MMED RESEARCH PROJECT

Prevalence of and Risk Factors for Cranial Ultrasound Abnormalities in Very Low Birth Weight Infants at CMJAH

INVESTIGATOR: Azra Ghoor MBChB (UCT)
STUDENT NUMBER: 0502838A
DEGREE: MMED (Paediatrics)

SUPERVISORS:

Professor Daynia Ballot
MBBCh (Wits), FCPaed (SA), PhD
Paediatric Neonatologist Charlotte Maxeke Johannesburg Academic Hospital

Professor Gail Scher
MBBCh (Wits), FCPaed (SA), MMed (Paeds) (Wits)
Paediatric Neurologist Charlotte Maxeke Johannesburg Academic Hospital

DECLARATION

I, Azra Ghoor, declare that this research report is my own original work. I am aware that plagiarism is wrong. I have followed the required conventions in referencing the thoughts and ideas of others. This report is being submitted for the degree of Master of Medicine in Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other institution.

A. Ghoor
05 December 2016

DEDICATION

To my parents, who were my first teachers.

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Vermont Oxford Network played no role in the design, conduct, analysis, interpretation or reporting of this study. The views, conclusions, and opinions expressed are solely those of the authors and do not represent those of the Vermont Oxford Network.

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Prevalence of and Risk Factors for Cranial Ultrasound Abnormalities in Very Low Birth Weight Infants at Charlotte Maxeke Johannesburg Academic Hospital

A Ghoor, MB ChB; **G Scher**, MBBCh, FCPaed (SA), MMed (Paeds); **D E Ballot**, MBBCh, FCPaed (SA), PhD

Department of Paediatrics and Child Health, University of the Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

***Corresponding author**: A Ghoor (azra.ghoor@gmail.com)*

ABSTRACT

Background. Intraventricular haemorrhage (IVH) and cystic periventricular leukomalacia (cPVL) contribute to neonatal mortality and morbidity. Low birth weight and gestational age are amongst the risk factors for IVH and cPVL.

Objectives. To assess how many very low birth weight (VLBW) infants had cranial ultrasound screening at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and to determine the prevalence of cranial ultrasound abnormalities. In addition, to compare the characteristics and risk factors of those VLBW infants with cranial ultrasound abnormalities to those with normal cranial ultrasound findings.

Methods. This was a retrospective case-controlled study of infants < 1 500g admitted to CMJAH from 1 January 2013 to 31 December 2015. Cases were identified as infants with IVH or cPVL. Controls were matched 1:2 based on birth weight and gender.

Results. Only 55% (856/1562) of VLBW infants had undergone cranial ultrasound screening. The prevalence of IVH was 26% (219/856). A total of 197 cases were identified and matched with 394 controls. Antenatal care was lower in cases (71% vs 79%; P=0.039). Sepsis, ventilation, metabolic acidosis and patent ductus arteriosus were all significantly higher in cases. The use of antenatal steroids was significantly higher in the grade I-II IVH/no IVH group vs grade III-IV IVH group (44% vs 25%; P=0.017).

Conclusion. The prevalence of IVH is consistent with that of developed countries. Improving antenatal care, infection control and adequate early resuscitation could decrease the incidence of IVH and cPVL. All VLBW infants should undergo cranial ultrasound screening.

Background

Periventricular-intraventricular haemorrhage (IVH) and white matter injury (WMI), particularly cystic periventricular leukomalacia (cPVL), are major contributors to mortality and long-term morbidity in preterm infants.[1,2] The immature blood-brain barrier combined with fluctuation in cerebral blood flow, or platelet and coagulation disorders, form the basis for IVH pathogenesis. Risk factors for IVH include low birth weight, gestational age, prematurity, lack of antenatal steroids, asphyxia, prolonged labour, respiratory distress syndrome, recurrent tracheal suctioning, hypoxia, hypercarbia, acidosis, patent ductus arteriosus (PDA), rapid infusion of sodium bicarbonate and inter hospital transfer.[3] Preterm infants with cystic PVL without IVH appear to have a different risk pattern, although the pathogenesis does involve both hypoxic-ischaemic and haemorrhagic processes. It also appears that intrauterine inflammation and cytokine release result in oxidative stress to white matter.[4,5]

IVH can be graded according to severity from grade I-IV, with the most commonly used classification being that of Papile et al.[6] The incidence of IVH in developed countries is about 20-25% of all very low birth weight (VLBW) infants. More than 50% of those with severe IVH develop intellectual disability or cerebral palsy.[7] Research done in Southern Africa, however, showed a higher incidence of between 20-50% of IVH in VLBW infants although the prevalence of severe IVH is similar to that of developed countries.[8-10]

Most neonatal units have a screening protocol in place to detect IVH or cPVL. The American Academy of Neurology suggests cranial ultrasound screening be performed at two time points for all infants with a gestational age less than 30 weeks: between week 1 and 2 of life and at 36 to 40 weeks post menstrual age.[7] More recent studies have evidence that Magnetic Resonance Imaging (MRI) done at term equivalent age could be helpful at identifying white matter abnormalities that could cause neurocognitive delay as a long-term outcome.[11] Cranial ultrasound, however, is still the first tool for assessing neurological injury in preterm infants as it allows for bedside investigation and sequential evaluation of evolving lesions.

As neonatal and obstetric care improves there is an increase in the survival of preterm infants and with this there is a newer burden of disease in the form of neurodevelopmental impairment.[2,12] In order to improve the screening and management of IVH at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) we first need to investigate the prevalence of IVH and cPVL and identify the specific risk factors important in our population. Low birth weight and gestational age are risk factors for IVH and therefore we chose to conduct a study that controlled for these possible confounders.[13]

Our aim was to assess how many VLBW infants had cranial ultrasound screening and determine the prevalence of cranial ultrasound abnormalities in our VLBW population. We also wanted to compare the characteristics, risk factors and short-term outcomes of those VLBW infants with cranial ultrasound abnormalities with VLBW infants with normal cranial ultrasound.

Methods

The study design was a retrospective case-controlled study using data from the CMJAH neonatal database. The study population included all VLBW infants admitted to the neonatal unit, including the intensive care unit, from 1 January 2013 to 31 December 2015. CMJAH is a tertiary hospital located in Johannesburg, South Africa. It acts as a referral centre for surrounding clinics and district hospitals. The study population included both inborn and outborn infants. Infants born with a birth

weight less than or equal to 1 500g qualify as very low birth weight. All VLBW infants who had the following ultrasound abnormalities were identified as cases: IVH, post-haemorrhagic hydrocephalous or cPVL. Cases were matched with control infants based on birth weight category and gender on a 1:2 basis. The two most suitable controls born closest to the study patient were selected. The grading of IVH was done according to the classification described by Papile et al.[6] Grade I includes bleeds restricted to the germinal matrix, grade II bleeds extend into the ventricles filling less than 50% of the ventricle, grade III bleeding causes ventricular dilatation, and grade IV includes parenchymal haemorrhage. Grade III and IV bleeds constitute severe IVH. There were four birth weight categories: less than or equal to 750g; 751 – 1 000g; 1 001 -1 250g and 1 251 – 1 500g. Infants with major congenital abnormalities of any organ system were excluded. Infants with cranial ultrasound revealing abnormalities such as absent corpus callosum, schizencephaly or findings with questionable significance such as periventricular echodensities were also excluded.

Data collection

Data was collected from the neonatal database REDCap (Research Electronic Data Capture) at CMJAH.[14] It is a secure web-based application that is linked to the Vermont Oxford Network (VON).[15] The VON includes about 1 000 centres around the world that submit data about high-risk newborn infants. It is a non-profit voluntary collaboration of health professionals aiming to improve neonatal care. Its members include both public and private units from North America, Brazil, Canada, Europe, the Middle East, Asia and Southern Africa, to name a few. Sixty-four units in South Africa are members of the VON.

The following maternal variables were extracted from the database for each infant: antenatal care, antenatal steroids, magnesium sulphate, chorioamnionitis, HIV, attempted termination of pregnancy, hypertension, diabetes and mode of delivery. Newborn variables were: place of birth (inborn, midwife obstetric unit (MOU), another hospital or home), gestational age, birth weight, head circumference, gender, multiple gestation, Apgar at 5 minutes, birth resuscitation, temperature on admission and metabolic acidosis. Birth resuscitation included oxygen, bag mask ventilation, intubation, cardiopulmonary resuscitation and/or intravenous adrenaline. Ultrasound findings were also recorded, particularly grade of IVH or presence of cPVL. The neonatal course was documented including respiratory diagnosis, respiratory support, days on continuous positive airways pressure (CPAP), days mechanically ventilated, surfactant therapy, supplementary oxygen on day 28, indomethacin or ibuprofen exposure and bacterial sepsis (early or late). Early sepsis constituted a positive blood culture within 72 hours of birth and late sepsis was a positive blood culture > 72 hours after birth. Other neonatal diagnoses noted were pneumothorax, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), neonatal jaundice, blood transfusion, HIV testing and major birth defects. Short term outcome namely survival to discharge was recorded. Well infants transferred to other hospitals were considered survivors.

Statistical methods

Statistical analysis was done using SPSS Statistics (IBM) version 23. Data was described using standard statistical methods. Continuous data with a normal distribution was described using mean and standard deviation, while skewed data was described using median and range. Categorical variables were described using frequencies and percentages. Univariate analysis was performed to describe differences between the case and control groups using the Pearson chi-squared or Fisher's exact test for categorical variables. Continuous variables were compared using independent t-tests or non-parametric tests (Mann Whitney) as appropriate, depending on data distribution. Basic demographic data of the group who had not undergone cranial ultrasound was compared to the final study sample that had undergone ultrasound to see if the sample selected was random. Sub-analysis

also included comparison between those with mild/no IVH to severe IVH and cPVL respectively. A p-value ≤ 0.05 was considered significant. The variables on univariate analysis with a p-value < 0.1 were analysed further in a stepwise logistic regression model to determine risk factors for IVH and cPVL.

Ethics

The Human Research Ethics Committee at the University of the Witwatersrand, Johannesburg, approved the study (Clearance certificate No. M151195).

Results

There were 1562 VLBW infants born between 1 January 2013 and 31 December 2015 at CMJAH (accessed 01 February 2016). Cranial ultrasounds were performed on 856 (55%) infants. The prevalence of cranial ultrasound abnormalities at CMJAH is shown in Table 1. Of the 856 patients with cranial ultrasounds, 13 were excluded from the study due to major birth defects. The remaining infants who underwent cranial ultrasound were then divided into normal (580) and abnormal (263) cranial ultrasound groups. Forty infants in the "abnormal" group (40/263, 15%) were excluded due to sonar findings that did not meet inclusion criteria. A further 26 infants with abnormal cranial ultrasounds had no matching control with the correct weight category or gender and were thus excluded. There were 186/580 (32%) in the "normal" group who could not be matched with an "abnormal" infant. There were thus 197 cases and 394 controls selected from the infants who had undergone cranial ultrasound (see Figure 1).

Table 1. Prevalence of ultrasound abnormalities in VLBW infants at CMJAH *n* (%)

	CMJAH
Cranial ultrasounds done	856 (54,8%)
Normal cranial ultrasound	580 (67,7%)
Grade I	63 (7,4%)
Grade II	91 (10,6%)
Grade III	34 (4%)
Grade IV	27 (3,2%)
Cystic PVL	8 (1%)

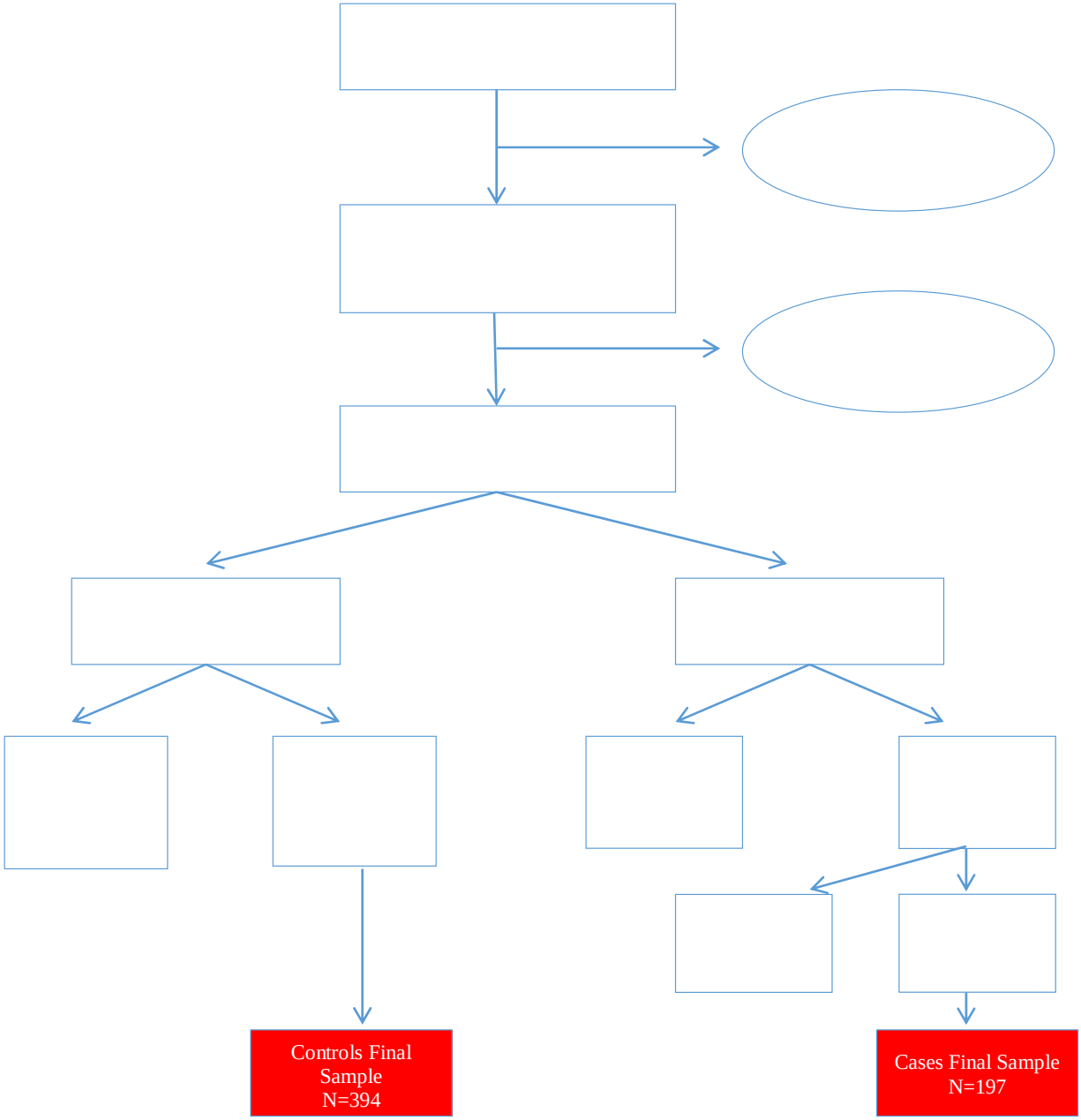

Figure 1. Flow diagram describing sample selection

Basic demographic data showed that 47% (729/1562) of infants admitted were males, median birth weight was 1150g and mean gestational age was 29 weeks. The mortality of the overall group was 27% (415/1562). There were less males in the group who had not undergone ultrasound (417/702; 45%) compared to the case/control group (303/591; 51%; P=0.029). The median weight was higher in the group with no ultrasound (1180g vs 1090g in the case/control group; P=0.05). The mean gestational age of 29 weeks was the same for both groups. Mortality in the group who had not undergone ultrasound was higher (279/706; 39% vs 99/591; 17%). This result had a significant p-value of 0.026. This higher mortality could be accounted for by the large amount of infants who were ≤750g in the group who had not undergone ultrasound (92/706; 13% vs 18/591; 3%). When comparing cases and controls we found that the gender distribution was the same with males constituting 49% in both groups. The mean birth weight for cases was 1097g and 1065g for controls.

The mean gestational age was 29 weeks for both groups. The above parameters had no statistical significance, which confirms that cases and controls were matched.

The univariate comparison between case and control groups is shown in Table 2. A higher proportion of cases were outborn. Sepsis, metabolic acidosis, ventilation and PDA were all significantly higher in cases. Antenatal care and Apgar at 5 minutes were lower in cases. However, there was no significant difference between the two groups when it came to antenatal steroids.

The logistic regression analysis included location of birth, antenatal care, maternal hypertension, maternal HIV, mode of delivery, Apgar at 5 minutes, initial resuscitation with oxygen, early and late bacterial sepsis, PDA and ventilation. The results are shown in Table 3. The analysis showed that antenatal care (odds ratio [OR]: 0.59; 95% confidence interval [CI]: 0.37–0.95) and Apgar greater than 7 at 5 minutes (OR: 0.53; 95% CI: 0.34–0.84) were associated with a lower risk of abnormal cranial ultrasound. Ventilation carried a higher risk of cranial ultrasound abnormality (OR: 2.44; 95% CI: 1.62–3.69) and early bacterial sepsis followed this trend (OR: 3.32; 95% CI: 1.3–8.34).

The rest of the variables were not significantly different between the groups.

Table 2. Overall characteristics of cases and controls

Characteristic	Controls (N=394)	Cases (N=197)	P-value
Outborn, *n* (%)	60/392 (15)	45/196 (23)	0.03
Mortality, *n* (%)	53/393 (14)	46/197 (23)	0.004
Maternal factors			
Antenatal care, *n* (%)	307/390 (79)	137/194 (71)	0.039
Antenatal steroids, *n* (%)	174/386 (45)	73/191 (38)	0.14
Maternal HIV, *n* (%)	111/392 (28)	72/197 (37)	0.059
Hypertension, *n* (%)	105/386 (27)	37/197 (19)	0.041
Mode of delivery, *n* (%)			0.054
Vaginal	139/385 (36)	83/185 (45)	
Caesarean	246/385 (64)	102/185 (55)	
Neonatal Factors			
Apgar at 5 min *n* (%)			0.002
Less than 7	65/360 (18)	52/173 (30)	
7 or greater	295/360 (82)	121/173 (70)	
Resuscitation at birth with oxygen, *n* (%)	324/394 (82)	148/197 (75)	0.037
Early bacterial sepsis, *n* (%)	10/392 (3)	13/197 (7)	0.023
Late bacterial sepsis, *n* (%)	156/394 (40)	99/197 (50)	0.02
Metabolic acidosis, *n* (%)	18/394 (5)	22/197 (11)	0.005
Mechanical ventilation, *n* (%)	102/380 (27)	95/197 (48)	<0.001
PDA, *n* (%)	57/393 (15)	45/192 (23)	0.015
Maximum Bilirubin level, mean (± SD)	167 (± 44)	179 (± 55)	0.036

*Valid cases reported for each variable (i.e. missing information was excluded)

Table 3. Parameters influencing the development of IVH, Severe IVH and cystic PVL, identified by logistic regression analysis

Parameter	OR	95% CI	P-value
All cases			
Antenatal care	0.59	0.37 - 0.95	0.03
Apgar ≥ 7 at 5 minutes	0.53	0.34 - 0.84	0.006
Early bacterial sepsis	3.32	1.32 - 8.34	0.011
Mechanical ventilation	2.44	1.62 - 3.69	<0.001
Severe IVH			
Outborn	3.0	1.22 - 7.41	0.017
Apgar ≥ 7 at 5 minutes	0.21	0.10 - 0.43	<0.001
Mechanical ventilation	3.64	1.73 - 7.62	0.001
Cystic PVL			
Sex (male)	0.11	0.01 - 1.22	0.072
Chorioamnionitis	45.73	6.27 - 333.68	<0.001
Mechanical ventilation	15.92	1.54 - 164.36	0.02

*Valid cases reported for each variable (i.e. missing information was excluded)

Sub-analyses

Severe IVH within the selected cases, was compared to mild/no IVH from within the case and control groups. Significant results are shown in Table 4. The use of antenatal steroids in the mild/no IVH group is higher (232/527; 44% vs 11/44; 25%: P=0.017). Logistic regression analysis revealed that both outborn and ventilated VLBW infants had a higher risk of severe IVH. An Apgar score of 7 or greater had indicated a lower risk of severe IVH. The results are shown in Table 3.

The sample of infants with cystic PVL was compared to those with mild/no IVH and results are detailed in table 5. The significant factors associated with cystic PVL on univariate analysis were sex (female), chorioamnionitis, blood transfusion, late bacterial sepsis as well as ventilation. Logistic regression analysis (Table 3) revealed that chorioamnionitis (OR: 45.73; 95% CI: 6.27–333.68) and ventilation (OR: 15.92; 95% CI: 1.54–164.36) hold a high risk of cystic PVL.

Table 4. Severe IVH compared to mild IVH/no IVH

Characteristic	Mild IVH/No abnormality (N=536)	Severe IVH (N=47)	P-value
Outborn, *n* (%)	81/534 (15)	17/47 (36)	0.001
Mortality, *n* (%)	78/535 (15)	17/47 (36)	<0.001
Maternal factors			
Antenatal care, *n* (%)	410/531 (77)	28/46 (61)	0.019
Antenatal steroids, *n* (%)	232/527 (44)	11/44 (25)	0.017
Neonatal factors			
Apgar at 5 min, *n* (%)			<0.001
Less than 7	91/485 (19)	24/41 (59)	
7 or greater	394/485 (81)	17/41 (41)	
Early bacterial sepsis, *n* (%)	18/535 (3)	5/47 (11)	0.031
Oxygen on day 28, *n* (%)	205/517 (40)	23/41 (56)	0.047
Metabolic acidosis, *n* (%)	31/536 (6)	7/47 (15)	0.026
Mechanical ventilation, *n* (%)	161/519 (31)	29/46 (63)	<0.001

*Valid cases reported for each variable (i.e. missing information was excluded)

Table 5. Cystic PVL compared to mild IVH/no IVH

Characteristic	Mild IVH/No abnormality (N=536)	Cystic PVL (N=8)	P-value
Sex (male), *n* (%)	275/536 (51)	1/8 (13)	0.035
Mortality, *n* (%)	78/535 (15)	4/8 (50)	0.001
Chorioamnionitis, *n* (%)	18/525 (3)	3/6 (50)	0.001
Blood transfusion, *n* (%)	308/532 (58)	8/8 (100)	0.024
Late bacterial sepsis, *n* (%)	224/536 (42)	7/8 (88)	0.012
Mechanical ventilation, *n* (%)	161/518 (31)	7/8 (88)	0.002

*Valid cases reported for each variable (i.e. missing information was excluded)

Discussion

The main objectives of this study were to look at the prevalence of cranial ultrasound abnormalities and associated risk factors. According to the screening protocol at CMJAH every VLBW should have an ultrasound within the first 7 days of life, at 10-14 days of life and one before discharge.[16] Only 55% of VLBW infants admitted in the study period had cranial ultrasounds, as compared to the VON where more than 90% of VLBW infants had cranial sonars.[15] Reasons for the low coverage rate in our unit include staff shortages at times but more importantly the lack of appropriate equipment to perform ultrasound. The unit only has one sonar machine that is often not functional.

It was shown that patients who did not undergo cranial ultrasound appeared to have a higher mortality rate than those who had undergone an ultrasound. This is partly explained by the fact that 92/706 (13%) of infants in that group were ≤ 750g. These infants already make up a high-risk group related to the extreme prematurity and are likely to have demised before an ultrasound could be performed. Well VLBW infants admitted with higher birth weights are often sent to the kangaroo mother care (KMC) ward and discharged quickly without undergoing cranial ultrasound screening.

The prevalence of IVH (26%) appears to be consistent with that of studies done in developed countries and is similar to that reported in the VON over the same time period.[7] With improvement of perinatal care the prevalence appears to have decreased compared to a study done at our sister unit Baragwanath Hospital in Soweto 20 years ago, which showed a prevalence of 52% in VLBW infants.[8] The prevalence of severe IVH in this study (7%) is also less than reported in the VON and studies from both developed and developing countries.[7-9]

This study confirms what is already known, that infants with IVH have higher mortality and that lack of antenatal care, birth asphyxia and sepsis appear to be associated with development of IVH. Mechanical ventilation and PDA also had an increased association with IVH and this can be explained by fluctuations in cerebral blood flow.[3] Inborn patients tended to have less IVH than those outborn and there are many factors that could explain the higher risk including delay in transfer, inadequate monitoring or lack of appropriate management at referral centres. Contrary to other studies, which show a decrease in IVH with antenatal steroids, our study did not show a significant difference between the use of antenatal steroids in the case and control groups.[3] This may be due to the fact that the administration of antenatal steroids in our setting is lower than other settings. Only 28% (431/1562) of mothers of VLBW infants had received steroids as compared to 83.5% coverage in the VON during the same period. The reason is possibly due to late presentation of unbooked mothers.[17] However, the sub-analysis showed that those with severe IVH had less exposure to antenatal steroids than the mild/no IVH group.

Maternal hypertension was also associated with a lower incidence of overall IVH and this is consistent with other studies.[13] In terms of the logistic regression analysis for all IVH cases, the major protective factors were antenatal care and Apgar ≥ 7 at 5 minutes. Sepsis and mechanical ventilation showed about a 3-fold increase in IVH and both of those factors can be modified by preventative measures. Severe IVH had similar association on logistic regression analysis to overall IVH, but infants that were outborn were shown to have a 3-fold risk of severe IVH and this could be prevented by transport of mothers in premature labour to centres with appropriate neonatal services before delivery.

In this study the prevalence of cystic PVL was only 1% although mortality was highest in this group which is consistent with previous studies.[2] As explained earlier MRI is a better tool to assess WMI, but in our setting this is not feasible due to lack of adequate MRI facilities to service the neonatal

unit. Studies seeking to describe a difference between cystic PVL and IVH have shown that the two are not mutually exclusive and there is a possible causal relationship between the two even though cystic PVL can be seen as a single pathology in some cases.[4,5] In this study the sub-analysis showed that the female gender, chorioamnionitis and blood transfusion had significant association with cystic PVL as well as sepsis and mechanical ventilation, which were both risk factors for IVH as well. However, on multivariate logistic regression analysis the gender association was shown to have an insignificant 95% CI and only chorioamnionitis and mechanical ventilation appeared significant, although confidence intervals were wide owing to the small sample.

Limitations

The retrospective study design was a limitation. The disadvantages include information bias and difficulty in establishing the temporal relationship between certain variables. Records that were incomplete or missing affect the dataset. Another limitation is the lack of resources, including both staff and equipment, which resulted in deviation from the ultrasound screening protocol and resulted in 45% of VLBW infants not being screened. WMI may be largely underestimated by cranial ultrasound alone. In our setting the access to MRI is inadequate.

Conclusion

This retrospective matched case-control study showed that the prevalence of IVH is consistent with that of developed countries and it is encouraging to note that severe IVH is lower in our unit. It confirmed the risk factors for IVH and cystic PVL at CMJAH are in keeping with that found globally. The increased mortality and morbidity in infants with IVH would suggest that we try to modify the risk factors found to be significant in our population. Access and awareness of early antenatal care is an important factor in preventing poor perinatal outcome. Neonatal resuscitation training in clinics and hospitals should be given priority as well as correct protocols for transfer of infants as well as possible early transfer of mothers in preterm labour to appropriate centres. Infection control and methods to decrease the need for mechanical ventilation are important interventions that could decrease the incidence of IVH. In terms of ultrasound screening, early detection of lesions gives infants a chance of early intervention services. Therefore, efforts should be made to ensure that all VLBW infants undergo ultrasound screening. Furthermore, early identification of patients with poor prognostic factors could assist with decision-making regarding the maximum level of care offered and allocation of resources in an equitable manner.

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APPENDIX 2 – PROTOCOL

MMED RESEARCH PROTOCOL

November 2015

PREVALENCE OF AND RISK FACTORS FOR CRANIAL ULTRASOUND ABNORMALITIES IN VERY LOW BIRTH WEIGHT INFANTS AT CMJAH

INVESTIGATOR: Azra Ghoor MBChB (UCT)
STUDENT NUMBER: 0502838A
DEGREE: MMED (Paediatrics)

SUPERVISORS:

Professor Daynia Ballot
MBChB (Wits), FCPaed (SA), PhD
Paediatric Neonatologist Charlotte Maxeke Johannesburg Academic Hospital

Professor Gail Scher
MBChB (Wits), FCPaed (SA), MMed (Paeds) (Wits)
Paediatric Neurologist Charlotte Maxeke Johannesburg Academic Hospital

CORRECTIONS TO PROTOCOL

Page 7: Paragraph 1, Line 10, ‘ten’ changed to ‘twenty’

Page 9: Paragraph 2, Line 2, the following was added; ‘’ For every case with IVH that is found, the next two babies born within the same weight category and gender, which have normal ultrasounds, will be taken as controls. ‘’

Page 10: Paragraph 2, Line 4, the following was added; ’’Maternal diabetes and hypertension will also be included.’’

Page 11: Paragraph 2, Line 7, the following was added; ’’Risk factors will be stratified to severity of IVH. The group of infants without cranial ultrasound will also be analyzed and compared with those who had ultrasounds.’’

Page 13: Paragraph 1, Line 4, the following was added; ’’Lastly, only the worst grade of IVH is recorded on the data sheet thus we will be unable to comment on risk factors associated with progression from a lower grade to a higher grade. The day the ultrasound is done is also not noted so temporality of the insult and IVH cannot be determined.’’

Page 16: Appendix A, ‘Date of birth’ was removed.

GLOSSARY OF TERMS

CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
VLBW	Very low birth weight
IVH	Intraventricular haemorrhage
WMI	White matter injury
cPVL	Cystic periventricular leukomalacia
PVHI	Periventricular haemorrhagic infarction
MRI	Magnetic Resonance Imaging
NICU	Neonatal Intensive Care Unit
REDCap	Research Electronic Data Capture

INTRODUCTION

Periventricular-intraventricular haemorrhage (IVH) and white matter injury (WMI), particularly cystic periventricular leukomalacia (cPVL), are major contributors to mortality and long-term morbidity in preterm infants. Preterm infants are at high risk for intraventricular haemorrhage. Intraventricular haemorrhage in the preterm infant generally has its onset in the ganglionic eminence also known as the germinal matrix (1). This area consists of neuronal and glial precursor cells. The vasculature in the sub ependymal germinal matrix is very dense and fragile owing to paucity of pericyctes, reduced fibronectin in the basal lamina and reduced glial fibrillary acidic protein expression in the astrocyte end feet. This immature blood-brain barrier combined with fluctuation in cerebral blood flow, or platelet and coagulation disorders, form the basis of IVH pathogenesis (2). Risk factors for IVH include prematurity, lack of antenatal steroids, asphyxia, prolonged labour, respiratory distress syndrome, recurrent tracheal suctioning, hypoxia, hypercarbia, acidosis, patent ductus arteriosus, rapid infusion of sodium bicarbonate and inter hospital transfer.

WMI occurs in a characteristic distribution with the cystic type comprising of focal necrosis in the periventricular white matter involving the loss of cellular elements. There is subsequent cyst formation that can be visualised on cranial ultrasound. Non-cystic WMI is a more diffuse process with paucity of oligodendrocytes. This type is not easily detected on cranial ultrasound and is better defined by Magnetic resonance imaging (MRI). Preterm infants with cystic PVL without evidence of IVH appear to have a different risk pattern, although the pathogenesis does involve both hypoxic-ischaemic and haemorrhagic processes (3,4). It also appears that intrauterine inflammation and cytokine release result in oxidative stress to pre-oligodendrocytes. However, studies seeking to describe a difference between WMI and IVH have shown that the two are not necessarily mutually exclusive and there is a possible causal relationship between the two even though cystic PVL can be seen as a single pathology in some cases (4,5).

The most commonly used classification for IVH is that of PapIle et al (6). This classification grades IVH according to severity from I-IV; grade I includes bleeds restricted to the germinal matrix, grade II the bleed extends into the ventricles filling less than 50% of the ventricle, grade III bleeding causes ventricular dilatation, and grade IV includes parenchymal haemorrhage. Many studies prefer to describe a grade IV as periventricular haemorrhagic infarction (PVHI) (1). In terms of WMI, it is often divided into cystic and diffuse PVL with the former being more easily detected on cranial ultrasound.

The incidence of IVH in developed countries is about 20-25% of all very low birth weight infants (VLBW) and more than 50% of those with severe IVH develop intellectual disability or cerebral palsy (7). Research done in Southern Africa, however, shows a higher incidence of between 20-50% of IVH in VLBW although the prevalence of severe IVH is similar to that of developing countries (8–10). The risk of poor neurological outcome increases with increasing grade of IVH. Cystic PVL, which may be a separate entity or a complication of IVH, is shown to result in cerebral palsy in up to 90% of cases (11).

Most neonatal units have a screening protocol in place to detect IVH or cPVL. The American Academy of Neurology suggests cranial ultrasound screening be performed at two time points for all infants with a gestational age less than 30 weeks: between week 1 and 2 of life and at 36 to 40 weeks post menstrual age (7). More recent studies have evidence that MRI done at term equivalent age could be helpful at identifying white matter abnormalities that could cause neurocognitive delay as a long term outcome (3,7). Cranial ultrasound, however, is still the first tool for assessing

neurological injury in preterm infants as it allows for beside investigation and sequential evaluation of evolving lesions.

It is clear that preventative measures aimed at improving neurological outcome are necessary. Early detection of lesions gives infants a chance of early intervention services. Furthermore, early identification of patients with poor prognostic factors could assist with decision-making regarding the maximum level of care offered and allocation of resources in an equitable manner (12). Early screening will also allow for appropriate counseling of parents about possible neurological impairment.

JUSTIFICATION OF THE STUDY

As neonatal and obstetric care improves we see an increase in survival of preterm infants (11) . With improved survival the morbidity rates increase and we begin to see a newer burden of disease in the form of cerebral palsy, cognitive and behavioural problems as well as neurosensory impairment (13). In order to improve the screening and management of IVH at Charlotte Maxeke Hospital (CMJAH) we first need to investigate the prevalence of IVH and cPVL and identify the specific risk factors important in our population. Once modifiable risk factors are identified we can address areas of concern and quantify the short-term sequelae. A previous study at Baragwanath Hospital published in 1994 showed relatively high prevalence of IVH and it would be informative to compare the findings at a sister unit twenty years later.

AIMS AND OBJECTIVES

AIM

The aim of this study is to evaluate the prevalence and risk factors of IVH and cPVL in VLBW infants at CMJAH.

OBJECTIVES

1. To determine how many VLBW infants had cranial ultrasound screening and how many ultrasounds were abnormal.
2. To compare the characteristics, risk factors and short-term outcome of those VLBW infants with cranial ultrasound abnormalities with VLBW infants with normal cranial ultrasound.

METHOD

STUDY DESIGN

A retrospective case-control study using data from the CMJAH neonatal database linked to the Vermont Oxford Network.

STUDY POPULATION

All VLBW infants admitted to the neonatal or NICU at CMJAH for the period of January 2013 to October 2015.

INCLUSION CRITERIA

Cases: All VLBW babies who had a cranial ultrasound with abnormal findings.

Controls: All VLBW babies who had normal cranial ultrasounds. Cases will be matched 1:2 on a birth weight and gender basis. For every case with IVH that is found, the next two babies born within the same weight category and gender, which have normal ultrasounds, will be taken as controls.

EXCLUSION CRITERIA

All babies without any information will be excluded as well as babies with major congenital abnormalities of any organ system.

DATA COLLECTION AND ANALYSIS

DATA COLLECTION

Data will be collected from the neonatal database REDCap (Research Electronic Data Capture) at CMJAH. It is a secure web-based application that is linked to the Vermont Oxford Network and uses it's coding. The data collected for this database is rigorously checked and verified before entered electronically. A data sheet representing data that is valid to this study will be attached (appendix A). The researcher will capture data using this sheet and all identifying data will be removed. Study numbers will be allocated to each data sheet. Data will be entered into STATISTICA for analysis.

The screening protocol for VLBW infants at CMJAH includes a cranial ultrasound to be done within the first 7 days of life, at 10-14 days of life and one before discharge (14). A paediatric neurologist or a neonatologist in the unit does the ultrasounds.

SAMPLE SIZE

The sample size was calculated using the number of patients with IVH that had antenatal steroids (a risk factor for IVH) and the number without IVH that had antenatal steroids in a similar case control

study done in 2003 (15). Considering a matched case control method with 1:2 ratio (case to control), p value of 0.05, β of 0.8, an assumed odds ratio of 4 and exposure to antenatal steroids in the control group of 70%, 57 subjects and 114 controls will be required.

DATA VARIABLES

The following maternal and neonatal characteristics will be looked at:

Maternal – Antenatal care, antenatal steroids, magnesium sulphate, chorioamnionitis, HIV, attempted termination of pregnancy and the mode of delivery. Maternal diabetes and hypertension will also be included.

Neonatal:

- Place of birth and gestational age
- Birth weight and head circumference
- Gender, multiple gestation and Apgar at 5 minutes
- Initial resuscitation and temperature
- Cranial ultrasound, grade of IVH, cystic PVL
- Metabolic acidosis and bacterial sepsis (early and late)
- Respiratory diagnosis, respiratory support, days on continuous positive airways pressure, days ventilated, surfactant therapy, day 28 on oxygen
- Indomethacin or Brufen exposure
- Pneumothorax, patent ductus arteriosus, necrotising enterocolitis or neonatal jaundice
- Blood transfusion, HIV testing
- Major birth defects
- Outcome

DATA ANALYSIS

Data will be described using standard statistical methods. Continuous variables will be described using mean and standard deviation where data is distributed normally and median and interquartile range will be used for non-parametric data. Categorical variables will be expressed as frequency or percentages. Comparison between case and controls will be done using unpaired t-test or Mann Whitney U-test. Categorical variables will be compared using Chi-squared analysis. A p-value of less than 0.05 will be considered significant. Risk factors will be stratified to severity of IVH. The group of infants without cranial ultrasound will also be analysed and compared with those who had ultrasounds.

ETHICS

This protocol will be submitted to the ethics committee of the University of Witwatersrand for research on human subjects. The Neonatal Database REDCap is confidential and has limited accessibility. There will be no identifying information for the patients in the dataset used and study numbers will be allocated to create anonymity. This will ensure confidentiality. There will no interaction with patients directly as this is a retrospective record review, thus there is no risk for patient exploitation. Consent for the study will be obtained from the Chief Executive Officer of CMJAH. Informed consent from the participants is not necessary as this is a retrospective review of records.

Approval from Human Research Committee is pending.

TIMING

	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept
Literature review												
Preparing protocol												
Protocol assessment												
Ethics application												
Collecting data												
Data analysis												
Writing up-Thesis												

FUNDING

The only financial considerations are printing and data usage estimated to be about R1000, the researcher would cover this expense.

LIMITATIONS

The retrospective study design is a limitation. The disadvantages include information bias and difficulty in establishing the temporal relationship between certain variables. The researcher relies on others for accurate record keeping and cannot control the exposure or outcome. If records are incomplete or missing it affects the dataset. Another possible limitation is that resource shortages and understaffing have made regular screening difficult so many VLBW infants may not be screened. Lastly, only the worst grade of IVH is recorded on the data sheet thus we will be unable to comment on risk factors associated with progression from a lower grade to a higher grade. The day the ultrasound is done is also not noted so temporality of the insult and IVH cannot be determined.

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DATASHEET

STUDY NUMBER			
Gestational age			
Gender			
Place of birth			
Head circumference at birth (cm)			
Maternal Data			
Antenatal care	YES	NO	UNKNOWN
Antenatal steroids	YES	NO	UNKNOWN
Antenatal Magnesium sulphate	YES	NO	UNKNOWN
Chorioamnionitis	YES	NO	UNKNOWN
Maternal HIV	YES	NO	UNKNOWN
Attempted Termination of pregnancy	YES	NO	UNKNOWN
Mode of delivery	YES	NO	UNKNOWN
Multiple gestation	YES	NO	UNKNOWN
Apgar score at 5 minutes			
Initial resuscitation			
Oxygen	YES	NO	UNKNOWN
Face mask ventilation	YES	NO	UNKNOWN
Endotracheal Tube Ventilation	YES	NO	UNKNOWN
Epinephrine	YES	NO	UNKNOWN
Chest compressions	YES	NO	UNKNOWN

Temperature in degrees Celsius	

Bacterial sepsis on or before day 3	YES		NO		UNKNOWN
Gram stain	POSITIVE		NEGATIVE		
Oxygen on day 28	YES		NO		UNKNOWN
Cranial sonar/CT/MRI	YES		NO		UNKNOWN
Worst grade of IVH	Normal	I	II	III	IV
cPVL	YES		NO		UNKNOWN
Metabolic acidosis (BE-16mmol/L)	YES		NO		UNKNOWN
Respiratory diagnosis					
Hyaline membrane disease	YES		NO		
Congenital pneumonia	YES		NO		
Atelectasis	YES		NO		
Pulmonary haemorrhage	YES		NO		
None	YES		NO		
Respiratory support after initial resuscitation	YES		NO		YES
CPAP duration					
IPPV duration					
Surfactant therapy	YES		NO		UNKNOWN
Pneumothorax	YES		NO		UNKNOWN
Patent ductus arteriosus	YES		NO		UNKNOWN
Necrotising enterocolitis	YES		NO		UNKNOWN
Blood transfusion	YES		NO		UNKNOWN

Neonatal jaundice requiring phototherapy	YES	NO	UNKNOWN
Neonatal jaundice requiring exchange transfusion	YES	NO	UNKNOWN
Sepsis after day 3	YES	NO	UNKNOWN
Gram stain	POSITIVE	NEGATIVE	
Indomethacin usage	YES	NO	UNKNOWN
Brufen usage	YES	NO	UNKNOWN
Major birth defects	YES	NO	UNKNOWN
HIV PCR if exposed	YES	NO	UNKNOWN
Outcome	DEATH	DISCHARGE	
Discharge head circumference (cm)			

APPENDIX 3 – ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Azra Ghoor

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151195

NAME: (Principal Investigator)	Dr Azra Ghoor
DEPARTMENT:	Paediatrics Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Prevalence and Risk Factors for Cranial Ultrasound Abnormalities in Very Low Birth Weight Infants at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	27/11/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Daynia Ballot and Prof Gail Scher
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	03/02/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 4 – AUTHOR GUIDELINES

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KEYWORDS

Breastfeeding Child development Children Congenital Developing countries HIV NICU Nigeria PICU Paediatrics South Africa child health children cytomegalovirus gestational age immunization infant feeding infants newborn noise prevention

Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472. **Internet references:** World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010). **Other references (e.g. reports)** should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'. **PROOFS** A PDF proof of an article may be sent to the corresponding author before publication to resolve remaining queries. At that stage, **only** typographical changes are permitted; the corresponding author is required, having conferred with his/her co-authors, to reply within 2 working days in order for the article to be published in the issue for which it has been scheduled. **CHANGES OF ADDRESS** Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication. **CPD POINTS** Authors can earn up to 15 CPD CEUs for published articles. Certificates may be requested after publication of the article. **CHARGES** There is no charge for the publication of manuscripts.

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APPENDIX 5 – TURNITIN REPORT

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MMED RESEARCH PROJECT Prevalence of and Risk Factors for

12**Cranial Ultrasound abnormalities in Very Low Birth Weight Infants**

at Charlotte Maxeke Hospital, Johannesburg INVESTIGATOR: Azra Ghoor MBChB (UCT) STUDENT NUMBER: 0502838A DEGREE: MMED (Paediatrics) SUPERVISORS: Professor Daynia Ballot MBBCh (Wits), FCPaed (SA), PhD Paediatric Neonatologist Charlotte Maxeke Johannesburg Academic Hospital Professor Gail Scher MBBCh (Wits), FCPaed (SA), MMed (Paeds) (Wits) Paediatric Neurologist Charlotte Maxeke Johannesburg Academic Hospital Prevalence of and Risk Factors for

12**Cranial Ultrasound abnormalities in Very Low Birth Weight Infants**

at Charlotte Maxeke Hospital, Johannesburg A Ghoor, MB ChB; G Scher,

4**MBBCh, FCPaed (SA),** MMed (Paeds); **D E Ballot, MBBCh, FCPaed (SA), PhD Department of Paediatrics and Child Health, University of the Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa Corresponding author:**

A Ghoor (azra.ghoor@gmail.com) ABSTRACT. Background. Intraventricular haemorrhage (IVH) and cystic periventricular leukomalacia (cPVL) contribute to neonatal mortality and morbidity. Low birth weight and gestational age are amongst the risk factors for IVH and cPVL. Objectives. To assess how many

9**very low birth weight (VLBW) infants**

had cranial ultrasound screening at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and to determine the prevalence of cranial ultrasound abnormalities. In addition we wanted to compare the characteristics and risk factors of those VLBW infants with cranial ultrasound abnormalities to those with normal cranial ultrasound findings.

5**Methods. This was a retrospective case-control study of**

infants < 1 500g

3**admitted to CMJAH between 1 January 2013** to **31**

December 2015. Cases were identified as infants with IVH or cPVL. Controls were matched 1:2 based on birth weight and gender. Results. Only 55% (856/1562) of VLBW infants had undergone cranial ultrasound screening. The prevalence of IVH was 26% (219/856). A total of 197 cases were identified and matched with 394 controls. Antenatal care was lower in cases (71% vs 79%; P=0.039). Sepsis, ventilation, metabolic

acidosis and patent ductus arteriosus were all significantly higher in cases. The use of antenatal steroids was significantly higher in the grade I-II IVH/no IVH group vs grade III-IV IVH group (44% vs 25%; P=0.017). Conclusion. The prevalence of IVH is consistent with that of developed countries. Improving antenatal care, infection control and adequate early resuscitation could decrease the incidence of IVH and cPVL. All VLBW infants should undergo cranial ultrasound screening. Background Periventricular-intraventricular haemorrhage (IVH) and white matter injury (WMI), particularly cystic periventricular leukomalacia (cPVL), are major contributors to mortality

6**and long-term morbidity in preterm infants.[** 1 **,2] The**

immature blood-brain barrier combined with fluctuation in cerebral blood flow, or platelet and coagulation disorders, form the basis for IVH pathogenesis. Risk factors for IVH include low birth weight, gestational age, prematurity, lack of antenatal steroids, asphyxia, prolonged labour, respiratory distress syndrome, recurrent tracheal suctioning, hypoxia, hypercarbia, acidosis, patent ductus arteriosus (PDA), rapid infusion of sodium bicarbonate and inter hospital transfer.[3] Preterm infants with cystic PVL without IVH appear to have a different risk pattern, although the pathogenesis does involve both hypoxic-ischaemic and haemorrhagic processes. It also appears that intrauterine inflammation and cytokine release result in oxidative stress to white matter.[4,5] IVH can be graded according to severity from grade I-IV, with the most commonly used classification being that of Papile et al.[6] The incidence of IVH in developed countries is about 20- 25% of all

1**very low birth weight (VLBW) infants. More than 50% of**

those with severe IVH develop intellectual disability or cerebral palsy.[7] Research done in Southern Africa, however, showed a higher incidence of between 20-50% of IVH in VLBW infants although the prevalence of severe IVH is similar to that of developed countries.[8-10] Most neonatal units have a screening protocol in place to detect IVH or cPVL. The American Academy of Neurology suggests cranial ultrasound screening be performed at two time points for all

6**infants with** a **gestational age less than 30 weeks:**

between week 1 and 2 of life and at 36 to 40 weeks post menstrual age.[7] More recent studies have evidence that

9**Magnetic Resonance Imaging (MRI)** done **at term equivalent age**

could be helpful at identifying white matter abnormalities that could cause neurocognitive delay as a long-term outcome.[11] Cranial ultrasound, however, is still the first tool for assessing neurological injury in preterm infants as it allows for beside investigation and sequential evaluation of evolving lesions. As neonatal and obstetric care improves we see an increase in the survival of preterm infants and with this we begin to see a newer burden of disease in the form of neurodevelopmental impairment.[2,12] In order to improve the screening and management of IVH at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) we first need to investigate the prevalence of IVH and cPVL and identify the specific risk factors important in our population. We already know that

8**low birth weight and gestational age are risk factors for IVH** and therefore **we** chose to conduct **a study**

that controlled for these possible confounders.[13] Our aim was to assess how many VLBW infants had cranial ultrasound screening and determine the prevalence of cranial ultrasound abnormalities in our VLBW population. We also wanted to compare the characteristics, risk factors and short-term outcomes of those VLBW infants with cranial ultrasound abnormalities with VLBW infants with normal cranial ultrasound. Methods The study design was a retrospective case-control study using data from the CMJAH neonatal

database. The study population included all VLBW infants admitted to the neonatal unit, including the intensive care unit, from 1 January 2013 to 31 December 2015. CMJAH is a tertiary hospital located in Johannesburg, South Africa. It acts

> 10**as a referral centre for surrounding clinics and** district **hospitals. The**

study population included both inborn and outborn infants. Infants born with a birth weight less than or equal to 1 500g qualify as

> 9**very low birth weight.** All **VLBW infants** who had **the**

following ultrasound abnormalities were identified as cases: IVH, post-haemorrhagic hydrocephalous or cPVL. Cases were matched with control infants based on birth weight category and gender on a 1:2 basis. The two most suitable controls born closest to the study patient were selected. The grading of

> 3**IVH was** done **according to the** classification **described by Papile et al.[**

6] Grade I includes bleeds

> 11**restricted to the germinal matrix, grade II** bleeds extend **into the**

ventricles filling less

> 11**than 50% of the ventricle,** grade III bleeding **causes ventricular dilatation,** and **grade IV**

includes parenchymal haemorrhage. Grade III and IV bleeds constitute severe IVH. There were four birth weight categories: less than or equal to 750g; 751 – 1 000g; 1 001 -1 250g and 1 251 – 1 500g. Infants with major congenital abnormalities of any organ system were excluded. Infants with cranial ultrasound revealing abnormalities such as absent corpus callosum, schizencephaly or findings with questionable significance such as periventricular echodensities were also excluded. Data collection Data was collected from the neonatal database REDCap (Research Electronic Data Capture) at CMJAH.[14] It is a secure web-based application that is linked to the Vermont Oxford Network (VON) (www.vtoxford.org). The VON includes about 1 000 centres around the world that submit data about high-risk newborn infants. It is a non-profit voluntary collaboration of health professionals aiming to improve neonatal care. Its members include both public and private units from North America, Brazil, Canada, Europe, the Middle East, Asia and Southern Africa, to name a few. Sixty-four units in South Africa are members of the VON. The following maternal variables were extracted from the database for each infant: antenatal care, antenatal steroids, magnesium sulphate, chorioamnionitis, HIV, attempted termination of pregnancy, hypertension, diabetes and mode of delivery. Newborn variables were: place of birth, gestational age, birth weight, head circumference, gender, multiple gestation, Apgar at 5 minutes, birth resuscitation, temperature on admission and metabolic acidosis. Birth resuscitation included oxygen, bag mask ventilation, intubation, cardiopulmonary resuscitation and/or intravenous adrenaline. Ultrasound findings were also recorded, particularly grade of IVH or presence of cPVL. The neonatal course was documented including respiratory diagnosis, respiratory support, days on continuous positive airways pressure (CPAP), days mechanically ventilated, surfactant therapy, supplementary oxygen on day 28, indomethacin or ibuprofen exposure and bacterial sepsis (early or late). Early sepsis constituted a

> 13**positive blood culture within 72 hours** from **birth and late sepsis** was a **positive blood culture > 72 hours after birth.**

Other neonatal diagnoses noted were pneumothorax, patent ductus arteriosus (PDA), necrotizing

enterocolitis (NEC), neonatal jaundice, blood transfusion, HIV testing and major birth defects. Short term outcome namely survival to discharge was recorded. Well infants transferred to other hospitals were considered survivors. Statistical methods

2**Statistical analysis was done using SPSS** Statistics (IBM) **version** 23. **Data** was **described using** standard **statistical methods. Continuous data with a normal distribution** was **described using mean and standard deviation,** while **skewed data** was **described using median and range. Categorical** variables **were described using frequencies and percentages.**

1**Univariate analysis was performed to** describe **differences between the** case **and control groups using the Pearson**

5**chi-squared or Fisher's exact test for categorical variables.**

Sub-analysis also included comparison between those with mild/no IVH to severe IVH and cPVL respectively. Continuous variables were compared using independent t-tests or non-parametric tests (Mann Whitney) as appropriate, depending on data distribution.

5**A p-value ≤ 0.05 was considered significant.** Basic demographic data **of the**

group who had not undergone cranial ultrasound was compared to the final study sample that had undergone ultrasound to see if the sample selected was random. The variables on univariate analysis with a p- value < 0.1 were analysed further in a stepwise logistic regression model to determine risk factors for IVH and cPVL. Ethics

3**The Human Research Ethics Committee at the University of the Witwatersrand, Johannesburg,** approved the study **(Clearance certificate** No. M151195). **Results There were** 1562 **VLBW infants**

born before or on 31 December 2015 at CMJAH (accessed 01 February 2016). Cranial ultrasounds were performed on 856 (55%) infants. The prevalence of cranial ultrasound abnormalities at CMJAH with a comparison to the VON is shown in table 1. Of the 856 patients with cranial ultrasounds, 13 were excluded from the study due to major birth defects. The remaining infants who underwent cranial ultrasound were then divided into normal (580) and abnormal (263) cranial ultrasound groups. Forty infants in the "abnormal" group (40/263, 15%) were excluded due to sonar findings that did not meet inclusion criteria. A further 26 infants with abnormal cranial ultrasound had no matching control with the correct weight category or gender and were thus excluded. There were 186 (186/580, 32%) in the "normal" group who could not be matched with an "abnormal" infant. There were thus 197 cases and 394 controls selected from the infants who had undergone cranial ultrasound (see Figure 1). Table 1. Prevalence of ultrasound abnormalities in VLBW infants at CMJAH n (%) Cranial ultrasounds done Normal cranial ultrasound

6**Grade I Grade II Grade III Grade IV**

Cystic PVL CMJAH 856 (54,8%) 593 (69,3%) 66 (7,7%) 92 (10,7%) 34 (4%) 27 (3,2%) 8 (1%) VON 91,1% 74,7% 10,5% 5,8% 3,5% 4,6% 2,8% Basic demographic data showed that the 47% (729/1556) of infants admitted were males, median birth weight was 1150g and mean gestational age was 29 weeks. The mortality of the overall group was 27% (415/1562). There were less males in the group who had not undergone ultrasound (417/702; 45%) compared to the case/control group (303/591; 51%; P=0.029). The median weight was higher in the group with no ultrasound (1180g vs 1090g in the case/control group;

P=0.05). The mean gestational age of 29 weeks was the same for both groups. Mortality in the group who had not undergone ultrasound was higher (279/706; 39% vs 99/591; 17%). This result had a significant p-value of 0.026. This higher mortality could be accounted for by the large amount of infants who were ≤750g in the group who had not undergone ultrasound (92/706; 13% vs 18/591; 3%). When comparing cases and controls we found that the gender distribution was the same with males constituting 49% for both groups. The mean birth weight for cases was 1097g and 1065g for controls. The mean gestational age was 29 weeks for both groups. The above parameters had no statistical significance, which confirms that cases and controls were matched. The univariate comparison between case and control groups is shown in Table 2. A higher proportion of cases were outborn. Sepsis, metabolic acidosis, ventilation and PDA were all significantly higher in cases. Antenatal care and Apgar at 5 minutes were lower in cases. However, there was no significant difference between the two groups when it came to antenatal steroids. The logistic regression analysis included location of birth, antenatal care, maternal hypertension, maternal HIV, mode of delivery, Apgar at 5 minutes, initial resuscitation with oxygen, early and late bacterial sepsis, PDA and ventilation.

1**The results are shown in table** 3. **The analysis** showed **that** antenatal care **(odds ratio [OR]:** 0.59; **95% confidence interval [CI]:**

0.37–0.95) and Apgar greater than 7 at 5 minutes (OR: 0.53; 95% CI: 0.34–0.84) were associated with a lower risk of abnormal cranial ultrasound. Ventilation carried a higher risk of cranial ultrasound abnormality (OR: 2.44; 95% CI: 1.62–3.69) and early bacterial sepsis followed this trend (OR: 3.32; 95% CI: 1.3–8.34). The rest of the variables we looked at were not significantly different between the groups. Table 2.

10**Overall characteristics of cases and controls Characteristic** Controls **(N=** 394) Outborn, **n**

(%) 60/392 (15) Mortality, n (%) 53/393 (14) Maternal factors Antenatal care, n (%) 307/390 (79) Antenatal steroids, n (%) 174/386 (45) Maternal HIV, n (%) 111/392 (28) Hypertension, n (%) 105/386 (27) Mode of delivery, n (%) Vaginal 139/385 (36) Caesarean 246/385 (64) Neonatal Factors Apgar at 5 min n (%) Less than 7 65/360 (18) 7 or greater 295/360 (82) Resuscitation at birth with oxygen, n (%) 324/394 (82) Cases (N=197) 45/196 (23) 46/197 (23) 137/194 (71) 73/191 (38) 72/197 (37) 37/197 (19) 83/185 (45) 102/185 (55) 52/173 (30) 121/173 (70) 148/197 (75) Early bacterial sepsis, n (%) 10/392 (3) 13/197 (7) Late bacterial sepsis, n (%) 156/394 (40) 99/197 (50) Metabolic acidosis, n (%) 18/394 (5) 22/197 (11) Mechanical ventilation, n (%) 102/380 (27) 95/197 (48) PDA, n (%) 57/393 (15) 45/192 (23) Maximum Bilirubin level, mean (± SD) 167 (± 44) 179 (± 55) P-value 0.03 0.004 0.039 0.14 0.059 0.041 0.054 0.002 0.037 0.023 0.02 0.005 <0.001 0.015 0.036 *Valid cases reported for each variable (i.e. missing information was excluded) Table 3. Parameters influencing the development of IVH, Severe IVH and cystic PVL,

1**identified by logistic regression analysis Parameter OR 95% CI**

P-value All cases Antenatal care 0.59 0.37 - 0.95 0.03 Apgar ≥ 7 at 5 minutes 0.53 0.34 - 0.84 0.006 Early bacterial sepsis 3.32 1.32 - 8.34 0.011 Mechanical ventilation 2.44 1.62 - 3.69 <0.001 Severe IVH Outborn 3.0 1.22 - 7.41 0.017 Apgar ≥ 7 at 5 minutes 0.21 0.10 - 0.43 <0.001 Mechanical ventilation 3.64 1.73 - 7.62 0.001 Cystic PVL Sex (male) 0.11 0.01 - 1.22 0.072 Chorioamnionitis 45.73 6.27 - 333.68 <0.001 Mechanical ventilation 15.92 1.54 - 164.36 0.02 *Valid cases reported for each variable (i.e. missing information was excluded) Sub-analyses We also looked further at severe IVH within the selected cases, compared with mild/no IVH from within the control group. Significant results are in Table 4. The use of antenatal steroids in the mild/no IVH group appears to be higher (232/527; 44% vs 11/44; 25%: P=0.017). Logistic regression analysis revealed that both outborn and ventilated VLBW infants had a higher

7**risk of severe IVH. An** Apgar score **of**

7 or greater had indicated

7a lower risk of severe IVH.

The results are shown in Table 3. The sample of infants with cystic PVL was compared to those with mild/no IVH and results are detailed in table 5. The significant factors associated with cystic PVL on univariate analysis were sex (female), chorioamnionitis, blood transfusion, late bacterial sepsis as well as ventilation. Multivariate analysis (table 3) revealed that chorioamnionitis (OR: 45.73; 95% CI: 6.27–333.68) and ventilation (OR: 15.92; 95% CI: 1.54–164.36) hold a high risk of cystic PVL. Table 4. Severe IVH compared to mild IVH/no IVH Mild IVH/No Characteristic abnormality (N=536) Outborn, n (%) 81/534 (15) Mortality, n (%) 78/535 (15) Maternal factors Antenatal care, n (%) 410/531 (77) Antenatal steroids, n (%) 232/527 (44) Neonatal factors Apgar at 5 min, n (%) Less than 7 7 or greater Early bacterial sepsis, n (%) Oxygen on day 28, n (%) Metabolic acidosis, n (%) Mechanical ventilation, n (%) Severe IVH P-value (N=47) 17/47 (36) 17/47 (36) 0.001 <0.001 28/46 (61) 0.019 11/44 (25) 0.017 <0.001 91/485 (19) 24/41 (59) 394/485 (81) 17/41 (41) 18/535 (3) 5/47 (11) 0.031 205/517 (40) 23/41 (56) 0.047 31/536 (6) 7/47 (15) 0.026 161/519 (31) 29/46 (63) <0.001 *Valid cases reported for each variable (i.e. missing information was excluded) Table 5. Cystic PVL compared to mild IVH/no IVH Characteristic Sex (male), n (%) Mortality, n (%) Chorioamnionitis, n (%) Blood transfusion, n (%) Late bacterial sepsis, n (%) Mechanical ventilation, n (%) Mild IVH/No abnormality (N=536) 275/536 (51) 78/535 (15) 18/525 (3) 308/532 (58) 224/536 (42) 161/518 (31) Severe IVH (N=8) 1/8 (13) 4/8 (50) 3/6 (50) 8/8 (100) 7/8 (88) 7/8 (88) P-value 0.035 0.001 0.001 0.024 0.012 0.002 *Valid cases reported for each variable (i.e. missing information was excluded)

8Discussion The main objectives of this study were to look at the

prevalence of cranial ultrasound abnormalities and associated risk factors. According to the screening protocol at CMJAH every VLBW should have an ultrasound within the first 7 days of life, at 10-14 days of life and one before discharge.[15] Only 55% of VLBW infants admitted in the study period had cranial ultrasounds, as compared to the VON where more than 90% of VLBW infants had cranial sonars. Reasons for the low coverage rate in our unit include staff shortages at times but more importantly the lack of appropriate equipment to perform ultrasound. The unit only has one sonar machine that is often not functional. It was shown that patients who did not undergo cranial ultrasound appeared to have a higher mortality rate than those who had undergone an ultrasound. This is partly explained by the fact that 99/706 (13%) of infants in that group were ≤ 750g. These infants already make up a high-risk group related to the extreme prematurity and are likely to have demised before an ultrasound could be performed. Well VLBW infants admitted with higher birth weights are often sent to the kangaroo mother care (KMC) ward and discharged quickly without undergoing cranial ultrasound screening. The prevalence of IVH (26%) appears to be consistent with that of studies done in developed countries and is similar to that reported in the VON over the same time period.[7] With improvement of perinatal care the prevalence appears to have decreased compared to a study done at our sister unit Baragwanath Hospital in Soweto 20 years ago, which showed a prevalence of 52% in VLBW infants.[8] The prevalence of severe IVH in this study (7%) is also less than reported in the VON and studies from both developed and developing countries.[7-9] This study confirms what is already known, that infants with IVH have higher mortality and that lack of antenatal care, birth asphyxia and sepsis appear to be associated with development of IVH. Mechanical ventilation and PDA also had an increased association with IVH and this can be explained by fluctuations in cerebral blood flow.[3] Inborn patients tended to have less IVH than those outborn and there are many factors that could explain the higher risk including delay in transfer, inadequate monitoring or lack of appropriate management at referral centres. Contrary to other studies, which show a decrease in IVH with antenatal steroids, our study did not show a significant difference between the use of antenatal steroids in the case and control groups.[3] This may be due to the fact that the administration of antenatal steroids in our setting is lower than other settings. Only 28% (431/1562) of mothers of VLBW infants had received steroids as compared to 83.5% coverage in the VON during the same period. The reason is possibly due to late presentation of unbooked mothers.[16] However, the sub-analysis of the group with severe IVH did show an association with antenatal steroids. Maternal hypertension also appeared to be

7associated with a lower incidence of overall IVH and this is consistent with

other studies.[13] In terms of the multivariate logistic regression analysis for all IVH cases, the major protective factors were antenatal care and Apgar ≥ 7 at 5 minutes (adequate resuscitation). Sepsis and

mechanical ventilation showed about a 3-fold increase in IVH and both of those factors can be modified by preventative measures. Severe IVH had similar association on multivariate analysis to overall IVH, but infants that were outborn were shown to have a 3-fold risk of severe IVH and this could be prevented by transport of mothers in premature labour to centres with appropriate neonatal services before delivery. In this study the prevalence of cystic PVL was only 1% although mortality was highest in this group which is consistent with previous studies.[2] As explained earlier MRI is a better tool to assess WMI, but in our setting this is not feasible due to lack of adequate MRI facilities to service the neonatal unit. Studies seeking to describe a difference between cystic PVL and IVH have shown that the two are not mutually exclusive and there is a possible causal relationship between the two even though cystic PVL can be seen as a single pathology in some cases.[4,5] In this study the sub-analysis showed that the female gender, chorioamnionitis and blood transfusion had significant association with cystic PVL as well as sepsis and mechanical ventilation, which were both risk factors for IVH as well. However, on multivariate logistic regression analysis the gender association was shown to have an insignificant 95% CI and only chorioamnionitis and mechanical ventilation appeared significant, although confidence intervals were wide owing to the small sample. Limitations The retrospective study design was a limitation. The disadvantages include information bias and difficulty in establishing the temporal relationship between certain variables. Records that were incomplete or missing affect the dataset. Another limitation is the lack of resources, including both staff and equipment, which resulted in deviation from the ultrasound screening protocol and resulted in 45% of VLBW infants not being screened. WMI may be largely underestimated by cranial ultrasound alone. In our setting the access to MRI is inadequate. Conclusion This retrospective matched case-control study showed that the prevalence of IVH is consistent with that of developed countries and it is encouraging to note that severe IVH is lower in our unit. It confirmed the risk factors for IVH and cystic PVL at CMJAH are in keeping with that found globally. The increased mortality and morbidity in infants with IVH would suggest that we try to modify the risk factors found to be significant in our population. Access and awareness of early antenatal care is an important factor in preventing poor perinatal outcome. Neonatal resuscitation training in clinics and hospitals should be given priority as well as correct protocols for transfer of infants as well as possible early transfer of mothers in preterm labour to appropriate centres. Infection control and methods to decrease the need for mechanical ventilation are important interventions that could decrease the incidence of IVH. In terms of ultrasound screening early detection of lesions gives infants a chance of early intervention services. Therefore efforts should be made to ensure that all VLBW infants undergo ultrasound screening. Furthermore, early identification of patients with poor prognostic factors could assist with decision-making regarding the maximum level of care offered and allocation of resources in an equitable manner. References: 1. Brouwer AJ, Groenendaal F, Benders MJNL, de Vries LS. Early and late complications of germinal matrix-intraventricular haemorrhage in the preterm infant: what is new? 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