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Neurodevelopmental Outcome Of Malaysian Very Low Birth Weight Infants: Predictive Value Of Cranial Ultrasound Appearances

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ABSTRACT

The aim of the study was to determine the predictive value of cranial ultrasound scans done in the neonatal period for neurodevelopmental outcome of the Malaysian very low birthweight (VLBW, <1500 grams) infants assessed at 12 months of corrected age. Of the 101 infants studied, 68 (67.3%) were neurodevelopmentally normal at one year of age, 18 (17.8%) had major and 15 (14.9%) had minor neurodevelopmental impairment. Neurodevelopmental outcome was normal in 66/88 (75.0%) infants who did not have severe intraventricular haemorrhage (IVH) or periventricular intraparenchymal echodensities (PVE) in the first week of life, and in 57/73 (78.1%) with uncomplicated scans at discharge. In contrast, 11/13 (84.6%) with parenchymal echodensities or severe intraventricular bleed in the early neonatal period and 17/28 (60.7%) with complicated scans at discharge had adverse sequelae. There was a significant association between lesions seen on cranial ultrasound in the neonatal period and subsequent neurodevelopmental impairment. Late neonatal ultrasound scans appear to be a better predictor of short-term neurodevelopmental outcome than early scans.

Keywords: cranial ultrasound, neurodevelopmental outcome, very low birthweight infants (VLBW), Malaysian, intraventricular haemorrhage (IVH)

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INTRODUCTION

Mortality rates for very low birthweight (VLBW, <1500 grams) infants in developed countries have fallen over the past decade[1]. While the majority of survivors do well, a proportion of them are disabled with neurological and cognitive disorders. Hence the need to determine early in life, factors for prognosticating adverse outcome so that appropriate advice and early anticipatory guidance can be given to parents. Clinical studies using cranial ultrasound have described little or no relationship between the amount of blood in the ventricles in the neonatal period and subsequent neurologic outcome[2,3] but have emphasised the importance of ventriculomegaly and parenchymal lesions as a critical determinant of early neurodevelopmental outcome[2-6].

There are few studies reported from developing countries documenting the morbidity among VLBW survivors , extent of cerebral lesions in the neonatal period and its correlation with outcome[7]. We had previously reported a high incidence of IVH and mortality in a group of VLBW Malaysian neonates[8].The objective of this study was to determine the value of both early and late ultrasound findings in predicting neurodevelopmental outcome at one year of age.

MATERIALS AND METHODS

Patient population

This prospective study was carried out between 1 December 1989 and 31 December 1992. All consecutive newborns with birthweight of less than 1,500 grams delivered in the Maternity Hospital Kuala Lumpur and admitted to the University unit during the study period were eligible for the study. Basic and clinical data of intrapartum and postnatal events during the period of hospitalisation were entered into a standard format. The gestational age was assessed based on the Ballard's score[9].

Cranial ultrasonography

Cranial ultrasound scans were performed, as described in a previous paper[8], on the fifth day of life, then weekly till the time of death or discharge. The scans, recorded on video and Polaroid photographs, were graded independently by each of the team members. In instances where there was a difference in opinion, the scans were reviewed together and a consensus opinion given. Classification of "early" scans (the findings on the fifth day of life were designated as "early" as an earlier study[8] had shown that all IVH had occurred by then) was based on the criteria by Volpe[10]: Grade 0 – no bleed; Grade 1 – germinal matrix haemorrhage with minimal or no IVH; Grade II – definite IVH but with neither lateral ventricle completely filled with blood; Grade III – IVH that completely filled and distended at least one ventricle: (Grade IV) – PVE with at least one dimension greater than 1 cm on the coronal or sagittal scan.

The ultrasonographic sequelae at the time of

Table I - Characteristics of the VLBW neonates

	No. studied (%) (n=101)	No. not studied (%) (n=73)
Race		
Malay	58(57.4)	35(47.9)
Chinese	14(13.9)	4 (5.5)
Indian	27(26.7)	18(24.9)
Others	2 (2.0)	16(21.9)
Birthweight (grams)		
<1000	8 (7.9)	4 (5.5)
1000-<1250	34(33.7)	15(20.5)
1250-<1500	59(58.4)	54(74.0)
SGA*	53(52.5)	37(52.9)
Gestation (weeks)		
<28	3 (2.9)	1 (1.4)
28-31	48(47.5)	23(31.5)
32-35	41(40.6)	41(56.1)
36 or more	9 (8.9)	8(11.0)
Mode of delivery		
SVD	49(48.5)	44(60.3)
Breech	15(14.9)	8(10.9)
LSCS	37(36.6)	21(28.8)
Ventilated	29(28.7)	20(27.4)
Early scans		
Grades 0-II IVH	88(87.1)	60(83.4)
Grades III/PVE	13(12.9)	13(16.6)

* Weight <10th centile based on Lubchenko et al 1963
PVE = periventricular intraparenchymal echodensity
IVH = intraventricular haemorrhage
SVD = spontaneous vertex delivery
SGA = small for gestational age
LSCS = lower segment caesarean section

discharge ("late" scans) in the surviving patients were classified using the criteria by Stewart[4] with minor modifications: 1) Uncomplicated – this could be i) normal, ii) resolving IVH without ventriculomegaly or iii) transient ventriculomegaly ; 2) Complicated – which could be i) ventriculomegaly – persistent ventricular dilatation whereby the depth of a frontal horn immediately anterior to the thalamo-caudate notch exceeded 3 mm, ii) hydrocephalus – marked dilatation of a lateral ventricle such that its width exceeded 5 mm above the 97th centile for this dimension[16] or iii) Cerebral atrophy – loss of brain tissue as a result of porencephalic cyst or multiple periventricular cysts.

Neurologic follow-up

The survivors were followed up at 3, 6 and 12 months of age, corrected for conceptional age. Neurological examination (using the method by Amiel-Tison)[11], developmental testing (Bayley Scales of Infant Development[12]), formal audiological (brain stem evoked responses) and ophthalmological assessments were carried out. At one year of corrected age, the infants were classified as[3]: i) Normal – normal neurological examination, no sensory deficits, Mental Developmental Index (MDI) ≥69; ii) Major impairment – defined as having an abnormality that interfered with normal function, ie, cerebral palsy, developmental delay with MDI<69, visual loss, severe sensorineural deafness (requiring a hearing aid) or multiple minor abnormalities; or iii) Minor impairment – defined as having one of the following, ie, minor abnormalities of tone and posture, squint/nystagmus, mild to moderate deafness (not requiring a hearing aid).

Statistical analysis

Differences in proportions of impairments with the different sonographic appearances were analysed using chi-squared tests or Fisher exact test for expected cell values <5. Other perinatal variables were also analysed using two-sample t-test for differences in means and chi-squared and Fisher exact tests for differences in proportions. Variables which were significant on univariate analysis were then analysed using stepwise logistic regression analysis (SPSS/PC statistical package) to determine risk factors significantly associated with neurological impairment. A p value of 0.05 or less was accepted as significant.

RESULTS

During the study period, there were 419 VLBW live births, of which 192 (45.8%) died before their first discharge from hospital and 52 (12.4%) were transferred out due to shortage of ventilators. Of the 175 survivors, 2 were excluded as they had Down syndrome, 26 were not subjected to ultrasound scanning before discharge and 47 defaulted assessment at 12 months. Table I shows the basic characteristics of the patients. The group studied comprised of patients who were of younger gestational age, had smaller birthweights, a higher incidence of instrumental deliveries and a smaller proportion of those classified ethnically as "others", (immigrants and aboriginal groups) than those not studied. The proportions of the different grades of IVH were similar in both groups.

There was a trend towards greater prevalence of abnormal scans at the time of discharge with increasing grades of IVH documented on the fifth day of life (Table II). Of the 88 patients with grades 0-II IVH, 54 (61.3%) were already normal or showed resolving bleed at the time of discharge; 19 (18.8%) developed transient and 14 (15.9%) persistent ventriculomegaly. Conversely, all 13 patients with PVE or grade III IVH in the first week of life developed adverse sonographic sequelae (61.5% developed hydrocephalus or cerebral atrophy).

At one year of corrected age, 68 (67.3%) were normal, 18 (17.8%) had major and 15 (14.9%) minor sequelae. Thirteen (12.9%) were diagnosed as having cerebral palsy (CP) – 7 were diplegic, 4 quadriplegic and 2 hypotonic. Twelve (92.3%) of the 13 patients with developmental delay were severely affected with MDI<50. Thirteen (12.9 %) had a sensory deficit (9 were visually impaired and 4 had severe sensorineural deafness). Twelve (66.7%) of those classified as having major impairment had multiple major deficits – 5 had 2 major deficits , 6 had at least 3 major (CP, severe developmental delay and a sensory deficit) and 1 had 4 major deficits. Of the 15 patients with minor impairment, 6 had abnormalities of tone, 6 had mild hearing loss and 3 had strabismus.

Table II - Relationship between early and late ultrasound findings

Early scans (grade of IVH)	Late scans: Uncomplicated N	S	T	Complicated V	H	C
0	5	0	0	0	0	0
I	5	2	2	1	0	0
II	21	21	17	13	1	0
III	0	0	0	2	1	0
PVE	0	0	0	3	2	5

N = Normal
S = Resolving IVH without ventriculomegaly
T = Transient ventriculomegaly
V = Ventriculomegaly
H = Hydrocephalus
C = cerebral atrophy

Table III - Relationship between early and late scans and neurodevelopmental outcome at one year

	Normal	Outcome (no.) Major & minor impairment	Major impairment only
Early scans			
Grade 0 IVH	6	0	0
Grades I-II IVH	61	22	8
Grade III/PVE	2	11	10
Late scans			
Normal/S	45	9	1
T	12	7	3
Ventriculomegaly	10	9	6
H/C	1	8	8

N = Normal
S = Resolving IVH without ventriculomegaly
T = Transient ventriculomegaly
H = Hydrocephalus
C = cerebral atrophy

Table III shows the relationship between the presence of neurological impairment at one year of age and early and late scan changes. All 6 patients who did not develop IVH went on to have normal scans at discharge and were subsequently normal on follow-up. Eleven (84.6%) of the 13 patients who had grade III IVH or PVE in early life were neurodevelopmentally impaired compared with 22/88 (25%) with grades 0-11 (odds ratio 16.5, 95% confidence interval 3.14-159.36, $p<0.0001$). The difference between the two groups was more significant when major impairment was used as a measure of outcome (76.9% versus 9.1%, odds ratio 33.3, 95% confidence interval 6.42-212.27). Similarly, 17/28 (60.7%) of those with complicated scans at the time of discharge had neurological impairment compared with 16/73 (21.9%) with uncomplicated scans (odds ratio 5.51, 95% confidence interval 1.95-15.7, $p=0.0005$). Again, the difference between the two groups was greater for major impairment (odds ratio 17.25, 95% confidence interval 4.39-79.65, $p<0.0001$). Most of the patients who were classified as having "uncomplicated scans" and who eventually developed adverse neurological sequelae in infancy actually had transient ventriculomegaly in the neonatal period.

Table IV shows the other potential perinatal risk factors that may have influenced neurological outcome. Univariate analysis showed that patients with adverse outcome tended to be of lower birth weight, with a lower Apgar score at 5 minutes, and had a longer duration of supplemental oxygenation and ventilatory support. They also had more problems related to tube blockage during mechanical ventilation. Logistic regression analysis of these variables together with the early and late scan variables showed that the only risk factor associated with neurodevelopmental (both major and minor) impairment was the presence of a complicated scan at discharge (odds ratio 2.11, 95% confidence interval 1.69-73.2, $p=0.0001$). The equation for the regression model was:- log (odds)= -2.7153 + 0.7194 (complicated scan), where the presence or absence of a complicated scan was designated –1 and 1 respectively.

DISCUSSION

It was not possible to compare the incidence of neurological impairment with others – as the results of our study were based on only 58% of the cohort, the denominator could not be precisely defined. Although the Maternity Hospital has annual deliveries exceeding 26,000[8], the patients were all inborn "graduates" from a specific perinatal unit and not derived from the general Malaysian population. This is a problem faced in follow-up studies of VLBW infants[13,14]. The fact that the patients studied were of lower birthweight (a potential confounding factor) suggests that the actual rate of handicap may even be lower.

Like others[3,15], we found that late ultrasound scan findings were a better predictor of outcome than early changes. The small number of patients in our study did not permit comparison as to whether ventricular size or parenchymal lesion was a better predictor of outcome. Others[15,16] have demonstrated the value of ultrasound in predicting cerebral palsy but not developmental delay – two-thirds of our patients with major impairment had both developmental delay and cerebral palsy, which made comparison of the two subcategories difficult.

It appears that while the predictive value for an individual baby with scans at extreme ends of the spectrum (completely normal throughout or hydrocephalus/cerebral atrophy at discharge) is good, it is less so for those with intermediate changes. Mild degrees of IVH associated with a normal scan at the time of discharge, while reassuring, do not exclude the subsequent development of neurological, especially minor, impairment. Serial scans are still preferable to a single scan done at the time of discharge for prognosticating outcome, as patients with transient ventriculomegaly have an intermediate risk of developing neurodevelopmental impairment. Nevertheless, neurological impairment at one year of age does not imply permanent disability. Two-thirds of our patients with major impairment had multiple major deficits resulting in disability, and this subgroup

Table IV - Perinatal risk factors and outcome at one year

Risk factor	All impairments (n = 33)	Normal (n = 68)	p
Mean birthweight, g (sd)	1199 (191.2)	1284 (146.9)	0.015
Mean gestation, weeks (sd)	31.1 (2.87)	31.9 (2.65)	0.155
Mode of delivery			
SVD	15	34	reference
Breech/LSCS	18	34	0.668
Race:			
Malays	20	38	reference
Others	13	30	0.652
Mean Apgar score, at 5 minutes (sd)	7.9 (1.12)	8.7 (1.31)	0.012
Ventilated	13	16	0.098
Experienced blocked endotracheal tube	4	1	0.038
Mean duration of ventilation, days (sd)	3.0 (4.94)	1.1 (2.43)	0.029
Mean duration of oxygen requirement, days (sd)	8.2 (8.53)	3.8 (5.25)	0.012

appears likely to remain disabled with age. However, minor neurological deficits are known to improve with time, although there is an association between "transient neurological dysfunction" in infancy with learning difficulties at a later age[11]. Long-term follow-up of this cohort is in progress to determine if this association between ultrasound changes and neurodevelopmental outcome continues into later childhood.

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