Clinical determinants distinguishing communicating and non-communicating hydrocephalus in childhood tuberculous meningitis at presentation

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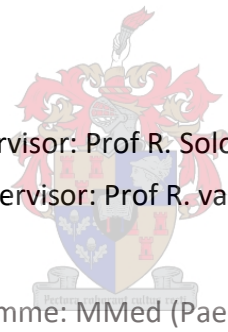

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Declaration

IBy submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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ABSTRACT

Introduction: Hydrocephalus occurs in up to 80% of children with tuberculous meningitis (TBM), of which the majority (70-80%) is of a communicating nature. Communicating hydrocephalus develops when cerebrospinal fluid (CSF) obstruction occurs at the level of the tentorium, whilst non-communicating hydrocephalus emanates from basal exudates that obstruct the outflow foramina of the fourth ventricle. Identifying the type of hydrocephalus is of critical importance since communicating hydrocephalus can be medically treated with diuretics whilst non-communicating hydrocephalus requires surgical CSF diversion. Conventional neuroimaging does not allow differentiation of the type of hydrocephalus. In resource-limited settings, air-encephalography is the only investigative modality that allows differentiation.

Objective: We aimed to investigate whether there are clinical features at baseline that allow differentiation between communicating and non-communicating hydrocephalus in children with TBM.

Design: A retrospective hospital-based cross-sectional study spanning 30 years (1985-2015).

Results: Out of 441 children with tuberculous hydrocephalus, 122 (27.7%) and 319 (72.3%) had non-communicating and communicating hydrocephalus respectively. Children with non-communicating hydrocephalus exhibited longer duration of symptoms (p=0.03) and were more inclined to develop hyponatremia (p=0.10). No children with TBM and HIV co-infection had non-communicating hydrocephalus. No differences were identified in relation to the age of onset, stage of TBM disease, Glasgow Coma Scale (GCS), cranial neuropathies, hemiplegia; signs and symptoms of raised intracranial pressure and/or brainstem dysfunction.

Conclusion: No clinical useful determinants were identified in children with tuberculous hydrocephalus that reliably allow differentiation between communicating and non-communicating hydrocephalus. This finding is explained by the fact that common TBM-related complications such as brainstem ischaemia and raised intracranial pressure (ICP) share similar clinical signs, thereby mimicking of each other's clinical determinants. The absence of non-communicating hydrocephalus in children with TBM and HIV co-infection likely reflects their defective host-inflammatory response. Air-encephalography remains the gold standard of determining the level of CSF block in resource-limited settings.

CHAPTER 1: BACKGROUND AND CONTEXT

1.1 EPIDEMIOLOGY OF TB IN SOUTH AFRICAN CHILDREN:

Tuberculosis (TB) has garnered a great quantity of research over the past decades, clearly exhibiting its ongoing relevance in the world today. According to the World Health Organization (WHO), there were approximately 10 million new cases of TB globally in 2019. South Africa ranks as one. In 2020 South Africa had reported an estimated incidence rate of 554 per 100 000; Children < 14 years comprised 7% of the case notifications (1, 2).

In children less than 12 months of age with TB disease, approximately 10-20% of cases are extra-pulmonary (3). Tuberculous meningitis (TBM) is the most severe common form of bacterial meningitis in children under 13 years, with significant morbidity and mortality, particularly in children under 5 years of age (4,5). Given the severity of this illness, it is vital that effective treatment be instituted as soon as possible, as any delay contributes to increasing morbidity and mortality (6).

1.2 PATHOPHYSIOLOGY OF CHILDHOOD TBM

Tuberculosis is spread via droplet inhalation and eventually deposited in the lung alveoli, where, depending on several bacterial virulence and host factors, it is either contained or disseminated throughout the body. Several factors including host genetics, HIV-co-infection, age and nutritional status influence whether the bacilli in the body will cause clinically evident disease. In central nervous system (CNS) TB, Rich foci (tuberculous foci) can be found on the meninges, spinal cord and brain, which when ruptured triggers a pronounced host-immune response; the release of IL-1, IL- 6, IL-12, TNF alpha and interferon gamma in TBM have been reported to be responsible for the change in the blood-brain barrier permeability and function (7). With rupture of the Rich foci into the subarachnoid space, a viscous exudate forms, which often impair flow and/or reabsorption of the cerebrospinal fluid (CSF), resulting in hydrocephalus. Hydrocephalus is a common complication of advanced TBM and if untreated it may contribute to morbidity and mortality (8).

1.3 PATHOGENESIS OF TUBERCULOUS HYDROCEPHALUS

Hydrocephalus occurs in up to 80% of children with TBM. In approximately 70-80% of cases, the hydrocephalus is of a communicating nature, which occurs when the exudate that fills the basal cisterns causes a bottleneck obstruction of the CSF pathways at the level of the tentorium. In 20% of cases, CSF obstruction occurs when the thick basal exudates obstruct the outflow foramina of the fourth ventricle resulting in non-communicating hydrocephalus. Less common causes may occur due to wrongly placed tuberculomas causing obstruction of the foramen of Munro or the Sylvian aqueduct (9). Neurologic sequelae of tuberculous hydrocephalus include impaired function and mobility, cognitive disturbances, epilepsy, endocrine disturbances and demise (10).

1.4 PREDICTORS OF TUBERCULOUS HYDROCEPHALUS

Clinical and neuroimaging risk factors of tuberculous hydrocephalus include advanced stage of disease, severe disability, duration of illness >2 months, diplopia, seizures, visual impairment, papilledema, cranial nerve palsy, hemiparesis, CSF total cell count >100/L, CSF protein >2.5 g/L, basal enhancement, tuberculoma and radiological ischaemic infarction (11). There is no literature published on studies which investigated predictors of the type of hydrocephalus.

1.5 DIAGNOSIS OF TUBERCULOUS HYDROCEPHALUS

Neuroimaging plays a crucial role in the early and accurate diagnosis of TBM and its disabling complications such as hydrocephalus and infarcts. In the early stages of TBM, neuroimaging often fail to reveal any abnormalities. Typical neuroimaging features of more advanced TBM include basal meningeal enhancement, ventriculomegaly due to hydrocephalus, basal ganglia-thalamic territory (tubercular zone) infarcts and the presence of tuberculomas. Magnetic resonance imaging (MRI) is considered superior to computed tomography (CT) in

detecting infarcts (especially in the brainstem) and small tuberculomas. However, CT is adequate for urgent evaluation of tuberculous-hydrocephalus, which often warrants urgent intervention. The presence and degree of hydrocephalus can be evaluated using the Evans' index, which is a ratio of the maximum width of the lateral ventricles and the internal biparietal diameter. An Evan's ratio of more than 0.3 is supportive of hydrocephalus (12). In communicating and non-communicating hydrocephalus pan-ventricular dilatation is observed on neuroimaging, and accurate identification of the level of the CSF block is challenging. Air-encephalography remains the most reliable way of determining the level of CSF obstruction in resource poor settings (See Figure 1).

1.6 TREATMENT OF TUBERCULOUS HYDROCEPHALUS

The treatment of tuberculous hydrocephalus depends on the level of CSF obstruction, which determines the type of hydrocephalus. Figure 2 illustrates the treatment algorithm for tuberculous hydrocephalus at Tygerberg hospital (9). Medical therapy consisting of furosemide (1 mg/kg/day) and acetazolamide (50 mg/kg/day) has been shown to normalize raised ICP within 7 days in children with communicating hydrocephalus (13). Carbonic anhydrase inhibitors (acetazolamide) and loop diuretics (furosemide) exert their effect on ICP by reducing CSF production at the choroid plexus. The experience at Tygerberg Hospital is that the majority (>90%) of children with communicating tuberculous hydrocephalus improve on diuretic therapy and only in a small percentage of cases warrant CSF diversion; usually in situations where communicating hydrocephalus over time becomes non-communicating. A 20-yr retrospective review of childhood TBM at our institution revealed that 70-80% of cases presented with hydrocephalus, with the vast majority of a communicating nature, and three quarters were successfully managed with medical therapy (14).

Children presenting with advanced (stage III) TBM with a GCS <10 and those with non-communicating hydrocephalus (on air encephalography) are treated surgically because of the risk of cerebral herniation. A ventriculo-peritoneal shunt (VPS), although lifesaving, is not without potentially serious complications. Broadly, the complications may be classified as: 1)

absorption-related problems such as ascites or loculation formation 2) flow-related issues such as low-pressure headaches, or subdural haemorrhage from CSF over drainage 3) shunt infections, which may be seen in up to 10% of shunt surgeries, particularly within the first year post-surgery and 4) mechanical problems such as blockage or shunt migration(15). The CSF shunt failure rates in children are estimated to be 30-40% at 1 year, and almost 50% at 2 years post-shunt (16).

Endoscopic third ventriculostomy (ETV) offers the benefits of CSF diversion without the risk of shunt complications. However, careful patient selection is important, as thick, tuberculous exudates may obscure important anatomical landmarks (vertebra-basilar artery) beneath the floor of the third ventricle (17).

1.7 OUTCOME OF TUBERCULOUS HYDROCEPHALUS

The effect of different treatment regimens on intracranial pressure (ICP), degree of hydrocephalus and clinical outcome was previously evaluated at our institution (18). Study findings were that the addition of acetazolamide and furosemide in children with communicating hydrocephalus was significantly more effective in achieving normal ICP than anti-tuberculous drugs alone and that no difference in outcome (mortality and morbidity) was noted when medical therapy was compared to CSF diversion. Determining outcome of tuberculous hydrocephalus in isolation is difficult as many of the neurological sequelae from TBM emanate from cerebral ischaemia (stroke) which often persist even after aggressive and rapid normalization of ICP.

CHAPTER 2: AIM OF THE STUDY

2.1 RESEARCH JUSTIFICATION

Hydrocephalus is a common complication of TBM occurring in up to 85% of children. Urgent CT imaging is usually requested for diagnostic confirmation (of hydrocephalus, basal enhancement, infarction, and pre-contrast basal hyperdensity) and to ascertain whether the raised ICP warrants neurosurgical intervention. Unfortunately, CT imaging cannot identify the level of the CSF block which may guide further therapy. Distinguishing the type of hydrocephalus is of critical importance as non-communicating hydrocephalus warrants urgent CSF diversion whilst communicating hydrocephalus is usually responsive to diuretic therapy. Air-encephalography remains the most reliable way of determining the level of CSF obstruction in resource-poor settings (9). The procedure involves a lumbar puncture which carries the risk of cerebral herniation. Neurosurgical care is often very limited in resource-poor settings and it would be valuable for clinicians to know whether there are clinical determinants which can identify the type of hydrocephalus and thus guide them to the most appropriate treatment modality.

2.2 RESEARCH HYPOTHESIS

Paediatric TBM patients with non-communicating hydrocephalus are more likely to present with more severe disease symptomatology (stage of disease, GCS, cranial neuropathy, ICP, and brainstem signs) and a shorter duration of onset. There may therefore be clinical determinants at disease onset which allow differentiation of the type of hydrocephalus.

2.3 RESEARCH QUESTION

Are there clinical determinants at disease onset which allow differentiation between non-communicating and communicating hydrocephalus without the need for formal neuroimaging and air-encephalography?

2.4 AIM

Given the importance of expediting management, the benefits of distinguishing between communicating and non-communicating hydrocephalus are obvious, particularly in resource-poor settings where any treatment delay has disastrous consequences. It would therefore seem pertinent to determine whether there is any evidence to aid clinicians in differentiating communicating from non-communicating hydrocephalus at presentation, prior to any neuroimaging and air-encephalography being performed. We sought to retrospectively examine a large cohort of children with TBM to investigate whether there are any clinical indicia that could be used to differentiate between communicating and non-communicating hydrocephalus; especially in settings where CT imaging and neurosurgical care is limited. The null hypothesis was that communicating and non-communicating hydrocephalus are indistinguishable at presentation without definitive neuroimaging and air-encephalography.

CHAPTER 3: METHODOLOGY

3.1 STUDY DESIGN

This was a retrospective cross-sectional study which evaluated and compared clinical features, biochemical and haematological markers at presentation in children with communicating and non-communicating tuberculous hydrocephalus.

3.2 SETTING

This study was conducted at Tygerberg Hospital in Cape Town, a tertiary referral and teaching centre affiliated with Stellenbosch University. The hospital is the largest in the Western Cape, serving a large area of the metropole as well as surrounding areas.

3.3 STUDY POPULATION, SAMPLING AND DEFINITIONS

The study population consisted of a cohort of 441 TBM children that were seen over a thirty-year period (1985-2015).

Inclusion criteria were children 3 months to 13 years with definite or probable TBM meningitis according to the uniform research case definition for TBM (19). **Definite TBM** was diagnosed when acid-fast bacilli were detected in the CSF, *M.tb* was cultured from CSF and/or a commercial nucleic acid amplification test of CSF was positive. A diagnosis of **probable TBM** was based on the uniform research definition for TBM using a scoring system considering clinical presentation, CSF findings, neuroimaging findings and evidence of extraneural TB. Children who did not meet criteria for definite or probable diagnosis of TBM (i.e. possible TBM) and those without tuberculous hydrocephalus or inadequate neuroimaging were excluded.

The **severity of TBM** was categorized using the refined British Medical Research Council (BMRC) stages of TBM: Stage I children have a normal GCS of 15, without focal neurological deficit; Stage IIa children have a GCS of 15 with focal neurological deficit; Stage IIb children

have a GCS of 11 to 14 with or without focal neurological deficit; whilst stage III children have a GCS less than 11 with or without focal neurological deficit (20, 21).

All children with drug-sensitive TBM were treated according to local standard of care with a **short, intensive four-drug regimen** consisting of daily isoniazid 20 mg/kg/day, rifampicin 20 mg/kg/day, pyrazinamide 40 mg/kg/day and Ethionamide 20 mg/kg/day for 6 months if HIV-uninfected and 9 month if HIV-infected. This treatment regimen has been used for more than 3 decades. Prednisone 2 mg/kg/day was given for the first month of treatment, followed by a 2 week tapering period.

Air-encephalography is routinely performed in all children with tuberculous hydrocephalus on CT imaging in the local setting, unless clinically contraindicated (Figure 2). The procedure entails installation of 5-10 ml of air into the subarachnoid space using a sterile needle and syringe after CSF analysis. The head of the child is then kept in an elevated position whereafter a lateral skull radiograph is taken 30 minutes to an hour later to evaluate the passage of the instilled air within the skull. **Communicating hydrocephalus** is diagnosed if air is seen within the lateral ventricles, whilst **non-communicating hydrocephalus** is demonstrated by air that is only visible in the basal cisterns. (Figure 1)

Hemiparesis was clinically defined as unilateral reduced movement and skill in the face and/or upper and lower limb consistent with arterial ischemic infarction of the motor cortex and/or corticospinal tracts. **Radiological arterial ischemic infarction** was defined as neuroimaging evidence of infarction, i.e. interruption of blood flow eventually resulting in focal encephalomalacia. As radiological arterial ischemic infarction is not always demonstrated on early neuroimaging, and CT is not the optimal modality to detect small areas of arterial ischemic infarction in the territory of the middle cerebral artery perforators, we considered hemiparesis (uni- or bilateral) and/or radiological arterial ischemic infarction as evidence of stroke (22).

Clinically, **raised ICP** was defined as the presence of a bulging fontanelle (in a younger child), setting sun sign and/or acute onset strabismus in infancy, and papilledema in an older child.

Brainstem dysfunction was defined as a constellation of signs and/or symptoms which included one or more of the following: marked depressed level of consciousness; impaired brainstem reflexes such as corneal, pupillary, dolls eye, oculovestibular, gag and cough; abnormal central breathing pattern; central autonomic instability and hemiplegia alternans.

3.4 DATA COLLECTION

The study utilised data that was previously collected in two prospective studies. (HREC reference numbers N10/11/367 and N11/01/006). Study participants were categorised into 2 groups; communicating versus non-communicating hydrocephalus. Recorded data was filtered reflecting demographic, clinical, laboratory and neuroimaging features in patients with TBM and confirmed communicating or non-communicating hydrocephalus (see Appendix 1).

3.5. STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 26 (SPSS Inc, Chicago, IL, USA). Numerical variables were summarized using medians and interquartile ranges. The X^2 test was used to assess the differences between categorical variables. The level of significance was set at $p < 0.05$ (2-sided).

3.6. ETHICAL CONSIDERATIONS

The MMed protocol was approved by the Stellenbosch University Health Research Ethics Committee (HREC) (Ref nr S20/07/180). Waiver of individual informed consent was granted as the data used was retrospectively analysed and anonymised and therefore no risk was posed to the participants of the study. The patients' identities were kept confidential and none of the investigators personally interacted with any of the patients directly regarding this research. Any identifying information was secured in a password-protected electronic file and access to this database was limited to essential investigators only.

CHAPTER 4: RESULTS

Of 441 children with TBM, median age 27.0 months (interquartile range (IQR):14.0 to 48.0) and 221 (50.1%) male; 319 (72.3%) presented with communicating and 122 (27.7%) with non-communicating hydrocephalus. **Table 1** illustrates the demographic, clinical, laboratory and neuroimaging features of children with communicating and non-communicating hydrocephalus. The median age at admission was 27 months (IQR: 14.0 to 50.0) and 26 months (IQR: 15.0 to 39.0) in patients with communicating and non-communicating hydrocephalus, respectively. Fifty-nine patients (18.5%) with communicating hydrocephalus met the criteria for definite TBM, while in those with non-communicating hydrocephalus 24 (19.7%) met criteria. HIV serology testing was performed in 190 children of which 9 proved positive (4.7% prevalence). Of interest was the absence of non-communicating hydrocephalus in TBM HIV-co-infected children.

Table 2 illustrates a univariate analysis of some of the clinical determinants between children with communicating and non-communicating hydrocephalus. No statistically significant differences were identified between the two groups in relation to age of onset, symptoms (vomiting, fever and convulsions), stage of TBM disease, Glasgow Coma Scale (GCS), stroke, cranial neuropathies, signs and symptoms of raised intracranial pressure and brainstem dysfunction, CSF cell count and biochemistry as well as the presence of tuberculomas and basal meningeal enhancement.

Children with non-communicating hydrocephalus exhibited longer duration of symptoms prior to diagnosis (p=0.03), and were more likely to be affected by moderate to severe hyponatremia (p=0.10).

CHAPTER 5: DISCUSSION

This study specifically investigated clinical factors associated with tuberculous hydrocephalus in general, such as advanced stage of disease, prolonged duration of illness, seizures, visual impairment (papilloedema), cranial nerve palsy, hemiparesis, high CSF total cell count and

high CSF protein (>1.0 g/l). CT features of interest were the presence of basal meningeal exudates, tuberculomas and infarcts. No clinico-radiologic-laboratory determinants were identified that could reliably identify the level of the CSF block in children with tuberculous hydrocephalus at admission.

The development of tuberculous hydrocephalus occurs secondary to the development of a dense and adhesive basal exudate that fills the basal cisterns and is usually most prevalent in the interpeduncular fossa and suprasellar region, as well as the ambient and prepontine cisterns and the spinal subarachnoid space. This process is time-dependent and could explain the study finding of non-communicating hydrocephalus associated with prolonged duration of symptoms before clinical presentation (> 5 days). However, quantifying disease duration in a chronic meningitis such as TBM is often challenging and subjective as it is dependent on the feedback obtained from the parents or caregiver. We therefore did not deem it a useful discriminator of the type of hydrocephalus.

Studies have furthermore shown that parenchymal brain stem injury may mimic the signs of raised ICP and that a poor correlation exists between signs of clinical raised ICP in children with TBM and monitored CSF pressure. The overlap/similarity in symptoms most likely accounts for the lack of clinical determinants in relation to the level of the CSF block.

Several observational studies comparing the clinical presentation of TBM in children with and without HIV infection have found that presenting symptoms such as fever, headache, vomiting, and weight loss are similar in both groups. Radiological studies on HIV infection in tuberculous meningitis (TBM) in children report that HIV-infected children are less likely to display meningovascular enhancement, tuberculoma formation and non-communicating hydrocephalus (23). The decreased likelihood of developing hydrocephalus associated with TBM in children who are infected with HIV is probably a consequence of the defective host-inflammatory response. Any ventricular dilatation seen in HIV-infected patients is therefore most likely to be secondary to cerebral atrophy, which protects against the development of raised intracranial pressure. In this study, HIV-serology was performed in 191 children of which 9 proved positive (4.7% prevalence). In this study no children with TBM and HIV co-infection developed non-communicating hydrocephalus.

In TBM patients, the CSF is often characterised by an elevated protein level, especially if a CSF block is present. A high CSF protein is therefore considered a predictor of hydrocephalus (in general) as well as a risk factor for subsequent shunt blockage. Of interest is that the study did not find any difference in CSF cell count or chemistry between the two tuberculous hydrocephalus subgroups. It is however important to appreciate that the CSF profile is dependent on the sampling site. Lumbar CSF profiles do not necessarily reflect ventricular CSF profiles in children with non-communicating hydrocephalus. However in this study, data on CSF sampling site was lacking, and it was presumed that the majority of CSF samples were obtained by lumbar puncture.

In this study, children with non-communicating hydrocephalus were more likely to develop hyponatremia (p=0.10). Two pathological conditions, namely the syndrome of inappropriate antidiuretic hormone (SIADH) and cerebral salt wasting syndrome (CSWS), have been implicated in the development of hyponatraemia in TBM. The underlying mechanism for CSWS in TBM is thought to be related to increased release of natriuretic factors such as atrial natriuretic peptide and brain natriuretic peptide (BNP). The release of BNP is thought to occur secondary to ventricular distention. The latter may occur more acutely and more severely in cases with non-communicating hydrocephalus, therefore the higher prevalence of hyponatremia.

Recently, many research studies has been conducted to identify raised ICP through minimally or non-invasive methods. Many studies have attempted to develop non-invasive methods to identify elevated ICP using techniques such as trans-ocular ultrasound, carotid artery Doppler, tympanic membrane pulsation, and cochlear aqueduct transmission (24). However, to date, none have proven to be reliable enough for clinical practice. Transcranial Doppler was investigated as a method to evaluate raised intracranial pressure in children with TBM, however it was not found to be a reliable measure (24). Newer MRI modalities and options to evaluate hydrocephalus have emerged in recent times, including options to employ techniques such as spin echo, turbo spin echo, 3D constructive interference in the steady state (3D CISS), and others, to review CSF flow and anatomy of cisterns. These modalities should be used in conjunction with conventional T1- &T2-weighted MRI imaging sequences

and are helpful to decide the most appropriate course of action if undertaking CSF diversion (25). Although CT is a very useful tool to detect hydrocephalus, a study undertaken in the Western Cape looking at the efficacy of CT to distinguish between communicating and non-communicating hydrocephalus in children with TBM was regrettably unable to show promising results for the case of CT superiority, with only age and a rounded 3rd ventricle showing a statistical difference (26). Thus air encephalography remains the gold standard for discerning the presence and level of CSF blockage in children with tuberculous hydrocephalus.

CHAPTER 6: STRENGTHS AND LIMITATIONS

The very large sample size and the fact that the data was prospectively collected data can be considered as study strengths. Study limitations include (1) the fact that the study was performed at a single hospital which may limit generalization of the study findings to other settings. (2) Routine HIV testing was not standard practice during the early years of the study period. In addition, the small number of HIV infected TBM children did not allow sub-group analysis. (3) The severity of the hydrocephalus was not quantified as data on Evan's index, hydrocephalus and bi-parietal diameter was limited. (4) A of communicating hydrocephalus evolving into non-communicating hydrocephalus is interesting, however data was lacking.

CHAPTER 7: CONCLUSION

Failure to accurately diagnose and manage TBM and its complications especially in the vulnerable paediatric population has both immediate and long-term deleterious effects. It is clear that clinical determinants alone are not enough to differentiate between communicating and non-communicating hydrocephalus. Apart from prolonged symptom duration that might point to a more likely diagnosis of non-communicating hydrocephalus, it is virtually indistinguishable at presentation from communicating hydrocephalus. Further, the absence of non-communicating in children with TBM and HIV co-infection highlights the defective host-inflammatory response resulting in CSF obstruction. After neuroimaging, air encephalography remains definitive and the gold-standard to differentiate communicating hydrocephalus from non-communicating hydrocephalus guiding often-urgent therapeutic options for the treatment of tuberculous hydrocephalus.

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APPENDIX 1.

Data collection sheet

	Admission	Week 1	Week 2	Week 3
Basic information				
Inclusion number				
Age in months				
Gender				
Definite or probable TBM				
TBM stage				
Duration of symptoms (days)				
HIV status				
Neuroimaging				
Hydrocephalus y/n				
Communicating/ Non-communicating				
Basal enhancement y/n				
Infarction y/n				
CSF analysis				
CSF volume taken (ml)				
CSF macroscopic appearance				
CSF Polymorphs cell/mm^3				
CSF Lymphocytes cell/mm^3				
CSF protein g/L				
CSF glucose mmol/L				
Other investigations				
Extra neural TB culture pos/neg				
Miliary TB CXR y/n				

LIST OF FIGURES AND TABLES

Figure 1. Air encephalography in tuberculous hydrocephalus

Figure 1A illustrates communicating hydrocephalus as air is visible (arrow) in the lateral ventricles; 1B illustrates non-communicating hydrocephalus as air is only visible in the basal cisterns. The latter finding warrants CSF diversion strategies.

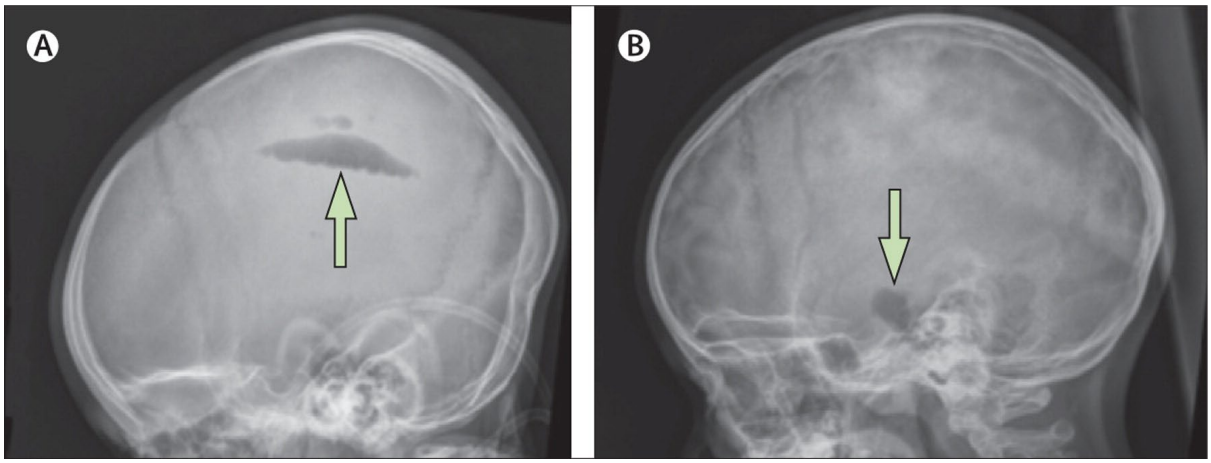
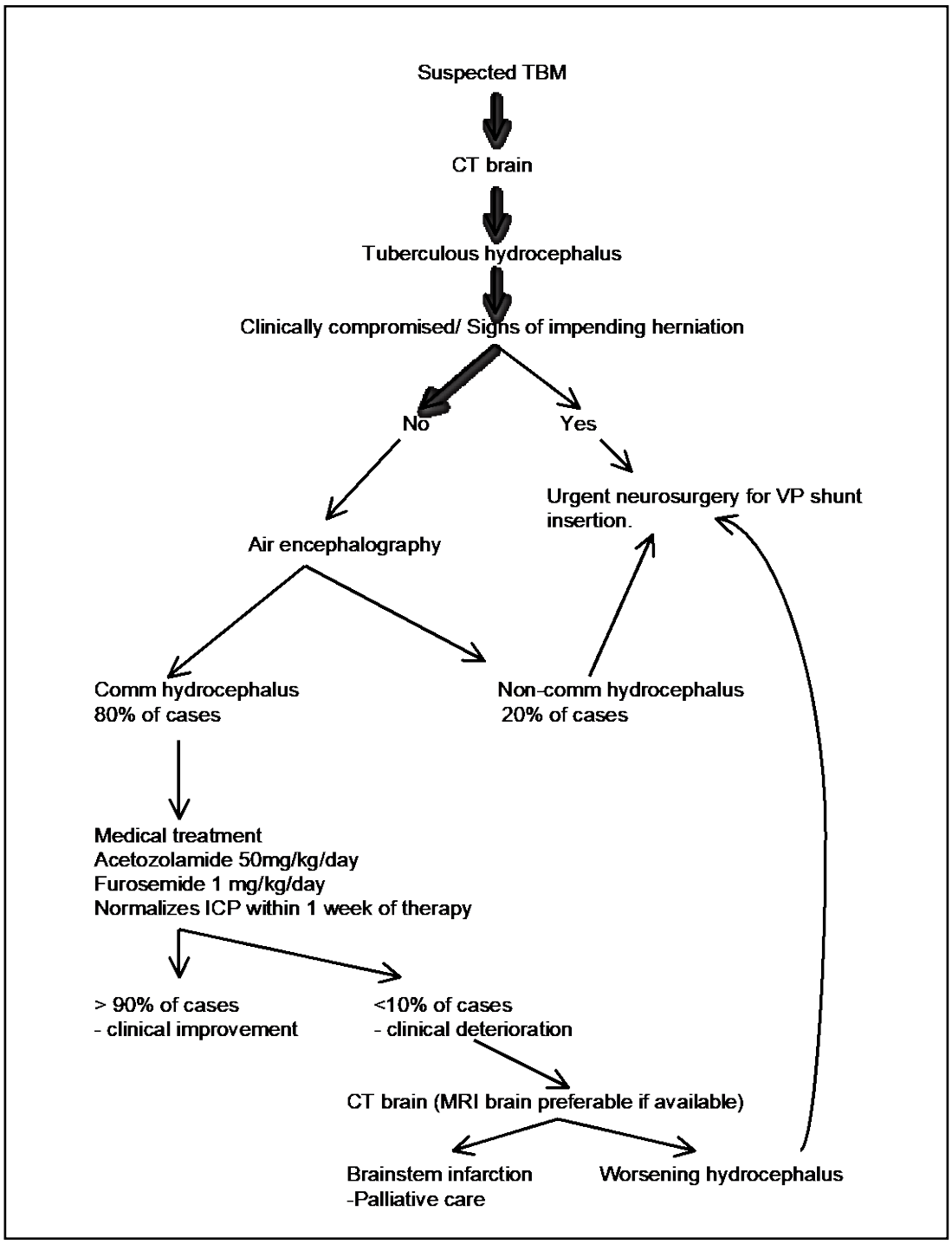


Figure 2. Tygerberg Hospital treatment algorithm for paediatric tuberculous hydrocephalus. (9)



Comm= communicating hydrocephalus; non-comm= non-communicating hydrocephalus; VPS= ventriculo-peritoneal shunt; ICP= intracranial pressure

Table 1.

Demographic, clinical, laboratory and neuroimaging features in paediatric tuberculous communicating and non-communicating hydrocephalus 1985-2015

		Communicating hydrocephalus (n=319) n/N (%)	Non-communicating hydrocephalus (n=122) n/N (%)
Definite TBM		59/319 (18.5)	24/122 (19.7)
Probable TBM		260/319 (81.5)	98/122 (80.3)
Male Gender		160/319 (50.2)	61/121 (50.4)
Age at admission in months	**median**	27.0: IQR 14.0-50.0	26.0: IQR 15.0-39.0
Vomiting		153/299 (51.2)	61/109 (56.0)
Fever		204/299 (68.2)	66/109 (60.6)
Convulsions		142/299 (47.5)	51/109 (46.8)
Headache		77/299 (25.8)	21/109 (19.3)
Symptom duration (days)	**median**	9.0: IQR 7.0-16.0	10.0: IQR 7.0-21.0
Symptom duration >5 days		268/314 (85.4)	110/118 (93.2)
Known TB exposure		183/319 (57.4)	62/122 (50.8)
TST	**Positive**	176/296 (59.5)	62/111 (55.9)
HIV status	**Infected**	9/133 (6.8)	0
Nutrition	**Weight faltering**	127/159 (79.9)	47/57 (82.5)
GCS <15		199/299 (66.6)	76/1090 (69.7)
TBM Stage	**Stage I**	4/319 (1.3)	0
	Stage IIa	9/319 (2.8)	2/122 (1.6)
	Stage IIb	144/319 (45.1)	39/122 (32.0)
	Stage III	162/319 (50.8)	81/122 (66.4)
Stroke		227/319 (71.2)	86/122 (70.5)
Cranial nerve palsy		86/312 (27.6)	39/120 (32.5)
Raised ICP		74/317 (23.3)	33/122 (27.0)
Brainstem dysfunction		124/319 (38.9)	50/122 (41.0)
Serum sodium (mmol/L)	**median**	131.0: IQR 127.0-135.0	130.5: IQR 125.0-134.0
Hyponatremia:	**mild 130-134mmol/L**	113/298 (37.9)	42/119 (35.3)
	moderate 120-129mmol/L	85/298 (28.5)	43/119 (36.1)
	severe <120mmol/L	17/298 (5.7)	7/119 (5.9)
CSF lymphocyte count (cells/L)	**median**	100.0: IQR 42.0-188.0	72.0: IQR 20.0-160.0
CSF neutrophil count (cells/L)	**median**	11.0: IQR 2.0-37.0	9.0: IQR 2.0-55.0
CSF protein concentration (g/L)	**median**	1.48: IQR 1.02-2.44	2.02: IQR 1.11-3.30
CSF glucose (mmol/L)	**median**	1.40: IQR 0.70-2.10	1.10: IQR 0.50-2.00
Culture positive for extraneural *M.tb*		79/319 (24.8)	30/122 (24.6)
Suggestive PTB on CXR		193/309 (62.5)	72/117 (61.5)
Basal meningeal enhancement		254/303 (83.8)	101/117 (86.3)
Tuberculoma(s)		37/299 (12.4)	13/115 (11.3)

TBM= tuberculous meningitis, IQR= interquartile range, GCS= Glasgow Coma Scale, BCG= Bacille Calmette-Guerin, ICP= intracranial pressure, *M.tb=Mycobacterium tuberculosis*

Table 2.

Analysis of clinical, laboratory and neuroimaging features in paediatric tuberculous non-communicating versus communicating hydrocephalus 1985-2015

	p-value	OR (95% CI)
Definite TBM	0.78	1.08 (0.64-1.83)
Male Gender	0.96	1.01 (0.67-1.54)
Mean age	0.25	
Vomiting	0.39	1.21 (0.78-1.89)
Fever	0.15	0.72 (0.45-1.13)
Convulsions	0.90	0.97 (0.63-1.51)
Symptom duration >5 days	**0.03**	2.36 (1.08-5.16)
TST	0.51	0.86 (0.55-1.34)
Weight faltering/loss	0.67	1.18 (0.54-2.60)
GCS <15	0.55	1.16 (0.72-1.86)
Advanced TBM Stage (2b/3)	0.21	2.55 (0.57-11.47)
Stroke	0.89	0.97 (0.61-1.53)
Cranial nerve palsy	0.31	1.27 (0.80-2.00)
Raised ICP	0.42	1.22 (0.76-1.96)
Brainstem dysfunction	0.69	1.09 (0.71-1.67)
Serum sodium <130mmol/L	0.10	1.44 (0.93-2.23)
CSF leucocytes 10-500 cells/L	0.73	0.90 (0.50-1.63)
CSF lymphocyte predominance	0.88	0.96 (0.55-1.70)
CSF protein >1g/L	0.51	1.19 (0.71-1.98)
CSF glucose <2.2 mmol/L	0.52	1.18 (0.72-1.94)
Culture positive for extraneural *M.tb*	0.97	0.99 (0.61-1.61)
Suggestive PTB on CXR	0.86	0.96 (0.62-1.49)
Basal meningeal enhancement	0.53	1.22 (0.66-2.24)
Tuberculoma(s)	0.77	0.90 (0.46-1.77)

TBM= tuberculous meningitis, OR= odds ratio, GCS= Glasgow Coma Scale, TB= tuberculosis, BCG= Bacille Calmette-Guerin, ICP= intracranial pressure, CXR= chest radiograph, CSF= cerebrospinal fluid, *M.tb=Mycobacterium tuberculosis,* CNS= central nervous system

LIST OF ABBREVIATIONS

BCG= Bacille Calmette-Guérin

BMRC=British Medical Research Council

CNS= central nervous system

CSF= cerebrospinal fluid

CXR= chest radiograph

ETV=Endoscopic third ventriculostomy

GCS= Glasgow Coma Scale

ICP= intracranial pressure

IQR= interquartile range

M.tb= mycobacterium tuberculosis

OR= odds ratio

CI= confidence interval

TB= tuberculosis

TBM= tuberculous meningitis

WHO= World Health Organisation

VPS=Ventriculoperitoneal shunt