ORIGINAL ARTICLE

Neonatal Head Ultrasound Abnormalities in Preterm Infants and Adolescent Psychiatric Disorders

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Context: Infants born prematurely are at risk for a perinatal encephalopathy characterized by white and gray matter injuries that affect subsequent cortical development and neural connectivity and potentially increase risk for later psychiatric disorder.

Objective: To determine the relation of perinatal brain injury, as detected by neonatal head ultrasound, to psychiatric disorders in adolescents who were born prematurely.

Design: Prospective cohort.

Setting: Community.

Participants: Adolescent survivors of a population-based low-birth-weight (<2000 g; 96% preterm; born 1984-1987) cohort (n=1105) screened as neonates with serial head ultrasounds. Neonatal head ultrasound abnormalities were categorized as either (1) germinal matrix and/or intraventricular hemorrhage or (2) parenchymal lesions and/or ventricular enlargement. Of 862 eligible survivors, 628 (72.9%) were assessed at age 16 years. The sample consisted of 458 nondisabled survivors assessed in person.

Main Outcome Measure: Adolescent current and lifetime psychiatric disorders assessed with parent report on the Diagnostic Interview Schedule for Children–IV.

Results: Compared with no abnormality, germinal matrix/intraventricular hemorrhage increased risk for current major depressive disorder (odds ratio, 2.7; 95% confidence interval, 1.0-6.8) and obsessive-compulsive disorder (9.5; 3.0-30.1). Parenchymal lesions/ventricular enlargement increased risk for current attention-deficit/hyperactivity disorder–inattentive type (odds ratio, 7.6; 95% confidence interval, 2.0-26.5), tic disorders (8.4; 2.4-29.6), and obsessive-compulsive disorder (7.6; 1.39-42.0). Parenchymal lesions/ventricular enlargement were not related to lifetime attention-deficit/hyperactivity disorder–inattentive type, but all other relations were similar for lifetime disorders. Control for other early risk factors did not alter these relations. Most of these relations persisted with control for concurrent cognitive or motor problems.

Conclusion: In preterm infants, 2 distinct types of perinatal brain injury detectable with neonatal head ultrasound selectively increase risk in adolescence for psychiatric disorders in which dysfunction of subcortical-cortical circuits has been implicated.

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THE CONCEPT THAT PERINATAL brain injury influences risk for later psychiatric disorder has been invoked in neurodevelopmental discussions of psychiatric disorders for more than 5 decades.[1-5] To date, however, studies having the prospective design, sample size, and brain imaging technique suitable for testing this concept have been rare.[4] Infants born prematurely (at <37 weeks' gestational age [GA]) constitute a large and growing subgroup of the population for whom this concept, if correct, has direct relevance.

Preterm infants, especially those born very preterm (<32 weeks' GA), are at high risk for perinatal brain injury because of zone-specific vascular and cellular vulnerabilities of the laminar fetal brain between 24 and 36 weeks GA.[6,7] As reviewed by others,[7,8] neuropathologic studies of preterm infants who died soon after birth have found that the anatomic sites most commonly injured are (1) the germinal matrix (GM), a transient fetal brain structure that proliferates cellular precursors, (2) the cerebellum, (3) immature white matter (WM), and (4) subcortical gray matter nuclei, including the basal ganglia and thalami. Although neuronal migration to the cortical mantle is nearly complete at birth in preterm infants, the neurons are largely unconnected, cortical tissue is minimal, and primary cortical lesions are described infrequently.[9] A secondary effect of subcortical gray matter and WM injury on cortical development by term age in preterm infants, however, is supported by (1) neuropathologic

findings of cortical neuronal abnormalities,[8,10-12] (2) structural magnetic resonance imaging (MRI) evidence of reduced cortical volumes,[13,14] and (3) functional connectivity MRI evidence of impaired neural network development.[15] Other neuroimaging evidence of impaired connectivity in preterm survivors has been reviewed recently by Ment et al.[16] Considering the neuropathologic and brain imaging evidence, Volpe[7,17] proposed the term *encephalopathy of prematurity* to describe "a complex amalgam of primary destructive disease and secondary maturational and trophic influences"[7(p111)] that affects neurodevelopmental outcomes. The consequences of the encephalopathy of prematurity have been studied most intensively with respect to motor and cognitive outcomes but may also have relevance for psychiatric disorders.

Although MRI is an invaluable tool for investigating the encephalopathy of prematurity,[14,16,18] the most common method of screening preterm infants for perinatal brain injury in the clinical setting is neonatal head ultrasound (HUS) directed through the anterior fontanelle.[19,20] This imaging technique can detect 2 early components of encephalopathy of prematurity: hemorrhagic injury to the GM and focal necrotic/ischemic injury to WM. Both types are of particular interest to psychiatry because they might be expected to disrupt normal brain development during the third trimester,[21-23] including the development of subcortical-cortical circuits that have been implicated in neurodevelopmental psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), tic disorders (TD), obsessive-compulsive disorder (OCD), major depression, and schizophrenia.[24]

The GM (also called the ventricular zone) is located between the ventricular wall and the periventricular zone. Past 27 weeks' GA, the GM proliferates predominantly glial precursors. The glial precursors become preoligodendrocytes and astrocytes.[25,26] The astrocytes migrate to the immature WM, where they assist in myelination, and to the outer layer of the cortex, where they play a role in cortical organization.[27,28] Because of its immature vasculature, the GM is vulnerable to hemorrhage that may extend into the ventricle.[29] Early enlargement of the lateral ventricle due to the presence of intraventricular blood, while sometimes catastrophic, is usually transient; lateral ventricular enlargement (VE) that persists to term is often a marker of injury to WM.[30] Head ultrasound–detectable GM and/or intraventricular hemorrhage (GM/IVH) without persistent ventricular dilatation occurs in at least 25% of infants of less than 32 weeks' GA and is typically diagnosable with HUS by 72 hours of age.[31] Although GM/IVH has been associated with lower cortical volumes at term[32,33] and transient neuropsychological deficits in infancy,[34,35] relatively short-term follow-up studies have not found it to be a predictor of major cognitive or motor disability or impairments in childhood.[36-40] This relative absence of effect may reflect repair and recovery.[41,42] Inder,[43] however, has warned that follow-up times may have been too short, or the measures used too insensitive, to detect an effect of GM/IVH.

The immature WM (also called the brain parenchyma or intermediate zone) is located between the subventricular zone and the cortical subplate. The parenchyma contains pre-oligodendrocytes and astrocytes as well as afferent and efferent fibers.[25,26] Between 24 and 37 weeks' GA, the pre-oligodendrocytes are vulnerable to injury from reactive oxygen species, particularly hydroxyl radicals, generated during infection and ischemia.[44,45] Hemorrhagic infarcts and necrotic foci, including the lesions often referred to as periventricular leukomalacia,[46] appear on HUS as echodense and echolucent parenchymal lesions (PL), respectively. Persistent, but not progressive, HUS-identified VE is associated on post mortem with all types of PL and often reflects loss of WM volume (hydrocephalus ex vacuo).[30,31] Neonatal HUS-detectable injury to immature WM as PL/VE occurs in up to 10% of preterm infants and is reflected on HUS typically within 1 week but may be evident as far out as 3 weeks.[31] Neonatal PL/VE is associated on post mortem with neuronal injury to basal ganglia and thalami; the neuronal injury is thought to be due to the same excitoxic factors that cause injury to the immature WM.[8,11,47] On MRI, PL/VE is associated with reduced subcortical gray matter volumes[14,48-50] and reduced cortical volumes[13] at term age. Parenchymal lesions/VE is an important predictor of major cognitive and motor disability,[19] as well as cognitive impairment and motor problems, as far out as adolescence.[39,51]

The present report on the psychiatric sequelae of ultrasound-detected GM/IVH and PL/VE is based on the adolescent follow-up of the Neonatal Brain Hemorrhage Study (NBHS) cohort. The NBHS cohort is the largest low-birthweight (<2000 g, 96% preterm) cohort to be systematically screened neonatally with serial HUS for GM/IVH and PL/VE[31] and followed up longitudinally into adolescence. Among the cohort survivors who did not have major motor or cognitive disability, PL/VE but not GM/IVH predicted increased risk for suboptimal motor and cognitive performance that was evident by age 6 years[38,40] and still present at adolescence.[39] At the 6-year follow-up of the NBHS cohort, neonatal PL/VE predicted ADHD and TD, whereas uncomplicated GM/IVH was unrelated to any psychiatric disorder.[51] In our report on psychiatric disorders at age 6, we suggested that with longer-term follow-up, a relation to later-onset disorders might emerge not only for PL/VE but also for GM/IVH.

Three questions are addressed in this report from the adolescent follow-up of the NBHS cohort. First, are neonatal HUS-detected GM/IVH or PL/VE related to current and lifetime psychiatric disorders by age 16 years? Second, if there are any such relations, do they withstand control for other potentially explanatory early biological and social risk factors? Third, do any such relations withstand control for concurrent cognitive and motor performance?

METHODS

BIRTH COHORT

Adolescent participants belong to the NBHS birth cohort.[31,52] The NBHS study prospectively enrolled 1105 consecutive infants with birth weights less than 2000 g who were born in, or admitted to, 3 New Jersey hospitals from September 1, 1984, through June 30, 1987. These 3 hospitals cared for 85% of in-

Table 1. Neonatal Head Ultrasound Abnormalities

Term	Definition
Germinal matrix hemorrhage (GMH)	A focal echodensity, on ≥1 scan, in the thalamocaudate groove, sometimes extending to the head of the caudate nucleus, just lateral to the frontal horns of the lateral ventricles.
Intraventricular hemorrhage (IVH)	An echodense focus or foci, on ≥1 scan, within the lateral, third, or fourth ventricles separate from, and at least as echodense as, the choroid plexus. Also diagnosed when irregularity of the choroid plexus margin indicated adherent intraventricular blood.
Parenchymal lesions (PL)	Focal or confluent echodense and/or echolucent areas, on at least 1 scan, in the parenchyma, replacing the normal pattern of alternating or interlaced gracile echogenic or echopoor lines.
Ventricular enlargement (VE)	At least moderate enlargement of at least one lateral ventricle, as read by the radiologist on the final scan obtained.

fants with birth weights from 501 to 2000 g and 90% of those with birth weights of 1500 g or less in 3 New Jersey counties. These counties were somewhat more affluent than the nation as a whole; 26% of the sample was black, but Hispanic and other minorities were uncommon.[31] All enrolled families were English speaking. All but 17 infants in the cohort were successfully entered into a protocol that screened for neonatal brain injury at 24 hours, 72 hours, and 7 days of life. (See eAppendix for description of HUS procedures; http://www.archgenpsychiatry.com) Of the 17 infants missing HUS, 14 had died before 12 hours.[31] Approximately half of the cohort also had later ultrasounds, most commonly just before discharge.[52]

AGE 16 FOLLOW-UP

At the 16-year follow-up, 212 (19.2%) of the original birth cohort were known to have died and 31 (2.8%) were adopted or in foster care, leaving 862 enrollees potentially eligible for follow-up. Of eligible enrollees, 628 (72.9%) participated in the adolescent follow-up, 83 (9.6%) refused, and 151 (17.5%) could not be located, 68 (45.0%) of whom had been lost to follow-up since hospital discharge.

Thirty-three participants with severe disability (IQ <55 and/or disabling cerebral palsy) are excluded from this report. Of the 595 participants who were not disabled, 474 (79.7%) were assessed on home visits and 121 (20.3%) by telephone. Participants assessed by telephone were not evaluated for psychiatric diagnoses; although slightly older, on average, than those assessed at home, they did not differ in any other respect, including frequency of behavior problems. Time constraints precluded a psychiatric interview for 16 participants seen at home, leaving 458 adolescents in the sample.

PROCEDURES

The New York State Psychiatric Institute Institutional Review Board approved this follow-up study; informed consent by parents or legal guardians, and assent, as appropriate, from the adolescents, was obtained before participation. During the home assessment, the primary caretaker was interviewed regarding the adolescent; the interviewers were masked to neonatal history, including HUS findings, apart from low-birth-weight status. Parents were masked to the study hypotheses although not to their child's neonatal history.

PREDICTORS

Neonatal HUS abnormalities are defined in **Table 1**. Head ultrasound abnormalities were categorized as follows: (1) NA, no abnormality; (2) GM/IVH, GM or IVH without either PL or VE; (3) PL/VE, PL and/or VE with or without GM/IVH. This categorization differs from the widely used Papile system, which rates severity of intracerebral hemorrhage on the basis of computed tomography.[53] The present system is more consistent with lesions observed post mortem[31,54] and has been used in follow-up studies of the Neonatal Brain Hemorrhage Study cohort[37-40,55] and other contemporary cohorts.[56,57] Other early risk factors (non-HUS prenatal, perinatal, and neonatal risk factors) that were of a priori theoretical importance or have been shown to be indicators of risk are listed in **Table 2** and defined in eTable 1.

OUTCOMES BY ADOLESCENCE

Parent-reported psychiatric disorders by age 16 years were assessed with the parent report version of the Diagnostic Interview Schedule for Children–IV (DISC-IVP).[58] The DISC-IVP is a structured, computer-assisted, psychiatric diagnostic interview that assesses current (past year) and lifetime mental disorders, as defined in the *DSM*-IV[59,60] for 26 current and lifetime disorders, not including the pervasive developmental disorders (**Table 3**; footnotes explain the definitions of diagnoses). Adolescents were not interviewed using the youth version of this instrument because cognitive testing was a higher priority; time considerations precluded doing both.

STATISTICAL ANALYSIS

Current and lifetime prevalence rates for each psychiatric disorder and for groups of disorders were calculated by dividing the number of positive cases by the number of cases assessed. The relation of HUS status to each disorder (or to a group of disorders) was examined by means of a priori contrasts using logistic regression. Head ultrasound was represented by 2 dummy variables, each encoding the comparison of those with no HUS abnormality to 1 of the 2 HUS abnormality groups (GM/IVH or PL/VE). Disorders with a prevalence of at least 15 cases (approximately 3% of the sample) at the threshold level (or, failing that, at the level of threshold plus subthreshold) on the DISC-IVP were examined in relation to HUS. Current subthreshold diagnoses are considered comparable to a *DSM-IV* diagnosis of "not otherwise specified" for a given disorder. Subthreshold levels were included to allow relations of rare but important psychiatric disorders to be tested. Relations of HUS status to groups of disorders were reported when there was an insufficient number of cases for analysis of any specific disorder within the group but a sufficient number for the group as a whole. The 2 HUS dummy variables were the sole risk factors for the unadjusted relations.

For adjusted relations, selected other early risk factors from Table 2 were included in the model as well. Variables ex-

Table 2. Risk Exposure for Preterm/LBW Nondisabled Adolescents in Sample vs Other Eligible Adolescents

Risk Factor	In Sample[a,b] (n = 458)	Other Eligible[b,c] (n = 371)	t_{df}/χ^2_{df}	*P* Value
Head ultrasound abnormality				
No abnormality	80.3	80.1		
Germinal matrix/intraventricular hemorrhage	15.1	14.0	$\chi^2_2 = 0.87$	.65
Parenchymal lesion/ventricular enlargement	4.6	5.9		
Maternal social risk	42.9	57.8	$\chi^2_1 = 18.28$	<.001
Male sex	51.7	48.2	$\chi^2_1 = 1.00$	.32
Birth weight, mean (SD), g	1482 (354)	1501 (355)	$t_{827} = 0.78$	.44
1500-1999	53.5	54.7		
1000-1499	34.7	34.0	$\chi^2_2 = 0.13$	.94
<1000	11.8	11.3		
Gestational age, completed wk, mean (SD)	31.2 (3.1)	31.3 (3.2)	$t_{827} = 0.19$	.85
>36	3.7	4.6		
34-36	19.9	18.3	$\chi^2_3 = 0.64$	.89
32-33	24.0	24.3		
<32	52.4	52.8		
Fetal growth ratio	0.8	0.9	$t_{827} = 0.93$	.35
Small for gestational age	32.5	33.4	$\chi^2_1 = 0.74$	.79
Multiple birth	29.7	21.0	$\chi^2_1 = 8.04$	<.001
Maternal smoking in pregnancy[d]				
No. of cigarettes/d, mean (SD)	3.8 (7.2)	3.8 (6.7)	$t_{698} = 0.09$	.93
None	68.6	64.2		
≤½ pack	19.0	25.1	$\chi^2_2 = 3.93$	.14
>½ pack	12.5	10.7		
Maternal drinking of alcohol in pregnancy[d]				
None	47.5	59.1		
<7 drinks/wk and <3 drinks/occasion	49.1	36.5	$\chi^2_2 = 10.82$	<.01
≥7 drinks/wk or ≥3 drinks/occasion	3.4	4.4		
Maternal hypertension				
None	70.5	72.3		
Preexisting hypertension	4.4	3.6	$\chi^2_2 = 0.22$	.90
PIH or preeclampsia	25.1	24.1		
Active labor	58.9	61.6	$\chi^2_1 = 0.57$	.45
Nonvertex presentation	31.5	32.5	$\chi^2_1 = 0.09$	.77
Low Apgar score	10.5	8.5	$\chi^2_1 = 0.97$	.33
Small head circumference at birth	33.7	33.0	$\chi^2_1 = 0.05$	.83
Base excess, mean (SD), mEq/L[c]	−4.7 (4.2)	−4.6 (3.6)	$t_{629} = 0.26$	.79
Thyroxine level, mean (SD), *z* score	−1.4 (1.0)	−1.5 (1.1)	$t_{789} = -0.30$	.13
Hypocapnia exposure[e]	24.5	24.6	$\chi^2_1 = 0.00$	.99
Hyperoxia exposure[e]	36.9	31.9	$\chi^2_1 = 2.15$	.14
Systolic hypotension[f]	34.5	34.0	$\chi^2_1 = 0.03$	.87
Diastolic hypotension[f]	23.0	23.1	$\chi^2_1 = 0.00$	.96
Peak bilirubin, first 8 d, mean (SD), mg/dL	9.2 (2.7)	9.1 (2.5)	$t_{768} = -0.26$	.80
Neonatal infection	31.4	26.1	$\chi^2_1 = 2.79$	.10
Prolonged ventilation	11.4	9.7	$\chi^2_1 = 0.59$	.44

Abbreviations: LBW, low birth weight; PIH, pregnancy-induced hypertension.
SI conversion factor: To convert bilirubin to micromoles per liter, multiply by 17.104.
[a] Preterm/LBW nondisabled adolescents assessed with the parent report on the Diagnostic Interview Schedule for Children–IV (DISC-IVP).
[b] Data are given as percentage of participants unless otherwise indicated.
[c] Preterm/LBW adolescents who were lost to follow-up (n = 151), refused (n = 83), assessed by phone (n = 121), or assessed at home but without DISC-IVP data (n = 16).
[d] The 3 categories were entered into regressions as a single variable, coded 0, 1, and 2, respectively.
[e] Highest 2 quintiles of time-weighted exposure; obtained only when clinically indicated (n = 387 for those in sample and n = 313 for other eligible adolescents).
[f] Any day(s) with hypotension.

cluded from the regression were (1) those too asymmetrically distributed, having very few positive cases (neonatal seizures, placenta previa, placental abruption, and chorioamnionitis); (2) those unrelated to any of the diagnoses of interest (maternal hypertension, low Apgar score, small head circumference at birth, peak bilirubin level during the first postnatal week, and neonatal infection), and (3) the variable of lesser theoretical importance of a redundant or highly correlated pair that posed a risk of multicolinearity (birth weight, which is redundant with GA when small-for-GA is also included, and diastolic blood pressure, which was highly correlated with systolic blood pressure, $r > 0.70$). All analyses were conducted using SPSS software (Chicago, Illinois)[61]; statistical tests were considered significant at the .05 level.

To conserve cases and power in the regressions, missing values were replaced using an expectation maximization algorithm with 200 iterations.[62] Only 6 non-HUS risk factors had more than 10% missing. Preliminary analyses using dummy-coded missing value indicators for these 6 measures had shown that none of the missing value indicators was related to any outcome of interest. Altogether, only 3.9% of the predictor values were missing.

Table 3. Prevalence of DISC-IVP *DSM-IV* Disorders in 458 Nondisabled Preterm/LBW Adolescents[a]

	No. (%) of Participants			
	Current Cases[b]		Lifetime Cases[c]	
Disorder Group/Specific Disorder	Threshold[d]	Threshold Plus Subthreshold[e]	Threshold[d]	Lifetime Threshold, Plus Current Subthreshold[e]
Attention-deficit/hyperactivity disorder-any-unmodified-refined[f]	25 (**5.5**)	89 (19.4)	57 (**12.4**)	105 (22.9)
Inattentive type-refined	17 (**3.7**)	69 (15.1)	49 (**10.7**)	89 (19.4)
Hyperactivity type-refined	0	4 (0.9)	22 (**4.8**)	26 (5.7)
Combined type-refined	8 (1.7)	16 (**3.5**)	No items	No items
Any disruptive disorder[g]	42 (**9.2**)	130 (28.4)	52 (**11.4**)	135 (29.5)
Oppositional defiant disorder	41 (**9.0**)	126 (27.5)	49 (**10.7**)	130 (28.4)
Conduct disorder	6 (1.3)	16 (**3.5**)	9 (2.0)	18 (**3.9**)
Any anxiety disorder[g]	43 (**9.4**)	73 (15.9)	69 (**15.1**)	91 (19.9)
Generalized anxiety disorder	4 (0.9)	13 (2.8)	17 (**3.7**)	25 (5.5)
Separation anxiety disorder	4 (0.9)	14 (**3.1**)	12 (2.6)	20 (**4.4**)
Social phobia	14 (**3.1**)	28 (6.1)	20 (**4.4**)	31 (6.8)
Specific phobia	22 (**4.8**)	28 (6.1)	31 (**6.8**)	36 (7.9)
Posttraumatic stress disorder	1 (0.2)	4 (0.9)	No items	No items
Panic disorder without agoraphobia	1 (0.2)	8 (1.7)	2 (0.4)	9 (2.0)
Panic disorder with agoraphobia	0	0	0	0
Agoraphobia without panic disorder	0	0	0	0
Selective mutism	1 (0.2)	2 (0.4)	2 (0.4)	3 (0.7)
Any mood disorder[g]	8 (1.7)	28 (**6.1**)	13 (2.8)	34 (**7.4**)
Major depression	4 (0.9)	22 (**4.8**)	12 (2.6)	29 (**6.3**)
Dysthymic disorder	3 (0.7)	12 (2.6)	No items	No items
Mania	1 (0.2)	5 (1.1)	1 (0.2)	5 (1.1)
Hypomania	0	No items	No items	No items
Any elimination disorder[h]	1 (0.2)	4 (0.9)	48 (**10.5**)	49 (10.7)
Nocturnal enuresis	1 (0.2)	4 (0.9)	40 (**8.7**)	41 (9.0)
Diurnal enuresis	0	0	1 (0.2)	1 (0.2)
Encopresis	0	0	9 (2.0)	9 (2.0)
Any tic disorder[h]	17 (**3.7**)	26 (5.7)	24 (**5.2**)	33 (7.2)
Transient tic disorder	5 (1.1)	No items	No items	No items
Motor/vocal tic disorder	11 (2.4)	No items	No items	No items
Tourette syndrome	1 (0.2)	No items	No items	No items
Other disorders[h]				
Pica	0	0	2 (0.4)	2 (0.4)
Obsessive-compulsive disorder	2 (0.4)	15 (**3.2**)	2 (0.4)	15 (**3.2**)
Trichotillomania	0	0	0	0
Any eating disorder	0	7 (1.5)	3 (0.7)	9 (2.0)
Schizophrenia	0	3 (0.7)	0	3 (0.7)
Any substance abuse/dependence	5 (1.1)	7 (1.5)	5 (1.1)	7 (1.5)
Any disorder	104 (**22.7**)	219 (47.8)	169 (**36.9**)	239 (52.2)
Multiple disorders	36 (**7.9**)	95 (20.7)	74 (**16.2**)	121 (26.4)

Abbreviations: DISC-IVP, parent report version of the Diagnostic Interview Schedule for Children–IV; LBW, low-birth-weight.

[a] Boldface indicates percentages for current and lifetime disorders qualifying for further analysis (threshold ≥3% or, failing that, threshold + subthreshold ≥3%).

[b] The DISC-IVP leaves the definition of caseness up to the investigator; here, caseness is defined by meeting the symptom criterion for a disorder (as defined for threshold and subthreshold levels; see footnotes *d* and *e*) with or without impairment. (See footnotes *f*, *g*, and *h*.) "Current" refers to symptoms present in the past year.

[c] Caseness is defined per footnote *b*. "Lifetime" refers to symptoms present from age 5 years on for most disorders (age 4 years for pica and encopresis).

[d] The threshold symptom criterion requires the full count of symptoms stipulated for a given disorder to be present.

[e] The subthreshold symptom criterion requires at least half, but not all, of the symptoms stipulated for a given disorder to be present.

[f] Current attention-deficit/hyperactivity disorder cases are defined per *DSM-IV-TR*, requiring the DISC-IVP impairment B criterion (intermediate to severe impairment in ≥2 domains) and onset of symptoms that caused impairment before 7 years of age as well as the relevant symptom criterion.

[g] For disruptive, anxiety, and mood disorders, cases are defined using the DISC-IVP impairment A criterion (intermediate to severe impairment in ≥1 domain), as well as the relevant symptom criterion.

[h] For elimination disorders, tic disorders, and other disorders, cases are defined using only the relevant symptom criterion, with no impairment required. The behaviors involved in these disorders were considered of sufficient clinical concern to define caseness irrespective of impairment.

RESULTS

SAMPLE DESCRIPTION

As shown in Table 2, the mean age at follow-up was 15.9 years (range, 15.3-18.8 years). Consistent with most longitudinal studies, those in the study sample were born at lower social risk than those eligible but not in the sample, particularly those lost to follow-up (75.5% of whom had ≥1 social risk factors). Of the medical risk factors, the 2 groups differed significantly only in respect to multiple births and moderate maternal prenatal

Table 4. Rates for Selected *DSM-IV* Disorders[a] by Neonatal Head Ultrasound Status in 458 Nondisabled Preterm/LBW Adolescents

Disorder	Current			Lifetime		
	NA (n = 368)	GM/IVH (n = 69)	PL/VE (n = 21)	NA (n = 368)	GM/IVH (n = 69)	PL/VE (n = 21)
Attention-deficit/hyperactivity disorder						
Inattentive type	3.0	2.9	19.0[b]	10.3	8.7	23.8
Hyperactive type	Unavailable[c]	Unavailable[c]	Unavailable[c]	4.1	7.2	9.5
Combined type	3.3	4.3	4.8	Unavailable[c]	Unavailable[c]	Unavailable[c]
Oppositional defiant disorder	9.3	8.7	4.8	11.1	8.7	9.5
Conduct disorder	3.3	2.9	9.5	3.5	4.3	9.5
Generalized anxiety disorder	Unavailable[c]	Unavailable[c]	Unavailable[c]	3.5	5.8	0.0
Separation anxiety disorder	2.4	5.8	4.8	3.8	7.2	4.8
Social phobia	3.5	1.4	0.0	4.9	1.4	4.8
Specific phobia	4.6	4.3	9.5	6.8	5.8	9.5
Major depression	4.1	10.1[d]	0.0	5.2	13.0[d]	4.8
Nocturnal enuresis	Unavailable[c]	Unavailable[c]	Unavailable[c]	7.6	13.0	14.3
Any tic disorder	2.7	4.3	19.0[b]	4.7	4.5	20.0[e]
Obsessive-compulsive disorder	1.4	11.6[b]	9.5[d]	1.4	11.6[b]	9.5[d]

Abbreviations: GM, germinal matrix; IVH, intraventricular hemorrhage; LBW, low birth weight; NA, no head ultrasound abnormalities; PL, parenchymal lesions; VE, ventricular enlargement.

[a] Data are given as percentages. Disorders having 15 or more cases (3% of the full sample) at the threshold level, or, failing that, at the threshold plus subthreshold level (Table 3).

[b] Greater than NA; $P \leq .001$.

[c] Disorder not defined or fewer than 15 cases in the full sample.

[d] Greater than NA; $P \leq .05$.

[e] Greater than NA; $P \leq .01$.

alcohol consumption, both more common in the study group. Of the 458 adolescents in the study sample, the overwhelming majority had been born prematurely (most extremely to moderately so). Based on age 16 motor and cognitive assessments described in detail elsewhere,[39] 14.6% of study participants scored in the top 2% on a standardized test of motor problems; 3.9% had full-scale IQ score in the range 55 to 69, 13.5% in the range 70 to 84, and 82.5% had scores of 85 or greater.

DESCRIPTIVE EPIDEMIOLOGY

Current Disorders

At the threshold level (Table 3, second column), 4 specific psychiatric disorders had sufficient prevalence (≥3.0%) to be considered further. In decreasing order of prevalence, these were oppositional defiant disorder, specific phobia, ADHD–inattentive type, and social phobia. The group of TD had a sufficient prevalence to be considered further, although none of the specific disorders within this group did.

When subthreshold levels of disorder were counted along with threshold levels (Table 3, third column), an additional 5 specific disorders had a prevalence of at least 3.0%: major depression, ADHD–combined type, conduct disorder, OCD, and separation anxiety disorder.

Lifetime Disorders

As expected, prevalence rates were greater for most individual disorders and for disorders overall when criteria for lifetime diagnoses at the threshold level were applied (Table 3, fourth column). For some disorders (eg, OCD), however, there were no additional cases. At the threshold level, 6 specific lifetime disorders had a prevalence of at least 3%: in decreasing order of frequency, these were oppositional defiant disorder, ADHD–inattentive type, nocturnal enuresis, specific phobia, ADHD–hyperactive type, social phobia, and generalized anxiety disorder. The group of lifetime TD had sufficient prevalence to be considered further, although none of the specific disorders within this group did. When current subthreshold diagnoses were added to the lifetime threshold diagnoses (Table 3, fifth column), 2 additional specific disorders (major depressive disorder [MDD] and separation anxiety disorder) met the prevalence criterion.

RELATION OF NEONATAL HUS STATUS TO PSYCHIATRIC DISORDERS

For those disorders with a prevalence qualifying for further analysis, the rates by neonatal HUS category are presented in **Table 4**. For disorders that did not qualify for further analysis, the number of adolescents with each disorder is provided in eTable 2 by HUS status. Germinal matrix and/or intraventricular hemorrhage was related significantly, without adjustment for other early risk factors, to current and lifetime MDD and OCD (**Table 5**). After adjustment, the significant relation of GM/IVH to lifetime MDD persisted, whereas that to current MDD did not. The significant relation to current and lifetime OCD also persisted. Overall, PL/VE was related significantly to ADHD-Inattentive Type, any TD, and OCD. Unadjusted for other early risk factors, PL/VE was related significantly to current (but not lifetime) ADHD-inattentive type, current and lifetime TD, and current and lifetime OCD. (As previously noted, all lifetime cases of OCD were also current.) After adjustment, the significant relation of PL/VE to current ADHD-inattentive type,

Table 5. Unadjusted and Adjusted[a] Relations of Head Ultrasound Abnormalities to Current and Lifetime Psychiatric Disorders

	Odds Ratio (95% Confidence Interval)			
	Unadjusted		Adjusted[a]	
Psychiatric Disorders	GM/IVH	PL/VE	GM/IVH	PL/VE
Current				
ADHD–inattentive type	0.97 (0.21-4.47)	7.64[b] (2.20-24.48)	1.01 (0.19-5.44)	6.83[c] (1.26-36.91)
Major depression	2.66[c] (1.04-6.78)	No cases[d]	2.23 (0.80-6.24)	No cases[d]
Tic disorders	1.63 (0.44-6.07)	8.42[e] (2.40-29.62)	1.89 (0.42-8.57)	9.77[c] (1.69-56.47)
Obsessive-compulsive disorder	9.52[b] (3.02-30.06)	7.64[c] (1.39-41.98)	11.85[b] (3.22-43.62)	15.32[c] (1.82-128.74)
Lifetime				
ADHD–inattentive type	0.83 (0.34-2.04)	2.71 (0.94-7.82)	0.64 (0.24-1.74)	1.13 (0.31-4.10)
Major depression	2.76[c] (1.19-6.38)	No cases[d]	2.59[c] (1.02-6.58)	No cases[d]
Tic disorders	0.95 (0.27-3.34)	5.07[e] (1.53-16.82)	0.85 (0.21-3.51)	5.02[c] (1.05-23.92)
Obsessive-compulsive disorder	9.52[b] (3.05-30.06)	7.64[c] (1.39-41.98)	11.85[b] (3.22-43.62)	15.32[c] (1.82-128.74)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; GM/IVH, germinal matrix and/or intraventricular hemorrhage without either parenchymal lesions or ventricular enlargement; PL/VE, parenchymal lesions and/or ventricular enlargement with or without GM/IVH.

[a] Adjusted for selected risk factors from Table 2, namely, the presence/absence of maternal social risk at birth, sex, completed weeks of gestation, fetal growth ratio, whether the participant was a member of a set of multiples at birth, maternal smoking during pregnancy, maternal drinking during pregnancy, presence/absence of active labor, nonvertex birth presentation, base excess from the first postnatal blood gas, thyroid status, hypocapnia, hyperoxia, systolic hypotension, and the presence/absence of prolonged ventilation. (See eTable 1 for definitions.)

[b] $P \leq .001$.

[c] $P \leq .05$.

[d] There were no cases of PL/VE having this disorder.

[e] $P \leq .01$.

Table 6. Current Diagnoses Related to Head Ultrasound Status Regressed on Head Ultrasound Controlling for WASI-FSIQ and Riley Motor Problems Inventory Scores

	Odds Ratio (95% Confidence Interval)[a]			
	Controlling for FSIQ		Controlling for Motor Problems	
Psychiatric Disorders	GM/IVH	PL/VE	GM/IVH	PL/VE
ADHD–inattentive type	0.86 (0.18-3.99)	5.04 (1.36-18.65)[a]	0.99 (0.21-4.62)	5.43 (1.32-22.40)[a]
Major depression	0.43 (0.16-1.11)	No cases[b]	0.40 (0.15-1.05)	No cases[b]
Tic disorders	1.54 (0.41-5.78)	7.01 (1.88-28.14)[c]	1.45 (0.38-5.48)	4.38 (1.05-18.23)[a]
Obsessive-compulsive disorder	8.68 (2.72-27.69)[d]	4.78 (0.83-28.10)	10.91 (3.13-37.99)[d]	3.58 (0.50-25.94)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FSIQ, full-scale IQ; GM/IVH, germinal matrix and/or intraventricular hemorrhage without either parenchymal lesions or ventricular enlargement; PL/VE, parenchymal lesions and/or ventricular enlargement with or without GM/IVH; WASI, Wechsler Abbreviated Scale of Intelligence.

[a] $P < .05$.

[b] There were no cases of this disorder with PL/VE.

[c] $P < .01$.

[d] $P < .001$.

current and lifetime TD, and to current and lifetime OCD, persisted. In the adjusted analyses, several other early risk factors had significant independent relations to current and lifetime disorders that were predicted by PL/VE and/or uncomplicated GM/IVH (eTable 3, A and B).

Because both cognitive and motor performance are also affected by HUS,[38-40] additional regression analyses were run for current disorders having a relation to HUS adjusting for Wechsler Abbreviated Scale of Intelligence Full-Scale IQ[39] and, separately, for the total problems score of the Riley Motor Problems Inventory,[63] both obtained at age 16. With control for IQ, all previously significant relations persisted except for that of GM/IVH to MDD and PL/VE to OCD (**Table 6**). With control for motor problems, all previously significant relations persisted, with the same 2 exceptions as for IQ (Table 6).

COMMENT

This prospective epidemiologic study of the relation of neonatal HUS abnormalities in preterm infants to adolescent psychiatric disorders has 3 principal findings. First, HUS-detected uncomplicated GM/IVH increased risk for current MDD and OCD, whereas PL/VE increased risk for current ADHD–inattentive type, any TD, and OCD. The results were similar for lifetime disorders, except for the relation of PL/VE to ADHD–inattentive type, which was not significant. Second, these relations withstood control for other potentially explanatory early biological and social risk factors. Third, these relations, for the most part, withstood control for cognitive and motor problems.

Although MRI is more sensitive to some abnormalities (eg, diffuse WM injury) than HUS and has played

an important role in understanding the encephalopathy of prematurity,[14] HUS is still the standard of care for evaluating preterm infants for brain injury in the newborn intensive care unit.[19,20] Because bedside HUS detects 2 important early component injuries of the encephalopathy of prematurity, namely GM/IVH and PL/VE, and is safe, relatively inexpensive, and widely available, it is an invaluable tool for prospective epidemiologic research.

COMPARISON WITH OTHER STUDIES

Comparison with other studies is complicated by differences in design, sample definition, and size; classification of brain injury; and outcome measures. Closest to the NBHS cohort in terms of birth years is a population-based Norwegian low-birth-weight (<1500 g) cohort, born from 1986 to 1988. Indredavik et al[64] recently reported on the relation of neonatal HUS-detected IVH (retrospectively obtained from hospital records) to psychiatric disorder and dimensional measures of psychiatric disorders and symptoms in this Norwegian cohort at age 14 years. Psychiatric disorder was assessed with a semistructured psychiatric diagnostic interview, the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), which covers a range of diagnoses comparable with the DISC-IVP used in the present study. Intraventricular hemorrhage, defined as either grades I or II (comparable with GM/IVH) or grades III or IV (comparable with PL/VE), was not related to psychiatric disorder but was related to inattentive symptoms on a questionnaire measure; the sample size, however, was small (n=65). The same group reported earlier that indicators of WM reduction on qualitative MRI obtained at age 14 years was related selectively to ADHD symptoms (≥75% of *DSM-IV* symptom criteria on the K-SADS) at age 14. The same group also reports that, on diffusion tensor imaging at age 14, lower fractional anisotropy values (a marker for disturbance of WM tracts) in several areas regarded as likely sites of perinatal WM injury were related to both symptoms and full diagnoses of ADHD at age 14.[65] These recent findings are consistent with those of Stewart et al,[66] who found that neonatal HUS abnormalities consistent with PL/VE were highly associated 14 years later with MRI indicators of WM injury, which, in turn, were associated with adolescent behavior problems.[66]

A recent report by the EPICure study group[67] of a very low-birth-weight cohort followed up prospectively found no relation of HUS status (or any other neonatal variable) to psychiatric disorder, as assessed with the Development and Well-being Assessment, but this may reflect the younger age and smaller size of their sample. A prospective study conducted by Luu et al[68] examined only severe brain injury (corresponding to PL/VE in the present study) and studied 375 premature infants using a dimensional outcome measure, the Achenbach Child Behavior Checklist at adolescence.[69] Compared with term controls, preterm infants with severe brain injury scored as a group in the clinical range on attention problems and on social and thought problems. It is noteworthy that Hille et al[70] found that attention, social, and thought problems were elevated in school-age children born weighing less than 1000 g, a group at high risk for the type of severe brain injury studied by Luu et al.[68] In light of our findings, the relation of GM/IVH, a brain injury category not examined by Luu et al, to the Anxious/Depressed Subscale of the Child Behavior Checklist and to a derived Obsessive-Compulsive Scale[71] would be of interest.

RELEVANCE FOR DEVELOPMENTAL NEUROPSYCHIATRY

This study provides strong evidence for the concept, first promulgated by Pasamanick et al,[1] that injury to the fetal-neonatal brain alters risk for later psychiatric disorder.

For the 2 components of the encephalopathy of prematurity studied here, the increase in risk was diagnostically quite specific: GM/IVH increased risk for OCD and MDD, whereas PL/VE increased risk for ADHD–inattentive type, OCD, and TD. Attention-deficit/hyperactivity disorder, TD, OCD, and MDD each belong to a group of disorders sometimes referred to as the neurodevelopmental frontostriatal disorders.[24] The importance of subcortical structures (particularly the basal ganglia) in childhood-onset forms of the neurodevelopmental frontostriatal disorders has recently been emphasized by others.[72-75] Structural and functional brain imaging studies of children and adolescents with frontostriatal disorders suggest that distinct neural circuits subserve ADHD, TD, MDD, and OCD. The finding here that PL/VE is related to ADHD and TD suggests that PL/VE affects the thalamocortical circuit implicated in ADHD[72,76-79] and the striatocortical circuits implicated in TD.[80-83] These possibilities are consistent with evidence of an association between PL/VE and postmortem findings of injury to the thalamus and basal ganglia[11,31] and quantitative MRI findings of reduced thalamic and basal ganglia volumes at term age.[48-50] The finding that GM/IVH is related to MDD suggests that GM/IVH may affect the amygdalo-striatal-dorsomedial prefrontal circuits whose dysfunction has been implicated in MDD.[73,84-86] This possibility is consistent, in turn, with the finding that uncomplicated GM/IVH is associated with lower cortical volumes at term on quantitative MRI[33] and with the suggestion that GM/IVH could affect development of the amygdala.[87,88] The finding that both GM/IVH and PL/VE are related to OCD supports the speculation that both may affect, possibly at different locations, the orbitofrontal-anterior cingulate-striatal circuit implicated in OCD[75,89-91] or (alternatively) globus pallidus–putamen-thalamus-prefrontal circuits.[73,92]

Other disorders that have been considered to be part of the neurodevelopmental frontostriatal group include autism, bulimia, and schizophrenia.[24,93-96] Autism as a diagnosis was not assessed at this follow-up. The low prevalence of bulimia and schizophrenia in this cohort at age 16 precluded analysis of their relation to HUS status. Perhaps most importantly, the emergence of new relations of GM/IVH to psychiatric disorders between the age 6 and age 16 follow-ups of the NBHS cohort suggests that further follow-up may find that GM/IVH and/or PL/VE may increase risk for disorders that typically have an even later onset. One such disorder, long thought to be at the "devastating intersection between development and disease,"[8] is schizophrenia.[2,93,97]

The relation of neonatal HUS status to adolescent psychiatric disorder in the NBHS cohort did not appear to be accounted for by other early medical risk factors. Concurrent cognitive and motor problems did not account for the relation of GM/IVH to OCD or the relation of PL/VE to ADHD or TD. The finding that the relation of GM/IVH to MDD and that of PL/VE to OCD did not withstand control for motor or cognitive problems may reflect a common cause or the presence of a neurodevelopmental syndrome; the exploration of these alternative possibilities is beyond the scope of this article.

The present findings may have relevance to some term infants as well. Preliminary evidence from fetal neuroimaging suggests that some fetuses sustain GMH/IVH and PL/VE in utero at the same GAs as preterm neonates, but are carried to term.[98] Term infants with certain forms of congenital heart disease show patterns of WM and gray matter injury similar to that seen in preterm infants.[6] Psychiatric outcomes in term infants who sustained prenatal injury and in term infants with congenital heart disease are not known but deserve study.

STRENGTHS AND LIMITATIONS OF THE STUDY

The strengths of this study are the (1) use of a large regional birth cohort, (2) rigor of the protocol for HUS, (3) prospective and systematic ascertainment of a rich set of early medical complications, (4) structured assessment of both common and rare psychiatric disorders in mid-adolescence, and (5) concurrent assessment of cognitive and motor functioning.

Limitations include (1) the lack of a normal birth weight or term control group, precluding determination of whether low-birth-weight/preterm infants, as a group, are at excess risk for psychiatric disorders; (2) the inability of HUS as used in this cohort to detect diffuse WM injury as well as cerebellar hemorrhages in preterm infants[14,99]; (3) the selective loss of those at greater social risk, which may have influenced the prevalence of disorders sensitive to social risk; (4) ascertainment of the cohort by birth weight rather than GA; (5) the reliance on parent report, which might underestimate internalizing disorders (ie, anxiety disorders and depression)[100]; and (6) the use of subthreshold criteria for some diagnoses.

In conclusion, HUS-detected uncomplicated GM/IVH and PL/VE in preterm neonates both selectively increase risk for the emergence of psychiatric disorders in which abnormal subcortical-cortical connectivity has been implicated.

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