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Topical Review

Toward Better Recognition of Early Predictors for Autism Spectrum Disorders

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ABSTRACT

BACKGROUND: Identification and diagnosis of autism spectrum disorders is essentially based on behavioral presentation and developmental history. The current average age at diagnosis is older than 3 years. **METHODS:** Over the past 15 years, there has been increasing documentation of the early signs of autism spectrum disorders through both individual retrospective parental reports and screening studies. Recent longitudinal studies have focused on early medical and behavioral features of children regarded at risk, namely younger siblings of children with autism spectrum disorders or children who required neonatal intensive care, with a later diagnosis of autism spectrum disorders. **RESULTS:** Potentially useful early neurological signs and developmental predictors for autism spectrum disorders could be identified, with a typical profile that evolved with age. **CONCLUSIONS:** Assessment of early social attention and communication skills with adapted scales in children before the age of 18 months in very large community-based settings may lead to high positive predictive values.

Keywords: autism, early signs, sibling prospective studies, NICU

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Introduction

Autism spectrum disorder (ASD) is a group of devastating developmental conditions whose prevalence may have increased over the past decades.¹ This increase may be related to changes in diagnostic criteria, comorbidity with other developmental disabilities, or a genuine rise in cases.¹ Diagnosis rests essentially on behavioral presentation and developmental history.² Difficulties in communication and reciprocal social behavior are the core characteristics of ASD. Motor and behavioral stereotypies, though prevalent. are not specific and are not commonly observed before the age of 2 years. The etiology and pathophysiological mechanisms of ASD remain largely unknown, although environmental toxins and genetic factors have been implicated. Early diagnosis is a necessary prerequisite to early intervention, but this approach is currently not evidence-based.³ Here we critically review the growing body of early signs documented in young children who go on to develop ASD.

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* Communications should be addressed to: Dr. Deconinck; Department of Neurology; HUDERF; Av. J.J. Crocq 15; 1020 Brussels, Belgium. E-mail address: nicolas.deconinck@huderf.be Clinical description

Autism was first described as a developmental disorder by Leo Kanner in 1943, in the form of a case study of 11 children.⁴ Since this first description, diagnostic criteria have been suggested and have evolved, resulting in the current criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).² In this version, the diagnostic criteria rest on two categories of symptoms, namely social and communication impairment, and fixed interests and repetitive behaviors, with particular attention given to the description of the sensory behaviors typically recorded in ASD. The autism spectrum categories characterized in the previous DSM-IV version are now subsumed under the wider term of "autism spectrum disorder" and rated on three degrees of severity based on the level of support children would require. 5,6 The categories of Asperger disorder and pervasive developmental disorder—not otherwise specified and the childhood disintegrative disorder officially disappear.⁷⁻⁹ Children are therefore no longer to be diagnosed as having "autism" versus pervasive developmental disorder-not otherwise specified or Asperger syndrome because all of these categories are nosographically conflated.¹⁰ However, individuals with ASD will be referred to as having one of three severity levels.²

An additional category of social communication disorder has been created for children in whom ASD was ruled out (absence of restricted, repetitive patterns of behavior, interests, or activities) but who show impairment of pragmatics with difficulties in the social uses of verbal and nonverbal communication in their daily lives.

Clinical red flags include lack of eye contact, social smiling, imitation, response to calling by name, interest and pleasure in others, emotional expression, directed vocalizations, joint attention skills, requesting behaviors, and gestures (e.g., waving, clapping, nodding, and shaking head). Imagination skills, such as pretend play, have also been found to be deficient in late infancy and toddler age in many children with ASD. 11,12 These features should prompt medical attention and may call for closer developmental guidance, follow-up or intervention.

In this review, unless stated otherwise, ASD will be used to refer collectively to autistic disorder (AD), Asperger disorder, and pervasive developmental disorder—not otherwise specified.

Epidemiology

Prevalence rates of ASD are currently 1:160 in Australia, 1:85 in the United States, and 1:100 in the United Kingdom. 1:13,14 The prevalence of AD is 1:500 with a 4:1 male to female ratio. 1:15,16 A striking increase in prevalence was observed in many countries in the early 2000s. 1:13,14,17 The reasons for this increase is still debated. Two main hypotheses have been suggested. First, there was an increased identification rate of ASD patients with growing clinical awareness and knowledge about ASD semiology. Second, the diagnostic spectrum of the condition has expanded from Kanner's typical description toward the wider DSM-IV concept of ASD.

Early clinical signs of autism

From a methodological point of view, reports of neurodevelopmental abnormalities that can be seen during the first months of life in children later diagnosed with autism are based on different sources: (1) parent-based retrospective studies; (2) examination of early medical and behavioral characteristics of children who required care in a neonatal intensive care unit and were later ascertained has having ASD; (3) prospective longitudinal studies in families with a sibling diagnosed with ASD; and, more recently, (4) prospective community-based studies.

Parent-based retrospective studies

Retrospective videotape analyses and parental report studies suggest that symptoms can be seen during infancy. About 50% of parents of children with ASD report having concerns before 12 months of age, and many more report they recognized abnormalities between 12 and 24 months. Parental recall of abnormalities in the first year of life include poor eye contact and lack of response to the parents' voices or attempts to play and interact. Extreme temperament and behavior, such as irritability or passivity, have also been described. Reviewing home videos of the first year of life, several authors reported significantly

reduced social interaction and orienting to faces and absence of social smiling as well as lack of spontaneous imitation and abnormal posture and movements patterns. ²⁰⁻²² Based on sequential review of the video material, they suggested three categories of onset patterns: "early-onset" presentation with low levels of social communication from early life, a "regression" category displaying initial high levels of social communicative behavior followed by a significant decrease over time, and a "plateau" trajectory characterized by normal initial levels of behavior but little progress in social communication with age.

Interesting as they may be in illustrating potentially relevant points, these retrospective parental report studies are inherently limited by recall biases (including as regards the timing of behavioral manifestations) and lack an appropriate control that would inform about typical development or early development in nonautistic developmental disorders in order to evaluate the specificity of these behavioral observations. Furthermore, the developmental sequence of these features has also been poorly reported, and the correspondence between parent report and home video remains low mainly as regards language areas.²²

Prospective studies

Behavioral characteristics of high-risk neonates

A strategy for avoiding the recall biases relies on designing longitudinal studies to document development trajectories in another group of infants who present an increased risk for ASD. Several studies identified a number of obstetric and neonatal factors resulting in neonatal intensive care unit admission as risk factors for ASD. When controlling for other developmental disorders, a multifold increase in ASD risk was identified as a result of low birth weight and gestational age.²³⁻²⁶ In low-birth-weight neonates, cranial ultrasound evidence of ventricular enlargement suggesting white matter injury seems to constitute a strong risk factor for developing subsequent ASD.²⁷ Karmel et al. performed a prospective study that examined early developmental differences between infants who later received a diagnosis of ASD and matched control participants from their sample of neonatal intensive care unit patients.²⁸ The authors conducted serial behavioral studies from birth as part of a prospective project to determine how brain organization interacts with autoregulatory processes over development. They found that ASD neonates showed persistent neurobehavioral abnormalities and higher incidences of asymmetric visual tracking and upper extremity muscle tone alterations as measured by the Rapid Neonatal Neurobehavioral Assessment. At 4 months, infants with ASD showed specific continued visual preference for higher amounts of stimulation than control infants on the Arousal Modulated Attention scale, behaving rather like typical newborn infants (Fig).²⁹ This continued higher attention to more stimulating events at 4 months was interpreted as a lack of transition to more mature levels beyond the neonatal period, providing evidence for atypical early development, including of the visual-perceptual system. Similar conclusions were reached regarding the importance of abnormal development of neurally mediated visual tracking and

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