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Can Neonatal Morbidity and 2 Year Outcome Predict Cognitive Delay at 5 Years in Extremely Low Birth Weight (ELBW) Infants?

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Abstract

Aim: To identify factors associated with cognitive delay in Asian ELBW survivors and evaluate the ability of significant delay at 2 years in predicting cognitive delay and need for rehabilitative services at 5.5 years.

Method: 213/295(72%) ELBW survivors were evaluated using the Mental Developmental Index (MDI) on the Bayley Scales of Infant Development (BSID II) and the Full Scale IQ (FSIQ) on Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) at 2 and 5.5 years respectively. Perinatal and neonatal factors associated with neurodevelopmental delay (MDI <70/ FSIQ scores <70) were estimated.

Results: Mean MDI and FSIQ scores were 77±18 and 89±13 respectively. 83 (39%) children had MDI<70, 20 (9%) had FSIQ<70. Thirteen (6%) had Neuro-Sensory Impairment (NSI) and 106 (50%) had major neonatal morbidity. On logistic regression, MDI<70 was significantly associated with lower birth weight [OR: 0.71(95% CI: 0.53-0.96)] and neonatal morbidity [OR 6.49 (95% CI: 2.95-14.21)]. Only NSI [OR: 15.36 (95% CI: 3.04-77.67)] and ethnic group [OR: 5.05 (95% CI: 1.06-23.94)] were independently significant in predicting FSIQ<70. MDI<70 had sensitivity of 0.81 specificity 0.65, positive predictive value 0.21 and negative predictive value 0.98 in predicting FSIQ<70. MDI<70 was independently associated with the need for rehabilitative services at 5.5 years (OR 5.52; 95% CI 2.59-11.76).

Conclusions: Neonatal morbidity was associated with delay at 2 but not at 5.5 years. NSI at 2 years was independently associated with significant cognitive delay at 5.5 years. Fewer ELBW survivors had significant delay at 5.5 years compared to 2 years. MDI<70 however predicted the need for rehabilitative services at 5.5 years.

What's known on this subject: MDI score<70 at 18-30 months is used to define significant delay and neurodevelopmental impairment in ELBW infants.

Significant delay at 2 years is commonly used for long term prognostication and formulation of perinatal guidelines.

What this paper adds: Major neonatal morbidity was associated with developmental delay at 2 years of age whereas neurosensory impairment and ethnicity were associated with cognitive delay at 5 years.

MDI<70 at 2 years was a poor predictor of cognitive delay beyond 5 years but was associated with the need for extra assistance at 5.5 years.

Keywords: Neonatal morbidity; Cognitive; Infants

Introduction

The striking improvement in survival of Extremely Low Birth Weight (ELBW) infants has not been accompanied by consistent improvement in long term neurodevelopmental outcome in survivors [1-8]. Continuing high rates of neurodevelopmental impairment [1], impaired executive functioning and poor academic performance [9-13], remain major concerns. The Bayley Scales of Infant Development (BSID, BSID-II and Bayley-III) are widely used for psychometric assessment in preterm Very Low Birth Weight (VLBW) children [6,10]. The Mental Developmental Index (MDI) from the BSID is commonly used in assessing the impact of neonatal intensive care, outcome of intervention [14-16], and formulation of perinatal guidelines [17].

Longitudinal follow up of preterm survivors is commonly limited to 24-30 months by cost and high attrition rates [18]. The ability of assessments at 2 years to precisely predict later cognitive function remains unclear. Roberts *et al.* [19] demonstrated a shift from no disability at 2 years to mild disability at 8 years, while a large

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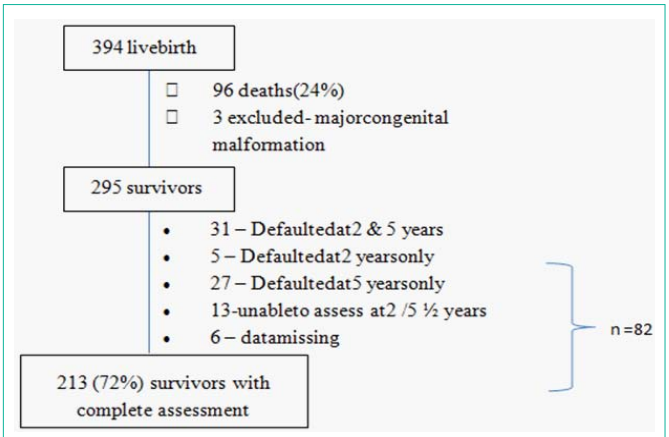

Figure 1: Sample flow chart of extremely low birth weight included in the present study.

proportion of children with moderate to severe disability at age 2 had improved at 8 years. Other longitudinal studies have also shown that early measures [20,21] are unduly pessimistic. However, a meta-analysis revealed a positive relationship between early MDI scores and later cognitive function [22] in VLBW children. Therefore, in this study, firstly, we aimed to identify factors associated with cognitive delay in a prospectively followed-up multi ethnic cohort of ELBW survivors and secondly, to further understand their developmental trajectory. We evaluated the predictive ability of an MDI score<70 in assessing cognitive delay and the need for rehabilitative services at 5.5 years.

Materials and Methods

This longitudinal cohort study was performed at the KK Women's and Children's Hospital in Singapore. Perinatal and neonatal data and follow up data was prospectively collected at 2, 5.5 and 8 years of age for ELBW survivors. Children with major congenital malformations were excluded. 213 ELBWs born between 2000 and 2004 and who completed assessments at both ages formed the study cohort (Figure 1). Of thirteen children excluded as they could not be assessed, 10 had NSI (cerebral palsy/deafness /blindness), one had selective mutism and nine needed extra assistance at 5.5 years. The hospital's institutional review board approved the study.

Maternal and neonatal demographic data and details of major neonatal morbidities postulated to have an impact on neurodevelopmental outcome, including severe cranial ultrasound abnormality [grade 3-4 Intra-Ventricular Hemorrhage/Peri-Ventricular Leukomalacia (sIVH/PVL)], Chronic Lung Disease (CLD) with oxygen dependency at 36 weeks corrected age, Necrotizing enterocolitis≥stage 2 (NEC>StII/ Focal Intestinal Perforation (FIP), severe retinopathy of prematurity≥stage III (ROP≥3) and culture proven sepsis were collected at discharge. The presence of one or more of these five morbidities (defined in a previous paper by the authors [23]) was defined as a major morbidity.

ELBW survivors had post-discharge follow up till 8 years of age, with physical and neurological examinations by the pediatrician and referral to rehabilitative services when clinically indicated.

Data on growth, health, and neurological and developmental status and the need for rehabilitative services at 5.5 years was collected. These services included physical, occupational or speech therapy in a hospital/community based setting. Data on the housing, family income and maternal education was collected from caregiver interviews. Maternal educational level was stratified as less than or more than 12 years of formal education (high school).

NSI at 2 years was defined as the presence of deafness (bilateral hearing loss needing amplification with hearing aids or cochlear implants), blindness (visual acuity of less than 6/60 in the better eye) or Cerebral Palsy (CP). Vision and hearing were assessed by pediatric ophthalmologists and audiologists. CP was classified as spastic diplegia/quadriplegia/ hemiplegia and functionally as ambulant or non-ambulant.

A psychologist performed formal psychometric assessments using the MDI of the BSID-II at 22-24 months corrected gestational age [24] and the Full Scale Intelligence Quotient (FSIQ) of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) [25] at 5.5 years. Index scores on both tests have a mean and standard deviation of 100+15. A cut off score of 70 (>2 SD below the mean) identified significant delay at both ages. Scoresbetween70-84 (>1SD below the mean) indicated mild delay.

Neurodevelopmental Impairment (NDI) was defined as the presence of any one of the following: MDI/FSIQ<70, cerebral palsy, deafness or blindness. Cases with no neonatal major morbidity or NSI were labeled as a "Well ELBW".

Statistical analysis

Distribution of sample characteristics was described using central tendencies for continuous data and proportions for categorical data. Univariate analysis using Independent 2-sample t-tests and Pearson chi-square tests was done to identify perinatal and neonatal factors associated with neurodevelopmental delay (MDI<70 and FSIQ scores<70) at 2 and 5.5 years. Perinatal and neonatal factors with a *p* value<0.05 on univariate analysis were included in the multivariate analysis using logistic regression. Important confounders such as birth weight (bw), Gestational Age (GA), gender, ethnicity and maternal educational status were included in the logistic regression models. We examined the independent and collective impact of major neonatal morbidity and NSI on significant cognitive delay at both ages.

Ability of the BSID-II MDI to predict FSIQ was evaluated using sensitivity, specificity and predictive values. All tests were two-tailed, with the level of statistical significance set at 0.05. Analyses were conducted using SPSS for Windows, version 22 (SPSS, Chicago, Illinois).

Results

Characteristics of the 213 children included in the study are described in Table 1. A significantly higher proportion of mothers from the minority Malay ethnic groups had<12 years of schooling compared to other races (38/40 *vs* 107/173; *p*<0.001; OR 11.33 (2.64-48.53). The 82 children who were excluded were more likely to be Malay compared with cases which were included. Gender, bw and GA at birth were similar in both groups of children (Supplementary Table 1).

Table 1: Demographic profile and neonatal morbidities of the overall study cohort and in children with psychometric cognitive scores<70.

	Overall cohort (n=213)	2 yrs MDI<70 (n=83)	5½ yrs FSIQ<70 (n=20)
Maternal age, years	31.3±5.2	30.3±5.4	30.3±6.7
Ethnicity			
Chinese	144 (68%)	49 (59%)	7 (35%)
Malay	39 (18%)	20 (24%)	9 (45%)
Indian	24 (11%)	11 (13%)	3 (15%)
Others	6(3%)	1 (4%)	1 (5%)
Monthly household income (SGD)	3546±2645	3125±2719	2263±1325
Maternal education>high school	67 (31.4%)	27 (32%)	3 (15%)
GA, weeks	26.8±2.1	26.42±2.31	25.8±2.29
Birth weight, g	825±126	780±144	755±144
Male gender	117 (55%)	51 (60%)	15 (75%)
CLD	58 (27%)	38 (45%)	13 (65%)
Culture proven sepsis	49 (23%)	33 (37%)	11 (55%)
Severe IVH	23 (10.7%)	12 (14%)	5 (25%)
NEC≥St II /FIP	18 (8.4%)	9 (15%)	3 (15%)
ROP≥St III	51 (24%)	33 (39%)	9 (45%)
≥1 Major morbidity	106 (50%)	65 (76%)	19 (95%)
Neurosensory impairment	15 (7%)	12 (14%)	9 (45%)

GA: Gestational Age; CLD: Chronic Lung Disease; IVH: Intra Venticular Haemorrhage; NEC≥St II/FIP: Necrotizing Entero Colitis≥stage II/Focal Intestinal Perforation; ROP≥stage III: Retinopathy of Prematurity≥stage III; MDI: Mental Developmental Index; FSIQ: Full Scale Intelligence Quotient.
Data presented in n (%) or mean±SD

Table 2: Risk factors for significant delay at 2 and 5.5 years.

	2 year MDI<70		FSIQ<70 at 5½ years	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†
Maternal age	0.93 (0.88-0.98)*	0.94 (0.88-1.01)	0.95 (0.87-1.04)	-
Ethnicity	0.71 (0.49-1.03)	0.69 (0.47-1.04)	1.95 (1.13-3.38)*	2.43 (1.17-5.05)*
Chinese	Reference	Reference	Reference	Reference
Malay	-2.04 (0.99-4.18)	1.45 (0.61-3.49)	5.87 (2.02-17.01)**	5.05 (1.06-23.94)*
Others	1.69 (0.76-3.75)	2.30 (0.90-5.91)	3.01 (0.82-11.03)	3.79 (0.98-14.66)
Male gender	1.42 (0.81-2.49)	1.37 (0.69-2.71)	2.04 (0.75-5.52)	2.98 (0.78-11.31)
Monthly household income	1.01 (0.99-1.02)	-	0.96 (0.93-0.99)*	0.97 (0.93-1.01)
Maternal Education>high school	0.63 (0.34-1.16)	0.64 (0.30-1.36)	0.35 (0.10-1.25)	0.56 (0.10-3.06)
Birth weight	0.66 (0.52-0.84)***	0.71 (0.53-0.96)*	0.74 (0.53-0.1.06)	0.86 (0.50-1.48)
Gestational Age	0.86 (0.75-0.98)*	0.84 (0.69-1.01)	0.79 (0.61-1.04)	1.10 (0.79-1.51)
≥1 Major Morbidity	6.36 (3.42-11.90)***	6.49 (2.95-14.21)***	6.62 (1.88-23.35)**	3.63 (0.71-8.51)
MDI<70	-	-	7.51(2.42-23.25)***	3.06(0.86-10.87)
NSI	5.81 (1.54-21.73)**	3.64 (0.81-16.13)	16.78 (4.92-57.23)***	15.36 (3.04-77.67)***

MDI: Mental Developmental Index; FSIQ: Full Scale Intelligence Quotient; NSI: Neuro Sensory Impairment; Major morbidity was defined as the presence of one or more of the following conditions: as every cranial ultra sound abnormality (grade3-4 Intra Ventricular Hemorrhage/Peri Ventricular Leukomalacia (sIVH/PVL); severe Chronic Lung Disease (CLD) with oxygen dependency at 36 weeks corrected age, Necrotizing Entero Colitis≥stage 2 (NEC>+St II/Focal Intestinal Perforation (FIP), severe Retinopathy of Prematurity≥stage 3 (ROP≥3) and culture proven sepsis.
†Adjusted for birth weight, gestational age, gender, ethnicity and maternal education, ***P<0.001, **P<0.01, *P<0.05

The mean MDI and FSIQ scores at 2 and 5.5 years were 77±18 and 89±13 respectively. 83 (39%) children had MDI<70 and 20 (9%) had FSIQ<70. Major neonatal morbidity was present in 106 (50%).

Thirteen (6%) children had NSI, including 9 with deafness, 8with CP (2 hemiplegia, 5 diplegia, 1 quadriplegia), 10 children with NSI in the form of CP (n=6), deafness (n=4) or blindness (n=2) were excluded from the study because they could not complete a formal psychometric assessment.

Risk factors for significant delay

At 2 years, maternal age, baby's birth weight and gestational age were significantly lower while major neonatal morbidity and NSI were higher in children with MDI<70 (Table 2). After adjusting for bw, GA, gender, ethnicity and maternal educational status, MDI<70 was significantly associated with lower birth weight and major neonatal morbidity.

Risk factors associated with FSIQ<70 are shown in Table 2. On univariate analysis, the unadjusted odds ratio for FSIQ<70 was higher

Table 3: Stratified analysis of the association between composite morbidity and significant delay at 2 and 5.5 years.

	2 year MDI<70		5 year FSIQ<70	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†
Well ELBWs^ versus those with neonatal morbidity or NSI	0.16 (0.08-0.29)***	0.14 (0.06-0.30)***	0.15 (0.04-0.54)**	0.25 (0.05-1.04)
ELBW with neonatal morbidity but no NSI versus well ELBWs^	5.55 (2.94-10.30)***	6.94 (3.17-15.35)***	3.67 (0.96-14.20)	2.79 (0.47-16.67)
ELBW with neonatal morbidity and NSI versus well ELBWs^	10.52 (2.29-47.6)**	8.56 (1.70-43.47)**	20.25 (5.64-72.66)***	19.51 (3.82-99.87)***

MDI: Mental Developmental Index; FSIQ: Full Scale Intelligence Quotient; ELBW: Extremely Low Birth Weight

†Adjusted for birth weight, gestational age, gender, ethnicity and maternal education

There were 106 ELBW without major neonatal morbidity and NSI (well ELBW^), 94 ELBW children with major neonatal morbidity but no NSI and 12 ELBW children with major neonatal morbidity and NSI

***P<0.001

**P<0.01

*P<0.05

Table 4: Classification of normal scores and categories of delay at 2 and 5 ½ years.

	5½ year FSIQ			
2 year MDI	**<70**	**70-84**	**≥85**	**Total**
<70	16 (19%)	32 (39%)	35 (42%)	83 (39%)
70-84	3 (5%)	17 (30%)	36 (64%)	56 (26%)
≥85	1 (1%)	7 (10%)	66 (89%)	72 (35%)
Total	20 (9%)	56 (26%)	137 (64%)	-

MDI: Mental Developmental Index; FSIQ: Full Scale Intelligence Quotient Data were presented in n (row percentages).

with lower monthly household income, MDI<70 and major neonatal morbidity and NSI. More Malay children had significant delay at 5.5 years (p=0.030). Upon logistic regression, only NSI and ethnic were independent predictors of FSIQ<70.

"Well ELBW"s, when compared with those with major neonatal morbidity or NSI, had a lower risk of having MDI<70 and FSIQ<70. Conversely, when compared with "well ELBW"s, cases with either major neonatal morbidity or NSI had higher odds to MDI<70 at 2 years. At 5.5 years, ELBWs with major neonatal morbidity in the presence of NSI continued to have a higher odds ratio of FSIQ<70 major neonatal morbidity alone were no longer independently associated with FSIQ<70 (Table 3).

Comparison of delay between 2 and 5.5 years

Table 4 shows the comparison of categories of delays on the MDI-BSID-II at 2 years with cognitive delay at 5.5 years. 83 (39%) cases had a MDI<70 and 65% had MDI<85 in comparison to 20 (9%) with FSIQ<70 and 35% with FSIQ<85.73 (35%) had no delay at 2 years while 137 (64%) were unimpaired at 5.5 years. Of the 83 children with an MDI score of<70, the cognitive scores of 16 (19%) children remained below 70 at 5.5 years. As shown in Supplementary Table 2 97 (46%) children at 5.5 years required rehabilitative services of which 59 (61%) had MDI<70 at 2 years.

MDI <70 had a sensitivity of 0.81 (95% CI 0.75-0.86), specificity of 0.65 (95% CI 0.58-0.71), Positive Predictive Value (PPV) of 0.21 (95%CI 0.13-0.31) and Negative Predictive Value (NPV) of 0.98 (95%CI 0.93-0.99) in predicting FSIQ<70. While MDI<70 was not associated with cognitive delay at 5.5years, it was associated with the need for rehabilitative services (OR 5.52; 95% CI 2.59-11.76, p<0.001) along with lower household income (OR 1.03; 95% CI 1.01-1.04. p=0.014).

Discussion

In our study composite neonatal morbidity was associated with delay at 2 but not at 5.5 years while NSI at 2 years was independently associated with significant cognitive delay at 5.5 years. Also, fewer ELBW survivors had significant delay at 5.5 compared to 2 years; especially for children without NSI.

Delay at 2 and 5.5 years

In our study, 39% of the cohort had MDI<70 which is similar to both single and multicenter data based on BSID II [2,20,26]. NSI rates of 6-8% in our cohort were also comparable to NICHD prevalence rates of CP (9%), deafness (2%) and blindness (1%) [2,27].

The presence of major neonatal morbidity and lower birth weight were independent significant predictors of MDI<70 at 2 years. This association of NDI with major neonatal morbidity is well documented internationally due to the possible effects of persistent inflammation, cytokine injury and brain damage [6,28-32]. But at age 5.5, we found that these earlier risk factors were no longer predictive of cognitive delay. This is consistent with a systematic review of prognostic factors for poor cognitive development in preterm children by Linsell [33]. Our strongest correlation of an FSIQ<70 was the presence of a NSI at age 2. It has been well documented that NSI in the first 2 years predicts persistent cognitive deficits at school age [20,31,34]. Notably, our rates of significant cognitive delay at 5.5 years dropped to 9%, similar to the trend seen by Hack *et al.* [20] who showed that despite 39% of ELBW survivors having significant delay at 2, only 16% were delayed at school age. We postulate that the decreasing rates of cognitive delay with increasing age may be attributed to the waning influence of biological risk factors and the increasing effect of environmental factors. This complex balance between biology, environment and neonatal illness has been described by Linsell [33] and Howard [35].

In our multi-ethnic population, there was a significant ethnic difference with a higher proportion of Malay children having significant delay at 5.5 years compared with the majority Chinese subgroup. We also showed that fewer Malay mothers had education>12 years. Internationally, minority races and ethnicities have been reported to be at a higher risk for delay, possibly mediated by environmental disadvantage [33,36]. Environmental factors (e.g. socioeconomic and educational status) are known to impact cognitive outcomes in preterm children [2,37,38], with Kilbride [39] demonstrating a difference of 12 IQ points favoring children from high socioeconomic households. Thus, preterm children with

biological or socio-environmental risk factors might benefit from early targeted intervention to optimize outcomes.

Predictive validity

Our predictive validity of an MDI score<70 at age 2 years for an FSIQ<70 at 5.5 years was poor, with a PPV of only 0.21. However, the high NPV, of MDI>70 continuing to have an IQ>70, was reassuring and potentially helpful in resource conservation and planning follow-up. Similar results were shown by Hack [20]. Kitchen *et al*. also demonstrated improving cognitive function in ELBW infants between 2 to 5 years and concluded that the 2 year assessment was unduly pessimistic [40]. A more recent study by the same group concurred with the poor predictive validity of a diagnosis of disability at age 2 compared with that at age 8 [19].

This observation may be due to a variety of reasons. One postulation is the effect of brain injury and developmental disruptions during the period of critical brain growth combined with neural plasticity and reorganization and recovery [41]. Thus, as suggested by Patel [6], the BSID II scores may be more a tool to measure developmental delays (which changes over time) rather than fixed impairment. The WPPSI is a more specific measure of intellectual function and IQ and this limits the possible comparisons between these two tools.

The EPI Cure study showed stability in the disability rate between 30 months and 6 years with 86% of children with severe disability at 30 months meeting the same criteria at age 6. However, their cohort was more preterm than ours and they defined severe disability as cognitive scores>3SD below the mean [42], a definition which may be more predictive of significant delay in school age. Accordingly, the NICHD-NRN and others have now reclassified categories of NDI from 2012 with Bayley 3 cognitive scores<55 defined as profound delay [6,10,19]. This may improve the predictive value of the 2 year psychometric assessment especially in children with no NSI. This is currently being done in our center for cohorts born after 2005 with introduction of the Bayley-III.

The need for rehabilitative services at 5.5 years

Although IQ scores assess general cognitive function, they may miss specific and subtle deficits of learning, attention and executive function [9]. Aylward [41] showed that, high prevalence/low severity dysfunctions were seen in 50-70% of non-disabled VLBW survivors. Learning disabilities, borderline to low average IQ scores, behavioral concerns and specific neuropsychological deficits become obvious only with increasing demands faced by the child with resulting effects on academic performance, social interactions and behavior regulation [41].

Thus, despite only 10% of our cohort having FSIQ<70, 46% needed rehabilitative services at 5.5 years. Although the MDI<70 could not predict FSIQ<70, it was independently associated with the need for rehabilitative services at 5.5 years. In other studies, 25-62% of school age ELBW infants have needed this extra assistance [43,44].

Our study's strength included its longitudinal design with a good follow up rate, of 87% at 2 years, 78% at 5.5 years and 72% at both the ages, with in the recommended 70-90% rates for valid interpretation of outcome studies [45]. Data capture included neonatal morbidity, parents' socioeconomic and educational status and the functional impact reflected by the need for rehabilitative services.

We recognize limitations imposed by single center data and absence of term controls. However, as our hospital manages two thirds of the national ELBW population, our study reflects the national cohort well. Another limitation was the lack of information about preschool attendance, parenting styles or ongoing medical concerns; lastly, our observation on the higher proportion of Malay children with significant delay may be biased due to their higher attrition rate on follow up.

Normal developmental scores at 2 years may be helpful to reassure parents and conserve resources in high risk follow-up programs. School age follow-up of ELBW survivors into is important as significant delay at 2 years is a poor predictor of cognitive delay beyond 5 years. IQ scores should not be the only outcome measure in the light of later high prevalence/low severity dysfunctions. Furthermore, predictive validity of the five-year assessment for later childhood and early adulthood outcomes needs further evaluation.

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