Autism Spectrum Disorders in extremely preterm children

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Samantha Johnson, *Ph.D, CPsychol.* Non-Clinical Lecturer in Academic Neonatology (Psychology), Institute for Women's Health, University College London, UK and Research Psychologist, School of Clinical Sciences, University of Nottingham, UK.

Chris Hollis, *PhD, MRCPsych*, Professor of Child and Adolescent Psychiatry, School of Community Health Sciences, University of Nottingham, UK.

Puja Kochhar, *BSc.* Academic Clinical Fellow, School of Community Health Sciences, University of Nottingham, UK.

Enid Hennessy, *MSc*. Senior Lecturer, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK.

Dieter Wolke, *Ph.D., Dipl-Psych, C.Psychol.* Professor of Developmental Psychology and Individual Differences, Department of Psychology and Health Sciences Research Institute, University of Warwick, UK.

Neil Marlow, *DM, FMedSci*. Professor of Neonatal Medicine, Institute for Women's Health, University College London, UK.

Corresponding author (and requests for reprints)

Dr Samantha Johnson

Non-Clinical Lecturer in Academic Neonatology (Psychology)

Institute for Women's Health

86-96 Chenies Mews

London, WC1E 6HX, United Kingdom

Email 1: s.j.johnson@ucl.ac.uk

Email 2: sam.johnson@nottingham.ac.uk

Tel: +44 (0) 20 7679 6313

Fax: +44 (0) 20 7383 7429

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Abstract

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

Study design. Prospective study of all births <26 weeks gestation in UK and Ireland, 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 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 (8%) extremely preterm children were assigned an ASD diagnosis compared with none of the classmates. By hospital discharge, male sex, lower gestation, vaginal breech delivery, abnormal cerebral ultrasound scan and not having had breast milk were independently associated with autism spectrum symptoms. By 6 years, independent associates were cognitive impairment, inattention, peer problems, withdrawn behaviour at 2½years and no breast milk.

Conclusions. Extremely preterm children are at increased risk for autism spectrum symptoms and disorders in middle childhood. These were associated with neurocognitive outcomes suggesting that ASD may result from abnormal brain development in this population.

Autism Spectrum Disorders (ASD) are a range of conditions that share core impairments in reciprocal social interaction, communication and a pattern of restricted/repetitive behaviours or interests. The most recent prevalence estimates for ASD range from 1/1000 to 4/1000 for narrowly-defined DSM-IV-TR autistic disorder and from 6/1000 to 9/1000 for the broader category of ASD(1, 2). Extremely preterm children are at high risk for neurodevelopmental disability(3), behaviour 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 recent studies have reported that 21%-25% of very preterm infants screened positive 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, three studies of school-aged outcomes have reported a 4% positive screening rate for autistic features in extremely low birthweight (ELBW <1000g) children(9) and 1-2% prevalence of diagnosed ASD in those born with very/low birthweight (VLBW/LBW)(10, 11).

As yet, the prevalence of ASD has not been systematically investigated in extremely preterm children. Autism spectrum symptoms may be secondary to the high prevalence of neurocognitive impairment in preterm children, particularly extremely preterm, reflecting a different aetiology and associated risk factors in this population(7, 10, 11). To advance the study of the aetiology of childhood mental disorders, both a dimensional and categorical approach has been proposed as many conditions develop on the basis of a dimensional liability in which boundaries extend more broadly than indicated by traditional diagnostic classifications(12).

Objective

Using both a dimensional and categorical approach, we have investigated the prevalence, correlates and antecedents of autism spectrum symptoms and disorders in extremely preterm children.

Participants

All babies born ≤25 weeks gestation across the UK and Ireland, March-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 (71%) were assessed (Median: 10y11m; range: 121m-145m). Longitudinal data were available for 213 and 202 children who were also assessed at 2.5y and 6y, respectively.

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

Method

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

Measures

Autism spectrum symptoms were assessed using the Social Communication Questionnaire (SCQ)(13), a parental screening questionnaire for identifying ASD. The SCQ yields sub-scale scores for Social Interaction (range 0-15), Communication (range 0-13) and Repetitive/Stereotyped Behaviour (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 using computer-generated scoring algorithms (www.dawba.com). Summary sheets and clinical transcripts were reviewed and diagnoses assigned by consensus between 2 clinicians blind to group allocation. This method has good reliability for diagnosing ASD.(15) As almost identical diagnostic criteria are applied in DSM-IV-TR and ICD-10, we refer only to DSM-IV-TR diagnoses: autistic disorder, Asperger's disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS), Rett's syndrome and childhood disintegrative disorder(16).

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

A standard paediatric evaluation was used to classify impairment (none, mild and serious) in neuromotor function, hearing and vision. Overall disability was classified using the most

severe rating in any of the four functional domains assessed (cognition, hearing, vision, motor) at 2.5y, 6y and 11y(21). Head circumference was measured at each age.

Parental ratings of behavioural problems were obtained at 2.5y using the Child Behaviour Checklist (CBCL)(22). Borderline and clinically significant problems were identified for Withdrawn, Anxious/depressed, Sleep problems, Somatic complaints, Aggressive behaviour, and for Internalising, Externalising and Total Behaviour problems. At 6y, parents and teachers completed the Strengths and Difficulties Questionnaire (SDQ)(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 discharge.

Statistical analyses

Data were double-entered, verified and analysed using SPSSv15.0 and Stata10 (SJ, EH). Group differences in SCQ scores were analysed using t-tests allowing for unequal variances and Fisher's exact tests for dichotomous outcomes. Differences between groups in SCQ scores were adjusted for IQ using linear regression. For extremely preterm children the effects of neonatal and neurodevelopmental variables on SCQ scores and ASD diagnoses were investigated using 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 three epochs: neonatal, outcomes by 2.5y and by 6y. Results are presented with 95% Confidence Intervals and 2-sided p-values. No adjustments were made for multiple comparisons. Classmates were assumed to have normal cerebral ultrasounds. All linear regressions used Huber White/sandwich estimates of variance to adjust for heteroscedasticity and/or non-normality in SCQ scores.

Results

Extremely preterm children not assessed (n=89) at 11y were more likely to be born at 25w to unemployed parents of non-white ethnic origin and to have more frequent cognitive

impairment at 2.5y and 6y than those assessed (n=219).(20) Extremely preterm children with missing SCQ (n=36) and DAWBA (n=18) 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 (86%) extremely preterm children and 140 (92%) classmates. 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 behaviour (Table 1). As expected, SCQ scores were positively skewed (Figure 1).

TABLE 1

Twenty-nine (15.8%) extremely preterm children and 4 (2.9%) classmates screened positive for ASD (SCQ ≥15; OR 6.3; CI 2.2,18.3; p<.001). The mean score for extremely preterm children with positive screens (22.0, SD 5.47) was significantly higher than classmates with positive screens (16.5, SD 1.7; Mean difference 5.5; CI 2.7,8.4). Of 29 extremely preterm children with positive screens, 14 (7.7%, CI 4.2%,12.5%) screened positive for autism (SCQ ≥22) compared with no classmates (CI: 0.0%,2.7%; p<.001) (Figure 1).

FIGURE 1

Antecedents of autism spectrum symptoms in extremely preterm children

On univariate analyses higher SCQ scores were significantly associated with male sex, breech delivery, birth <25w, last cerebral ultrasound scan being abnormal and increasing weeks in NICU (Table 2). Preterm rupture of membranes and receipt of any breast milk were significantly associated with lower SCQ scores. At 2.5y and 6y, cognitive and functional disability and behaviour problems had strong associations with increased SCQ scores. Larger

head circumference at 2.5y was significantly associated with lower SCQ scores and was the same order of magnitude at 6y although non-significant (Table 2).

TABLE 2

Variables in Table 2 were tested to establish factors independently associated with SCQ scores at 3 sequential epochs. By discharge being male, <25w, breech delivery, abnormal cerebral ultrasound and non-receipt of breast milk were independently associated with higher SCQ scores and thus greater autism spectrum symptomatology (Table 3). By 2.5y, after inclusion of the highly significant functional disability and withdrawn behaviour scores, male sex, birth <25w and abnormal ultrasound remained significant but with weaker associations. By 6y, non-receipt of breast milk and withdrawn behaviour scores retained independent associations in addition to cognitive impairment, hyperactivity/inattention and peer problems (Table 3).

TABLE 3

Prevalence and correlates of Autism Spectrum Disorder diagnoses

DAWBA interviews were available for 201 (92%) extremely preterm children and 143 (93%) classmates. Sixteen (8%) extremely preterm children were diagnosed with ASD: 13 (6.5%) with autistic disorder and 3 (1.5%) with PDD-NOS. No classmates received an ASD diagnosis. Extremely preterm children with ASD were more likely to be male, have cognitive impairment, SEN and poorer academic attainment than their preterm counterparts (Table 4). Only 1/12 children with functional disability and ASD did not have cognitive impairment but had an isolated hearing impairment.

TABLE 4

Antecedents of Autism Spectrum Disorders in extremely preterm children

Male sex was the only significant neonatal risk factor (Table 2). At 2.5y, functional disability and aggressive behaviour were significant and at 6y, cognitive impairment, functional

disability, attention/hyperactivity and peer problems were significant associates. None of the 56 children without cognitive impairment at 6y had ASD at 11y (0%; 0%,6.4%), 4/65 with mild impairment had ASD (6.1%; 1.7%,15.0%) and 6/34 in both the moderate and severe categories had ASD (17.6%; 6.8%,34.5%).

On multivariate analyses in three sequential epochs, only male sex (adjusted-OR 3.85; 1.20,12.4) was independently associated with ASD at discharge from hospital. After adjustment for sex, breech delivery and abnormal cerebral ultrasound and any breast milk were marginally associated ($p<0.10$), the first two positively and breast milk negatively. By 2.5y, only withdrawn behaviour score (adjusted-OR 1.20 per point; 1.05,1.37) was independently associated, but male sex, abnormal neonatal cerebral ultrasound, breast milk and sleep problem score were each close to significance (p values 0.05-0.10). By 6y, only cognitive impairment (adjusted-OR 2.0 per category; 1.05,3.7; $p=0.035$) and pervasive peer problems (adjusted-OR 5.3; 1.4,19; $p=0.012$) were independent predictors.

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 around 65 times higher than community populations, and the prevalence of ASD 4 to 12 times higher(2, 24). As hypothesised, the prevalence of diagnoses in the present study is higher than in other studies of ASD in VLBW/LBW children(10, 11). This is likely to be due to the increased risk of cognitive and neurodevelopmental impairment(25) and ASD with decreasing gestational age(26). It is unsurprising that no extremely preterm children had Asperger's disorder. Given the high rate of developmental delay in this population, extremely preterm children are unlikely to fulfil 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 on many extremely preterm children rather than on a small sub-group who have ASD 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 have previously been associated with a range of neurodevelopmental outcomes in this population(28). By 2.5y of age, withdrawn behaviour scores and functional disability, the latter largely accounted for by the high burden of cognitive impairment, were independent associates of SCQ scores. By 6y 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 NICU 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 of 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).

While in the general population ASD are generally considered 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 disorder 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-haemorrhagic injury in very preterm infants with positive autism screens(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 behavioural 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 due in part to 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 as scores on standardised 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 utility 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 sub-set identified at-risk, and diagnoses were made by consensus between psychiatrists blind to group allocation. The collection of validated outcomes from birth also enabled the investigation of risk factors for ASD in middle childhood.

Conclusions

Autism spectrum symptoms and disorders are highly prevalent among 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.

Abbreviations:

ASD	Autism Spectrum Disorders
EP	Extremely preterm (≤25 weeks gestation)
LBW	Low Birthweight (<2500g)
VLBW	Very Low Birthweight (<1500g)
ELBW	Extremely low birthweight (<1000g)
SCQ	Social Communication Questionnaire
DAWBA	Development and Well Being Assessment
OR	Odds Ratio
CI	Confidence Interval

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Figure legend

Figure 1. 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 (n=137).

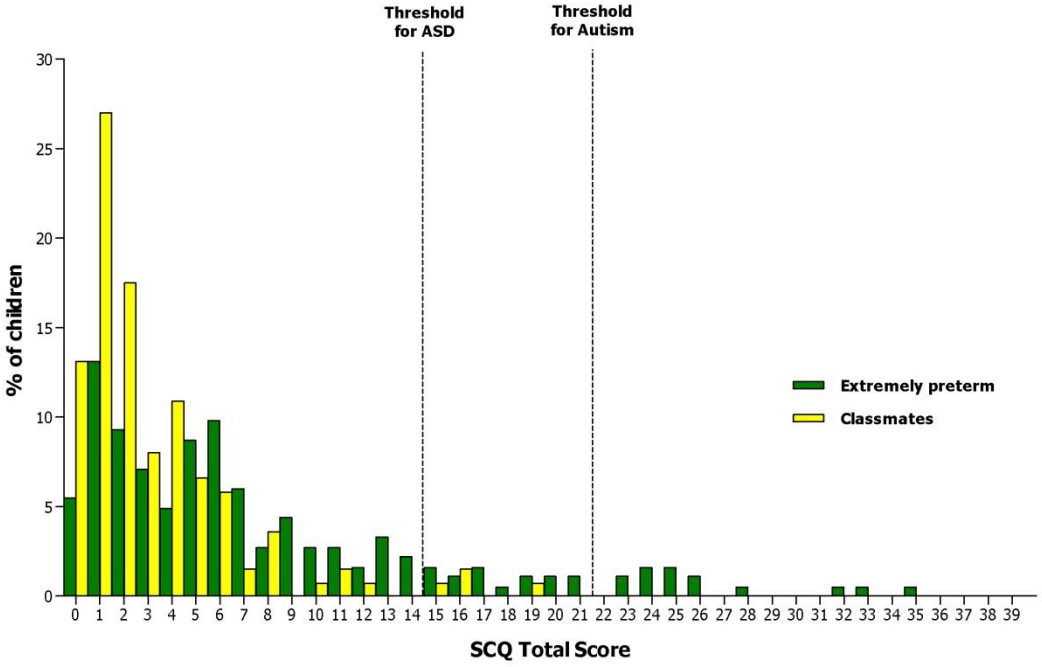
Threshold for ASD
Threshold for Autism
% of children
SCQ Total Score
Extremely preterm
Classmates

Figure 1.