Predicting Autism Spectrum Disorder in Very Preterm Infants

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Children born preterm are known to be at higher risk for developing autism spectrum disorder (ASD) compared with their term-born counterparts, with an estimated 7% prevalence of ASD based on a recent large prospective study and a meta-analysis.[1,2] This high prevalence is in contrast to the currently estimated prevalence of ASD in the United States of 1.8% in the general population.[3] ASD has been shown to be associated with a variety of prenatal, perinatal, and neonatal risk factors, including a variety of maternal health risk factors and medications and neonatal risk factors such as seizures, birth asphyxia, and low birth weight.[4] Previously identified perinatal risk factors for ASD specific to preterm infants include factors such as low birth gestational age and birth weight, intracranial hemorrhage, and acute and chronic lung disease (CLD).[5]

The article by Chen et al[6] in this issue of *Pediatrics* provides the first prospectively obtained data regarding whether there is an early developmental trajectory of prematurely born children that predicts who will develop ASD. The authors tested 319 preterm children prospectively with Bayley Scales of Infant Development examinations at 6, 12, and 24 months and used group-based trajectory modeling to assess whether early-life developmental trajectory predicted autism at 5 years of age. The approach of looking at developmental trajectory has been used in other high-risk populations, such as infant siblings of children with ASD[7] or those with a specific genetic disorder (tuberous sclerosis complex) with a high prevalence of ASD.[8]

The authors provide the first data revealing that although a small percentage of preterm infants who develop ASD have a similar early-life trajectory to that of term-born children, with decline in mental development from age 12 to 24 months,[9,10] the highest-risk group was identified as having low cognitive scores at 6 months, with further decline over time, allowing for early identification and intervention. The converse finding that infants with low cognitive scores who improve to >85 and those with stably high cognitive scores are at lower risk of developing ASD enables the clinician to provide reassurance to families.

Their analysis also illuminates risk factors for ASD related to preterm birth by comparing the 29 children who developed ASD with the 290 children without ASD. Notably, their study identified both nonmodifiable (eg, male sex, gestational age, and birth weight) and potentially modifiable risk factors (eg, CLD and duration of oxygen therapy) for the development of ASD. As the authors discussed, CLD is known to be a risk factor for developmental delay and cognitive impairment and/or disability, but it is unclear the extent to which the risk associated with CLD is related to brain injury and altered brain development.

One acknowledged limitation of the study was the lack of neuroimaging data, so it is unknown whether there was a contribution of identifiable brain injury to the development of ASD in their subjects. It is likely that at least

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some of the infants in the low cognitive score group had easily detected brain injury, such as large cerebellar injury[11] or cerebral injury and/or impaired brain development,[12–14] both of which are associated with low IQ and are suspected to increase the risk of ASD. Additionally, there were no data regarding genetic risk factors for ASD, which could contribute a "second hit" to risk factors related to prematurity. Numerous genes have now been identified to be associated with ASD and/or intellectual disability and could have contributed to some cases of ASD in this study. Male sex remains a strong risk factor for ASD in both preterm and term-born children, and particularly in preterm children, male sex may contribute to inherent genetic risks related to sex as well as increased vulnerability to complications of preterm birth that also increase the risk of ASD. The importance of neuroimaging and genetic data relates in part to the observation that preterm and term-born children with ASD have been shown to have important phenotypic differences. In one study, boys with ASD born preterm had higher rates of seizures, attention-deficit/hyperactivity disorder, and sleep apnea,[15] suggesting a potentially different neural substrate for ASD than term-born children.

Perhaps most importantly, these findings provide an opportunity for initiating interventions in early life to mitigate ASD before the diagnosis of ASD can be definitively established. Identification of a constellation of prenatal and neonatal risk factors could help clinicians target infants at highest risk, while providing reassurance to parents whose infants are at low risk. Identification of high-risk infants with low cognitive scores at 6 months of age or those with declining scores over time could provide another opportunity to intensify early intervention services aimed at mitigating manifestations and/or symptoms of ASD. Importantly, identification of high-risk infants by neonatal discharge and/or 6 months of age could improve research into novel therapies to mitigate the manifestations of ASD, such as communication and social-emotional deficits or impairments.

ABBREVIATIONS

ASD: autism spectrum disorder
CLD: chronic lung disease

REFERENCES

1. Hirschberger RG, Kuban KCK, O'Shea TM, et al; ELGAN Study Investigators. Co-occurrence and severity of neurodevelopmental burden (cognitive impairment, cerebral palsy, autism spectrum disorder, and epilepsy) at age ten years in children born extremely preterm. *Pediatr Neurol*. 2018;79:45–52
2. Agrawal S, Rao SC, Bulsara MK, Patole SK. Prevalence of autism spectrum disorder in preterm infants: a meta-analysis. *Pediatrics*. 2018;142(3):e20180134
3. Maenner MJ, Shaw KA, Baio J, et al. Prevalence of autism spectrum disorder among children aged 8 years - Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2016. *MMWR Surveill Summ*. 2020;69(4):1–12
4. Hisle-Gorman E, Susi A, Stokes T, Gorman G, Erdie-Lalena C, Nylund CM. Prenatal, perinatal, and neonatal risk factors of autism spectrum disorder. *Pediatr Res*. 2018;84(2):190–198
5. Kuzniewicz MW, Wi S, Qian Y, Walsh EM, Armstrong MA, Croen LA. Prevalence and neonatal factors associated with autism spectrum disorders in preterm infants. *J Pediatr*. 2014;164(1):20–25
6. Chen LW, Wang ST, Wang LW, et al. Early neurodevelopmental trajectories for autism spectrum disorder in children born very preterm. *Pediatrics*. 2020;146(4):e20200297
7. Landa RJ, Gross AL, Stuart EA, Faherty A. Developmental trajectories in children with and without autism spectrum disorders: the first 3 years. *Child Dev*. 2013;84(2):429–442
8. Spurling Jeste S, Wu JY, Senturk D, et al. Early developmental trajectories associated with ASD in infants with tuberous sclerosis complex. *Neurology*. 2014;83(2):160–168
9. Nishimura T, Takei N, Tsuchiya KJ. Neurodevelopmental trajectory during infancy and diagnosis of autism spectrum disorder as an outcome at 32 months of age. *Epidemiology*. 2019;30(suppl 1):S9–S14
10. Nishimura T, Takei N, Tsuchiya KJ, Asano R, Mori N. Identification of neurodevelopmental trajectories in infancy and of risk factors affecting deviant development: a longitudinal birth cohort study. *Int J Epidemiol*. 2016;45(2):543–553
11. Limperopoulos C, Bassan H, Gauvreau K, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? *Pediatrics*. 2007;120(3):584–593
12. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol*. 2009;8(1):110–124
13. Padilla N, Eklöf E, Mårtensson GE, Bölte S, Lagercrantz H, Ådén U. Poor brain growth in extremely preterm neonates long before the onset of autism spectrum disorder symptoms. *Cereb Cortex*. 2017;27(2):1245–1252
14. Stolp HB, Fleiss B, Arai Y, et al. Interneuron development is disrupted in preterm brains with diffuse white matter injury: observations in mouse and human. *Front Physiol*. 2019;10:955
15. Bowers K, Wink LK, Pottenger A, McDougle CJ, Erickson C. Phenotypic differences in individuals with autism spectrum disorder born preterm and at term gestation. *Autism*. 2015;19(6):758–763

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