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Autism Spectrum Disorder is associated with ventricular enlargement in a Low Birth Weight Population

Tammy Z. Movsas, MD, MPH [Medical Director],

Midland County Dept of Public Health Clinical Assistant Professor of Pediatrics & Human Development, Michigan State University 220 West Ellsworth St Midland, MI 48640

Jennifer A. Pinto-Martin, PhD, MPH,

Univ of Pennsylvania School of Nursing and School of Medicine

Agnes H Whitaker, MD,

New York State Psychiatric Institute, Dept of Psychiatry, Columbia Univ Medical Center

Judith F Feldman, PhD,

New York State Psychiatric Institute, Dept of Psychiatry, Columbia Univ Medical Center

John M Lorenz, MD,

Dept of Pediatrics, College of Physicians and Surgeons, Columbia Univ Medical Center

Steven J Korzeniewski, PhD,

Perinatal Research Unit, Wayne State University

Susan E Levy, MD, and

The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine

Nigel Paneth, MD, MPH

Dept of Epidemiology & Biostatistics and Pediatrics & Human Development, College of Human Medicine, Michigan State Univ.

Abstract

Objective—To determine the relation of neonatal cranial ultrasound abnormalities to autism spectrum disorders (ASD) in low birthweight (LBW) adult survivors, a population at increased ASD risk.

Study design—This is a secondary analysis of a prospectively-followed regional birth cohort of 1105 LBW infants systematically screened for perinatal brain injury with cranial ultrasound in the first week of life and later assessed for ASD using a two-stage process [screening at age 16 years (N=623) followed by diagnostic assessment at age 21 years of a systematically selected subgroup of those screened (N=189)]; 14 cases of ASD were identified. For this analysis, cranial ultrasound

Corresponding Author:tmovsas@gmail.com, Phone: 1-989-430-7437 Fax: 1-866-519-7510.

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abnormalities were defined as ventricular enlargement (indicative of diffuse white matter injury), parenchymal lesions (indicative of focal white matter injury) and isolated germinal matrix/intraventricular hemorrhage (GM/IVH).

Results—Compared with no cranial ultrasound abnormalities, any type of white matter injury (ventricular enlargement and/or parenchymal lesion) tripled the risk for screening positively for ASD [3.0 (2.2, 4.1)]. However, the risk of being diagnosed with ASD depended on type of white matter injury. With ventricular enlargement, the risk of ASD diagnosis was almost seven-fold that of no cranial ultrasound abnormality [6.7 (2.3, 19.7)], and no elevated risk was found for parenchymal lesion without ventricular enlargement [1.8 (0.2, 13.6)]. Isolated GM/IVH did not increase risk for a positive ASD screen or diagnosis.

Conclusion—In LBW neonates, cranial ultrasound evidence of ventricular enlargement is a strong, and significant risk factor for subsequent development of rigorously-diagnosed ASD.

Keywords

preterm; autism screening; ventricular enlargement; autism diagnosis

Converging lines of evidence suggest that autism spectrum disorders (ASD) reflect genetic predispositions modified by other risk factor interactions (gene-gene or gene-environment interactions) occurring pre-, peri- and/or post-natally (1-2). Consistent with the known importance of pre-, peri- and neonatal factors, the risk for ASD in low birth weight (LBW)/preterm children is two to five fold higher than in the general population (3-6). Medical complications of prematurity may contribute to the increased risk of ASD in these infants. Among these complications are forms of perinatal brain injury that are detectable with cranial ultrasound in the first week of life. Because neonatal cranial ultrasound abnormalities are associated with several adverse neurodevelopmental and neuropsychiatric outcomes (7-10), a potential relation of cranial ultrasound abnormalities to ASD is of particular interest.

Neonatal cranial ultrasound is the most widely used imaging technique for screening preterm and LBW infants for perinatal brain injury (11-12). Aimed through the anterior fontanelle, cranial ultrasound can detect three types of abnormalities that may occur in isolation or in combination: germinal matrix and/or intraventricular hemorrhage (GM/IVH), parenchymal lesions that reflect focal ischemic or hemorrhagic injury to white matter, and ventricular enlargement. Ventricular enlargement may sometimes represent post-hemorrhagic hydrocephalus, but more commonly, it reflects diffuse loss of white matter volume (hydrocephalus ex vacuo) (13).

The Neonatal Brain Hemorrhage Study is a longitudinal, prospective study of a regional low birth weight population systematically screened for neonatal cranial ultrasound abnormalities. Previous reports on this cohort have shown that neonatal cranial ultrasound abnormalities are powerful predictors of disabling cerebral palsy by age two, severe cognitive deficiency at age 6 and certain neuropsychiatric disorders (attention deficit hyperactivity disorder, tic disorders, obsessive-compulsive disorder, and major depressive disorder) by age 16 (7-10). These disorders are thought to reflect disturbance of corti-

subcortical circuits. Because ASD is also thought to involve abnormalities of these circuits, we hypothesized that neonatal cranial ultrasound abnormalities may be associated with ASD.

Methods

This secondary data analysis of longitudinal Neonatal Brain Hemorrhage Study data was approved by the Institutional Review Board of Michigan State University.

Enrollment in the Neonatal Brain Hemorrhage Study consisted of 1105 infants weighing between 500 g and 2000 g who were born-in or transferred into three Central New Jersey study hospitals between 8/27/1984 and 6/30/1987. In the first year of the study 598/687, (87%) of all babies < 2000 g born in one of the three counties of Central New Jersey (Middlesex, Monmouth, Ocean) were enrolled (7). Of the 1105 infants enrolled, 212 were known to have died and 31 were known to have been adopted. Of the 862 remaining children, 628 were recruited for a followup assessment at age 16. All but five completed autism screen, leaving 623 as the study population at age 16. Of note, there were no significant differences in mean gestational age, birth weight, or small for gestational age status between the cohort screened for ASD (N=623) and those eligible for screening but not screened for ASD (N=239) (14). The two groups differed significantly only with respect to lower maternal social risk at birth in those screened (14).

Cranial Ultrasonography

Three cranial ultrasounds were performed: at age 4 hours, 24 hours and 7 days. Among 1105 enrolled infants, 1088 (98.5%) received at least one protocol ultrasound scan. The specific methodology for the ultrasound protocol has been previously described (15). Data recorded on each ultrasound included: presence of germinal matrix (GM) hemorrhage; intraventricular hemorrhage (IVH); presence and location of ultrasonographic parenchymal echogenic or echolucent lesions; and moderate or severe ventricular enlargement. Although we are aware that sonographers often make pathologic diagnoses based on ultrasound images, it has been our practice in all papers regarding the Neonatal Brain Hemorrhage Study project to describe the ultrasound images and not to assign diagnoses to them. With that said, what is generally referred to as periventricular leukomalacia on ultrasound would be encompassed by what we here refer to as parenchymal lesions, and would not be reflected in the finding of ventricular enlargement. Though about half of enrollees had additional cranial ultrasound performed at a later date, only protocol ultrasound scans were used in this analysis.

Films were read first by a radiologist at the infant's hospital and then submitted to second reader from another hospital. Concordance between the first two readers as to the presence of GM/IVH and parenchymal lesions and ventricular enlargement was achieved in 836 of 1014 reviewed scan sets (82.4%) (15). When first two readers disagreed as to the presence of GM/IVH hemorrhage or parenchymal lesion and/or ventricular enlargement, the infant's entire scan file was submitted to a third reader from the pool. In such cases, the final diagnosis reflected the consensus of two of three readers (15).

ASD Screening Procedure at Age 16 Years

As part of a larger psychiatric follow up study(10), parents of 623 study participants completed at least one of two research-validated ASD screening instruments: the Social Communication Questionnaire and the Autism Spectrum Screening Questionnaire. As described in detail elsewhere (14), a participant in the 16 year follow-up was considered “screen positive” if he/she met any of the following criteria: (a) a score of 9 or above on the Social Communication Questionnaire, (b) a score of 12 or above on the Autism Spectrum Screening Questionnaire, or (c) history of professional diagnosis of ASD. The cut-points for the screening tools at age 16 were designated to cast as wide a net as possible, and were thus lower than the customary values of 15 for the Social Communication Questionnaire (16) and 22 for the Autism Spectrum Screening Questionnaire (17). Using one or more of these criteria, 117/623 (18.8%) of the cohort screened positive for ASD. Also available for this analysis were the Wechsler abbreviated scale of intelligence and Riley Motor Problem Inventory scores from the age 16 follow-up (18).

ASD Diagnostic Procedure at Age 21 Years

As described in detail elsewhere (14), 189 cohort members of the 623 who had been screened for ASD were assessed at age 21 years for a diagnosis of ASD with The Autism Diagnostic Observation Schedule (ADOS) and/or Autism Diagnostic Interview-Revised (ADIR). An ASD diagnostic assessment was completed on 60% (70/117) of those who had screened positive for ASD at age 16 and a sample of 119 of the 506 (24 %) who had screened negative. Characteristics of those who were and were not retained in the sample from 16 to 21 years of age were not dependent upon ASD screen status except for one component of maternal social risk (receipt of public assistance); sex, birth weight, gestational age, and small-for-gestational-age status have been previously been shown not to be significantly related to the diagnosis of ASD(14).

The diagnosis of ASD was considered present if the young adult scored positive on the ADOS or ADIR using published algorithms. Of the 189 study participants assessed, 14 (7.4%) were diagnosed with ASD. The screen positive sample yield 11 cases (15.7 %), and the screen negative sample yielded 3 cases (2.5%).

Statistical Analyses

Contingency tables were constructed to calculate ASD risk and statistical analyses were performed with SAS statistical software (SAS Institute Inc, Cary, NC). Due to the small number of participants who screen positive for ASD (total of 14) and ventricular enlargement (total of 12) in our dataset, only univariate analyses were performed with the exception of the construction of one contingency table stratified by sex.

Results

Characteristics of the Cohort

Table I compares characteristics of the study participants who were assessed for ASD at age 21years (N=189) by ASD status; Table I includes many of the obstetric, birth, and postnatal factors that have been shown to be associated with higher incidence of ASD (19-20). We

found that a significantly higher percentage of study participants who screened positive for ASD had been born to mothers with maternal hypertension. We also found that the percentage of cerebral palsy and/or motor impairment in ASD positive young adults was significantly higher than that of the young adults who screened negative for ASD.

Risk of ASD Positive Screen by cranial ultrasound status

Compared with participants who had no evidence of neonatal cranial ultrasound abnormalities, the risk for screening positively for ASD with cranial ultrasound evidence of white matter damage was tripled. This risk did not vary by presence of ventricular enlargement. Isolated GM/IVH did not increase risk of positive screen. The association of ventricular enlargement with ASD positive screen did not differ by sex (data not shown).

Ultrasound Findings of young adult cohort assessed for ASD by ASD Diagnosis

A significantly different percentage of abnormal cranial ultrasound was found between those with and without ASD. However, a significant difference in abnormal cranial ultrasound did not exist between those from original cohort who were not followed till age 21 (N=916) compared with this young adult group who were assessed for ASD (N=189; data not shown). The prevalence of ASD was found to be significantly higher in young adults who had neonatal ventricular enlargement compared with those with no neonatal US abnormalities. Of note, only one of the 12 cases of ventricular enlargement in the cohort assessed for ASD was isolated; the other 11 had been accompanied by other cranial ultrasound abnormalities.

Risk of ASD Diagnosis by cranial ultrasound status

The risk of being diagnosed with ASD depended upon type of white matter damage. With ventricular enlargement, the risk of ASD diagnosis rose almost seven-fold over those with no evidence of neonatal cranial ultrasound abnormality, and no significantly elevated risk was found for parenchymal lesion without ventricular enlargement. The risk for ASD diagnosis with any combination of ventricular enlargement and/or parenchymal lesion was the same as the risk for ventricular enlargement alone. Isolated GM/IVH did not increase risk of ASD diagnosis.

Discussion

In a prospective study of low birth weight infants assessed for ASD at 21 years of age with validated instruments, we found a strong and significant association between the presence of ventricular enlargement on cranial ultrasound in the newborn period and risk of ASD. The data did not allow a definite conclusion to be drawn regarding the relationship of parenchymal lesion to the diagnosis of ASD. However, both forms of white matter injury (parenchymal lesion and ventricular enlargement) were associated with screening positively for ASD in adolescence. GM/IVH did not increase the risk for either ASD screening positivity or ASD diagnosis.

The only prior study to investigate the relation between neonatal cranial ultrasound abnormalities and ASD used only an ASD screening tool (21). That study reported that in

very preterm infants, cranial ultrasound abnormalities (without further specification as to type of cranial ultrasound abnormality) were associated with higher ASD screening scores on the Social Communication Questionnaire (21).

Damage to immature white matter identified on neonatal cranial ultrasound, such as parenchymal lesion and/or ventricular enlargement, has been previously shown in this cohort to increase risk for several developmental neuropsychiatric disorders (attention deficit-hyperactivity disorder, attention deficit hyperactivity disorder, obsessive-compulsive disorder, and depressive disorder) in which disturbances of circuits involving the cortex and striatum have been implicated (8, 10). ASD is also considered to be a neurodevelopmental disorder of cortico-striatal circuits (22). Our finding that both parenchymal lesion and ventricular enlargement increase the risk of screening positively for ASD may suggest an overlap between some ASD characteristics short of the ASD diagnostic threshold and other developmental neuropsychiatric disorders. However, for diagnosed ASD, the only cranial ultrasound abnormality significantly associated with ASD is ventricular enlargement. Ventricular enlargement seen in preterm infants is a generally a mark of diffuse white matter damage and loss of white matter volume (13, 23-25). One caveat, however, is that some forms of diffuse white matter injury are not readily seen on cranial ultrasound (26-27). Thus, ventricular enlargement and/or parenchymal lesion visible on cranial ultrasound is probably only part of the full spectrum of white matter damage (28-31).

The present results are consistent with those from a recent MRI imaging study of high functioning children with ASD aged between 7 and 15 years (32). That study found that, on average, the total brain and grey matter volume was 6% greater in individuals with ASD, and ventricular volume was 40% larger in ASD than in controls matched for sex, age, IQ, height, weight, handedness and parental education (32). Even after correction for the increased brain volume, the ventriculomegaly remained significant. Furthermore, others have shown that children with ASD exhibit white matter reduction in the frontostriatal pathways (25).

Diffusion tensor imaging of individuals with ASD in general (both preterm and term) demonstrates abnormal white matter microstructures, signifying impaired neural network development (33-35). However, several anatomic likelihood estimation analyses have demonstrated that alterations in brain morphology of ASD extend beyond white matter abnormalities. Anatomic likelihood estimation analyses enable the identification of consistent foci of disturbances across the brain. One recent anatomic likelihood estimation meta-analysis of 277 patients with ASD and 303 controls identified six significant clusters of brain structure disturbances in ASD including the lateral occipital lobe, the pericentral region, the media temporal lobe, the basal ganglia, and an area proximate to the right parietal operculum (36).

Other anatomic likelihood estimation meta-analyses have identified grey matter reductions in individuals with ASD in areas including the left putamen, medial prefrontal cortex, cerebellar tonsil, inferior parietal lobule, right amygdala, insula, middle temporal gyrus; increases in grey matter were reported in regions such as the lateral pre frontal cortex, cerebellum, and caudate head (25, 37). An MRI study of low birth weight infants,

(birthweight <1500 g) demonstrated that cerebellar involvement (either isolated or in associated with other brain involvement) at mean age of 39.2 weeks significantly increased the likelihood of screening positive for ASD (19). It is clear that ASD reflects abnormalities within multiple, spatially distributed, neural systems such as in the limbic system, frontostriatal system, frontotemporal, frontoparietal and cerebellar systems (37) and the extent to which different neural systems are involved may potentially differ for preterm and term children with ASD.

The strengths of this study are its population-based sample and its longitudinal design, which provided prospective data collection of many risk factors and outcomes in a standardized fashion for over two decades. The generalizability of our findings is broader than in other preterm follow-up studies because the cohort was not restricted to lower extremes of birth weight and gestational age. In addition, whereas many ASD studies rely on screening instruments, this study implemented rigorous ASD diagnostic procedures with research-validated instrument (14).

Despite the small number of study participants diagnosed with ASD (14 total) and the small number with ventricular enlargement (12 total), we found significance between ventricular enlargement and ASD ; thus, our study was not underpowered to demonstrate this linkage between ventricular enlargement and ASD. However, the small sample size prevented adequate exploration of potential interactions. Only 67% (623/931) of the original birth cohort who were still alive and living with biological parents underwent autism screening, and, of these, only 60% of adolescents who screened positive and an systematically selected sample of 23% who screened negative were diagnostically evaluated for ASD as young adults. However, those eligible for but not screened for ASD differed significantly only with respect to lower maternal social risk at birth from those screened (14). Furthermore, characteristics of those who were and were not retained in the sample from 16 to 21 years of age were not dependent upon screen status except for one component of maternal social risk (i.e. receipt of public assistance) (14). However, those not retained in the sample at age 21 years of age (n=434) were more likely than those retained in the sample (n=189) to be at greater risk for suboptimal neurodevelopmental outcomes (14).

Our results are based upon cerebral ultrasound technology of the 1980's which has since undergone improvements. Also, our results are based upon cranial ultrasounds performed only within the first seven days of life. Sometimes, ventricular enlargement manifests itself only on ultrasound scans that are completed 4-6 weeks after birth (38-40). Therefore ventricular enlargement may not have been detected in some LBW infants. However, whether or not ventricular enlargement first becomes manifest after 4-6 weeks of life should not depend upon ASD status, and therefore the relationship between ventricular enlargement and ASD should not be affected by this.

Some adolescents did not receive all parts of the three-part screen (14). Moreover, due to distance or scheduling issues, some of the young adults were evaluated only by parental phone interview using the ADIR. However, the proportions of the individuals who screened positively and negatively interviewed by phone were similar (14).

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Abbreviations

ADIR	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
ASD	Autism Spectrum Disorder
GM/IVH	Isolated germinal matrix/intraventricular hemorrhage
LBW	Low Birth Weight

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Table 1

Characteristics of Study Participants Assessed For ASD at Age 21 (N=189)

Characteristics	ASD-Negative (N=175)	ASD-Positive (N=14)
<i>Maternal/Obstetric</i>		
Maternal Age (years)	28.9 [SD 5.0]	29.3 [4.5]
Education Beyond High School	62.0%	69.2%
Cesarean Delivery	54.9%	57.1%
Singleton Birth	66.9%	69.2%
Cord pH<7.25	18.3%	14.3%
Cord Abnormality	9.7%	14.3%
Maternal Hypertension * (with or without pre-eclampsia)	16.0%	42.9%
<i>Infant/Perinatal</i>		
White Race	86.3%	78.6%
Male	53.7%	78.6%
Gestational Age (weeks)	31.3 [SD 3.1]	31.2 [4.1]
Head Circumference at Birth (cm)	28.2 [2.6]	27.6 [2.1]
Birth Weight (grams)	1487 [372]	1314 [304]
5 minute Apgar Score <7	13.7%	21.4%
Duration of Ventilation (Days)	13.1 [19.4]	18.9 [1.5]
Serum Bilirubin At 60 hrs of life (mg/dl)	7.7 [2.7]	7.3 [2.3]
Small for Gestational Age	22.9%	42.9%
Bronchopulmonary Dysplasia	11.4%	14.3%
<i>Toddler/Childhood</i>		
Cerebral Palsy * [assessed at 2 yrs old]	7.4%	21.4%
Motor Impairment (Riley Motor Problems Inventory Score >=5) * [assessed at 16 yrs old]	30.1%	80.0%
Cognitive Impairment (IQ<70) [Assessed at 16 yrs old]	4.9%	10.0%

* Significant difference (p<0.05) between study participants with and without ASD

Table 2

Risk of ASD-positive screen in the young adult cohort who were assessed for ASD by CUS abnormalities (N=189)

	Risk of +ASD Screen	Risk Ratio [95% CI]
Normal CUS	41/141 (29.1%)	1.0 [Referent]
Isolated GM/IVH	13/30 (43.3%)	1.5 [0.9, 2.4]
+VE	11/12 (91.7%)	3.2 [2.3, 4.3]
+PEL	10/11 (90.9%)	3.1 [2.3, 4.3]
+PEL and/or +VE	15/17 (88.2%)	3.0 [2.2, 4.1]

Abbreviations Used in Above Table:

ASD= Autism Spectrum Disorder

CUS= Cranial Ultrasound

GM/IVH=Intracranial Hemorrhages (Germinal Matrix and/or Intraventricular Hemorrhage)

PEL= Parenchymal Echolucent or Echodense Lesions

VE= Ventricular Enlargement

Table 3

Cranial Ultrasound Abnormalities for the young adult cohort who were assessed for ASD (N=189)

<i>CUS Abnormalities</i> *	ASD Negative (N=175)	ASD Positive (N=14)
<i>Normal</i> ** (% Cohort)	134 (76.6%)	7 (50.0%)
<i>GM/IVH</i> (% Cohort)	38 (21.7%)	6 (42.9%)
<i>VE</i> ** (% Cohort)	8 (4.6%)	4 (28.6%)
<i>PEL</i> (% Cohort)	10 (5.7%)	1 (7.1%)

Abbreviations Used in Above Table:

ASD= Autism Spectrum Disorder

CUS= Cranial Ultrasound

GM/IVH=Intracranial Hemorrhages (Germinal Matrix and/or Intraventricular Hemorrhage)

PEL= Parenchymal Echolucent or Echodense Lesions

VE= Ventricular Enlargement

* Ultrasounds may have one or more than one abnormality; therefore, total % of abnormalities >100%

** Significant difference between ASD Negative and ASD positive group (p<0.05)

Table 4

Risk of ASD-positive diagnosis in the young adult cohort who were assessed for ASD by CUS Abnormalities (N=189)

	Risk of +ASD Diagnosis	Risk Ratio [95% CI]
Normal CUS	7/141 (5.0%)	1.0 [Referent]
Isolated GM/IVH	2/30 (6.7%)	1.3 [0.3, 3.2]
+VE	4/12 (33.3%)	6.7 [2.3, 19.7]
+PEL	1/11 (9.1%)	1.8 [0.2, 13.6]
+VE and/or +PEL	5/18 (2.8%)	6.6 [2.0, 15.8]

Abbreviations Used in Above Table:

ASD= Autism Spectrum Disorder

CUS= Cranial Ultrasound

GM/IVH=Intracranial Hemorrhages (Germinal Matrix and/or Intraventricular Hemorrhage)

PEL= Parenchymal Echolucent or Echodense Lesions

VE= Ventricular Enlargement