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Autistic traits at neurodevelopmental assessment for very preterm infants

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Abstract

Aim

The aim of this study was to establish the prevalence of autistic traits at childhood neurodevelopmental assessment in a premature cohort and to assess associated perinatal exposures.

Methods

An observational retrospective case-control study was conducted in a single tertiary neonatal unit. All infants born weighing ≤1500 grams and/or ≤32/40 weeks who attended for neurodevelopmental assessment in 2019 were eligible.

Results

96 preterm infants met the inclusion criteria. 22 (23%) in the case group demonstrated clinical features of autism at early childhood assessment. The remaining 74 acted as a control group. In the case group 18 (82%) were male. There was no difference in rate of multiple births between the groups. There was no statistically significant difference in maternal age or indication for delivery.

Male phenotype (p=0.003), non-Irish ethnicity (p=0.005), vaginal delivery (p=0.005) and abnormal cranial ultrasound (p=0.009) occurred more frequently in the case group. Use of assistive reproductive technologies occurred less frequently in the case group (p=0.047). In the case group, 10/14 of the composite scores measured on Bayleys-3 at a median (IQR) age of 32 (31-35) months showed statistically significant differences (p<0.003).

Discussion

Our study strongly supports increasing awareness of the association between prematurity and autism. It highlights the need for targeted neurodevelopmental follow-up to support early detection of autism, allowing for timely intervention. Further investigation in a larger prospective cohort may further delineate the various perinatal risk factors for autism.

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Introduction

Preterm birth is associated with a higher incidence of autism[1-5]. A meta-analysis published in 2018 included 18 studies with a total of 3,366 preterm infants and reported a 7% prevalence rate for autism[6].

Pinto-Martin et al utilizing a validated autism diagnostic test revealed that low birth weight infants had approximately a five times increased prevalence rate of autism compared to the general population[7]. There appears to be a significant correlation between birth week and the risk of autism, with increasing risk at lower gestations[5,8]. The EPICURE follow-on study reported 1 in 12 extreme premature infants were diagnosed with autism[9].

The aim of this study was to establish the prevalence of autistic traits at early childhood neurodevelopmental assessment in a cohort of very-low birth weight and/or very preterm infants and to assess the perinatal exposures potentially associated with autistic traits in this population.

Methods

This study is an observational retrospective case-control study performed in a single tertiary neonatal intensive care unit (NICU). Our early childhood neurodevelopmental assessments are scheduled at 2 years corrected gestational age (CGA). All children who attended this assessment from January 2019 to December 2019 were screened for inclusion. Inclusion criteria were infants born ≤1500 grams (g) and/or ≤32/40 weeks gestational age. There were no exclusion criteria. A retrospective chart review was performed to extract demographic details, perinatal and neonatal factors. Early childhood neurodevelopmental assessment was completed by a senior clinical psychologist who was blinded to the neonatal course of the children and has experience in the diagnosis of autism spectrum disorder (ASD). Assessment included clinical observation, the child-behavioural parental checklist (ages 1 ½ - 5) and the Bayley Scales of Infant and Toddler Development (Edition 3). Clinical observation was guided by the DSM 5 299.00 diagnostic criteria for autism, as well as other relevant DSM 5 childhood developmental disorders and incorporated parental reports on the child's typical presentation in various environments. Criteria A: persistent deficits in social communication and –interaction requires evaluation of social-emotional reciprocity, joint attention and peer relationships. Criteria B: restricted, repetitive behaviours, activities and requires evaluation of stereotypical, repetitive motor movement, speech, use of objects, etc.

Children with suspected autism were referred according to a pre-determined care pathway to a developmental paediatrician for further assessment. Children with isolated low scores on language subdomains with no other concerns for social development were identified as having isolated speech delay rather than autistic traits and not included in our case numbers.

Ethical approval for this study was provided by the Research Ethics Committee of The Rotunda Hospital, Dublin.

Statistical analysis was performed using Statacorp LLC Stata 15.1. Patient demographic data is expressed as summary statistics by median (interquartile range (IQR)), n/n (percentage) as

appropriate. For neurodevelopmental outcome, available scaled and composite scores from the Bayley assessment are reported.

Between group differences are analysed by Mann Whitney U test for continuous variables and Chi-squared or Fisher's exact test for categorical variables. Perinatal factors significant for group differences between cases and controls were tested as independent variables in a logistic regression analysis. A Bonferroni corrected p value of $p<0.01$ was applied for variables added to the logistic regression analysis. Due to low numbers the variable ethnicity was recoded as a binary Irish and Non-Irish outcome for logistic regression. Similarly, mode of delivery was regrouped as a binary vaginal or operative delivery. Significant variables within the model are reported as odds ratios (OR) and 95% confidence intervals (95% CI).

Results

137 children were invited for an early childhood neurodevelopmental assessment in 2019. Of these, 113 children (82%) attended at a median (IQR) age of 32 (31-35) months.

17 were excluded due to birth weight or gestational age outside the inclusion criteria. 96 infants were included in the final cohort. 22/96 (23%) were identified as having features of autism during assessment and the remaining 74/96 (77%) acted as a control group.

The total cohort was 52/96 (54%) male, with a median (IQR) gestational age at birth of 29+1/40 (28+1/40 – 30+6/40) and a birth weight 1.15 kilograms (0.99kgs – 1.37kgs). Patient demographics, perinatal and neonatal risk factors are summarised in Table 1. The cohort included 51/96 (53%) infants from multiple births. Table 2 displays data on twins and triplets for cases and controls.

Male phenotype (p=0.003), non-Irish ethnicity (p=0.005), vaginal delivery (p=0.005) and abnormal cranial ultrasound (p=0.009) occurred more frequently in the case group. Use of assistive reproductive technologies (ART) occurred less frequently in the case group OR (95% CI) of 4.8 (1.1-22.0), p=0.047. However, this lost significance once Bonferroni correction was introduced. Non-Irish ethnicities in the case group included Chinese, Brazilian, African and Polish. One child's ethnicity was not available.

The only neonatal parameter that demonstrated a statistically significant difference between cases and controls was the finding of an abnormal cranial ultrasound scan which included intraventricular haemorrhage (IVH) or peri-ventricular leukomalacia (PVL) reported on cranial ultrasound at any time during the initial neonatal period. Eight out of 22 (36%) in the case group had abnormal cranial ultrasound reports: two with grade 1, three grade 2, one grade 3, one grade 4 IVHs and one with a small focus of PVL which was not seen on subsequent imaging. In comparison, 9/74 (12%) had an abnormal cranial ultrasound in the control group. This included two babies with grade 1 IVH, four babies with grade 2 IVH, two babies with grade 3/4 IVH and a single baby with bilateral symmetrical foci of PVL. Therefore, four perinatal factors and one neonatal factor were included in the logistic regression analysis.

Through the logistic regression analysis, ethnicity and mode of delivery lost statistical significance. Male phenotype showed an OR (95% CI) of 6.3 (1.6-25.4) to have a higher association with autistic features. Having an abnormal cranial ultrasound had an OR (95% CI) of 7.9 (1.7-35.7) of having

autistic features at follow-up. Bayley-3 assessment scores showed a statistically significant difference on 10/14 subscales (p<0.003) (*Table 3, Figure 1*).

The outcomes of follow up assessments of cases were obtained. Five children have received a formal diagnosis of autism. A further nine children continue to show features of autism and have been waitlisted for a formal assessment. Two sets of parents declined assessment for autism. Three children's outcome were unknown as they were accessing local services in another region after their Bayley assessment. A further three children were discharged, with two receiving ongoing speech and language therapy.

Perinatal Characteristics	**Total (n=96)**	**Case (n=22)**	**Control (n=74)**	**p-value**
Maternal Age (yrs)				0.56
Median (IQR)	34 (30.5-38)	33 (31-37)	35 (30-38)	
Range	20-49	21-44	20-49	
GA at Birth				0.47
Median (IQR)	29+1/40 (28+1/40 – 30+6/40)	28+5/40 (26+1/40 – 31+0/40)	29+4/40 (28+1/40 – 30+6/40)	
Range	23+4/40 – 34+3/40	25+0/40 – 32+5/40	23+4/40 - 34+3/40	
BW (kg)				0.18
Median (IQR)	1.15 (0.99- 1.37)	1.11 (0.93-1.27)	1.20 (1.02-1.41)	
Range	0.5-1.91	0.72 – 1.91	0.5 – 1.84	
Weight Centile				0.75
Median (IQR)	48 (19-68)	52 (16-72)	48 (19-64)	
Range	0.9-98	0.9-90	3-98	
Male phenotype n (%)				0.003*
Male/Female	52 (54%)/44 (46%)	18 (82%)/4 (18%)	34 (46%)/40 (54%)	
Birth Multiplicity n (%)				1.00
Singleton	45 (47%)	10 (45%)	35 (47%)	
Twin	46 (48%)	11 (50%)	35 (47%)	
Triplet	5 (5%)	1 (5%)	4 (5%)	
IUGR n (%)				0.71
Yes	11 (11%)	3 (14%)	8 (11%)	
Ethnicity n (%)				0.005*
Irish	75 (78%)	12 (55%)	63 (85%)	
Non-Irish	20 (21%)	9 (40%)	11 (15%)	
Not available	1 (1%)	1 (5%)	0 (0%)	
ART n (%)				0.047
Yes	39 (41%)	5 (23%)	34 (47%)	
Mode of Delivery n (%)				0.005*

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Vaginal	18 (19%)	9 (41%)	9 (12%)	
Operative	78 (81%)	13 (59%)	65 (88%)	
Delivery Indication n (%)	19 (20%)	6 (27%)	13 (18%)	0.30
Spontaneous labour	8 (8%)	3 (14%)	5 (7%)	
Breech in labour	10 (10%)	4 (18%)	6 (8%)	
Chorioamnionitis	12 (13%)	1 (5%)	11 (15%)	
Maternal Indication	41 (43%)	7 (32%)	34 (46%)	
Fetal Indication	6 (6%)	1 (5%)	5 (7%)	
APH				
Apgar 1 min				0.76
Median (IQR)	7 (5-8)	7 (4-9)	7 (5-8)	
Range	1-9	2-9	1-9	
Apgar 5 min				0.35
Median (IQR)	9 (8-10)	9 (8-10)	9 (8-10)	
Range	4-10	7-10	4-10	
Ventilation n (%)				0.64
Yes	65 (68%)	14 (64%)	51 (69%)	
Sepsis n (%)				0.22
Yes	19 (20%)	2 (9%)	17 (23%)	
NEC medical n (%)				0.13
Yes	6 (6%)	3 (14%)	3 (4%)	
NEC surgical n (%)				0.55
Yes	3 (3%)	1 (5%)	2 (3%)	
PDA medical n (%)				0.95
Yes	17 (18%)	4 (18%)	13 (18%)	
PDA surgical n (%)				0.20
Yes	7 (7%)	3 (14%)	4 (5%)	
ROP requiring treatment n (%)	4 (4%)	2 (9%)	2 (3%)	0.22
Yes				
Abnormal CRUSS n (%)				
Yes	17 (18%)	8 (36%)	9 (12%)	0.009*

Table 1: Perinatal characteristics. IQR = inter-quartile range. GA = gestational age. BW = birth weight. IUGR = intra-uterine growth restriction. ART = assisted reproductive therapy. SVD = spontaneous vaginal delivery. APH = antepartum haemorrhage. NEC = necrotising enterocolitis. PDA = patent ductus arteriosus. ROP = retinopathy of prematurity. CRUSS = cranial ultrasound. Maternal indication for delivery includes maternal PET, HELLP syndrome, fetal indication for delivery includes poor growth, abnormal umbilical dopplers and abnormal fetal cardiac monitoring.

Twin/Triplet Results	Case (n=22)	Control (n=74)
DCDA twins n (%)	7 (32%)	25 (34%)
MCDA twins n (%)	4 (18%)	8 (11%)
MCMA twins n (%)	0	2 (3%)
DCTA triplets n (%)	1 (0.5%)	4 (5%)
Total n (%)	12 (55%)	39 (53%)

Table 2: Twin and triplet data in the case and control groups. MCDA = monochorionic, diamniotic. DCDA = dichorionic, diamniotic. MCMA = monochorionic, monoamniotic. DCTA = dichorionic, tri-amniotic.

Neurodevelopmental Outcome	Total (n=96)	Case (n=22)	Control (n=74)	p-value
Cognitive Scaled Score				
Median (IQR)	9 (7-12)	5 (3-9)	10 (8-12)	0.000*
Range	1-18	1-16	6-18	
Missing	8	3	5	
Cognitive Composite Score				
Median (IQR)	95 (85-108)	80 (65-95)	100 (90-110)	0.000*
Range	55-140	55-130	80-140	
Missing	8	3	5	
Receptive Language Scaled Score				
Median (IQR)	9 (7-11)	6 (4-9)	9 (8-11)	0.000*
Range	1-15	1-12	3-15	
Missing	11	4	7	
Expressive Language Scaled Score				
Median (IQR)	9 (6-10)	5 (3-8)	9 (7-10)	0.004
Range	1-13	1-11	3-13	
Missing	13	4	9	
Language Composite Score				
Median (IQR)	94 (79-103)	73 (62-91)	96 (89-103)	0.000*

Range	47-118	47-109	62-118	
Missing	12	4	8	
Fine Motor Scaled Score				
Median (IQR)	8 (6-9)	5 (3-8)	8 (7-9)	0.007
Range	1-16	1-12	1-16	
Missing	9	3	6	
Gross Motor Scaled Score				
Median (IQR)	8 (5-10)	4 (3-9)	8 (6-10)	0.019
Range	2-18	2-16	3-18	
Missing	9	3	6	
Motor Composite Score				
Median (IQR)	85 (76-97)	73 (59-85)	88 (79-97)	0.003
Range	55-121	55-121	56-121	
Missing	9	3	6	
Social-Emotional Scaled Score				
Median (IQR)	10 (5-12)	5 (2-7)	10 (7-13)	0.000*
Range	1-18	1-11	2-18	
Missing	12	0	12	
Social-Emotional Composite Score				
Median (IQR)	98 (75-105)	75 (60-85)	100 (85-115)	0.000*
Range	55-140	55-105	60-140	
Missing	10	0	10	
General Adaptive Composite				
Median (IQR)	92 (78-105)	75 (54-83)	96 (86-106)	0.000*
Range	48-137	48-121	59-137	
Missing	10	1	9	
Conceptual Composite				
Median (IQR)	99 (84-111)	71 (59-95)	103 (90-112)	0.000*
Range	49-137	49-129	53-137	
Missing	11	1	10	
Social Composite				
Median (IQR)	96 (83-108)	68 (59-93)	99 (90-108)	0.000*
Range	50-145	50-118	55-145	
Missing	11	1	10	
Practical Composite				
Median (IQR)	83 (76-101)	68 (58-77)	92 (80-104)	0.000*
Range	49-142	49-109	57-142	
Missing	11	1	10	

Table 3: Bayley scales of infant development: 3rd edition, cognitive, language and motor scores. Bayley scales of infant development: 3rd edition, social-emotional and adaptive behaviour scores.

Conceptual composite, social composite and practical composite scores are derived from combined subscales within the adaptive behaviour report.

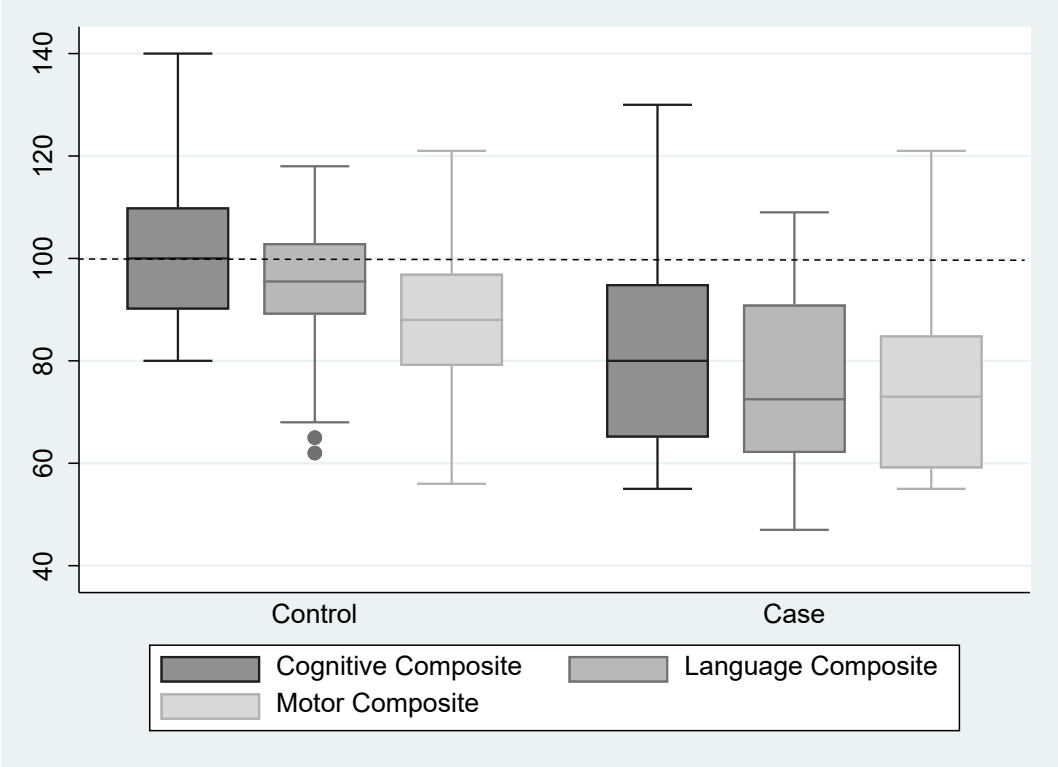

Figure 1: Boxplot comparing cognitive, language and motor composite scores from the Bayley Scales of Infant and Toddler Development (Edition 3) between case and control children. Solid blocks represent median and IQR while whiskers represent 95% CI. Dashed line represents the normed median score of all three scales at 100.

Discussion

Our cohort included premature infants, 23% were identified as having autistic traits at early childhood developmental assessment. Male phenotype, non-Irish ethnicity, vaginal delivery and abnormal cranial ultrasound occurred more frequently in the case group. Only male gender and abnormal cranial ultrasound remained significant following logistic analysis. Likewise, the use of ART lost significance once correction for multiple analysis was applied. Birth weight and gestation at delivery were not of significance.

Previous studies have shown high rates of autism on follow up of the preterm population[10,11]. Our study suggests that many more may be at risk of more subtle disturbances with social interaction and communication. This is in keeping with studies showing preterm cohorts score poorly when screened using questionnaires assessing social interaction and communication skills[12]. Of concern,

there is evidence to suggest that these disturbance in social interaction, communication and other psycho-affective disorders may not be transient difficulties[1] .

In keeping with our findings, Johnson et al identified male sex and abnormal cranial ultrasound results as risk factors for impacting on later social communication scores[12]. Guinchat et al. identified prematurity, low birth weight, breech presentation, planned caesarean section and low Apgar scores as neonatal risk factors for autism[13]. Other identified risk factors include chorioamnionitis, acute intrapartum haemorrhage, illness severity on admission to NICU and abnormal magnetic resonance imaging (MRI) studies[3,14-16].
In our study, an abnormal cranial ultrasound scan during the infant's in-patient course increased the odds of autistic features at follow-up assessment. Similar to our study, Kuzniewicz et al. (2014) identified that infants less than 34 weeks and with intra-ventricular haemorrhage were at higher risk of autism[4]. Buchmayer et al. (2009) also identified intracranial bleeding as a risk[17]. Movsas et al. (2013) identified ventricular enlargement on cranial ultrasounds in low-birth-weight infants as a significant risk factor for autism[18].

It is well accepted that cognitive impairment and atypical neurodevelopment are linked to preterm delivery[12]. Uterine inflammation may be an important contributing factor to the long-term neurodevelopmental risk to the foetus[19]. Though chorioamnionitis was a documented indication for delivery in 18% of cases compared to 8% of controls, the numbers affected are too small for further statistical evaluation.

Bokobza et al comprehensively reviewed the role of inflammation in the perinatal period and a genetic predisposition to abnormalities of connectivity that may prime the preterm brain towards an autistic trajectory[20]. This study also suggested a differing phenotype of autism in those born preterm. A further study by Chen et al. supports this hypothesis[21]. Preterm children diagnosed with autism may have differences in qualitative abnormalities in reciprocal social interaction. Therefore, current modes of testing and diagnosing autism may need to expand their criteria or the assessor may need to be mindful of the differences between term and preterm children. In our study children with autistic traits scored lower on 10/14 subscales of the Bayley Scales of Infant and Toddler Development (Edition 3). This may reflect an interplay between autism and global developmental delay in the preterm brain or the limitation of the assessment tool to adequately measure developmental progress in the neurodiverse brain. Premature children are at increased risk for an atypical social-behavioural profile, which reflects many similarities to autism and therefore the diagnosis may be difficult.

Improving MRI techniques including structural and functional measurements, may enhance our knowledge of prematurity-related brain injury and could possibly aid in understanding the pathogenesis of autistic features in preterm infants[14]. Areas of interest include the cerebellum, frontal lobes and amygdala[22].

Autism has historically been described as a male dominated condition which was reflected in our study with 82% of the case group being male. A study by Allen et al. (2020) highlighted that with lower gestational ages there was a higher risk of female infants developing autism[8]. Joseph et al (2017) noted a lower male to female ratio 2:1 in their premature cohort compared to the general population[5]. A study by Teoh et al shows no difference in the rates of preterm birth between males and females in developing autism. Higher rates of diagnosis in males may reflect differing

presentations in females[23]. Girls may not fit the DSM-5 diagnostic features which are associated with autism in early childhood.

ART have been associated with higher rates of prematurity, low birth weight and multiple births. In our study, the use of ART was protective. However, when Bonferroni correction was applied this lost statistical significance. Previous studies have linked ART with a risk of autism[24]. However, a study by Mainburg et al (2007) reported a lower risk of autism if ART was used[25]. Our study did not identify a significant difference in maternal age between the case and control groups. Paternal age was not delineated in our study but would be of interest[13.]

Almost one quarter of our cohort had lower scores on the Bayley assessment, identifying this group as a high-risk cohort for developmental delay (*Figure 1*). While a useful tool for assessing neurodevelopmental progress, the Bayley's cannot differentiate specific learning or neurodevelopmental difficulties.

Strengths of our case-control study include assessment by a clinical psychologist; a contemporaneous control group and detailed data on neonatal course in both cases and controls.

There are several important limitations of our study. Firstly, it is a retrospective study and the case numbers are small. The neurodevelopmental assessment was not designed to formally diagnose autism. Important variables such as a family history of autism and/or neurodisability were not routinely included at the time of assessment.

Given that 50% (11/22) of children identified as displaying autistic traits are still awaiting formal assessment or have parents who declined assessment, we cannot say what proportion of preterm infants who display autistic traits at early follow up go on to receive a formal diagnosis of autism.

Our study identifies a similar increased occurrence of autistic traits in very premature infants (23%) comparable to other studies. This is despite using the Bayley-3 assessment tool which can underestimate neurodevelopmental impairment. Male phenotype and abnormal cranial ultrasound occurred more frequently in the case group following logistic analysis. Awareness of the association between prematurity and autistic traits can help guide targeted neurodevelopmental follow-up and early intervention. Further prospective studies incorporating early autism screening and diagnostic assessment are needed to improve detection and differentiation of autistic traits in ex-premature children.

Declarations of Conflicts of Interest:

None declared.

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Ethical approval:

Ethical approval for this study was provided by the Research Ethics Committee of The Rotunda Hospital, Dublin. This study was performed in accordance with the Declaration of Helsinki.

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