ORIGINAL ARTICLE

Risk Factors Associated With Chronic Lung Disease in Malaysian Very Low Birthweight Infants

S A K M Ameenudeen, MMed-Paed*, N Y Boo, FRCP, L G Chan, MRCP***

*Department of Paediatrics, Sarawak General Hospital, Kuching, Sarawak, ** Clinical School, International Medical University, Jalan Rasah, 70300 Seremban, Kebangsaan Malaysia, Kuala Lumpur

SUMMARY

To determine the significant risk factors associated with development of chronic lung disease (CLD) in Malaysian very low birthweight (VLBW, <1501g) infants. A prospective observational study was carried out at the Sarawak General Hospital (SGH) in Kuching, over a period of 29 months from 1 April 2003 to 31 August 2005. Infants with birthweight between 600g to 1500g admitted to this hospital were recruited. The progress of these infants was followed till discharge. CLD was defined as the persistent need for oxygen therapy to maintain oxygen saturation above 88% at 36 weeks of postmenstrual age. Of the 224 infants recruited, 36 (14.8%) had CLD. Logistic regression analysis showed that lower birth weight (adjusted odds ratio (OR) =0.996, 95% confidence intervals (CI) =0.994, 0.998; p=0.001), male infants (adjusted OR=3.9, 95% CI =1.6, 11.7; p=0.02), chorioamnionitis (adjusted OR=9.0, 95% CI = 1.6, 50.8; p=0.01), severe respiratory distress syndrome of grades 3 or 4 (adjusted OR=4.6, 95% CI =1.6, 13.2; P=0.005) and patent ductus arteriosus (adjusted OR= 4.3, 95% CI =1.5, 12.8; p=0.007) were significant risk factors associated with development of CLD. A number of treatable conditions are associated with development of CLD in Malaysian VLBW infants.

KEY WORDS:
Chronic lung diseases, Malaysian, Very low birthweight infants, Bronchopulmonary dysplasia

INTRODUCTION

Chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD) was first described in 1967 by Northway *et al* [1] in prematurely born infants with severe respiratory distress syndrome (RDS) following treatment with prolonged mechanical ventilation and high concentration of oxygen. Bancalari *et al* [2] and later Shennan *et al* [3] proposed well-defined criteria for diagnosis of CLD. Bancalari *et al* defined CLD as a condition present in infants who after mechanical ventilation remained oxygen dependent for more than 28 days and who had persistent abnormal changes in their chest radiographs[2]. Shennan *et al* defined CLD to be present in an infant when there was persistent oxygen requirement up to 36 weeks of postconceptional age as they noticed that oxygen dependency at 36 weeks of postconceptional age was more predictive of later pulmonary morbidity[3].

The reported incidence of CLD varies from 10-35% in very low birthweight infants (VLBW, <1501g). The precise aetiology of CLD, however, remains unknown and is thought to be multi-factorial. Numerous antenatal, perinatal and neonatal risk factors have been reported to be associated with CLD in preterm and/or VLBW infants in developed countries. These include abruptio placenta at birth,[4] poor intrauterine growth,[5] maternal indomethacin therapy for preterm labour,[6] maternal chorioamnionitis,[7,8] low Apgar score at 1 or 5 minutes of life,[9] low birth weight and gestation,[5,10] patent ductus arteriosus (PDA),[11,12] nosocomial infection,[11-13] high fluid intake,[14] presence of extrapulmonary air leak,[15] severe RDS,[1,16] high ventilation rate at 96 hour and low PaCO2 at 48 hour birth, [9,16] and male sex[17]. In Malaysia, the incidence of CLD in the VLBW infants is reported to vary around 15-20%[18]. However, no studies have reported on risk factors associated with CLD in Malaysian VLBW infants. As CLD is associated with long-term morbidity and mortality in VLBW infants, this study aimed to determine the significant risk factors associated with the development of CLD in Malaysian VLBW infants with the ultimate objectives to reduce this condition and improve the long-term outcome of VLBW infants in this country.

MATERIALS AND METHODS

This was a prospective observational study carried out in the nursery and neonatal intensive care unit (NICU) at the Sarawak General Hospital (SGH) in Kuching, over a period of 29 months from 1 April 2003 till 31 August 2005.

Infants with birth weight between 600g to 1500g admitted to the NICU during the study period were recruited. The exclusion criteria were infants with gross congenital abnormalities, major cardiac lesions other than patent ductus arteriosus (PDA) and/or who died before 28 days of life. After recruitment into the study, the progress of the infants in the ward was followed till discharge.

The gestation of infants was calculated based on their maternal last menstrual period or, in infants whose mothers

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Corresponding Author: Boo Nem Yun, Department of Paediatrics, Clinical School, International Medical University, Jalan Rasah, 70300 Seremban, Negeri Sembilan

were unsure of their dates, by the Ballard score[19]. For the purpose of this study, CLD was defined, based on the criteria of Shennan *et al*,[3] as the persistent need of oxygen therapy to maintain oxygen saturation above 88% up to 36 weeks of postmenstrual age in the presence of radiological pulmonary changes. RDS was defined as the development of respiratory distress within four hours of life associated with characteristic chest radiological changes. Severity of RDS was graded according to chest radiograph changes:[20] grade 1 was diagnosed in the presence of fine reticular granular mottling with good lung expansion, grade 2 when there was mottling with air bronchogram sign, grade 3 when there was diffuse mottling with just discernible heart border and prominent air bronchogram sign, and grade 4 when there was bilateral confluent opacification (or whiteout) of lungs. Sepsis was diagnosed in the presence of clinical signs and positive blood culture. Chorioamnionitis was diagnosed in the presence of maternal fever, AND maternal tachycardia, foetal tachycardia, uterine tenderness or foul smelling liquor, AND raised maternal total white count or raised C-reactive protein. PDA was diagnosed in the presence of a pan-systolic murmur, bounding pulse and characteristic echocardiographic findings. Pregnancy induced hypertension (PIH) was defined as a diastolic blood pressure of ≥90mm Hg, a systolic blood pressure ≥140mm Hg or as an increase in the diastolic blood pressure of at least 15mm Hg or in the systolic blood pressure of 30m Hg when compared to previous pre-pregnancy blood pressures. Gestational Diabetes Mellitus was diagnosed based on the result of oral glucose tolerance test following the new diagnostic criteria proposed by 'Expert Committee in the Diagnosis and Classification of Diabetes Mellitus'[21]. Antepartum hemorrhage was defined as bleeding from the genital tract after the 24th week of pregnancy. Small for gestational age (SGA) was defined as when the birth weight of a newborn infant was below 10th percentile for a given gestational age. Anemia in pregnancy was defined as hemoglobin level of less than 11g/dl during pregnancy. Premature rupture of the membranes was defined as spontaneous rupture of membrane prior to the onset of labor at any stage of gestation[22]. Antenatal steroids use was considered complete if a mother received a course of 4 doses of intramuscular Dexamethasone of 6mg every six hourly or 2 doses of 12mg every 12 hourly. Hypoxic ischemic encephalopathy was defined according to the grading system by Sarnat & Sarnat[23]. Congenital pneumonia was diagnosed in the presence of coarse opacity in chest radiograph during the first 48 hours of life. Air leak was diagnosed in the presence of radiological evidence of pulmonary interstitial emphysema or pneumothorax.

Statistical analysis

Statistical package SPSS (version 10.1) was used for analysis of data. Variables between infants with and without CLD were compared. The Chi square test (or Fisher exact test for expected value of less than 5) was used for analysis of categorical variables. The Student independent t-test was used for analysis of continuous variable with normal (Gaussian) distribution. Mann-Whitney test was used for analysis of continuous variables with skewed distribution. Variables with $p<0.05$ based on univariate analysis in Tables I - IV were entered into a multivariate logistic regression model to determine the significant risk factors associated with the development of CLD. P value of less than 0.05 was considered statistically significant.

RESULTS

During the study period, 229 infants with birthweight between 600g to 1500g were admitted to the neonatal intensive care unit. Of these, 48 died before 28 days of life and were excluded from the study. Among the remaining 244 infants, 103 (42.0%) were Malay, 90 (37.0%) were native Sarawakian, 47 (19.3%) were Chinese, and 4 (0.8%) were of other ethnic groups. Their mean birth weight was 1141 (SD=237) g and mean gestational age was 29.7 (SD=2.7) weeks.

Of these 224 infants, 36 (14.8%) developed CLD. Chest radiographs taken at the age of either 28 days or 36 weeks showed grossly abnormal findings in 30 (83.3%) of the 36 infants with CLD. Infants with CLD had significantly lower mean birth weight, mean gestational age, and mean Apgar score at 1 and 5 minutes of life ($p<0.001$) than those without CLD. A significantly higher percentage of infants with CLD were males. There was no significant difference in the ethnic distribution between the two groups of infants (Table I).

Significantly higher proportion of infants with CLD had maternal premature rupture of membrane, chorioamnionitis and antepartum hemorrhage ($p<0.05$). There was no significant difference in pregnancy-induced hypertension, gestational diabetes mellitus, maternal anaemia, use of antenatal steroid and intrauterine growth retardation between the two groups of infants (Table II).

A significantly higher percentage of infants with CLD had severe RDS with grades 3 or 4 radiological changes during the first week of life, PDA and sepsis than those without CLD (Table III). Furthermore, a significantly higher percentage of infants with CLD had surfactant therapy and ventilatory support shortly after birth. However, there was no significant difference in the prevalence of airleak syndrome, hypoxic ischaemic encephalopathy, congenital pneumonia and timing of onset of sepsis between the two groups of infants.

Infants with CLD were given significantly higher fluid intake during all the first five days of life than those without CLD (Table IV).

Infants with CLD required significantly longer duration of ventilation ($p<0.001$), higher peak inspiratory pressure ($p<0.001$), higher peak mean airway pressure (MAP) ($p=0.004$) and higher peak fractional inspiratory concentration of oxygen (FiO2) than infants without CLD. Infants with CLD also tend to have a significantly higher partial pressure of carbon dioxide during the first four days of ventilation ($p<0.001$) than those without CLD (Table V).

There was no significant difference in the proportion of infants with family history of bronchial asthma between infants with (n=5 or 13.9%) and without CLD (n=48 or 23.4%) ($p=0.2$). A significantly higher percentage of infants with CLD (n=22 or 61.1%) received postnatal steroid therapy for respiratory problems than those without CLD (n=5, or 2.4%) ($p<0.001$).

Table I: Comparison of basic variables of infants with and without chronic lung disease (CLD)

Basic variables	Infants with CLD n=36	Infants without CLD n=208	95% CI of difference between means	p values
Birthweight, g				
Mean (SD)	923 (205)	1178 (222)	-330, -179	<0.001*
Gestation in weeks				
Mean (SD)	27.2 (2.2)	30.2 (2.5)	-3.7 , -2.1	<0.001*
Apgar at 1 min	n=34	n=195		
Mean (SD)	6.2 (1.6)	7.0 (1.3)	-1.4, -0.3	0.007*
Apgar at 5 min	n= 34	n= 195		
Mean (SD)	7.6 (1.4)	8.4 (1.1)	-1.3, -0.3	<0.001*
Ethnic groups (%)				
Malay	15 (41.7)	88 (42.3)	____	0.2
Chinese	11 (30.6)	36 (17.3)		
Native Sarawakian	10 (27.8)	80 (38.5)		
Others	0 (0.0)	4 (1.9)		
Gender (%)				
Male	26 (72.2)	100 (48.1)	___	0.007*
Female	10 (27.8)	108 (51.9)		

95% CI = 95% confidence intervals, SD= standard deviation, *denotes statistical significance

Table II: Comparison of antenatal factors between infants with and without chronic lung disease (CLD)

Antenatal variables	Infants with CLD n=36 (%)	Infants without CLD n=208 (%)	p value
PROM	n=34	n=202	
	12 (35.3)	39 (19.3)	0.04*
Chorioamnionitis	n=34	n=202	
	7 (20.6)	8 (4.0)	0.002*
PIH	n=34	n=199	
	11 (32.4)	63 (31.5)	0.9
Gestational DM	n=34	n= 202	
	0 (0.0)	16 (7.9)	0.08
Antepartum	n=34	n=201	
Hemorhage	10 (29.4)	31(15.4)	0.047*
SGA	n=34	n=199	
	3 (0.0)	37 (18.5)	0.3
Maternal anemia	n=34	n=202	
	0 (0.0)	17 (8.4)	0.06
Antenatal	N=36		
Steroids			
No	10 (27.8)	43 (21.3)	0.6
Completed	14 (38.9)	94 (46.5)	
Not Completed	12 (33.3)	65 (32.2)	

PROM= premature rupture of membrane, PIH= pregnancy-induced hypertension, DM=diabetes mellitus, SGA=small for gestational age, * denotes statistical significance.

Table III: Comparison of neonatal problems or treatment received in infants with and without chronic lung disease (CLD)

Neonatal problems or treatment received	Infants with CLD n=36 (%)	Infants without CLD n=208 (%)	p value
Severe RDS	18 (51.4)	22 (10.7)	0.0001*
Abnormal chest radiograph during first week of life	34 (94.4)	117 (56.5)	0.0001*
Surfactant therapy	36 (100)	124 (86.1)	0.02*
Ventilated	36 (100)	129 (62.9)	<0.0001*
Airleak syndrome	1 (2.8)	1 (0.5)	0.3
Patent ductus arteriosus	27 (75.0)	55 (26.8)	0.001*
Sepsis	12 (33.3)	28 (13.5)	0.002*
Sepsis during the first week of life	32 (88.9)	164 (90.1)	0.8
Hypoxic ischaemic encephalopathy	1(2.8)	0 (0)	0.1
Congenital Pneumonia	1 (2.9)	6 (3.0)	1.0

RDS= respiratory distress syndrome, * denotes statistical significance

Table IV: Comparison of total fluid (ml/kg/day) intake of infants with and without chronic lung disease (CLD) during first five days of life

Total fluid intake (ml/kg/day)	Infants with CLD n=36	Infants without CLD n=208	95% CI of difference between means	p value
Day 1		n=206		
Mean (SD)	118.3 (36.8)	91.5 (28.5)	13.82, 39.90	<0.001*
Day 2	n=35	n=206		
Mean (SD)	144.3 (33.0)	117.1(27.0)	15.34, 39.10	<0.001*
Day 3	n=35	n=206		
Mean (SD)	173.1(39.7)	147.0 (26.9)	12.04, 40.23	0.001 *
Day 4	n=35	n=206		
Mean (SD)	188.9(38.7)	173.1 (30.8)	1.87, 29.69	0.027*
Day 5	n=35	n=205		
Mean (SD)	205.0 (35.9)	186.4 (29.1)	5.65, 31.47	0.006*

CI= confidence intervals, SD= standard deviation, *denotes statistical significance

Table V: Comparison of ventilation parameters of infants with and without chronic lung disease (CLD) during the first 4 days of life.

Variables	Infants with CLD n=36 (%)	Infants without CLD n=208 (%)	95% C.I. of difference between means	p value
Age when ventilation started, days	n=35	n=122		
(Median, IQR)	1.0(0)	1.0 (0)	----	0.9
Duration of ventilation, days	n=34	n=126		
Median (IQR)	30.0(34.0)	3.50(8.00)	----	<0.001*
Highest PIP , cm H2O	n=34	n=120		
Mean (SD)	21.4 (6.6)	17.69 (3.5)	1.34, 6.1	<0.001*
Highest MAP, cm H2O	n=35	n=118		
Median (IQR)	5.0 (4.0)	4.5 (1.0)	----	0.004*
Highest FiO2, %	n=34	n=121		
Median (IQR)	60.0(43.0)	50.0 (20.0)	----	0.0098
Highest PaC02, mmHg	n=32	n=109		
Median (IQR)	58.9 (22.9)	47.5 (17.6)	---	<0.001*
Lowest PaCO2, mmHg	n=32	n=108		
Mean (SD)	30.6 (7.4)	28.16 (6.2)	-0.43, 5.37	0.093

C.I.= confidence intervals, SD= standard deviation, IQR= interquartile range, PIP= positive inspiratory pressure, MAP= mean airway pressure, PaCO2= partial pressure of arterial carbon dioxide, *denotes statistical significance

Furthermore, a significantly higher percentage of infants with CLD developed retinopathy of prematurity than those without CLD (69.4% versus 11.8%, p<0.001). A higher percentage of infants with CLD died before discharge (CLD= 5.6%, no CLD =0.5%), although this difference was not statistically significant (p=0.06).

Logistic regression analysis showed that birth weight (adjusted odds ratio (OR) =0.996, 95% confidence intervals (CI) =0.994, 0.998; p=0.001), male infants (adjusted OR=3.9, 95% CI =1.6, 11.7; p=0.02), chorioamnionitis (adjusted OR=9.0, 95% CI = 1.6, 50.8; p=0.01), severe RDS of grades 3 or 4 (adjusted OR=4.6, 95% CI =1.6, 13.2; p=0.005) and PDA (adjusted OR= 4.3, 95% CI =1.5, 12.8; p=0.007) were significant risk factors associated with the development of CLD after controlling for the various potential confounders. Gestation age, Apgar scores at 1 and 5 minutes of life, anteparteum haemorrahge, sepsis, surfactant therapy, ventilatory support, and total fluid volume received during the first five days of life were not significant risk factors.

DISCUSSION

The incidence of CLD in the present study was much lower than those reported by other investigators. This could be partly due to the fact that the study population reported elsewhere [12,24] recruited only infants of gestation less than 32 weeks, whereas the present study included more mature infants of gestation greater than 31 weeks whose risk of CLD was therefore much lower. Secondly, extremely low birth weight infants weighing between 500 to 600 gram, who commonly had more severe RDS, were excluded from our study. Thirdly, the level of oxygen saturation achieved by the infants when oxygen therapy was weaned off could be different from those reported elsewhere. Differences in clinical practices such as targeting higher or lower oxygen saturation have been shown to significantly affect the length of oxygen supplementation. Ellsbury *et al* pointed out that clinicians have no consistent criteria for which an infant at 36 weeks needed oxygen[25]. Much of the variability in CLD incidence between units could be an artifact of oxygen use. Wash *et al* [26] proposed a new strategy for determining the presence or absence of CLD based on a physiologic test of the need for supplemental oxygen to achieve a pre-specified target oxygen saturation values over a test period. In their test, infants receiving 30% or less oxygen underwent a stepwise 2% reduction in supplemental oxygen to room air while under continuous observation and oxygen saturation monitoring. Infants were considered not oxygen dependent when they could maintain an oxygen saturation of 88% or more for 60 minutes when breathing air. With this approach infants receiving mechanical support or FiO2 > 30% would be designated as having CLD and infants receiving FiO2< 30% would receive their diagnosis designation based on the results of the oxygen challenge test.

The inclusion of relatively more mature infants in the present study could also explain why gestation was not a significant risk factor associated with CLD in the Malaysian infants, unlike that reported elsewhere[5 ,10, 24]. The relatively small sample size of infants with CLD recruited in the present study could be another explanation why gestational age was not identified as a significant risk factor based on multivariate analysis. This is because we found severity of RDS, which is known to be closely influenced by gestation, is a significant risk factor identified in the present study.

Our findings showed that VLBW infants with lower birth weight were significantly associated with higher risk of developing CLD. Furthermore infants born to mothers with chorioamnionitis have 9 times the risk of developing CLD than those without chorioamnionitis. Infants with severe RDS have 4.6 times the risk of CLD; infants with PDA have 4.3 times the risk while male infants have 3.9 times the risk than females of developing CLD. These findings were consistent with those reported by other investigators[1,5,7,8,11,12,16,17,24,27]. Presence of PDA and the resulting left to right shunt decreased lung compliance and increased airway resistance requiring higher ventilatory support. The higher ventilatory support predisposed infants to more lung injury and consequently higher risk of CLD. Some investigators speculated that the presence of chorioamnionitis not only accelerated lung maturation but also caused lung inflammation and lung injury leading to the development of CLD[28].

We did not find any significant association between use of antenatal steroids and CLD. This could be because usage of antenatal steroid was not high among our patients (only 72.2% in the CLD group) and the sample size of cases were not large enough to detect any differences. One of the reasons for the relatively low usage of antenatal steroid could be due to the fact that a large number of mothers were admitted at a late stage of preterm labour and thus precluding time for the drug to be administered. Although our findings were in agreement with those of Marshall *et al*[11] and Van Marter *et al*,[29] a recently published large multicenter trial by Gagliardi *et al*[30] showed that infants treated with antenatal steroid had a lower risk of CLD after proper adjustment for other confounding factors. The authors suggested that the lack of protective effect of antenatal steroid on CLD could be due to over-adjustment during analysis, caused by controlling for factors that were in the causal pathway between treatment and outcome.

Although the present study has identified a number of preventable and/or treatable conditions associated with the development of CLD, the main limitation of this study was the relatively small number of CLD infants recruited which was under-powered to detect some of the other potentially significant risk factors and erroneously identify others as significant. For instance, we did not find ventilatory support as significant risk factors associated with the development of CLD, after controlling for various potential confounders. In order to determine the types of ventilatory parameters which could be significant risk factors associated with the development of CLD, further studies should target only the ventilated infants to identify the incriminatory ventilatory factors.

In conclusion, a number of preventable and/or treatable conditions associated with CLD in Malaysian infants have been identified in the present study. However, larger national studies should be carried out to confirm these findings before policy changes take place.

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