Türk Pediatri Arşivi
Turkish Archives of Pediatrics

Review / Derleme

Is it autism? Some suggestions for pediatricians

Otizm mi? Pediatristler için bazı öneriler

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Cite this article as: Posar A, Visconti P. Is it autism? Some suggestions for pediatricians. Turk Pediatri Ars 2020; 55(3): 229–35.

Abstract

An early diagnosis of autism spectrum disorder, leading to a timely enabling intervention, is associated with a better long-term prognosis and allows the early detection of any medical comorbidities that are sometimes found in individuals with autism. It is, therefore, an important challenge to begin the diagnostic procedure of these children as soon as possible. Nowadays, much progress has been made in this respect compared with the past, but considerable work remains. A fundamental role in starting a correct and timely diagnostic procedure is obviously played by the pediatrician. Today, many tools are available for the early screening of autism in the general population, but unfortunately, their real effectiveness has yet to be established. In this narrative review, we address the topic of the early diagnosis of autism spectrum disorder, emphasizing, in particular, those that are now considered the first warning signs. We list a few of the most important signs to consider when a child aged around 18 months presents to a pediatrician, subdivided into three subgroups: social-communication skills; patterns of behavior, interests, or activities; and sensory behaviors and reactivity/temperament. We deal separately with the possible presence of slight motor signs, which can also go unnoticed, but probably they should be considered as very early signs appearing even before social-communication deficits.

Keywords: Autism spectrum disorder, diagnosis, early signs, neurodevelopmental disorders, screening

Öz

Otizm spektrum bozukluğunun zamanında müdahaleye olanak tanıyan erken tanısı, uzun vadede daha iyi bir prognozla ilişkili olup, bazen otizmli kişilerde bulunan komorbiditelerin erken saptanmasına da olanak tanır. Bu nedenle, bu çocuklarda tanısal prosedürün mümkün olduğu kadar erken başlatılması önemli bir sorundur. Geçmişle kıyaslandığında, günümüzde bu açıdan oldukça fazla ilerleme kaydedilmiştir, ama bu konuda halen önemli ölçüde çaba sarfetmek gerekmektedir. Tanısal prosedürün doğru şekilde ve zamanında başlatılması açısından temel rol açık bir şekilde pediatristlere düşmektedir. Günümüzde, genel popülasyonda otizmin erken taraması için birçok araç vardır, ama maalesef bunların gerçek etkinliği henüz belirlenmemiştir. Bu anlatısal derlemede, otizm spektrum bozukluğunun erken tanısı konusunu ele almaktayız ve özellikle ilk uyarı işaretleri olarak kabul edilen bulgulara odaklanmaktayız. Yaşı 18 ay civarında olan bir çocuk pediatriste muayeneye geldiğinde göz önüne alınması gereken en önemli bulgulardan bazılarını üç alt grup şeklinde sıralıyoruz: sosyal-iletişim becerileri; davranış modelleri, ilgi ya da aktiviteler; ve duyusal davranışlar ve tepkisellik/mizaç. Gözden kaçabilecek olan hafif motor bulguların olası varlığı konusunu ayrıca ele alıyoruz. Ancak, bu bulgular muhtemelen sosyal-iletişim kusurlarından bile önce ortaya çıkan çok erken bulgular olarak kabul edilmelidir.

Anahtar sözcükler: Erken bulgular, nörogelişimsel bozukluklar, otizm spektrum bozukluğu, tanı, tarama

Introduction

Autism spectrum disorder (ASD) is characterized by an early-onset, severe impairment of social-communication skills, as well as by repetitive interests and activities (1). In recent decades, the prevalence of ASD has increased dramatically, reaching 16.8 per 1000 8-year-old children, according to a multicenter study in the United States of America (2). This increase is partly apparent due to improved ASD knowledge, and partly real, probably due to multiple environmental factors adding up to the genetic factors that play a predominant role in the etiopathogenesis of ASD, as suggested for example by the persistent prevalence of affected males compared with females (3).

An early diagnosis of ASD, leading to a timely enabling intervention, is associated with a better long-term prognosis (4) and allows the early detection of any medical co-

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Received/Geliş Tarihi: 13.09.2019 **Accepted/Kabul Tarihi:** 17.01.2020

DOI: 10.14744/TurkPediatriArs.2020.59862

morbidities that are sometimes found in individuals with autism (5). It is, therefore, an important challenge to begin the diagnostic procedure of these children as soon as possible. Nowadays, significant progress has been made in this respect compared with the past, but much work remains. In fact, also today, it can happen that less severe cases of ASD, especially at younger ages, are confused with language disorders (1). It is still possible that a parent worried about the development of his/her child hears reassuring phrases like: "Don't worry, you'll see that he/she will speak, there are children who speak first and others who do it later...". In some cases of language delay, the simple wait is followed by a prompt recovery, in others, especially when language impairment is only one aspect of the developmental problem, the waiting leads to an unjustified and potentially harmful diagnostic delay. A fundamental role in starting a correct and timely diagnostic procedure is played by the pediatrician. It is the pediatrician who the parents, worried about the development of their child, usually turn to for the first time. Also, it is the pediatrician who first has to assess the initial suspicion of ASD, starting the diagnostic procedure if necessary.

In this narrative review, we address the topic of the early diagnosis of ASD, emphasizing, in particular, those that are now considered the first warning signs, based on literature data and our personal experience. We considered the most relevant articles published about this topic from January 2008 to August 2019, available on PubMed (United States National Library of Medicine), achieved using the following combinations of terms: autism spectrum disorder and early diagnosis, autism spectrum disorder and early symptoms, autism spectrum disorder and early signs, and autism spectrum disorder and screening.

What meaning could a language delay have?

Language delay is one of the most frequent early warning signs reported by parents. In these cases, one of the first questions to be asked is trivial but at the same time crucial: has the child a clinically significant language delay that requires him/her to undertake a diagnostic procedure or is his/her language development still within the limits of the wide variability that can be normally present from individual to individual? There are enough precise criteria to answer this question. For example, for the Italian language, the delay is considered significant if at the age of 18 months the child does not yet pronounce isolated words or if at 30 months he/she does not yet pronounce two words together. If the child has a clinically significant language delay, however, this is only a very non-specific sign, as it can be the prelude to many situations extremely different from one another in terms of etiopathogenesis, features, severity, prognosis and treatment. It may be a simple language delay, for which full recovery is the rule or it may be the first sign of a developmental language disorder, which will need a speech therapy intervention and whose prognosis is not always favorable. It may be the consequence of early and severe hearing loss, which can be caused by various (genetic or acquired) etiologic factors. It may be the first and most marked sign of a global developmental delay, in which social-communication skills are delayed but not atypical, and that often represents the prelude to a more or less severe intellectual disability (1). Alternatively, in rare cases, it may be the first sign of a neurodegenerative disease such as neuronal ceroid lipofuscinosis type 2, before the appearance of clear signs of cognitive, motor and visual deterioration (6). Finally, it may be the first sign (or one of the first signs) of ASD. What are the possible associated signals that can suggest this latter type of diagnosis in an infant? We will try to answer this question by summarizing the vast and variegated literature findings available on the subject and focussing on the fundamental aspects that can particularly interest the pediatrician in his/her daily clinical practice.

How does ASD begin?

Autism spectrum disorder does not begin in the same way in all children. At least four onset patterns have been identified. In many cases, social-communication abnormalities appear early, already during the first year or so of life: this is the 'early-onset' pattern. In other cases, autistic signs appear later, during the second year of life, mostly between 16 and 20 months, associated with a loss of acquired social-communication skills: this is 'regressive autism.' These two are the longest and best known ASD onset patterns, as well as the most frequent (especially the first one), but they are not the only ones. There is another group of children who show an onset pattern with mixed features, both early delays and later losses of social-communication skills. Further, some children display an onset pattern of a 'developmental plateau,' characterized early by a normal social development or by non-specific abnormalities (including eating and sleeping problems), followed by a failure to acquire new social-communication skills (7). Moreover, other onset patterns have also been described: the typical pattern of the so-called childhood disintegrative disorder, recognized as an independent diagnostic category in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, 1994) in the context of pervasive developmental disorders (but no longer in the DSM-5, 2013) (1), characterized by an initial period of at least 2 years of typical development, followed by a loss of acquired skills (not only in the social-communication domain) and the onset of autistic symptomatology (8). Although childhood disintegrative disorder is not recognized as such in the DSM-5 (1), some rare cases of ASD present a clinical course of this type.

From an etiopathogenetic perspective, it should be kept in mind that especially in ASD cases presenting a more or less early regression at onset, underlying neurobiologic conditions should be excluded, including several neurometabolic diseases (e.g. organic acidurias) and an electroencephalographic picture of subcontinuous/continuous paroxysmal abnormalities during sleep (even in the absence of seizures) (9), also because in the latter case a drug therapy can be effective. However, in most cases with regression at onset, it is not possible to find a clear etiology. Furthermore, the presence of regression at onset seems to be associated with a worse long-term outcome, but this finding is not supported by all the studies mentioned in the literature on the subject (10).

Never underestimate what the parents report!

Faced with the concerns of parents regarding the development of their child, any physician, including pediatricians, of course, would like to have valid arguments to reassure those in front of them. This situation can sometimes lead to an unintended underestimation of some warning signs. However, parents should always be listened to very carefully because in most cases their concerns have a foundation. Already in 1994, the American Academy of Pediatrics emphasized the importance of careful attention to the observations and concerns of parents about their child's development (11). As pointed out by Filipek et al. (12) as early as in 2000, the parental concerns about developmental issues have both high sensitivity (75–83%) and high specificity (79–81%) in detecting the presence of global developmental deficits, so they should always be seriously considered. It should never be forgotten that, although parents may misrepresent the behavior of their children due to their inevitable emotional involvement, they have the opportunity to catch warning signs during daily life that are is impossible to detect during a visit, however accurate.

When, on the contrary, parents do not appear to be aware of the problem of their child's development, the pediatrician can play an equally important role leading them to a closer observation of the child's skills and behaviors and thus enabling them to realize the problem (11). This last situation, although less frequent, is not at all rare even today.

In both situations mentioned above, a fundamental function of the pediatrician is to promptly start the diagnostic procedure aimed at confirming or eliminating the suspicion of a developmental disorder, including an ASD. In Italy, this diagnostic procedure is conducted by the child neuropsychiatrist, usually supported by the psychologist.

Screening tests for ASD

Today, various standardized ASD screening tests have the advantage of reducing the margin of arbitrariness in the clinical judgment of the child's behavior. There are two types of tests for ASD early screening, respectively Level 1 and Level 2 screeners. Level 1 autism screening instruments are used at a general population level, e.g. to all children coming to a pediatrician's office, which therefore constitute 'unselected' or 'low-risk' samples. These tools are usually used by the pediatrician. Examples of Level 1 ASD screening instruments are the First-Year Inventory, Infant-Toddler Checklist, Pervasive Developmental Disorders Screening Test, Checklist for Early Signs of Developmental Disorders, and the Early Screen for Autism Traits (13). Level 2 ASD screening instruments are used to distinguish ASD among children considered at high risk for developmental disabilities, who include children who failed a Level 1 ASD screening instrument; the ASD children's younger siblings, in which ASD prevalence is significantly higher than the general population; and children with a congenital or genetic condition that is associated with a higher risk for ASD. These tools are usually used by clinicians experienced in developmental disorders (in Italy they are child neuropsychiatrists and psychologists). Examples of Level 2 ASD screening instruments include the Autism Observation Scale for Infants, Screening Test for Autism in Two-Year-Olds, Parent Observation of Early Markers, and Autism Detection in Early Childhood (13).

In Italy, still today one of the ASD screening tools most used by pediatricians is the CHAT (CHecklist for Autism in Toddlers), which historically represents the first tool of Level 1 for autism screening, suitable for children aged 18 months (14). CHAT includes nine questions for parents and five items that depend on the direct semi-structured observation of the child's behavior by the pediatrician. Depending on in which and how many items the child has a failure, the result is considered indicative of a high, medium or low risk of autism. This is an easy and quick administration tool, but it has a certain margin of error, showing a high specificity (the presence of few false positives), but a low sensitivity (the presence of many false negatives) (15). Therefore, a modified version of CHAT was developed and came into use, the Modified Checklist for Autism in Toddlers (M-CHAT) (16), a 23-item checklist for parents of children aged 18-24 months, which provides a more complete account of the child's skills and behaviors than CHAT, also showing an increased sensitivity. To increase the M-CHAT specificity (due to an excessive number of false positives), the authors suggested making a structured telephone follow-up interview with the parents of children who failed the M-CHAT (16). The Q-CHAT (where "Q"

stands for "quantitative"), a 25-item checklist for parents of children aged 18–24 months, represents a further step forward because it considers both the presence and the frequency of atypical behaviors (17), but the real efficacy of this tool has not yet been established.

For the purpose of a very early diagnosis, some screening tools have been built for children, even those younger than 18 months. Here, we mention the First-Year Inventory (FYI), a 63-item checklist for parents of children aged 12 months that investigates the frequency and mode of reaction of the child to a series of situations: 46 items are characterized by a scale that includes four possible answers: "never", "seldom", "sometimes", and "often"; other 14 are multiple-choice items; further, there is one item about the sound production of the child; and finally there are two open-ended items about the concerns regarding child development and the possible presence of unusual physical or medical features of the child, respectively. The FYI items cover the social-communication domain and the sensory-regulatory domain, respectively (18, 19). Unfortunately, the sensitivity of FYI seems to be too low for an ASD screening instrument and the efficacy of this tool is yet to be established.

Based on their systematic review about ASD early screening instruments, Towle and Patrick concluded that the evidence base of these early screeners is not strong enough and therefore their development requires further improvements. From a clinical point of view, the authors recommended continuing careful ASD surveillance from the first year of life onward, but using the screening instruments only for children considered at high risk for ASD rather than for the general population (13).

Some practical suggestions for pediatricians

Regardless of the results of standardized ASD screening tests, which as we have seen are not infallible tools, several important clinical features must be taken into account when a child aged around 18 months first comes to the pediatrician with the suspicion of ASD. In Table 1, we list some of these features, subdivided into three subgroups, related respectively to the following domains: social-communication skills; patterns of behavior, interests, or activities; and sensory behaviors and reactivity/temperament. This subdivision is the result of a way of interpreting clinical data that could be further improved. The signs listed in Table 1 summarize those taken into consideration by the tests most used for early autism screening (13). The possible presence of the various signs listed in Table 1 should be investigated both through the interview with the parents and through the direct observation of the child's behavior. In fact, what parents report may be less objective than what the examiner is able to see directly, but provides data about the child's daily life in the environments in which he/she lives. At the same time, direct observation of the child's behavior can highlight something that parents are not yet aware of: this is especially true if the child is an only child and therefore it is more difficult for parents to have terms of comparison to evaluate his/her development. Based on literature data, the signs that better distinguish between ASD, developmental delay, and typical development in infants (even before the appearance of a speech impairment) concern the following behaviors, which are related to social-communication skills: orienting to name; looking at the faces of other persons; joint attention, that is when the child shares focus with someone else on the same object; sharing of affects; and imitation (7). An impairment of at least some of these behaviors should inevitably lead to a further diagnostic investigation, which should be carried out by a physician experienced in developmental disorders in order to confirm (or eliminate) the diagnosis of ASD as soon as possible.

The early ASD signs that we have listed, if present, should be evaluated and interpreted based on the clinical context of the individual child. If they recur in the absence of other severe neurologic signs, ASD is highly suspected. If instead they recur in a child in association with clear neurologic signs, such as severe motor delay, tetraparesis, marked microcrania or macrocrania, aposturality, severe hypotonia, it is likely to hypothesize the presence of encephalopathy causing a global developmental delay, which often represents the prelude to intellectual disability in the following years.

Pay attention to motor development too!

In addition to the classically recognized early signs of ASD mentioned in Table 1, attention should also be paid to the possible presence of slight motor signs, which have, particularly in the last years, started to be properly valued. These signs can also go unnoticed, but probably they should be considered as very early as they may appear even before social-communication deficits. Motor impairments could represent the first signs of atypical development and they may contribute to the social-communication abnormalities in ASD, due to the critical role of the motor system for engaging with the environment (20). According to several studies, already in the first year of life, there may be a delay in the acquisition of both gross and fine motor skills (21–23). Note that, as suggested by numerous literature data (24, 25), the development of motor skills may be related to the development of both verbal and non-verbal communication skills, which are impaired by definition in ASD. However, in addition to

Table 1. possible early signs of autism spectrum disorder in children aged around 18 months, subdivided into three subgroups

Social-communication skills	Patterns of behavior, interests, or activities	Sensory behaviors and reactivity/temperament
Impaired eye contact	Stereotyped movements and behaviors	Dislikes touching and cuddling
No reciprocal social smile	Unusual postures	Overly sensitive to touch
Lack of understandable and appropriate emotions	Overreaction to change or other events	Ignores loud or startling sounds
No differential response to facial emotion	Enjoys staring at bright lights or making objects spin over and over	Spits out certain textures of foods
Does not look when their name is called	Gets stuck on playing with a part of a toy	Presses against things
Does not follow/point to object	Stares at fingers while wiggling them	Enjoys rubbing or scratching objects
Lack of anticipatory posture for being picked up	Lack of functional object use	Enjoys kicking feet over and over
Does not speak words for attention or help	Difficulty in shifting attention from one event to another	Altered reaction to pain
Does not share interest and enjoyment	Does not explore new toys and environments	Fearful of objects that move or make noise
Does not point to request or to share interests	Atypical use of words	Altered sleep-wake and feeding patterns
Does not coordinate gaze and point	No pretend play	Lack of mood stability
Does not point in response to a question		Not consolable when hurt
Does not respond to verbal command		Altered activity level
Does not show objects for social attention		
Does not initiate joint attention		
Does not look at the face of parents for comfort		
Does not imitate		
Does not take turns		
Does not play with peers		
Lack of attachment to parents		
Does not recognize parents' voice		

a delay in motor development, which is relatively easy to diagnose in itself, some peculiarities at the motor level, that are more difficult to detect in the daily clinical practice, have been reported very early in children with autism. For example, as suggested by Esposito et al. (26), during the first 5 months of life, children with ASD may show significantly less both static and dynamic symmetry during lying. According to literature data, as reported by Purpura et al. (27), an increased frequency of repetitive movements could be considered as an early sign of ASD, from 12 months of life. Also, Purpura et al. (27) retrospectively found in infants with ASD aged 6 to 12 months a higher frequency and duration of bilateral repetitive movements with arms, hands, fingers, and lower limbs. They suggested that especially repetitive movements with hands and fingers could be considered highly sensitive target behaviors in ASD early screening instruments. Also, some early patterns of repetitive movements may prevail in infants with ASD. For example, Loh et al. (28) found that "arm waving" at 12 and 18 months of life was more frequent in infants with ASD. Morgan et al. (29) found in infants with ASD aged 18 to 24 months a higher rate as well as a larger inventory of so-called repetitive and stereotyped movements both with objects (swiping, rubbing/squeezing, rolling/knocking over, rocking/flipping, spinning/wobbling, collecting, moving/placing, lining up/stacking, and clutching) and without objects (flapping, rubbing body, patting body, and stiffening). Instead, in the first few months of life, Phagava et al. (30) found a lower variation and a higher monotony in spontaneous motor activity of children with ASD.

Conclusions

A strong suspicion of ASD has reason to exist when an infant with a verbal language delay has an associated impairment of social-communication skills, especially in the following behaviors: orienting to name, looking at the faces of other persons, joint attention, sharing of affects, and imitation (7). Due consideration should be also given to the possible presence of other signs that are part of the atypical patterns of behavior, interests, or activities and sensory abnormalities. Even the possible presence of slight motor signs must be taken into account. A suspicion of this kind inevitably entails sending children to a physician experienced in developmental disorders for correct diagnostic classification. All this, regardless of the

results of the ASD early screening tests, which, although they can be very useful for a first diagnostic approach, have a margin of error in terms of sensitivity and specificity that should not be underestimated, and are not always easily feasible in the daily clinical practice. We stress once again the fundamental role in starting a correct diagnostic procedure played by the pediatrician.

Acknowledgment: The authors would like to thank Cecilia Baroncini for help in editing the text.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.P., P.V.; Design - A.P.; Literature Review - A.P.; Writing - A.P.; Critical Review - A.P., P.V.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Teşekkür: Metni düzenlemeye yardım ettiği için Cecilia Baroncini'ye teşekkür ediyoruz.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - A.P., P.V.; Tasarım - A.P.; Literatür Taraması - A.P.; Yazıyı Yazan - A.P.; Eleştirel İnceleme - A.P., P.V.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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