CLINICAL, LABORATORY AND RADIOLOGIC FEATURES OF TUBERCULOUS MENINGITIS IN CHILDREN AT THE UNIVERSITY TEACHING HOSPITAL, DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH

By

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DECLARATION

I hereby declare that this dissertation represents my own work and has not been presented either wholly or in part for a degree at the University of Zambia or any other university.

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APPROVAL

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ABSTRACT

Introduction: Tuberculosis (TB) is one of the top 10 reasons for admission in the University Teaching Hospital (UTH), Department of Paediatrics, accounting for 4 -8 % of all admissions. The relative incidence of tuberculous meningitis (TBM) in developing countries has been reported to range from 7–12% of all cases of TB. Because TBM can mimic other meningitides or common illnesses like cerebral malaria, diagnosis is often delayed, resulting in poor outcome.

Objective: To describe the clinical, laboratory and radiological features of TBM in children admitted to the UTH department of Paediatrics and Child health.

Methods: Prospective descriptive case series carried out from February 2007 to November 2007. Twenty one children were recruited. Clinical case definition of TBM was based on the following:

Abnormal neurologic signs and/or symptoms, and ≥2 of the following:

1. History of adult source case with TB who had contact with child
2. Presence of tuberculin skin test (TST) reaction ≥10 mm of induration in HIV un-infected, or ≥ 5 mm of induration in HIV infected children
3. CSF abnormalities without evidence of other infectious cause
4. A chest radiograph consistent with primary TB infection, such as miliary picture, hilar lymphadenopathy or mediastinal adenopathy
5. Failure of sustained response to antibiotic and/or anti-malarial treatment

Clinical, laboratory and radiologic features of the 13 children with TBM were evaluated and documented for the study. The 8 non-TBM children were excluded from the analysis.

Results: Of the 13 children, 7 (53.8%) were male and 6 (46.2%) were female, the majority of whom (69.3%) were less than 43 months old. All the children had history of fever, 53.8% had TB contact, 69.2% had weight loss, 92.3% had meningeal signs and 46.2% were TST positive. More HIV negative children test TST positive than HIV

negative children (55.6% versus 25%). Eleven (92.3%) of the children had ESR >50mm/hr. Four (30.8%) of the children were HIV positive. The chest radiographs were abnormal in 6/12 (50%) of the children. Gastric lavage was negative for Acid and Alcohol Fast Bacilli (AAFB) in all children tested. CSF protein was elevated in 10 (76.9%) patients and CSF to blood glucose was reduced <0.6 in 10 (76.9%) children. Both CSF microscopy and Mycobacteria Growth Indicator Tube (MGIT) culture yielded no AAFB. All children had at least two courses of antibiotics before Anti Tuberculous Treatment was commenced.

Conclusion: Definitive diagnosis of TBM continues to be difficult as none of the children had tubercle bacilli isolated from sputum or CSF. Moreover, abnormal CSF protein and sugar, positive TST and failure of adequate response to initial antibiotics were the major criteria used for the diagnosis of probable TBM in UTH.

DEDICATION

This dissertation is dedicated to my late dad who believed in me so much and my mum for her continued words of encouragement on many a frustrating times. To my long suffering husband, Robert Andrew Marsden, who endured long days and nights without his wife, friend and confidant. For all the hours of being left alone to be mum and dad to our son, Thank you. To my son Aiden Chawanzi Marsden who spent many hours without his mother. Who knew the sentence 'are you going to work, mama?' as soon as he could talk, Thank you for the wonderful hugs and kisses at the end of numerous exhausting days.

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TABLE OF CONTENTS

ABBREVIATIONS

MTB	Mycobacterium Tuberculosis
TB	Tuberculosis
WHO	World Health Organisation
UTH	University Teaching Hospital
PTB	Pulmonary Tuberculosis
TST	Tuberculin Skin Test
HIV	Human Immunodeficiency virus
EPTB	Extrapulmonary Tuberculosis
ATT	Antituberculous Treatment
CSF	Cerebral Spinal Fluid
AAFB	Acid alchohol Fast Bacilli
CT	Computer Tomography
ZN	Ziehl Nelson
LJ	Lowestein Jensen
MGIT	Mycobacterial Growth Indicator Tube
ESR	Erythrocyte Sedimentation Rate
LIP	Lymphoid Interstitial Pneumonitis
NTB	Non Tuberculous Mycobacterium
DTH	Delayed Type Hypersensitivity
DOTS	Directly Observed Therapy Short Course
CXR	Chest Xray
TU	Tuberculin Units
PPD	Purified Protein Derivative
WCC	White Cell Count

AIDS	Acquired immunodeficiency syndrome
BCG	Bacille Calmette Guerin

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CHAPTER 1

INTRODUCTION

1.1 BACKGROUND INFORMATION

Mycobacterium Tuberculosis (MTB) infects nearly one-third of the global population, i.e. two billion people. More than eight million people develop active tuberculosis (TB) every year and about two million die.[1] The World Health Organization (WHO) estimates that tuberculosis causes 6% of all deaths worldwide, making it the most common cause of death resulting from a single infectious agent.[2] On a global scale, there are 22 countries that are considered high burden countries for tuberculosis and Zambia is ranked 24th based on estimated number of cases.[3]

Tuberculosis remains one of the major causes of admission to hospitals in Zambia and is among the top ten leading causes of morbidity and mortality in children at the University Teaching Hospital (UTH).[4] Between 1999 and 2002, TB accounted for between 4% and 8% of all paediatric admissions in UTH and mortality during this same period ranged from 1% and 16%.[4] Historically in Zambia, the prevalence rate of TB remained constant at around 100 per 100,000 population between 1964 and 1984, indicating a steady-state situation. During the period 1984-1994, the absolute number of notified cases (all forms) increased from about 8,000 in 1985 to over 38,000 in 1996, tripling the case-definition rate from about 100 to over 400 per 100,000 population.[5] The trends have continued to increase with notification rates (all forms) of 442 in 1999 to 499 in 2003 per 100,000 population.[5] During the same period smear positive cases of TB rose from 114 in 1999 to 175 in 2003. As of 2003, the prevalence rate (all forms) of TB rose to 638 per 100,000 population with a mortality rate of 122 per 100,000 population in the same year.[5]

Children are usually infected with TB by an adult or an older child with sputum smear-positive pulmonary tuberculosis (PTB), often a family member. Less commonly, they may be infected by contact with smear-negative (often culture-positive) cases. They can present with TB at any age, but the most common age is between 1 and 4 years. In contrast, children aged 5-14 years often have been referred to as the "favoured age" since they have lower rates of TB than any other age group. The majority of infected children do not develop TB disease in childhood. The only evidence of infection may be a positive tuberculin skin test (TST).[6]

The likelihood of developing disease is greatest shortly after infection and declines steadily with time. If an infected child does develop disease, the majority will present with symptoms within one year of infection. For infants particularly, the time-span between infection and disease may be as little as 6-8 weeks. Various immunosuppressive illnesses may facilitate progression of infection to disease, including Human Immunodeficiency Virus (HIV) infection, measles, whooping cough and severe malnutrition. These conditions are also most common in infancy and early childhood.[6]

The frequency of childhood TB depends on the intensity of the epidemic, the age structure of the population, the available diagnostic tools and whether contact tracing is routinely undertaken. Case notifications of childhood TB usually represent 6-20% of all TB cases registered with National Tuberculosis Programmes.[6] WHO only reports smear positive cases of TB for children less than 15 years. The notification rates for children in Zambia have risen from 10 per 100,000 population in 2000 to 14 per 100,000 population in 2003. This translated into an absolute number of 499 and 594 children respectively. These figures made Zambia the third highest country globally after South Africa and Angola.[3]

The rates of TB (all forms) in Zambia have been increasing over the years. The reasons for these increases include high rate of HIV in sexually active age groups, poverty and over crowding in homes, failure to identify cases early by the health providers, failure to adhere to treatment and problems with data collection. Over diagnosis due to reliance on clinical and radiological findings rather than on sputum microscopy have also contributed to these high rates.[5] Of all the risk factors, HIV has

become the single most important risk factor for the development of TB. In Zambia, as of 2003 the percentage of tuberculosis cases that were HIV positive in the age group 15-49years was 56 %.[3] The rate of HIV in children with TB was shown to be 70% by Chintu et al in a study done in UTH between 1990 and 1991.[7]

The ratio of PTB to extrapulmonary tuberculosis (EPTB) in children is usually around 1:3 but varies depending on factors such as age, ability to examine contacts and possibly genetic factors.[6] In Zambia, PTB was shown to be the commonest clinical feature of tuberculosis when compared to the extrapulmonary forms in both HIV positive and negative children.[8] Unfortunately, statistics released by the Zambian Ministry of Health and WHO do not differentiate between pulmonary and extra pulmonary tuberculosis (EPTB). In fact, information on children with tuberculous meningitis regarding incidence, morbidity and mortality in Zambia is sadly lacking. Despite this, the relative incidence of tuberculous meningitis (TBM) in developing countries has been reported as 7–12% of all cases of TB.[9] In addition, studies in some African countries have shown that 20-30% of meningitis cases in children are due to TBM.[10]

1.2 STATEMENT OF THE PROBLEM

Tuberculosis is one of the major causes of admission in the UTH. The burden of the disease has continued to increase resulting in high bed occupancy by patients in the hospital. The diagnosis of TBM in children in our environment continues to pose difficult challenges. This situation is worsened by the fact that most of the investigative tools are either time consuming or do not add value. In UTH, the diagnosis of TBM is usually made clinically. Because TBM can mimic other meningitides or common illnesses like cerebral malaria, children are usually initially treated for these conditions. When no response to appropriate therapy is seen, they are frequently commenced on Anti Tuberculous Therapy (ATT). Unfortunately, too often, by the time this treatment is commenced, serious and irreversible neurological sequelae have already set in.

The definitive diagnosis of TBM should be made by examining Cerebral Spinal Fluid (CSF) for Acid Alcohol Fast Bacilli (AAFB) by microscopy and culture. This is the 'gold

standard' for the diagnosis of TBM. In UTH, however, lumbar punctures have long been associated with death by parents resulting in refusal to consent to the procedure on their children. In addition, microscopy and cultures for AAFB are not routinely done on all specimens resulting in reduced sensitivity for the diagnosis of TBM. Finally, Computer Tomography (CT) scans which can be diagnostic are not routinely done due to their high cost. The majority of our patients cannot afford the immense cost of these CT scans.

1.3 LITERATURE REVIEW

1.3.1 PATHOGENESIS

TBM usually arises from the formation of a metastatic caseous lesion in the cerebral cortex or meninges that develops during the lymphohematogenous dissemination of the primary infection. The initial lesion increases in size and discharges small numbers of tubercle bacilli into the subarachnoid space. The resulting gelatinous exudates infiltrate the corticomeningeal blood vessels, producing inflammation obstruction and subsequent infarction of cerebral cortex.[11] Regardless of where the discharging tuberculous focus may be, the resultant exudative inflamatory reaction is always most marked at the base of the brain.[12]

The three features which dominate the pathology of TBM include:[12,13]

1. Proliferative, inflammatory predominantly basilar meningeal exudate which usually centres around the interpeduncular fossa, enveloping the optic nerves at the chiasma. It also extends over the pons and cerebellum.
2. Vasculitis of arteries and veins traversing this exudate often resulting in ischaemic cerebral infarction.
3. Disturbance of CSF circulation and resorption to the basilar cisterns, leading to a communicating hydrocephalus.

The combination of vasculities, infarction and hydrocephalus results in the severe damage that can occur gradually or rapidly. The brain stem is often the site of greatest involvement with cranial nerve six being the most frequently affected by TBM.[13]

Papilloedema is the most common visual effect of TBM. In children, papilloedema may progress to primary optic atrophy and blindness due to direct involvement of the optic nerves and chiasma by basal exudates. Other causes of visual impairment include chorioretinitis, optic neuritis, internuclear ophthalmoplegia and, occasionally, abrupt onset of painful ophthalmoplegia.[14] Profound abnormalities in electrolyte metabolism, due to salt wasting or the syndrome of inappropriate antidiuretic hormone secretion, also contribute to the pathophysiology of TBM.[11]

1.3.2 CLINICAL MANIFESTATIONS

TBM is the most life-threatening form of extrapulmonary tuberculosis. It commonly arises as a complication of primary infection. The highest incidence occurs in the first three years of life and is uncommon below six months. Fifty to sixty percent of cases have been shown to be below three years.[15]

Congenital TB is rare mainly because the most common result of female genital tract TB is infertility. However, Schaaf et al did describe four cases of PTB occuring in the neonatal period thought to have been caused by maternal urogenital transmission.[16] Congenital transmission occurs most commonly from a lesion in the placenta through the umbilical vein though it can be caused by aspiration or ingestion of infected amniotic fluid. Primary infection in the mother just before or during pregnancy is more likely to cause congenital infection than is reactivation of a previous infection.[11] Congenital TBM usually occurs within the first two months of life compared with postnatally acquired TBM which is practically never seen in infants less than four months of age. Four cases of infants less than 3 months of age were described by Watchi et al , the youngest of whom was a five week old infant.[17]

TBM in its classical form, is characterised by a prodromal stage lasting 2 -3 weeks, sometimes a month or two, where there is a history of vague ill health. This is followed by a stage of meningeal irritation leading to a final stage of diffuse or focal cerebral involvement.[15] The clinical progression of TBM may be rapid or gradual. Rapid progression tends to occur more often in infants and young children, who experience symptoms for only several days before the onset of acute hydrocephalus, seizures and

cerebral oedema.[11] The three stages were of TBM were classically described by the British Medical Research Council in 1948[18]

Stage 1 (early):	Nonspecific symptoms and signs. No clouding of consciousness. No neurologic deficits.
Stage 2 (intermediate):	Lethergy or behavioral changes. Meningeal irritation. Minor neurologic deficits such as cranial nerve palsies.
Stage 3 (late):	Stupour or coma. Abnormal movements, seizures and severe neurologic deficits such as pareises.

Researchers in some studies, however, have reported that only 13% to 19% of their patients with TBM had fever.[19,20,21] Therefore, absence of fever should not exclude the possibility of TBM.

1.3.3 DIAGNOSIS

The diagnosis of TBM can be difficult early in its course requiring a high degree of suspicion on the part of the clinician. Early diagnosis followed by effective treatment may prevent neurologic damage or fatal outcome.[22]

1.3.3.1 Sputum

Collecting sputum from children is not only difficult and time consuming but the sensitivity of gastric lavage is low. Studies have shown low sensitivities (in the range of 15-30%) but with very high specificities (in the range of 90-99%).[23,24,25] The yield of mycobacteria is high when the samples are repeated, in extensive pulmonary disease and in infants, where it is up to 70 per cent.[26] The yield of conventional culture of gastric aspirate varies from 30-52% in children with TB.[23,27,28] This yield drops to zero per cent in children when only hilar adenopathy is observed on X-ray film of chest.[28] Higher yields (up to 70%) have been reported in infants and children with extensive disease.[26]

1.3.3.2. Cerebral spinal fluid

The most important laboratory test for the diagnosis of TBM is examination and culture of lumbar CSF. The gold standard for making the diagnosis of TBM involves isolation of AAFB in CSF. Although there has been warning of herniation precipitated by lumbar puncture, it carries no risk in the absence of hemiparesis or papilloedema[26] whether cerebrospinal fluid pressure is raised or not.[29,30]

The CSF findings in TBM often demonstrate reduced glucose concentration, increased protein level, and elevated leukocyte counts. It is generally reported to be under mild pressure, clear and colourless or 'ground glass' in appearance while, on standing, a delicate web like clot is often said to form. [15,12] CSF biochemistry reveals low glucose in 90% of cases, <2.5 mmol/l in more than 80% of cases [12,31] or a CSF: Blood sugar ratio <0.6.[32] Simultaneous testing of blood sugar levels helps to avoid confusion in diabetics or those on intravenous alimentation. Protein levels in the CSF are typically high, being less than 1 g/l in 25% of patients, 1–5 g/l in most and >5 g/l in 10% of patients. Very high protein concentrations of >5 g/l suggest a subarachnoid spinal block, and are often associated with a poor prognosis. [12,31]

The cell count in the CSF reflects moderate pleocytosis, ranging from 10–1000/µl; it is <500/µl in 90% of patients, and rarely exceeds 1000/µl. Lymphocytes generally predominate, but early in the course of the disease a polymorphonuclear reaction may be found, making differential diagnosis from acute bacterial meningitis difficult.[12,31] Although the lumbar CSF is grossly abnormal, ventricular CSF may have normal chemistries and cell counts because this fluid is obtained from a site proximal to the inflammation and obstruction.

The success of the microscopic examination of Ziehl Nelson (ZN) stained CSF and mycobacterial culture is related directly to the volume of CSF sample collected. Examination or culture of small amounts of CSF is unlikely to demonstrate MTB. When more than 6ml of lumbar CSF can be obtained, the acid-fast stain of the CSF sediment is positive in up to 80% of cases. In addition, spending at least 30min when examining a sample also increases the chances of finding positive results.[33]

1.3.3.3 Culture – conventional, semi-automated and automated

Conventional culture on Lowenstein Jensen (LJ) media takes 7-10weeks for detection of acid fast bacilli. It is for this reason that other techniques have been developed like BACTEC radiometric assay, Septicheck AFB system, and Mycobacterial Growth Indicator Tube (MGIT) system.

The BACTEC 460 is a semi-automated radiometric system improves the yield of positive cultures from clinical specimen while the time taken to detect MTB is 9-14 days.[34] The capability of performing rapid mycobacterial drug sensitivity is an additional advantage of the BACTEC system. The limitations of BACTEC system include high cost of instruments, inability to observe colony morphology and detect mixed cultures, overgrowth by contaminants, need for disposal of radioactive material and extensive use of needles. [35]

BACTEC 960/MGIT is a fully automated system which uses an oxygen sensitive fluorescent sensor embedded in silicone base to serve as an indicator of mycobacterial growth. The tube contains 4 ml of modified Middlebrook 7H9 broth enriched with 0.5 ml of a nutritional supplement and 0.1 ml of an antibiotic cocktail to suppress growth of contaminating micro-organisms. As the actively growing and respiring mycobacteria consume the dissolved O_2, the sensor glows indicating mycobacterial growth. This is observed by using an ultra violet lamp with a wave length of 365 nm.

A meta-analysis of 10 studies of BACTEC 960/MGIT and BACTEC 460 systems showed sensitivities and specificities of 81.5% and 99.6% and 85.8% and 99.9% respectively.[36] Most of the earlier studies were mainly on pulmonary specimens but in recent years extrapulmonary specimens have also been evaluated. Extrapulmonary specimens have included gastric aspirates, pleural fluid, stool, urine and CSF. The greatest detection rates for MTB have been recovered with MGIT (range 80 – 90.3%), followed by BACTEC 460 (75%) and lastly by LJ media (69 -72.6%).[37,38] In children with HIV infection even lower yields of mycobacterial culture are obtained,[23] although this difference may not be significant.[39]

1.3.3.4. Erythrocyte Sedimentation Rate

Elevated erythrocyte sedimentation rate (ESR) is usually used by most paediatricians as a indication of TB infection. However, Al-Marri and Kirkpatrick showed that 32% of the children studied had a normal ESR (<10 mm/hr) and 43% had an ESR of <20 mm/hr at the time of diagnosis. Children with symptomatic TB and culture proven TB did have higher ESR's.[40] ESR should therefore be interpreted with caution when used as a diagnostic tool for TB (EPTB or PTB).

1.3.3.5 Tuberculin skin test

The tuberculin skin test (TST) is the only routinely available and comparatively cheap method for detecting individuals infected with MTB. In view of evidence indicating the variability of tuberculin reactivity under different conditions and among different populations, the definition of a criterion for a positive TST is problematic.[41] A positive TST indicates active or latent infection with MTB, although infection with environmental mycobacteria can cause false-positive reactions.[42] Traditional cut off points of 10mm have been derived from countries with low prevalence TB where interference from non tuberculous mycobacteria (NTM) and Bacille Calmette-Guerin (BCG) vaccine is low.

There are additional factors that might influence the degree of tuberculin reactivity which include age, exposure to active TB, country of birth, immune-competence, HIV status, protein energy malnutrition, chest X-ray appearance and socio-economic status.[42,43] In the absence of an independent means of determining whether or not a person is infected with MTB, the sensitivity and specificity of TST in detecting LTBI cannot be determined with absolute accuracy.[44] However, some studies have shown a sensitivity of approximately 80%.[45,46]

Regarding BCG, most individuals who receive a BCG vaccination become only transiently (6 months to 5 years) reactive to tuberculin; 80 - 90% are of children who received BCG as infants have a non reactive TST at 5 years of age.[47] Mean TST size in BCG-vaccinated children varies with factors including the strain and dose of BCG used, interval since vaccination, number of BCG vaccinations administered,

subsequent TST placement, and age and nutritional status of the child at the time of vaccination. It is generally agreed that a positive test result to the standard dose of tuberculin is 10 mm or more in unvaccinated children and 15 mm or more in BCG-vaccinated children. However, several studies have shown no difference in induration size between BCG vaccinated and non vaccinated children. [48 - 51]

A negative TST does not rule out TB disease in a child. Approximately 10% of otherwise normal children with culture-proven TB do not react to TST initially.[28,52] These rates are higher in those who are tested soon after becoming infected with severe TB, in children with debilitating illness or advanced immunosuppression, malnutrition, in infancy and if poor technique is used. [26,53] The prevalence of negative TST in patients with TBM can be as high as 70%.[54] In particular, patients with HIV infection and protein energy malnutrition commonly have anergy to TST resulting in false negative interpretation.[42,55,56] Anergy results from immunosuppression of the delayed type hypersensitivity (DTH) reaction which is the hallmark of the TST reaction.

Patients who have initial anergy to the TST can have repeat tests done within 1 to 5 weeks of the initial test. The phenomenon of a positive TST after an initial negative result is thought to be due to immunologic recall of preexisting delayed type hypersensitivity to mycobacterial antigens (boosting).[57] It is important, however, to distinguish boosting effect from conversion effect. Conversion is defined as the development of new DTH to mycobacterial antigens following new infection with MTB , nontuberculous mycobacteria (NTM), or BCG vaccination.[57]

There are three possible methods to distinguish boosting from conversion:[57]

1. The clinical situation: When increase in size of induration occurs after 1-5 weeks when there has been no possibility of exposure.
2. The size of second test reactions: A second reaction of ≥10mm and an increase of at least 6 mm from the initial TST.
3. The predictive value of a positive second test

1.3.3.6 Chest radiograph

A number of features may suggest TB but none is diagnostic with the exception of miliary tuberculosis.[58] In addition 20 – 50% of children may have normal chest xrays.[11] Typical post-primary cavitating tuberculosis is unusual in children but is occasionally seen in teenagers. The most typical feature is hilar or paratracheal lymphadenopathy. In addition, adolescents seem to be particularly prone to pleural TB.[58] Up to 31% of children with TBM may show a micro-nodular appearance typical of miliary TB and in those without miliary mottling, 86% can have abnormal radiographs; the commonest being hilar or paratracheal adenopathy, followed by segmental or lobar opacification.[59]

1.3.3.7 Computer tomography Scan

Computer Tomography (CT) scan of the brain has emmerged as an important diagnostic tool for patients with TBM. However, 15-25% of CT scans may be entirely normal during the early stages of the disease.[13,60] It is for this reason that it might be important to repeat CT scans at least 6 weeks after the initial scan as features like hydrocephalus , infarcts, or tuberculomas may appear during the follow up period especially when treatment is commenced.[60] As disease progresses, basilar enhancement and communicating hydrocephalus with signs of cerebral oedema or early focal ischaemia are the most common findings.

Basal enhancement may be subtle on CT scanning and has variable appearances. It has ill-defined edges compared with normal vessel enhancement and usually affects the suprasellar, middle cerebral artery and sylvian cisterns.[11] Basilar enhancement is the most sensitive feature of TBM with various studies showing sensitivies ranging from 82 - 93%.[32,61,62] In addition, several studies have shown that hydrocephalus is a common feature of TBM with ranges of 72 – 100% of paediatric patients having this sign. [32,61 - 64,

Hyperdensity in the basal cisterns prior to intravenous contrast medium administration is the most specific sign of TBM (100%) and similar appearances are only found in patients who have subarachnoid haemorrhage, intrathecal contrast medium and Neisseria meningitidis infection.[62] A combination of features (hydrocephalus, infarction

and basal enhancement) is as specific as precontrast hyperdensity, but has a lower sensitivity(41%).[62] In countries with financial constraints, being able to make a diagnosis on non-contrast scanning may be essential for preserving resources.

Although computed tomography is more informative, cranial sonography has been demonstrated to be useful,[65] Tung et al demonstrated that ultrasound of the brain was able to detect hydrocephalus in 100% of their infants.[22] In their study, they conclude that if hyponatremia and hydrocephalus are detected, any ill infant presenting with a cerebrospinal fluid leukocyte count of less than 500 cells/mm3 and lymphocyte predominance should be immediately treated with antituberculosis medication.

1.3.4 TREATMENT

The only effective treatment of TB is adequate chemotherapy, by which is meant;

- An appropriate combination of anti TB drugs
- Given in the correct dosages
- Taken regularly by the patient under supervision
- For the stipulated duration of treatment

It follows therefore that the success of tuberculosis chemotherapy depends on the strict application of the Directly Observed Therapy Short Course (DOTS) strategy.[5]

The DOTS strategy is applicable to all patients with tuberculosis, including children. High success rates (over 95%) are achievable in children with PTB and less severe forms of EPTB such as TB lymphadenopathy. Thioacetazone which can cause severe and often fatal reactions in HIV-infected children has been replaced by ethambutol. There has been understandable caution with the use of ethambutol in children too young to report early visual deterioration, but ethambutol has been safely used in infants and young children at recommended dosages.[6] The treatment guidelines for TB in Zambia have been outlined in the Ministry of Health Tuberculosis manual. (Appendix 1)

1.3.5 PROGNOSIS

Childhood TBM is a neuroinfection with a reported mortality ranging from 4 to 60 per cent. This significant difference in mortality could possibly be due to multiple factors such as severity of illness, time of initiation of treatment and supportive therapy.[66]
The prognosis of TBM correlates most closely with the clinical stage of illness at the time treatment is initiated. The majority of patients in stage 1 have an excellent outcome, whereas most patients in stage 3 who survive have permanent disabilities, including blindness, deafness, paraplegia, diabetes insipidus or mental retardation. Mahadevan et al have also found that younger age, tonic posturing, papilloedema, and focal neurological deficit affect adversely the prognosis independently in children with TBM. The strong association of papilloedema with poor outcome was observed in this study although this observation was not emphasized in earlier studies.[66] Infarcts, due to the vasculitis which complicates TBM, are also determinants of prognosis, with bilateral basal ganglia infarcts having a very poor prognosis.[67]

1.3.5 IMPACT OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

HIV testing can be helpful in the diagnosis of TB, especially if the result is negative, as it increases the likelihood of a diagnosis of TB. This is because HIV positive children are more at risk of diagnostic error as well as delayed diagnosis of their TB.[68] Chintu et al showed that HIV positive children can have co-mobidities with the four most common findings being acute pyogenic pneumonia (39.1%), Pneumocystis jiroveci pneumonia (27.5%), TB (18.8%) and cytomegalovirus (20.2%).[69] The implication of this is that children may clinically improve on anitbiotics for pneumonia while still harbouring TB resulting in delayed diagnosis. Conditions like Lymphoid interstitial pneumonitis (LIP) have similar radiologic appearances to TB and it may be difficult to distinguish between the two, requiring good clinical judgement.[70]

The impact of the HIV epidemic on paediatric TB has been reported in several studies. A prospective cohort study of children with TB diagnosed in Addis Ababa from December 1995 to January 1997 in which HIV-positive children were compared with HIV negative children, reported that HIV-positive children were younger, more

underweight and had a 6-fold higher mortality than HIV-negative children. TST is less sensitive and chest radiograph less specific in HIV-infected patients.[68] Adherence to treatment was high (96%), and the cure rate were 58 per cent for HIV-positive and 89 per cent for HIV-negative paediatric TB patients. Clinical manifestations were more severe and progression to death was more rapid in HIV-positive children than in HIV-negative children. Weight for age may be used to identify children at high risk of a fatal outcome.[68]

In another retrospective study of 118 culture proven TB patients in Durban, South Africa; 57 (48%) children were detected to be HIV-1 infected, 44 (37%) non-HIV-1-infected, and in 17 (14%) HIV- 1 status was not determined. In contrast to previous studies, this study has shown that co-infection in children is common (48% of all culture proven cases), the presentation of TB may be acute (43%), and supportive tests are individually useful in confirming the diagnosis in a third of cases. All culture for MTB were positive by 8 week, clubbing and age over 2 yr were the most reliable indicators of underlying HIV-1 disease, while clinical features, radiology and supportive tests were found to be similar between HIV-infected and non infected TB cases. Hospital-related mortality was higher (17.5%) in HIV-1-infected children compared to that in non-infected group (11.4%).[71]

The changing pattern of presentation of childhood TB and the high prevalence of TB in HIV endemic areas have made it imperative to maintain a high index of suspicion, with culture evaluation being an important part of clinical practice. HIV makes diagnosis and management of TB in children more difficult for the following reasons:

- Other HIV-related diseases, such as LIP, may present in a similar way to PTB or miliary TB.
- Interpretation of tuberculin skin testing and CXR is less reliable.
- When TB/HIV co infection is common in adults, a positive contact history is less specific if the contact is the child's parent. The child is at risk of transmission of either or both diseases.
- Children with TB and advanced HIV disease may not respond as well to TB treatment.

CHAPTER 2

STUDY OBJECTIVES

General Objective

To describe the clinical, laboratory and radiological features of TBM in children admitted to the UTH department of Paediatrics and Child health.

Specific objectives

1. To describe the frequency of various clinical and laboratory features of TBM in children at UTH.
2. To document the TST reaction of children with TBM at UTH
3. To determine the frequency of HIV infection in children with TBM
4. To document the CD4count/percentage of children with HIV/TBM co-infection

CHAPTER 3

METHODOLOGY

3.1 Study Design and site

This study was a prospective descriptive case series set at the UTH, Department of Paediatrics and Child Health.

3.2 Study population

Inclusion criteria:

1. Children aged between 6 months and 12years inclusive.
2. Children admitted with abnormal neurological signs and symptoms suspected to have TBM based on clinical case definition.
3. Children diagnosed with cerebral malaria despite a negative blood slide, who did not respond to quinine therapy by day 7.

Exclusion criteria

1. Children with proven bacterial or fungal meningitis by CSF gramstain and/or culture
2. Refusal to consent to Lumbar Puncture

3.3 Sample size

Using Epi info Version 6 software Statcalc for a population survey or descriptive study using random (not cluster) sampling:

Population size:	292 patients (Average number of children diagnosed with meningitis from 2004 to 2006, obtained from the UTH Health Management Information Systems)
Expected frequency of disease:	14% (Average percent of children with TBM of the children admitted with meningitis from 2004 to 2006 in UTH)
Worse acceptable frequency:	30%
Confidence interval:	95%
Sample size:	17 cases

3.4 Study procedure

Children were screened for recruitment from the outpatient rooms, admission ward, and from the various in-patient wards. Each child recruited had 5 ml of blood drawn for the following investigations: Full blood count, ESR and random blood sugar. In addition, every child was sent for routine HIV test using the antibody test, Abbot Determine. Only those children less than 18 months who tested positive for HIV antibody had a confirmatory test done using the DNA PCR test as is the current protocol in the UTH Paediatrics Department. This was followed by a lumbar puncture where 3ml of CSF was obtained. This CSF was immediately sent to the UTH Microbiology, Biochemistry and TB laboratory for examination.

In the Microbiology laboratory, the CSF was examined under direct microscopy for white cell count and differential, gram stain for organisms, Indian ink stain for Cryptococcus species, and then cultured for gram negative or positive organisms. In the biochemistry laboratory, estimation of CSF glucose and protein was done. In the

TB laboratory, the CSF was examined directly under ZN stain and then cultured on both the LJ and MGIT for isolation of AAFB.

Three sputum samples were collected in those children with a history of cough by gastric lavage on three consecutive days. Older children were simply asked to cough up sputum into a specimen bottle. Furthermore, every child had a Tuberculin Skin Test carried out by the investigator. This involved having a 0.1ml intradermal injection of 2 T.U. PPD RT 23 SSI on the left forearm. The diameter of induration was measured 72hours later by the investigater. Finally, every child had a chest radiograph done.

The children that were screened for recruitment were managed by the attending UTH paediatrics department physicians. All test results were copied to the attending physicians who were left to manage and follow up the children. Those children whose CSF results isolated organisms other than MTB were excluded from the final study analysis.

3.5 CASE DEFINITION

The case definition for TBM was made by either microbilogical or clinical criteria according to Doerr et al[72], modified as follows:

Microbiologic case definition

One of the following:

1. Isolation of MTB from CSF
2. Abnormal neurologic signs and symptoms or CSF findings consistent with CNS TB, and isolation of MTB from any site

Clinical case definition

Abnormal neurologic signs and/or symptoms, and ≥2 of the following:

1. History of adult source case with TB who had contact with child
2. Presence of TST reaction ≥10 mm of induration in HIV un-infected, or ≥ 5 mm of induration in HIV infected children
3. CSF abnormalities without evidence of other infectious cause

4. A chest radiograph consistent with primary TB infection, such as miliary picture, hilar lymphadenopathy or mediastinal adenopathy
5. Failure of sustained response to antibiotic and/or anti-malarial treatment

3.6 Study Duration

The study was carried out February to November 2007, covering a total of 9 months

3.7 Data collection and analysis

A detailed questionnaire was administered to the guardian/parent of the children who fitted the inclusion criteria. Information regarding history, examination and results of investigations carried out were also entered on the questionnaire. (Appendix 2)

Data collected was entered and analysed using Epi Info Version 6. The clinical and laboratory features of TBM were analysed. For the continuous variables, median values are shown. For categorical variables, data was represented by number of patients with the finding.

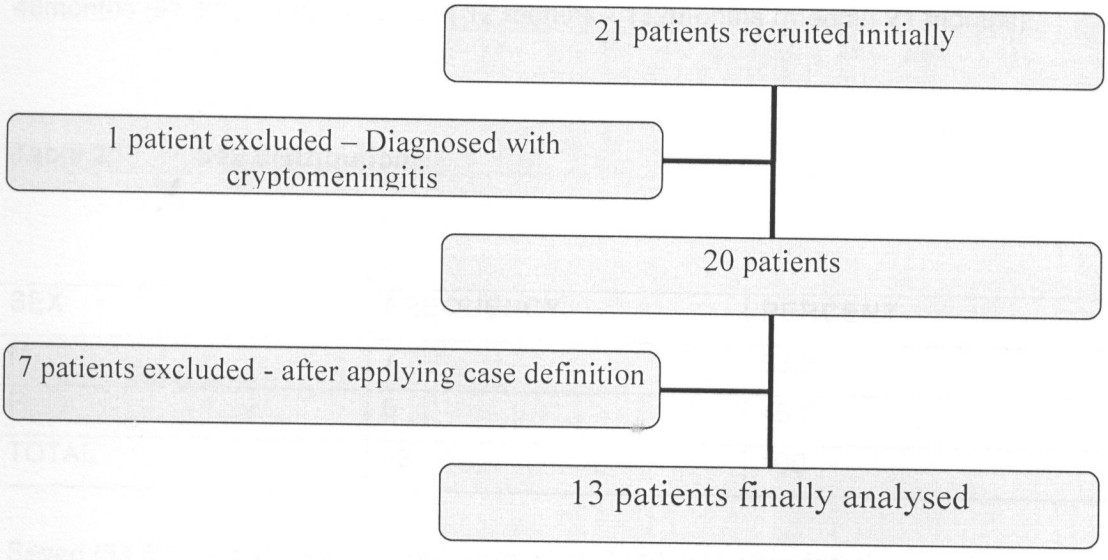
3.8 Ethical consideration

Permission to conduct the study was sought from the University of Zambia Research Ethics Committee. The proposal was approved by the Department of Paediatrics and Child Health and the University of Zambia School of Medicine through the Graduate Studies Forum. Informed consent was obtained from the parents/guardians of the children who were recruited for the study through a written consent form (Appendix 3). The form explained the purpose of the study and all the procedures that were carried out. It also explained the risks involved and the complications associated with the different procedures.

CHAPTER 4

RESULTS

During the study period 21 patients were initially recruited. From these 21, one patient was excluded after isolation of Cryptococcus species from the CSF. Upon further follow up, and using the TBM case definition, 7 patients were excluded. The final analysis involved 13 patients with TBM.



4.1 DEMOGRAPHIC CHARACTERISTICS

Of the 13 patients, 10 came from the high density compounds within Lusaka City, 1 came from the low density township and 2 came from the periurban areas around Lusaka city.

Table 1: Age distribution

AGE (MONTHS)	FREQUENCY	PERCENT
≤12	1	7.7
13 – 48	8	61.6
49 - 144	4	30.8
TOTAL	**13**	**100**

Table 1 shows that almost two thirds of children who had TBM were between 13 and 48months (61.6%); range was from 12 months - 132months (median 21 months).

Table 2: Sex distribution

SEX	FREQUENCY	PERCENT
M	7	53.8
F	6	46.2
TOTAL	13	100

Seven (53.8%) of the children were male while 6 (46.2%) were female.

4.2 CLINICAL CHARACTERISTICS

Table 3: History at presentation

PRESENTATION	FREQUENCY (n=13)	PERCENT
Fever	13	100
History of BCG at birth	13	100
Weight loss	9	69.2
Convulsions	9	69.2
TB contact	7	53.8
Cough	7	53.8
History of antibiotics prior to admission	6	46.2
Neck stiffness	5	38.5
Night sweats	5	38.5

All the children with TBM presented with a history of fever and had received BCG vaccine. Almost two thirds of the children had history of convulsions and weight loss prior to admission and half had history of TB contact.

Table 4: Clinical signs

FEATURE		FREQUENCY n=13	PERCENT
Temperature ≥37.6		7	53.9
Weight For Height	>Median	1	7.7
	≤Median	4	30.8
	≤-1	4	30.8
	≤-2	2	15.4
	≤-3	2	15.4
Lymphadenopathy		1	7.7
BCG Scar		9	69.2
TST reaction	Negative	7	53.8
	Positive	6	46.2
Fundal optic atrophy		1	7.7
Coma		5	38.5
Decerebrate posturing		5	38.5
Meningeal signs		8	61.5
Increased tone		7	53.8

Over half of the children with TBM had fever (temperature >37.5) on admission. Six (46.2%) of the children had mild to moderate malnutrition on admission while 2 (15.4%) had severe malnutrition. All the children had received BCG in infancy but only about two thirds of them (69.2%) had a BCG scar. Five (38.5%) children presented with coma and 5 (38.5%) had decerebrate posturing. Eight (61.5%) children had meningeal signs at presentation: 4 (50%) with bulging anterior fontanelle, 3 (37.5%) had kernig's sign positive and 1 (12.5%) had Brudzinski positive. The tone was increased in 7 (53.8%) of the patients.

Table 5: Tuberculin skin test result verses patient HIV status

HIV STATUS	TST INDURATION (mm)	TST RESULT
Positive	0	Negative
Positive	0	Negative
Positive	5.5	Positive
Positive	0	Negative
Negative	0	Negative
Negative	0	Negative
Negative	0	Negative
Negative	0	Negative
Negative	15	Positive
Negative	13.5	Positive
Negative	15.5	Positive
Negative	15.4	Positive
Negative	16.5	Positive

The TST result showed 6 of the thirteen children (46.2%) had a positive result while 7 (53.8%) had a negative result. A larger percentage of the HIV negative children tested positive to TST compared to the HIV positive children; 55.6% versus 25%.

Diagnosis on admission

Nine patients (69.2%) were admitted with meningitis as the primary diagnosis, two had a primary diagnosis of severe malaria and two were diagnosed with encephalitis. Only one patient was diagnosed with disseminated TB from the outset i.e TBM and PTB. However, two patients had TBM as part of the differential diagnosis.

4.3 LABORATORY FINDINGS

Table 6: Haematological features

FEATURE		FREQUENCY (n=13)	PERCENT
High Total Leucocyte Count		4	30.8
ESR	10 - 49	1	7.7
	50 - 99	7	53.8
	≥100	5	38.5

Only 4 (30.8%) patients had an abnormally raised total leucocyte count for their age and the rest had normal total leucocyte counts. All the children had raised ESR, with the majority 12 (92.3%) having ESR ≥50.

Table 7: CD4 counts for HIV positive patients

AGE (MONTHS)	CD4 COUNT (CELL/μL)	CD4 PERCENT
14	383	14.1
15	155	1.1
21	662	21.8

Only four (30.8%) of the thirteen children tested positive for HIV infection. In addition, of the 4 patients, 3 had CD4 counts done. Two children of the three had severe immunodeficiency and 1 had advanced immunodeficiency as defined by WHO immunologic classification. (Appendix 4)

Table 8: **CSF WCC and biochemistry**

CSF FINDINGS		FREQUENCY (n=13)	PERCENT
WCC cells/mm^3	0	11	84.6
	4	2	15.4
Protein (g/L)	Normal	3	23.1
	0.4 - <1	7	53.8
	1 – 5	2	15.4
	>5	1	7.7
CSF:Blood glucose ratio	<0.6	10	76.9
	≥0.6	3	23.1

None of the children had lumbar punctures done on the day of admission. Six of the thirteen (46.1%) had lumbar punctures done within one week of admission; four (30.8%) within two weeks and three (23.1%) after two weeks of admission.

Regarding the CSF results, eleven (84.6%) had no white cells isolated from the CSF, protein was elevated in 10 (76.9%) and CSF glucose was reduced to less than 60% of blood glucose in 10 (76.9%) of patients.

AAFB isolation

1. Sputum

Eight out of thirteen children had sputum collected for AAFB. Of these eight, all were collected via gastric lavage and their sputum were negative for AAFB.

2. Cerebral spinal fluid

All the specimens of CSF examined for AAFB were negative. In addition, all the specimens did not grow any bacilli when cultured in MGIT.

4.4 CHEST XRAY

Twelve out of thirteen children had chest x-rays done. Of these, six (50%) had a normal xray, 2 (16.7%) had hilar adenopathy and 4 (33.3%) had wide mediastinum. Three of the four children with wide mediatinum were below the age of fifteen months.

4.5 TREATMENT

Table 9: Hospital treatment

NUMBER OF ANTIBIOTICS PRIOR TO COMMENCEMENT OF ATT	FREQUENCY (N=13)	PERCENTAGE
2	6	46.1
3	5	38.5
4	2	15.4

All patients received a minimum course of two different antibiotics while in hospital prior to commencement of ATT. Five (38.5%) patients were treated with three and 2 (15.4%) were treated with 4 antibiotics. First line antibiotics were Penicillin G (Xpen) or chloramphenicol, or a combination of Xpen/Gentamicin or Xpen/Chloramphenicol. Second line antibiotics were Cefotaxime or Ciprofloxacin. Additionally six (46.1%) patients were treated with quinine. The diagnosis of TBM was made within a week of starting antibiotics in two of thirteen children (15.4%) , within 2 weeks in eight (61.5%) and within a month in three (23.1%) of the children.

CHAPTER 5

DISCUSSION

TBM continues to be a difficult diagnosis to make in UTH as all the children in this study had no microbiological proof from the CSF. Therefore, they were all probable TBM and not definite TBM. This study was carried out between February 2007 and November 2007.

5.1 CLINICAL CHARACTERISTICS

In this study, the majority of the children presented to the hospital with symptoms and signs of meningitis. Prominent features in the history included fever (100%), weight loss (69.2%), convulsions (69.2%), TB contact (53.8%) and neck stiffness (38.5%). Prominent clinical signs included meningeal signs (61.5%), low weight for height (69.2%) and fever (53.9%). comparable results have been found in studies done in the developing world.[39,72] An exception was vomitting which was not a prominent feature of this study (15.4%).

Almost 50% of the children in this study received antibiotics prior to admission. Additionally, serioulsly ill children referred from the local clinics are often given stat doses of injectable penicillin G. In such instances, guardians to these children are often not even aware that antibiotics were given. Antibiotic treatment prior to admission usually prolongs the course of partially treated bacterial meningitis, can render CSF sterile and even result in lymphocytic predominance in the CSF.[73] This situation results in diagnostic confusion at initial presentation.

On admission to UTH, the initial diagnosis usually entertained is partially treated bacterial meningitis in view of prior antibiotic exposure. Other differential diagnoses

frequently made in UTH include viral encephalitis, HIV encephalopathy, cryptococcal meningitis and cerebral/severe malaria especially in a comatose child. This scenario is similar to that seen in other developing countries. Kumar et al found that 30% of their meningitis patients had diagnostic confusion between TBM and pyogenic meningitis.[73]

In our high TB prevalence environment, maintaining a high index of suspicion is very important to rapid diagnosis. This is because the 'gold standard' for diagnosis, isolating AAFB in CSF usually has low yields. This should start with the age range; TBM is common in children 6 months to 4years. In this study, 61.6% of the children were in this age range. Additionally, history of fever, recent weight loss, TB contact and history of convulsions were common manifestations of TBM. Children acquire TB from close contact with an adult with active TB, therefore history of contact is very important. However, it is equally important to note that this history may not always be documented; only 42% - 65% of paediatric cases. [32,73,74]

In UTH, TST is not routinely used as a diagnostic tool for all forms of TB. In this study, 7 children (53.8%) had a negative TST result and 6 (46.2%) had a positive result. The higher percentage of negative result to TST could have been due to the the fact that these children had a severe form of TB and most were malnourished. Both of these factors have been shown to reduce TST positivity.[42,54]

The HIV positive children had a higher negative TST (75%) result than the HIV negative children (44.4%). A major contributory factor could have been true anergy in HIV positive children as a result of their immunosuppresion. This causes an inability to mount a delayed type hypersensitivity reaction. The prevalence of anergy was shown to be as high as 72% in HIV positive children compared with 51% in HIV negative children.[55] Additionally, studies have shown an inverse relationship between CD4 count and TST reactivity.[55,56,75] Although the numbers were small, two of the three HIV positive children who had CD4 counts done were severely immunosuppressed and this could have contributed to the negative TST result.

Children with an initial negative TST would benefit from the boosting effect of a second TST 1-3 weeks later. This helps to distinguish whether the child had true exposure as opposed to having new infection as it takes about 6 weeks after tubercle infection for

the TST to become positive.[76] In this study only one TST was done on each child, therefore, it is not known whether the negative test was a true negative or could have been explained by anergy.

5.2 LABORATORY CHARACTERISTICS

5.2.1 White cell count and ESR

The majority of the children in this study had normal total leucocyte counts for age. Only 4 (30.8%) had abnormally high counts in support of a bacterial infection. Al-Marri and Kirkpatrick showed that the majority of children studied had normal or mildly elevated ESR counts at the time of diagnosis.[40] All the children in this study had very high ESR results, 5 (38.8%) above 100. A lot of emphasis is usually placed on the degree of elevation of ESR in UTH but as has been noted, it can be normal in as many as 32% of children with TB.[40] Sputum collected from children in this study yielded negative results for AAFB. This is not surprising as previous studies have shown such low yields from gastric aspirates.[23,27,28]

5.2.2 HIV serology and CD4 count

The majority of children with TBM in this study were HIV negative. Four (30.8%) tested positive for HIV infection. In a study done in Harare in adults and children diagnosed with meningitis (5% children), 12% of the patients had TBM; 88% of whom were HIV positive.[77] Two of the three patients with HIV in this study had WHO immunological staging of severe immunodeficiency and 1 had advanced immunodeficiency. TB (all forms) can occur at any stage of HIV infection but is more common and more severe with advanced immunodeficiency. This is particularly true for TBM and disseminated TB whose frequency increases in severe immunodeficiency.[78]

In this study, the numbers of HIV positive children were small and comparisons between the HIV positive and HIV negative groups would not be meaningful. Van der Weert et al showed no significant difference in clinical symptoms between the HIV infected and uninfected group. However, lymphadenopathy, hepatosplenomegaly and

clubbing occurred more frequently in the HIV positive group. Furthermore, significantly more HIV negative children had impaired consciousness than in the positive group.[39] In a similar study in Ethiopian children, HIV-positive children were younger, underweight and had a 6-fold higher mortality than HIV-negative children. The tuberculin skin test was less sensitive and chest radiography was less specific in HIV-infected patients.[23]

5.2.3 CSF findings

Eleven of the thirteen children (84.6%) had no white cells detected in their CSF whereas 2 (15.4%) had normal white cell counts. The usual finding is CSF pleocytosis, the majority of patients having <500cells/μL.[12,31]The CSF protein showed elevated levels in 10 (76.9%) of patients and the CSF glucose was less that 60% of blood glucose in 10 (76.9%) of patients. This CSF: blood glucose ratio was very reduced in 70% of child to ≤0.3. These findings are consistent with expected CSF glucose and protein levels in patients with TBM. [12,31,32] Because of previous antibiotic exposure, the leucocyte counts may not be reliable markers of pleocytosis in patients with TBM as was seen in this study were all the patients had normal CSF white cell counts.

All the specimens of CSF that were examined for AAFB microscopically were negative. Furthermore, culture on conventional LJ media and MGIT did not isolate any bacilli. This result is not surprising as the volumes of CSF that were collected for examination and culture were small. Collecting less than 2mls of CSF isolates 40% of M.tb from CSF compared with 65% and 80% when 4-5.9mls and 6 – 7.9mls of CSF is collected.[33] Regardless, previous studies have shown low pick up rates from direct staining and microscopy ranging from 1.7 – 58%.[10,11,33]

Simultaneous LJ/MGIT culture is standard operating procedure in UTH for culturing specimens for isolation of mycobacteria. Initially the majority of specimens cultured on MGIT were from sputa from adults but now extrapulmonary specimens like gastric aspirates, pleural aspirates and CSF specimens are routinely being cultured. MGIT is highly sensitive and specific (81.5% and 99.6% respectively) with high detection rates (range 80 – 90.3%) [36,37,38] and when used in combination with LJ, pick rate improve further.

5.3 CHEST XRAY

Fifty percent of the children in the study had normal chest xrays. With abnormal xrays more children, 4 (33.3%) had wide mediastinum. It is very important to do chest xrays in all children with suspected TBM as they might show miliary features or other abnormal features of PTB.[59] Although mediastinal lymphadenopathy was a common feature of this study, it is very important to keep in mind that in children less than 2 years thymic enlargement also presents as a mediastinal shadow. This can easily happen in children where it is sometimes difficult to get well centred chest xrays.

5.4 DIAGNOSIS

Only one child in the study was diagnosed with TBM as part of a disseminated TB from the outset. The rest of the children were diagnosed with meningitis, encephalitis or sever malaria. The diagnosis of TBM was usually made on the basis of low CSF glucose and high protein findings since the leucocyte counts were normal in all the patients. However, these CSF findings might be difficult to differentiate from partially treated Bacterial Meningitis. In addition, the other main criterion that was used to diagnose TBM was failed response to either antimalarials and antibiotics or two - three courses of antibiotics. Obviously, this results in delay in diagnosis which usually results in poor outcome.

Various studies have tried to come up with diagnostic criteria for TBM some of which have included response to treatment.[73,79,80] Kumar et al found the following to be independently associated with TBM: prodromal stage ≥7 days, fundal optic atrophy, focal deficit, extrapyramidal movements and CSF leucocytes <50% polymorphs. The sensitivity dropped from 98.4 to 54.5% as predictor variables increased and the specificity increased from 43.5% to 98.3% as predictor variables increased. Seth and Sharma modified the Ahuja Criteria to formulate diagnostic criteria for TBM in children. Ahuja et al used PCR, isolation of AAFB, autopy findings and response to treatment to validate their criteria for diagnosis in adults. Modifying the criteria to suit children, Seth and Sharma found sensitivity and specificity of 83% and 63% respectively. The draw back, of course in the modified criteria is that validation was made by response to treatment alone.

CHAPTER 6

CONCLUSIONS

6.1 STUDY CONCLUSIONS

TBM continues to pose diagnostic challenges in our environment. Because it can mimic other meningitides like partially treated meningitis, fungal meningitis and viral meningoencephalitis a high index of suspicion is necessary. Furthermore, using every available diagnostic tool, including response to treatment is cardinal as bacteriological proof might not be forthcoming. Important pointers to diagnosis include young age, TB contact, positive TST, high CSF protein, very low CSF/blood glucose level and lack of adequate response to antibiotics.

6.2 STUDY LIMITATIONS

1. Small sample size due to following factors:
   a. Refusal to consent to LP despite adequate counseling on safety, indications, side effects, and caregiver fears.
   b. Refusal to consent to TST despite adequate counseling.
2. Lack of serology and PCR to rule out viral meningoencephalitis
3. Due to continuous breakdown of CT scan machine and inadequate funding, CT scan was removed from the procedures carried out on the children who were recruited. This would have been a helpful additional tool to the rapid diagnosis of TBM.
4. Due to insufficient funding, continued follow up of patients could not be done to evaluate the long term outcome of those children who were started on ATT.

6.3 STUDY RECOMMENDATIONS

1. Incorporate TST as an additional diagnostic tool for children with suspected TBM. In those children that have negative TST, carry out a second test to maximise on the boosting phenomenon.
2. Hospital to carry out radio and television education programmes on the benefits of lumbar puncture to allay fears of death. This is very important as lack of CSF examination delays diagnosis and contributes to poor outcome.
3. Encourage doctors to routinely request AAFB microscopy and MGIT culture in children between 6 months and 4years with meningitis especially those with clear CSF. Waiting for 1 or 2 weeks of lack of response to antibiotics results in delay in diagnosis and poor outcome.
4. Encourage doctors to collect at least 6ml of CSF for analysis to improve the pick up rate of AAFB by microscopy and culture. This should be specific for the CSF going to the TB laboratory and not in its entirity.
5. Carry out a larger study with a comparison group to evaluate a diagnostic criteria for the diagnosis of TBM and to assess the discriminating ability of the individual tests carried out.

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APPENDICES

APPENDIX 1: ZAMBIAN TUBERCULOSIS TREATMENT GUIDELINES

Category 1: New cases of smear-positive PTB and other newly diagnosed seriously ill patients with severe forms of TB (Severe forms include TBM, disseminated tuberculosis, miliary tuberculosis and spinal disease with neurological complications)

Intensive phase: 2 months of ethambutol, isoniazid, rifampicin and pyrazinamide

Continuation phase: 6 months of continuation phase of ethambutol and isoniazid.

Category 2: Relapses and treatment failures (smear positive)

Intensive phase: 2 months of Isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin

Continuation phase: 1 month of isoniazid, rifamicin, pyrazinamide, and ethambutol, then

5 months of rifampicin, isoniazid and ethambutol.

Category 3: Pulmonary smear negative TB and EPTB (other than the clinical forms considered in category 2)

Intensive phase: 2 months of rifampicin, isoniazid, and pyrazinamide

Continuation phase: 6months of ethambutol and isoniazid

Category 4: Paediatric tuberculosis (Children 12 years and below)

Intensive phase: 2 months of daily rifampicin, isoniazid and pyrazinamide

Continuation phase: 4 months of daily isoniazid and rifampicin

For severe forms of TB:

Intensive phase: 2 months of streptomycin, rifampcin, isoniazid and pyrazinamide

Continuation phase: 10 months of rifampicin and isoniazid

Trial therapy

The number of patients being put on TB trial has been increasing. This is partly due to the increasing number of AIDS patients who present with atypical symptoms and signs. The danger of the practice of trial therapy is the potential to develop multi-drug resistant tuberculosis in the long run.

In situations where the diagnosis is challenging, it is important to take the following steps:

- Investigate thoroughly
- Use a broad spectrum antibiotic for at least two weeks observing the patients for improvement or otherwise
- Exclude HIV related conditions like Kaposi's sarcoma, Lymphoid Interstitial Pneumonitis (LIP)

After extensive investigations and use of broad spectrum antibiotics, if no improvement is seen, a full course of ATT may be started. Under no circumstances should ATT be considered if a full course is not going to be given.

APPENDIX 2: QUESTIONNAIRE

Study no..... Date of recruitment:.....

General information

1. Patients initials: .....
2. File No: .....
3. Date of birth:.....
4. Age: .....
5. Sex: M / F
6. Date of admission: .....
7. Physical Address:.....
   .....
8. Contact No:.....

History

1. TB contact: Y / N If yes, sputum Neg / Pos / DK
2. Duration of contact: .....
3. Cough: Y / N If Y, duration .....
4. Fever: Y / N If Y, duration .....
5. Weight loss or failure to thrive: Y / N If Y, duration.....
6. Night sweats Y / N If Y, duration.....
7. Headache: Y / N / DK If Y, duration .....
8. Vomiting: Y / N If Y, duration.....
9. Neck stiffness Y / N / DK If Y, duration.....
10. Convulsions: Y / N If Y, generalised / focal
11. Were antibiotics taken prior to admission? Y / N / DK. If Y, what abx
    .....
    ..... DK
12. UFC:
    a. Available / Not available
    b. Weight: gain / loss / static Duration .....
    c. BCG given Y / N
13. Other.....

Examination

1. Temp .....
2. Weight.....
3. Height.....
4. SD Score:.....
5. Oedema 0 + ++ +++
6. BCG Scar seen Y / N
7. OFC (<2yrs) ..... N/A
8. Lymphadenopathy: Y/ N if Y, where.....
9. Level of consciousness:
    a. Conscious
    b. If unconscious, using Blantyre Coma Scale (5yr & below).....
    c. If unconscious, using Glasgow coma scale (>5yr).....
10. Posture: Decerebrate / Decorticate / Normal
11. Ophistotonus: Y / N
12. Meningeal signs: kernigs brudzinski nuchal rigidity Bulging AF None
13. Fundoscopy:
    a. Normal
    b. Optic atrophy
    c. Papilloedema
    d. Other:.....
14. Cranial nerve palsy: Y / N if Y, which nerve .....
15. Tone:
    a. Upper limbs increased / reduced / normal
    b. Lower limbs increased / reduced / normal
16. Reflexes
    a. Upper limbs increased / reduced / normal
    b. Lower limbs increased / reduced / normal
17. Abnormal chest findings: Y / N if Y, describe.....

.....

Diagnosis on admission:.....

.....

.....

Investigations

1. FBC
    a. WCC .....
    b. Hb .....
    c. Platelets .....
    d. MCV .....
    e. MCH .....
    f. Lymphocytes.....
    g. Polymorphs.....
    h. Monocytes .....
2. ESR: .....
3. Blood sugar: .....
4. HIV Status:
    a. HIV test: Pos / Neg
    b. DNA PCR Pos / Neg / NA
    c. CD4 Count.....
    d. CD4 % .....
5. Tuberculin induration:.....cm
6. Gastric lavage Y / N if yes, AAFB Pos / Neg
7. CXR Y / N (Date done:.....)
    a. Hilar adenopathy
    b. Military mottling
    c. Normal
    d. Other:.....
8. Lumbar puncture:

    Date done:.....

    CSF findings:

    Colour: Clear / Cloudy / Xanthochromic / other .....

    Pressure..... (rough)

    WCC.....

    Lymphocytes.....

    Neutrophils.....

    Protein.....

    Glucose.....

AAFB.....

Indian ink.....

Gram stain.....

Microbiology Culture results: ....

MGIT Culture results: .....

9. Other test results:

.....

.....

.....

Treatment initiated

1. Antibiotics initiated on admission:

   .....

   .....

   .....

2. ATT Date started: .....
3. Intensive phase: Drugs: S H R Z
4. Prednisolone: yes / no
5. Did diagnosis change during the course of treatment? Y / N if Y, what was the new diagnosis.....

APPENDIX 3: CONSENT FORM

Principle investigator: DR EMILIA JUMBE-MARSDEN

University Teaching Hospital
Department of Paediatrics and Child Health
Private Bag RW1X
Lusaka

Information sheet for parents/guardians of children between 6 months and 12years admitted to the University Teaching Hospital, Paediatrics Department, participating in the research 'Evaluation of criteria for Tuberculous Meningitis at the University Teaching Hospital Department of Paediatrics'.

I am a postgraduate student working in the Department of Paediatrics, University Teaching Hospital. I will be carrying out a study to look at how the diagnosis of tuberculous meningitis is made at this hospital with the hope of improving on the tools currently being used.

Purpose of the study

Meningitis is a serious infection of the coverings of the brain and can be caused by many different germs. The one that is the most severe and devastating is that which is caused by Tuberculosis (TB). The diagnosis of TB meningitis in University Teaching Hospital continues to provide difficulties resulting in delay. This situation results in children staying long periods on the wards and having terrible complications like blindness, deafness, fits, paralysis and most seriously death.

The aim of this study is to look at what features of TB meningitis are being used to make this diagnosis in UTH.

Procedures

Children between the ages of 6 months and 12 years with symptoms and signs of TB meningitis will be recruited. These patients will have blood taken (just over a teaspoon full) from a vein in the arm or groin, should this fail, looking for signs of TB meningitis. Fluid from the back of the spine (Lumbar puncture) will also be taken (about a teaspoon full) at the same sitting. In addition, chest Xrays, eyes will be checked and a special skin prick test (Tuberculin) will be done. Children who are coughing will have sputum collected via a tube that will be passed through the nose into the stomach (gastric lavage). This is done because children cannot cough and spit out their sputum into a collecting container. Parents/guardians will also be counseled for an HIV test to be carried out on the participant. All these tests will be done once unless errors are made, and sent to the laboratory looking for signs of TB. Any results that are positive for TB meningitis will be relayed to the admitting doctor for further management and follow-up.

Risks

There will be minimal risk and discomfort on the participant. Collection of blood has a small risk of bleeding if correct pressure is not applied after the procedure is completed. In addition, in the rare patient with a bleeding disorder, this bleeding if not addressed could be fatal to the patient. Lumbar puncture is a very safe test. Sometimes we are not able to get fluid and may have to try more than once. A small number of children may have a headache, backache or numbness for a day or two after the test. The risk of any serious complications (bleeding or infection, damage to nerves, breathing difficulties or death) is extremely small. Gastric lavage is another procedure which is very safe. It might cause some irritation on the throat when inserting and rarely bleeding if too forcefully put. The tuberculin test can cause irritation or itching on the area of skin on which it is carried out. It is important to note that these procedures will all be carried out by well trained and fully qualified doctors and nurses highly skilled in carrying them out. Should any complications arise from any of these procedures, they will be handled in the Department on Paediatrics with the available equipment and expertise.

Benefits

Less time will be spent in the hospital as tests will be done more promptly helping to reduce the risk of complications for the patient. Participation in this study will hopefully help in finding features which will help other patients in future to be diagnosed and managed earlier.

Confidentiality

Information obtained will be kept confidential. Should it be deemed necessary this information will only be shared with the doctors treating the patient, ethics committee and the Department of Paediatrics.

Compensation

Patients will not be expected to incur additional costs for any tests carried out by the researcher which will not be requested for by the doctors handling their care. E.g. CT Scan. The tests that will be carried out by the researcher are all tests that are part of routine medical care. However, any complications arising from these tests will be handled in the institution with the available expertise at no cost to the patient.

Contacts

For any questions regarding the study, contact:

The Chairman,
Prof J.T. Karashani
Research Ethics Committee
University of Zambia,
School of Medicine
Phone: 256067

Dr Emilia Jumbe-Marsden
Department of Paediatrics and Child Health
A block
Pri Bag RW 1X Tel: 095-860217

Participation in this study is entirely voluntary and if you feel that you do not want to take part, no penalty will be levied against you. You will still receive the best medical attention provided by the hospital.

I have read the aforementioned information or it has been read to me and I have had the opportunity to ask questions which have been answered to my satisfaction. I agree to my child taking part in this study voluntarily and understand that I have the right to withdraw from this study at any time. I also understand that should I do so, this decision will not affect the medical care given to my child. In addition, I will not be given any gifts or payments for taking part in this study.

Name of participant:..... Study ID no:.....

Name of parent/guardian:.....

Signature:..... Thumbprint(if cannot sign).....

Date:.....

Name of witness: .....

Signature:.....

Date:.....

Researcher.....

APPENDIX 4: WHO CLASSIFICATION OF HIV-ASSOCIATED IMMUNODEFIENCY IN INFANTS AND CHILDREN

Classification of HIV-associated immunodeficiency	Age related CD4 values			
	<11 months (%)	12–35 months (%)	36–59 months (%)	>5 years (cells/mm3)
Not significant	>35	>30	>25	500
Mild	30–35	25–30	20–25	350–499
Advanced	25–29	20–24	15–19	200–349
Severe	<25	<20	<15	200 or <15%