An analysis of the relationship between Myelomeningoceles, Hvydrocephalus and Chiari Malformations.

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Medicine in Neurosurgery

2021

Johannesburg

Declaration

I, Ian Noel Human, declare that this dissertation is my own work. It is being submitted for the Degree of Master of Medicine in the branch of Neurosurgery. It is being submitted at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature : .....

29 day of July 2021 in Johannesburg

Dedication

Dedicated to God.

Dedicated to my family, my beautiful wife Norma, my son Luca, my parents Lester and Geraldine and my brother Dylan.

Acknowledgements

The neurosurgical consultants Prof J Ouma and Dr C Profyris for their advice and guidance. The past and present staff from the Department of Neurosurgery and Neonatology at the Chris Hani Baragwanath Academic Hospital.

ABSTRACT

The study reports on 45 patients with myelomeningoceles that were operated at Chris Hani Baragwanath Academic Hospital (CHBAH) between 1 January 2015 and 31 December 2018. There was a total of 29 males and 16 females with most of the myelomeningoceles (MMC's) within the lumbosacral region. None of the patients operated on during this period had cervical MMC's whilst 3 had thoracic MMC's. Hydrocephalus was present in 77,8 % of patients that were operated on and 66 ,7 % were diagnosed with Chiari II malformations. 30 Patients had colpocephaly which works out to 66,7% of those patients that had MMC's. Differences between female and male patients were not identified apart from the incidence of Chiari Type II malformation. Seven patients are known to have demised.

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LIST OF ABBREVIATIONS

1.AFP - alpha-fetoprotein

2. APGAR -Appearance, Pulse, Grimace, Activity and Respiration

2.ARV'S - Antiretroviral drugs

3.CHBAH – Chris Hani Baragwanath Academic Hospital

4.Chiari II - Chiari Type II malformation

5.CSF - Cerebral Spinal Fluid

6.FOCM - folate one-carbon metabolism

7.GWAS - genomewide association studies

8.HCP - Hydrocephalus

9.HIV - Human Immunodeficiency Virus

10.HOD - Head of department

11.HREC - Human Research Ethics Committee (Medical)

12.IQ - Intelligence Quotient

13.MMC's - Myelomeningoceles

14.MOMS - Management of Myelomeningocele Study

15.5-MTHF - **5** Methyltetrahydroxyfolate

16.MTHFR - Methylene tetrahydrofolate reductase

17. NVD – Normal Vaginal Delivery

17.PACS - Picture Archiving and Communicating System

18.PCP - planar cell polarity pathway

19.UK – United Kingdom

20.USA - United States of America

21.US - United States

1. INTRODUCTION

1.1 Background

Definitions

Neural Tube Defects (NTD's) are common congenital malformations that affect the brain and spinal cord which is a result of a failure of the neural tube to close during embryogenesis(1).

NTD's may be classified as "open" or "closed" depending on whether neural tissue is exposed or not. Open NTD's are mostly Anencephaly which is at the cephalad end whilst Myelomeningoceles are found at the caudal end of the neural tube(1).

Anencephaly is defined as a congenital malformation resulting from the failure of closure of the cranial neuropore where there is abnormal vascularisation of the embryonic brain(2).

Myelomeningoceles are defined as congenital malformations resulting from the failure of fusion of one or all of the midline mesenchymal and bony elements resulting in exposure of the neural tissue. Sometimes also referred to as spinal dysraphism(3).

Closed NTD's is where the neural tube has disjoined from the ectoderm and an intact layer of skin lies between the environment and the underlying neural tissue(2). It is often associated with overlying cutaneous manifestations such as naevi, hypertrichosis, skin dimples or haemangiomas. Clinical manifestations of closed NTD's based on this definition include unfused spinous processes, intradural lipoma, filum terminale fibrolipoma, filum terminale thickening and shortening, myelocystocoele and lipomyelomeningocoele(4, 5).

Older and now seldomly used terminology for the outpouching of the spinal canal through the open spinal column, due to its failure to close, is known as spina bifida(4). Spina bifida may either be spina bifida aperta, which are open spinal defects and spina bifida occulta, which are the closed spinal defects(1). The development of open neural tube defects is a problem of primary neurulation, which is when the flat neural plate becomes cylindrical(3).

Hydrocephalus is a clinical condition that results from the progressive expansion of the cerebral ventricles due to the deficient passage of cerebral spinal fluid(CSF) from the choroid plexus, the site of CSF synthesis, to its sites of absorption into the systemic circulation but may also result from hypersecretion of CSF(6). There are two well accepted terms defining hydrocephalus namely:

Non-communicating or obstructive hydrocephalus is when the flow of CSF from the ventricles to subarachnoid space is blocked(7).

Communicating or non-obstructive hydrocephalus is when the flow is not obstructed, nonetheless CSF is incompetently reabsorbed in the subarachnoid space(7).

Chiari malformations are a group of defects associated with congenital caudal displacement of the cerebellum and brainstem and were divided into four distinct forms by Chiari according to his autopsy series(8, 9).

Types I to IV of Chiari malformations are not seen as a spectrum of the same disease process but rather completely different entities(8).

Chiari Type I - peg-like cerebellar tonsils displaced into the upper cervical canal through the foramen magnum(10).

Chiari Type II - displacement of the medulla, fourth ventricle and cerebellar vermis through the foramen magnum which is usually associated with myelomeningoceles(10).

Chiari Type III - features similar to Chiari II but with an occipital and/or high cervical encephalocele(10).

Chiari Type IV - severe cerebellar hypoplasia without the displacement of the cerebellum through the foramen magnum(10). Myelomeningoceles (MMC's) are commonly associated with hydrocephalus as well as Chiari type II malformations, although the exact relationship and percentages between these conditions are not known and vary according to different academic institutions and authors.

1.2 Epidemiology

The worldwide incidence of neural tube defects ranges from 1.0 -10.0 per 1000 births and is evenly distributed between anencephaly and myelomeningoceles(11). Northern Ireland has the highest incidence of MMC's which is almost 8.7 per 1000 live births(3). In the United States, as from 1989, the incidence was 0.6 per 1000 live births and 0.14 – 1.99 per 1000 live births in Africa(3, 12). In South Africa it is estimated to be 0.98 per 1000 births(13). The prevalence of MMC's since the 1980's have become quite difficult to determine with the availability of prenatal diagnosis and the elective termination of pregnancies(14).

1.3 Risk Factors

A few environmental risk factors implicated include, maternal deficiencies in folate as well as hyperthermia. Vitamin abnormalities which include deficiencies in Vitamin C and zinc; and either a lack or overdose of vitamin A are also known contributors(3). Included in this is a previous history of a child born with a NTD, partner with a NTD, the use of anti-epileptic and traditional medication and although not a strong correlation , diabetic mothers on insulin, Human Immunodeficiency Virus (HIV) mothers on Antiretroviral drugs (ARV's), radiation exposure, anaesthetic agents, agricultural pesticides and chemicals, lead, tobacco smoke and cleaning solvents and disinfectants(13, 15). Anti-epileptic drugs associated with MMC's are Valproic Acid and Carbamazepine. These drugs possibly interfere with folate metabolism(14).

Maternal periconceptual folate supplementation reduces the incidence of neural tube defects and therefore throughout the world, food fortification became mandatory. This started in 1998 in the United States(US) and Canada(12). In South Africa this started in 2003, resulting in a 30 - 46% reduction in neural tube defects(12). In the US, food producers were mandated to fortify flour with 140 micrograms of folic acid per 100 grams(16).

The correct dosage of folic acid prior to conceiving and within the first few months, reduces the chance of having offspring with MMC's. NTD's however follow a multifactorial inheritance pattern therefore not all women taking folic acid will be exempt from having a foetus with an open neural tube defect. It is accepted that neural tube defects aggregates within families with an estimated recurrence risk between 2% and 6%(13). In the Gauteng population, the recurrence risk is 2,28% for the subsequent child of couples who had 1 child with an MMC and 4,12% after 2 affected siblings(13).

Not one single genetic locus is responsible for familial aggregation of MMC's, but rather, a complex genetic trait determined by many genes. This is then attributed to how these genes interact with the environment(16). Another factor in the Gauteng and North West population, particularly Klerksdorp where there are Uranium mines. Even inoperable mines can cause adverse effects due to wind erosion from poorly covered heaps and tailings, leaky tailing dams and contamination of water, radioactive particles can enter the body either through inhalation or ingestion of radioactive particles. These particles can lead to various types of carcinomas, leukaemias and birth defects. In Navajo Indian Reservation and parts of Colorado, Uranium mining developed in the 1940's. At the Public Health Service/ Indian Health Service Hospital in the Colorado area, a total of 320 different congenital defects were discovered in the review of clinical records over a 30 year period as a result to the exposure of Uranium or it's by-products(17).

1.3.1 FOLIC ACID HYPOTHESIS

The method in which folic acid prevents MMC's is not clearly understood as well as why thousands of women around the world who take folic acid still have foetuses with MMC's(4).

One hypothesis is that there is a problem with the folate receptors and therefore by flooding the system with folic acid, some folic acid is taken up by these receptors leading to the prevention of MMC development(4).

Folic acid is the synthetic form of Vitamin B9 and unlike most folate, the majority of folic acid is not converted to the active form 5 Methyltetrahydroxyfolate (5-MTHF) in the digestive system but rather in the liver and other tissues(18). In the digestive system the majority of folate is converted into 5-MTHF before it enters the blood stream(18). Folate participates in two metabolic pathways, the synthesis of nucleic acids and also

in a series of methylation reactions(14). Disturbances in folate metabolism can lead to increased homocysteine levels which can lead to disastrous complications of the neural tube(14).

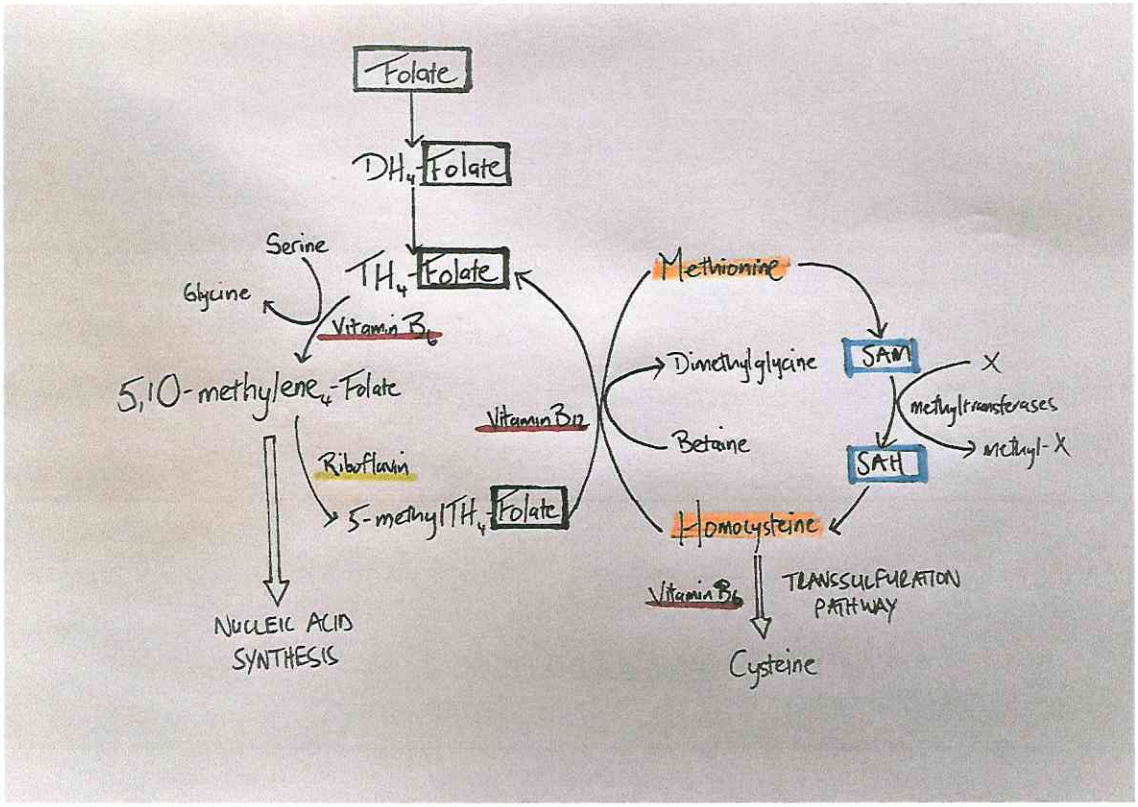

Figure 1.1 Folic Acid Metabolic Pathway(19)

1.3.2 GENETICS

It is difficult to discern exactly how genetic factors play a role in the development of MMC's because no clear- cut mode of inheritance for Neural tube defects (NTD's) can be determined(20). In mice over 200 genes are responsible for the closing of the neural tube with new genes being discovered regularly(4). The human disease phenotype of MMC's is not replicated by the numerous animal models, nor do the genes demonstrated

in mice MMC's cause MMC's in humans and vice versa(11, 20). This phenomenon suggests gene- gene interaction, dosage effect and gene- environment interactions are all involved in causing NTD's(20). These genes associated with MMC's belong to various molecular pathways and display a variety of Phenotypes(4). Through studying the genetic make-up of MMC's, many of the amino acid mutations were found not to be present in normal individuals(20). The planar cell polarity pathway (PCP) and folate one-carbon metabolism (FOCM) pathway have verified to be linked with an array of NTD's(20). Homocysteine is converted to methionine by the enzyme Methylene tetrahydrofolate reductase (MTHFR)(20). The 677C>T variant reduces the activity of MTHFR which can result in NTD's, especially if the folate is low(20). Not all studies have similar conclusions due to limitations in study design therefore possible avenues, to avoid this could be the genomewide association studies (GWAS) and the whole genome sequencing, to identify genes that affect risk for human NTD's(11).

1.4 Literature Review

According to a study by Khattak H.A et al in Abbottabad, Pakistan, myelomeningoceles (MMC's) are commonly associated with hydrocephalus as well as Chiari type II malformations, with the incidence of hydrocephalus seen in 11,8% of patients born with MMC's(13). In their specific series though, they found that MMC's were associated with Chiari type II in 75% of cases whilst hydrocephalus was associated with 85,4% of cases(13).

In other series in Georgia, United States of America (USA), by Stevenson K.K, patients with MMC's and Chiari type II had an 80% incidence of developing hydrocephalus

with 10 - 20% of patients never developing hydrocephalus and therefore do not need any CSF diversion(9).

According to Shrot S et al in Baltimore, USA, MMC patients that had Chiari II, were seen in 60% of patients who concomitantly had hydrocephalus, with the other 40% showing no signs of ventriculomegaly(14). The incidence of hydrocephalus increases with time, the repair of MMC's and with a higher spinal lesion(14). Hydrocephalus in Chiari type II malformations is multifactorial(14). Obstructive hydrocephalus may develop when there is an occlusion of the fourth ventricle as well as at the cranio-cervical junction, preventing the passage of CSF(14). Dysplastic tectal plates may lead to aqueductal stenosis or occlusion which may lead to another form of obstructive hydrocephalus(14). Communicating hydrocephalus in Chiari II may develop due to a hypoplastic posterior cranial fossa and cerebellar herniation, which in turn may decrease the venous outflow thereby impacting CSF absorption(14).

All these findings, namely the correlation between MMC's, Chiari Type II Malformations and Hydrocephalus were replicated by Copp A.J et al in a combined USA and United Kingdom (UK) study(4). They mention that although Chiari Type II Malformations are present in most individual with MMC's, only about 30% are clinically symptomatic. With regards to the level of the lesion, all thoracic lesions needed Ventriculoperitoneal shunting, 85% of lumbar lesions and 70% of sacral lesions(4). The article also mentions variations of statistics within a country with respect to race and ethnic groups(4).

A case study by Takamiya S et al, done in Sapporo, Japan, identified that myelocystoceles are associated with a more severe form of hydrocephalus as opposed to MMC's(15).

Copp A.J et al also mentions that along with the higher level of the lesion, the worse the hydrocephalus is as well as the severity of the neurological fallout(4). Hydrocephalus is directly proportional to cognition and motor outcome, that is, the worse the hydrocephalus, the worse the cognition and motor function(14).

Interestingly these findings were contradicted according to Cinalli G according to his studies in Naples, Italy which stated that there is no correlation between the level of the lesion and the presence of hydrocephalus(5). The Italian study does however concede that according to some authors a higher incidence is suggested with thoracic lesions (97%), as compared to lumbar (87%) and sacral lesions (37%)(5).

Along with hydrocephalus, Chiari II malformations also affects cognition as well as motor function(14). Neurocognitive difficulties can be observed from 6 months of age and intellectual disability affect approximately 20 - 25% of patients with MMC's often after the complication of hydrocephalus(14). Children with mild to moderate ventriculomegaly with a head circumference within the normal range, can be treated conservatively but monitored with regards to head circumference and neuropsychological development(14). In children with no clinical or radiological evidence of acute hydrocephalus but steady intellectual decline observed through serial Intelligence Quotient (IQ) and psychomotor monitoring should receive CSF diversion(14). The slow and insidious nature of this disease may cause the clinician to miss such subtle changes(14).

Because of these subtle changes that could occur with regards to developing Hydrocephalus, Kim et al conducted a retrospective study. In the article, Kim et al mentions a study with 297 individuals which showed there was a difference in the placements of VP Shunts. The patients with a higher level of the lesion was associated with more VP Shunts being placed as compared to those with a lower level of the

lesion(21). In another study however within the same article, there were contrary findings which showed no relation with the amounts of VP Shunts placed with regards to the level of the lesion and this was a retrospective study of 72 patients(21). Additional parameters were looked into, namely gender distribution which says that there might be a female dominance.

Other factors such as gender, race and APGARS have been associated with hydrocephalus. According to Kim et al of 4448 individuals in their study, 2308(51,9 %) were females as compared to males which was 2140 (48,1 %)(21). Timson et al in their analysis of 3521 cases of MMC's found a female predominance of 65,5 % as compared to males at 34,5 %(22). Maria M.M et al alludes to a female preponderance in their article but according to their own study where they analysed 31 patients with MMC's only 16 were females and 15 were males. Some other parameters also mentioned within this study besides gender is race where there is a Caucasian majority, mean maternal age of 25 years of age, caesarean section rate of 74 %, mean gestational age of 39 weeks and mean infant weight of 3009 gm. More parameters studied were the APGARS for which only one was below 6 at 5 minutes, 97 % had hydrocephalus and 32 % had a Chiari Type II malformation(23).

Cinalli G in his study in Italy, maintains that hydrocephalus is almost exclusively associated with open spinal lesions but does concede that it may also be associated with non- terminal myelocystoceles, sometimes as high as 44 - 62% as previously mentioned in the case report from Japan(14).

1.4.1 Chiari Type II Malformations

Chiari Type II malformation is commonly associated with MMC's. It accounts for more deaths associated with MMC's before the age of 2 years old than any other cause(9). It may also be associated with myelocystoceles in some cases(16). Symptoms range from life threatening to very subtle changes needing timely monitoring and management to prevent significant morbidity and mortality(9). Chiari II involves the entire brain and surrounding structures, including the bones and meninges, but more especially the posterior fossa(9). The cerebellar vermis is displaced below the foramen magnum and has the appearance of a "peg." Along with the vermis there may also be caudal displacement of the cerebellar tonsils and caudal brainstem through the funnel- shaped foramen magnum into the cervical canal(16). A "medullary kink" can also be observed secondarily to the mobile medulla with a relatively fixed spinal cord by the dentate ligaments(16). Cerebellar "inversion" is often noted, or the cerebellum could just appear small on the whole. The abnormal shape of the cerebellum along with the absence of the cisterna magna produces the "banana sign" which is appreciated on prenatal ultrasonography(9). Cerebellar folia are absent along with heterotopias which may be present. The term "crowded" posterior fossa is used to describe the posterior fossa in patients with Chiari II malformations, even though the cerebellum may be small and this is due to the small compartment size(9). Lastly the tentorium is typically hypoplastic and inserts below the torcular herophili just above the foramen magnum(16).

1.4.2 Evan's Ratio

Ventricles constitute 2 percent of the brain and 82 % of the ventricular volume is contained in the lateral ventricles(24).

Hydrocephalus can be diagnosed using Evan's ratio which is a ventriculographic index. The ratio compares the maximum width of the frontal horns of the lateral ventricles to the maximum transverse diameter of the inner table of the skull. The ratio is deemed positive for hydrocephalus if it exceeds >0.3(24).

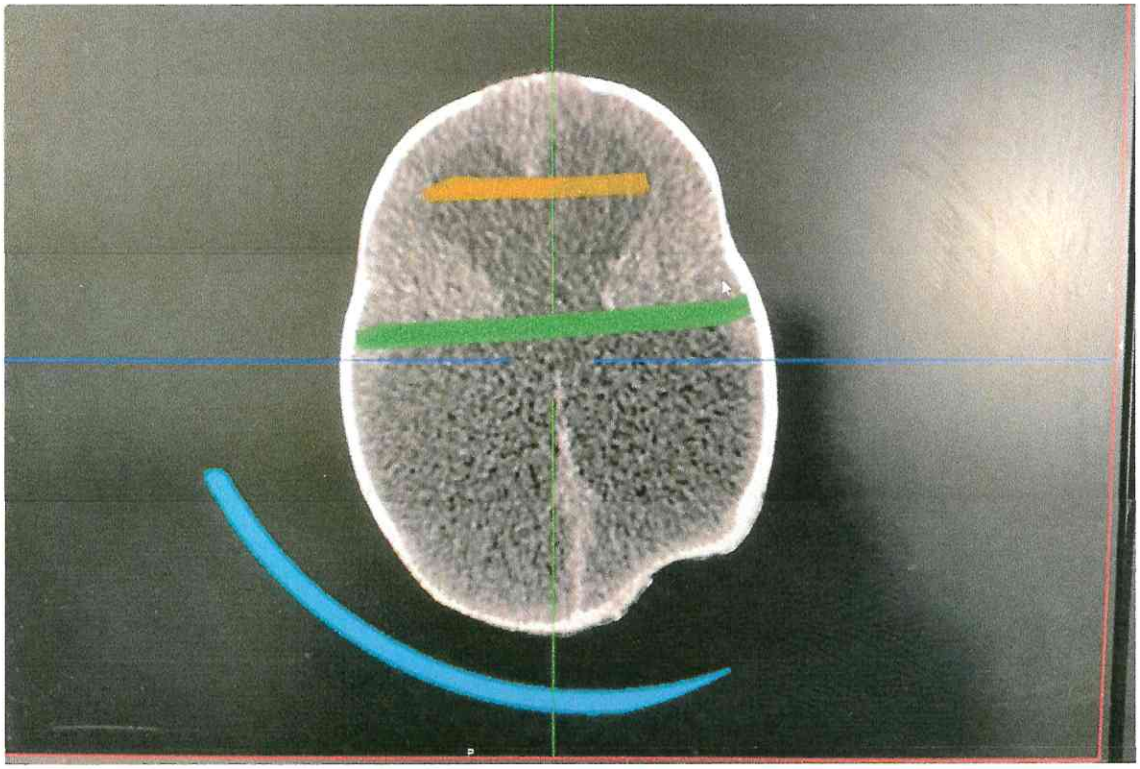

Figure 1.2 :Evan's Ratio. Maximum ventricular width (yellow line) divided by the largest biparietal distance between the inner tables of the skull (green line).

1.4.3 Colpocephaly

Colpocephaly is defined as an abnormal enlargement of the occipital horns of the lateral ventricles with normal frontal horns sometimes defined as the persistence of the foetal configuration of the lateral ventricles(25, 26). An embryological mechanism proposed for the development of colpocephaly states that lateral ventricles arise from the telencephalic vesicle. In normal development, these ventricles which are cavities, decrease in size only after the formation of the Foramen of Magendie as this causes the ventricular decompression(26). The surrounding structures like the corpus callosum and so forth help mould the occipital horns by increasing in size and volume(26). It is suggested that in colpocephaly, an unknown mechanism disrupts this process leading to enlarged occipital horns(26). Agenesis of the corpus callosum is the leading malformation with others including myelomeningoceles, which in itself is associated with Chiari type II malformations and this is known to be associated with agenesis of the corpus callosum along with other cerebral malformations(25).

Clinical symptoms associated with colpocephaly include, varying degrees of mental retardation, seizures and motor and visual disturbances(26).

Colpocephaly is often misdiagnosed as hydrocephalus although the two conditions can occur simultaneously.

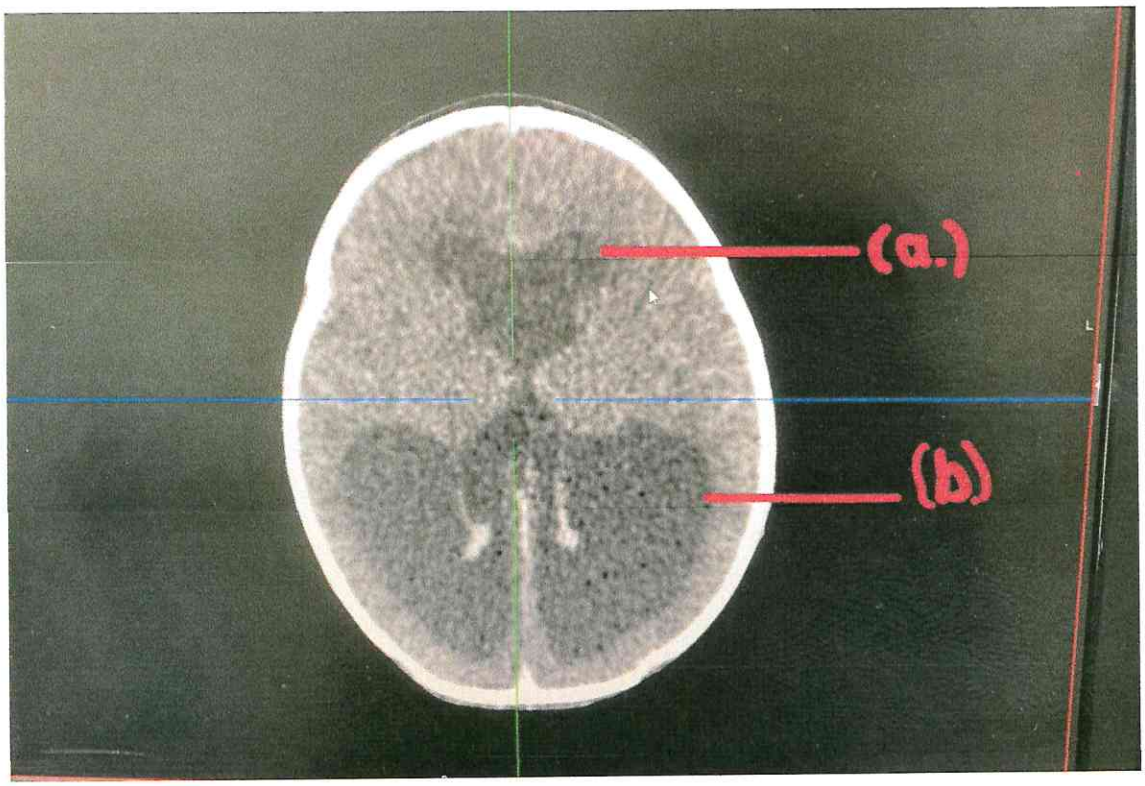

Figure 1.3: CT Brain depicting Colpocephaly (a)Smaller frontal lateral horns as compared to, (b) dilated occipital lateral horns depicted.(27).

1.5 Embryology

1.5.1 Spine Embryology

The framework on which the CNS develops is known as the neural tube. The blastula which are hollow cells, transform into an embryo by a process known as gastrulation. Post gastrulation is when the neural tube develops. An opening in the blastula, the blastopore is formed and this whole process is regulated by the signalling centre on the axial side. At this point the embryonic disc is composed of ectoderm, mesoderm and endoderm and is surrounded dorsally by amniotic fluid and ventrally by the yolk sac(28). A primitive node with a primitive streak is formed. The primitive node by thickening of the rostral end whilst the primitive streak, a thickened linear band of primitive mesoderm elongates caudally. The primitive groove forms in the primitive streak which is continuous with the primitive pit of the primitive knot(28). On days 16-17 post-conception, the notochord in the midline of the embryonic mesoderm develops as a solid structure when the primitive groove is invaded. The embryo is now made up of the endoderm, mesoderm and ectoderm(28).

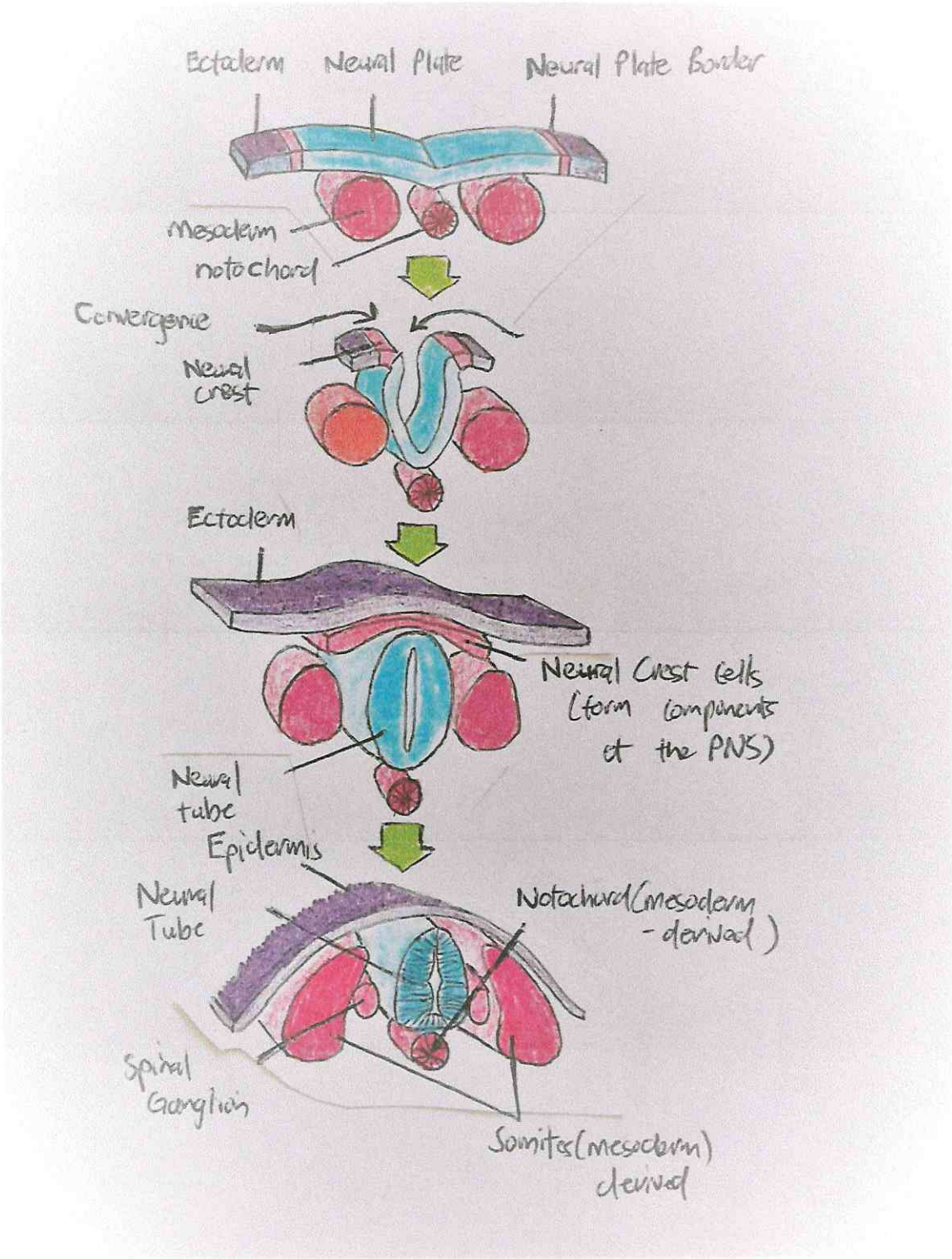

Figure 1.4: Neural Tube Development(29)

1.5.2 Neurulation and Neurogenesis

The notochord is formed at Day 16 in the midline of the rostral end of the embryo by mesoblastic cells that migrate from the primitive node. The embryo is about 1.5mm in length at the beginning of the third week of intrauterine life. The notochord induces a strip of columnar ectodermal cells along the central axis of the embryonic disc(3).

The strip called the neural plate, consists of neuroectodermal cells, which undergo rapid proliferation. This is one of the causes of longitudinal and transverse 'bending' of the early embryo. At the edges of the plate, columnar cells meet flattened ectodermal cells, which will become the surface ectoderm. The surface ectodermal cells will later form the lining of the amniotic cavity and epidermis of the body(3).

Rapidly multiplying cells of the neural plate become heaped at the junction with the surface ectoderm to form the neural fold. These neural folds invaginate to form the neural groove. As the neural fold enlarges and bend towards each other, the neural groove deepens and when they meet, they fuse in the middle of the neural plate. This is now the beginning of the neural tube(3).

Fusion begins between somite levels 4 and 6 and then proceeds in a cranial and caudal direction until the tube is complete. There will be two openings present at the cephalad and caudal ends known as the anterior and posterior neuropores which remain open temporarily into the ectodermal (amniotic) cavity(28).

While neural folds are developing, a special group of cells called neural crest cells differentiate in the crest of the fold. The neural crest cells give rise to a multiple of structures in various parts of the adult body which they reach via a process of migration in the embryo. These structures include melanocytes, craniofacial cartilage and bone as

well as smooth muscle, peripheral and enteric neurons and glia. When the neural folds fuse, the neural crest cells lie on the dorsolateral sides of the tube, becoming the spinal and sympathetic ganglia, while others migrate to other parts of the embryo(28).

By the end of week 4 of intrauterine life, the neural folds have fused completely and the neuropores have closed. At this stage the surface ectoderm has separated from the neural tube. The surface ectoderm fuses and becomes continuous dorsal to the neural tube preserving the ectodermal (amniotic) cavity. This ensures that the neural tube and neural crest become independent of the ectoderm from which they arose(28).

1.5.3 Primary Neurulation

Primary Neurulation begins with the formation of the neural plate as a thickening of the dorsal ectoderm(1). The neural tube then bends, elevates and begins to move towards the midline(1). The ends come together in a zipper - like fashion and fuse to form the neural tube which, thereafter, is covered by epidermal ectoderm(1). Neural tube defects can result from failure of any part of this sequence of neurulation events and are typically open defects(1).

1.5.4 Secondary Neurulation

Secondary Neurulation forms the part of the spinal cord below S1 and includes sacral spinal segments, conus medularis and the cauda equina – see Figure 1.5.

It is composed of two stages:

1) Tail bud canalisation of the medullary cord, which occurs between days 28 -48.
2) Regression, which occurs from day 48 up until birth.

During tail bud canalisation, the tail bud is derived from a primitive streak remnant, which contains an undifferentiated cell mass under the ectoderm.

This mass forms vacuoles that coalesce to form the terminal ventricle and subsequently the distal neural tube. The distal neural tube then ascends to fuse with the neural tube formed by Primary Neurulation(5, 30). Primary Neurulation forms the Central Nervous System (CNS) from telencephalon to S1 and Secondary Neurulation forms the CNS from S1 to the cauda equina(5, 30).

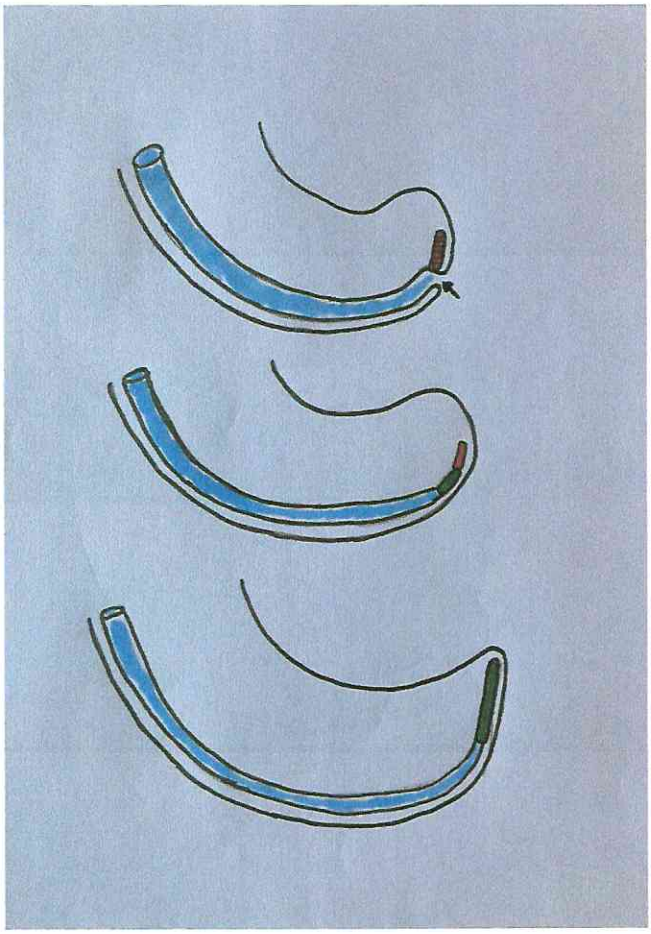

Figure 1.5: Diagrammatic representation of secondary neurulation showing tail bud canalisation. From top to bottom. Primary Neural Tube(blue) completed at the caudal neuropore(arrow); medullary cord(red) appears. First formation of Secondary Neural Tube(green) by canalisation of medullary cord. Completion of Secondary Neurulation prior to regression of the tail. (4).

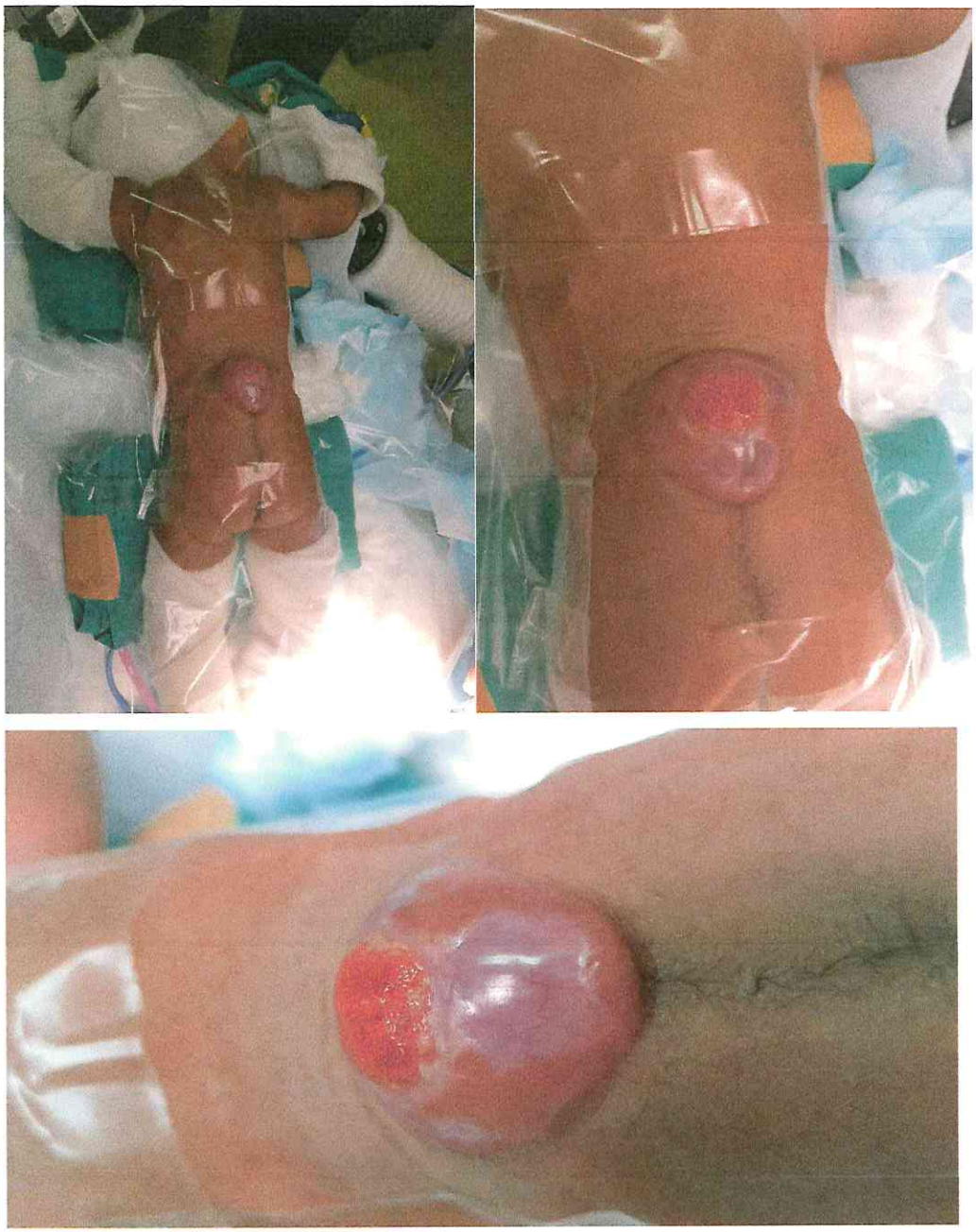

Figure 1.6: Photos of MMC'S seen at CHBAH

1.5.5 Embryology of Chiari malformations

Four main theories exist that attempt to explain Chiari type II malformation. Chiari attributed the hindbrain herniation to hydrocephalus and even though hydrocephalus is present in Chiari type II malformations and MMC's, it fails to explain many features of Chiari II malformations. On prenatal screening, Chiari II is often present prior to the development of hydrocephalus(9). Cleland postulated Primary Dysgenesis of the hindbrain to help explain the CNS anomalies in the posterior fossa but was unable to explain the supratentorial malformations(9). Overcrowding of the posterior fossa due to a mesenchymal disorder has been proposed as the reason there is a low- lying vermis and brainstem herniation. Leaking of CSF chronically from the spinal cord has also been postulated as a cause of the small posterior fossa which again doesn't explain the CNS abnormalities seen in the patient. In the fourth theory, proposed by Penfield the CNS abnormalities again is failed to be explained this time by the traction theory which states that the development of Chiari II is due to the pulling of the hindbrain by the tethering and open spinal cord(9). McClone and Klopper combined all four of these theories together to form the unified theory of Chiari II. The theory states that the incomplete spinal occlusion and neural tube defects allow the CSF to drain through the central canal. The CSF is therefore not maintained in the ventricular system and therefore does not exert a ventricular CSF driving force, therefore not allowing the calvarium and neural structures to develop as well as the posterior fossa due to the lack of ventricular distention(9). Later the rhombencephalon grows rapidly, forcing the cerebellum cephalad and caudal along the brainstem. Other manifestations occur due to the lack of ventricular distention in the telencephalon causing polymicrogyria, enlargement of the massa intermedia, low-lying tentorium and torcular herophili and base of skull abnormalities(9). In this theory, hydrocephalus develops due to obstruction of the CSF pathway due to

impaction of the posterior fossa at the Foramen Magnum, Foramen of Luschka and the Foramen of Magendie(9).

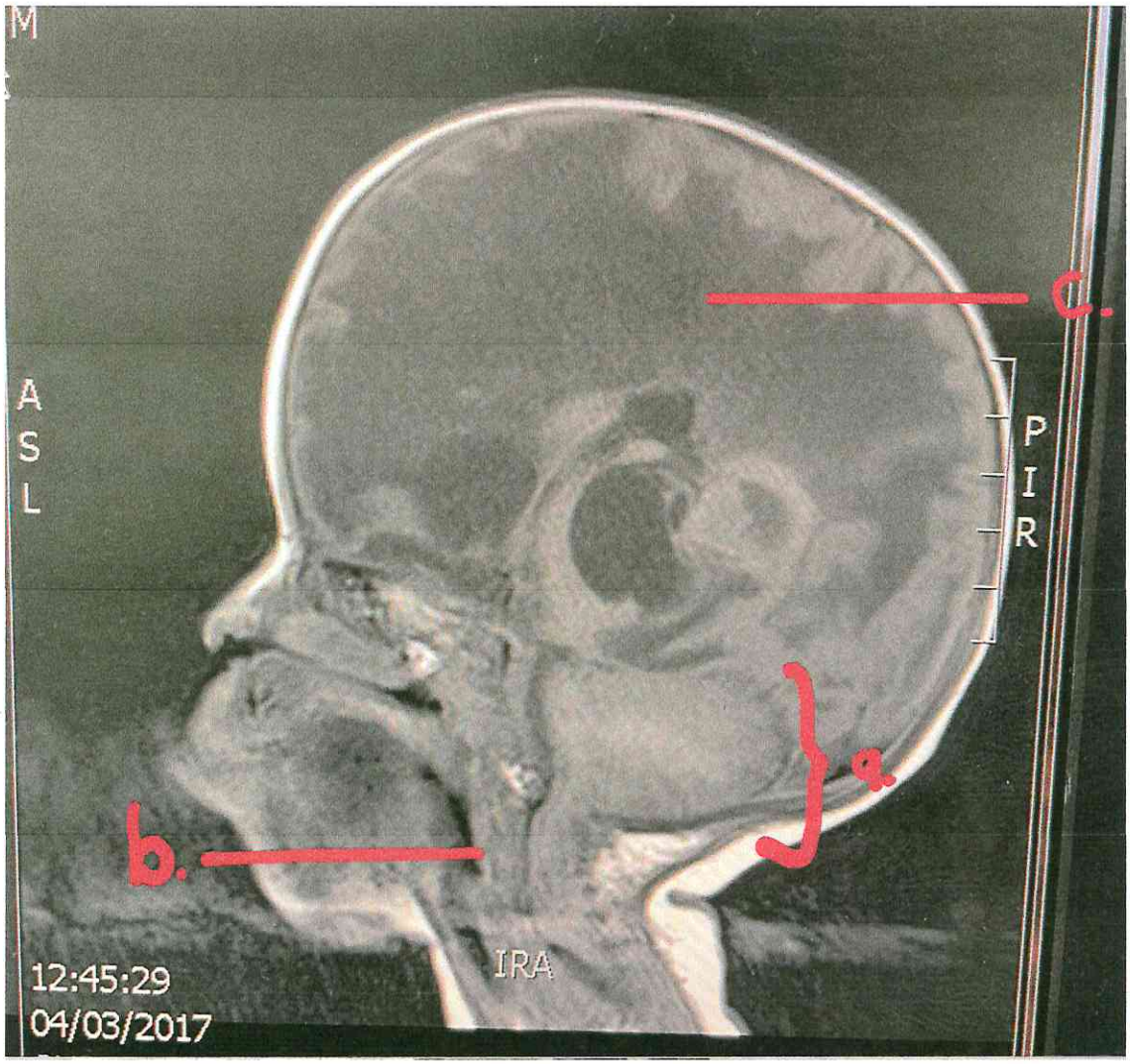

Figure 1.7: Sagittal T1-weighted image showing Chiari II malformation; the features include elongated brainstem that extends into the cervical spinal canal; (a)Smaller Posterior Fossa with downward herniation of the cerebellar tonsils into cervical spinal canal; (b)elongated brainstem extending into cervical spinal canal and just above that a small fourth ventricle; (c)There is also a thinned out, almost absent corpus callosum(24).

1.6 CLINICAL PRESENTATION

Neonates with MMC's are prone to numerous developmental abnormalities. These can be broadly divided into cranial abnormalities, spinal abnormalities and other. Spinal abnormalities can be partial motor and partial sensory function below the lesion or there can be complete paralysis(4)

Under cranial abnormalities, neonates can have hydrocephalus which may present with macrocephaly and have signs and symptoms of raised intracranial pressure(16). On imaging there may be associated colpocephaly as previously discussed(16). Chiari type II malformations are common in patients with MMC's and may present with stridor, apnoea, opisthotonos or even sudden death(16). Chiari II is the most common cause of death in patients with myelomeningocele who are younger than 2 years of age(9). Approximately one third of patients with Chiari II develop signs and symptoms of brainstem compression up to the age of 5 years, and more than one third of these patients do not survive(9). Gastrointestinal disturbances which are as prevalent as respiratory symptoms, are more insidious in nature(9). Lower cranial nerves are frequently affected and manifest as neurogenic dysphagia leading to chronic aspiration which may lead to frequent bouts of pneumonia(9).

Other abnormalities may be bladder and bowel pathology which has a prevalence of 60%(31). Low IQ's can also be of a concern in later life which may be further complicated by untreated hydrocephalus and meningitis(16). During growth spurts, children with MMC's may present with new onset neurology secondary to tethering of the spinal cord(32). Urological pathology includes horseshoe kidney, hydronephrosis and renal failure secondary to the effects of neurogenic bladder. The musculoskeletal system may be affected secondary to kyphosis or scoliosis, congenital hip dysplasia and clubfoot.

Cutaneous lesions may be present such as various forms of naevi or hairy tufts around the lumbar region. This is more associated with closed NTD's. Neural arch defects especially the posterior arch may also be present(33). This is more commonly associated with spina bifida cystica, along with other developmental errors of the vertebra namely segmental defects of the vertebral bodies, anterior vertebral body defects and minor fusion anomalies(33). Neonates with MMC's may also have anal sphincter dysfunction, rectal prolapse and finally are commonly affected with latex allergies(4, 30)

1.7 PRENATAL SCREENING AND DIAGNOSIS

MMC's along with their associated conditions, namely hydrocephalus and Chiari II have potentially devastating consequences. This has led to active screening protocols so that any complications can be detected early. Maternal serum alpha-fetoprotein(AFP) is detectable from week 12 of pregnancy and steadily increases up to week 32. If serum alpha-fetoprotein between weeks 15 and 20 is double the normal amount, the risk for an NTD increases from baseline by 224-fold(34). The sensitivity of AFP for MMC's is 91%, whereas it is 100% with anencephaly. If there is any uncertainty from the prenatal ultrasound or serum AFP measurements, amniocentesis can be utilised to quantify the amniotic AFP. It usually peaks between weeks 13 – 15(34). Acetylcholine esterase can also be used as a NTD marker and combining both AFP along with acetylcholine esterase measurements as a screening tool for MMC's achieves a sensitivity of 99%. Unfortunately, amniocentesis carries a miscarriage risk of up to 6%(35). The Second - trimester foetal anatomic survey, sometimes referred to as the foetal abnormality scan or prenatal ultrasound imaging has sensitivity of 98% in detecting MMC's(36).

The advantage of the prenatal ultrasound is that it's non-invasive in nature and has the ability to detect associated anomalies such as hydrocephalus, Chiari type II malformations, kyphoscoliosis and clubfoot(36). With appropriate views in the relevant planes, example axial, coronal and sagittal planes the spine can be completely assessed and a potential MMC can be fully detected and even characterised. Detailed assessments of the lower limbs and characterisation of flexion and extension motions at the hip, knee and ankle joints can provide crucial information that could predict neurological compromise. This information can be vital for pregnancy termination counselling and postnatal care for the future foetus(36). The development of heavily T2-weighted MRI sequences that can be acquired in very short acquisition times – half -Fourier single-shot turbo spin-echo (HASTE) sequence – has increased the scope for foetal MRI in MMC assessment and has become an established adjunct to foetal ultrasound(37). The HASTE sequence is a trademark of Siemens. Other MRI companies may refer to a similar sequence by another name as there has not been a uniform system of nomenclature for these type of MRI sequences. Foetal MRI is best considered following the first trimester to avoid the theoretical risk for teratogenesis and is particularly useful in settings such as maternal obesity, oligohydramnios and suboptimal foetal positioning(37).

1.8 MMC MANAGEMENT

1.8.1 Preconceptual management

In 1991 a major trial funded by the Medical Research Council (MRC) showed that folic acid could prevent NTD's. According to the MRC study, the administration of 4mg/day of folic acid in families prone to NTD's decreased the risk by 72%(38). In addition to fortified dietary staples, women should supplement before conception with 0,4- 1mg of

folic acid daily as part of their multivitamins(39). Fortification of flour and wheat led to a worldwide reduction of MMC's.

The Canadian Task Force on Preventative Health Care gives further recommendation in that women should maintain a healthy folate-rich diet. All women in the reproductive age group should be made aware of the benefits of folic acid in general health visits and should know their particular risks regarding previous NTD's or partners who have had any NTD's in their family(40).

1.8.2 Post Delivery Management

Caesarean section deliveries are associated with less neurological damage and is superior to vaginal mode of delivery in preventing further neurological damage in foetuses who have been antenatally diagnosed with an MMC(41). A planned caesarean section also prevents further injury to the CSF filled MMC, which could lead to a CSF leak and infection from the birth canal. Following the birth, the MMC should be covered with a non- adhesive silicone-based dressing with a piece of sterile gauze on top and then sealed with a plastic wrap to prevent urine or faecal contamination. The dressings should be changed daily until surgery and the neonate should be nursed in a prone position or on its side(42). According to the latest literature from the Guidelines Task Force, there is no concise evidence that the MMC should be closed within 48 hours to prevent infection but does advocate that if it takes longer than 48 hours to close that antibiotics should be initiated(43). During the first 24 hours of life, the neonate is stabilised and assessed for any other associated abnormalities, some of which, may have been identified prenatally(42). Pending the neonate being stable, blood is cross-matched and surgery for the repair of the MMC is planned. It was previously thought and still implemented in

many institutions that the MMC closure should occur within the first 24- 48 hours of birth. This strategy was thought to decrease the risk of CNS infections like meningitis(42). The exact frequency associated between hydrocephalus, Chiari II malformations and MMC's is unknown but if hydrocephalus is present whilst the MMC is being repaired, there are advocates for simultaneously inserting the Ventricular Peritoneal Shunt(VP Shunt) immediately(44). Others however advocate for watchful waiting after the MMC has been repaired(44). If hydrocephalus does not develop, the potential complications from VP Shunts are therefore avoided. Warf successfully treated a number of patients in Uganda who had both MMC's and hydrocephalus with Endoscopic Third Ventriculostomies and Choroid Plexus Cauterizations(45). This avoided the huge costs involved in VP Shunts and is an accredited alternative treatment(45). A multidisciplinary team is essential for care of the neonate post MMC repair(4). The Urology team will care for any renal tract pathologies and will require a renal tract ultrasound along with urodynamic studies as well as a vesico -urethrogram(31). Parents are generally taught how to perform intermittent clean catheterisation whilst anti-muscarinic agents are commenced(31). Orthopaedic surgeons treat and give input with regards to the congenital hip dysplasia and clubfoot which could be concerns(4). Finally, psychological support for the family is quite pertinent(46).

1.8.3 Surgical Management

For MMC repairs, prevention of hypothermia is key. It is recommended that the theatre is kept at 28 degrees Celsius and that the neonate is kept warm with warming pads, cotton rolls, and aluminium foil to cover the head and limbs(4). Occlusive plastic sheets are used to cover the non-operative site and the intravenous fluids given should be warm saline(4). The neonate is proned, pressure points padded, and attention paid to

maintaining a free abdomen. Anaesthetists should pay special attention to monitoring intra-operative haematocrit and serum glucose(4). The primary treatment of myelomeningoceles remains early surgical closure of the defect(47). Surgical repair of MMCs requires precise dissection, meticulous haemostasis, minimal electrocautery and repair under magnification(42).

Once the placode is free and the proximal junction defined with the normal spinal cord, it is reconstructed into a neural tube with a non-absorbable 6-0 monofilament suture.

In some centres the neural placode is amputated as there is little evidence of regained motor function with sparing it.

Lorber et al reported a 100% mortality if the MMC was left untreated, however some children survived greater than 6 months(48).

Myelomeningoceles that have not been closed at birth will epithelialize if the

child survives. The treatment strategy for repairing these MMC's is slightly different in that the epithelialized placode is separated so that the placode is spared and reintegrated back into the neural tube(47). A prime example on when to spare the placode would be if there are functional nerve rootlets below the MMC. Two different types of myelomeningoceles were observed during surgery in a Turkish hospital. Type I, the rootlets of cauda equina was terminated at the level of MMC by attaching to the membrane and to the dural sac(49). No rootlets were lying below the level of myelomeningocele and therefore, there was no function below(49). In Type II, there were some rootlets lying below the level of the MMC. These rootlets were functional and the patients had some neurological functions below the MMC(49). When operating on these patients electro-neurophysiology monitoring is essential(49).

The surgical technique is as follows. An incision is made along the junction of the placode with the dysplastic skin and care is taken to excise remnants of dysplastic skin along the junction as it could lead to future inclusion dermoid cysts. It is the surgeon's choice with regards to amputating the neural placode or re-integrating it into the neural tube. The dura is dissected free from the MMC cavity and then closed in a watertight fashion with a non-absorbable 5-0 monofilament suture. The repair is tested for CSF leaks with a Valsalva manoeuvre. The subcutaneous tissue is undermined widely and depending on the available subcutaneous tissue one or two further layers are closed with a 4/0 absorbable suture. Finally, residual dysplastic skin is excised, dog-ears are neatened, and skin is closed with 5-0 nylon interrupted sutures. The wound is dressed with an occlusive dressing and the neonate is nursed prone for seven to ten days until the skin has healed and sutures are removed. Large dorsal defects following MMC repair require closure with local flaps. Data from plastic surgery suggest that the minimal sized defect requiring a flap is 18 cm2(50).

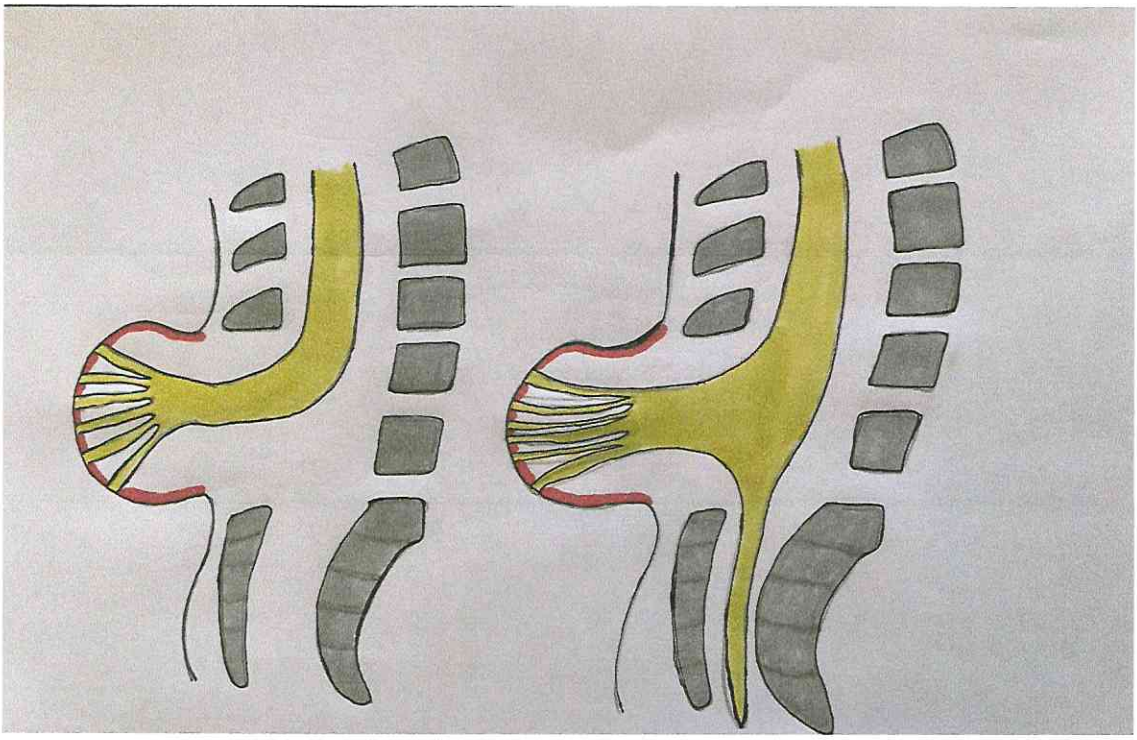

Figure 1.8: Types of Myelomeningoceles(49).Left is Type 1 MMC and Right is Type 2 MMC.

1.8.4 Long term management

It is estimated that the lifetime medical and non- medical costs of an individual with a NTD is $560000 United States Dollars(51). From a Neurosurgical point of view, close follow-up is required for children who have shunts inserted and to monitor for tethered cord syndrome, that might require a future release(32). Urinary catheter management is handled by the parents after they are taught with future bladder augmentation advised by some urologists(31, 52). Orthopaedic input is generally ongoing in the early years in

the setting of clubfoot and congenital hip dysplasia(52). Psychological support is very important; initially for the parents and then for the child with the MMC, as they grow older(46). Although many advances have been made the treatment of MMC's, resulting in improved quality of life and increased life expectancy, no treatment exists that will completely eliminate the serious disability or premature mortality associated with it(51). About 82% of adults achieve independence in activities of daily living, 30% attend or finish University and 32% are gainfully employed(32). Multidisciplinary care is lifelong.

1.9 PRENATAL MMC REPAIR (MOMS TRIAL)

The Management of Myelomeningocele Study (MOMS) was initiated in 2003(53). MOMS was a multicentre prospective randomised clinical trial comparing treatment outcomes between prenatally and postnatally repaired MMC's. The hypothesis was that in utero surgery may improve lower extremity, bowel and bladder function, ameliorate the Chiari Type II malformations and decrease the need for post- natal shunting(54). The centres where the foetal surgery was performed were Vanderbilt University, University California San Francisco and at the Children's Hospital of Philadelphia(53). Initially the sample size was going to be 200 patients but the trial was stopped earlier at 183 by the Data Safety and Monitoring Board as it was concluded that prenatal intrauterine repair of MMC's between weeks 19-25 of gestation was superior to standard postnatal Neurosurgical repair in terms of long-term outcomes(53). The initial article stated that there was a successful decrease in rate of shunting when comparing the postnatal surgical group with the prenatal surgical group from 82% to 40%(55). However, according to the pre-specified criteria substantially more patients actually met the criteria

than actually underwent shunt placement (92% vs. 65%)(55). In 2015 the revision of the CSF Shunting criteria was suggested and now is as follows :

Table 1. MOMS Primary and Revised Shunting Criteria(52)

Primary Criteria	**Revised Criteria**
1) Meeting at least two: • (a) an increase in the circumference/crossing percentiles • (b) a bulging fontanelle or split sutures or sunsetting sign • (c) an increasing hydrocephalus on consecutive imaging studies • (d) head circumference >95th percentile	**1)** Bulging fontanelle or split sutures or sunsetting sign AND one of the following: • (a) an increase in the circumference/crossing percentiles • (b) an increasing hydrocephalus on consecutive imaging studies • (c) head circumference >95th percentile
2) Syringomyelia with ventriculomegaly	**2)** Syringomyelia with ventriculomegaly
3) Ventriculomegaly and symptoms of Chiari II Malformation	**3)** Ventriculomegaly and symptoms of Chiari II Malformation
4) Persistent CSF leakage from the myelomeningocele wound or bulging at the repair site	**4)** Persistent CSF leakage from the myelomeningocele wound or bulging at the repair site

Finally, hindbrain herniation was significantly reduced in the prenatally repaired group, potentially protecting this group from the severe sequelae of Chiari Type II malformation(53). Many risks are elucidated to the MOMS trial pertaining to surgery for the mother namely an increased risk of spontaneous rupture of membranes,

oligohydramnios, preterm delivery and uterine thinning or dehiscence. All these risks factored in, prenatal surgery was still deemed to be a very good option if the proper criteria and conditions are met and done in a high volume centre(53, 55). Costs involved in setting up for such a procedure is considerable and has only been done once on the African continent at Mediclinic Morningside Hospital led by Professor Mike Belfort from the US(53, 56).

1.10 SURGICAL COMPLICATIONS

There are three main complications associated with MMC's which can be quite significant but to a large extent can also be preventable with meticulous planning(57).

1.10.1 CSF Leak

Leakage of CSF through the surgical site increases the risk for wound dehiscence as well as meningitis along with its accompanying complications. The reported frequency of CSF leaks varies from institution to institution.

1.10.2 Wound Dehiscence

Wound dehiscence is a common complication of MMC repair surgery and the poor nutritional status of the neonate increases the risk for this adverse outcome(57-59). Neonates with MMC's are disadvantaged due to their low birth weights, negative nitrogen balance, hypoalbuminaemia and low lymphocyte counts. These factors are associated with a catabolic state that resolves quite slowly. Local factors that affect wound healing, leading to wound dehiscence is larger flaps with higher tension of suture lines. Kyphosis can lead to decreased blood supply leading to necrotic skin edges. Skin flap necrosis is

also known to happen when significant subcutaneous undermining is needed. This can all be quite challenging to treat(59).

1.10.3 Infection

Like CSF leaks, the exact incidence of infections varies with some series quoting from 1 to 37%(5, 16, 60-62). Infection can be divided into extradural and intradural where extradural infections arise secondary to contamination of the wound by skin commensals, faeces or urine. Intradural infections tend to be worse and can lead to meningitis and even ventriculitis. Prompt employment of antibiotics is necessary in both cases but more so in intradural infections. CSF samples should be obtained and sent for cultures and sensitivity so that the correct antibiotics can be commenced(5). The new guidelines, as mentioned previously, states that closure within 48 hours does not reduce the risk of infection in a leaking MMC(43).

1.10.4 Other Complications

Less frequent post-operative complications following MMC surgery may include ileus, particularly in the setting of large defects requiring widespread undermining and use of myocutaneous flaps. This complication is usually self-limiting. Rarely pneumothorax can occur following deep dissection of the latissimus dorsi in the thoracic region which is also more frequent following closure of large defects. Finally, necrotising enterocolitis which is slightly more frequent post MMC repair(5).

1.11 STUDY AIMS AND OBJECTIVES

It is quite evident from the above literature that there is no consensus with regards to the exact relationship between MMC's, Chiari Type II malformations and hydrocephalus. This therefore brings us to the question, "What is the association with MMC's, Hydrocephalus and Chiari Type II malformations in our surgical setting?"

The aim is to determine the prevalence of Hydrocephalus and Chiari type II malformations in patients who present with MMC's whom had operations.

The objectives are to determine the number of MMC patients that were operated on from 2015 to 2018.

To determine whether the patient has a Chiari type II malformation and/or hydrocephalus alone.

Then to determine the severity of the Hydrocephalus with regards to the level of the MMC lesion.

2. METHODS

- **2.1 STUDY DESIGN**

Retrospective Study of Patient Records

- **2.2 STUDY SITE**

The study was conducted at the Neonatal and Neurosurgery Departments at Chris Hani Baragwanath Academic Hospital.

- **2.3 STUDY POPULATION**

All patients with MMC's that were operated at CHBAH between 1 January 2015 and 31 December 2018.

- **2.4 SAMPLING**

The number of patients seen was 45.

- **INCLUSION CRITERIA**

  - Patients with MMC's that were operated at the CHBAH

- **EXCLUSION CRITERIA**

  - Patients with MMC's that were not operated for any reason

  -Incomplete patient records

- **2.5 DATA COLLECTION**

Medical records were obtained from CHBAH.

The names of patients were obtained from the theatre books which are regarded as legal documents.

Patients' files were then obtained from Records and the Neonatal Data Bank

(a departmental data bank compiled by the Neonatologists at CHBAH).

Gestation, maternal information and birthing details were obtained from the patients' clinic books.

Scans were obtained either from the local CHBAH Picture Archiving and Communicating System(PACS) or the referral hospital if a scan was done there.

Cranial ultrasounds were obtained from patient files.

Data was recorded on a data collection sheet – see Appendix A - and then managed in a Microsoft Excel database. Data recorded and presented includes demographic details which includes (Race, Gender, Gestation period, Mother's Age), birthing details (Mode of Delivery, Birth Weight, Length, Head Circumference and Appearance, Pulse, Grimace, Activity and Respiration (APGAR) Scores), clinical details (Hydrocephalus, Chiari Type II Malformation, Colpocephaly, Level of the Lesion (MMC) and CSF Leak) and operative details (Date of Surgery, Time of Surgery and Mode of Delivery.)

- **2.6 DATA ANALYSIS**

Data was checked for incompleteness and inconsistencies and was analysed using the statistical software Stata/SE, version 16. Since all the variables were categorical, bivariate analyses were performed using Chi-squared tests to identify if associations existed between these variables. For cells less than 5 in cross tabulations, Fisher's exact test was used. P-values are reported. For all analyses, significance level was set at $p < 0.05$.

Exposure variables included socio-demographic and clinical variables. All the variables are categorical, and they include gender, MMC's, the level of lesion (MMC) and whether there are Chiari type II malformations, hydrocephalus and colpocephaly.

Descriptive statistics consisting of mean and standard deviation were calculated for birth weight, length, head circumference, APGAR score and Timing of MMC Repair.

For descriptive and analytical purposes age was categorized to allow for calculations of frequencies and proportions. Continuous data (age of mothers), was checked for normality using the Kolmogorov – Smirnov Test of Normality and plotted in a histogram.

- **2.7 SOURCES OF BIAS**

Only those patients who had MMC's that were operated will be included in the study.

- **2.8 ETHICS**

An application for ethics clearance was submitted to the Human Research Ethics Committee (Medical) at the University of Witwatersrand. The study was approved, and the researcher was subsequently issued with a clearance certificate **M190420** (Appendix B). Consent to use hospital patient records was obtained from the medical superintendent at the Chris Hani Baragwanath Academic Hospital (Appendix C).

Consent was obtained from the HOD of Neonatology to conduct research on the MMC patients and to use the Neonatal Data Bank of records (Appendix E).

3. RESULTS

3.1 RECORDS REVIEWED

A total of 45 patients with MMC's were identified who were operated at CHBAH between the period of 1 January 2015 and 31 December 2018. Their medical records were obtained and reviewed.

3.2 SERIES DEMOGRAPHICS

Demographics pertaining to the study population are summarised in Table 3.1. The gestational period ranged from 34 weeks to 40 weeks. Most of the patients were of African descent with 2 being Coloured and none were of Caucasian or Indian descent. Gender distribution showed that there were 29 males and 16 females.

Table 3.1: Series Demographics

Variables		Results
Gestation		38.78 weeks +/- 1.71(n=39)
Race		
	African	95,6 % (n=43)
	Coloured	4,4 % (n=2)
	Caucasian	0 % (n=0)
	Asian/ Indian	0 % (n=0)
Gender		
	Male	64,4 % (n=29)
	Female	35,6 % (n=16)

3.3 SERIES OF BIRTHING DETAILS

The mode of delivery (MOD) for 64,9 % of the neonates was via a Normal Vaginal Delivery (NVD) with 35,1 % through a Caesarean Section. The lightest neonate was 1490 grams and the heaviest was 4100 grams. The neonates' length's ranged from 35 centimetres to 57 centimetres with the Head Circumferences ranging from 30 centimetres to 40 centimetres. The lowest APGAR at 1 minute was 4 and the lowest APGAR at 5 minutes was 7. See table 3.2 for the summary of the birthing details.

Table 3.2 : Series of Birthing Details

Variables	Results
Mode of delivery	
Caesarean Section	**35,1 % (n=13)**
NVD	**64,9 % (n=24)**
APGARS	
1 Minute	**7,6 ± 1,32 (n=38)**
5 Minutes	**9,6 ± 0,63 (n=38)**
Birth Weight	**2885,9 g ± 510,71 (n=40)**
Birth Length	**46,72cm ± 4,32 (n=39)**
Head Circumference	**36,1cm ± 2,26 (n=39)**

3.4 APGAR SCORES AT 1 MINUTE AND 5 MINUTES COMPARING THE SIGNIFICANCE WITH REGARDS TO MODE OF DELIVERY

3.4.1 APGAR score at 1 minute for neonates born with MMC's via normal vaginal delivery (NVD) was compared to neonates born via caesarean section (C-section) in Table 3.3. The result was not significant at $p < 0,05$ where the t-value = -0,24 and the p- value = 0,41.

Table 3.3 : Unpaired student *t* test comparing APGAR scores at 1 minute for neonates born via NVD vs. C-section

Group	NVD	C- section
Mean APGAR at 1 minute	7,7	7,8
Standard Deviation	2,11	1,42

Sum of Difference squared	42,29	15,67
N	21	12

3.4.2 APGAR score at 5 minutes for neonates born with MMC's via normal vaginal delivery (NVD) was compared to neonates born via caesarean section (C-section) in Table 3.4. The result was not significant at $p < 0,05$ where the t-value = -1,12 and the p- value = 0,13.

Table 3.4 : Unpaired student *t* test comparing APGAR scores at 5 minute for neonates born via NVD vs. C-section

Group	NVD	C- section
Mean APGAR at 5 minutes	9,6	9,8
Standard Deviation	0,56	0,15
Sum of Difference squared	11,14	1,67
N	21	12

3.5 CLINICAL CHARACTERISTICS

No neonates were born with a cervical MMC. Only 3 neonates had thoracic MMC's with the majority, 84,4 % in the study having lumbar , whilst 4 had sacral MMC's. The majority had Colpocephaly, Chiari Malformation and Hydrocephalus. Most MMC's did not have CSF leak at birth. See table 3.3 for the summary of the clinical characteristics.

Table 3.5: Clinical characteristics of our sample, N=45

Characteristic	Frequency	Percentage
Chiari Malformation - Type II		
No	15	33.33
Yes	30	66.67
Hydrocephalus		
No	10	22.22
Yes	35	77.78
Colpocephaly		
No	15	33.33
Yes	30	66.67
Level of lesion		
Sacral	4	8.89
Lumbar	38	84.44
Thoracic	3	6.67
CSF Leak		
No	27	69.23
Yes	12	30.77

3.6 CLINICAL CHARACTERISTICS BY GENDER

82,8 % of males had Chiari Type II malformations whereas 62,5 % of females did not have a Chiari Type II malformation. 76% of males had Hydrocephalus along with most females, that is, 81% as well. Both males and females predominantly had lumbar MMC's.24 males and 14 females which work out to 83% and 87% respectively.

Approximately two thirds of patients had Colpocephaly, that is, 19 males (66%) and 11 females (69%). See below for the summary of the clinical characteristics in table 3.6.

Table 3.6: Clinical characteristics by gender

Characteristic	Males	Females	P-value
Chiari Malformation - Type II			
No	5 (17.2)[1]	10 (62.5)	0.002
Yes	24 (82.8)	6 (37.5)	
Hydrocephalus			
No	7 (24.1)	3 (18.7)	0.677
Yes	22 (75.9)	13 (81.3)	
Level of lesion			
Sacral	3 (10.34)	1 (6.25)	0.892
Lumbar	24 (82.76)	14 (87.5)	
Thoracic	2 (6.9)	1 (6.25)	
Colpocephaly			
No	10 (34.5)	5 (31.3)	0.826
Yes	19 (65.5)	11 (68.7)	

[1]All values are frequencies with percentages in parenthesis

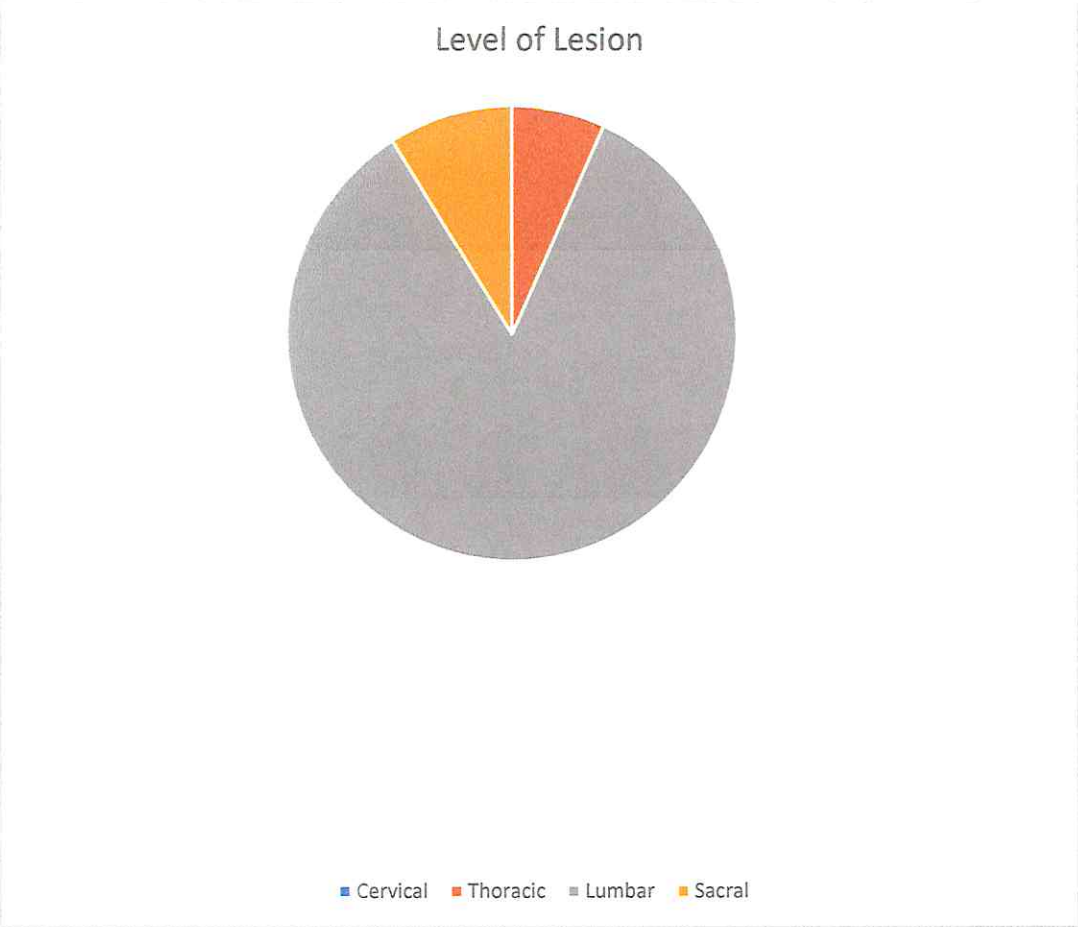

Figure 3.1 Distribution of the level of the lesions

3.7 GENDER DISTRIBUTION ACCORDING TO YEARS

The average number of neonates born with MMC's are 11.25 per year. The most prominent year in which MMC's were born was in 2015 which is equal to 40% then followed by 2018 which is 28.9%. The year with the least amount of MMC's was in 2016 with 2017 close behind. A summary of the details can be found in Table 3.7

Table 3.7: Gender distribution according to years

Gender	2015	2016	2017	2018	totals	Average	%
Male	11	4	7	6	28	7	62,22%
Female	7	2	1	7	17	4.25	37.78%
Totals	18	6	8	13	45	11.25	

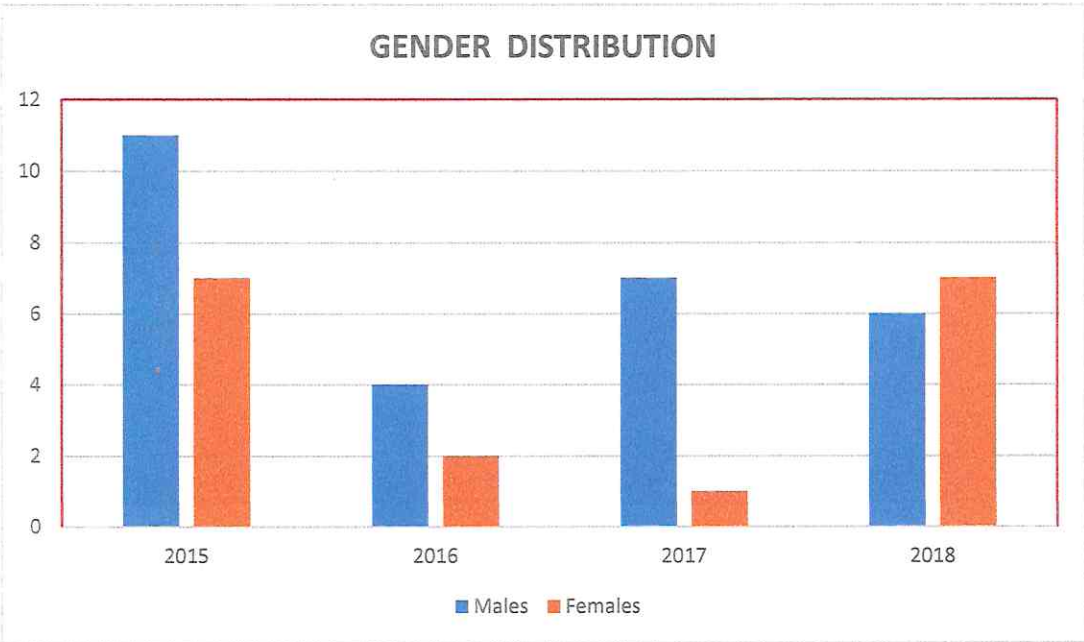

Figure 3.2 Gender distribution according to years

3.8 GENDER DISTRIBUTION ACCORDING TO MMC VARIABLES

See tables 3.8.1 to 3.8.6 for summaries

Table 3.8.1: Gender distribution of patients with Chiari II Malformation with and without Hydrocephalus

The Fisher Exact test statistic value is 0,5614. The result is not significant at $p < 0,05$

Gender	Chiari II with Hydrocephalus	Chiari II without Hydrocephalus	Marginal Row Totals
Male	21	4	25
Female	6	0	6
Marginal column totals	27	4	31(grand total)

Table 3.8.2: Gender distribution of patients without a Chiari II Malformation with or without Hydrocephalus

The Fisher exact test statistic value is 0,2821. The result is not significant at $p < 0,05$.

Gender	No Chiari II with Hydrocephalus	No Chiari II with NO Hydrocephalus	Marginal Row totals
Male	1	3	4
Female	7	4	11
Marginal column totals	8	7	15(grand total)

Table 3.8.3: Gender distribution of patients with Chiari II malformation and Hydrocephalus according to the level of the lesion.

Gender	Chiari II,HCP and Lumbar MMC	Chiari II,HCP and Thoracic MMC	Chiari II,HCP and Sacral MMC
Male	17	2	2
Female	6	0	0

Table 3.8.4: Gender distribution of patients with Chiari II malformations without Hydrocephalus according to the level of the lesion.

Gender	Chiari II, No HCP and Lumbar MMC	Chiari II, No HCP and Thoracic MMC	Chiari II, No HCP and Sacral MMC
Male	4	0	0
Female	0	0	0

Table 3.8.5: Gender distribution of patients without Chiari II malformation with Hydrocephalus according to the level of the lesion.

Gender	No Chiari II,HCP and Lumbar MMC	No Chiari II,HCP and Thoracic MMC	No Chiari II,HCP and Sacral MMC
Male	1	0	0
Female	6	0	0

Table 3.8.6: Gender distribution of patients without Chiari II malformation nor Hydrocephalus according to the level of the lesion.

Gender	No Chiari II, No HCP and Lumbar MMC	No Chiari II, No HCP and Thoracic MMC	No Chiari II, No HCP and Sacral MMC
Male	2	0	1
Female	2	1	1

3.9 TIMING TO MMC SURGERY

Timing to surgery is presented in table 3.10 and a frequency distribution relation to timing intervals to surgery is presented in Figure 3.4.

Table 3.9: Timing to MMC surgery

Variable	Result
Mean timing to MMC surgery	**42,93 ±75,21 (n=45)**

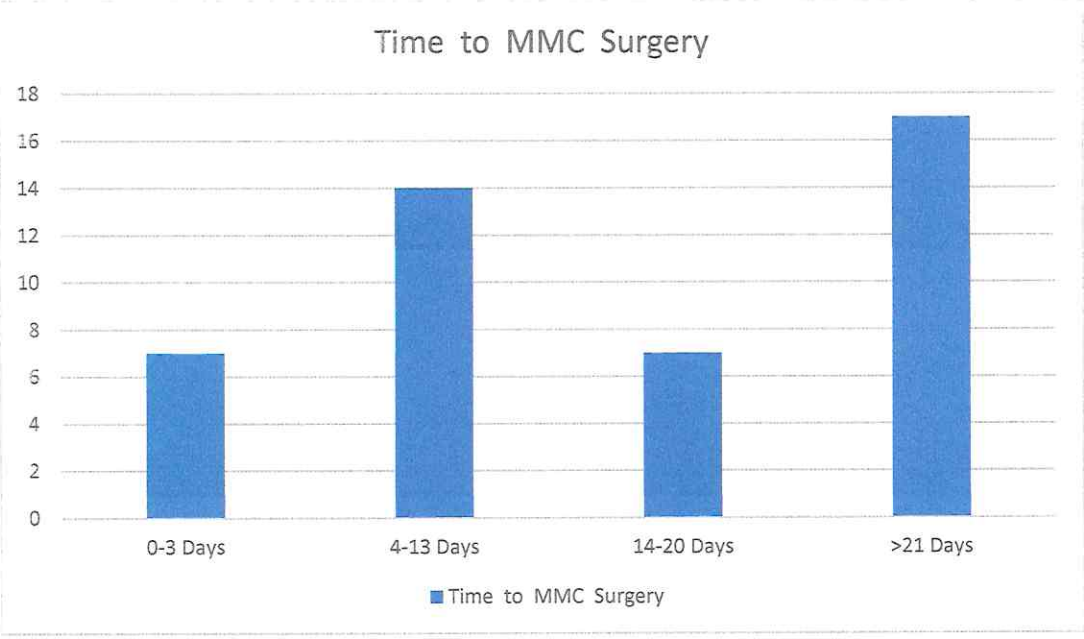

Figure 3.3: Timing to MMC Surgery

3.10 MATERNAL PARAMETERS

The maternal distribution of age, which number pregnancy this was,

that was associated with an MMC and number of children was tabulated and summarised in table 3.11.

Table 3.10: Maternal Parameters

Variables	Results
Maternal age distribution	Mean 28,18 ±5,68 (n=38)
Number of this pregnancy	Mean 2,14 ±1,11 (n=37)
Number of children	Mean 2,16 ±1,04 (n=37)

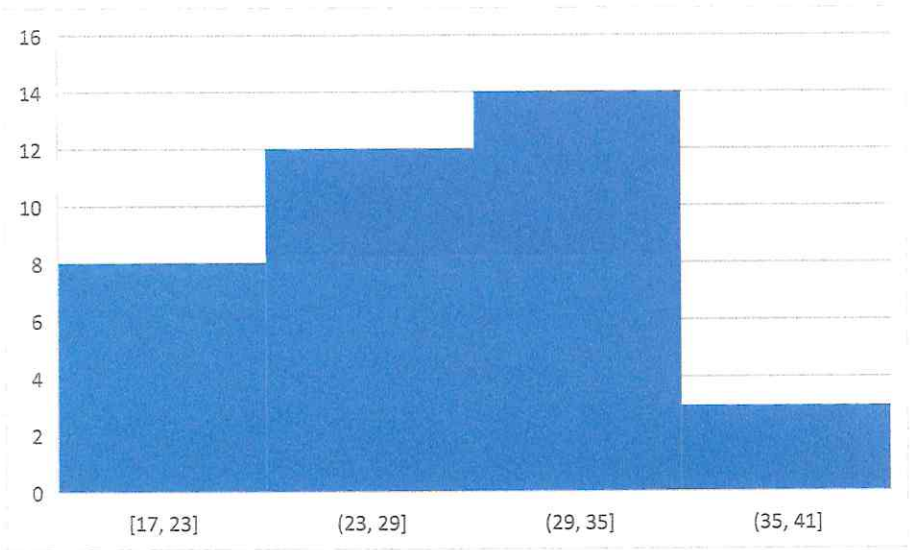

FIGURE 3.4: Maternal Age

4. DISCUSSION

4.1 SAMPLE SIZE

This was a not a large study even though it was retrospective spanning over 4 years. All patients born with MMC's during this time were not taken into account as not all patients met the inclusion criteria. Another factor influencing the number was the fact that only those patients with MMC's who were operated was included in this study. Mirzai H et al in a Turkish study reported 190 MMC Repairs done over a 15 year period which works out to about 12 repairs per year(63).

The current study reports on 45 patients, which works out to 11 per year, which is in keeping with the numbers from the Turkish study. According to the MOMS trial of which 183 patients were operated across 3 Centres over a 7-year period, 8 were operated a year, but this number may be skewed due to the very stringent inclusion criteria.

4.2 SERIES DEMOGRAPHICS

Analysis of the demographics revealed that the mean gestational period was 38,78 weeks with a standard deviation of ± 1,71. This is in keeping with the median time from ovulation to birth according to Jukic A.M et al from Durham, USA. This is above the 37 week mark, which defines preterm labour(64). The demographics regarding race is quite skewed towards those of African descent as the CHBAH is situated in Soweto which is a predominantly African populated district. There are 2 neonates of Coloured descent as well with no other racial groups represented. One cannot say whether the percentage of neonates of African descent, 95,6 %, would remain as high if a National Audit was made as to the prevalence of MMC's with regards to racial groups. With

regards to the sample size, 29 were males and 16 were females that had MMC repairs between 2015 and 2018. This works out to an almost 2 is to 1 ratio (2:1) which is not in keeping with most studies where there is a female predominance. Protzenko T et al in a Brazilian study showed a slight female predominance of 55.4% in their study(65).

4.3 SERIES OF BIRTHING DETAILS

Most of the births were via NVD at 64,9 % and not via C-section. This is in line with the predominantly postnatal as opposed to prenatal diagnosis of MMC's in South Africa(52).

Analysis of the MMC cohort's mean weight, mean length and mean head circumference revealed that the means were within normal range for neonates(66) . The APGAR scores at 1 minute and 5 minutes were both within the normal range, with mean scores of 7.6 and 9.6 respectively. When a comparison was made between APGAR scores for neonates born via NVD vs. neonates born via C-section, it appeared that APGAR scores were better at both 1 minute and 5 minutes for neonates born via C-section as opposed to NVD. The difference was a mean APGAR score of 7,8 as opposed to 7,7 at 1 minute and 9,8 and 9,6 at 5 minutes which were both in fact negligible. These results, although not significant, potentially highlight the importance of a planned C-section for neonates born with MMC's.

4.4 CLINICAL CHARACTERISTICS

Chiari type II malformations were common in this series cohort with a percentage of 66,67 %. This is in keeping with the worldwide literature on Chiari II with regards to MMC's although it may be slightly on the lower side of the reference range. Stevenson

et al from Georgia, USA found that Chiari II was associated with MMC's 80 % of the time whilst another US study in Baltimore by Shrot et al found it was only associated in 60 % of their cases. The rate of Hydrocephalus in this series was 77,78 % and was in line with the studies conducted by both the Georgia and Baltimore groups. Colpocephaly has been widely touted as to be associated with myelomeningoceles and in this study this statement appears to be quite accurate with 66,67 % of these patients having colpocephaly(25, 26). There is a higher incidence of lumbar MMC's which is in keeping with literature from the rest of the world which makes sense as these are also more compatible with life. This was based on a clinical observation as not all MMC patients at CHBAH had MRI scans due to the poor resource situation in South Africa and the long waiting times to have MRI scans done. According to Copp et al, the higher the level of the lesion, the worse the neurology and more marked hydrocephalus thus needing repeated shunt revisions(4, 65). In this particular study, no such correlation was made. There were only 3 patients with thoracic MMC's, 1 of which had neither a Chiari Type II malformation nor hydrocephalus. Of the lumbar and sacral MMC's, most had hydrocephalus. If we take it that the level of the lesion works out to more marked hydrocephalus and hence worse neurology, it stands to show that there should be no chance of even 1 patient with a thoracic MMC not having any hydrocephalus. If we break this down further, it equates to only 66,7% of patients with thoracic MMC's having hydrocephalus with the rest being normocephalic in this study. This however cannot be permitted as the study sample for this particular variable is so small and is therefore not of any statistical significance. No cervical MMC's were operated in the time frame of this study. This could mean that these MMC's are significantly more fatal than the other sites for MMC's in that these neonates do not survive to have a chance of a repair for which ever reason. Either the foetus may have demised in the

womb, or very soon after birth or even that the pregnancy was terminated for fear of a poor prognosis. The last point is the least likely in our population as most of the women either booked to late, so therefore could not terminate or decided against having a termination of pregnancy. This being said, it was not possible to correlate a higher level of the lesion with poorer outcome neurologically, worse hydrocephalus or even death. CSF leak at birth was present in 30,77 % of neonates in this series. In comparison to the series by Sattar et al from Pakistan, this is quite a high rate(67). Sattar et al reported a rate of 3.8 %(67). The high rate may be explained by the low rate of C-section deliveries in this series leading to birth trauma of the MMC sac via NVD.

4.5 CLINICAL CHARACTERISTICS BY GENDER

Chiari Type II malformation was the only variable that showed a significant relationship associated with sex (p-value = 0,002). It was found to be strongly associated with males when compared to females. In literature the opposite is true. In addition, results from the Fisher's exact test suggest that there was no statistically significant association between level of lesion and hydrocephalus (p-value= 0.796). There are no other significant findings that could be deduced with regards to the relationship between MMC,s, hydrocephalus, Chiari Type II malformation, colpocephaly and the level of the lesion when comparing males and females.

4.6 GENDER DISTRIBUTION ACCORDING TO YEARS

According to Table 3.9 and Fig 3.2 there was a male predominance for all the years except 2018. The most prominent year for MMC's was 2015. It tapered off again in

2016 and 2017 with a slight incline in 2018. CHBAH has many feeder hospitals including Klerksdorp in the North West Provence. High risk pregnancies are referred to CHBAH as well as neonates that need Neurosurgical intervention. In 2014 the Uranium mines in Klerksdorp re-opened which brought along with it, all its environmental problems. This could in part be the cause of the increase in Neonates seen at CHBAH in 2015. Equally in 2016, the first set of Neurosurgery Registrars were sent to work in Klerksdorp-Tshepong Hospital Complex. Having these Registrars rotating there could have assisted with the decline in patients seen in 2016 and 2017, with 2018's value not being particularly high but rather in keeping with the number of patients repaired globally.

4.7 GENDER DISTRIBUTION ACCORDING TO MMC VARIABLES

In this series cohort, 21 males had both Chiari II and hydrocephalus compared to only 6 females. None of the females who had a Chiari Type II malformation were normocephalic. Of the total number of neonates that had MMC's, only 8 suffered with Hydrocephalus alone, one of which was male with 7 being female. A further 7 patients had neither Hydrocephalus nor Chiari Type II malformation. Thoracic MMC's were scarce in this series cohort as in keeping with data demonstrated worldwide with 3 being repaired,2 male and 1 female. The majority of males and females both had lumbar MMC's with the second highest frequency being sacral MMC's. There was no statistical significance with regards to the MMC variables tabulated in this series except that of the Chiari Type II Malformations being predominant in the male population. This finding is directly correlated with the male predominance overall and is in contrast to the

findings by Messing- Junger et al where there were more females with MMC's and related to Chiari II with a frequency of 56 %(68).

4.8 TIMING TO MMC SURGERY

The mean time to MMC repair was 42.93 days and only 7 of the 45 cases were operated upon at less than 72 hours, which is the generally accepted gold standard; although, as addressed according to the latest literature by Beier et al with the Guidelines Task Force, there is no evidence to support a decreased risk of wound infection or ventriculitis(43, 60). This less than desirable timing is the result of multiple factors. Delayed referrals, transfer from peripheral hospitals to CHBAH and availability of the operating theatre were all systemic factors that delayed repair times. Delays based on medical grounds, for medical optimisation prior to surgery, was responsible for the longest delays especially with regards to those neonates that was born premature. This has skewed the results quite significantly by increasing both the mean and standard deviation which was 75,21. Unfortunately, in the current series there were 17 neonates that were repaired beyond or on day 21. Although timing to repair in the current series is not ideal it is interesting to note that of the 45 who underwent an MMC repair, only 7 have since demised. As a comparison, Atenello et al from the United States reported on the timing of MMC repairs based on countrywide databases as 19% after the 48 hour mark(61). Idowu and Apemiye from Nigeria commented that the majority of patients were repaired after day 7 of life and Sattar et al from Pakistan reported that their average time to repair was 4 weeks(67, 69).

4.9 MATERNAL PARAMETERS

The mean maternal age was 28,18 with a standard deviation of 5,68. The Skewness was -0,145 with Kurtosis being -1,08 therefore when calculating the Kolmogorov-Smirnov Test of Normality, the result indicated that age was distributed normally with a p- value of 6,28 and the K-S test statistic (D) = 0,124. These statistics fall with the age of women who are of childbearing age. According to Vieira et al age is a risk factor with regards to having a child with an NTD. This is reserved for woman at the ends of the spectrum, that is, young woman below 19 years of age as well as older women above 40 years of age(70). The reason for these 2 peaks may be due to the fact that younger females are less likely to attend antenatal clinic and therefore may not be taking periconceptual folic acid whilst woman in their forties are more prone to having genetic mutations. In this particular study however, this is not the case.

4.10 LIMITATIONS

The small sample size of 45 patients limited the statistical tests aiming to compare the parameters of interest. Future studies expanding on this study would probably yield more statistically relevant results especially if all patients born with MMC's are taken into account rather than just those that were operated. As this was a retrospective study, data was very difficult to attain due to poor record keeping therefore a prospective study would greatly assist with this limitation. The author reviewed all the data pertaining to this study and could therefore be a source of bias.

4.11 CONCLUSION

The study provided good insight into the relationship between MMC's, Hydrocephalus and Chiari Type II Malformations as well as the implication of the level of the lesion and the association with Colpocephaly. There was a high male predominance as compared to females seen in this study but the rest of the data correlates fairly closely with those seen in international studies. A strong recommendation from this study is that all neonates born with MMC's seen at CHBAH should have cranial ultrasounds and that it may be uploaded on the PACS system. If the cranial ultrasound is difficult to interpret that a CTB be performed. Colpocephaly can be differentiated from Hydrocephalus avoiding over treatment of enlarged ventricles. This will therefore also assist in preventing the complications associated with shunts. If the patients are too ill to undergo a CT Brain scan, the scan be delayed until such time the patient is well enough. According to the latest literature, even if the MMC is leaking, the closure can be delayed as long as the patient is started on adequate antibiotics(43).In CHBAH patients are inadvertently delayed from having their repairs done due to many constraints in the public sector. What is good is that this long waiting time has been shown not to affect the outcomes of these patients. Of the 45 patients, only 7 known to the author have demised. What is not known was whether these patients had leaking MMC's and when the repair was done although statistically, if only 15.6% demised this again attests to the above-mentioned statement. What can be recommended is if there is a delay in closure, antibiotics should be started. What should also be implemented is not only clinical and radiological check-ups but psychosocial and cognitive tests as well. That means working hand in hand with the allied health professionals which could in turn lead to the neonate being shunted when appropriate and therefore become a contributing member to society.

Prevention strategies in South Africa are geared more towards preventing the development of MMC's with preconception use of folic acid in women of child bearing age. These strategies do not take into account the roles of other environmental factors nor does it take into account how these environmental factors actually interact with genetic factors. Women should also be counselled with regards to the fairly higher percentages of having children with genetic mutations with advanced maternal ages. This may be another avenue to explore with regards to the prevention of MMC's.

In Johannesburg the dosage of periconceptional use of folic acid is 400mcg for low risk woman and 5mg daily for high risk women 3 months prior and after conceiving. This is thought to now be universally accepted. State hospitals stock Pregamal tablets which contains 400mcg of folic acid in addition to the iron.

The folate status may be obtained by various biological markers namely Red Cell Folate, Serum or Plasma folate and homocysteine(18). Future studies could be focussed on the environmental factors associated with our population leading to the development of MMC's.

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APPENDIX A

DATA SHEET

RESEARCH NUMBER: _____

AGE :_____ DOB :_____ DOS:_____ TTS:_____ RACE :_____

SEX : M/F _____ BIRTH WEIGHT: _____ LENGTH:_____ GESTATION:_____

APGARS: 1 MIN_____ 5 MIN_____ HEAD CIRCOMFERENCE:_____

MODE OF DELIVERY:_____

CHIARI MALFORMATION: Type I _____ None_____

Type II _____

Type III _____

Type IV _____

HYDROCEPHALUS : Yes _____ No _____

COLPOCEPHALY : Yes _____ No _____

LEVEL OF LESION : Cervical _____

Thoracic _____

Lumbar _____

Sacral _____

APPENDIX A

MATERNAL PARAMETERS

MOTHER'S AGE: _____

NUMBER OF PREGNANCIES:_____ NUMBER OF CHILDREN:_____

WHAT NUMBER WAS THIS PREGNANCY:_____

NUMBER OF CHILDREN WITH MMC's :_____

APPENDIX B

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr I Human

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M190420

NAME: (Principal Investigator)	Dr I Human
DEPARTMENT:	School of Clinical Medicine Department of Surgery Division of Neurosurgery Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	An analysis of the relationship between Myelomeningoceles, Hydrocephalus and Chiari Malformations
DATE CONSIDERED:	2019/04/26
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr JR Ouma
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2019/05/27

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 on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore reports and re-certification will be due early in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

28/06/2019.
Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

APPENDIX C

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 18th March 2019

TITLE OF PROJECT: An analysis of the relationship between Myelomeningoceles, Hydrocephalus and Chiari Malformations,

UNIVERSITY: Witswatersrand

Principal Investigator: Dr IN Human

Department: Neurosurgery

Supervisor : Dr C Profyris

Permission Head Department (where research conducted): Yes

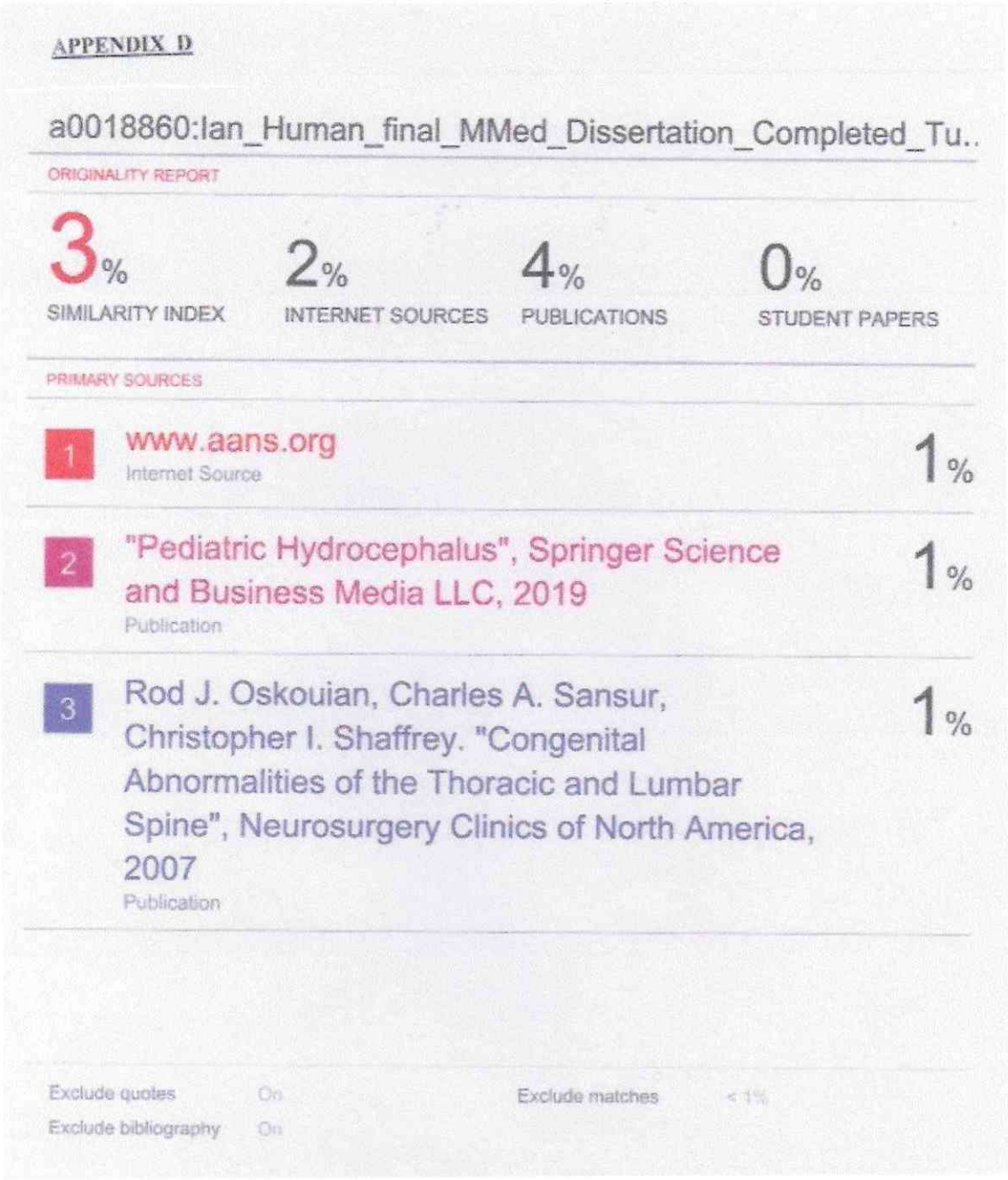
The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 18/03/2019

Approved/~~Not Approved~~
Hospital Management
Date: 26/03/2019

APPENDIX D



APPENDIX D

a0018860:Ian_Human_final_MMed_Dissertation_Completed_Tu..

ORIGINALITY REPORT

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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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2	"Pediatric Hydrocephalus", Springer Science and Business Media LLC, 2019 Publication	1%
3	Rod J. Oskouian, Charles A. Sansur, Christopher I. Shaffrey. "Congenital Abnormalities of the Thoracic and Lumbar Spine", Neurosurgery Clinics of North America, 2007 Publication	1%

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APPENDIX E

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Dr IAN NOEL HUMAN (Student number: 1732178) am a student registered for the degree of MMED (NEUROSURGERY) in the academic year 2019.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 20/11/2019

APPENDIX F

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Department of Paediatrics and Child Health
Metabolic Unit
Chris Hani Baragwanath Academic Hospital
P. O. Bertsham
2013

14 May 2019

The Research Protocol Review Committee
Chris Hani Baragwanath Academic Hospital
Soweto
Johannesburg
South Africa

Dear Madam/ Sir

I would like to inform you that **Ian N. Human** has been given a permission to conduct his research study in the Department of Paediatrics at Chris Hani Baragwanath Academic Hospital. The title of his study is: **"An analysis of the relationship between Myelomeningoceles, Hydrocephalus and Chiari Malformations."**

While he has been given permission to conduct this study, he cannot start with data collection until he has provided the Department with Ethics Committee Clearance Certificate.

Yours Sincerely

Professor SC Velaphi
Head of Department of Paediatrics
Chris Hani Baragwanath Academic Hospital