Autism Spectrum Disorders in Extremely Preterm Children

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Objectives To investigate the prevalence, correlates, and antecedents of autism spectrum disorders (ASD) in extremely preterm children.

Study design We conducted a prospective study of all births <26 weeks gestation in the United Kingdom and Ireland in 1995. Of 307 survivors at 11 years, 219 (71%) were assessed and compared with 153 term-born classmates. Parents completed the Social Communication Questionnaire (SCQ) to assess autism spectrum symptoms, and ASD were diagnosed by using a psychiatric evaluation. An IQ test and clinical evaluation were also administered. Longitudinal outcome data were available for extremely preterm children.

Results Extremely preterm children had significantly higher SCQ scores than classmates (mean difference, 4.6 points; 95% CI, 3.4-5.8). Sixteen extremely preterm children (8%) were assigned an ASD diagnosis, compared with none of the classmates. By hospital discharge, male sex, lower gestation, vaginal breech delivery, abnormal cerebral ultrasound scanning results, and not having had breast milk were independently associated with autism spectrum symptoms. By 6 years, independent associates were cognitive impairment, inattention and peer problems, withdrawn behavior at 2.5 years, and not having had breast milk.

Conclusions Extremely preterm children are at increased risk for autism spectrum symptoms and ASD in middle childhood. These symptoms and disorders were associated with neurocognitive outcomes, suggesting that ASD may result from abnormal brain development in this population. *(J Pediatr 2010;156:525-31)*.

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Autism spectrum disorders (ASD) are a range of conditions that share core impairments in reciprocal social interaction, communication, and a pattern of restricted/repetitive behaviors or interests. The most recent prevalence estimates for ASD range from 1 in 1000 to 4 in 1000 for narrowly defined *DSM-IV-TR* autistic disorder and from 6 in 1000 to 9 in 1000 for the broader category of ASD.[1,2] Extremely preterm children are at high risk for neurodevelopmental disability,[3] behavior problems and social difficulties,[4] and impairment in executive functions,[5] all of which are also impaired in children with ASD.

The first studies of ASD in preterm survivors are only now emerging. Two studies have reported that 21% to 25% of very preterm infants had positive results on screening tests for autistic features.[6,7] However, the specificity of screening in infancy is confounded by the high rate of developmental delay in this population; thus the prevalence of confirmed diagnoses may be considerably lower later in childhood.[8] Accordingly, 3 studies of school-aged outcomes have reported a 4% positive screening rate for autistic features in extremely low birthweight (ELBW; <1000 g) children[9] and 1% to2% prevalence of diagnosed ASD in children born with very low birth weight/low birth weight (VLBW/LBW).[10,11]

As yet, the prevalence of ASD has not been systematically investigated in extremely preterm children. Autism spectrum symptoms may be associated with the high prevalence of neurocognitive impairment in preterm children, particularly extremely preterm children, reflecting a different etiology and associated risk factors in this population.[7,10,11] To advance the study of the etiology of childhood mental disorders, both a dimensional and categorical approach has been proposed, because many conditions develop on the basis of a dimensional liability in which boundaries extend more broadly than indicated with traditional diagnostic classifications.[12] With both a dimensional and categorical approach, we have investigated the prevalence, correlates, and antecedents of autism spectrum symptoms and disorders in extremely preterm children.

ASD	Autism spectrum disorders
DAWBA	Development and Well Being Assessment
ELBW	Extremely low birthweight
LBW	Low birth weight
OR	Odds ratio
SCQ	Social Communication Questionnaire
VLBW	Very low birth weight

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Methods

All babies born <26 weeks gestation in the United Kingdom and Ireland from March through December 1995 were recruited to the EPICure Study. Of 307 survivors at 11 years of age, 11 (4%) moved abroad, and the parents of 77 (25%) did not respond or declined consent. The remaining 219 children (71%) were assessed (median age, 10 years 11 months; age range, 121-145 months). Longitudinal data were available for 213 and 202 children who were also assessed at 2.5 years and 6 years, respectively.

At 6 years, for each extremely preterm child in mainstream school, a term-born classmate was randomly selected from 3 classmates of the same sex and ethnic group and closest in age to the preterm child. Of 160 classmates evaluated at 6 years, 110 (69%) were re-assessed at 11 years. When the extremely preterm child attended a different school or the 6-year-old classmate declined to participate, a new classmate was selected at 11 years by using the same method (n = 43). Thus, 153 classmates were assessed at 11 years (median age, 131 months; age range, 117-147 months). There were no significant differences in age, sex, and ethnicity between extremely preterm children and classmates.

The study was approved by the Southampton and South West Hampshire Research Ethics Committee. Parents and children received study information sheets, and parents provided written informed consent. Children were assessed at school (87%), a hospital or home (13%) by a pediatrician and psychologist blind to group allocation. Parents and teachers completed questionnaires and parents participated in a diagnostic psychiatric interview.

Measures

Autism spectrum symptoms were assessed by using the Social Communication Questionnaire (SCQ),[13] a parental screening questionnaire for identifying ASD. The SCQ yields subscale scores for social interaction (range, 0-16), communication (range, 0-13), and repetitive/stereotyped behavior (range, 0-8) and total SCQ scores (range, 0-39). Higher scores indicate higher frequency of symptoms. Total scores are used to screen for autistic disorder (≥22) and ASD (≥15).

Parents completed, by telephone interview or online, the Development and Well Being Assessment (DAWBA),[14] a semi-structured diagnostic interview to assign ASD diagnoses. Potential cases were identified by using computer-generated scoring algorithms (www.dawba.com). Summary sheets and clinical transcripts were reviewed, and diagnoses were assigned by consensus of 2 clinicians blind to group allocation. This method has good reliability for diagnosing ASD.[15] Because almost identical diagnostic criteria are applied in DSM-IV-TR and *International Statistical Classification of Diseases, 10th Revision*, we refer only to DSM-IV-TR diagnoses: autistic disorder, Asperger's disorder, pervasive developmental disorder-not otherwise specified, Rett's syndrome, and childhood disintegrative disorder.[16]

IQ was assessed by using the Kaufman-Assessment Battery for Children.[17] Impairment (scores <–2SD) was defined by using the distribution of classmate scores to account for the secular drift in IQ with time.[18] Cognitive impairment was assessed at 6 years with the same methodology and at 2.5 years with the Mental Development Index of the Bayley Scales of Infant Development II and classified by using test norms.[19] At 11 years, attainment in reading and mathematics was assessed with the Wechsler Individual Achievement Test-II^{UK}. Information about special educational needs was obtained from teacher questionnaires.[20]

A standard pediatric evaluation was used to classify impairment (none, mild, and serious) in neuromotor function, hearing, and vision. Overall disability was classified with the most severe rating in any of the 4 functional domains assessed (cognition, hearing, vision, motor) at 2.5 years, 6 years, and 11 years of age.[21] Head circumference was measured at each age.

Parental ratings of behavioral problems were obtained at 2.5 years with the Child Behaviour Checklist.[22] Borderline and clinically significant problems were identified for withdrawn, anxious/depressed, sleep problems, somatic complaints, aggressive behavior, and for internalizing, externalizing, and total behavior problems. At 6 years, parents and teachers completed the Strengths and Difficulties Questionnaire.[23] Congruence between parent- and teacher-based classifications of clinically significant difficulties was used to identify pervasive problems in each domain.[4] Data describing neonatal course were collected for extremely preterm children at the time of discharge from the hospital.

Statistical Analyses

Data were double-entered, verified, and analyzed with SPSS software version 15.0 (SPSS Inc., Chicago, Illinois) and Stata software version 10 (StataCorp, College Station, Texas) (S.J., E.H.). Group differences in SCQ scores were analysed with *t* tests allowing for unequal variances and Fisher exact tests for dichotomous outcomes. Differences between groups in SCQ scores were adjusted for IQ with linear regression. For extremely preterm children, the effects of neonatal and neurodevelopmental variables on SCQ scores and ASD diagnoses were investigated with univariate and multivariate linear regression. Logistic regression was used for ASD diagnoses. A forward stepwise procedure was used to identify independent factors associated with SCQ scores and diagnoses in 3 epochs: neonatal, outcomes by 2.5 years and by 6 years. Results are presented with 95% CIs and 2-sided *P* values. No adjustments were made for multiple comparisons. Classmates were assumed to have normal cerebral ultrasound scanning results. All linear regressions used Huber White/sandwich estimates of variance to adjust for heteroscedasticity, non-normality in SCQ scores, or both.

Results

Extremely preterm children not assessed (n = 89) at 11 years of age were more likely to be born at 25 weeks to unemployed

parents of non-white ethnic origin and to have more frequent cognitive impairment at 2.5 years of age and 6 years of age than children who underwent assessment (n = 219).[20] Extremely preterm children with missing SCQ (n = 36) and DAWBA (n = 18) assessments had lower IQ scores (15 and 5 points, respectively); these differences were 0 (n = 16) and 4 (n = 10) points for classmates with missing data.

Prevalence and Correlates of Autism Spectrum Symptoms

SCQ questionnaires were returned for 189 extremely preterm children (86%) and 140 classmates (92%). Mean (SD) SCQ scores were significantly higher for extremely preterm children, indicating a higher frequency of symptoms. After adjustment for IQ, group differences were at least halved and remained significant for social interaction, communication, and total scores, but not repetitive/stereotyped behavior (Table I). As expected, SCQ scores were positively skewed (Figure).

Twenty-nine extremely preterm children (15.8%) and 4 classmates (2.9%) had positive screening results for ASD (SCQ ≥15; odds ratio [OR], 6.3; 95% CI, 2.2-18.3; $P < .001$). The mean score for extremely preterm children with positive screening test results (22.0; SD, 5.47) was significantly higher than for classmates with positive screening results (16.5; SD, 1.7; mean difference, 5.5; 95% CI, 2.7-8.4). Of 29 extremely preterm children with positive screening results, 14 (7.7%; 95% CI, 4.2%-12.5%) had positive screening results for autism (SCQ ≥22), compared with no classmates (95% CI, 0.0%-2.7%; $P < .001$; Figure).

Antecedents of Autism Spectrum Symptoms in Extremely Preterm Children

With univariate analyses, higher SCQ scores were significantly associated with male sex, breech delivery, birth <25 weeks gestation, last cerebral ultrasound scanning results being abnormal, and increasing weeks in the neonatal intensive care unit (Table II; available at www.jpeds.com). Preterm rupture of membranes and receipt of any breast milk were significantly associated with lower SCQ scores. At 2.5 years of age and 6 years of age, cognitive and functional disability and behavior problems had strong associations with increased SCQ scores. Larger head circumference at 2.5 years of age was significantly associated with lower SCQ scores and was the same order of magnitude at 6 years of age, although non-significant (Table II).

Variables in Table II were tested to establish factors independently associated with SCQ scores at 3 sequential epochs. By the time of discharge from the hospital, being male, <25 weeks gestation, breech delivery, abnormal cerebral ultrasound scanning results, and non-receipt of breast milk were independently associated with higher SCQ scores and thus greater autism spectrum symptomatology (Table III). By 2.5 years of age, after inclusion of the highly significant functional disability and withdrawn behavior scores, male sex, birth <25 weeks gestation, and abnormal ultrasound scanning results remained significant, but with weaker associations. By 6 years of age, non-receipt of breast milk and withdrawn behavior scores retained independent associations, as did cognitive impairment, hyperactivity/inattention, and peer problems (Table III).

Prevalence and Correlates of ASD Diagnoses

DAWBA interviews were available for 201 extremely preterm children (92%) and 143 classmates (93%). ASD was diagnosed in 16 extremely preterm children (8%): 13 (6.5%) with autistic disorder and 3 (1.5%) with pervasive developmental disorder-not otherwise specified. No classmates received an ASD diagnosis. Extremely preterm children with ASD were more likely to be male, have cognitive impairment, have special educational needs, and have poorer academic attainment than their preterm counterparts (Table IV). Only 1 of 12 children with functional disability and ASD did not have cognitive impairment but had an isolated hearing impairment.

Antecedents of ASD in Extremely Preterm Children

Male sex was the only significant neonatal risk factor (Table II). At 2.5 years of age, functional disability and aggressive behavior were significant, and at 6 years of age, cognitive impairment, functional disability, attention/hyperactivity, and peer problems were significant associates. None of the 56 children without cognitive impairment at 6 years of age had ASD at 11 years of age (0%; 95% CI, 0-6.4%), 4 of 65 children with mild impairment had ASD (6.1%; 95% CI, 1.7-15.0%), and 6 of 34 children in both the moderate and severe categories had ASD (17.6%; 95% CI, 6.8-34.5%).

With multivariate analyses in 3 sequential epochs, only male sex (adjusted-OR 3.85; 1.20-12.4) was independently

Table I. Social Communication Questionnaire scores at 11 years of age

	Classmates			Extremely preterm				
SCQ scores*	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	Mean difference (95% CI)	Mean difference adjusted for IQ† (95% CI)
Total SCQ score	137	3.2 (3.4)	2 (1-4)	183	7.8 (7.4)	6 (2-11)	4.6 (3.4-5.8)	1.9 (0.6-3.1)
Social interaction	138	1.0 (1.5)	0 (0-1)	185	2.8 (3.4)	1 (0-4)	1.8 (1.3-2.4)	0.7 (0.1-1.3)
Communication	139	1.7 (1.7)	1 (0-3)	186	3.4 (2.7)	3 (1-5)	1.7 (1.2-2.2)	0.8 (0.3-1.3)
Repetitive behavior	139	0.4 (0.9)	0 (0-0)	186	1.3 (1.9)	0 (0-2)	0.9 (0.6-1.2)	0.3 (−0.0-0.6)

IQR, Interquartile range.
*Total SCQ scores range from 0 to 39; social interaction scores range from 0 to 16; communication scores range from 0 to 13; repetitive behavior scores range from 0 to 8.
†Two extremely preterm children did not have IQ scores and are not included in the results for this column. IQ refers to Mental Processing Composite scores of the Kaufman Assessment Battery for Children.

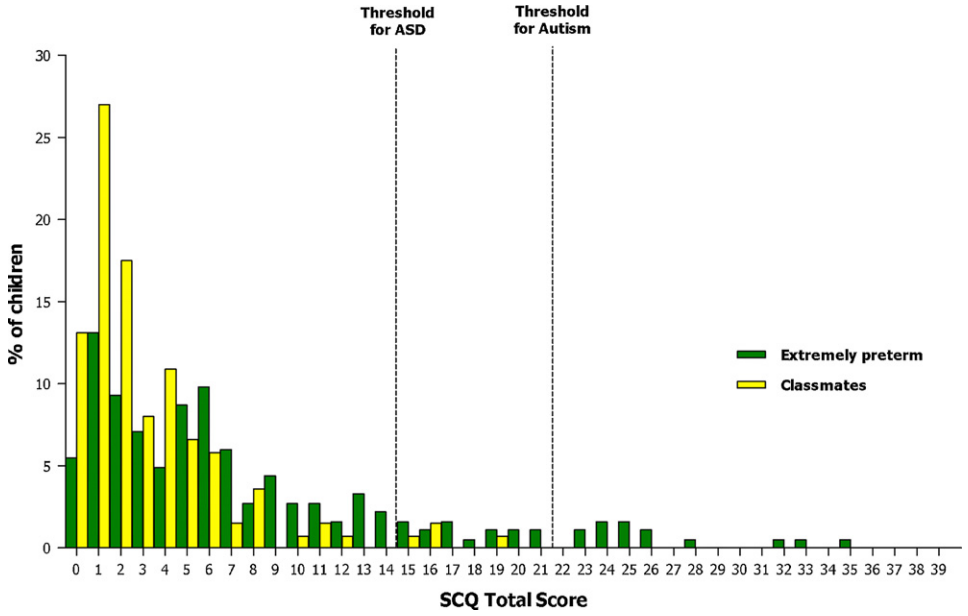

Figure. Frequency distribution showing proportion of children with each total SCQ score in the extremely preterm cohort (n = 183) and term-born classmates at 11 years of age (n = 137).

associated with ASD at discharge from hospital. After adjustment for sex, breech delivery, and abnormal cerebral ultrasound scanning results and receiving any breast milk were marginally associated ($P < .10$), the first 2 positively and breast milk negatively. By 2.5 years of age, only withdrawn behavior score (adjusted-OR, 1.20 per point; 1.05-1.37) was independently associated, but male sex, abnormal neonatal cerebral ultrasound scanning results, receiving breast milk, and sleep problem score were each close to significance (P values = .05-.10). By 6 years of age, only cognitive impairment (adjusted-OR, 2.0 per category; 1.05-3.7; $P = .035$) and pervasive peer problems (adjusted-OR, 5.3; 1.4-19; $P = .012$) were independent predictors.

Table III. Factors independently associated with total Social Communication Questionnaire scores in extremely preterm children at 11 years of age (n = 183) in stepwise multiple regression.

Variable	SCQ score	95% CI	P
Step 1: neonatal (n = 181) r^2 = 19.7%			
Male sex	3.4	1.3-5.4	.002
Gestational age ≤24 weeks	3.3	1.2-5.3	.002
Any breast milk	−4.7	−8.6–−0.8	.019
Abnormal cranial ultrasound scanning results	4.2	0.7-7.8	.020
Vaginal breech delivery	3.5	1.0-5.9	.006
Step 2: neonatal and outcome at 2.5 years (n = 166) r^2 = 38.8%*			
Male sex	2.8	1.0-4.7	.003
Gestational age ≤24 weekds	2.3	0.4-4.3	.017
Abnormal cranial ultrasound scanning results	2.9	0.01-5.8	.049
Functional disability (per category)	2.1	1.0-3.3	<.001
CBCL: withdrawn (per point)	1.0	0.6-1.3	<.001
Step 3: neonatal and outcomes at 2.5 and 6 years (n = 146) r^2 = 51.5%			
Any breast milk	−4.4	−7.8–−1.0)	.012
CBCL: withdrawn (per point)	0.9	0.6-1.2	<.001
Cognitive impairment at 6 years (per category)	1.7	0.7-2.6	.001
SDQ: pervasive hyperactivity/inattention	3.7	1.6-5.8	.001
SDQ: pervasive peer problems	3.6	1.0-6.1	.006

CBCL, child behavior checklist.
Functional disability at 2.5 years is for categories: none–other–severe. Cognitive impairment at 6 years is for categories: none–mild–moderate–severe.
Regressions were analyzed by using the robust option in Stata10 software to allow for heteroskedasticity and skewness.
*Withdrawn behavior scores at 2.5 years alone accounted for 23.9% of the variance.

Discussion

This large population-based study confirms that extremely preterm children are at increased risk for autism spectrum symptoms and disorders. The prevalence of narrowly defined autistic disorder is approximately 65-times higher than community populations, and the prevalence of ASD are 4- to 12-times higher.[2,24] As hypothesized, the prevalence of diagnoses in this study is higher than in other studies of ASD in VLBW/LBW children.[10,11] This is likely because of the increased risk of cognitive and neurodevelopmental impairment[25] and ASD with decreasing gestational age.[26] It is not surprising that no extremely preterm children had Asperger's disorder. Because of the high rate of developmental delay in this population, extremely preterm children are unlikely to fulfill diagnostic criteria for Asperger's disorder in which cognitive and language development is unimpaired in infancy.[16]

Extremely preterm children also had a significantly higher frequency of ASD symptoms, as has been reported for LBW children.[10] The distribution of SCQ scores was stretched to the right in extremely preterm children, yielding generally higher scores and greater variability compared with both classmates and the general population.[27] This suggests that increased liability to ASD symptoms impacts many extremely preterm children rather than a small subgroup who have ASD

Table IV. Correlates of autism spectrum disorder diagnoses in extremely preterm children (n = 201) at 11 years of age

Characteristics	No ASD diagnosis (n = 185) n (%)	ASD diagnosis (n = 16) n (%)	OR (95% CI)	P
Male	81 (44%)	12 (75%)	3.9 (1.2-12.4)	.019
Gestation <25 weeks	76 (41%)	8 (50%)	1.4 (0.5-4.0)	.60
Serious cognitive impairment	69 (37%)	11 (69%)	3.7 (1.2-11.1)	.017
Serious neuromotor impairment	17 (9%)	2 (13%)	1.4 (0.3-6.7)	.65
Serious hearing impairment	2 (1%)	1 (6%)	6.1 (0.5-71.2)	.22
Serious visual impairment	12 (6%)	3 (19%)	3.3 (0.8-13.3)	.10
Serious functional disability*	77 (42%)	12 (75%)	4.2 (1.3-13.6)	.016
Attends special school	18 (10%)	6 (38%)	5.6 (1.8-17.2)	.006
Special educational needs†	107 (59%)	16 (100%)	>11.1 (>1.8-NA)§	.001
Special educational needs support	105 (58%)	16 (100%)	>11.6 (>1.9-NA)§	<.001
Statement of special educational needs‡	52 (29%)	13 (93%)	32 (4.1-254)	.001
	Mean (SD)	**Mean (SD)**	**Difference in means (95% CI)**	**P**
IQ score	85 (17)	71 (18)	14.7 (5.8-24)	.001
Reading standardized score	82 (20)	68 (21)	13.8 (2.9-25)	.013
Math standardized score	73 (21)	54 (15)	18.9 (10.7-27)	<.001
Height (z-score)	−0.52 (1.0)	−0.62 (0.97)	0.10 (−0.39-0.59)	.70
Weight (z-score)	−0.40 (1.3)	−0.42 (1.2)	0.02 (−0.59-0.63)	.95
OFC (z-score)	−1.22 (1.2)	−1.44 (1.4)	0.22 (−0.47-0.92)	.53

*Serious functional disability is a composite classification of the most severe impairment in any of the 4 functional domains in rows above.
†Special educational needs data were available for 197 children (no ASD n = 181; ASD n = 16).
‡A statement of special educational needs is a legal local authority document outlining a child's special educational needs and mandating provision. Data were available for 195 children (no ASD n = 181; ASD n = 14). IQ, Reading and Math scores are standardized test scores (Mean, 100; SD, 15). OR are for univariate analyses.
§Cornfield approximation, upper limit of CI not defined.

diagnoses. Diagnosed ASD thus appear to be the extreme end of a distribution of symptoms that are generally increased in extremely preterm children. This results in a significant number of extremely preterm children who may have clinically important social and communication difficulties that fall below the diagnostic threshold for ASD.

Neonatal factors that were independently associated with a higher frequency of autism spectrum symptoms previously have been associated with a range of neurodevelopmental outcomes in this population.[28] By 2.5 years of age, withdrawn behavior scores and functional disability (the latter largely accounted for by the high burden of cognitive impairment) were independent associates of SCQ scores. By 6 years of age, cognitive impairment alone replaced a composite measure of functional disability, and inattention/hyperactivity and peer problems became additional significant associates. Having received any breast milk during neonatal intensive care unit admission was associated with lower autism spectrum symptomatology. This association is complex and must be interpreted with caution; it is impossible to determine whether this is a marker of parental aspiration, poor early attachment and reduced social contact, neurological difficulties, or a critical role of breast milk in neuronal development. Factors most strongly associated with SCQ scores were also close to significance for associations with ASD diagnoses on both univariate and multivariate analyses and are thus likely to be true relationships. The lack of significant associations with ASD diagnoses is likely to be a result of low statistical power for this binary outcome.

In extremely preterm children, ASD appear to be associated with different factors compared with the general population.[12] Almost all extremely preterm children with diagnoses had cognitive impairment, and IQ accounted for more than half the excess of social and communication difficulties in these children. Poor cognitive processing may underpin difficulties in social integration,[10] and attentional difficulties, also prevalent in preterm populations,[4,5] may be a primary underlying factor in impaired social interactions.[11]

Although in the general population ASD are generally considered to be genetic in origin, environmental factors such as obstetric complications[29] and extreme prematurity may play an important etiologic role. The correlates of ASD symptoms and disorders, in particular the high prevalence of cognitive impairment and reduced head circumference, are consistent with autistic disorders in which there is identifiable non-genetic structural or functional brain abnormalities[30] and suggests a different pathogenic pathway involving global impairment in brain development and cerebral connectivity. Extremely preterm birth confers both an insult to normal brain development and the superimposed risk of acquired brain injury. There is some evidence of white matter reduction and ventricular dilatation in VLBW children with symptoms of Asperger's disorder[31] and cerebellar-hemorrhagic injury in very preterm infants with positive autism screen test results.[6]

A high prevalence of autism spectrum symptoms has been reported in Romanian orphans who experienced early severe global privation.[32] Autistic features in these children were strongly associated with cognitive impairment, inattention/hyperactivity and attachment disorder. There is thus a striking similarity between the behavioral and cognitive profiles of Romanian adoptees and extremely preterm survivors. Furthermore, both have experienced highly abnormal physical and psychosocial environments during a potentially critical period in the development of the social

brain. We speculate, therefore, that ASD symptoms in extremely preterm children may be caused in part by physical and psychosocial environmental factors affecting early brain development.

The results from this study are conservative and robust. Classmates, although selected only from mainstream schools, were representative of the normal population because scores on standardized tests of academic attainment were remarkably close to population standards.[20] The lack of ASD diagnoses in classmates is consistent with the sample size and national prevalence. Rigorous methods were used to assess cognitive outcomes by psychologists blind to study group allocation. The SCQ has good diagnostic usefulness for identifying ASD,[27,33] and the DAWBA is a well-validated diagnostic psychiatric interview[14] that was the principal measure of psychopathology and ASD prevalence in the British Mental Health Survey.[15,24] Psychiatric data were collected for all children, rather than a subset who were identified as being at-risk, and diagnoses were made by consensus of psychiatrists blind to group allocation. The collection of validated outcomes from birth also enabled the investigation of risk factors for ASD in middle childhood.

Autism spectrum symptoms and disorders are highly prevalent in extremely preterm children and are part of a wider profile of global functional, cognitive, and attention deficits in this cohort. The increased risk in this population is suggestive of an environmental origin for ASD that is associated with aberrant brain development. Screening for ASD in extremely preterm children may help identify those at risk for a range of adverse social and educational outcomes and facilitate early planning for professional, educational, and domestic support. ■

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References

1. Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res 2009;65:591-8.
2. Williams JG, Brayne CEG, Higgins JPT. Systematic review of prevalence studies of autism spectrum disorders. Arch Dis Child 2006;91:8-15.
3. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005;352:9-19.
4. Samara M, Marlow N, Wolke D. Pervasive behavior problems at 6 years of age in a total-population sample of children born at <25 weeks of gestation. Pediatrics 2008;122:562-73.
5. Anderson P, Doyle L. Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s. Pediatrics 2004;114:50-7.
6. Limperoloulos C, Bassan H, Sullivan NR, Soul JS, Robertson RL, Moore M, et al. Positive screening for autism in ex-preterm infants: prevalence and risk factors. Pediatrics 2008;121:758-65.
7. Kuban KCK, O'Shea TM, Allred EN, Tager-Flusberg H, Goldstein DJ, Leviton A. Positive screening on the Modified Checklist for Autism in Toddlers (M-CHAT) in extremely low gestational age newborns. J Pediatr 2009;154:535-40.
8. Johnson S, Marlow N. Positive screening results on the Modified Checklist for Autism in Toddlers: implications for very preterm populations. J Pediatr 2009;154:478-80.
9. Hack M, Taylor HG, Schlichter M, Andreias L, Drotar D, Klein N. Behavioral outcomes of extremely low birth weight children at age 8 years. J Dev Behav Pediatr 2009;30:122-30.
10. Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk AM. Psychiatric symptoms and disorders in adolescents with low birth weight. Arch Dis Child Fetal Neonatal Ed 2004;89:F445-50.
11. Elgen I, Sommerfelt K, Markestad T. Population based, controlled study of behavioural problems and psychiatric disorders in low birthweight children at 11 years of age. Arch Dis Child Fetal Neonatal Ed 2002;87:F128-32.
12. Happe F, Ronald A, Plomin R. Time to give up on a single explanation for autism. Nature Neurosci 2006;9:1218-20.
13. Rutter M, Bailey A, Lord C. The Social Communication Questionnaire. Los Angeles, CA: Western Psychological Services; 2003.
14. Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. J Child Psychol Psychiatry Allied Disciplines 2000;41:645-55.
15. Fombonne E, Simmons H, Ford T, Meltzer H, Goodman R. Prevalence of pervasive developmental disorders in the British nationwide survery of child mental health. J Am Acad Child Adolesc Psychiatry 2001;40:820-7.
16. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fourth edition, text revision. 4th ed. Washington, DC: American Psychiatric Association; 2000.
17. Kaufman AS, Kaufman NL. Kaufman Assessment Battery for Children. Circle Pines, MN: American Guidance Service; 1983.
18. Wolke D, Ratschinski G, Ohrt B, Riegel K. The cognitive outcome of very preterm infants may be poorer than often reported: an empirical investigation of how methodological issues make a big difference. Eur J Pediatr 1994;153:906-15.
19. Bayley N. Bayley Scales of infant development. 2nd ed. San Antonio, TX: Psychological Corporation; 1993.
20. Johnson S, Hennessy E, Smith R, Trikic R, Wolke D, Marlow N. Academic attainment and special educational needs in extremely preterm children at 11 years. The EPICure Study. Arch Dis Child Fetal Neonatal Ed 2009;94:F283-9.
21. Johnson S, Fawke J, Hennessy E, Rowell V, Thomas S, Wolke D, et al. Neurodevelopmental disability through 11 years in children born before 26 weeks of gestation: the EPICure Study. Pediatrics. In press 2009.
22. Achenbach TM. The manual for the Child Behaviour Checklist/4-18 and 1991 Profile. Burlington, VT: University of Vermont, Department of Psychiatry; 1991.
23. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. J Am Acad Child Adolesc Psychiatry 2001;40:1337-45.
24. Green H, McGinnity A, Meltzer H, Ford T, Goodman R. Mental health of children and young people in Great Britain. Basingstoke, Hampshire: National Statistics; 2005.
25. Johnson S. Cognitive and behavioural outcomes following very preterm birth. Semin Fetal Neonatal Med 2007;12:363-73.
26. Moster D, Terje R, Markestad T. Long-term medical and social consequences of preterm birth. N Engl J Med 2008;359:262-73.
27. Chandler S, Charman T, Baird G, Simonoff E, Loucas T, Meldrum D, et al. Validation of the Social Communication Questionnaire in a population cohort of children with autism spectrum disorders. J Am Acad Child Adolesc Psychiatry 2007;46:1324-32.

28. Wood N, Costeloe K, Gibson A, Hennessy E, Marlow N, Wilkinson A. The EPICure Study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. Arch Dis Child Fetal Neonatal Ed 2005;90:F134-40.
29. Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. Br J Psychiatry 2009;195:7-14.
30. Rutter M, Bailey A, Bolton P, Le Couter A. Autism and known medical conditions: myth and substance. J Child Psychol Psychiatry 1994;35:311-22.
31. Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Brubakk AM. Psychiatric symptoms in low birth weight adolescents, assessed by screening questionnaires. Eur J Child Adolesc Psychiatry 2005;14:226-36.
32. Rutter M, Anderson-Wood L, Beckett C, Bredenkamp D, Castle J, Groothues C, et al. Quasi-autistic patterns following severe earlly global privation. J Child Psychol Psychiatry 1998;40:537-49.
33. Berument SK, Rutter M, Lord C, Pickles A, Bailey A. Autism screening questionnaire: diagnostic validity. Br J Psychiatry 1999;175:444-51.

50 Years Ago in The Journal of Pediatrics

Ristocetin, a Laboratory and Clinical Evaluation in Children

Pries CP, Koch R. J Pediatr 1960;56:498-504

Ristocetin, a glycopeptide antibiotic, was isolated from *Amycolatopsis orientalis* shortly after the discovery of vancomycin, a similar glycopeptide. Ristocetin's antibacterial properties were described in 1955,[1] and the drug was widely used as an antistaphylococcal drug until the early 1960s. In this 1960 article, Pries and Koch describe the clinical response to ristocetin in 55 children, including pharmacokinetic studies. Serious staphylococcal infections were effectively treated, but one-third of the patients had mild toxicities (eosinophilia, leukopenia, skin rash, and local reactions). Interestingly, none developed thrombocytopenia, but other reports of ristocetin-induced severe thrombocytopenia eventually led to ristocetin's discontinuation as an antimicrobial drug.[2]

Although platelet toxicity was risocetin's clinical undoing as an antibiotic, years later the drug found a role in the investigation of von Willebrand disease (VWD), as the key reagent for testing functional interactions between von Willebrand factor (VWF) and the platelet GPIb-IX-V complex. In this VWF ristocetin cofactor assay (VWF:RCo), ristocetin induces measurable platelet aggregation in the presence of VWF. The VWF:RCo assay is sensitive to the presence of large and intermediate VWF multimers and is abnormal in patients with VWD and also in those with Bernard-Soulier disease, an inherited deficiency of the GPIb-IX-V complex. Although this assay has multiple shortcomings (ie, cumbersome, lack of optimal control of reagent platelets, high coefficient of variation, inaccurate at low levels of VWF, and significant interlaboratory variation), it remains central to the evaluation for VWD, because ristocetin remains the sole reagent capable of assessing this specific VWF function.

It is noteworthy that ristocetin and vancomycin have biological and structural similarities. But the ristocetin aglycon methyl ester derivative lacks the platelet side effect while conserving the antimicrobial property, thus making ristocetin a lead compound for developing new antibiotics against vancomycin-resistant bacteria.[3]

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References

1. Philip JE, Schenck JR, Hargie MP. Ristocetins A and B, two new antibiotics: isolation and properties. Antibiot Annu 1956;699-705.
2. Gangarosa EJ, Landerman NS, Rosch PJ, Herndon EG Jr. Hematologic complications arising during ristocetin therapy: relation between dose and toxicity. N Engl J Med 1958;259:156-61.
3. McComas CC, Crowley BM, Hwang I, Boger DL. Synthesis and evaluation of methyl ether derivatives of the vancomycin, teicoplanin, and ristocetin aglycon methyl esters. Bioorg Med Chem Lett 2003;13:2933-6.

Appendix

A study steering group chaired by Professor Peter Brocklehurst (Oxford) monitored the progress of the study. Ms Rebecca Smith, Ms Rebecca Trikic, Dr Samantha Johnson (psychologists), Dr Joseph Fawke, Dr Susan Thomas, and Dr Victoria Rowell (pediatricians) conducted data collection for this study. Mrs Heather Palmer was the study manager. Support for DAWBA data collection and analysis were provided by Professor Robert Goodman (London). Co-investigators for the EPICure Studies were Professor Neil Marlow (University of Nottingham; principal investigator), Professor Kate Costeloe (Queen Mary, University of London), Mrs Enid Hennessy (Queen Mary, University of London), Professor Janet Stocks (University College London), and Professor Elizabeth Draper (University of Leicester). The study website can be viewed at www.epicure.ac.uk.

Table II. Univariate associations with total Social Communication Questionnaire scores and autism spectrum disorder diagnoses in extremely preterm children at 11 years of age

Neonatal variables	Total SCQ scores (n = 183)				ASD diagnoses (n = 16)			
	n	Coefficient	95% CI	*P*	n	OR	95% CI	*P*
Male	183	3.2	1.0-5.4	**.005**	201	3.85	1.20-12.39	**.024**
Gestational age (≤24 weeks)	183	2.58	0.3-4.8	**.025**	201	1.43	0.52-4.00	.49
Birthweight (per 100 g)	183	−0.5	−1.5-0.5	.32	201	2.42	0.03-199	.67
Head circumference (per cm)	125	−0.0	−1.0-1.0	.99	139	1.25	0.85-1.85	.25
Singleton	183	1.6	−0.6-3.8	.16	201	0.81	0.27-2.46	.72
White ethnic origin	182	−0.7	−3.2-1.8	.57	200	1.53	0.33-7.06	.59
Any antenatal steroids	181	−0.3	−2.9-2.4	.83	199	0.99	0.27-3.66	.99
Preterm premature rupture of membranes	180	−2.6	−4.8–−0.3	**.025**	198	0.63	0.17-2.29	.48
Breech delivery	182	2.7	0.1-5.4	**.042**	200	2.55	0.90-7.3	.079
Chorioamnionitis (suspected or proven)	180	−2.1	−4.5-0.3	.083	198	1.18	0.36-3.87	.78
Fetal heart rate >100 bpm @ 5 minutes	179	1.6	−2.0-5.1	.38	197	1.36	0.17-11.0	.78
Temperature <35°C	174	1.8	−0.8-4.4	.18	191	1.55	0.50-4.77	.45
CRIB score (per point)	182	0.2	−0.1-0.5	.20	200	1.03	0.89-1.19	.69
Transferred with 24 h of birth	182	1.9	−0.9-4.7	.18	200	1.89	0.50-7.21	.35
Abnormal cranial ultrasound scanning results	182	3.8	0.0-7.7	**.049**	200	2.76	0.88-8.60	.079
Necrotizing enterocolitis	182	5.3	−4.5-15.0	.29	200	2.24	0.26-22	.44
Any postnatal steroids for CLD	182	1.5	−0.9-3.8	.22	200	0.78	0.26-2.35	.65
Postnatal steroids (per week) for CLD	180	0.3	−0.1-0.7	.17	197	1.06	0.93-1.21	.36
Bronchopulmonary dysplasia (02 @ 36 weeks)	183	1.0	−1.5-3.4	.43	201	0.82	0.27-2.46	.72
Any breast milk	181	−4.4	−8.6–−0.3	**.037**	199	0.33	0.10-1.04	.058
Duration of NICU admission (per week)	135	0.3	0.0-0.5	**.027**	151	1.07	0.99-1.17	.098
Maternal age (per 10 years)	181	−0.4	−2.5-1.8	.73	199	1.39	0.55-3.47	.50
Maternal education post-16 years	170	0.7	−2.4-3.8	.66	187	2.35	0.79-7.02	.13
Outcome at 2.5 years								
Serious cognitive impairment*	169	8.6	5.0-12.3	**<.001**	183	1.83	0.47-7.11	.39
Functional disability	180	5.3	3.1-7.6	**<.001**	197	3.58	1.10-11.7	**.034**
Head circumference (per SDS)	178	−0.9	−1.8–−0.1	**.034**	195	0.82	0.56-1.20	.31
Internalizing behavior problems†	166	6.0	1.9-10.0	**.004**	183	2.86	0.90-9.07	.074
Externalizing behavior problems†	166	6.0	2.3-9.8	**.002**	183	2.08	0.54-8.09	.29
Anxious/depressed† (per category)	166	4.8	1.8-7.8	**.002**	183	2.15	0.95-4.88	.066
Somatic complaints† (per category)	166	1.4	−0.5-3.2	.15	183	1.93	0.98-3.78	.056
Withdrawn† (per category)	166	6.5	3.8-9.2	**<.001**	183	2.09	0.95-4.61	.066
Sleep problems† (per category)	166	1.5	−0.7-3.8	.18	183	2.07	0.98-4.37	.057
Aggressive behavior† (per category)	166	4.5	2.1-6.8	**<.001**	183	2.23	1.05-4.76	**.037**
Total behavior problems†	166	6.7	2.1-5.5	**<.001**	183	4.19	1.41-12.48	**.010**
Outcome at 6 years								
Serious cognitive impairment‡	171	6.5	3.9-9.1	**<.001**	189	6.27	1.94-20.31	**.002**
Serious functional disability	171	5.5	3.0-7.9	**<.001**	189	4.75	1.47-15.33	**.009**
Head circumference (per SDS)	171	−0.8	−1.8-0.2	.14	188	0.95	0.63-1.43	.82
Pervasive emotional problems§	149	2.0	−1.2-5.3	.22	158	0.96	0.20-4.64	.96
Pervasive conduct problems§	148	4.9	0.1-9.8	**.047**	157	1.46	0.30-7.16	.65
Pervasive attentional problems§	151	6.1	3.1-9.2	**<.001**	161	6.08	1.77-20.83	**.004**
Pervasive peer problems§	149	7.5	4.1-10.9	**<.001**	158	7.95	2.30-27.50	**.001**
Pervasive total behavior problems§	147	6.8	2.8-10.8	**.001**	156	4.47	1.38-14.53	**.013**

CRIB, Clinical Risk Index for Babies; *NICU,* neonatal intensive care unit; *SDS,* standard deviation score; *CLD,* chronic lung disease.

*Bayley Scales of Infant Development 2nd Edition, Mental Development Index score –2SD (scores <70).

†Assessed with Child Behavior Checklist (CBCL). Regression for internalizing and externalizing problems is for risk of clinically significant behavior problems. Regression for subscales is for 3 categories: none, borderline, clinically significant problems defined using published cutoffs.

‡Kaufman Assessment Battery for Children, Mental, Processing Composite (MPC/IQ) score–2SD of classmates (scores <82).

§Assessed with Strengths and Difficulties Questionnaire (SDQ).

P values in bold denote significance at .05 level.