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Screening for autism spectrum disorder in very preterm infants during early childhood

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ABSTRACT

Aim: The aim of the study was to screen very preterm infants for autism spectrum disorder (ASD) with comparisons to a group of term controls. The study also aimed to identify maternal and neonatal risk factors, development and behaviour associated with a positive screen in the preterm group.
Method: Preterm infants born ≤30 weeks gestation and term infants were recruited at two years of age. The mothers were posted the questionnaires and completed the Modified Checklist for Autism in Toddlers (M-CHAT), the Child Behaviour Checklist (CBCL) and the Depression, Anxiety and Stress Scales (DASS). Previously collected data from the mothers at 12 months — the Edinburgh Postnatal Depression Scales (EPDS) were analysed. The children had neurodevelopmental assessment including the Bayley-III. Infants positive on M-CHAT screen had an M-CHAT follow-up interview by phone and then were assessed by a developmental paediatrician as indicated with a diagnosis of autism being made on clinical judgement.
Results: 13 (13.4%) of the 97 preterm infants screened positive on the M-CHAT compared to three (3.9%) of the 77 term infants ($p = 0.036$). On follow-up interview, three of the preterm infants remained positive (one was diagnosed with autism) compared to none of the term infants. The preterm infants who screened positive were born to younger, non-Caucasian mothers and were of lower birth weight and had a higher incidence of being small for gestational age (SGA). The infants had lower composite scores on Bayley-III and had more internalising and externalising behaviours on the CBCL. The mothers had more emotional problems on the DASS and higher scores on the EPDS. On multivariate analysis, SGA, greater internalising behaviours and higher EPDS scores remained statistically significant.
Conclusions: A positive screen on the M-CHAT occurs more commonly in very preterm infants than those born at term. Internalising behaviours and maternal mental health are associated with a positive screen in the preterm cohort.

1. Introduction

Autism spectrum disorder (ASD) is a major psychiatric disorder seen in childhood. The diagnosis is clinical and based on specific social, language and behavioural characteristics. The reported prevalence of ASD is 6–10/1000 children [1,2]. ASD is generally a lifelong disorder associated with substantial co-morbidities affecting development, learning and behaviour, along with long term effects on the individual and family quality of life. Its aetiology is unknown, though it is considered to be a disorder of brain development [3] with genetic and environmental factors playing a role [4]. The strength of the relationship between preterm birth and ASD is controversial. In a meta-analysis on perinatal and neonatal risk factors for autism, Gardener et al. [5] found that preterm birth was not associated with autism, though there was a positive association between low birth weight and the risk of autism. When very preterm infants of <30 weeks gestation were assessed at the age of 7 years, 4.5% of the cohort were diagnosed with ASD [6], while 8% of children born <26 weeks gestation were diagnosed with the condition at 11 years [7]. With early identification of children with ASD and subsequent intervention, there is evidence of improvement in cognitive performance and language skills [8,9]. Thus,

Abbreviations: ASD, autism spectrum disorder; M-CHAT, Modified Checklist for Autism in Childhood; CRIB, Clinical Risk Index for Babies; GMFCS, Gross Motor Functional Classification System; CBCL, Child Behaviour Checklist; DASS, Depression, Anxiety, Stress Scale.

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screening of very preterm infants could be important as they are considered to be at high risk for ASD.

The Modified Checklist for Autism in Toddlers (M-CHAT) has been used widely as a screening tool for both term [10] and preterm populations. Positive screening has been found in 21–41% of very preterm infants [11–13]. The children in these studies, however, had a relatively high rate of developmental impairment which may have led to a falsely high positive M-CHAT screen rate [14]. Therefore, it is recommended that a follow-up interview be conducted [15], followed by a formal diagnostic assessment if indicated.

The aim of the present study was to screen very preterm infants for ASD using the M-CHAT with comparisons made with a group of term controls. The infants with a positive screen had a follow-up interview, with diagnostic evaluation to establish a diagnosis as indicated. The study also aimed to identify maternal and neonatal risk factors, developmental outcomes and other behavioural and family characteristics associated with a positive screen in the preterm group.

2. Methods

2.1. Participants

The mothers of the very preterm (gestation ≤30 weeks) and term infants recruited in the current study had participated in a study of parenting stress, when their infants were 4 and 12 months (corrected for prematurity) for the preterm group [16,17]. The preterm infants born between June 2007 and February 2009 had been managed in the Neonatal Unit at the Mater Mothers' Hospital, Brisbane. The mothers of the preterm infants were approached to join the Parenting Stress study when their infants were stable and were receiving care in the Special Care Nursery. Mothers with multiple pregnancies more than twins, mothers with twins where one twin died, mothers with a baby with a major congenital abnormality or were not expected to survive to hospital discharge and mothers who were not English speaking were excluded from the study. Consent was obtained prior to discharge. The control group of infants were born at term (≥37 weeks gestation), also at the Mater Mothers' Hospital. In a similar time frame to the recruitment of the mothers of preterm infants, the term mothers were also approached while in hospital, but for the most part consent was obtained after discharge home.

Prior to the second birthday (corrected for prematurity for the preterm cohort) of the infants, the mothers who participated in the Parenting Stress study were contacted inviting them and their infants to participate in the current study related to the screening for ASD in early infancy. Of the 124 preterm infants recruited into the parenting study, 97 participated in the ASD screening study. Of the 120 term infants recruited into the parenting study, 77 participated in the current study. The study was approved by the Mater Health Services Human Research Ethics Committee, with all mothers giving written consent for the participation of their child in the study.

2.2. Procedures

Perinatal data including maternal demographic variables, pregnancy complications and neonatal morbidities were obtained at hospital discharge. Small for gestation age (SGA) was defined as having a birth weight <10th percentile by gestational age using Australian National Data [18]. Cranial ultrasonography was performed on the preterm infants at 5–7 days of age, 21–28 days of age and at 34–36 weeks (corrected for prematurity) for infants with birth weight <1000 g, with additional scans as clinically indicated. Ultrasound abnormalities including peri-intraventricular haemorrhage, cystic periventricular leukomalacia and cerebellar haemorrhage were recorded. Bronchopulmonary dysplasia was diagnosed with an ongoing requirement for supplemental oxygen after 36 weeks corrected for prematurity. The Clinical Risk Index for Babies (CRIB) [19] was also calculated for each baby. When the children were 12 months of age, the mothers had completed the Edinburgh Postnatal Depression Scale (EPDS) [20] as previously described [17]. The EPDS is a 10-item self-report screening tool for depression after child birth. It may be used for mothers 12 months after delivery and beyond [21]. Scores ≥12 indicate probable depression.

At 2 years (corrected for prematurity for the preterm cohort) the infants underwent a neurological examination, with cerebral palsy being diagnosed according to standard criteria [22]. Those with cerebral palsy had a Gross Motor Functional Classification System (GMFCS) [23] assessment. The GMFCS is a standardised classification system which grades gross motor skills in a child with cerebral palsy and categorises children into five different levels. The emphasis is on sitting and walking, with advancing levels indicating more severe limitations in motor function. The Bayley Scales of Infant and Toddler Development-III (Bayley-III) [24] were administered by trained examiners who were blinded to whether the children were preterm or term. The Bayley-III assessment examines the cognitive, language (receptive and expressive communication) and motor (gross and fine motor) abilities of children during infancy. The standardised norm for each of the three components of the Bayley-III is 100 (standard deviation [SD], 15).

2.3. Questionnaires

These were posted to the mothers and were completed at home. They were returned by mail or brought along to the clinic at the time of the clinical assessment.

2.3.1. Modified-Checklist for Autism in Toddlers [10]

This is a 23 item checklist that was developed as a screening test for symptoms of ASD in which parents report on child behaviours (yes/no). There are six items that are considered to be 'critical'. When any three items or two or more 'critical' items are failed the child is considered to have screened positive with further assessment being indicated. The positive predictive value for the M-CHAT has been reported as 0.36 [25].

2.3.2. Modified-Checklist for Autism in Toddlers — follow-up interview [12]

This was performed by telephone interview with the mothers for the children who screened positive on the M-CHAT, enabling clarification of the mothers' responses to the failed behaviours using relevant specific examples. Using the 2-stage screen, the M-CHAT has been shown to be reliable with a positive predictive value of 0.74 [25].

Only the three children who remained positive on the M-CHAT interview were assessed by experienced developmental paediatricians at the Mater Children's Hospital. A diagnosis of pervasive developmental disorder was made on clinical grounds following interview with the mother and medical assessment of the child, according to DSM-IV criteria. Additional multidisciplinary assessments were undertaken as clinically indicated, though no formal additional assessments were consistently performed. Clinical judgement by an experienced clinician is considered to be the 'gold standard' for autism diagnosis [26].

2.3.3. Child Behaviour Checklist (CBCL) 1.5–5 [27]

This is a 100 item parent report that measures problem behaviours of pre-school children. Problem items are converted into syndrome scale scores which can be assigned a corresponding T-score from which internalising and externalising problem scales may be derived. The internalising problem scale is comprised of items from withdrawn, somatic and anxious/depressed behaviours, while the externalising problem scale is comprised of items from delinquent and aggressive behaviours.

2.3.4. Depression, Anxiety, Stress Scale (DASS) [28]

A 42 item self-report questionnaire designed to measure the emotional states of depression, anxiety and stress was completed by the