Dr. Oswald's Corner

Comments on recent autism-related research reports

Epidemiology of Autism

A recent paper published in the *Annual Review of Public Health* (Lyall et al., 2017) offers a summary of the state of the science with respect to the epidemiology (i.e., the incidence, distribution, and possible control) of autism. This abstract quotes the main conclusions of that paper.

PHENOTYPE AND DIAGNOSIS

- Onset of ASD symptoms typically occurs by age 3, although symptoms may not fully manifest until school age or later; symptoms can emerge between 6 and 18 months of age.
- Common ASD-associated impairments include intellectual disability [currently estimated to occur in ~30% of cases and historically estimated at ~70%] and attention deficits (occurring in ~30–40% of cases).
- The conceptualization of ASD as a discrete phenotype is being increasingly questioned. The NIMH Research Domain Criteria initiative encourages researchers to focus on core behavioral and neurobiologic features that cross diagnostic categories.

PUBLIC HEALTH IMPACT

- The annual total costs associated with ASD in the United States approach $250 billion
- Lifetime individual ASD-associated costs: $1.5 to $2.5 million.

PATHOPHYSIOLOGY

- The neural mechanisms underlying the impairments observed in ASD remain unknown.
- Evidence of early brain overgrowth in ASD fairly consistently supported . . . Imaging studies have indicated changes in functional connectivity and hypoconnectivity across brain structures. Anatomic differences in brain substructures (cerebral cortex and cerebellum), continue to be found
- Metabolism, gut, and immune function abnormalities have been frequently described in ASD.

DESCRIPTIVE EPIDEMIOLOGY

- In the U.S. in 2012, the CDC estimated that approximately 1.5% of children aged 8 years had an ASD
- Nonwhite race, Hispanic ethnicity, and low socioeconomic status (SES) have been associated with lower ASD prevalence and delayed diagnosis
- The World Health Organization estimated that 0.76% of the world's children had ASD in 2010

GENETIC EPIDEMIOLOGY

- The genetic contribution to ASD etiology is strongly supported . . . Recent heritability estimates in the United States and Europe ranging from 50% to 95%. Estimates of recurrence risk among siblings of autistic children range from 3% to 18%.
- Genetic studies have been quite successful at identifying rare genetic variation related to autism or autistic features. However, observations of specific rare de novo and inherited CNVs have been limited to a small portion (about 10%) of children with nonsyndromic autism [i.e., autism not related to a known genetic disorder].
- Gene-by-Environment Interaction: Conflicting evidence about the contribution of environmental factors to the etiology of ASD. . .[e.g.,] interactions between the MET gene risk variant and prenatal exposure to air pollutants, variants in the one carbon metabolism pathway and maternal use of prenatal vitamins, and ASD-associated CNVs and maternal prenatal infection.
- Epigenetics: molecular information that sits on top of the DNA sequence and regulates cellular processes, including imprinting, gene expression, and organismal development. . .findings highlight the future potential for epigenetics to serve as a biomarker of disease.
- Genomics and Neurobiology: Analysis of rare [genetic] variants linked to ASD has revealed three common biological pathways—chromatin remodeling, synaptic cell adhesion and scaffolding, and neuronal signaling and development.

ENVIRONMENTAL RISK FACTORS

- Prenatal and Perinatal Factors
  - Increased parental age is one consistently identified perinatal risk factors for ASD
  - Interpregnancy interval. Increased risk with a <12 months interpregnancy interval (IPI); although evidence is more limited, three studies reported increased risk from long IPI.
  - Immune factors. Maternal hospitalization with infection during pregnancy and familial history of autoimmune disease associated with increased risk of ASD.
  - Medication use. Recent associations between ASD and prenatal medications have included antidepressants, antiasthmatics, and antiepileptics. Antidepressants, particularly selective serotonin-reuptake inhibitors (SSRIs), are the medications most investigated; evidence is conflicting, with six studies reporting increased risk and five finding no association. Recent studies of antiepileptics and B2AR antiasthmatics have consistently identified increased risk of ASD or autistic traits with exposure during pregnancy.
  - Lower gestational age/preterm birth and small- or large-size-for-gestation independently increase risk of ASD. . . increased ASD risk from maternal metabolic conditions (including gestational weight gain, diabetes, and hypertension) . . .Other factors less consistently associated with increased ASD risk include caesarian delivery and assisted conception.
  - Increasing numbers of suboptimal conditions in pregnancy generally pose increasing risk of ASD and adverse developmental outcomes
- Maternal Dietary and Lifestyle Factors
  - Folic acid and related nutrients. Two studies have suggested an approximately 40% reduction in risk for ASD with periconceptional folic acid supplement use.
  - Other prenatal nutrients. Other nutrients have been associated with ASD, but to date their examination during the prenatal period has been extremely limited.
- Alcohol and Smoking
  - Evidence from the existing literature suggests that maternal prenatal use of these substances does not affect ASD risk.
- Environmental Chemicals
  - Prenatal exposure to air pollution has emerged as a candidate risk factor for ASD.
  - Evidence with respect to early life exposure to endocrine-disrupting chemicals (EDCs) and ASD risk remains sparse, and findings are inconsistent.
  - Heavy metals such as lead and mercury are established neurotoxicants with documented impacts on cognitive and developmental outcomes; some metals may also act as EDCs. ASD risk following prenatal exposure to mercury through fish or other sources has received little study, but it has not been associated with ASD in available evidence. . . Epidemiologic evidence to date has consistently shown no increased risk of ASD with vaccines.

FUTURE DIRECTIONS AND CONCLUSIONS

- Challenges in ASD descriptive epidemiology for the next decade include characterization of the impact of the shift to DSM-5; deeper exploration of the interplay of race, ethnicity, and SES on ASD distribution and addressing of diagnostic disparities related to these factors as well as to sex; more robust comparisons of ASD characteristics across sexes; and enhanced effort to describe the epidemiology of ASD over the life course and in developing nations around the world. Population-level surveillance efforts could increase tracking of key continuous traits underlying the ASD phenotype (in addition to the condition itself), which could have potentially profound implications for research and public health.
- Recent developments continue to reveal complexity in the genetic epidemiology of ASD.
- Epidemiologic investigation of potentially modifiable risk factors has grown markedly over the past decade.
- The innovation around biomarkers of exposure and exposure response prompted by increased interest in the field of exposomics [the study of all the exposures of an individual in a lifetime and how those exposures relate to health] might catalyze further advances.

Lyall, K., Croen,L., Daniels, J., Fallin, M.D., Ladd-Acosta, C., Lee, B.K., Park, B.Y., Snyder, N.W., Schendel, D., Volk, H., Windham, G.C., & Newschaffer, C. (2017). The Changing Epidemiology of Autism Spectrum Disorders. *Annual Review of Public Health, 38*:9.1–9.22. doi: 10.1146/annurev-publhealth-031816-044318

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