Early Infant Development and Intervention for Autism Spectrum Disorder

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Abstract

Objective: The objective is to overview recent findings on early detection/diagnosis of autism spectrum disorders, as well as clinical trials of early interventions for toddlers at risk for/diagnosed with autism spectrum disorder. Findings: Prospective studies of infants at high risk of autism spectrum disorder have yielded significant advances in understanding early development in autism spectrum disorder. Findings from prospective studies indicate that abnormalities in social communication and repetitive behaviors emerge during the second year, whereas additional "prodromal features" (motor and sensory abnormalities) emerge in the first year. Subsequently, exciting progress has been made in establishing the efficacy of autism spectrum disorder–specific interventions for toddlers as young as 15 months. Finally, efforts occur to characterize autism spectrum disorder–specific characteristics in genetic syndromes with concurrent autism spectrum disorder symptomatology. Conclusion: Substantial progress in characterizing early developmental trajectories as well as the identification of specific behavioral markers has aided early detection. Work remains to ensure that research findings are translated into clinical practice for uptake in the health care system.

Keywords
early identification, infant siblings, early intervention, autism spectrum disorder, review

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The heterogeneity of autism spectrum disorders, both clinically and etiologically, creates challenges in identifying a set of early risk markers that would be informative across the continuum of severity and complexity of affected children. However, despite these challenges, there are many reasons to continue to strive toward earlier detection and diagnosis of the disorder. First, there is an unacceptable delay between parents’ first concerns and confirmation of a diagnosis of autism spectrum disorder,1,2 which creates added stress for families and may adversely impact on subsequent engagement with health care providers.3 Second, earlier diagnosis creates opportunities for children with autism spectrum disorder to benefit more fully from earlier initiation of intervention, which benefits both the child and the community.4,5 There is also broader scientific relevance to delineating the earliest expression of the autism spectrum disorder phenotype in terms of understanding underlying mechanisms, and in particular, to be able to study the neurological features of autism spectrum disorder early in development.

Early detection efforts have benefitted from recent advances in research, including broad implementation of prospective study designs involving high-risk infants6 and technological advances in assessing early brain structure and function.7-9 Indeed substantial progress has been made in characterizing early behavioral and neurobiological markers of autism spectrum disorder in high-risk infant cohorts.10,11 In addition, there is exciting progress in establishing the efficacy of autism spectrum disorder–specific interventions for toddlers as young as 18 months.4,12 Finally, efforts have been made to characterize autism spectrum disorder–specific characteristics in genetic syndromes with concurrent autism spectrum disorder symptomatology.13-15 These efforts together bring us closer to the core mechanisms underlying autism spectrum disorder. The authors summarize advances in each of these areas in this review.

Prospective Design: Application to Studies of Early Development of Autism Spectrum Disorder

Prospective studies of high-risk infant cohorts (generally, younger siblings of children diagnosed with autism spectrum disorder) are well suited to understand early development in autism spectrum disorders.
autism spectrum disorder. The prospective, high-risk design has been used to study other disorders, such as schizophrenia, but the advantage of utilizing this method in autism spectrum disorder is the early onset of the disorder. The prospective design offers additional advantages. First, infants can be followed from a very early age, allowing examination of early systems, such as motor development and visual attention. Second, behaviors can be studied longitudinally to age at diagnosis, which may help address questions regarding developmental trajectories of autism spectrum disorder. Third, clinical assessments can be correlated with neurobiological phenomena, such as underlying EEG measurement. Fourth, early behavioral signs of autism spectrum disorder can be measured under standardized conditions, allowing greater comparability both within and between individuals over time. Finally, interventions can be implemented at an earlier age in infants and toddlers who show behavioral signs of autism spectrum disorder.

To what degree can younger siblings be considered “high risk”; that is, what is the recurrence risk of autism spectrum disorder (ie, the likelihood of autism spectrum disorder for each later-born sibling) compared to general population risk? One of the first epidemiological studies of recurrence risk in autism spectrum disorder was completed in the 1980s at the University of Utah. The recurrence risk was estimated at 8.6%. More recently, a multisite international network, the Baby Siblings Research Consortium reported on 664 infant siblings of children with autism spectrum disorder followed to age 3, when they were classified as having or not having autism spectrum disorder. Overall, the recurrence rate was 18.7%. However, 3 recent large population-based studies have reported lower recurrence rate estimates. A Danish birth cohort study involving 1.5 million children born between 1980 and 2004, estimated recurrence rate for autism spectrum disorder at only 6.9%. Similarly, recurrence rate was 10.1% among younger siblings of individuals with autism spectrum disorder in a 1990-2003 California birth cohort (n = 6616). and 12.9% in a population-based cohort of Swedish children born between 1982 and 2006 (n = 2 049 973). Despite this broad range of recurrence risk estimates (roughly 8-18%), it is clear that the rate of autism spectrum disorder among younger siblings is higher than that in the general population, most recently estimated at 1.5% (or 1 in 68 children) by the US Centers for Disease Control and Prevention (CDC).

### Prospective Studies of Infants at Risk of Autism Spectrum Disorder: Key Findings

Converging findings from prospective studies of infants at risk of autism spectrum disorder (younger siblings) suggest that “diagnostic” symptoms (that is, behavioral features that related to diagnostic criteria defined by current frameworks such as the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders) are expressed by 12-18 months in many children with autism spectrum disorder. However, “prodromal” (ie, earlier) symptoms, such as sensory and motor impairments, emerge during the first 12 months, and atypical brain development and function are apparent in the first 12 months and may precede behavioral symptoms. Each set of findings will be discussed in turn.

### Diagnostic Symptomatology

Abnormalities in social communication include deficits in social reciprocity, nonverbal communication, developing relationships, and verbal communication. By 12 months of age, high-risk infants show reduced orienting to name, gazing to faces, and directed vocalizations, and by 18 months of age, showed reduced social smiling and social engagement. In addition, deficits in responding to referential cues during joint attention occur early in the second year of life for children who later are diagnosed with autism spectrum disorder. Other nonverbal skills, such as the use of gestures, also show early impairments. High-risk infants later diagnosed with autism spectrum disorder are less likely to show an object or use directed pointing at 12 months of age, and have a smaller inventory of gestures. High-risk infants who are later diagnosed with autism spectrum disorder also show reduced attentiveness to their mother during naturalistic interactions, as well as reduced dyadic mutuality. Several studies have reported delays in receptive language by 12 months of age in infants who are later diagnosed with autism spectrum disorder. Parents of these children report fewer words on the Communicative Developmental Inventories, as well as understanding fewer phrases with or without accompanying gestures on the Mullen Scales of Early Learning. In addition to receptive problems, language production is also impaired in children who are later diagnosed with autism spectrum disorder. Parents of these children report fewer words on the Communicative Developmental Inventories at 18 months of age, and these children score lower on the expressive language component of the Mullen Scales of Early Learning.

Abnormalities in restricted interests or repetitive behaviors include repetitive motor movements, atypical use of objects, and atypical sensory interests. Reports of repetitive movements suggest that they lack early specificity in autism spectrum disorder. Loh and colleagues analyzed repetitive movements during a semistructured assessment and identified the frequency of arm waving as the only item that distinguished 12- and 18-month-old siblings who were later diagnosed with autism spectrum disorder from other high-risk and low-risk samples. In contrast, for use of objects, 12-month-olds often use play materials in stereotyped, self-stimulatory ways (eg, an infant might wave a string of beads in front of his/her eyes). Similarly, Ozonoff and colleagues noted that 12-month-old high-risk infants later diagnosed with autism spectrum disorder showed more atypical uses of objects, particularly unusual visual exploration of objects, rotating, and spinning, but did not differ on throwing or mouthing of objects. High-risk children later diagnosed with autism spectrum disorder also show additional reactivity and sensory issues. Parents of these infant
siblings later diagnosed with autism spectrum disorder reported atypical auditory processing and lower sensory registration on the Infant-Toddler Sensory Profile at 24 months of age.\textsuperscript{38}

**Prodromal Symptoms**

A growing literature suggests that early sensory and motor differences, and possible emotional regulation differences, form a prodrome of autism spectrum disorder that manifests in the latter half of the first year of life.\textsuperscript{39-42} before the appearance of social-communication and restrictive behavioral differences more directly related to autism spectrum disorder diagnostic criteria (reviewed in Zwaigenbaum et al\textsuperscript{11}).

**Motor.** Prospective studies of high-risk siblings who are later diagnosed with autism spectrum disorder identify delays in gross and fine motor skills on the Mullen Scales of Early Learning at 14 and 24 months of age, but not at 6 months.\textsuperscript{26,34,43} Zwaigenbaum and colleagues\textsuperscript{25} also report lower fine and gross motor scores on the Mullen Scales of Early Learning compared with nondiagnosed high-risk infants and controls at 12 and 18 months, but not at 6 months.\textsuperscript{27}

Rather than looking at scale scores, Libertus and colleagues\textsuperscript{42} assessed toy play during the Mullen Scales of Early Learning and found that high-risk infants exhibited less mature object manipulation and reduced grasping activity than infants with no family history of autism spectrum disorder at 6 months, with grasping activity increasing in high-risk infants between 6 and 10 months. Additional evidence of atypical motor development include reduced motor maturity at 3 and 6 months in high-risk infants versus low-risk infants (without outcome information) using the Alberta Infant Motor Scales,\textsuperscript{44} and pronounced head lag during pull-to-sit at 6 months, delayed independent sitting, reduced postural stability, and reduced rhythmic arm movements in high-risk infant siblings.\textsuperscript{45,46} Further clarification is needed on whether abnormalities in high-risk infants are specific to those who later are diagnosed with autism spectrum disorder or are shared by a broader group of high-risk infants who show later social-communication impairments.\textsuperscript{44}

**Sensory.** Coding of home videos of children who are diagnosed with autism spectrum disorder show differences in sensory behaviors at 9 and 12 months of age, particularly visual exploration of their visual environment, differentiated infants with autism spectrum disorder from those who had developmental disabilities or who were typically developing.\textsuperscript{39} Similar findings come from prospective studies of high-risk infant siblings of children with autism spectrum disorder. Ozonoff and colleagues\textsuperscript{37} reported that 12-month-old high infants who were later diagnosed with autism spectrum disorder were different from children with developmental disability and typically developing infants in atypical uses of objects, such as rotating, spinning and unusual visual exploration. Atypical sensory-oriented behaviors at 12 months (including intense visual inspection) were also identified as an early risk marker of autism spectrum disorder in high-risk infants assessed by Zwaigenbaum and colleagues\textsuperscript{25} using a semistructured play assessment. Similar findings are seen in computer based visual assessments.\textsuperscript{36,47} Elsabbagh et al\textsuperscript{48} reported that high-risk infants who were diagnosed with autism spectrum disorder at 24-36 months showed increases in their latency to disengage when looking at objects between 7 and 14 months, whereas disengagement latencies in typically developing children and high-risk infants without autism spectrum disorder decreased or remained the same. In addition, Elison et al\textsuperscript{49} found longer latencies to disengage attention from objects in 7-month-old infants with high Autism Diagnostic Observation Schedule scores at 24 months. In addition to prolonged disengagement from objects, autism spectrum disorder is associated with diminished attention to faces (no relative difference in eyes versus mouth) in videotaped social scenes at 6 months of age in high-risk infants who are later diagnosed with autism spectrum disorder.\textsuperscript{48} Similarly, a prospective longitudinal study of infants later diagnosed with autism spectrum disorder show declines in percentage of time gazed at eyes versus mouth on a face shown on a video during early infancy. In fact, the severity of decline between 2 and 6 months of age was informative for autism spectrum disorder risk.\textsuperscript{49}

**Temperament.** Prospective studies have shown evidence of reduced positive affect in high-risk infants who are later diagnosed with autism spectrum disorder by the first birthday when compared to nondiagnosed siblings and low-risk controls.\textsuperscript{29,50} Zwaigenbaum and colleagues\textsuperscript{25} reported fewer observed positive affective responses and increased distress in high-risk infants with autism spectrum disorder at 12 months, as coded from the Autism Observation Scale for Infants, compared to those with typical development, consistent with concurrently collected parental reports of temperament. In a subsequent analysis of high-risk infant siblings (n = 138) and low-risk infants (n = 73), Garon et al\textsuperscript{51} examined the relationship between temperament at 24 months and 3-year outcomes. Using discriminant function analysis, they identified profiles that were informative for general differences between high-risk siblings and low-risk comparison infants, and that were specific to siblings subsequently diagnosed with autism spectrum disorder. A profile that included poor regulation of negative emotions, and difficulty with attention control (increased attention shifting) distinguished the high-risk sibling group (as a whole) from comparison infants, whereas a second profile that included low positive affect and increased duration of attention, was associated specifically with autism spectrum disorder. Similarly, Clifford and colleagues\textsuperscript{52} noted that parents of high-risk infants later diagnosed with autism spectrum disorder reported reduced positive affect, but not increased negative affect, as characterizing beginning at 7 months. As well, Feldman and colleagues\textsuperscript{53} noted that community diagnosed children with autism spectrum disorder were rated by the parents as more difficult when waiting to have their needs met at 9, 12, and 18 months of age. These results suggest that emotional regulation differences may precede the core symptomatology of autism spectrum disorder.
Neurobiological Markers

Atypical brain development and function are evident in the first 12 months in high-risk infants who are later diagnosed with autism spectrum disorder using magnetic resonance imaging (MRI) and electroencephalogram (EEG).

MRI. Hazlett and colleagues\textsuperscript{54} compared brain volumes at 2 and 4 years of age in children at high risk of autism spectrum disorder and without familial risk of autism spectrum disorder. They reported generalized cortical enlargement in children with autism spectrum disorder at both 2 and 4 years of age, and after controlling for total brain volume, children with autism spectrum disorder had disproportionate enlargement of temporal lobe white matter. The authors note that there was no significant difference from controls in the rate of brain growth at this age interval, suggesting that the brain enlargement took place prior to 2 years of age.\textsuperscript{54} Investigation of white matter tract organization from 6 to 24 months of age in children at high risk of autism spectrum disorder showed higher fractional anisotropy values at 6 months, followed by slower changes over time in comparison to infants without autism spectrum disorder. In a related investigation, measuring visual orienting latencies in 7-month-old infants at high risk for autism spectrum disorder and associating outcomes with the microstructure of the corpus callosum, Elison and colleagues\textsuperscript{9} found that high-risk infants who were later diagnosed with autism spectrum disorder showed longer disengagement latencies than both high-risk negative infants and control infants. Furthermore, the disengagement latencies were associated with the microstructure organization of the splenium of the corpus callosum in the control infants, but this association was not apparent in high-risk infants later diagnosed with autism spectrum disorder, suggesting early atypical development in autism spectrum disorder. Finally, Lewis and colleagues\textsuperscript{55} measured differences in brain connectivity in autism spectrum disorder at 24 months of age, an age at which the diagnostic features of autism spectrum disorder become clear. Network efficiency was analyzed by measuring the length and strength of connections between anatomical regions, resulting in significantly decreased local and global efficiency over the temporal, parietal, and occipital lobes in high-risk infants classified as autism spectrum disorder. The authors suggest that delays or deficits in network efficiency are associated with the impairments in audition, visual processing, language, and nonlinguistic social stimuli.

EEG. A prospective longitudinal study of infants at high risk of autism spectrum disorder examined whether neural responses to eye gaze at 6-10 months of age was associated with autism spectrum disorder symptomatology.\textsuperscript{7,56} Event-related potentials were recorded in response to infants viewing faces with the eye gaze either directed toward or away from the infant and noted that changes to the characteristic of the event-related potential response, specifically the P400 response, was associated with an outcome of autism spectrum disorder. In a subsequent study, the authors measured the P400 response to directed or averted eye gaze in 7-month-olds and compared it to infants’ overt behavior during a caregiver-child dyadic free play session.\textsuperscript{57} The results suggested that infants with more positive affect exhibited stronger differentialization to gaze stimuli in respect to P400 responses to directed gaze versus averted gaze. These results suggest the integrity of the neural response is associated with overt, observed behavioral phenomenon.

Other. Increased head circumference in children with autism spectrum disorder is one of the most consistent findings in autism spectrum disorder. Yet, this association is now in question due to problems in interpretation related to using CDC norms for comparison. A systematic review by Raznahan et al\textsuperscript{58} identified 5 independent longitudinal cohorts of typically developing children that demonstrate trajectories in head circumference z scores that deviate from CDC norms.\textsuperscript{59} To understand whether head growth in the first 3 years differed between high-risk infants later diagnosed with autism spectrum disorder versus high-risk infants who were not diagnosed with autism spectrum disorder and community controls, Zwaigenbaum and colleagues\textsuperscript{60} obtained prospective and growth-records of head circumference from 492 high-risk infants (77 of whom were later diagnosed with autism spectrum disorder) and 333 low-risk community controls. Overall, there were no significant differences comparing head growth between high-risk infants (regardless of outcome) and low-risk controls in the first 3 years of life. Furthermore, there were no differences in head growth related to clinical outcome within the high-risk group (when subtyping based on autism spectrum disorder, developmental disability, and typical outcomes). The authors concluded that head growth was largely uninformative as a risk-marker for autism spectrum disorder, at least within the reported high-risk cohort.

Early Intervention for Autism Spectrum Disorder

As detailed above, prospective studies of high-risk infants who are later diagnosed with autism spectrum disorder indicate impairments appear early in development for sensory and motor ability, visual attention, social-emotional regulation, and communication. The atypical development of these domains may lead to disruptions in early interactions with the environment, resulting in cascading effects during the first 3 years of life. Moving forward, it becomes necessary to develop earlier interventions to coincide with earlier identification of autism spectrum disorder and improve lifelong outcomes for these children. For a recent review of potential treatment targets for interventions, see Brian et al,\textsuperscript{12} and for a recent review article that summarizes key feature shared in common across recently reported interventions for infants and toddlers with autism spectrum disorder or at risk of autism spectrum disorder, see Schreibman et al.\textsuperscript{5}

Clinical Trials

Dawson and colleagues\textsuperscript{61} provided the first randomized controlled trial to demonstrate efficacy for a behavioral
intervention for toddlers with autism spectrum disorder. Children diagnosed with autism spectrum disorder between 18 and 30 months (n = 48) were enrolled in a randomized, controlled trial to evaluate the efficacy of the early start Denver model, a comprehensive developmental behavioral intervention for improving outcomes of toddlers diagnosed with autism spectrum disorder. Following random assignment in 1 of 2 groups (Early Start Denver model for 2 years versus ‘treatment as usual’ [typical community intervention]), those children who received Early Start Denver model showed significant improvements in IQ, adaptive behavior, and autism spectrum disorder diagnosis (showing fewer autism spectrum disorder symptoms) compared to the treatment as usual group. Carter et al\(^6\) reported a randomized controlled trial comparing Hanen’s ‘More Than Words’, a parent-implemented intervention for 3.5 months, to a ‘treatment as usual’ group in 20-month-old children diagnosed with autism spectrum disorder (n = 62). Overall, there were no main effects of the More Than Words intervention on parental responsivity or children’s communication ability compared to the treatment as usual group receiving community intervention, but the More Than Words intervention showed differential effects on child communication depending on their baseline performance. Wetherby et al\(^6\) completed a randomized control trial of the ‘Early Social Interaction’ Project for 16- to 20-month-old toddlers diagnosed with autism spectrum disorder. Children were matched on nonverbal developmental level and were randomly assigned to an individualized Early Social Interaction treatment (1-on-1 parent coaching 2-3 times per week) or group Early Social Interaction treatment (group parent coaching offered once per week) conditions for 9 months. The children enrolled in the individualized Early Social Interaction treatment showed improvements on observational measures of social communication and receptive language skills, parent-reported measures of communication, daily living, social skills, and stability over time. In contrast, children enrolled in the group Early Social Interaction treatment showed worsening or no changes to these skills, highlighting the importance of parent coaching in an individualized environment. Similarly, Kasari et al\(^4\) performed a randomized control trial on a parent-mediated intervention for 15- to 21-month-old toddlers at high risk of autism spectrum disorder. Parents were enrolled in 12 sessions of individualized parent education intervention or to a control group involving 4 sessions of behavioral support for 3 months. Parental responsiveness improved significantly in the individualized treatment group compared to the control group over the 3-month period, however it had declined in the 12-month follow-up. Although children in both groups made gains in cognitive and language ability over the 12 months, there were no treatment effects on joint attention for the individualized treatment group. Finally, Brian and colleagues\(^1\) completed a clinical trial on a parent-mediated intervention, the ‘Social ABCs’, based on adapted pivotal response treatment principles and strategies. The intervention relied on in-home, parent-mediated strategies with in-vivo coaching by a trained interventionist.

Parents completed 12 weeks of in-home training and children were followed up 24 weeks later to examine communication ability and shared positive affect. Overall, children showed improved language performance and functional verbalizations, with increases in responsivity, initiations, social orienting, and shared smiling.

**Other Intervention Studies**

Pivotal response treatment is an evidence-based, manualized intervention for individuals with autism spectrum disorder with empirical support for use with preschool children with autism spectrum disorder.\(^6\) Steiner and colleagues\(^6\) developed an adaptation of pivotal response treatment and piloted, via a brief parent-training model, the intervention with 12-month-old infants at risk for autism (n = 3). The results provided preliminary support for the feasibility and utility of pivotal response treatment for very young children at risk for autism spectrum disorder. That is, utilizing a multiple baseline design, the introduction of pivotal response treatment resulted in increases in the infants’ frequency of functional communication and parents’ fidelity of implementation of pivotal response treatment procedures. Landa et al\(^6\) reported on a sample of 2- and 3-year-old children with autism spectrum disorder (n = 48) who participated in a research-based, 6-month comprehensive intervention at 10 hours per week within a nursery classroom. Parents received weekly on-site education and monthly home-based coaching on teaching strategies. From pre- to postintervention, significant gains were made in IQ and communication scores on the Vineland, as well as a reduction in autism spectrum disorder severity scores. Measurements completed at 6-month and long-term follow up after intervention found that IQ and communication stabilized, but autism spectrum disorder severity scores increased. Pre- to post-follow-up trajectories showed that robust gains were observed for both IQ and communication scores, with no changes in autism spectrum disorder symptom severity. Recently, Rogers et al\(^4\) developed and piloted the feasibility of a manualized, parent-delivered intervention for infants aged 6-15 months who were highly symptomatic for autism spectrum disorder (n = 7 high risk and n = 7 low risk for autism spectrum disorder). The intervention aimed at 6 target symptoms (visual fixation, repetitive behaviors, communicative acts, turn taking, phonemic development, and gaze) and consisted of 12 weekly, 1-hour sessions. Follow-up at 36 months showed that the treatment group had lower rates of autism spectrum disorder symptomatology and fewer developmental quotients under 70 on the Mullen Scales of Early Learning than high-risk infants with autism spectrum disorder who were not enrolled in the treatment intervention. Overall, the results of the intervention studies reviewed above underscore the importance of early detection of autism spectrum disorder, noting promising outcomes of short and long-term intervention in toddlers with autism spectrum disorder.
Genetic Disorders and Autism Spectrum Disorder

Specific genetic syndromes associated with autism spectrum disorder represent other potential high-risk groups that can be studied prospectively beginning in infancy. However, the question of co-occurring autism spectrum disorder in genetic syndromes can be complex, as reported prevalence rates vary widely,14,15 and may be driven by particular behavioral symptoms. One possible reason for variability in reported prevalence could be the use of different assessment tools, including autism spectrum disorder screening questionnaires68-70 and gold standard autism spectrum disorder diagnostic tools,71-73 as well as parent report surveys.74,75 Although a complete review of genetic syndromes associated with autism spectrum disorder is beyond the scope of this article, for illustration, the following section reports on 3 syndromes with elevated incidence of autism spectrum disorder: fragile-X syndrome, Down syndrome, and Prader-Willi syndrome.

Fragile-X Syndrome

On a national parent survey in the United States, more than 1000 parents of children with fragile-X syndrome were asked about co-occurring conditions. In total, parents reported that 40% (46% of males and 16% of females) had a diagnosis of autism spectrum disorder,74 consistent with a recent review citing a range of 21-50% of autism spectrum disorder in genetic disorders.14 The results from the national parent survey also found that fragile-X syndrome and autism spectrum disorder were rarely reported in isolation; rather, they frequently coincided with attention problems, anxiety, and hyperactivity.74 Assessing the clinical utility of using the CHAT to identify autism spectrum disorder in young children with fragile-X syndrome, Scambler et al76 noted that using the Denver Criteria,77 the CHAT showed high levels of sensitivity (75%) and specificity (92%) in identifying those children with fragile-X syndrome who also had concurrent autism spectrum disorder prior to age 3. Similarly, Rogers et al78 compared children with autism spectrum disorder, developmental delays, and fragile-X syndrome on two gold-standard autism spectrum disorder instruments and noted that the subgroup of children with fragile-X syndrome but without autism spectrum disorder performed similarly to the children with developmental delays, whereas the subgroup of children with fragile-X syndrome and autism spectrum disorder were virtually identical to the children with autism spectrum disorder. Overall, children with fragile-X syndrome and autism spectrum disorder have a similar profile of scores on the Autism Diagnostic Observation Schedule79 as children with autism spectrum disorder; however, the individuals with fragile-X syndrome and autism spectrum disorder also perform significantly lower on performance and verbal IQ.13 These studies and a longitudinal study of boys with fragile-X syndrome find that autism spectrum disorder can be reliably diagnosed in fragile-X syndrome during the preschool years.80

Down Syndrome

Prevalence of autism spectrum disorder in Down syndrome was reported as 18% (24% of males and 9% of females), based on clinical diagnosis of autism spectrum disorder in a cohort of 123 individuals with Down syndrome,81 also coinciding with the review by Moss and Howlin,14 reporting 5-39% of individuals with Down syndrome had co-occurring autism spectrum disorder. Interestingly, it appears as though autism spectrum disorder is most frequently found in children with Down syndrome who also have intellectual disability. Indeed, the Moss and Howlin14 review found that individuals with Down syndrome who met criteria for autism spectrum disorder also fell within the “moderate to severe” degree of intellectual disability. Molloy et al82 found that the deficits in social communication and restricted and repetitive behaviors are not entirely explained by the intellectual disability, suggesting that the autism spectrum disorder in Down syndrome is not directly caused by cognitive impairment. Rather, children with Down syndrome and autism spectrum disorder begin to display atypical behaviors during infancy or toddlerhood, including social disinterest, lack of sustained joint attention, few gestures, repetitive motor behavior, self-injurious behaviors, sensory seeking, and unusual play with objects.83 As with fragile-X syndrome, diagnosis of autism spectrum disorder in Down syndrome can also reliably be performed in the preschool years.81

Prader-Willi Syndrome

The prevalence of autism spectrum disorder in Prader-Willi syndrome was reported as 25% in a recent systematic review,84 confirming previous findings.85 One interesting recurring finding is a higher prevalence of autism spectrum disorder symptoms in the uniparental disomy genetic subtype of Prader-Willi syndrome when compared to the deletion subtype,86,87 presumably due to the correlation between chromosome 15q11-13 and autism spectrum disorder.88,89 Specifically, adolescents and adults with the uniparental disomy subtype have scored similar in autism spectrum disorder symptomatology to comparison groups with autism spectrum disorder, and higher than those with the deletion subtype.86 Of note, individuals with Prader-Willi syndrome and autism spectrum disorder display repetitive behaviors, a need for sameness, verbal perseverations, poor peer relations, and anxiety, symptoms also present in autism spectrum disorder.90 However, there is paucity in the literature concerning autism spectrum disorder in younger children with Prader-Willi syndrome. To date, no study investigating autism spectrum disorder in Prader-Willi syndrome has had a mean age below 8 years. Recent research has suggested that autism spectrum disorder symptoms might not emerge in Prader-Willi syndrome until children are older,81,92 but further research is required to confirm these findings.

Summary

Prospective studies of autism spectrum disorder with high-risk infants have been informative for identifying early behaviors that are predictive of autism spectrum disorder. Interestingly,
such studies have proposed that the diagnostic characteristics of the disorder, social-communication and restricted interests and repetitive behaviors, may be preceded by prodromal symptoms, specifically, sensory and motor impairments. Indeed, early differences have been identified in the brains of children who will later be diagnosed with autism spectrum disorder as early as 6 to 9 months of age, appearing prior to or concurrently with symptom onset. There has been progress in establishing developmentally appropriate and evidence-based interventions, yet scholars still have a long way to go toward the goal of earlier diagnosis and intervention for all children with autism spectrum disorder. As such, research findings need to be translated into clinical practice must address health systems issues, including access to specialized care.

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LRS and LZ developed the objectives for this review article. LRS, JAB and LZ drafted initial sections of the manuscript and LRS integrated the sections into an overall first draft. LRS, JAB and LZ critically revised the manuscript and approved of its final version.

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