Title
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Beyond baby siblings – Expanding the definition of "high risk infants" in autism research

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Abstract

Purpose of review: Much of our understanding of early development in children with autism spectrum disorder (ASD) comes from studies of children with a family history of autism. We reviewed the current literature on neurodevelopmental profiles and autism prevalence from other high-risk infant groups to expose gaps and inform next steps. We focused on infants with early medical risk (e.g., preterm birth) and genetic risk (Tuberous Sclerosis Complex [TSC]).

Recent findings: About 7% of very preterm infants are later diagnosed with ASD. Prospective studies of early development outside of familial-risk infants are rare; however, recent work within preterm and TSC infants suggests interesting similarities and differences from infants with a family history of ASD.

Summary: It is essential that we extend our knowledge of early markers of ASD beyond familial-risk infants to expand our knowledge of autism as it emerges in order to develop better, more individualized early interventions.

Keywords

Autism spectrum disorder; high-risk infants

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder defined by core deficits in social communication and the presence of restricted and repetitive behaviors[1]. There is increasing evidence that ASD emerges very early in life, with atypical brain maturation, organization, and network formation likely beginning before birth[2]. ASD does not, however, clinically manifest until one to two years of age, opening a promising window of opportunity to improve developmental trajectories by intervening prior to the full behavioral expression of ASD. Testing the efficacy of targeted treatments for at-risk infants has posed some challenges, including accurate, scalable methods to identify infants who would most benefit from early intervention, identification of the unique needs and treatment targets for early intervention, and clinical outcome measures that are sensitive to change in early infancy.

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Studies of early identification and intervention have leveraged opportunities to prospectively follow infants with elevated risk for ASD. Although there are many underlying risk factors, such as genetic conditions, prematurity or other perinatal medical complications requiring a Neonatal Intensive Care Unit (NICU) stay, epileptic encephalopathies, and family history, prospective studies have primarily focused on infant siblings of children with ASD. These infants can be identified prior to birth, based simply on their older sibling's diagnosis of ASD, facilitating early monitoring. Clinical characteristics of these infants have been well described through decades of studies supported by an international collaboration known as the Baby Siblings Research Consortium (BSRC). These studies have found that approximately 20% of infant siblings will meet criteria for ASD by age 3[3], and another 20% may show subclinical symptoms of ASD or other developmental delays[4,5]. Children with a multiplex family history (i.e., more than one older sibling with ASD) carry a two-fold likelihood of an ASD outcome, relative to children who have only one older sibling with ASD[6].

These BSRC studies have generated important insights regarding early behavioral differences associated with the emergence of ASD. The first signs of atypical development appear between 6 and 12 months of age, mostly in motor and nonverbal communicative behaviors, with clearer signs of autism emerging in the second year of life[7–9]. Prospective studies of infant siblings have also revealed changes in brain structure and function that may precede clinical evidence of ASD. Through the Infant Brain Imaging Study, a multi-site neuroimaging consortium, investigators have identified patterns of functional brain connectivity at age 6 months[10] and trajectories in structural brain development from 6 to 12 months[11] that predict ASD outcomes[12]. More recent studies using electroencephalography (EEG) have demonstrated atypical connectivity in distributed brain networks as early as 3 months of age in infants that develop ASD symptoms[13]. These studies underscore the feasibility and relevance of multimodal investigation of early infancy in ASD, but the degree to which these findings extend beyond infant siblings remains unknown.

Here, we propose that this early detection study design could be applied effectively to other risk groups already under medical attention, including those with early medical challenges and those with causative genetic conditions. These populations often face additional medical challenges and comorbidities, such as epilepsy, and they may exhibit a broader range of neurodevelopmental outcomes that include not only ASD but also global developmental delay and intellectual disability. These additional clinical features ultimately will improve the generalizability and clinical relevance of early detection and prediction research. Here, we review the recent literature on early predictors and ASD prevalence in these "other" risk groups. We then propose a series of guidelines and considerations for next steps in studies of early neurodevelopment in high-risk infants.

Early Medical Risk

Given their clinical heterogeneity and public health relevance, infants who experienced early medical challenges are particularly well suited for prospective studies aimed at widening our understanding of the early emergence of ASD and neurodevelopmental disabilities.

We discuss two groups: Neonatal Intensive Care Unit (NICU) graduates, with a focus on preterm infants, and infants with congenital heart disease (CHD).

NICU Graduates

Newborns requiring extended NICU hospitalizations often enter their social environment with biological risk factors related to preterm birth, medical complications, neurological injuries during or shortly after birth, or genetic risk factors, all of which can adversely impact healthy brain development. Infants with these initial biological vulnerabilities then experience additional environmental challenges, as the NICU setting often precludes the close social contact between infants and caregivers that typically defines the first weeks and months of life. Disruptions to the social environment may continue during the transition home due to parental stress following early, and possibly ongoing, medical complications and physical separation. NICU graduates also are more likely to experience socioeconomic risk factors given racial/ethnic and economic disparities in preterm birth and NICU admission rates[14,15]. This complex array of variables may disrupt early social learning and development which may then cascade into higher level impairments in social communication and social-emotional development. While many of these challenges are shared among NICU graduates, the level and mechanisms of risk for ASD and other neurodevelopmental disabilities are expected to vary, at least partially, based on the unique circumstances of an infant's medical diagnosis and course. With regard to the existing literature, much of what is known about neurodevelopmental outcomes in NICU graduates to date comes from studies of very preterm (28–32 weeks gestation) and extremely preterm (<28 weeks gestation) infants.

Preterm infants—Several studies have reported an increased prevalence of ASD in preterm infants compared to healthy, term-born children. A recent meta-analysis of studies examining ASD in preterm infants ranging from 25 to 31 weeks gestational age (GA) found that the average likelihood of an ASD diagnosis across 18 studies was 7%, although there was substantial variability in the diagnostic rate among the included studies[16]. This rate is meaningfully higher than a recent estimated population rate of 1.7% ASD in the United States[17]. Other neurodevelopmental disabilities, such as cognitive impairment or intellectual disability, are generally reported to occur at higher rates than ASD in the preterm population. For instance, Hirschberger et al. found a 25% prevalence of cognitive impairment in a sample of extremely preterm children at 10 years old[18]. A meta-analytic review reported a pooled prevalence of cognitive impairment of almost 17% in young very preterm children, with mild impairments noted to be more common than more severe delays[19]. Generally, the likelihood of neurodevelopmental disabilities, such as ASD and intellectual disability, increase with decreasing gestational age and lower birth weight[20,21]. The relatively high rates cognitive impairment in the preterm population have likely contributed to unexpectedly high rates of elevations on ASD screeners, such as the Modified Checklist for Autism in Toddlers (M-CHAT)[22–25]. That being said, there is initial evidence of subclinical ASD symptoms and broader social deficits in preterm and low birth weight infants and children, including delayed social Competence[26], delays in joint attention[27–29], atypical social orienting[30], and empathy[31]. While these infants are often followed closely

by medical professionals, early social delays may be overlooked and require more focused monitoring[32].

Much of the research in NICU graduates to date has focused on cross sectional examination of the prevalence of ASD diagnosis among preterm and low birth weight infants rather than on early developmental trajectories or comparison with different risk groups. Recent work by Chen and colleagues, however, has uniquely sought to describe the development and phenotype of children born very preterm who are later diagnosed with ASD. In the first of these studies, the investigators followed a cohort of 246 very preterm infants in Taiwan (mean GA=28 weeks, mean birthweight=1066 g), of whom 7.7% met criteria for ASD at age 5[33]. The 18 preterm-born children with ASD were then matched to 44 term-born children with ASD and compared using direct assessment through the Autism Diagnostic Observation Schedule (ADOS) and caregiver report through the Autism Diagnostic Interview-Revised (ADI-R). While the groups did not differ in their ADOS severity scores or cognitive abilities, differences were identified via parent report on the ADI-R. Interestingly, the preterm ASD group was reported to be more symptomatic in the nonverbal communication domain, but less so in social-emotional reciprocity. The authors suggested that there may be unique neurobiological pathways to ASD in preterm children.

Chen and colleagues also examined early developmental trajectories using the Bayley Scales of Infant Development in a group of 319 very preterm infants, 29 (9.1%) of whom had ASD at age 5[34]. Infants fell into one of three groups, based upon a combined score derived from the Bayley cognitive and language scales, that differed by ASD rate: low declining (35% ASD), high declining (9%), and high stable (3%). Infants in the low declining group, in which scores were initially lower at 6 months then showed a decline between 12 and 24 months, were 15 times more likely to have ASD in comparison to those in the high stable group. Infants who were male, from families with lower maternal education, and had a longer duration of oxygen treatment were most likely to fall in the low declining group. These findings are strikingly consistent with studies examining developmental trajectories in familial-risk infants[11,35] and children with Tuberous Sclerosis Complex[36], reinforcing the importance of prospectively examining change over early infancy rather than just a cross-sectional snapshot. Studying these trajectories has the potential to deepen our understanding of how ASD unfolds in the first years of life across risk groups, and in many cases thus far has proved more accurate in predicting clinical outcomes than relying on a single time point.

Congenital heart disease

Rapid advances in effective surgical approaches to repair complex congenital heart disease (CHD) either prenatally or in early infancy have necessitated more attention to neurodevelopmental outcomes in these children[37]. This area is decidedly less well researched than the preterm population. Almost 1% of infants are born with a CHD[38], with survival rates of the more critical cases improving over the past several decades[39]. Given the direct biological effects of CHDs (such as early hypoxia), medical treatments (e.g., surgery), higher rates of associated genetic syndromes, and environmental stressors, it is not surprising that children with CHD have a higher likelihood of developmental delays and neurodevelopmental disabilities[40]. There is increasing evidence that ASD is more

common in these children than the general population. A recent large case-control study (ASD n=8760, Control n=26,280) based on documented CHD and ASD within a United States military database found that children with ASD had significantly higher odds of having CHD (4.6%) vs. control patients (2.5%), which remained after controlling for other relevant variables (e.g., genetic syndrome, preterm birth, low birth weight)[41]. Atrial septal and ventricular septal defects in particular were found to be more likely in the ASD group[41]. These findings are consistent with previous studies suggesting a modestly higher rate of ASD in children with CHD[42,43]. To our knowledge, there is not yet any published work that longitudinally examines infants with CHD with respect to their developmental trajectories or that has characterized differences and similarities in ASD phenotype in young children with CHD, although this research may be forthcoming[44].

Genetic Risk

Genetic testing is the only routinely recommended medical workup for a child with ASD, with hundreds of causative copy number variants and single gene disorders having been identified. Each of these genetic conditions is, individually, rare, accounting for less than 1% of the entire autism spectrum, but taken together these “syndromic neurodevelopmental disorders” do share some common features, such as a higher likelihood of global developmental delay, particularly motor deficits, and increased prevalence of medical comorbidities, such as epilepsy. These infants often are identified early in life, sometimes in utero, either through routine prenatal screening or after anomalies are identified on prenatal ultrasound, which has afforded the opportunity to study their early development.

As an example of the opportunities for early detection and intervention provided by early genetic testing, here we share insights gained through studies of the single gene disorder, Tuberous Sclerosis Complex (TSC). These infants are particularly well suited to the prospective examination of the emergence of ASD given the timing of TSC diagnosis and the high prevalence of ASD in this population.

TSC is a rare autosomal dominant disorder caused by mutations in the TSC1 or TSC2 genes. TSC is commonly diagnosed during infancy or even prenatally based on clinical presentation, usually due to the identification of cardiac or brain hamartomas[45–47]. Infants with TSC often first present with cardiac rhabdomyomas and/or skin lesions, with epilepsy presenting in most children within the first year of life[46]. TSC is strongly associated with neurodevelopmental disabilities. The two most common diagnoses are intellectual disability and ASD. Up to 80% of children with TSC experience some level of cognitive impairment, from milder learning disabilities to severe intellectual disability, and rates of ASD approach 60%[48–50].

To our knowledge, there have been two prospective, longitudinal studies of development in infants with TSC[36,51]. These infants demonstrate early delays in nonverbal cognition and social communication skills, and these delays are most prominent in those who develop ASD. By 9 to 12 months of age, social communication delays differentiate infants later diagnosed with ASD from those without ASD[52,53]. Moreover, TSC infants with ASD outcomes demonstrate a significant decline in their nonverbal cognitive abilities, relative

to peers, from 12 to 36 months of age, suggesting a greater divergence from typical development in the second and third years of life[36]. Early differences in brain development have also been identified, such as long range hypoconnectivity as quantified through resting state EEG[54,55]. Initial examination of the ASD phenotype in young children with TSC have revealed that core features of ASD are relatively similar in children with TSC vs. idiopathic autism[50,53], although more detailed examinations may reveal subtle differences in behaviors. These early detection studies in TSC have paved the way for the first randomized controlled trial of early behavioral intervention for social communication deficits in TSC (NCT02687633).

Implications for Next Steps

We have entered an era of precision health in neurodevelopmental disorders, with the promise of therapies that may target putative genetic mechanisms that underlie ASD, intellectual disability, and related conditions. However, we contend that the concept of precision should not be limited to the treatment target. Rather, it can also apply to the timing of treatment, founded on the overarching principle that the earlier we intervene, the more likely we are to exact meaningful, long term change. Certainly, more rigorous, large scale early intervention trials will be necessary to prove such a contention, but, in the meantime, studies of early detection can greatly improve our understanding of the exact timing at which interventions should be initiated. These studies have historically focused on infants with older siblings with ASD, but, as discussed in this review, other populations of high-risk infants warrant prospective investigation, such as NICU graduates and those with genetic syndromes that are known to be highly penetrant for neurodevelopmental disorders.

These expanded risk populations are more closely monitored medically and often are well integrated into larger health care systems due to comorbidities, a situation which presents both obstacles and opportunities. Sometimes the emphasis on more urgent medical issues, such as cardiac disease, upcoming surgeries, or epilepsy management appropriately distract attention away from neurodevelopmental trajectories. However, over time, as the medical concerns become less imminent or critical, the deprioritization of neurodevelopmental monitoring may persist and, as a result, emerging early signs of ASD or cognitive impairment can be missed, as might be the initiation of needed early interventions. Instead, the close surveillance these infants receive could be leveraged through the initiation and expansion of early developmental monitoring that accompanies routine medical care. These large scale developmental surveillance programs could then directly integrate with early intervention trials or programs.

Another promising area of progress includes increased availability of prenatal genetic testing that might identify ASD risk genes. As these rare causative variants and mutations are identified[56–58], research infrastructures will be necessary to support prospective developmental monitoring, scalable and rigorous common measures to be collected across conditions (including not only behavioral assays but also objective, quantitative biomarkers through methods such as EEG, eye tracking, and motor assessments) that ultimately could serve as “gold standard” screening tools. These tools need not have high predictive value for specific diagnoses, rather they would further stratify infants into risk categories that

would guide decisions around level of developmental surveillance or initiation of early interventions.

Lastly, as briefly described earlier, these studies of early detection can directly inform early intervention clinical trials, with creative designs such as staggered enrollment and longitudinal baselines that mitigate the need to wait for natural history studies to be complete before beginning treatment studies. In 2016, the US Preventative Services Task Force (USPSTF) was commissioned to review the literature on early screening and intervention for ASD. They found 26 randomized controlled trials of early intensive behavioral and developmental interventions for ASD in young children, but there was so much variability in intervention design, method of delivery, comparators, and outcomes measured, along with heterogeneity in the age, types of symptoms, and symptom severity of the children enrolled in trials, that they ultimately concluded that there was "insufficient evidence to assess the benefits and harms of screening for ASD in young children"[59]. This statement led to considerable public concern about the implication that the USPSTF was advocating against screening. However, the USPSTF responded by emphasizing that their findings should encourage more research in early detection and intervention, and we would add that these studies should include not only community screened or familial-risk infants but also a broader, albeit more complex cohort of infants with varying medical and genetic risk factors for neurodevelopmental disabilities. Moreover, as targeted therapeutics for specific genetic etiologies are developed, we will need to find ways to establish safety and feasibility of drug delivery in infants and toddlers to allow for enrollment of younger ages into these trials. Such efforts already have begun in conditions such as TSC (with MTOR inhibitors) and Angelman Syndrome (with the upcoming Antisense oligonucleotide trials).

Conclusions

In summary, it is essential that we move beyond studying only infants with a family history of ASD in our pursuit to understand autism as it emerges in the first years of life. The prospective study design that has been applied so successfully to the investigation of infant siblings of children with autism can be applied to other risk groups, including those with early medical challenges and genetic risk factors, to broaden our understanding and improve our ability to detect and appropriately intervene with at-risk infants at the earliest possible point. With improved precision in timing of risk detection across a broader range of infants, we will be able to develop and test monitoring and treatment strategies that can fundamentally improve long term clinical outcomes. Ongoing research will require multisite and multidisciplinary collaborations to improve sample sizes and to include these heterogeneous, clinically relevant risk groups.

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