a compreensão dos principais sinais de alerta do TEA em crianças de 0 a 6 anos e com isso pode auxiliar na detecção e possível diagnóstico precoce pelos profissionais de saúde.

**Palavras-chave:** Transtorno do Espectro do Autismo, diagnóstico precoce, características do TEA em crianças, sinais de aviso.

**1 INTRODUCTION**

According to the Diagnostic and Statistical Manual of Mental Disorders - DSM-5 - from American Psychiatric Association (2013)¹, Autism Spectrum Disorder (ASD) is the first diagnostic consideration for individuals with neurocognitive development delays. Individuals with ASD may present restricted/repetitive patterns of behavior, interests or activities and deficits in communication and social interaction. In addition to typical neurobiological changes, which become striking signs before three years old, the disorder is much more frequent in males.¹

ASD has shown exponential growth over the last few years. In 2012, the world's mean prevalence of the disorder was 62 for 10,000 children. On the other hand, the current numbers have risen from 100 to 10,000 infants, once people began to be more attentive to some signs
and consequently seek out health professionals’ assistance about their concerns. This fact has led to early diagnosis, which contributes to a better prognosis in developmental disorders.

The age of detection of ASD has been extensively explored by researchers in order to determine characteristics for a stable and reliable diagnosis, which still remains in the mean of 2 to 4 years of age. However, the world literature points to a variable diagnostic age group. Nevertheless, recent studies have pointed out the possibility of diagnostic stability for autism from 14 months on, which sets precedents for very early management.

Called as Warning Signs for Autism Spectrum Disorder (WSASD), some atypical behaviors observed in children may indicate possible alterations related to ASD and other neurodevelopmental disorders and should be early observed by professionals who are aware about child development marks. Knowledge about the presence of these signs enables a faster beginning of interventions, constituting a benefit for the patients.

Recognizing a warning sign is a first-level risk screening for ASD. In view of this fact, this systematic review aims to gather the best scientific evidence to analyze and identify the most prevalent warning signs in children with ASD in early childhood.

2 MATERIAL AND METHODS

This systematic review was initially registered at PROSPERO database under CRD number 42022355585 and followed the recommendations of the Reporting Preferred Items for Systematic Reviews and Meta-analyses (PRISMA).

This review was designed using an adaptation of the PICO strategy (P - Population; I - Interest; C - Context. Thus, P - Families with children; I - Warning signs of ASD in the 1st childhood (0-6 years) for early diagnosis; C - Context of family daily life; and the led question of the research was "What evidence is available about the Warning Signs of Autism Spectrum Disorder (WSASD), which can help the seek for an early diagnosis?"

The searches were conducted between January 2017 and June 2022, in the Portuguese and English language, into the SCOPUS, MEDLINE, Lilacs, Web of Science, ScienceDirect and SCIELO databases. Chart 01 presents the keywords regarded from Mesh Terms delimiting the search according to each database.
We included studies that reported early signs in children aged 0-6 years with Autism Spectrum Disorder or screened for it and involved the perspective of family members in the perception of these signs. Exclusion criteria included dissertations, theses, review articles, conference reports, congresses, book chapters, books, letters, erratum, experience reports and editorials.

For the selection of the studies identified in the databases, the PRISMA Statement® (Transparent Reporting of Systematic Reviews and Meta-analysis) checklist was used, which is structured in the stages of Identification, Screening and Inclusion. In the identification stage, duplicate records were removed using the free online available tool for systematic reviews Rayyan© from Qatar Computing Research Institute single version. For the later steps, titles and abstracts were read by two independent reviewers, with the blinding tool activated on the Rayyan platform.

The publications evaluated for eligibility were fully read to define their inclusion or exclusion. For the management of references, the Mendeley application was used.

The studies selected for complete reading had their methodologies and results analyzed in detail in order to avoid the occurrence of "distorted results", "confusions" and "random occurrence". For each study value determining process, the following questions were answered: "Were the results biased?"; "Are there confounding or distorting factors present or lack of standardization among the study participants?" and "Is there a possibility that the results have arisen by chance?". "YES" and "NO" answers were given. If the answers were NO to the three questions, the research was considered reliable with low risk of bias.

The evidence level was determined using the GRADE (Grading of Recommendations Assessment, Development and Evolution) which is based on a subjective confidence demonstrated by the authors to the readers. Therefore, it could grade the quality of evidence.
and the strength of the recommendations. Grade has four levels of evidence: very low, low, moderate and high that considers issues such as risk of bias, inconsistency, inaccuracy and if publication bias is serious, very serious or not serious.

3 RESULTS

After searching the databases, following the previously mentioned PRISMA strategy, 452 records were found among the 6 databases considered, however after reading only 43 articles were part of the systematic review, as described in the Figure 01.

Figure 01 – Flowchart Schematic of the systematic review which includes the steps taken to collect all the studies included in the review.

Then, the subjective evaluation of the quality of the studies was applied based on the risk of bias, confounding factors and random occurrence. In this sense, 110 studies were considered of low methodological quality and classified as high risk of bias, the other 43 articles were classified as low risk of bias.

After data extraction based on the collected instructions, the studies included in the review presented the following profile: United States was the country of origin of the majority articles (13), followed by Italy (5) and China (3), however, there were no Brazilian studies that fit the pre-established clinical question. All articles were published in English.

Regarding the design of the analyzed studies, the vast majority consisted of a non-experimental design (67.4%), including cross-sectional, longitudinal, prospective and retrospective and observational cohort studies in general. Many experimental studies (30.2%) have also been obtained, which consist of testing the feasibility and/or efficacy of a screening tool for ASD in populations. A single qualitative study was also detected (2.3%).

Concerning the sample of the studies, the most observed form of selection was convenience (67.4%). On the other hand, randomized searches represented a minority of cases (13.9%).

The survey with lower N included 23 participants and the survey with higher N included 35,732 participants. Among the studies, five articles did not mention the N of the sample. The mean initial N among the articles was 2175.42 participants (median: 225), while the final was 532.59 participants (median:128).

Regarding the participants evaluated in the studies, as shown in Table 01, most were children with a previous diagnosis of ASD, but also reports obtained through screening tools for parents of children with previous diagnosis of ASD and children without previous diagnosis, submitted or not to screening warning signs for ASD.

<table>
<thead>
<tr>
<th>Participant</th>
<th>N</th>
<th>%</th>
<th>Gender of children of N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with previous diagnosis of ASD</td>
<td>22</td>
<td>51,1</td>
<td>Male</td>
<td>5548</td>
</tr>
<tr>
<td>Parents of children with previous diagnosis of ASD</td>
<td>10</td>
<td>23,2</td>
<td>Female</td>
<td>2374</td>
</tr>
<tr>
<td>Children without previous diagnosis</td>
<td>8</td>
<td>18,6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Authors
The age of the children evaluated in the studies ranged from 0 to 204 months, with intervals ranging from a mean of 12.5 months in the initial samples (median: 12 months; mode: 0 months) and in the final samples 58.97 months (median: 40 months; mode: 36 months). Regarding the gender of the children evaluated in the study, the high prevalence of male children was observed in comparison to the female sex among the participants included in the study, as shown in Table 01.

Considering the experimental studies included, the type of intervention most performed was the application of a screening tool for detection and ASD diagnosis. The Table 02 shows which checklist tool was used and their frequency in the included articles. However, a considerable number of articles did not specify which checklists were used.

<table>
<thead>
<tr>
<th>Checklists used</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism Diagnostic Observation Schedule (ADOS-2)</td>
<td>16</td>
<td>37,2%</td>
</tr>
<tr>
<td>Mullen Scales of Early Learning (MSEL)</td>
<td>8</td>
<td>18,6%</td>
</tr>
<tr>
<td>Vineland Adaptive Behavior Scales (VABS)</td>
<td>5</td>
<td>11,6%</td>
</tr>
<tr>
<td>Modified Checklist for Autism in Toddlers (M-CHAT)</td>
<td>3</td>
<td>6,98%</td>
</tr>
<tr>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition</td>
<td>3</td>
<td>6,98%</td>
</tr>
<tr>
<td>Unspecified</td>
<td>10</td>
<td>23,2%</td>
</tr>
</tbody>
</table>

Source: Authors

Regarding the results of the evaluated articles, the behavioral signs observed as a warning for diagnosis of autism in children aged 0-6 years were categorized and presented based on their prevalence in the articles, which is presented through Table 03.

<table>
<thead>
<tr>
<th>Warning Signs - ASD</th>
<th>Articles N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeated and stereotyped movements (shaking hands, running aimlessly, rotating objects)</td>
<td>43</td>
<td>100</td>
</tr>
<tr>
<td>Avoid eye contact // Social isolation</td>
<td>24</td>
<td>55,81</td>
</tr>
<tr>
<td>Speech disorder // Speech delay</td>
<td>14</td>
<td>32,56</td>
</tr>
<tr>
<td>Sensory hypersensitivity</td>
<td>13</td>
<td>30,23</td>
</tr>
<tr>
<td>Does not answer the name // Fixation by objects</td>
<td>12</td>
<td>27,91</td>
</tr>
<tr>
<td>Resistance to get out of the routine // Doesn't understand gestures // Does not make and understand facial expressions // Learning difficulties</td>
<td>10</td>
<td>23,26</td>
</tr>
</tbody>
</table>

Table 03 - Warning Signs for Autism Spectrum Disorder found in the results of the studies included in the review.
## DISCUSSION

The results of this review showed that most relevant articles for the theme were published by authors coming from the United States and Italy centers, which reflects the scarcity of financial resources for scientific research and improvements in health systems in underdeveloped or developing countries. It also means that in the medium and long term, in countries with the highest investment in research, there may be greater progress in screening and consequently in the diagnosis of ASD.

Moreover, the fact that most studies occur in countries with better social indicators can lead the scientific community to take as standard the typical development of children from these developed countries, generalizing indiscriminately patterns for children in a lower quality of life.

Regarding age, the included scientific literature reported that, although ASD diagnosis is given more safely at 2 years of age, this identification can happen even before 1 year of age, with this early detection strict relationship with the best prognosis. However, even though this possibility of early diagnosis was found several times throughout the review, the age of the participants in the final samples of the included studies was 36 months, which reveals the need to conduct investigations with an even younger population. It is possible that this difficulty of access to this even younger audience is related to parents’ inability in detecting signs by the of the children studied, since many tools used the description of parents to compute autism scores.

<table>
<thead>
<tr>
<th>Difficulty maintaining relationships</th>
<th>9</th>
<th>20.93</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not make social smile</td>
<td>8</td>
<td>18.6</td>
</tr>
<tr>
<td>Echolalia // Sensory hyposensitivity // Motor delay // Difficulty playing games and “pretending” interpretation</td>
<td>7</td>
<td>16.28</td>
</tr>
<tr>
<td>Shows no affection // Motor damage // Non-verbal communication regression // Difficulty keeping joint attention // Does not point</td>
<td>6</td>
<td>13.95</td>
</tr>
<tr>
<td>Does not imitate // Verbal communication stagnation and regression // Receptive language damage // Anger/Whining</td>
<td>5</td>
<td>11.63</td>
</tr>
<tr>
<td>Food selectivity // Sleep problems // Stereotyped speech // Attention deficit // Apathy // Preferring objects than people</td>
<td>4</td>
<td>9.3</td>
</tr>
<tr>
<td>Does not comply commands // Does not share objects</td>
<td>3</td>
<td>6.98</td>
</tr>
<tr>
<td>Low muscle tone // Does not follow someone pointing visually // Does not ask // Aggressiveness // Lack of danger sense // Impulsiveness // Difficulty starting and answering joint attention</td>
<td>2</td>
<td>4.65</td>
</tr>
<tr>
<td>Does not cry // Extreme attachment to someone // Hyperactivity/Hipoactivity // Does not like sounds // Restlessness</td>
<td>1</td>
<td>2.33</td>
</tr>
</tbody>
</table>

Source: Authors
This difficulty occurs because the parents, unlike health professionals and educators, do not have contact over a long time with children, making it difficult to comparatively analyze what is or is not expected for a given age group. Moreover, even at a young age, infants express characteristic landmarks of each stage of their development, which are more visible in social interaction with other children. Thus, signs of autism could happen with more facility in a non-domestic environment, such as preschool, not favoring the analysis of parents and guardians. 12

Another important variable analyzed was the gender of the study participants. The results revealed male prevalence, which may reveal an underreporting of early signs of autism in girls, since the manifestations of the disorder are different between the sexes 13, and only recently these gender differences were questioned, making most of the screening tools currently used not sensitive for autism detection in female children, which may be going unnoticed by current studies. 12

Regarding the types of studies included in this review, it is observed that screening studies were often recurrent of which tools were used to quantify early signs of alertness to autism and, through comparison between children, analyze the intensity with which these signs are presented by each child. This restricted to pre-established tools analysis caused poor mentioning about certain signs because they were not frequent in these traditional tools, such as sensory hyperreactivity, which was more commonly reported in observational studies with caregivers or educators. 14 In this context of possible excessive standardization of screening tools, many studies have investigated whether some checklists tools could be used in not samples different from the originally designed for it, without prejudice to the annulment of the individuality of each population studied. A successful example was the use in Spanish children of a tool originally designed for the Anglo-Saxon people. 15

The research in question aimed to identify in the literature what were the warning signs for a possible diagnosis of ASD in early childhood. A diverse type of signs, from behavioral to socio-communication/language and learning signs were observed, demonstrating the versatility of the studies included. However, signs relevant to non-verbal communication, such as lack of eye contact, not understanding gestures, non-responsiveness when calling by name and changes in joint attention skills, etc., were more related to early diagnosis 15,16,17, which aligns with the results obtained, considering the average age found, which also report these signs frequently. On the other hand, signs related to verbal communication such as speech disorders or delays and difficulties in social interaction with other people are more identified in a late diagnosis 16,18, which can be explained by the expectation created around the older child, who already probably attends places such as schools and day care centers where these activities are expected.
Motor and behavioral signs, excepted repetitive and stereotyped movement, were less observed. Although they do not present correlation with early or late diagnosis patterns, these types of signs are more refined for detection, having been more related to the perception of a specialist, since they are elucidated in behaviors such as hypo or hypersensitivity, and others. 19,20

In relation to behavior patterns, factors such as food selectivity, social isolation, fixation by objects and repetitive movements with these objects and with one’s own body are considered more subjective and likely cultural patterns analysis, which diverge between countries. 17,21,22 However, the most prevalent finding in this study was related to stereotyped and repetitive movement, which suggests an increase in knowledge related to behavior patterns and developmental marks by parents and guardians.

It is also worth mentioning that most of the studies presented selection biases, related to the place of collection, the absence of sampling and/or the absence of randomization. The existence of these elements compromises in part the safety and reliability of the results, such as a study in which the physicians who conducted the research asked parents and guardians of children during a consultation if they agreed to participate in an experimental analysis. 15 In this sense, it is likely that there may be interferences of measurement and execution in the studies due to the proximity between examiner and sample, and a possible solution is the use of double-blind methodologies, which did not exist among the records included in this review. In addition, selection biases lead an incomplete population, excluding people who could not access the research centers. In cases where samples were collected from particular hospitals, health insurance and even reference centers, it increases a lot. The presence of memory bias was also remarkable, since some studies questioned the presentation of signs in children many years after diagnosis; and the presence of measurement bias, such as the study in which IQ test was used to compare groups of children with and without the diagnosis of ASD, ignoring the individual differences present in each group.

5 CONCLUSION

This systematic review was able to categorize the main behavioral signs observed as a warning for the diagnosis of autism in children aged 0-6 years and with this it may help in the detection and possible early diagnosis by health professionals.

Strengths of this research highlight the innovation of the theme and the methodology applied, which, because of the systematic design, presents a high level of scientific evidence.
Moreover, the ASD differential diagnosis approach will also be useful in combating the stigma and standardization that often accompanies the diagnosis process.
REFERENCES


