PERIVENTRICULAR LEUCOMALACIA/ INTRAVETRICULAR HAEMORRHAGE AND ASSOCIATED PERINATAL FACTORS AMONG VERY LOW BIRTH WEIGHT INFANTS AT MUHIMBILI NATIONAL HOSPITAL (MNH)

BY

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DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE IN PAEDIATRICS AND CHILD HEALTH OF THE UNIVERSITY OF DAR ES SALAAM

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CERTIFICATION

THE UNDRESIGNED CERTIFY THAT THEY HAVE READ AND HEREBY RECOMMEND FOR ACCEPTANCE BY THE UNIVERSITY OF DAR ES SALAAM A DISSERTATION ENTITLED: PERIVENTRICULAR LEUCOMALACIA/ INTRAVENTRICULAR HAEMORRHAGE AND ASSOCIATED PERINATAL FACTORS AMONG VLBW INFANTS AT MNH, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE IN PAEDIATRICS AND CHILD HEALTH

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I, Peter M Swai, declare that this dissertation is my own original work and that it has not been presented to any other University for a similar or any other degree award.

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ABSTRACT

Introduction and review of literature

Periventricular leucomalacia and intraventricular haemorrhage are two most important antecedents of neurodevelopmental outcome in very low birth weight infants

Study objective

To determine the incidence of PVL/IVH and it's associated perinatal factors among very low birth weight (VLBW) infants admitted at neonatal unit Muhimbili National Hospital.

Material and methods

Prospective study with a nested case-control study was conducted at the neonatal unit from May to November 2000. A total of 4539 neonates were admitted to the neonatal unit during the study period and among these 443 (9.8%) were VLBW. Three hundred seventy two VLBW neonates were recruited to the study on admission to the neonatal unit. The neonates were followed up to the postnatal age of 4 weeks or death depending on which came first. All 372 neonates had initial cranial-ultrasound examination within 72 hours of life. Cranial-ultrasound was done on179 and151 neonates at the postnatal age of 2 weeks and 4 weeks respectively. At the end of the follow up study some neonates had developed PVL and or IVH. Records of all 372 neonates were reviewed to determine the presence or absence of the various perinatal factors.These

data was analysed as case-control study with case and control as shown below:-

Case: Any VLBW who had been recruited in the follow up study and had Diagnosis of either PVL or IVH or both by cranial ultrasound.

Control: Any VLBW who had been recruited in the follow up study without a Diagnosis of either PVL or IVH by cranial ultrasound

Results

The incidence of VLBW was 9.8% and two hundred fifty seven (58%) out the 443 VLBW neonates died before the postnatal age of 4 weeks. The overall incidence of PVL was121/372 (32.5%) and that of IVH was 230/372 (61.8%). Most of the PVL and IVH occurred during the first 3 days of life. All neonates with grade IV IVH died before the postnatal age of 4 weeks. Forty-seven neonates (12.6%) developed posthaemorrhagic hydrocephalus. Maternal haemoglobin and neonatal haemoglobin showed significant `association with PVL and IVH respectively.

Conclusion and Recommendations

There is high incidence of VLBW, IVH and PVL. IVH grade IV carries high mortality. Routine cranial-ultrasound on all VLBW neonates along with clinical follow up for long-term neurodevelopmental outcome is recommended. Residents in paediatrics should be thought how to perform cranial-ultrasound examination during their postgraduate training.

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ABBREVIATIONS

ABD-Assisted Breech Delivery

BA-Birth Asphyxia

BP-Blood Pressure

cm-centimetre

CT scan-Computerised-Tomography scan

dl-decilitre

ELBW-Extreme Low Birth Weight

gm-gram

HIE-Hypoxic Ischaemic Encephalopathy

IPPV-Intermitent Positive Pressure Ventilation

IVH-Intraventricular Haemorrhage

LBW-Low Birth Weight

LCVE-Lower Cavity Vacuum Extraction

LSCS-Lower Segment Cesarean Section

MNH-Muhimbili National Hospital

MRI-Magnetic Resonance Imaging

OFC-Occipito-Frontal Circumference

PROM-Premature Rupture of Membranes

PVL-Periventricular Leucomalacia

RDS-Respiratory Distress Syndrome

VLBW-Very Low Birth Weight

WORKING DEFINITIONS:

1. Antepartum haemorrhage.-bleeding from the genital tract after the twenty- eight week of gestation and before onset of labour.
2. EPH gestosis/Pre-Eclampsia/Pregnancy induced hypertension (Oedema, proteinuria and hypertension during pregnancy).
   Hypertension: diastolic Bp> 90mm Hg or systolic BP>140mmHg or both. *Diagnostic criteria:.*-Hypertension plus presence of oedema or proteinuria or both
3. Eclampsia.-A state of coma associated with convulsions and usually occurs in late pregnancy commonly preceded by pre-eclampsia
4. Premature rupture of membranes (PROM).-Rupture of membranes for more than 24 hours prior to delivery
5. Hypothermia.-Axillary temperature <35^{0}C
6. Respiratory Distress Syndrome (RDS). Diagnostic criteria (clinical), evidence of prematurity and appearance of any two of the following beginning within the first three hours of life and lasting for at least 24 hours or until death
   - ❖ Respiratory Rate of 60 or more in one minute
   - ❖ Expiratory grunting
   - ❖ Sternal or intercostal recession and the need for supplemental oxygen

8. Oxygen therapy.-If at any time during admission the neonate is given oxygen

1.0.1 INTRODUCTION AND LITERATURE REVIEW:

1.1.1 Introduction

Very low birth weight refers to infants born with a weight of less than 1500 gm (1) while Extreme Low Birth weight are infants born weighing less than 1000 gm (1). Premature infant is any live-born infant delivered before 37 completed weeks of gestation (1,2).

Premature birth in itself may prejudice later development. In general the greater the immaturity and the lower the birth weight the greater the likehood of intellectual and neurologic deficit. The incidence of neurologic and developmental handicap in VLBW infants ranges from 10-20% including cerebral palsy (3-6%), moderate to severe hearing and visual defects (1-4%) and learning difficulties (20%) (1).

The neurologic and developmental handicap is related to two major neurological insults, which are:

Periventricular leucomalacia (PVL)

Intraventricular haemorrhage (IVH)

1.1.2 Periventricular Leucomalacia (PVL) refers to necrotic areas in the periventricular white matter especially in regions just adjacent to the outer angles of the lateral ventricles. These involve particularly the white matter adjacent to the frontal horn and body and the occipital and temporal horns. It is due to ischaemia affecting a watershed region of the brain between two arterial sources, this watershed disappears with

advancing maturity due to effective anastomosis. Clinically PVL correlates strikingly with the spastic diplegia type of Cerebral palsy, which is characteristic motor deficit of the preterm infant (3). PVL is usually evident by 17-21 days (4).

Four stages of PVL have been identified by ultrasonography as shown in table 1 below

Table 1 Stages of PVL

Stage	Features
Stage I	Congestion (increased echogenicity)
Stage II	Relative return to normal
Stage III	Development of cysts
Stage IV	Resolution of cyst with presence of ventricular enlargement

Characteristic clinical findings associated with PVL include mental retardation and severe motor and sensory deficit which generally become apparent months after the child has left the nursery. Spastic diplegia or quadriplegia, visual and auditory deficit and convulsive disorders may develop later, but during the neonatal period there are no specific neurological abnormalities which are pathognomonic of PVL (5,6).

Major neurodevelopmental handicaps have been shown to be strongly associated with the presence of PVL. A clear relationship has been established between the type and severity of the dysfunction and the site and extent of the cerebral lesion. Parietal involvement leads to motor dysfunction, while occipital lesions lead to visual impairment (7).

The prognosis for survival correlates reasonably well with the staging system above (Table 1) (3).

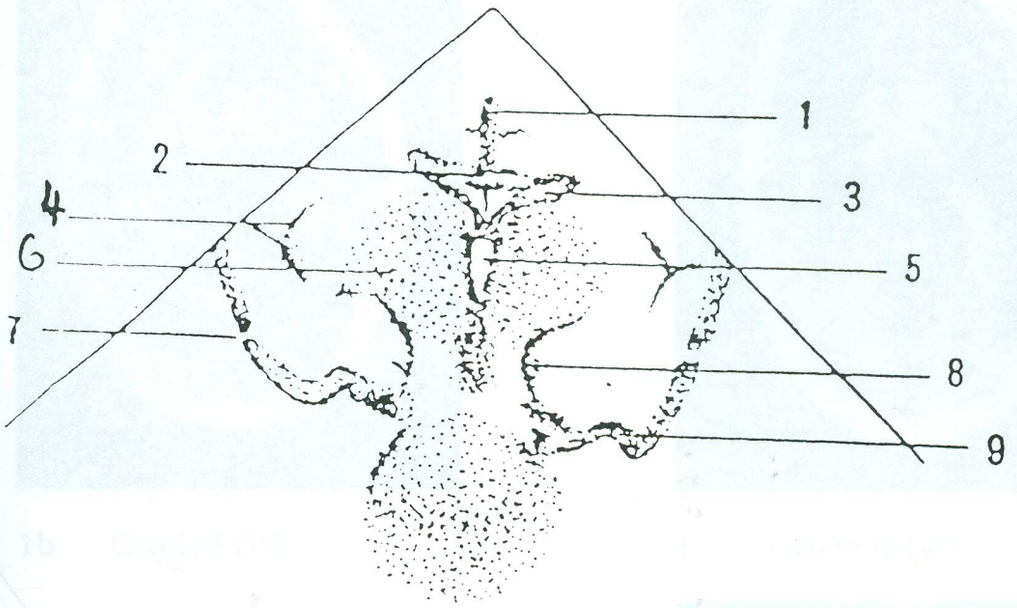
1.1.3 Intraventricular haemorrhage (IVH) is a condition often associated with prematurity and is related to the rupture of capillaries within the germinal matrix (2-4,8). IVH most frequently occurs on the second or third day after birth (3,9).

The severity of IVH can be classified into four grades (3,10,11), see table 2 and figure 1 below.

Table 2 Classification of IVH

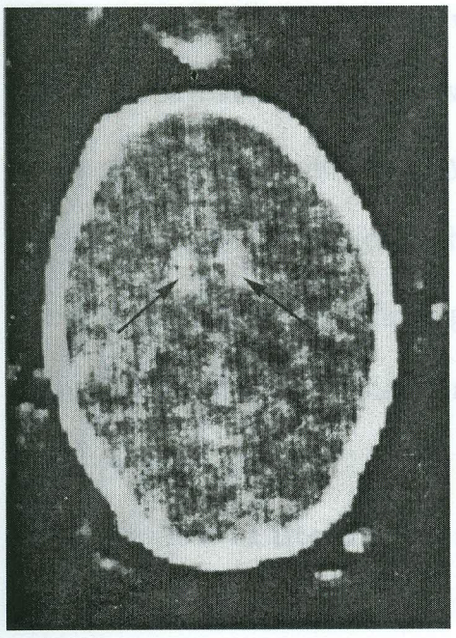
Grade	Features
Grade I	subependymal haemorrhage
Grade II	IVH without ventricular dilatation
Grade III	IVH with ventricular dilatation
Grade IV	IVH with parenchymal haemorrhage.

Figure 1 Classification of IVH

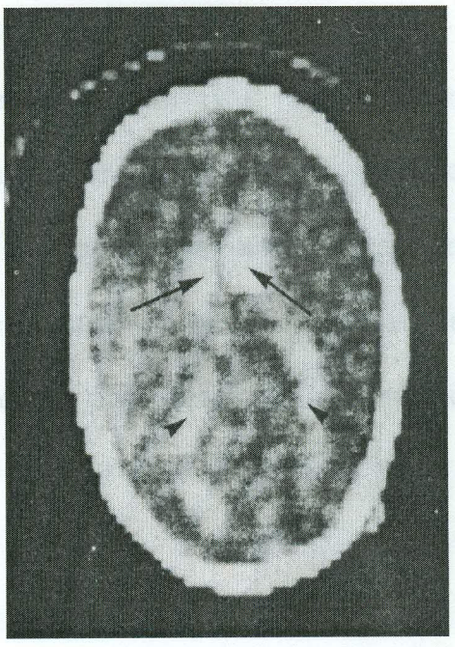


1a Coronal section through the foramen magnum

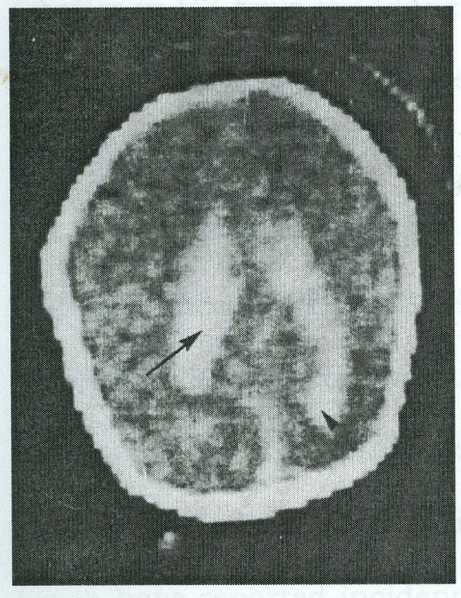
1.Falx cerebri-interhemispheric fissure
2.Corpus callosum
3.Lateral ventricle (body)
4.Sylvian fissure
5.Third ventricle
6.Thalamus
7.squamoparietal suture
8.Hippocampus gyrus
9.Pars-petrosa



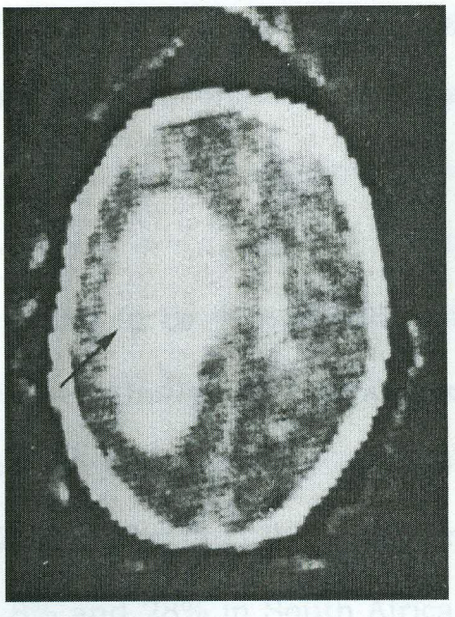
1b Grade I IVH



1c Grade II IVH



1d Grade III IVH



1e Grade IV IVH

Figures 1b to 1e shows section of the brain on CT scan indicating various grade of IVH

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Clinical deterioration occurs when the blood enters the ventricles (3) Clinical feature associated with the acute phase of IVH ranges from rapid deterioration (coma, hypoventilation, decerebrate posturing, fixed pupils bulging fontanelle, hypotension, acidosis and acute drop in haematocrit) to a more gradual deterioration with more subtle neurological changes to absence of any specific physiologic or neurologic signs (4).

1.2.0 Review of literature

1.2.1 Incidence of PVL

The incidence of PVL has been found to be 34% in VLBW in USA (6). Studies in UK have found incidence of 13.5-26% (8,12) .The incidence of PVL has been reported to be 26.4% among VLBW neonates in Nigeria (13).

1.2.2 Incidence of IVH

The incidence of IVH in VLBW has been found to be 43% and36% in USA and UK respectively (11,14). Researchers in India and China have estimated the magnitude of 26.3% and 36% respectively (15,16). Mohamed et-al reported an incidence 0f 20% in Oman (17). Studies in Africa have reported incidence of 53%, 42.8% and 28% in South Africa, Cameroon and Nigeria respectively (13,18,19).

1.2.3 Perinatal factors associated with PVL/IVH

The risk factors for IVH in newborn are well documented, and although a large number of variables have been reported to predispose to haemorrhage many studies have agreed on a relatively few commonly associated conditions, these include respiratory distress syndrome, pneumothorax, acidosis, hypercapnia, and coagulation disorders (8). There are considerably less data available concerning the risk factors predicting the onset of PVL (8). A study in Oman found that Apgar score at 1 and 5 minutes, mechanical ventilation (IPPV), blood transfusion, administration of boluses of sodium bicarbonate for correction of metabolic acidosis, the degree of acidosis, the degree and duration of hypercapnia were significantly associated with IVH (17). Sandler and colleagues reported from South Africa a significant correlation of IVH with lower 5-minute Apgar score, the need of active resuscitation at birth, the occurrence and severity of hyaline membrane disease, the requirement for mechanical ventilation in the first 48 hours of life and the development of pneumothorax (18). Researchers in Australia found severe bruising at birth, low birth weight, short gestational, ratio of arterial oxygen pressure (Pao_2), fractional inspired oxygen (Fio_2), haematocrit on admission, RDS, assisted-ventilation, pneumothorax, administration of tubocurarine, hypercapnea, hypoxaemia and

hypotension were significant antecedents of IVH in infants weighing 1250 gm or less at birth (20).

A study in UK found that perinatal hypoxia, acidosis, hypercapnia and hypoxia after birth were significantly associated with IVH and hypoxia at birth and maternal antepartum haemorrage were significantly associated with PVL (21).

Calvert et.al reported from Canada that antepartum haemorrhage and hypocarbia during the first 72 hours of life were significantly associated with PVL (22). Severe maternal bleeding in late pregnancy and hypocarbia could significantly reduce cerebral perfusion and cause area of ischaemia and infarction resulting in PVL (22).

1.2.4 Diagnosis of PVL/IVH

Before 1956 the diagnosis of intracranial lesions was solely by autopsy but from then on non-invasive procedures such us ultrasound, CT scan and MRI have become increasingly in use (3,11, 23-25).

Ultrasound is a safe and non-invasive method of diagnosing intraventricular haemorrhage and PVL with high degree of accuracy of up to 90% (25,26). Routine screening may be delayed until the second week without compromising patient care (9, 27). A single scan performed when a preterm baby is discharged from the special baby care unit might prove to be the most cost-effective use of ultrasound brain imaging (28).

1.2.5 The need for evaluating VLBW infants

One of the problems of neonatal neurology is the lack of clinical signs associated with the development of cerebral lesions in the newborn infants. This has allowed gross intracranial lesions to go undiagnosed in the neonatal period and may be responsible for much persisting confusion over the causes of cerebral palsy (29).

It has been proposed that evaluation of the outcome in VLBW and ELBW children should be given priority in pediatric research (30).

Motor development is an important area to monitor in preterm infants since one third of all cases of cerebral palsy occur in children born prematurely (31). Accurate prediction of outcome for prematurely born children is important since early identification enables intervention while the child is still young (32). It has been suggested that measures taken to increase the survival rate of infants of very low birth weight would result in an increasing number of handicapped children entering the community, where they would become a burden on their families and upon society (22,33).

It has been found that prematurity is one of the most significant contributory factor in the development of cerebral palsy (34,35).

The risk for infants weighing less than 1500 grams at birth is about 9 to 22 times that of normal birth weight (34, 35).

The incidence of low birth weight (LBW) in Tanzania is 16% and nearly 40% o f these are less than 1500g (36).

In LBW infants who survive the critical neonatal period, post neonatal mortality is nearly 20% (36). In a Dar es salaam study, low birth weight was found to be one of the leading causes of cerebral palsy (37).

The incidence of neonatal bleeding disorders has been estimated to be 10.7% but intraventricular haemorrhage was not included in this study. Low birth weight was one of the factors which were significantly associated with bleeding. Coagulation indices and platelet count were not significantly associated with bleeding (38).

There is therefore a need to see the outcome of VLBW infants admitted in the neonatal unit and perform this simple non-invasive examination (ultrasound) in order to identify affected infants early

2.0 Rationale of the study:

It is envisaged that this study will provide basic data of the magnitude and associated risk factors at our setting. Knowing the predictors will help in intervention of the factors for preventing development of PVL/IVH

There is a need to recognise predictors of PVL/IVH, which can in turn lead to neurodevelopmental handicap like cerebral palsy. This is of importance in counseling the parents/care-takers, close follow up and

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early institution of rehabilitative measures when neurological disability is identified.

3.0 OBJECTIVES:

3.1 Broad Objective.

To determine the incidence of PVL/IVH and it's associated perinatal factors among VLBW infants admitted at neonatal unit Muhimbili National Hospital.

3.2 Specific Objectives:

1. To determine the incidence of PVL among very low birth weight infant admitted at neonatal unit Muhimbili National Hospital.
2. To determine the incidence of IVH among very low birth weight infant admitted at neonatal unit Muhimbili National Hospital.
3. To determine perinatal factors associated with PVL among VLBW infants admitted at neonatal unit Muhimbili National Hospital.
4. To determine perinatal factors associated with IVH among VLBW infants admitted at neonatal unit Muhimbili National Hosptal.

4.0 MATERIAL AND METHODS:

4.1 Study Design:

Prospective study with a nested case-control study.

4.2 Study site: Neonatal ward and High-Risk postnatal clinic at Muhimbili National (MNH). MNH is the referral Hospital located in the city of Dar es salaam and it is the teaching hospital for the Muhimbili

University College of Health Sciences (MUCHS). Most patients treated at MNH are referred from peripheral hospitals within the city both government and private owned. Few patients are referred from other regions. The hospital has a 70 bed neonatal unit which admits neonates from within the hospital and from outside the hospital.

Criteria for admission to the neonatal unit

- All neonates with birth weight of less than 2500 gm
- Neonates with APGAR score of less than 7at 5 minutes
- Neonates born by Cesarean Section or Vacuum extraction
- Sick neonates
- Neonates born with congenital anomalies like meningomyelocele, cleft lip/palate etc.
- Abandoned newborns and orphans

High Risk Postnatal clinic provides follow up services for neonates who were admitted in the neonatal ward for various reasons and few neonates from outside the hospital who do not have indications for admission to the neonatal unit.

4.3 Inclusion criteria:

Birth weight < 1500 gm.

4.4 Exclusion criteria:

Presence of major congenital malformations particularly those affecting the central nervous system like meningomyelocele, encephalocele.

Neonates who died before cranial-ultrasound could be performed.

4.5 Sample Size:

$$\eta = 4\pi(100-\pi) \div \varepsilon^2 \quad (39)$$

η=sample size

π= Incidence

ε = margin of error

Consider the incidence of PVL/IVH of 30% and ε of 5%

$\eta = 4 \times 30(100-30) \div 5^2 = 336$ plus 10% correction for loss to follow up giving a sample size of **370** neonates

According the 1999 statistics the total number of admissions of LBW in the neonatal ward was 2488 hence average admissions per month was 207 and 40% of LBW neonates are VLBW, giving an average of 83 VLBW per month.Survival of VLBW is about 40%, hence the number of VLBW infants who would be followed up at the High-risk postnatal clinic was estimated to be about 154

4.6 Data Collection:

4.6.1 Recruitment

All neonates who met the inclusion criteria were recruited into the study on admission to the neonatal ward.and this was done daily.

Data was collected by carrying out interviews, physical examination and reviewing various records related to the subjects

4.6.2 **Interview**

Mothers/caretakers of the neonates who met the inclusion criteria were interviewed by the investigator by using structured questionnaire (Appendix I)

4.6.3 Physical examination

Thorough physical examination was done by the investigator.

All the neonates who were included in the study had Gestational age assessment by using Dubowitz method (see appendix II) except in very sick neonates in this cases the Parkins method was used (Appendix III).

4.6.4 Anthropometric measurements

Weight

Weight was measured by seca beam balance to the nearest 10g and the infants were completely naked during the measurement.

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Occipito-frontal circumference (OFC)

OFC was measured by non-stretchable nylon measuring tape from the occiput passing just above the eyebrows to the nearest 0.1cm.

Length

Length was measured by a wooden length board, which had a fixed head plate and a movable footplate. The neonate was laid on supine position. One assistant was holding the neonate's head in contact with the head plate. The legs were straightened by the investigator and the feet were turned upward at right angles to the legs, the foot plate was brought in contact with the heels and finally the length was determined and recorded to the nearest 0.1cm

Records

Partogram and MCH card number 4 were used to retrieve some of the maternal factors like time of rupture of membranes, colour of the liquor, haeomglobin level during the third trimester and EPH gestosis and neonatal factors e.g. APGAR score at birth (see appendix I)

4.6.5 Cranial ultrasound

Cranial ultrasound was done to all VLBW infants who had been recruited to the study within 72 hours of life and was repeated at two weeks and 1month postnatal age. The ultrasound scan was performed by the investigator by using Toshiba 5MHZ probe through the anterior

fontanelle for both coronal and sagittal sections under supervision of a neonatologist who is experienced in cranial ultrasound.

4.6.6 Laboratory investigations

Full blood picture was done in neonates on admission; 1millitre of blood was taken from each neonate by venepuncture at the dorsum of the arm after thorough cleansing the site with 70% alcohol.

Other investigations were done depending on clinical presentation of the concerned neonate.

4.6.7 Management of the neonates

The neonates were managed according to the management protocol of the neonatal unit depending on the coexisting morbidity.

4.6.8 Follow up

The neonates were followed up to discharge or death. In case of death the cause was established by clinical judgment, relevant laboratory information and circumstances of death. Neonates who had survived up to the discharge were followed up to 1month postnatal age at the High Risk Postnal clinic by the author.

At the end of the follow up some neonates had developed IVH and or PVL. Records (patient's file, questionnaires from the follow up study, patogram, admission /discharge book in the neonatal ward) were reviewed to determine the presence or absence of the various perinatal

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factors. These data was analysed as case –control study with case and control as shown below

Case- Any VLBW who had been recruited in the follow up study and had Diagnosis of either PVL or IVH or both by cranial ultrasound.

Control- Any VLBW who had been recruited in the follow up study without a Diagnosis of either PVL or IVH by cranial ultrasound

Both surviving VLBW infants and those who had died were included into the analysis as long as case/control definition had been met.

Perinatal factors associated with PVL/IVH.

The following perinatal factors were included in the analysis:

Maternal factors	*Neonatal factors*
Age	Sex
Parity	Birth weight
EPH gestosis	Gestational age
Eclampsia	APGAR SCORE
Antepartum haemorrhage	convulsions
Haemoglobin in the third trimester	Hypothermia
Premature rupture of membranes	Oxygen therapy
Meconium stained liquour	Birth asphyxia
Mode of delivery	RDS
Place of delivery	Haemoglobin
	Platelet count

4.7 Ethical clearance

Ethical clearance was sought from the MUCHS High Degree, Research and Publication Committee. Informed verbal consent was obtained from the mothers/caretakers prior to the inclusion to the study.

4.8 Disposal of infants

All infants who survived up to the end of the study were handed over to the Paediatricians in the High Risk postnal clinic for usual regular follow up.

4.9 Data analysis

Data analysis was done by a computer using Epiinfo version 6 program .All data were checked for consistency and entry errors before data analysis. Students t-test was used for numerical variables except in cases where Bartlett's test for homogenicity of variance showed the variances in the sample to differ where the Kruskal-Wallis H test was applied. x^2 was applied for the categorical variables and in the cases were the expected value less than 5 Fisher exact test was applied accordingly

P value of <. 05 was considered statistically significant.

5.0 RESULTS

A total of 4539 neonates were admitted to the neonatal unit from May to November 2000. Four hundred forty three (9.8%) were VLBW. Sixty-nine neonates died before a cranial ultrasound examination could be performed, two neonates had gross Central nervous system anomalies (spina bifida and Patau syndrome) and were excluded from the study.

The study sample therefore consisted of 372 neonates. One hundred eighty one neonates (48.7 %) were born at MNH, 152 (40.9 %) were born at other health facilities in Dar es salaam and 39 (10.8 %)neonates were born at home or on the way to MNH. Characteristcs of the study sample are summarized in table 3.

One hundred fifty one (40.6 %) neonates survived up to the postnatal age of 4 weeks, 188(50.5%) died in the ward before the age of 4 weeks. One hundred fifty eight (84%) of the 188 neonates who died in the ward died before the postnatal age of 2 weeks. Thirty five neonates were not brought for follow up at the postnatal age of 2 weeks but 2 of 35 neonates were available during the follow up at 4 weeks; therefore leaving 33 (8.9%) neonates who were lost to follow up.

All 372 neonates had initial cranial ultrasound examination within 72 hours of life.

Cranial ultrasound examination was done on 179 and 151 at the postnatal age of 2 weeks and 4 weeks respectively as illustrated by tables 4 and table 5.

Table 3: Characteristics of the study sample

	Female (203)		Male (169)	
	Range	Mean ± sd	Range	Mean ± sd
Birth weight (gm)	500-1490	1170±240	600-1490	1190±210
Gestational age (weeks)	26-37	30±3	26-36	30±2
OFC (cm)	21.1-32.0	27.8±2.2	20.5-32.0	28.1±2.0
Length (cm)	29.5-46.0	37.5±3.1	28.0-48.0	38.1±3.0

5.1 INCIDENCE OF PVL

The overall incidence of PVL was 121/372(32.5%). All PVL were of stage 1 as shown in table 4 below. See appendix iv for photographic illustration of PVL

Table 4: Distribution of PVL according to initial cranial ultrasound examination, at two weeks and 4 weeks

	+Initial PVL	PVL at 2 week	PVL at 4 weeks
	Number (%)	Number (%)	Number (%)
Stage 1	75 (20.2)	*30 (16.8)	**48 (31.8)
No PVL	297 (79.8)	149 (83.2)	103 (27.7)
Total	372 (100)	179 (100)	151 (100)

* 10 PVL persisted from the initial PVL therefore new cases of PVL were 20
** 22PVL persisted from the previous PVL hence new cases of PVL were 26
+ PVL at cranial ultrasound examination within the 72 hours of life

5.2 INCIDENCE OF IVH

The overall incidence of IVH was 230/372(61.8%) Classification of the IVH according to Papile's method and postnatal age at cranial-ultrasound examination is summarized in table 5.

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Table 5: Distribution of IVH according to its grade and postnatal age at cranial examination

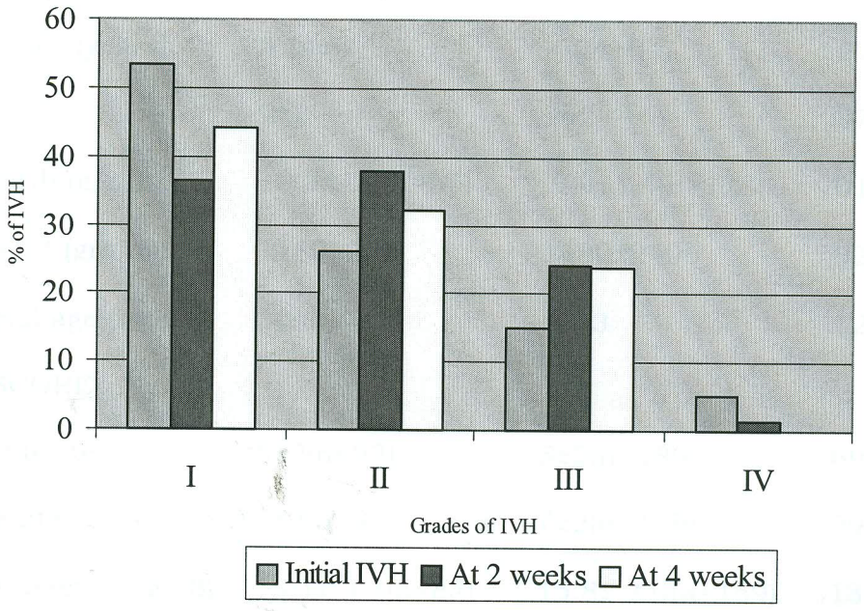
	+ Initial IVH Number (%)	IVH at two weeks* Number (%)	IVH at 4 weeks** Number (%)
Grade I	100 (26.9)	26 (14.5)	37 (24.5)
Grade II	49 (13.2)	27 (15.1)	27 (17.9)
Grade III	28 (7.5)	17 (9.5)	20 (13.2)
Grade IV	10 (2.7)	1 (.6)	0
No IVH	185 (49.7)	108 (63.3)	67 (44.4)
Total	372(100)	179 (100)	151 (100)

* 44 IVH persisted from the initial IVH therefore new cases of IVH were 27
**58 IVH persisted from the previous IVH hence new cases of IVH were 16
+IVH at cranial ultrasound examination within the 72 hours of life

Figure 2 below shows the distribution of neonates who developed IVH according to its grade and time at cranial ultrasound examination. Grade 1 and 2 constituted 79.7%, 62.6% and 76.2% at initial, two week and 4 weeks respectively. Grade IV IVH was seen in 10 (5.3%) infants at the initial cranial examination and in 1 (1.4%) infant at two weeks of age. The neonate who had grade 4 IVH at two weeks postnatal age had grade 3 IVH at the initial cranial examination. All neonates who had

grade 4 IVH at the initial cranial examination died before the postnatal age of 2 weeks and the one that progressed to grade 4 died before the postnatal age of 4 week.

Figure 2. Distribution of IVH according to grades and time at cranial ultra sound examination



5.3 Perinatal factors associated with PVL

The results of analysis of various perinatal factors in relation to PVL is summarised in table 4 and table 5. Only maternal Haemoglobin was found to have difference, which was statistically significant. Mothers of the neonates who developed PVL had mean haemoglobin of 10.3g/dl

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compare to 9.9g/dl of the mothers whom their neonates did not develop PVL.

Table 6: Association of PVL with numeric perinatal factors

Risk factors	PVL		
	Present (n=121)	Absent (n=251)	p-value
Maternal age (years)	✳24±6	✳ 24±6	.275
Parity	2±2	2±2	.375
Maternal Hb (g/dl)	10.3±1.0(n=67)	9.9±1.4(n=128)	.0106
Birth weight (grams)	1180±200	1180±240	.521
Gestational age (weeks)	30±2	30±3	.121
APGAR SCORE			
At one minute	5±2(n=93)	5±2(n=189)	.694
At 5 minutes	7±2(n=93)	7±2(n=189)	.997
Hb of the neonate (g/dl)	15.1± 3.3(n=83)	15.8± 3.0(n=159)	.13
Platelets	222±75(n=82)	210±81(n=153)	.27
Duration of oxygen (days)	3±3	2±2	.538

✳ =*Mean ± standard deviation*
Note the total number of cases was 121 and controls 251 except in some variables as indicated in the table as these variables were not done or were not available in the records

Table 7: Association of PVL with categorical perinatal factors

Risk factors	PVL		
	Present (n=121)	Absent (n=251)	p-value
EPH gestosis	4	13	.418
Eclampsia	2	8	.315
APH	0	5	.178
PROM	1	2	.694
Me conium stained liquor	1	0	.325
Mode of delivery			
SVD	103	212	
LSCS	3	11	
ABD	15	28	.638
Place of delivery			
MMC	58	122	
Other health facilities	54	98	
Home	9	31	.292
Sex			
Female	66	137	
Male	55	114	.916
Fit	3	6	.605
Hypothermia	2	8	.315
Oxygen therapy	49	109	.596
RDS	38	64	.259
Birth asphyxia	30	48	.208

Table 8: Association of IVH with numeric perinatal factors

Risk factors	IVH		
	Present (n=230)	Absent (n=142)	p-value
Maternal age (years)	✳24±6	✳25±6	.275
Parity	2±2	2±2	.307
Maternal Hb (g/dl)	10.1±1.1(n=117)	9.9±1.5(n=78)	.171
Birth weight (grams)	1190±210	1160±250	.289
Gestational age (weeks)	30±2	30±3	.841
APGAR SCORE			
At one minute	5±2(n=173)	6±2(n=109)	.084
At 5 minutes	7±2(n=173)	8±2(n=109)	.107
Hb of the neonate (g/dl)	15.1± 3.3(n=149)	16.3± 2.6(n=93)	.00811
Platelets	219±80(n=146)	205±77(n=89)	.182
Duration of oxygen (days)	2±3	2±2	.05

✳ =*Mean ± standard deviation*
Note the total number of cases was 230 and controls 142 except in some variables as indicated in the table as these variables were not done or were not available in the records

Table 9: Association of IVH with categorical perinatal factors

Risk factors	IVH		
	Present (n=230)	Absent (n=251)	p-value
EPH gestosis	9	8	.44
Eclampsia	6	4	.572
APH	3	2	.632
PROM	3	2	.235
Meconium stained liquor	1	0	.618
Mode of delivery			
SVD	193	122	
LSCS	10	4	
ABD	27	16	.739
Place of delivery			
MMC	110	70	
Other health facilities	99	53	
Home	21	19	.33
Sex			
Female	132	71	
Male	98	71	.164
Fit	5	4	.472
Hypothermia	6	4	.573
Oxygen therapy	92	66	.219
RDS	64	38	.765
Birth asphyxia	51	27	.467

5.4 Perinatal factors Associated with IVH

Table 6 and Table 7 above shows the result of the analysis of the perinatal factors in relation to IVH. Neonates who developed IVH had lower mean haemoglobin 15.5g/dl compared to the neonates who had not developed IVH (16.3g/dl) the difference was statistically significant (P=0.00811). In the remaining 20 factors either there was no difference of association between the neonates with IVH and those who had not developed IVH and even where these was a difference, it was not statistically significant.

6.0 DISCUSSION

The incidence of VLBW was 9.8%, which was higher compared to that of 1to1.2% from developed countries (1,2). The higher incidence of VLBW is probably due to low social economic status and the existence of causes/factors associated with intrauterine growth retardation and or prematuriy like maternal malnutrition, maternal anaemia, maternal infections particularly malaria and maternal age (below 16 years and above 35 years) (2).

Sixty-nine neonates died before cranial ultrasound could be done and 188 neonates died during the follow up. Therefore 257 (58%) VLBW neonates died before reaching postnatal age of 4 weeks.

VLBW caries high mortality (58%) and this contributed 32.0% of the 794 deaths, which occurred in the neonatal unit during the study period. This contributes to a high percentage of perinatal mortality as most deaths occurred during early neonatal period. Researchers in South Africa have reported mortality rate of 34% and 76% for infants with birth weight 1000 to 1499 grams and less than 1000 grams respectively at 12 to 18 months of age (40). In the current study survival rate at the postnatal age of 1 month was 42%, which is very low compared to rates from developed countries. Survival rate is between 85 to 90% for infants with birth weight between 1250 and1500 grams and 20 % for those with birth weight between 500 and 600 grams in USA (1). Survival rate is 85%, 60%, and 20% for infants with birth weight 1000 to 1250 grams 750 to 1000 grams and below 750 grams respectively in UK (2). The low survival rate in developing countries is perhaps due to lack of modern neonatal intensive care units. Most common causes of death were RDS, HIE, pneumonia, septicaemia and prematurity. Thirty-three (8.9%) of the 372 neonates were lost to follow up. These neonates could have died or migrated. The follow up of these neonates were beyond the scope of the investigator due to financial constraints. Manji et al found that 31(10.6%) of the total 291 neonatal deaths of low birth neonates had occurred at home (36).

6.1 INCIDENCE OF PVL

The incidence of PVL was 32%, which is comparable with other reports of 13.5-34% (6,8,12,13). Seventy-five out of 121 neonates (62%) had PVL within the first 72 hours of life. Absence of PVL at birth does not necessarily mean that the infant will not develop PVL. This is evidenced by the 46 neonates who had normal initial cranial-ultrasound examination but subsequently developed PVL. Twenty-five neonates who were noted to have PVL at initial cranial ultrasound examination or at two weeks postnatal age had their PVL disappeared by the postnatal age of 4 weeks, showing PVL is not necessarily permanent. The neonates who had their PVL reverting to normal could have been on stage 2 which is known to relatively return to normal (5). The absence of other stages of PVL could be due to short duration of follow up. Bowerman et al reported that periventricular cysts were noted in 3 neonates at the postnatal age 26 to 44 days in a prospective follow up of 8 preterm neonates (6). It has been found that cysts may not always be recognized even by regular scanning. This is attributed to the inability of the ultrasound to visualize cysts less than 2mm in diameter. Absence of cysts does not imply absence of permanent tissue damage as neonates with only increased echogenicity of ventricles (stage 1 PVL) during the neonatal period were eventually shown to have signs of cerebral palsy at the postnatal age of 9 months (5). It has been noted that PVL is the

second most frequent lesion of the neonatal brain after IVH (6). The same trend has been observed in this study as the incidence of IVH was higher than that of PVL.

Long term sequelae in this study is not known but other studies have shown that PVL is strongly associated with major neurodevelopmental handicaps like cerebral palsy, severe visual impairment and mental retardation (3,7).

6.2- INCIDENCE OF IVH

The incidence of IVH in this study (61.8%) is higher than most previous reports of 28 to 53 % (11,13-19). Cranial-ultrasound examination was done on every neonate during the first 72 hours of life and 187 (50.3%) of the neonates had developed IVH. Only 43(11.3%) developed IVH after the first 72 hours of life. This trend is consistent with previous report of most of IVH occurring on the second or third day of life (3,9). Grade III or IV IVH occurred in 56 neonates (15.1%), this is slightly higher than 12% that was found by Sandler et al in South Africa (18). One hundred and four (53.3%) of the neonates who died during the follow up had IVH. Forty-seven (12.6%) neonates developed posthaemorrhagic hydrocephalus and 17 (32.2%) of them died before the postnatal age of 4 weeks. Four (8.5%)of the 47 neonates with posthaemorrhagic hydrocephalus were lost to follow up and 26 (53.3%) are being followed up at the high risk postnatal clinic.

All 11 neonates who had grade IV IVH and 17 neonates who had grade III IVH died meaning that the higher the grade of IVH the higher the risk of death. In a study in Oman all 4 neonates who had IVH grade IV died and in a study in South Africa only one of the 11 neonates with grade IV IVH survived to hospital discharge (11,18). Grade III or IV IVH usually leads to decreased haematocrit and shock. Grade IV IVH wich extends to the parenchyma lead to massive brain damage which in turn aggravates cerebral hypoxia. Hypoxia leads to metabolic acidosis and if these metabolic derrangement are not corrected they will culminate into death.

Forty-five neonates who were revealed to have IVH at the initial cranial-ultrasound examination or at 2 two weeks, had their IVH regressed to normal before the postnatal age of 4 weeks. It has been shown that ventricular dilatation appears to reach maximum between 1 and 2 two weeks after the initial bleed but most return to normal over the next 1 to 2 months. (9,18). None of the neonates with ventriculomegaly required ventriculo-peritoneal shunting during the study period.

Long-term outcome in this study is not known but previous studies elsewhere have shown that IVH is associated with abnormal neurodevelopmental outcome (16,31).

6.4 PERINATAL FACTORS ASSOCIATED WITH IVH.

Many perinatal factors have previously been implicated in the causation of IVH in VLBW infants but many studies have agreed on relatively few commonly associated factors, these include RDS, pneumothorax acidosis, Hypercapnia and Coagulation disorders (8).

In this study only haemmmoglobin of the neonates had significant association with IVH (p=0.00811). Neonates who developed IVH had lower mean haemoglobin compared to neonates without IVH. This could be an outcome of IVH rather than predictor of IVH. RDS and Birth asphyxia are among the factors that have been commonly reported to have significant association with IVH (8,17,18,20)

In our study, neonates with IVH were more likely to have RDS and Birth Asphyxia but the association was not statistically significant (p=0.765 and 0.467 respectively).

Neonates with IVH had lower APGAR Score at one minute and five minutes but the difference was not statistically significant (p=0.084 and 0.107 respectively). Bassionny MR et.al found that lower APGAR Score at one minute and five minutes had significant association with IVH (17). Researchers in South Africa found lower APGAR Score at one minute to have significant association with IVH. Acidosis, hypercapnia, and mechanical ventilation could not be evaluated in our study due to lack of facilities for measuring P^{H} and blood gases. There is no

mechanical ventilator at our neonatal unit. None of the neonates had diagnosis of pneumothorax.

6.5 PERINATAL FACTORS ASSOCIATED WITH PVL.

Maternal Haemoglobin during the third trimester was the only factor that had significant association with PVL (p=0106). For unknown reasons neonates who developed PVL, their mothers were more likely to have higher haemoglobin during the third trimester. Previous studies have shown APH and Hypocarbia during the first 72 hours of life to have significant association with PVL. It has been speculated that APH and Hypocarbia could significantly reduce cerebral perfusion and thereby leading to ischaemia and infarction (8,22).

7.0 CONCLUSION

There was high incidence of VLBW and a high mortality was observed in these VLBW infants.

There was high overall incidence of IVH particularly grades I and II and majority of haemorrhages occurred on the first 3 days of life.

IVH grade IV carries high mortality. The incidence of PVL is comparable to that from other centers. Marternal haemoglobin in the third trimester and haemoglobin of the neonate showed significant association with PVL and IVH respectively.

8.0 RECOMMENDATIONS

Incidence of IVH and PVL is high in VLBW neonates at MNH. In early stages most are asymptomatic therefore routine cranial-ultrasound to all VLBW neonates at discharge from the unit is recommended. The cranial-ultrasound findings should be documented on discharge summary so that the infants can be followed at the High Risk Postnatal clinic.

The cohort under the study should be followed up for longterm neurodevelopmental outcome.

Residents in paediatrics should be taught how to perform cranial-ultrasound examination during their postgraduate training. Cranial-ultrasound machine should be available at referral and regional hospitals.

The presence of very high incidence of VLBW at the neonatal unit probably reflects the low social economic status and existence of preventable causes of VLBW. Antenatal care should be improved with emphasis on intervention of preventable causes like malaria and anaemia in pregnancy.

The high mortality among VLBW infants at the neonatal unit is likely due to lack of intensive neonatal care. Improvement of facilities like availability of mechanical ventilator and machine for measuring P^H and blood gases are highly recommended.

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