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Multiple neonatal factors associated with autism spectrum disorders in infants

Sara Jane Webb

Seattle Children's Research Institute & University of Washington, Seattle, Washington, United States

Aetiology

Lower gestational age increases risk of autism spectrum disorder

Summary of the study

Participants

195 021 infants (24 weeks gestation) who survived until discharge from hospital. The following were excluded: infants with missing data on maternal age, gestational age or gender; infants who changed hospitals during birth hospitalisation; infants who were no longer in the Kaiser Permanente (KP) health plan at two years. Participants were representative of the general population (except for highest and lowest income earners). Children subsequently diagnosed with autism spectrum disorder (ASD; ICD-9), either at a KP ASD evaluation centre, or by a specialist or general practitioner, were identified from the KP Autism registry, which contains details of all children diagnosed with ASD. Children with symptoms indicating possible ASD but without formal evaluation were excluded.

Setting

Kaiser Permanente Northern California hospitals; recruitment January 1 2000 to December 31 2007.

Exposure

Gestational age from obstetrically assigned estimated date of confinement. For infants with a gestational age of <34 weeks, procedures performed (mechanical ventilation, transfusion, inotropic support or chest compressions) and diagnoses (intracranial haemorrhage, cystic periventricular leukomalacia, bacteraemia or necrotizing enterocolitis (Bell stage II)). Data were collected retrospectively.

Follow up period

Three years minimum.

Competing interests

None

Outcomes

Prevalence of ASD

Overall, 2457 children were diagnosed with ASD (1.26%). Prevalence of ASD was significantly higher among infants born at <37 weeks (1.78%) compared with infants born 37 weeks (1.22%; $p<0.001$).

Risk factors for ASD

Gestational age of 24 to 26 weeks significantly increased risk of ASD compared with term (gestational age 37 to 41 weeks) (hazard ratio (HR)=2.7, 95% confidence interval (CI) 1.5 to 5.0; adjusted for covariates of maternal age and education, sex, and being small for gestational age (SGA) and caesarean delivery). Infants born at 27 to 33 weeks were also at significantly increased risk of ASD compared with term infants (HR=1.4, 95% CI 1.1 to 1.8), as were infants born at 34 to 36 weeks (HR=1.3, 95% CI 1.1 to 1.4).

Independently of gestational age, SGA significantly increased risk of ASD (HR=1.5, 95% CI 1.1 to 1.9). However, in infants born at <34 weeks the risk association between SGA and ASD increased (HR=3.0, 95% CI 1.4 to 6.3). Among infants born at <34 weeks, risk of ASD was also significantly increased with presence of intracranial haemorrhage (HR=1.9 for grade 1 or 2 bleed (95% CI 1.1 to 3.4) and HR=3.4 (95% CI 1.4 to 8.6) for grade 3 or 4 bleed) and need for high frequency ventilation (HR=2.2, 95% CI 1.1 to 4.6).

Commentary

What is already known on this topic?

Autism spectrum disorders (ASD) have a prevalence rate of at least 1 in 68 among children;¹ with genetic, familial (eg, maternal and paternal age), prenatal (eg, low birth weight and prematurity) and perinatal factors associated with an increased risk for later development of ASD.^{2,3}

What does this paper add?

- The likelihood of an ASD diagnosis increased with decreasing gestational age and decreasing birth weight. High frequency ventilation and intraventricular cranial hemorrhages (ICH) were also related to increased risk.
- ASD outcome was established through a combination of tools; results were stable regardless of diagnostic pathway.

Limitations

- Not all potentially confounding variables were available on all infants; for example, only 76% of infants <34 weeks had an ultrasound examining ICH.
- Premature children who developed ASD were more likely to have other developmental disabilities, reinforcing our understanding that this may be a particularly vulnerable group.
- The findings do not address the mechanisms or causal pathway to ASD.

What next in research

Sex (ie, being male) and familial history (ie, having an older sibling with ASD) represent the greatest known risks for development of ASD. A number of genetic mechanisms have also been found to be contributors to an ASD diagnosis. Incorporation of genetic findings with specific assessment of prenatal and neonatal factors will help to focus our understanding of the factors that contribute to ASD outcomes.^{2,3} Genetic vulnerabilities may be exacerbated by specific environments, resulting in an atypical cascade of neural development that is specific to ASD.

Elucidation of the causal pathway to ASD is complex and likely heterogeneous. Further understanding of the biological mechanisms that result in prematurity, as well as those that protect against it, will be important to examine in relation to other ASD risk characteristics.

Could these results change your practices and why?

No. However, this supports the emphasis on early monitoring of children born premature and with medical complications. As well, better implementation of integrated electronic medical records that include information about psychological and intellectual functioning will allow us to examine the sensitivity and specificity of developmental trajectories resulting in ASD.

These data suggest that infants with specific prenatal or neonatal events such as prematurity, small for gestational age, ICH, and ventilation may be more vulnerable to poor outcomes and should be monitored so that early concerns can be quickly addressed through reference to specialized early evaluation and treatment programs.

References

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