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SINGLE SURGEON SERIES OF MYELOMENINGOCOELE REPAIRS: FACTORS INFLUENCING OUTCOMES

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

Johannesburg, 2018

DECLARATION

I, Christos Profyris, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Neurosurgery at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature: 

..17th day of…February….2018……in……Parktown……

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Dr John Ouma for his sound advise and guidance.

The past and present staff from the Paediatric and Neurosurgery Departments at the Chris Hani Baragwanath Academic Hospital.

The administration staff at the Chris Hani Baragwanath Academic Hospital.

My wife Isabel, Liko and my parents Nikolaos and Matina for their unwavering support.

PRESENTATIONS AND PUBLICATIONS ARISING FROM THIS STUDY

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ABSTRACT

This study reports on 24 Myelomeningocoeles (MMC) repaired at Chris Hani Baragwanath Hospital by a single surgeon.

Mean gestation was 38.13 weeks, most MMCs were in the lumbosacral region and mean MMC surface area was 19.4cm^2. Cerebrospinal Fluid (CSF) leak at birth was present in 50%, lower-limb neurology in 71%, lower cranial nerve dysfunction in 13% and hydrocephalus in 54%. Clubfoot was present in 71%, congenital hip dysplasia in 24%, neurogenic bladder in 82% and cutaneous abnormalities in 12%.

Mean time from birth to MMC repair was 13.6 days, 46% of infants had ventriculoperitoneal shunt insertion and latex allergy was absent.

Complication wise, wound dehiscence arose in 21%, CSF leak in 12.5% and infection in 25%. Neonates with CSF leak subsequently developed both wound dehiscence and CSF infection.

Maternal HIV prevalence within the series was 28% and there was potential correlation between CSF infection and birth to a positive mother.

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LIST OF ABBREVIATIONS

APGAR	Appearance, Pulse, Grimace, Activity and Respiration
BMP	Bone Morphogenic Protein
C	Caesarean
CHBH	Chris Hani Baragwanath Hospital
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
EVD	External Ventricular Drain
HIV	Human Immunodeficiency Virus
L	Lumbar Level
MMC	Myelomeningocoele
MOMS	Management of Myelomeningocoele Study
MRI	Magnetic Resonance Imaging
NTD	Neural Tube Defect
NVD	Normal Vaginal Delivery
VP	Ventriculoperitoneal

1. INTRODUCTION

Myelomeningocoele (MMC) is a central nervous system (CNS) malformation that belongs to the group of anomalies that encompass spinal dysraphism.[1] Following congenital heart anomalies, spinal dysraphism forms the second most frequent group of birth malformations.[2]

1.1 Epidemiology

Incidence of spinal dysraphism varies greatly according to geographical location and varies between 1 per 200 live births to 1 per 10,000 live births.[3] Aetiology is largely multi-factorial with genetic and environmental interplay. Mothers that have conceived a child with an MMC have 3% risk in subsequent pregnancies and mothers that have conceived two children with an MMC have a 10% subsequent risk.[4] Folate deficiency is a well-known cause for MMC development and has received considerable attention as preventative treatment – *see section 1.5.1*.[5] Anti-epileptic medication increases the risk of neural tube defects (NTDs), with sodium valproate increasing the risk 20-fold.[6] Other factors thought to increase the risk of MMCs include diabetes, obesity, heat exposure, fever, alcohol, tobacco and illicit substance abuse.[4]

1.2 Pathology

1.2.1 Neural Tube Development

The neural tube is the embryonic scaffold upon which the future CNS develops. Development of the neural tube is a post-gastrulation event, at which point the embryonic disc is composed of ectoderm, mesoderm and endoderm and is surrounded by the amniotic cavity dorsally and yolk sac ventrally. On days 16-17 post-conception, the notochord in the midline of the embryonic mesoderm develops as a solid structure.[7,8] The notochord secretes nogin, chordin and folliculostatin. These molecules act as inhibitors to Bone Morphogenic Protein (BMP) – 4 and block the binding of BMP-4 to its receptor on the ectoderm.[1,8] By day 20 post-conception, this process induces the dorsally overlying ectoderm to fold inwards and form the neural groove centrally and plates laterally. This marks commencement of *Primary Neurulation* – see Figure 1.1.[7,8]

Following initiation of *Primary Neurulation*, the lips of the neural folds disjoin to form the neural crest and then proceed to unite with their contralateral counterpart to form the neural tube. Once formed, the neural tube lies deep to overlying ectoderm and mesodermal derived vertebral arches encircle the neural tube to form the future lamina and spinous processes. In a zipper-like manner, this process proceeds along the cephalo-caudal axis of the embryo until only cranial and caudal neuropores are present. These neuropores form transient connections between the neural tube lumen and the amniotic cavity. Eventually, the cranial neuropore closes on day 25, its remnant the lamina terminalis and the caudal neuropore closes on day 28, its remnant at lumbar spine level one (L1). Enclosure of the neural tube marks completion of *Primary Neurulation*.[7,8]

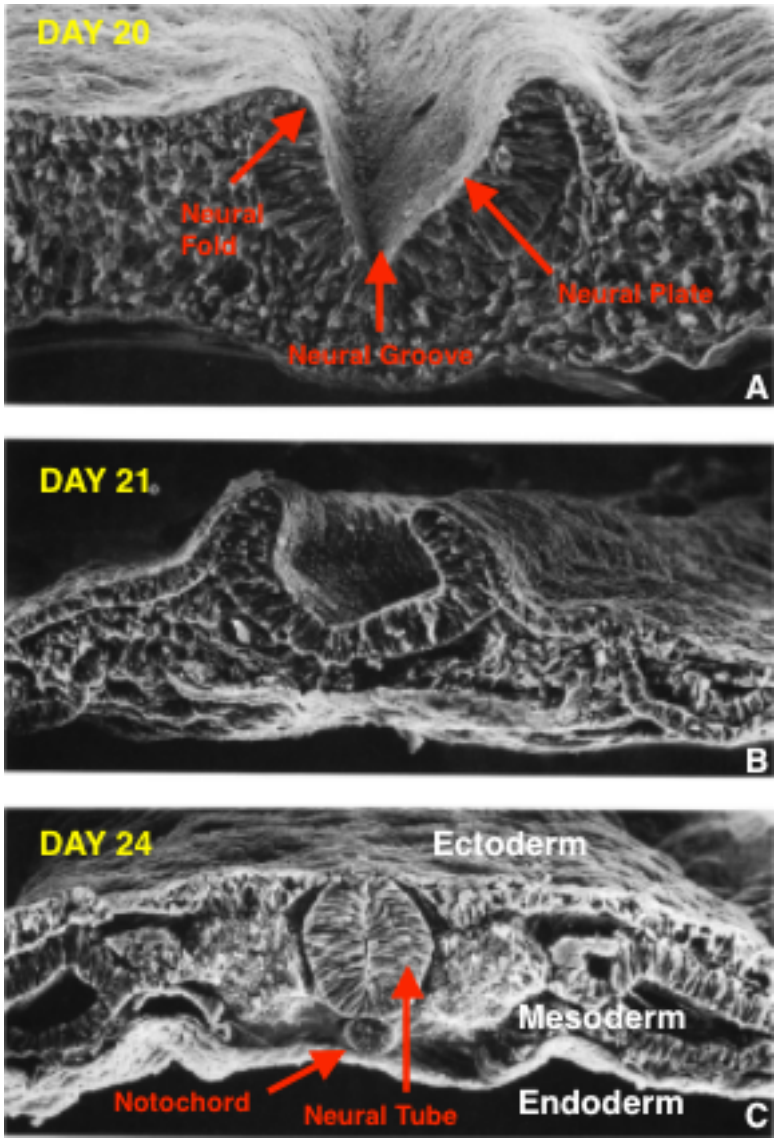


Figure 1.1: Scanning electron micrograph depicting primary neurulation in a chick embryo. Days in top left corner indicative of days post-conception in a human equivalent. **A** Neural folds commence folding and forming neural groove. **B** Progression of neural groove folding. **C** Completion of neural tube formation.[53]

Secondary Neurulation forms the part of the spinal cord below S2 and includes lower sacral spinal segments, conus medularis and the cauda equina – see Figure 1.2. It is composed of two stages: Tail bud canalisation of the medullary cord, which occurs between days 28-48 and *regression*, which occurs from day 48 up until birth. During *tail bud canalisation* the tail bud derives 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 distal neural tube. Following formation, the distal neural tube ascends to fuse with the neural tube formed by *Primary Neurulation*.[7,8]

In summation, *Primary Neurulation* forms the CNS from telencephalon to L1 and *Secondary Neurulation* forms the CNS from L1 to the cauda equina.[7,8]

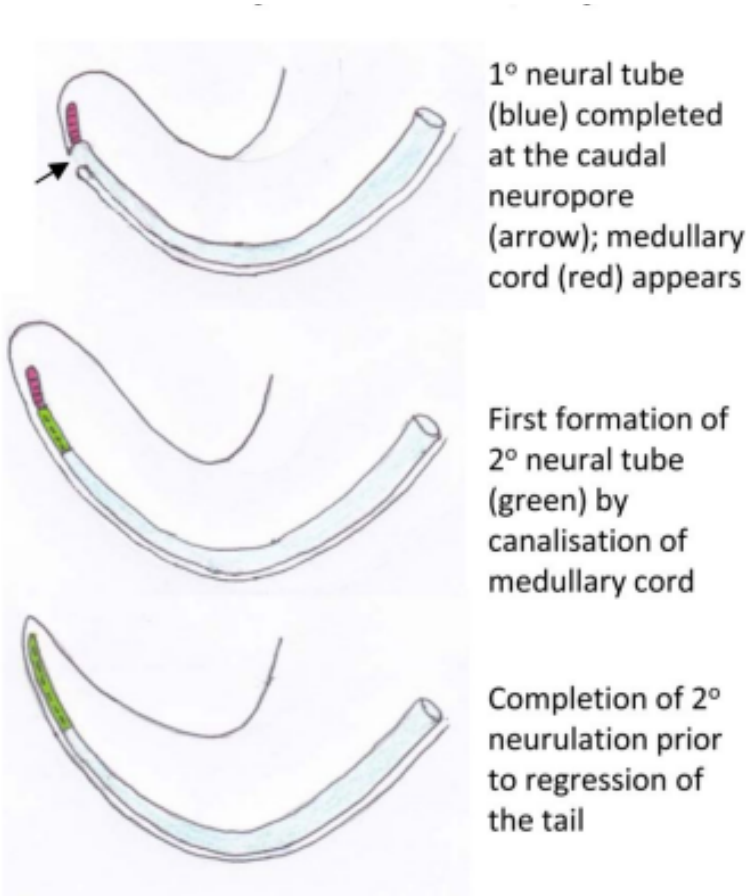


Figure 1.2: Diagrammatic representation of secondary neurulation showing tail bud canalisation.[54]

1.2.2 Embryopathology of Spinal Dysraphism and MMCs

Spinal dysraphism is a congenital anomaly that arises from defective neural arch formation and ensuing herniation of meninges, neural elements or a combination of the two. Depending on the presence of covering skin and the contents of the herniated sac there are a variety of clinical manifestations. In broad terms, spinal dysraphism can be subdivided into *closed spinal dysraphism* and *open spinal dysraphism*.[4,9]

In *closed spinal dysraphism*, the neural tube has disjoined from the ectoderm and an intact layer of skin lies between the environment and the underlying anomaly. It is often associated with overlying cutaneous manifestations such as naevi, hypertrichosis, skin dimples or haemangiomas. Clinical manifestations of *closed spinal dysraphism* based on this definition include unfused spinous processes, intradural lipoma, filum terminale fibrolipoma, filum terminale thickening and shortening, myelocystocoele, lipomyelomeningocoele, meningocoele and dermal sinus tracts with or without epidermoids and dermoids.[4,9]

In the *open* variety of dysraphism there is failure of disjunction between the ectoderm and neural folds. This leads to exposed meninges or neural elements and is clinically confined to open MMCs The remainder of this discussion will focus on MMCs.[4,9]

Embryologically, MMC is the manifestation of aberrant primary spinal neurulation. The caudal neuropore fails to disjoin from the ectoderm leaving the neural placode exposed. This prevents mesodermal derived vertebral arches from migrating dorsally and enclosing the future spinal cord. Consequently, the placode is exposed to amniotic fluid, which hinders neurodevelopment by causing neuronal apoptosis and deranged axonal connections. Ultimately, there is a malformed spinal cord and an MMC presentation at birth.[4,9]

1.2.3 Molecular Biology of MMCs

Honing in on candidate genes responsible for MMC formation has been a difficult task. This is likely the result of a multifactorial interplay between multiple candidate genes and environmental factors.[1] Multiple strategies, including genome-wide association, whole exome sequencing and whole genome sequencing have been employed in the endeavour to find responsible genes. These efforts have

yielded more than 200 genes that are implicated in MMC formation.[10] The function of these genes includes apoptosis, cell cycle signalling, cytoskeletal architecture, glucose metabolism, methylation, to name a few.[10] Despite this complexity, there are several signalling pathways that have received particular attention in regard to MMC formation. These signalling pathways are the planar cell polarity signalling pathway, sonic hedgehog pathway, BMP pathway, grainyhead-like gene pathway and retinoid signalling pathway.[1]

1.3 Clinical Presentation

Neonates born with MMCs are prone to numerous developmental abnormalities. Neurologically, neonates may have partial motor and sensory function below the lesion or have complete spinal cord paralysis.[4] This is associated with neurogenic bladder prevalence of up to 60%.[11] Hydrocephalus develops in 80-90% of neonates born with MMCs and presents with associated symptoms and signs of macrocephaly and increased intracranial pressure.[12] Imaging wise, apart from features of hydrocephalus there is increased prevalence of colpocephaly – enlargement of the occipital horns.[12] The Chiari Type II malformation is also common in neonates with MMCs and presents with opisthotonos, stridor, apnoea and even sudden death.[12] In later life, during growth spurts, children with MMCs may present with new onset neurological defecit secondary to a tethered spinal cord.[5] Eighty precent of children with MMCs attain a normal intelligence quotient (IQ) score; however this may be adversely affected by early onset meningitis.[13,14]

Apart from the CNS, numerous other organ systems may be affected in children with MMCs. Urological pathology includes horseshoe kidneys, hydronephrosis and renal failure secondary to the effects of a neurogenic bladder. Faecal incontinence may arise. The musculoskeletal system may be affected secondary to kyphosis or scoliosis, congenital hip dysplasia and clubfoot. Cutaneous lesions may also arise with various forms of naevi or hairy tufts around the lumbar region. Finally, neonates with MMCs may present with anal sphincter dysfunction or rectal prolapse and are commonly affected by latex allergy.[1,4,7]

Post-delivery, neonates with MMCs have a high risk of meningitis secondary to bacterial colonisation of their exposed neural placode. Meningitis in these neonates may progress to ventriculitis with ensuing cortical injury and a high

degree of morbidity and mortality.[1,4,7] In fact, not treating MMCs with surgical repair has a documented survival rate of 10-12% largely due to infective sequelae.[15]

1.4 Prenatal Screening and Diagnosis

The potentially devastating consequences of MMCs and their associated conditions has led to active screening protocols.

Maternal serum alpha-fetoprotein is detectable from week 12 of pregnancy and steadily increases up to week 32. At weeks 15-20, if serum alpha-fetoprotein is twice the normal amount, the risk for a NTD increases from baseline by 224-fold. Sensitivity for spina bifida is 91%, whereas sensitivity for anencephaly is 100%. [16]

Amniocentesis, to quantify amniotic alpha-fetoprotein, is also utilised. It peaks between 13-15 weeks of gestation and is recommended if a mother has had a previous child with a NTD or there is any uncertainty from the serum alpha-fetoprotein measurements and prenatal ultrasound. In addition to alpha-fetoprotein, acetylcholine esterase can also be measured as a NTD marker. Combining alpha-fetoprotein and acetylcholine esterase measurements as a screening tool for spina bifida achieves a sensitivity of 99% with a false-positive rate of 0.34%. Unfortunately, amniocentesis carries a miscarriage risk of up to 6%.[17]

Second-trimester foetal anatomic survey with prenatal ultrasound imaging has sensitivity of 98% in detecting spina bifida.[18] The advantage of prenatal ultrasound is its non-invasive nature and ability to detect associated anomalies such as hydrocephalus, clubfoot, Chiari malformation and kyphoscoliosis. With appropriate windows in the axial, coronal and sagittal planes the spine is completely assessed and a potential MMC can be fully characterised. Importantly, detailed assessment of the lower limbs and characterisation of flexion and extension motions at the hip, knee and ankle joints can provide crucial information that predicts neurological compromise. This information can be vital for pregnancy termination counselling and postnatal care for the future fetus.[18]

Foetal magnetic resonance imaging (MRI) has become an established adjunct to foetal ultrasound.[19] 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. It is particularly useful in settings such as maternal obesity, oligohydraminos and suboptimal foetal positioning where ultrasound evaluation may be limited. Although safe, foetal MRI is best considered following the first trimester to avoid the theoretical risk for teratogenesis and improve the quality of images with a larger fetus.[19]

1.5 MMC Management

1.5.1 Pre-conception Management

The mainstay of MMC prevention is folic acid supplementation.[20] Folic acid administration during pregnancy was established by two randomised control trials in the early nineties. The Medical Research Council Vitamin Study Group demonstrated that administration of 4mg/day of folic acid in families with a history of previous NTDs had a 72% protective effect.[21] Czeizel *et al.* went on to demonstrate that 0.8mg/day of folic acid supplementation introduced prior to conception reduced the incidence of NTDs.[22] These two studies firmly established pre-conception folic acid administration in order to reduce incidence of NTDs and led to worldwide policies to fortify flour with folic acid. In fact, countries that established folic acid fortification had a marked reduction in NTD incidence.[20]

1.5.2 Post-Delivery Management

When MMCs have been detected prenatally, planned caesarean section delivery is advised. This ensures that the cerebrospinal fluid (CSF) filled MMC is not injured along the birth canal, which may lead to a CSF leak and subsequent infection. Following birth, the MMC should be covered with a non-adhesive silicone based dressing, layered on top with a piece of sterile gauze and then sealed with a plastic wrap. This prevents urine and faecal contamination. The dressing should be changed daily until surgery and the neonate nursed prone or on its side. Some centres advocate pre-operative antibiotic cover and if very early surgery is planned, some centres do not initiate oral feeds in order to prevent faeces and the potential for contamination.[23]

The first 24 hours of life are used to stabilise the neonate and assess for any other associated abnormalities, some of which, may have been identified prenatally. Pending the neonate is stable, blood is cross-matched and surgery for repair of the

MMC is planned within 48-72 hours of birth. This strategy has been developed to decrease the risk of meningitis secondary to CSF infection.[23] Controversy exists in regard to the timing of CSF diversion.[23,24] There are proponents of a simultaneous MMC repair and ventriculoperitoneal (VP) shunt insertion.[24] However, others advocate MMC repair followed by watchful waiting. If hydrocephalus arises a VP shunt is inserted; however for the 20% of patients that do not develop hydrocephalus, VP shunting and potential shunt complications are avoided.[23] Interestingly, Warf has demonstrated that endoscopic third ventriculostomy combined with choroid plexus cauterisation can treat 76% of infants with hydrocephalus secondary to MMC without the need for further surgery.[25] This can drastically reduce the requirement for shunting.[25]

Post MMC repair, multidisciplinary care is essential.[4] Urology wise, the neonate will require a renal tract ultrasound, urodynamic studies and a vesicourethrogram.[11] Parents will need to be taught how to perform intermittent clean catheterisation and anti-muscurinic agents are commenced.[11] Orthopaedic wise, input is required if the neonate has clubfoot or congenital hip dysplasia.[4] Finally, psychological support for the family is pertinent.[26]

1.5.3 Surgical Techniques for MMC repair

As MMC repair is neonatal surgery, special attention must be given to preventing hypothermia. It is recommended that theatre is kept at 28 degrees Celsius and that the neonate is kept warm with warming pads, cotton rolls, aluminium foil to cover the head and limbs, occlusive plastic sheets to cover the non-operative site and warm saline.[27] The neonate is proned and attention paid to pressure points and maintaining a free abdomen. Anaesthesia wise, special attention must also be given to monitoring intra-operative haematocrit and serum glucose.[27]

Surgical repair of MMCs requires precise dissection, meticulous haemostasis, minimal electrocautery and repair under magnification.[23] The junction of the neural placode with the surrounding dysplastic skin is defined and the narrow groove that bisects the placode in the midline identified. This represents the primitive ventral sulcus and is continuous with the central canal of the closed spinal cord proximal to the placode. 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 dermoids. Once the placode is free and the proximal junction of the placode with the normal spinal cord defined, the placode is reconstucted into a neural tube with a non-absorbable 6-0 monofilament suture. Following, 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 – *see Figure 1.3*.[23]

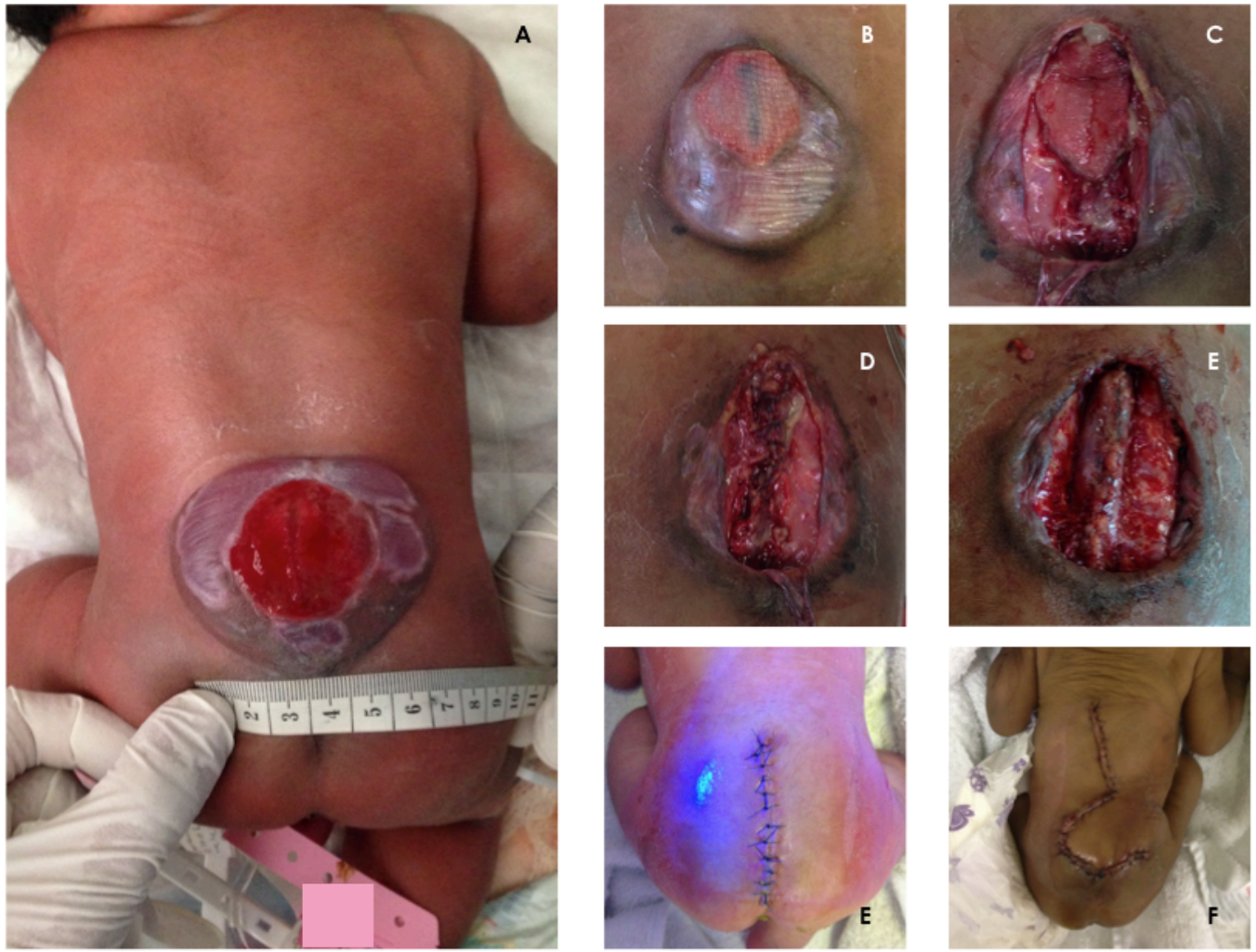


Figure 1.3: A Neonate with typical MMC from the series. **B** MMC placode and surrounding membrane with dysplastic skin. **C** Placode freed from surrounding dysplastic skin. **D** Reconstruction of placode into neural tube. **E** Dura was dissected off MMC cavity and closed primarily over the reconstructed placode. **F** Primary closure of MMC skin defect. **G** Author elected to utilise a Limberg flap as defect was large. NOTE: consent was obtained from parents for the presented photographs.

Of note, Albright *et al.* reported on distal cordectomy, whereby the placode is not reconstructed but rather excised at its proximal end, as an option for MMC repair.[28] They reported that the majority of infants treated with distal cordectomy retained preoperative motor function after surgery and proposed this technique as a viable option for the treatment of MMCs.[28] Distal cordectomy may be a procedure of choice in the setting of delayed MMC presentations.[28]

1.5.4 Long-Term Management

As children born with MMCs have multisystem involvement and are often disabled, on-going multidisciplinary care is essential.[29] It is estimated that the lifetime medical and non-medical costs of an individual with a NTD are $560,000 United States Dollars.[30]

Following discharge, neonates with MMCs are best followed-up under dedicated clinics that bring together all specialists involved in their care.[4,26,29] From a Neurosurgical standpoint, close monitoring is required for children with shunts and to anticipate symptoms related to a tethered cord syndrome that will require future release.[5] Urology wise, patients need to be followed-up for urinary catheter management and advised on a future bladder augmentation procedure.[11,29] Orthopaedic input is generally ongoing in the early years in the setting of clubfoot and congenital hip dysplasia.[29] Finally, psychological support is very important; initially for the parents and then for the child with the MMC, as they grow older.[26]

Despite disability, a considerable amount of neonates born with MMCs progress to become contributing members of society.[5] Some 82% of adults achieve independence in activities of daily living, 30% attend or finish University and 32% are gainfully employed.[5]

1.6 Prenatal MMC Repair: The MOMS Trial

Advancement in the field of foetal surgery inspired considerable interest in prenatal repair of MMCs.[31] Proponents of *in utero* repair advocated the *two-hit hypothesis* whereby the *first hit* comes about from failure of neural tube closure and the *second hit* comes about secondary to exposure of a normal spinal cord to amniotic fluid, direct trauma and hydrodynamic pressure. Based on this *two-hit hypothesis*, proponents argued that early foetal surgery ameliorates the second hit

by covering the spinal cord and protecting it from the effects of progressive exposure.[31]

On this background, the Management of Myelomeningocoele Study (MOMS) was initiated in 2003.[32] MOMS was a multicenter prospective randomised clinical trial comparing treatment outcomes between prenatally and postnatally repaired MMCs. Foetal surgery was performed at Vanderbilt University, University California San Francisco and at the Children's Hospital of Philadelphia. The planned sample size was 200 patients but the study was stopped early in 2010 after 183 patients by the Data Safety and Monitoring Board.[32]

The MOMS study concluded that prenatal intrauterine repair of MMCs between weeks 19-25 of gestation was superior to standard postnatal Neurosurgical repair in terms of long-term outcomes.[32] At one year of age following foetal surgery 40% of prenatally repaired MMCs required a VP shunt compared to 82% of postnatally repaired MMCs. At 30 months, 42% of prenatally repaired MMCs were walking independently compared to only 21% of the postnatally repaired group. Finally, hindbrain herniation was significantly reduced in the prenatally repaired group, potentially protecting this group from the severe sequelae of an Arnold Chiari Type II malformation.[32]

The MOMS trial also elucidated the risks in relation to foetal surgery for MMCs.[32] In the prenatally repaired group there was an increased risk of spontaneous rupture of membranes, oligohydraminos, preterm delivery and uterine thinning or dehiscence. These factors considered, the potential benefits obtained with prenatal surgery still led the investigators to conclude that prenatal repair is beneficial in the long-term.[32]

Despite these important findings, it must be appreciated that foetal surgery is resource intense and requires considerable expertise in surgical, foetal and maternal care.[31,32] Costs involved for the setup and care are considerable, which in less developed settings make the procedure, to a large extent, prohibitive.[31,32]

1.7 MMC Repair Outcomes and Complications

1.7.1 Large Surgical Series

Survival rate for MMCs born before the nineteen sixties was between 10-12%.[15] Treatment was typically postponed until the age of two and survival was based on a self-selected cohort. Antibiotic availability, development of the VP shunt and neuropathic bladder management drastically improved survival in neonates born with MMCs and led to a paradigm shift that advocated MMC repair within 48-72 hours.[15] In fact, Pinto *et al.* demonstrated that repair immediately after birth, termed "time zero repair" yields even better long-term results.[33] Based on this paradigm shift, at least 75% of children born with MMCs can be expected to reach early adulthood.[15]

Notably, series by Lorber analysing post-operative results in 524 MMC cases, McLone analysing 100 consecutive cases and Mirzai *et al.* analysing 190 MMC patients have provided important baseline information on the condition and surgical outcomes following open MMC repair.[34-36]

1.7.2 Complications

Extracting from the aforementioned studies, postoperative mortality following MMC repair is low. However, morbidity post repair can be significant and to a large extent is preventable with meticulous preoperative planning.[37]

1.7.2.1 Wound Dehiscence

Wound Dehiscence is a common complication post MMC repair.[38,39] Poor nutritional status and unfavourable local wound factors are responsible for this adverse outcome.[38]

Nutritionally these neonates are at a disadvantage secondary to low birth weights, negative nitrogen balance, hypoalbuminaemia and low lymphocyte counts. These factors can lead to a catabolic state and recovery from this state does not occur until one-month post MMC repair. Compounded on this are potential feeding problems secondary to hydrocephalus, Arnold Chiari malformation and postoperative ileus. As a whole, the aforementioned factors may lead to poor post-operative wound healing, which intern increases the risk of wound

dehiscence. As such, proactive nutritional management of neonates born with MMCs is essential.[38]

Local factors are also extremely important predictors for wound dehiscence. Large skin defects lead to higher tension on the suture line of MMC repairs. This can decrease cutaneous blood supply and lead to necrotic edges with subsequent dehiscence. In a similar manner, Kyphosis can also compromise blood supply to the surgical wound by stretching the wound posteriorly in the ventral-dorsal plane. Importantly, when wide subcutaneous undermining or local flaps are required dehiscence can ensue secondary to skin flap necrosis. This can be challenging to address.[38]

1.7.2.3 CSF Leak

Following watertight closure of the dural sac there is a post-operative risk of CSF leak. There is wide range of reported CSF leakage rates in the literature, with several large series not quantifying the phenomenon.[37,38] Chand *et al.* reported a CSF leak rate of 8.1% and Fazal *et al.* had a CSF leak rate of 12.72%. [39,40] Leakage of CSF through the surgical wound increases the risk for wound dehiscence as well as meningitis with its accompanying complications. As a result, it must be identified early and managed aggressively. In addressing the potential for this complication, meticulous surgical technique, testing the repair with a Valsalva manoeuvre, multilayered closure and CSF diversion in the setting of hydrocephalus are essential practises.[23,37]

1.7.2.4 Infection

MMC infection rates, depending on the series, are quoted as between 1 to 37%.[23,37,41,42] Infections can be subdivided into extradural and intradural infections. Extradural infection arises secondary to contamination of the wound by skin commensals, faeces or urine. Clinically, extradural infection is suspected when erythema arises around the wound and the infection is treated aggressively with antibiotics. Intradural infections are more serious and tend to progress to meningitis and subsequently ventriculitis. Gram-negative enteric pathogens tend to be the source of most CSF infections in this setting. Intradural infections require prompt use of antibiotics and frequent CSF cultures in order to obtain antibiotic

sensitivities.[37] CSF infection in the setting of MMCs can have devastating consequences. As aforementioned, McLone *et al.* firmly established, hydrocephalus independent, deterioration of IQ scores in neonates that suffered from meningitis or ventriculitis.[14]

Based on the severe consequences of CNS infection for neonates born with MMCs, prophylaxis with broad-spectrum antibiotics is commonly employed.[43] By employing this strategy, ventriculitis risk is reduced and neonates have better outcomes.[43]

Early surgery is also crucial in reducing the risk of CNS infection. Incidence of ventriculitis is at 7% with early closure as opposed to 37% with closure beyond 72 hours.[23] These findings, further stress the importance of early closure.

1.7.2.4 Other Complications

Less frequent post-operative complications following MMC repair also occur. Post-operative ileus may occur, particularly in the setting of large defects requiring widespread undermining and use of myocutaneous flaps. This complication is usually self-limiting. Pneumothorax may arise following deep dissection of latissimus dorsi in the thoracic region; again, this is more frequent following closure of large defects. Finally, necrotising enterocolitis is slightly more frequent post MMC repair.[37]

1.8 MMC Literature in South Africa

1.8.1 Epidemiological Studies in South Africa

Addressing the needs of children born with MMCs in South Africa and providing care for these children in a multidisciplinary setting has been instituted as early as the 1960s.[29] An epidemiological study in Cape Town has documented the incidence of NTDs between 0.63 – 1.74 per 1000 births, with prevalence highest in the local Caucasian population.[44] In Gauteng, a study looking at NTD recurrence risk, identified a 2.28% recurrence risk following one child with a NTD and a 4.16% risk following birth of two affected children.[45] These rates are lower than the international literature. Lebese *et al.* reported on the National Congenital Disorder Surveillance System, analysing data from 2006-2014.[46] During this time period there

were 787 NTDs reported. However, the authors commented that reporting to the surveillance system is erratic and inadequate.[46]

1.8.2 Prenatal Prevention and Diagnosis in South Africa

In 2003, South Africa initiated folic acid fortification of staple foods.[47] Following implementation of this program, incidence of NTDs decreased from 1.41 to 0.98 per 1000 births. Spina Bifida specifically, declined by 41.6%.[47]

For the most part, MMC diagnosis in South Africa is made postnatally.[29] This is attributed to low maternal awareness and uptake of measures that prevent NTDs. In a study sampling a sub-Saharan population of mothers that had neonates with NTDs, only 18.8% were aware that folic acid reduced the incidence of NTDs and only 10.7% had dietary multivitamin supplementation.[48] Of the defects analysed in this study, only 17.8% were diagnosed prenatally. Interestingly, 23% of mothers reported that they might have requested for termination of the pregnancy.[48] In a similar manner, Sayed *et al*. demonstrated in a cohort of pregnant women in Cape Town that only 20.6% had heard of folic acid and only 11.1% related it to birth defects.[49] Clearly, these studies demonstrate that more needs to be achieved from a public health perspective in relation to NTD prevention in sub-Saharan Africa.

1.8.3 Surgical MMC Repair Series in South Africa

To the author's knowledge, there is no published surgical series from South Africa analysing post-operative MMC repair results. Narotam *et al.* from Durban, published a 22.4% incidence of wound complications and 14.8% incidence of sepsis post NTD repair.[50] These rates were extracted from a broader study analysing operative sepsis in Neurosurgery.

1.8.4 Long-term Follow-up Post MMC Repair in South Africa

Follow-up of children born with MMCs is important in analysing the success of local infrastructure in addressing the needs of these children. Buccimazza *et al.* followed-up a cohort of children born with MMCs from Cape Town and compared them to children born with MMCs in rural areas.[51] By analysing the general development quotient at 5 years, they found that there was no significant

difference in outcomes between children from urban areas and the rural areas. Caesarean section delivery and early MMC closure led to a higher general development quotient, whereas CNS infection and placement of more than one shunt led to a lower quotient.[51]

1.9 MMCs and Human Immunodeficiency Virus Infection

MMC literature in relation to human immunodeficiency virus (HIV) infection is limited. There is some literature to support that maternal exposure to the anti-retroviral drug, efavirenz, increases the incidence of NTDs.[52] Aside from this, there is a paucity of literature. To the author's knowledge, there are no studies that have investigated post-operative MMC repair results in neonates born to mothers with HIV infection.

1.10 Study Aims and Objectives

It is evident from the literature that MMCs affect a considerable population at great human and financial cost. As prenatal diagnosis in South Africa remains a challenge, it is important to understand factors that lead to good post-operative results following MMC repair. This is essential to improve both neonatal care and to also save on health care costs by reducing patient days in hospital. To address this need, a retrospective study of all the MMCs that were repaired by that author (Dr Christos Profyris) at Chris Hani Baragwanath Hospital (CHBH), from 1 January 2014 to 1 August 2015 was undertaken. The rational behind investigating patients repaired by a single surgeon is to compare patient outcomes following a standardised and identical repair technique.

To the author's knowledge, there are no published surgical series from South Africa analysing post-operative MMC repair results. This is important, as unique challenges faced in a South African context may influence outcomes. Furthermore, there are no studies that have investigated post-operative MMC repair results in neonates born to mothers with HIV infection. Upon this background, the present study aims to contribute to the MMC literature by:

1. Describing base-line clinical characteristics of neonates born with MMCs at CHBH or referred to CHBH
2. Analysing surgical outcomes following MMC repair by a single surgeon at CHBH
3. Identifying factors that may influence post-operative complications related to MMC surgery at CHBH
4. Investigating if maternal HIV infection leads to different outcomes in neonates born with MMCs

2. METHODS

2.1 Study Design

This study was structured as a retrospective clinical audit of all MMCs repaired at Chris Hani Baragwanath Hospital by the author from 1 January 2014 to 1 August 2015. During this period, the author repaired all the MMCs referred to the Department of Neurological Surgery at CHBH.

All MMCs were repaired with the technique described in *Section 1.5.3* and VP shunting was undertaken if the neonate developed signs and symptoms of hydrocephalus.

2.2 Sample

All patients with MMCs that were either born at CHBH or referred to CHBH from peripheral hospitals and operated upon by the author were included in the study. Pending the above criteria were met, there were no exclusionary criteria.

Prior to this series the author had performed a further fifteen MMC repairs and had been trained by a consultant to perform the procedure independently. The current series of cases was performed by the author as the primary surgeon.

2.3 Data Collection

Following review of the author's surgical logbook during the period 1 January 2014 to 1 August 2015, suitable patients for the study were identified. Hospital files of the identified patients were collected from the Division of Neonatology at CHBH. Relevant data was collected from both the author's logbook and the collected hospital files.

Data was recorded on a data collection sheet – *see Appendix A* – and then recorded onto a Microsoft Excel 2010 spread sheet. Data recorded and presented includes demographic details (gestation period, gender and referral route), birthing details (mode of delivery, birth weight, length, head circumference and Appearance, Pulse, Grimace, Activity and Respiration (APGAR) scores), pre-operative status (MMC spinal region, MMC surface area, pre-operative CSF leak and kyphosis), neurological abnormalities (lower limb weakness, clinical aspiration or dysphagia, Chiari Type II malformation, and hydrocephalus), non-neurological abnormalities (clubfoot, congenital hip dysplasia, neurogenic bladder and

cutaneous abnormalities), timing to MMC repair, operative parameters (utilisation of flap for closure, pre and post operative haemoglobin, blood transfusion volume and post-operative intensive care unit admission), post operative course (VP shunt insertion, external ventricular drain (EVD) insertion and latex allergy), post-operative complications (CSF leak, wound dehiscence and infection) and maternal parameters (HIV status and antiepileptic drug use during pregnancy).

2.4 Data Analysis

Statistical analysis was undertaken using the *GraphPad Prism* software package. Descriptive statistics consisting of mean and standard deviation were calculated for birth weight, length, head circumference, APGAR score, MMC surface area, timing to MMC repair, pre and post operative haemoglobin, and blood transfusion volume. Absolute numbers expressed as proportions were calculated for gender, referral route, mode of delivery, MMC spinal region, pre-operative CSF leak, kyphosis, lower limb weakness, clinical aspiration or dysphagia, Chiari Type II malformation, hydrocephalus, clubfoot, congenital hip dysplasia, neurogenic bladder, cutaneous abnormalities, utilisation of flap for closure, post-operative intensive care unit admission, VP shunt insertion, EVD insertion, latex allergy, CSF leak, wound dehiscence, infection, maternal HIV status and maternal antiepileptic use during pregnancy.

Cross tabulation between variables of interest was performed. Association between continuous data variables was tested with an unpaired student *t* test. Categorical data variables had a low frequency of events and as such, a Fischer's exact test was used to assess statistical significance. Statistical significance was considered significant when a p-value was less than 0.05.

2.5 Ethics

This study was approved by the Human Research Ethics Committee (Medical) at the University of the Witwatersrand with Clearance Certificate Number M151101 – *see Appendix B*. Informed consent was not required as data was acquired from existing hospital files and no interaction with patients occurred. All identifying information such as names and hospital numbers were removed from the data sheet and only a study number was used.

3. RESULTS

3.1 Records Reviewed

A total of 24 patients were identified that had their MMC repaired by the author at Chris Hani Baragwanath Hospital during the period of 1 January 2014 to 1 August 2015. Their medical records were obtained and reviewed.

3.2 Demographic and Birthing Details

Demographic data and birthing details pertaining to the study population are summarised in Table 3.1.

Gestational period ranged from 35 weeks to 40 weeks. Delivery wise, 6 of the infants were recorded as being in breech position and there was one set of twins, whereby only one of the infants was affected by an MMC. The lightest neonate was 2,300 grams and the heaviest 3,600 grams. Neonate length ranged from 45 to 50 centimetres and head circumference ranged from 31 to 37 centimetres. The lowest APGAR score at 1 minute was 5 and the lowest APGAR score at 5 minutes was 8.

Table 3.1: Demographic and Birthing Details

VARIABLE	RESULT
MEAN GESTATION PERIOD (weeks)	38.13 +/- 1.6 (n=15)
GENDER	
Male	66.67% (n=16)
Female	33.33% (n=8)
MODE OF DELIVERY	
Natural Vaginal Delivery	56% (n=9)
Caesarean Section	44% (n=7)
MEAN WEIGHT (grams)	2821 +/- 340 (n=16)
MEAN LENGTH (cm)	47.8 +/- 1.5 (n=12)
MEAN HEAD CIRCUMFERENCE (cm)	34.9 (n=16)
MEAN 1 MINUTE APGAR SCORE	7.8 +/- 1.5 (n=13)
MEAN 5 MINUTE APGAR SCORE	9.4 +/- 0.7 (n=13)
REFERRAL ROUTE	
In Hospital (CHBH)	53% (n=8)
Peripheral Hospital Referral	47% (n=7)

APGAR score at 1 minute for neonates born with MMCs via natural vaginal delivery (NVD) was compared to neonates born via caesarean section (C-section) in Table 3.2. There was no statistically significant difference with a p Value of 0.095.

Table 3.2: Unpaired student *t* test comparing APGAR scores at 1 minute for neonates born via NVD vs. C-section

GROUP	NVD	C-Section
Mean 1 minute APGAR	7	8.4
Standard Deviation	1.9	0.8
Standard Error of the Mean	0.8	0,3
N	6	7

APGAR score at 5 minute for neonates born with MMCs via NVD was compared to neonates born via C-section in Table 3.3. There was no statistically significant difference with a p Value of 0.48.

Table 3.3: Unpaired student *t* test comparing APGAR score at 5 minutes for neonates born via NVD vs. C-section

GROUP	NVD	C-Section
Mean 1 minute APGAR	9.2	9.4
Standard Deviation	0.4	0.8
Standard Error of the Mean	0.2	0,3
N	6	7

3.3 MMC Characteristics

Characteristics related to the presenting MMCs of the infants involved in the study are summarised in Table 3.4.

The smallest MMC had a surface area of 3 cm^2 and the largest had a surface area of 36 cm^2. Surface are was approximated by multiplying the height by width of the MMC

Table 3.4: MMC Characteristics

VARIABLE	RESULT
MMC REGION	
Cervical	0% (n=0)
Thoracic	4% (n=1)
Lumbar	58% (n=14)
Sacral	38% (n=9)
MEAN MMC SURFACE AREA (cm^2)	19.4 +/- 9.7 (n=9)
CSF LEAK ON PRESENTATION	
Yes	50% (n=9)
No	50% (n=9)
KYPHOTIC DEFORMITY	
Yes	33.33% (n=6)
No	66.67% (n=12)

3.4 Associated Neurological Abnormalities

Neurological abnormalities that were present in the neonates with MMCs in this series are summarised in Table 3.5. Chiari II malformation and hydrocephalus were diagnosed with the use of neuroimaging.

Table 3.5: Associated Neurological Abnormalities

VARIABLE	RESULT
LOWER LIMB NEUROLOGY	
Lower Limbs Intact	29% (n=5)
No Movement below Ankle	0% (n=0)
No Movement below Knee	12% (n=2)
No Movement below Hip	6% (n=1)
Complete Paralysis	53% (n=9)
CLINICAL ASPIRATION/DYSPHAGIA	
Yes	13%(n=2)
No	87% (n=15)
RADIOLOGICAL CHIARI TYPE II MALFORMATION	
Yes	94% (n=16)
No	6% (n=1)
HYDROCEPHALUS	
Yes	54% (n=13)
No	46% (n=11)

3.5 Associated Non-Neurological Abnormalities

Non-neurological abnormalities that were present in the neonates with MMCs in this series are summarised in Table 3.6.

There were two cutaneous abnormalities in the series and both were located over the lower back in the vicinity of the MMC; one was a capillary haemangioma and the other was a fawn's tail – a hairy patch.

Other congenital abnormalities that were identified within the series were a horseshoe kidney in one infant and rectal prolapse in another infant. One neonate also had bilateral femur fractures.

Table 3.6: Associated Non-neurological Abnormalities

VARIABLE	RESULT
CLUBFOOT	
Yes	71% (n=12)
No	29% (n=5)
CONGENITAL HIP DYSPLASIA	
Yes	24%(n=4)
No	76% (n=13)
NEUROGENIC BLADDER	
Yes	41% (n=7)
No	59% (n=10)
CUTANEOUS ABNORMALITY	
Yes	12% (n=2)
No	88% (n=15)

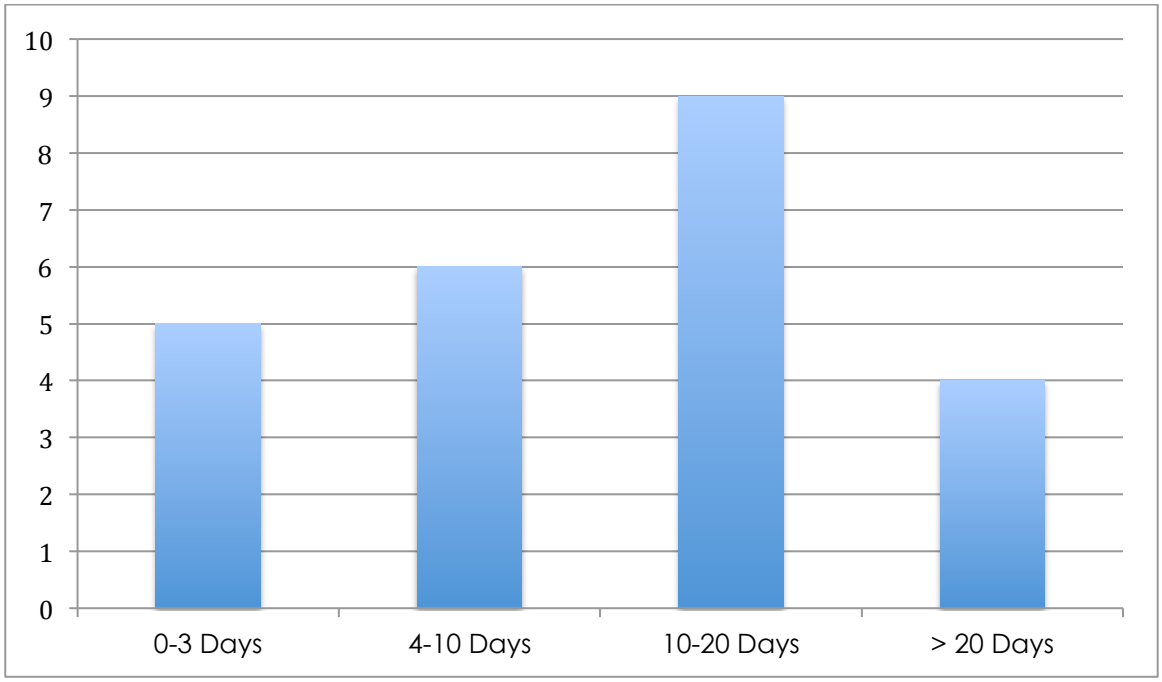
3.6 Timing to MMC Repair

Timing to surgery is presented in Table 3.7 and a frequency distribution in relation to timing intervals to surgery is presented in Figure 3.1

Table 3.7: Timing to MMC Repair

VARIABLE	RESULT
MEAN TIMING TO MMC REPAIR	13.6 +/-11.2 (n=24)
MEDIAN TIMING TO MMC REPAIR	11

Figure 3.1: Frequency Distribution in relation to days from birth until MMC Repair



3.7 Operative Parameters

Operative parameters relating to requirement for a local flap for closure, perioperative haemoglobin values, requirement for transfusion and intensive care unit admission are presented in Table 3.8.

Of the 4 flaps presented in Table 3.8, 2 utilised a Limberg flap and 2 a reading man flap. The largest haemoglobin drop between pre-operative and post-operative values was 5.5 g/dL from 17.5 g/dL to 12 g/dL. The largest transfusion volume was 60 mls of packed red blood cells.

Table 3.8: Operative Parameters

VARIABLE	RESULT
LOCAL FLAP FOR CLOSURE	
Yes	17% (n=4)
No	83% (n=20)
HAEMOGLOBIN	
Mean Pre-Operative Value (g/dL)	14.3 +/-2.3 (n=18)
Mean Post-Operative Value (g/dL)	12.7 +/-2.2 (n=17)
TRANSFUSION	
Yes	44% (n=4)
No	56% (n=5)
Mean Transfusion Volume (ml)	41 +/-13.3 (n=4)
POST-OPERATIVE INTENSIVE CARE UNIT ADMISSION	
YES	59% (n=10)
No	41% (n=7)

3.8 Post-Operative Course

Post-operative course in relation to requirement for VP shunt, EVD insertion and latex allergy is presented in Table 3.9.

Two revision VP Shunt procedures were performed.

Table 3.9: Post-Operative Course

VARIABLE	RESULT
VP SHUNT INSERTION	
Yes	50% (n=12)
No	50% (n=12)
EVD INSERTION	
Yes	9% (n=2)
No	91% (n=22)
LATEX ALLERGY	
Yes	0% (n=0)
No	100% (n=24)

3.9 Post-Operative Complications

Post-operative complications arising in the current series under investigation are presented in Table 3.10.

Of the 6 infections that arose, 5 were CSF infections and 1 was a superficial wound infection

All 3 of the patients with a CSF leak went on to complicate with both a wound dehiscence and CSF infection.

Reoperation to address complications was performed for 2 of the 5 patients with wound dehiscence and 2 of 3 the patients with CSF leak.

There were two mortalities in this case series. One was in a neonate with a large MMC requiring a flap for closure. There was wound dehiscence and CSF leak with subsequent CSF infection and systemic sepsis leading to mortality. The other neonate had episodes of apnoea, stridor, aspiration and dysphagia on a background of Chiari Type II malformation and demised secondary to respiratory arrest.

Table 3.10: Post-Operative Complications

VARIABLE	RESULT
WOUND DEHISCENCE	
Yes	21% (n=5)
No	79% (n=19)
CSF LEAK	
Yes	12.5% (n=3)
No	87.5% (n=21)
INFECTION	
Yes	25% (n=6)
No	75% (n=18)

3.10 Maternal Parameters

Maternal HIV infection status and pregnancy antiepileptic use are presented in Table 3.11.

Four of the five mothers with HIV were aware of their status prior to pregnancy and one was diagnosed following birth of her child.

Both mothers on anti-epileptics were on sodium valproate.

Table 3.11: Maternal Parameters

VARIABLE	RESULT
HIV INFECTION	
Yes	29% (n=5)
No	71% (n=12)
PREGNANCY ANTIEPILEPTIC USE	
Yes	11% (n=2)
No	89% (n=16)

3.11 Factors Influencing Complication Outcomes

3.11.1 Wound Dehiscence and Gestation Period

Wound dehiscence in relation to gestation period was compared in Table 3.12. There was no statistically significant difference with a p Value of 0.58.

Table 3.12: Unpaired student *t* test comparing gestation period for patients with wound dehiscence vs. patients without wound dehiscence

GROUP	Dehiscence	No Dehiscence
Mean gestation period (weeks)	37.8	38.3
Standard Deviation	1.5	1.6
Standard Error of the Mean	0.8	0.5
N	4	11

3.11.2 Wound Dehiscence and Birth Weight

Wound dehiscence in relation to birth weight was compared in Table 3.13. There was no statistically significant difference with a p Value of 0.10.

Table 3.13: Unpaired student *t* test comparing birth weight for patients with wound dehiscence vs. patients without wound dehiscence

GROUP	Dehiscence	No Dehiscence
Mean birth weight (grams)	3078.8	2740.0
Standard Deviation	381.7	307.4
Standard Error of the Mean	190.9	92.7
N	4	11

3.11.3 Wound Dehiscence and Maternal HIV status

Wound dehiscence in relation to maternal HIV status was compared in Table 3.14. There was no statistically significant difference with a p Value of 0.54.

Table 3.14: Fischer's exact test comparing maternal HIV status to wound dehiscence.

GROUP	Dehiscence	No Dehiscence	Total
HIV Positive	2	3	5
HIV Negative	2	10	12
Total	4	13	17

3.11.4 CSF Infection and Time to Surgery

Presence of CSF infection in relation to timing to MMC repair was compared in Table 3.15. There was no statistically significant difference with a p Value of 0.15.

Table 3.15: Unpaired student *t* test comparing timing to surgery for patients with CSF Infection vs. patients without CSF infection

GROUP	CSF Infection	No CSF Infection
Mean days to surgery	16.4	10.8
Standard Deviation	9.4	7.0
Standard Error of the Mean	4.2	1.6
N	5	19

3.11.5 CSF Infection and Gestation Period

CSF infection in relation to gestation period was compared in Table 3.16. There was no statistically significant difference with a p Value of 0.87.

Table 3.16: Unpaired student *t* test comparing gestation period for patients with CSF Infection vs. patients without CSF infection

GROUP	CSF Infection	No CSF Infection
Mean gestation period (weeks)	38.3	38.1
Standard Deviation	1.5	1.6
Standard Error of the Mean	0.8	0.5
N	4	11

3.11.6 CSF infection and Birth Weight

Presence of CSF infection in relation to birth weight was compared in Table 3.17. There was no statistically significant difference with a p Value of 0.76.

Table 3.17: Unpaired student *t* test comparing birth weight for patients with CSF Infection vs. patients without CSF infection

GROUP	CSF Infection	No CSF Infection
Mean birth weight (grams)	2775	2837.5
Standard Deviation	246.0	374.5
Standard Error of the Mean	123.0	108.1
N	4	12

3.11.7 CSF Infection and Maternal HIV status

Presence of CSF infection in relation to maternal HIV status was compared in Table 3.18. There was no statistically significant difference with a p Value of 0.11.

Table 3.18: Fischer's exact test comparing maternal HIV status to CSF Infection.

GROUP	CSF Infection	No CSF Infection	Total
HIV Positive	3	2	5
HIV Negative	2	10	12
Total	5	12	17

4. DISCUSSION

4.1 Study Sample

By international standards, the current study was not a very large series of cases – 24 in total.[34-36] However, the patients within the series were operated upon by a single surgeon. When analysing outcomes, this removes the confounding factor of surgical technique variation, which may arise, when multiple surgeons operate upon patients within a single series.

In comparing this series to the reported literature, it becomes clear that CHBH has a reasonable volume of MMC presentations. For instance, in the series by Mirzai *et al.* from Turkey, they reported on 190 MMC repairs over a 15 year period, which equates to about 12 per year.[36] When one considers the MOMS trial, which was a multicentre trial between three centres, there were 183 patients included in the trial from February 2003 to December 2010.[32] Although one must consider exclusion criteria, the MOMS numbers would equate to about 8 MMC repair operations per centre per year. The current series under investigation has a rate of about 15 MMC presentations requiring surgery per year. This number is actually higher if one also considers the MMCs that presented after the neonatal period that were not operated upon at the neonatal unit at CHBH and therefore not included in this series. These patients were operated upon by different surgeons and not by the author.

Unfortunately, given the retrospective nature of this study, a lot of the patients had incomplete data for the variables under investigation. This is limiting in terms of data extrapolation and restricts some of the conclusions that may be drawn from the discussion that will follow. This limitation will be discussed further – *see section 4.12*.

4.2 Demographic and Birthing Details

Demographic analysis of the series reveals that the mean gestation of 38.13 weeks was within normal limits and over the 37 week mark, which defines pre-term labour.[55] Gender distribution was skewed toward male neonates at 66.67%, which may have been the result of a small series and is not inline with the reported female preponderance. Timson analysed 3521 cases of MMCs and found female predilection for the condition at 65.5%.[56]

Unfortunately, the majority of births were via NVD at 56% and not via C-section. This is in line with the predominantly postnatal as opposed to prenatal diagnosis of MMCs in South Africa.[29]

Analysis of the MMC cohort's mean weight, mean length and mean head circumference revealed that the means were within normal range for neonates.[57] APGAR scores at both 1 minute and 5 minutes were also within normal range, with mean scores of 7.8 and 9.4 respectively. When 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 one minute for neonates born via C-section as opposed to NVD. The difference was a mean APGAR score of 8.4 as opposed to 7; however, this was not statistically significant with a p value of 0.095. The difference in APGAR score was negligible by 5 minutes. These results, although not significant, potentially highlight the importance of a planned C-section for neonates born with MMCs.

In regard to MMC referral patterns to CHBH, referrals from peripheral hospitals accounted for almost half of the MMCs operated upon at CHBH.

4.3 MMC Characteristics

The majority of MMCs in this series were located in the lumbar region, with a frequency of 58%. This is comparable to the series by Mirzai *et al.* from Turkey who had a similar frequency for the lumbar region at 59.5%.[36] Following the lumbar region, the sacral region was the second most common area in the current series and there was only one thoracic MMC. There were no cervical MMCs in this series, which correlates with the relatively low frequency of MMCs at this region.[58,59]

Location was based largely on clinical observation, with few of the neonates having had a spinal MRI. This was the result of resource restraints at CHBH. It was deemed that an MRI was not essential to proceed with MMC repair surgery and waiting for an MRI led to unnecessary delays in the treatment of these neonates. As a result, it is possible that some of the MMCs classified as lumbar may have been sacral in nature if imaged with MRI.

Based on the data that was available (n=9), the mean surface area of MMCs in this series was 19.4 cm^2. This is somewhat smaller than surface area means reported in other series. Idowu and Apemiye from Nigeria had a mean MMC

surface area of 26.4 cm^2 in their operative series and Lee *et al.* from Korea had a mean MMC surface are of 47 cm^2.

CSF leak at birth was present in 50% of neonates in this series. In comparison to the series by Sattar *et al.* from Pakistan this is quite a high rate.[62] Sattar *et al.* reported a rate of 3.8%.[62] The high rate may be explained by the low rate of C-section delivery in this series leading to birth trauma of the MMC sac via NVD.

Finally, the rate of kyphosis in the current series was 33.33%. This is higher than the rate of 15% quoted in the literature and is possibly the result of a small sample.[63]

4.4 Associated Neurological Abnormalities

Assessment for lower limb neurological deficits revealed that 71% of neonates had lower limb deficits and only 29% were intact. In comparison, Sattar *et al.* from Pakistan had a 46% rate of intact neurology.[62] Interestingly, a study by Bartonek and Saraste from Sweden, analysing neurological outcome in 56 children born with MMCs found only 3 children that were completely intact.[64] They used two classifications to asses neurological function, that by Sharrard[65] and that by Smith and Smith[66]. These are both detailed classifications that can pick up subtle deficits. Perhaps, application of these scales would have revealed a lower percentage of completely intact children.

Lower brainstem dysfunction presenting as aspiration and/or dysphagia was present in 13% of the series and Chiari type II malformation was identified radiologically, via CT or MRI, in the majority of patients, at 94%. These numbers are in line with the literature, whereby Chiari Type II malformation is present in about 90% of children with MMC and where about 5% of neonates with Chiari Malformation suffer from lower cranial nerve dysfunction.[4,67] Importantly, one of the two children suffering from lower cranial nerve dysfunction within the series demised secondary to respiratory failure.

The rate of hydrocephalus within the series at 54% was low. This is below the 80-90% rate of hydrocephalus quoted within the general literature.[12] The reason is potentially multifactorial, with the small size of the series being a strong factor. However, the strategy in the current study of repairing the MMC and only VP shunting if hydrocephalus arose may have decreased the requirement for VP shunting and thereby the associated diagnosis of hydrocephalus. Alternatively,

follow-up was undertaken until the newborns were discharged and therefore some of the discharged neonates may have represented with hydrocephalus. Although this would have led to underreporting, the author is not aware of any such cases within this current series. In addressing the need to accurately predict which neonates born with MMCs develop hydrocephalus Phillips *et al.* studied various parameters in search of useful predictors.[68] They found that head circumference velocity greater than 0.32cm/day, head ultrasonography mean ventricular index of 2.33cm and mean thalamo-occipital distance of 4.04cm were associated with development of hydrocephalus.[68] By using these parameters, the authors commented that it is possible to identify which neonates born with MMCs require CSF diversion and thereby shorten the period of watchful waiting and which neonates do not require CSF diversion and thereby avoid unnecessary procedures.[68]

4.5 Associated Non-neurological Abnormalities

Analysis of associated non-neurological abnormalities revealed that 71% of the neonates in the series had associated clubfoot deformity. This prevalence was higher than the 30-50% prevalence reported by Swaroop and Dias.[69] The prevalence of congenital hip dysplasia in the current series was lower than clubfoot at 24%. This is lower than the 30-50% prevalence quoted by Westcott *et al.*[70] Evidence of clinically manifested neurogenic bladder was present in 82% of the neonates examined in this series. This result is inline with the expected high prevalence of neurogenic bladder in neonates born with MMCs.[29] Finally, cutaneous abnormality was present in 12% of neonates within the series – These abnormalities included hyperpigmentation and/or hypertrichosis(faun's tail). This is inline with their relatively low prevalence.[3]

4.6 Timing to MMC Repair

Mean time to MMC repair was 13.6 days, median was 11 days and only 5 of the 24 cases were operated upon at less than 72 hours, which is the generally accepted gold standard;[23] although, as addressed in the introduction, some authors have pushed for time zero repair.[33] This less than desirable timing is the result of multiple factors. Delayed referrals, transfer from peripheral hospitals to CHBH (47% in this

series) and availability of the operating theatre were all systemic factors that delayed repair times. Delay based on medical grounds, for medical optimisation prior to surgery, was not a common reason for delays. Unfortunately, in the current series there were 4 neonates that were repaired beyond 20 days, which increased the standard deviation to 11.2 days and also increased the aforementioned mean.

Although timing to repair in the current series is not ideal it is interesting to note that Atenello *et al.* from the United States reported on MMC repair timing based on countrywide databases.[41] They found that 19% of MMC repairs occur outside the 48 hour mark. Their results in regard to timing are much better than the results from the current series, however they do demonstrate that even in a highly developed setting it is not easy to repair all MMCs within the first few days of life. For comparison, Idowu and Apemiye in their series from Nigeria commented that the majority of patients were operated upon after 7 days of life and Sattar *et al.* from Pakistan reported that their average age of repair was 4 weeks.[60,62]

4.7 Operative Parameters

Closure of large MMC defects is potentially challenging and requires Plastic Surgery techniques that utilise flaps for closure.[23] In the current series, 17% required closure with a flap. This is lower than that reported in other series. Kemaloğlu *et al.* reported a 40% rate of closure requiring flaps.[71] However, the mean MMC surface area reported in this series is somewhat smaller than that reported in other series – *see Section 4.3*. This may account for the smaller percentage of flap utilisation in the current series. Of note there was one flap breakdown; however this child had an extensive myelomeningocoele.

Data in regard to mean pre-operative and post-operative haemoglobin levels and the need for transfusion revealed a drop in mean haemoglobin following surgery. However the drop was modest at 1.6g/dL. Transfusion was required for 44% of neonates, however this percentage was derived from only 9 patients of the series total of 24. To the author's knowledge, there are no other series that have documented mean haemoglobin values for comparative analysis.

Post-operative admission was most frequently at the neonatal intensive care unit as opposed to the high care unit – 59% vs. 41%. For the majority of neonates,

discharge from the intensive care unit occurred on the following post-operative day.

4.8 Post-Operative Course

Post MMC repair 12 patients had a VP shunt inserted and 2 patients had an EVD inserted. Comparatively, 13 patients had hydrocephalus. The two patients that had an EVD inserted had concomitant CSF infection with their hydrocephalus and the EVD was used as a temporising measure. Of the two patients with the EVD, one survived and went on to have a VP shunt inserted and thereby the total number of VP shunts in the series was 12. The other patient was one of the two mortalities in the series and never had a VP shunt inserted – *see Section 3.9*. Follow up was up until 01 January 2016.

There was no documented latex allergy. Although an effort was made to avoid latex products in these patients, this policy was not strictly adhered to. Interestingly, although the incidence of latex allergy in MMC patients is thought to by high, a study from Cape Town also found a low incidence.[72] Their rate of latex allergy was 16.7%.[72]

4.9 Post-Operative Complications

Within the current series there was a 21% rate of wound dehiscence. This amounted to 5 cases of which the dehiscence in 3 of the patients was minor, with skin edge necrosis that was treated conservatively. If this is taken into account the rate is modified to 8.3%. Comparatively, Chand *et al.* had a wound dehiscence rate of 5.4% and Lee *et al.* had a rate of 10%.[39,61]

CSF leak rate within the series was at 12.5%. This is inline with other series. Chand *et al.* had a CSF leak rate of 8.1% and Fazal *et al.* had a CSF leak rate of 12.5%.[39,40]

Infection occurred in 25% of the patients within the series. Of the 6 infections within the series 5 were CSF infections, giving the series a CSF infection rate of 21%. This is a high rate. Comparatively, Demir *et al.* had a CSF infection rate of 16.4%, Attenello *et al.* in their nation-wide United States study had an 18% infection rate and Narotam *et al.* from Durban had an infection rate of 14.8%.[41,42,50]

As expected, the three patients that had a CSF leak went onto also complicate with wound dehiscence and CSF infection. This is well recognised and has been reported in other operative MMC series as well.[38,61,73]

4.10 Maternal Parameters

With prevalence of HIV in Soweto being potentially as high as 30%, HIV prevalence in mothers giving birth to neonates with MMCs was investigated.[79] In line with this, 29% of mothers had HIV in this series. If the observation of CSF infection being more common in neonates born to mothers with HIV stands – *see Section 3.11.7*, identifying neonates born to mothers with HIV is clinically significant.

Finally, two mothers within the series were using sodium valproate as an epileptic treatment during their pregnancy. This is likely to be reflective of problems with patient education on perinatal anti-epileptics use and is an extension of a known underlying theme of poor maternal awareness of perinatal MMC risk factors in sub-Saharan Africa.[48,49]

4.11 Factors Influencing Complication Outcomes

With the aim of gaining insight into potential reasons behind the complications within the series, variables of interest were analysed for statistical significance. Unfortunately, the small number of patients within the series made attainment of statistical significance difficult; however, some trends did emerge.

4.11.1 Wound Dehiscence and Gestation Period

Based on reasoning that neonates born at an earlier gestation period may have been less developed and this may have impacted on wound healing, a comparison was made between infants with dehiscence and those without dehiscence to see if the neonates with dehiscence were born earlier. Although the mean gestational period for neonates with dehiscence was slightly less at 37.8 weeks as opposed to 38.3 weeks for the non-dehiscence group this was not statistically significant with a p Vale of 0.58.

4.11.2 Wound Dehiscence and Birth Weight

On the assumption that neonates born with a low birth weight might be at higher risk of wound dehiscence due to their smaller size, birth weight comparison between infants with dehiscence and those without dehiscence was investigated. Interestingly, neonates with dehiscence were actually born heavier than the

neonates without dehiscence with mean birth weights of 3078.8 grams and 2740.0 grams respectively. This was not statistically significant with a p Value of 0.10.

4.11.3 Wound Dehiscence and Maternal HIV Status

There is limited evidence that patients with HIV may have delayed healing capacity.[74,75] Interestingly, there is also evidence that neonates born to mothers with HIV have lower antibody responses when compared to neonates born to mothers without HIV.[76] As wound healing is based on an inflammatory response, which utilises components of the immune system, it was of interest to evaluate wound dehiscence rates between neonates born to HIV infected mothers and those born to non-infected mothers. Following statistical analysis however, wound dehiscence did not appear to correlate with maternal HIV infection status – p Value was 0.54.

4.11.4 CSF Infection and Time to surgery

The correlation between delayed MMC repair and subsequent infection is well established and has been discussed elsewhere – *see Section 1.7.2.4*. As such, an analysis of timing to surgery between neonates with CSF infection and neonates without CSF infection was undertaken. Mean days to surgery for the CSF infected group was 16.4 days, whereas mean days to surgery for the non-CSF infected group was 10.8. Although the p Value of 0.15 was not significant, it would be expected that with a larger study sample, the p Value would veer towards significance.

4.11.5 CSF Infection and Gestation Period

Premature infants have reduced immunity.[77] Based on this premise gestational period was compared between infants with CSF infection and infants without CSF infection. There was no difference in mean gestation period between the two groups, with the CSF infection group having a mean gestation period of 38.3 weeks and the non-CSF infection group having a mean gestation period of 38.1 weeks. The p Value was 0.87 and not significant.

4.11.6 CSF Infection and Birth Weight

On evidence that low birth weight can lead to impaired immunity, birth weights were compared between infants with CSF infection and infants without CSF infection.[78] Birth weight for infants with CSF infection was slightly lower at 2775 grams as opposed to 2837.5 grams for the non-infected group; however, this was not significant with a p Value of 0.76.

4.11.7 CSF Infection and Maternal HIV status

Based on the aforementioned evidence that neonates born to mothers with HIV have lower antibody responses when compared to infants born to mothers without HIV, correlation between maternal HIV status and CSF infection was investigated.[76] Although the series cohort was small, p Value was approaching significance at 0.11 in support of higher infection incidence in MMC neonates born to mothers with HIV. This might be due to impaired passive neonatal immunity and warrants further investigation with a larger study size.

4.12 Limitations

The small sample size of 24 patients in the current series limits statistical tests aiming to compare parameters of interest. Future studies expanding on the current series would likely achieve more meaningful data by increasing the cohort number.

As the study is retrospective, data collection for a lot of the parameters was incomplete. This led to many of the parameters of interest not having data equivalent to 24 patients, which was the complete patient number in this series. Again, this limits data interpretation. A prospective study design would greatly assist with this limitation.

The author reviewed all of the files, which had information pertaining to the author's post-operative results. This could potentially lead to bias in result reporting.

4.12 Conclusion

To the author's knowledge, this is the first surgical series from South Africa to analyse post-operative MMC repair results. This is important, as unique resource related challenges faced both in a South African and Sub-Saharan African context have been probed. This series also provides vital information on the standard of care provided for neonates born with MMCs at CHBH and will aid in Improving care for these patients.

The series reported on a total of 24 neonates that were born with MMCs and operated upon by a single surgeon at CHBH. Mean gestation was 38.13 weeks, the majority of neonates were male at 66.67% and 56% were born via NVD. Mean weight, length and head circumference were within normal limits and mean APGAR scores at 1 and 5 minutes were 7.8 and 9.4 respectively. Referral route to Neurosurgery services was almost equal between in-hospital referral at 53% and peripheral hospital referral at 47%.

The majority of MMCs in this series were in the lumbosacral region and mean surface area was 19.4cm^2. CSF leak was present in 50% of patients on presentation and kyphotic deformity was present in 33.33%. Neurologically, 71% of neonates had lower limb neurology, 13% had evidence of lower cranial nerve dysfunction and 54% had hydrocephalus. Chiari Type II malformation was present radiologically in 94% of neonates. Analysis of non-neurological abnormalities revealed prevalence of clubfoot at 71%, congenital hip dysplasia at 24%, neurogenic bladder at 82% and cutaneous abnormalities at 12%.

Mean time from birth to MMC repair was 13.6 days with only 5 out of 24 neonates repaired within 72 hours. The majority of neonates (59%) were admitted to intensive care post-operatively. Closure wise, 17% required a flap to close the defect. Mean preopeative haemoglobin was 14.3 g/dL and this dropped to a mean of 12.7 g/dL postoperatively. Transfusion was initiated in 44% of patients with a mean transfusion volume of 41mls.

Within the series, 46% went on to have a VP shunt inserted and 9% had an EVD. Latex allergy was absent.

Post-operatively there were 2 mortalities in the series, one secondary to Chiari Type II malformation and lower cranial nerve dysfunction and the other was due to sepsis. Complication wise, wound dehiscence arose in 21% of neonates, CSF leak

in 12.5% and infection in 25%. Of note, of the three patients with CSF leak, all three went on to have wound dehiscence and CSF infection.

Evaluation of maternal parameters within the series revealed 28% were HIV positive and 11% used anti-epileptics during their pregnancy.

On analysis of factors influencing complications there was no statistical significance between wound dehiscence and gestation period, wound dehiscence and birth weight, wound dehiscence and maternal HIV status, CSF infection and gestation period and CSF infection and birth weight. Although not statistically significant, results trended toward significance for CSF infection and increased time to MMC repair surgery and CSF infection and birth to a HIV positive mother. The potential correlation between CSF infection post MMC repair and birth to a HIV positive mother has not been reported previously.

Following these results, it is apparent that CHBH treats a relatively high volume of neonates born with MMCs. It is also clear that the time period between birth of these neonates and repair of their MMC needs to be reduced. This study may have also identified that neonates born to mothers with HIV are at higher risk for CSF infection postoperatively. Based on these insights, a further prospective study collecting variables of interest in relation to MMC patients, maternal HIV status and their treatment is recommended, especially if this is combined with an active protocol that aims to repair all neonates born with MMCs within 72 hours. Such a study could compare complication rates based on a 72-hour repair strategy to the current study and investigate if such a protocol improves outcomes. Ultimately, further work in this area will improve patient care for neonates born with MMCs at CHBH.

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APPENDIX A – DATA COLLECTION SHEET

Study Number (De-identified for confidentiality)	
Gestational Age	
Birth Weight	
Gender	
Evidence of CSF Leak Preoperatively	
Administration of Preoperative Antibiotics	
Days to Surgery	
Utilisation of a Flap for Closure	
Hydrocephalus	
Ventriculoperitoneal Shunt Insertion	
Kyphosis	
Size of MMC – Height (Height in millimeters)	
Size of MMC - Width (Width in millimeters)	
Spinal Region of MMC (Thoracic/Lumbar)	
Blood Transfusion Volume	
Maternal Diabetes	
Maternal HIV Status	
CSF Leak Postoperatively	
Wound Infection	
Meningitis	
Encephalitis	
Operative Wound Dehiscence	
Other	

APPENDIX B – ETHICS APPROVAL

R14/49 Dr Christos Profyris

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151101

NAME: (Principal Investigator)	Dr Christos Profyris
DEPARTMENT:	Neurosurgery Chris Hani Baragwanth Academic Hospital
PROJECT TITLE:	Single Surgeon Series of Myelomeningocoele Repairs: Factors Influencing Outcomes
DATE CONSIDERED:	27/11/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr John Ouma
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	12/10/2016

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in November and will therefore be due in the month of November each year.

Principal Investigator Signature

Date 15/10/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C – PLAGIARISM REPORT

ResearchReportCProfyris.pdf

ORIGINALITY REPORT

%1	%1	%0	%0
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.dovepress.com Internet Source	%1

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23 November 2016

The Chair

Graduate Studies Committee

Faculty of Health Sciences

Re: Turn-it-in Report: Dr Christos Profyris – MMED: Single Surgeon Series of Myelomeningocoele Repairs: Factors Influencing Outcomes

I have reviewed the Turn-it-in report, which identifies a similarity index of 8%. When matches of less than 1% are removed, the similarity index drops to 1%. The vast majority of similarities relate to definitions, references and the words "statistical significance." I am satisfied that this degree of similarity does not constitute plagiarism.

Yours sincerely,

John R Ouma
Supervisor

Chief Specialist & Head of Department
Department of Neurological Surgery
University of the Witwatersrand, Johannesburg
& Chris Hani Baragwanath Academic Hospital, Soweto