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Probability of an Autism Diagnosis by Gestational Age☆,☆☆

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ABSTRACT

Early preterm infants (EPT) (<33 6/7 weeks) are at increased risk for autism spectrum disorders (ASDs) but prevalence estimates vary widely across studies. Furthermore, there are very few studies addressing the association between late preterm (LPT) births (34–36 6/7 weeks) and ASDs. To address the question of whether LPT infants carry the same risk for ASDs as full-term infants, this study aimed to estimate the relative probability of an ASD diagnosis using Bayes rule. A retrospective cohort analysis of 406 children was undertaken to look at gestational age, ASDs, and birth history. The application of Bayes rule was used, given that there is not sufficient information about the joint probabilities related to prematurity and autism. Using the estimated gestational age proportions within ASD diagnosis, plus national estimates of ASDs, probabilities for ASDs within a given gestational age were calculated. Among these 406 children with ASDs, 6.7% were EPT and 10.6% were LPT. In comparison to full term, EPT children are at 1.9 multiplicative increase in risk (95% CI [1.3, 2.5]). While the probability of ASDs for LPT children was higher than that for term, the estimated relative risk of the LPT infants was not statistically significant (95% CI [0.9, 1.5]). EPT infants were significantly more likely to be diagnosed with ASDs compared to their term peers. While the relative probability of ASD diagnosis among children born LPT was not statistically significant in this limited sample, the results indicate a possible elevated risk. A larger cohort is needed to adequately estimate this risk.

Autistic spectrum disorders (ASDs) are neurodevelopmental disorders characterized by impaired communication, social interaction, and behavior.[1] According to the Centers for Disease Control & Prevention (CDC), the prevalence of ASDs has increased over the past two decades and is estimated to affect one in 88 children in the United States.[2] Major advances in autism research have led to the development of validated autism screening tools that have facilitated early autism detection for children at risk for these disorders. Recent evidence suggests that early preterm birth (<32 weeks) is a risk factor for autism.[3–7] Like autism, the prevalence of preterm infants, particularly moderate (32–33 6/7 weeks gestation) to late preterm (34–36 6/7 weeks), has increased in the last two decades.[8,9] Moderate to late preterm infants make up 70% of all preterm births and are at risk for poor neurodevelopmental sequelae.[10] However, studies estimating the prevalence of ASDs in late preterm infants (34–36 6/7 weeks) are lacking.[8]

To address the gap in knowledge of whether late preterm infants are at higher risk for ASDs than full-term infants, this study estimated the relative probability of an ASD diagnosis by gestational age using Bayes rule in a cohort of patients screened at a large autism center in the southeastern United States between March 2009 and December 2010.

Background and Significance

Autism spectrum disorders (ASDs) are a group of complex developmental syndromes of the central nervous system that are characterized by restricted behaviors and deficits in communication and social interactions. Although neuropathology of ASDs varies across cases, the most consistent pathology includes curtailment of normal development of the limbic system and abnormal development of the cerebellum and associated nuclei.[11,12] While the pathogenesis of ASDs is not fully understood, evidence supports the hypothesis that ASDsdevelop in children with a genetic susceptibility who experience abnormal stressors during a critical period of brain development.[6]

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Research points to the potential role of neurological insults in preterm infants in the development of ASDs. Preterm birth is associated with high rates of perinatal brain injury and interrupts a critical period for brain growth and structural differentiation.[13,14] A significant proportion of brain growth and development, including that of cortical gray matter, white matter, and the cerebellum, occurs during the last six weeks of gestation.[15] Knowledge regarding brain development in preterm infants derives primarily from the large body of literature surrounding infants born less than 32 weeks gestation and very low birth weight infants (<1500 g).[3–7] Neurodevelopmental abnormalities are well recognized among very low birth weight and very preterm infants (<32 weeks) and a growing line of evidence supports prematurity as a risk factor for ASDs.

Multiple prospective studies of very preterm or very low birth weight children screened for autism at less than 3 years of age demonstrate an elevated prevalence of autism in the preterm population compared to the general population. Estimated prevalence ranged from 12% to 41%.[3–7] Similarly, preterm toddlers born <30 weeks gestation scored higher on the Quantitative Checklist for Autism in Toddlers, indicating greater restrictive, stereotyped, and repetitive behavior as well as greater social communication difficulties.[16] These deficits seem to persist throughout childhood into adolescence as shown by Pinto-Martin et al.[17] In a regional and longitudinal cohort study, prevalence of autism in 623 adolescents with a history of birth weight <2000 g was 5%, approximately five times higher than the CDC reported prevalence for the general population.[17] The prevalence estimates of ASDs for early preterm infants vary widely, with estimates varying from 5% to 41% depending on the study referenced.

While much is known about the neurodevelopment of very preterm infants, less is known regarding brain development and cognitive outcomes of late preterm infants[18–20] despite the fact that late preterm infants comprise the largest and fastest growing segment of premature infants.[8,21] Typically, late preterm infants are perceived to be at similar risk for developmental issues as full-term infants and are often clinically treated in the same manner as their term counterparts. Emerging evidence suggests that neurologic morbidity and ASDs may also be a problem in late preterm infants.[22–25]

Few studies have examined ASD diagnosis across the spectrum of gestational age, however, there have been some studies that have shed light onto this subject using ASD screening tools. Pinto-Martin et al. found higher rates for autism screening and autism diagnosis in infants born less than two kilograms and Guy et al. found that late and moderately preterm infants are at increased risk for a positive autism screen at 2 years, but did not go on to discuss findings related to autism diagnosis. Kuzniewicz and colleagues demonstrated higher prevalence of ASDs in all preterm infants, including moderate and late preterm infants, relative to term infants at two years of age.[23,26] In a recent study, 4100 mothers with children with an already diagnosed ASD voluntarily completed two validated ASD questionnaires that screen for autistic characteristics.[25] Results indicated a higher degree of autism characteristics for preterm (<37 weeks) infants than for infants born at a normal gestational age.[25] These results suggest that normal gestational age at birth mitigates the severity of symptomology of ASDs. Further studies to confirm these findings are needed.

As described above, research estimating diagnosis of ASDs in late preterm infants is sparse and estimates of ASDs in all preterm children vary greatly. Identification of risk factors can lead to early diagnostic evaluations and referrals needed to receive support and interventions to minimize poor neurologic outcomes. Despite the need to better understand the relationship between prematurity and ASDs, estimation of this relationship is difficult. Direct estimation of the probability of ASDs in relation to gestational age is complicated by both the inherent variation in diagnosis and the relatively low joint prevalence of ASDs and prematurity. This issue is illustrated in a study by Kuban et al. who reported that prevalence of autism rates in extremely preterm children was reduced when children with sensory and cognitive impairments were excluded from analysis.[5] This highlights the need to develop alternative ways of estimating risk in preterm populations.

The application of Bayes Rule in estimating the probability of given conditions in a clinical sample using known population parameters has a long history.[27,28] The application of Bayes rule in this study is appropriate, given that there is not sufficient information about joint probabilities related to prematurity and autism. The rule of Bayes Rule calculates a posterior probability, or the probability of a diagnosis given knowledge of certain conditions, by taking into account empirical data from an experiment and known probabilities from other sources.

Using Bayes rule does not assume that the clinical information is completely accurate and thus accounts for the possibility of both false positive and false negative ascertainment of a disease status and may therefore provide a more robust assessment of the probability of ASDs given gestational age.[29] However, there is little evidence in the literature of its application toward estimation of risk factors associated with ASDs. In this study, we estimate the probability of an ASD diagnosis in preterm children across the range of gestational ages, including late preterm infants, using Bayes rule.

Methods

Sample & Measures

This study involved a retrospective analysis of data ascertained from a cohort of children treated at the Pediatric Neurodevelopmental Clinic (PNC) at a large center for excellence in autism in the southeast portion of the United Sates. The center provides approximately 2500 diagnostic evaluations annually and served 4823 children during 2010, 28% of whom were African American and 70% of whom relied on Medicaid. For this study, IRB approval was obtained and data were abstracted from in-depth medical records to obtain ASD diagnosis and phenotype, gestational age, and timing of autism diagnosis. In addition, demographic information and birth history were also obtained from medical records. The inferences made in this study are on the population of referred children, a population with a higher proportion of ASDs than the general population.

ASD diagnosis was identified in the medical record based on multidisciplinary assessments conducted by the PNC. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) describes five categories of disorders that collectively comprise the Pervasive Developmental Disorders (PDD). PDD is widely used by professionals to refer to children with autism spectrum disorders (ASDs). In the DSM-IV, the term "PDD" is not a specific diagnosis but an umbrella term under which these disorders are included: Autism, Childhood Disintegrative Disorder, Rett's Syndrome, Asperger's Disorder and Pervasive Developmental Disorder Not-Otherwise-Specified. According to Autism Speaks, "psychologists and psychiatrists sometimes use the term pervasive developmental disorders and autism spectrum disorders interchangeably".[30] While there are slight differences in the configuration of symptoms in each of these categories of PDD, diagnostic labels are used to indicate commonalities among individuals. The diagnosis of ASDs indicates qualitative impairments in social interaction and communication, and the presence of restricted, repetitive and stereotyped patterns of behavior, interests and activities. Most importantly, whether a child is diagnosed with a PDD, his/her treatment will be similar (Autism-society.org). Children with any of the diagnoses noted above were included in our sample as having a diagnosis of autism spectrum disorders (ASDs).

All assessments were conducted by a pediatric psychologist and either a developmental pediatrician or pediatric nurse practitioner. In addition to a review of records, thorough medical and family history, and a physical exam, each child received a battery of psychological tests. The specific battery of tests was chosen by the psychologist based on the individual child's presenting concerns, age, and level of skill. Most assessments included a structured diagnostic play session (most commonly