

Early Detection and Intervention of Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder typically identified in early toddlerhood. Both retrospective and prospective follow up studies of high risk infants reveal early risk signs of ASD at 12-24 months of age. The most frequently replicated early signs of ASD are atypical visual tracking and coordination, lack of social reciprocity, abnormal social communication and unusual patterns of manipulating objects, atypical sensory exploration, expressed as uncoordinated eye contact, unresponsiveness to naming, lack of social smile, delayed development of nonverbal communication and joint attention, less sharing interest, and unusually repetitive use of objects. Early intervention, before 2 years of age, appears to change the underlying developmental trajectories of the brain in individuals with ASD. In this review, the early risk signs of ASD in infancy and toddlerhood, along with early intervention and their implications, are discussed.

Key Words: Autism Spectrum Disorder; Prodromal Symptoms; Early Medical Intervention

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by persistent deficits in social communication and social interaction, as well as by restricted, repetitive patterns of behavior, interests, or activities from early childhood [1]. The prevalence of ASD has tended to increase over the last few decades, from 4-10/10,000 in the early 1990s, 20-116/10,000 after the year 2000, to 1 in 68, based on a recent report [2]. Although the prevalence rate differs among nations depending on the research methodologies used, the incremental trend is regarded as a global phenomenon. As the prevalence may accumulate due to the chronic nature of the disease, the cost to society increases markedly, up to 137 billion USD per year in 2012 [3].

In the previous version of the standard diagnostic criteria (DSM-IV-TR), autistic disorder should manifest before 36 months of age, but the specification of the age of onset has been removed from the diagnostic criteria in the DSM-5, because the age of onset is not easily specified in some high-functioning individuals with ASD.

However, ASD is still regarded as manifesting by toddlerhood, typically between 12 and 24 months of age, and some of the “red flag” signs can be observed even before 12 months [4]. Early identification and intervention for ASD is becoming a public health issue, considering the high prevalence and high cost to the community. This review aims to summarize current studies on the early identification of ASD, evidence-based treatment for ASD in infants and toddlers, and the clinical implications and further applications of such interventions.

WHEN & HOW CAN WE CATCH THE EARLY SIGNS?

ASD is the end-product of altered gene-environmental interaction; when a fetus with vulnerable genes is exposed to environmental risk factors, such as intrauterine infections, toxins, advanced maternal/paternal age, air pollution, organophosphates, puerperal complications, or other idiopathic hazardous factors, gene-environmental interactions or epigenetic modification of the expression of risk genes can occur. These influence the neurobiological

trajectories of the fetus in terms of neuronal organization, synapse formation and development, cortical network development, and brain growth. The changes in brain function can then manifest as the specific symptomatology of ASD, including communication, social, and behavioral deficits after birth [5].

Even though the brain dysfunction starts before birth, there is a lag between birth and when red flag signs can be observed. Many parents report that they were unable to detect their children's "different" behavior until toddlerhood or later. Hypothetically, the reasons for this "delay in notice" can be explained as follows. First, certain atypical behaviors are present from the very early years, but those are not observed clearly enough to distinguish its typicality. This notion is particularly appropriate for the explicit social and communicative behaviors necessary for interacting with other people. Second, brain changes are cumulative, and the brain may attempt to compensate for the changes, but if these compensatory processes are insufficient to overcome the accumulated dysfunction, the behavioral symptoms may manifest [6].

1. Retrospective studies

Some studies have attempted to optimize the *timing* and *behavioral repertoire* for identification of the earliest signs of ASD. The first era of such studies was devoted to retrospective analyses of home videotapes of infants. For example, Adrien et al. compared home videotapes of children with and without ASD before and after their 1st birthday, using the Infant Behavioral Summarized Evaluation Scale. The children with ASD ignored other people, preferred being alone, and made no eye contact in a socialization context [7]. They showed a lack of vocal communication, lack of appropriate facial expressions, no social smile, a lack of gestures, and no or poor imitation of others, as compared to typically developing children. Using similar methodology, Osterling & Dawson identified 4 key behaviors that could differentiate children with and without ASD with 90% accuracy: low frequency of looking at others (including eye contact), low frequency of orienting to name call (at 8 months), absence of showing objects, and a lack of pointing. Repetitive motor actions could also differentiate ASD and intellectual disability [8]. The age of identification has been reduced, as many studies have been performed, as deficits in social smiling and eye contact at 6 months are significant indicators of the development of ASD [9].

Retrospective parental reports also provided similar insights into the early signs of ASD in the 1st year of life. In a retrospective

parental interview using the First Year Inventory, Baranek et al. [10] suggested that markers differentiating ASD from developmental delay include markers involving social attention and communication, including orienting to name call, following pointing, social orientation, interest in their age, social smiling, facial expression, playing peek-a-boo, and demanding attention from the caregiver. Imitation, expressive communication, sensory processing, regulatory patterns, reactivity, and repetitive behaviors were found to be nonspecific signs, which can only differentiate ASD and developmental delay from typical development.

The first retrospective studies set the first milestones for early identification, emphasizing 1) the existence of early risk markers around 1 year of age and 2) the value of deficits in social communication and attention as early signs of ASD. However, these studies were limited by generalization, such as sampling biases and a lack of standardized social situations in home videos, incorrect recall, recall biases, distortion of events, biases related to parental alertness in recognizing behaviors, socioeconomic status, personality, intelligence, and parental mental health.

2. Prospective studies

To compensate for the limitations of the retrospective studies, prospective infant follow-up studies have been performed in the past decade. Those studies focused on high-risk infants, i.e., the infants believed to have a higher chance of developing ASD than the general population. The first such subjects studied were neonates who had been cared for in neonatal intensive care units (NICUs) due to neonatal or obstetric causes. As the published prevalence of ASD among these high-risk infants is 1.3-3.2%, it may be debatable whether they actually have significantly higher risk of developing ASD than typical infants. However, birth complications, low birth weight, or prematurity have consistently been replicated as risk factors for ASD, and infants who have been hospitalized in NICUs are candidates for prospective surveillance of the effectiveness of follow-up studies.

The second, more feasible and reliable subjects for prospective studies are infants who are the younger siblings of children diagnosed with ASD. The sibling concordance rate is high, up to 10%, and there is an increased recurrence risk of ASD in siblings. A recent, large prospective follow-up study explored 664 younger siblings who have elder siblings diagnosed with ASD. The recurrence rate of ASD in the siblings was as high as 18.4%, and the risk was even higher if the sibling was male or from multiplex families in-

cluding two or more older siblings with ASD [11]. Typically, babies were followed up in parallel with low-risk infants who did not have any older siblings with ASD, from 6 months of age up to 3 years, with specific attention to the first 18-24 months of development. Such a design is desirable, as it avoids the recall bias of the parents, provides multiple time points for grasping very early signs from the youngest age, and makes it possible to apply experimental measures as well as rating scales and observational instruments. Moreover, from a clinical perspective, this design allows early intervention if the subject shows significant red flag signs.

A few population-based prospective follow-up studies have also been performed. Such a research design is ideal for following up high risk behaviors in the general population, but not in those with high risk, who share genetic vulnerabilities and possible broad autism phenotypes, and may allow identification of red flag signs without the influence of genetic traits. However, such a design requires a very large cohort, time, and personnel, and more importantly, a consolidated system in the community for registering and following up subjects consistently and reliably.

EARLY RISK SIGNS FROM PROSPECTIVE STUDIES: CONSENSUS

In the high-risk neonate studies, the most consistently proposed early markers are signs of abnormal development of the neutrally-mediated visual tracking and attention systems, including atypical attention to stimuli, impaired ability to disengage, and a lack of typical developmental transitions in the visual system [12-14]. In a recent large scale study involving 2,197 NICU graduates with a 1.3% prevalence of ASD, the infants who developed ASD showed continued visual preference for more stimulation at 4 months of age, persistent neurobehavioral abnormalities, and higher incidences of asymmetric visual tracking than controls. The study emphasized that infants with ASD showed declining mental and motor performance by 7 to 10 months, similar to children with severe brain dysfunction [15]. Those findings implicate that dysfunction in visual and motor development may be very early risk signs of future social-communication abnormalities.

Atypical visual exploration was replicated as a very early marker in infant sibling studies; unusual sensory-oriented behaviors, such as intense visual inspection of objects at 12 months, were also suggested as an early risk marker of ASD in several case-control studies and case series studies [16,17]. Additionally, accumulating evi-

dence indicates that atypical face processing, as manifested by eye gaze and visual engagement patterns at age 6 to 10 months, are risk signs of future ASD [18,19]. This atypicality in visual tracking and eye gaze is consistently reported, but it is limited by its relative value compared to typically developing children. This behavior also varies among individuals, and it is virtually impossible to set a threshold that can differentiate between the two groups. Markers with more clinical applicability would be social-communication behaviors, which tend to be accumulated between 12 and 24 months.

In the infant sibling studies using the Autism Observation Scale for Infants (AOSI), infants diagnosed with ASD ("High-Risk ASD infants; HR ASD infants) generally did not show significantly different behavioral indices or showed only a slight difference in social communication as compared to infants who were not diagnosed with ASD ("High-Risk non-ASD Infants"; HR non-ASD infants) at 6 months. However, these differences are more prominent at 12-14 months, particularly in terms of reduced social engagement, social orienting, shared enjoyment, and non-verbal communication [20-22]. Decreased sharing of positive affect and the use of gesture in communication are also proposed as strong markers around 12-18 months of age [23-26].

Joint attention is one of the important developmental achievements in toddlerhood. It involves using gestures and gaze alteration to share attention to interesting objects or events with other people, within the continuum of intentional communication. In typically developing children, gaze alteration appears in all children at 15 months, and communicative pointing emerges in 80% of children by 18 months and all typically developing children by 24 months [27-29]. It includes two inter-related behaviors: response to joint attention and initiation of joint attention. Thus, lack of, or delayed development of joint attention (both initiation and response) by 14-18 months is a very strong predictor of the future development of ASD [26,30-32]. Furthermore, the rate of growth of weighted triadic communication has been reported to predict the later degree of social impairment in individuals diagnosed with ASD [32].

In terms of repetitive behavior and restricted interests, specific behavioral items that are associated with ASD risk tend to be relatively inconsistent as compared to items in the social-communication domain. One of the representative studies, including 30 HR ASD infants (vs 75 HR non-ASD and 53 Low Risk infants) showed that an increased rate of stereotyped motor mannerisms may rep-

resent an early behavioral marker of ASD at 12 months, while the manner of manipulating objects could not differentiate HR ASD from non-ASD infants [33]. As there are other studies showing different play patterns between these groups, this area should be explored further to reach a consensus.

Overall, the consistently replicated predictive features of ASD at the age of 12-18 months can be summarized as listed below [23,34, 35]. The risk signs range from a lack of typical behaviors to the presence of abnormal behaviors at a certain developmental stage. There is no single highly specific red flag sign, but multiple behavioral abnormalities should be considered collectively. The high risk behaviors by age 0 to 24 months are summarized in Fig. 1.

- Impairments in social-communication development: atypicalities in eye gaze, orienting to name, social smiling, social interest, and affect, and reduced expression of positive emotion by 12 months (AOSI)
- Repetitive interest and behaviors: atypical exploration of toys and other objects, prolonged visual examination, unusually repetitive actions
- Delays in play skills: motor imitation and functional use of toys, more non-functional play, less functional other-directed play
- Response to other’s distress: less attention and less change in affect in response by 12 and 36 months
- Parental concern: Concerns at 12 and 18 months (not 6 months)

are predictive of later ASD diagnosis

1. Community-based prospective study: Social Attention and Communication System (SACS)

One of the noteworthy attempts to identify risk signs and screen infants in the community is the development of the SACS [36], which was based on a previously established developmental surveillance system, including Maternal and Child Health (MCH) nurses and related practitioners in Australia. The MCH service is a free public service provided to all families with children younger than 6 years of age, with the focus on child and maternal health surveillance and screening. The authors provided a draft of the SACS highlighting potential early risk signs of ASD, in infancy and toddlerhood, selected from the literature, and trained MCH nurses to administer the instrument. The MCH nurses screened 20,770 children, a total of 216 subjects were referred for confirmation of diagnosis as “at-risk” infants, and the positive-predictive value of the SACS was found to be 81%, with a sensitivity of 69-84% and a specificity of 99.9% [37].

The SACS is one of the most efficient early screening instruments for ASD. It measures red flag signs of ASD at multiple points of development (8, 12, 18, and 24 months), compensating for the age limit of the Checklist of Autism for Toddlers (CHAT) and the Modified CHAT. It covers the risk signs of early ASD comprehensively,

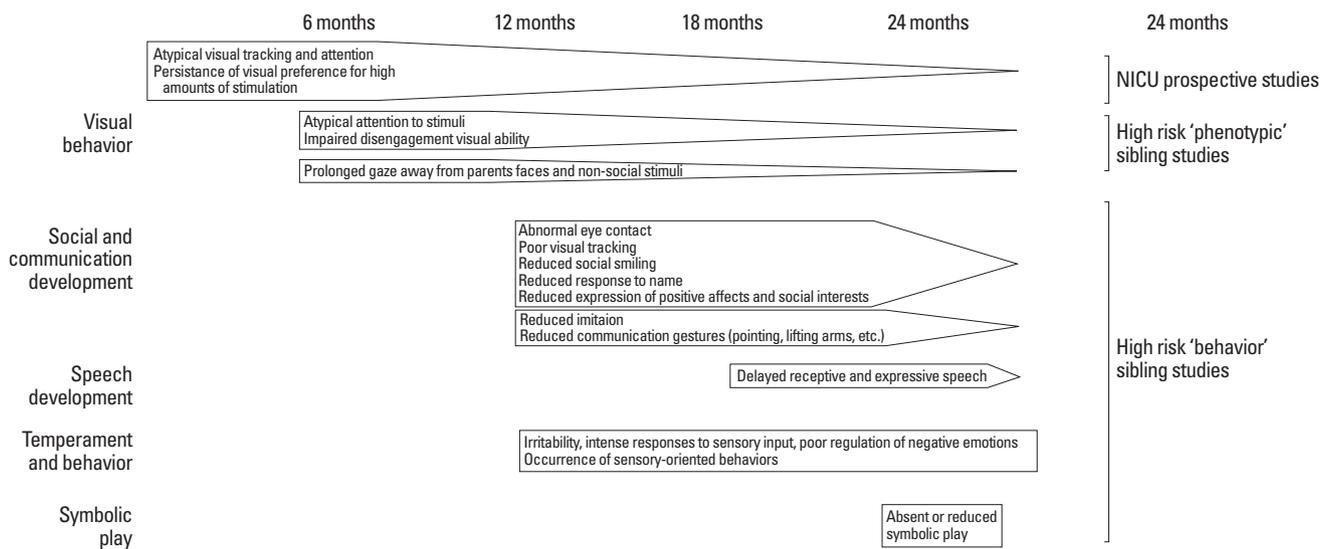


Fig. 1. Schematic representation of the emergence of early clinical signs of autism spectrum disorders. Presented features correspond to findings obtained in prospective studies conducted in infants systematically followed after admission in neonatal intensive care units (NICU; signs recorded from the age of 4 months)[49-51] or from prospective studies of siblings at high risk, either phenotypic [52-54] or behavioral [52-62]. Reprinted from Pediatric Neurology, Volume 49, Issue 4, Deconinck et al. (2013), Toward Better Recognition of Early Predictors for Autism Spectrum Disorders, pp225-231. Ref. 63 with permission from Elsevier.

including social response, communication, reciprocity, imitation, pointing, joint attention, and developmentally appropriate interactive play. It is a combined rating scale and direct instrument, which can be administered by trained mental health professionals. The Korean translated version is also now available.

DOES EARLY INTERVENTION WORK?

Early intervention of ASD starts with early identification; early intervention in infancy and toddlerhood reduces the burden of impairment and enhances quality of life of the subjects and family, reducing the social costs across the lifespan [38]. Secondary compensatory behavior problems and secondary neurological disturbances can be prevented by early therapeutic intervention, because of early brain plasticity and the potential for modification of abnormalities in the reward circuitry in infancy [39-41].

The general principles of early intervention are, first, that interventions should be tailored to the individual child's behavioral profiles, language level, and adaptive functioning; second, the skills learned in the treatment program should be generalizable to the daily life setting, and family support and involvement are important. Early intervention models based on diverse theoretical and methodological backgrounds have been proposed and tested. These interventions are based on behavioral therapy, an educational approach, or both. There are also interventions emphasizing natural developmental processes or environmental support. *Comprehensive* intervention programs aim at remediating multiple core deficits simultaneously and allow for potential synergistic effects of the components of the intervention [42]. Moreover, there are programs that address the specific deficits of ASD, such as social communication, social skills, or behavioral problems.

Comprehensive behavioral programs based on Lovaas/applied behavioral analysis (ABA), also referred as Early Intensive Behavioral Intervention (EIBI), are some of the well-studied treatments for ASD in toddlerhood. Studies using EIBI have shown a reduction in the severity of core symptoms, and increases in IQ, adaptive behavior, and language [43,44]. Strategies for Teaching Based on Autism Research (STAR), the Walden Toddler Program, the Early Start Denver Model (ESDM), and Structured TEACCHing (TEACCH) are other examples that have been reported to result in improvements in the core deficits of ASD [45]. Parent education and training, as well as parent-mediated treatment are increasingly being emphasized, because parents should learn to deliver inter-

ventions in their home and/or community and to provide individualized intervention to their child in order to improve or increase a wide variety of skills and/or to reduce interfering behaviors within the family context [46].

Generally, experts emphasize the efficacy of intervention before 2 years of age. In a neurobiological context, early intervention is believed to have an effect on the plasticity of the developing brain, to promote early learning, and to provide opportunity for changing the connectivity and organization of the brains of individuals with ASD [47]. However, as a randomized control design is not generally possible due to methodological/ethical issues, it remains unclear how and whether early intervention changes brain circuitry and developmental processes in individuals with ASD in infancy [48].

In a recent investigation, Dawson et al. [48] tested the effects of ESDM on forty-eight 18- to 30-month-old children with ASD in a randomized controlled trial, comparing these to children receiving a community-based intervention and age-matched typically developing children as control groups, over a period of 2 years. After each intervention, event-related potentials and spectral power on EEGs were measured during the presentation of faces versus objects. In addition to improvements in the core symptoms of ASD, IQ, language, and adaptive behaviors, the ESDM group and typical children showed increased cortical activation when faces were presented, while the community intervention group showed the opposite pattern. This means that early behavioral intervention is associated with normalized patterns of brain activity. Additionally, greater cortical activation during the presentation of faces was quantitatively associated with increased social behavior [48]. Although this study is one of only few studies examining changes in brain function after early intervention of ASD, it suggests that early intensive treatment may reverse brain changes in ASD as hypothesized

CONCLUSION

There is consensus that early risk signs of ASD can be detected between 12 and 24 months of age; these encompass early behaviors related to social communication, ranging from a lack of normal behavior to the presence of abnormal, atypical behaviors, by a certain developmental stage. There is evidence that early intervention is essential for improving the prognosis of ASD, but further randomized controlled trials and studies of the neural mechanisms

underlying the effects of early intervention are needed.

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