TUBERCULOUS MEININGITIS IN QUEEN SIRIKIT NATIONAL INSTITUTE OF CHILD HEALTH, THAILAND

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Thematic paper
entitled

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Bilal Ahmad Rahimi

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TUBERCULOUS MENINGITIS IN QUEEN SIRIKIT NATIONAL INSTITUTE OF CHILD HEALTH, THAILAND

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ABSTRACT

The objective of this retrospective descriptive study was to evaluate the clinical features, treatment, and outcomes of tuberculous meningitis among a sample of children. The study cohort comprised 30 children (age 11 months to 14 years) with tuberculous meningitis, who were admitted to Queen Sirikit National Institute of Child Health, Bangkok, Thailand, during the period 2003-2009.

Ninety-six percent of the patients had a positive history of Bacillus Calmette-Guérin (BCG) vaccination. Forty, 27, and 33% of the patients were in stages I, II, and III, of tuberculous meningitis on admission, respectively. On admission, fever, weakness, neck stiffness, headache, vomiting, and seizures were present in 83, 62, 53, 43, and 40% of patients, respectively. Of the 30 patients, 70% were positive by tuberculin skin test.

Overall, the results of this study agreed with typical cerebrospinal fluid (CSF) findings. Leukocytes >5 cells/mm^3, protein >100 mg/dl, CSF glucose < 50% of plasma glucose, increased opening pressure, and increased mononuclear cells, were present in 91, 69, 78, 95, and 82% of patients, respectively. Acid-fast stain and polymerase chain reaction (PCR) analysis of CSF for *Mycobacterium tuberculosis* were positive in 5 and 26% of patients, respectively.

Six- and 9-month anti-tuberculous drug regimens were used for 28 and 39% of patients, respectively. Sixty-seven percent of the patients underwent a combination-regimen of 4 anti-tuberculous drugs (isoniazid, rifampicin, pyrazinamide, and streptomycin). Ninety percent were administered steroids, while 30% received a ventriculo-peritoneal (VP) shunt.

The case fatality rate was 10%; all fatal cases had hyponatremia on admission. Fifty percent had neurological sequelae, of which 33% were temporary and 17% permanent.

KEY WORDS: TUBERCULOUS MENINGITIS / NEUROLOGICAL SEQUELAE /CLINICAL MANIFESTATIONS

100 pages

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LIST OF ABBRIVIATIONS

Abbreviation/Symbol	Term
AFB	Acid fast bacilli
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AV shunt	Atrio-ventricular shunt
BAL	Broncho-alveolar lavage
BCG	Bacillus Calmette-Guérin
BMRC	British Medical Research Council
BUN	Blood urea nitrogen
Cl	Chloride
Ca	Calcium
C/S	Culture and sensitivity
CSF	Cerebrospinal fluid
DLC	Differential Leukocyte Count
EMB	Ethambutol
et al	And others
F	Female
g	Gram
GGT	γ-Glutamyltransferase
GW	Gastric washing
HCO_3^-	Bicarbonate
H_2O	Water
hr	Hour
IM	Intramuscular

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LIST OF ABBRIVIATIONS (cont.)

Abbreviation/Symbol	Term
INH	Isoniazid
IV	Intravenous
K	Potassium
kg	Kilogram
M	Male
MKD	Milligram/Kilogram body weight/Day
mg	Milligram
ml	Milliliter
mm^3	Cubic millimeter
Mos	Months
N	No
Na	Sodium
NA	Data Not Available
Neg	Negative
PCR	Polymerase chain reaction
PMN	Polymorphonuclear (leukocytes)
Pos	Positive
Pt.	Patient
Pts.	Patients
PZA	Pyrazinamide
QSNICH	Queen Sirikit National Institute of Child Health
RIF	Rifampicin
SM	Streptomycin
TBM	Tuberculous meningitis
TB	Tuberculosis

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LIST OF ABBRIVIATIONS (cont.)

Abbreviation/Symbol	Term
VP shunt	Ventriculo-peritoneal shunt
Y	Yes
%	Percent
>	More than
≥	More than or equal to
<	Less than
≤	Less than or equal to

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CHAPTER I
INTRODUCTION

Tuberculous meningitis (TBM) is a severe and life-threatening form of tuberculosis, caused by acid fast bacilli *Mycobacterium tuberculosis.* The mortality rate from TBM is 30% and is increased in individuals who are co-infected with HIV/AIDS. (Yorsangsukkamol et al., 2009).

M. tuberculosis bacilli enter the host body by droplet inhalation, the initial point of infection being in alveolar macrophage. Escalating localized infection within the lung, with dissemination to the regional lymph nodes, produces the primary complex. During this stage, there is a short but significant bacteremia that can seed tubercle bacilli to other organs in the body (Thwaites et al., 2000). Tubercle bacilli distribute into all parts of the central nervous system during lymphohematogenous spread. TBM arises from the caseous foci, often very small ones, situated in the brain or meninges (Krugman's Infectious Diseases of Children, 2004).

Currently, nearly 2 billion people (one third of the world population) are infected with tuberculosis, out of which about 10% develop clinical disease (Thwaites et al., 2000). Eight million people develop active disease each year and about three million die every year (Farinha et al., 2000).

Thailand is in the top 18th of the world high-burden countries of TB (WHO Report, 2009). Although in Thailand TBM is a relatively rare disease, it is still a cause of morbidity and mortality in Thai children. In Thailand, the tuberculosis prevalence (per 100,000 population) was actually declining between 1985 and 1989 from 150 to 80; but between 1990 and 2005 it did not decrease, rather it increased slightly. Due to the HIV/AIDS epidemic, tuberculosis is becoming a public health problem in Thailand. The TB-HIV co-infection prevalence has increased from 14.5% in 1989 to 28.7% in 2005 (Thailand Health Profile, 2007).

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TBM mostly occurs in children and the peak age is 6 months to 4 years (Nelson Textbook of Pediatrics, 2007). TBM is a rare disease in developed countries, but in developing countries TBM is still a serious cause of morbidity and mortality. Meanwhile, the incidence of TBM is directly related to the prevalence of tuberculous infection in a community, which in turn is dependent on the socio-economic conditions of the community. TBM occurs in approximately 7 – 12% of the patients with pulmonary tuberculosis. TBM is seen more often in Africans than the other races of the world (El Sahly et al., 2007).

The diagnosis of TBM is very difficult because of the low mycobacterial yield in the CSF and the lack of adequate alternative methods for the diagnosis of TBM (Garcia-Monco et al., 2005). Moreover, the differential diagnosis of TBM from bacterial meningitis by clinical features alone is often impossible (Youssef et al., 2007). In low-incidence geographical areas, clinicians should suspect TBM in immigrants from high-incidence areas, immunosuppressed patients, and patients who are alcohol or drugs abused.

Clinical features of TBM are not very specific and can be confused with other diseases easily. Onset of fever is gradual and fluctuating. Lassitude, weight loss, behavior changes, headache, and vomiting are mostly observed in the patients. If diagnosis is delayed then neurologic deficits, loss of consciousness or convulsions can occur (Donald et al., 2004).

The gold standard test for the diagnosis of TBM is CSF culture. Lumbar puncture is necessary for these patients. The typical CSF profile of TBM includes leukocytes count 10-500/mm^3 (sometimes the leukocyte count may increase), with a predominant of lymphocytes (but predominated neutrophils may be observed at the beginning of the disease), an elevated protein concentration of 100 – 3,000 mg/dl (or even higher in the presence of CSF pathway blockage), and a low glucose concentration of <50 mg/dl (80%). However, in 10–20% of cases, the glucose concentration may be normal (Nelson Textbook of Pediatrics, 2007). Tuberculin test can be negative in TBM. Abnormal chest X-Ray compatible with tuberculosis is found in 50-80% of cases (Donald et al., 2004).

For the treatment of TBM, it is strongly recommended to use a combination of four anti-tuberculosis drugs, i.e., INH (10-15 mg/kg/day), Rifampicin

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(10-20 mg/kg/day), Pyrazinamide (15-30 mg/kg/day), and Ethambutol (15-20 mg/kg/day) or Streptomycin (15 mg/kg/day). Pyridoxine (vitamin B_6) should be given with INH therapy (Thwaites et al., 2005). The evidence supporting the use of corticosteroids along with the anti-TB drug for children with tuberculosis is still controversial. However, according to most of the experts, corticosteroids are indicated in children with TBM, because corticosteroids may decrease the mortality and long-term neurologic impairment (Red Book, 2009).

The results of this study emphasize the clinicians to diagnose TBM in its early stage and provide early appropriate management to prevent the severity and therefore the sequelae of the disease.

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CHAPTER II
OBJECTIVES

2.1 Primary objective

To evaluate the clinical features of TBM in children in a pediatric tertiary referral hospital.

2.2 Secondary objectives

1. To describe the treatment and outcome of TBM in children.
2. To find the proportion of bacteriological positive in TBM.

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CHAPTER III
LITERATURE REVIEW

3.1 Prevalence and epidemiology

Tuberculous meningitis (TBM) is a severe and life-threatening form of tuberculosis, caused by acid fast bacilli *Mycobacterium tuberculosis.*

Today nearly 2 billion people (one third of the world population) are infected with tuberculosis, out of which about 10% develop clinical disease (Thwaites et al., 2000). Eight million people develop active disease each year and about 3 million die every year (Farinha et al., 2000).

According to WHO report (2009), the highest estimated rates of TB incidence are in African countries. According to this report, most of the African countries have ≥ 300 new TB cases (all forms) per 100,000 people. Estimated TB incidence rates, by country, in 2007 were shown in figure 3.1.

According to WHO report (2009), estimated number of new TB cases (all forms) is increased in India and China as compared to the other countries of the world. In each of these two countries, estimated number of new TB cases is ≥ 1,000,000 cases (Figure 3.2).

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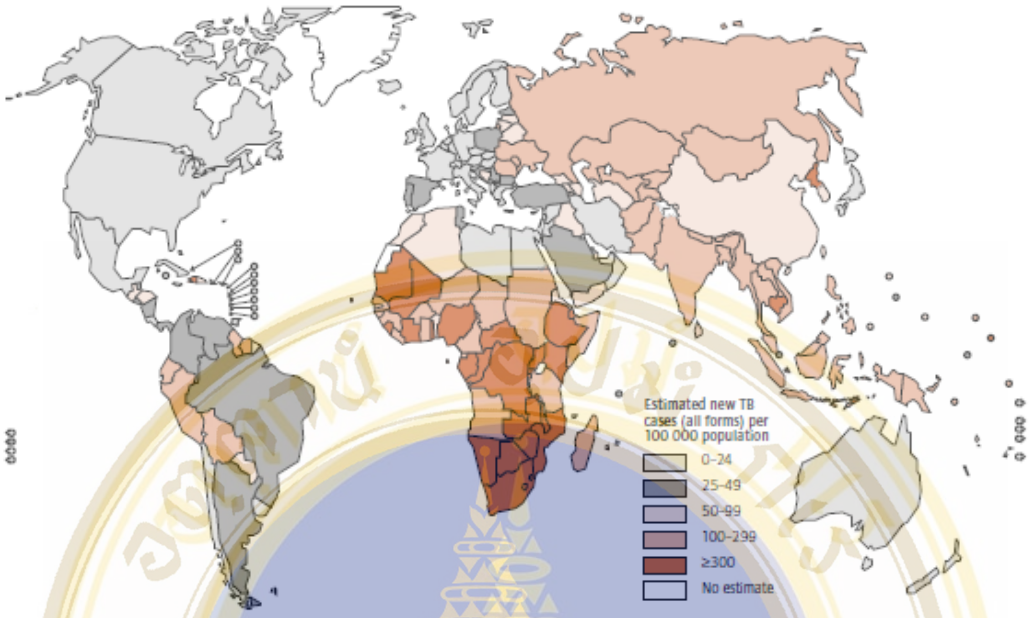

Figure 3.1 Estimated TB incidence rates, by country, 2007

Source: WHO Report, 2009

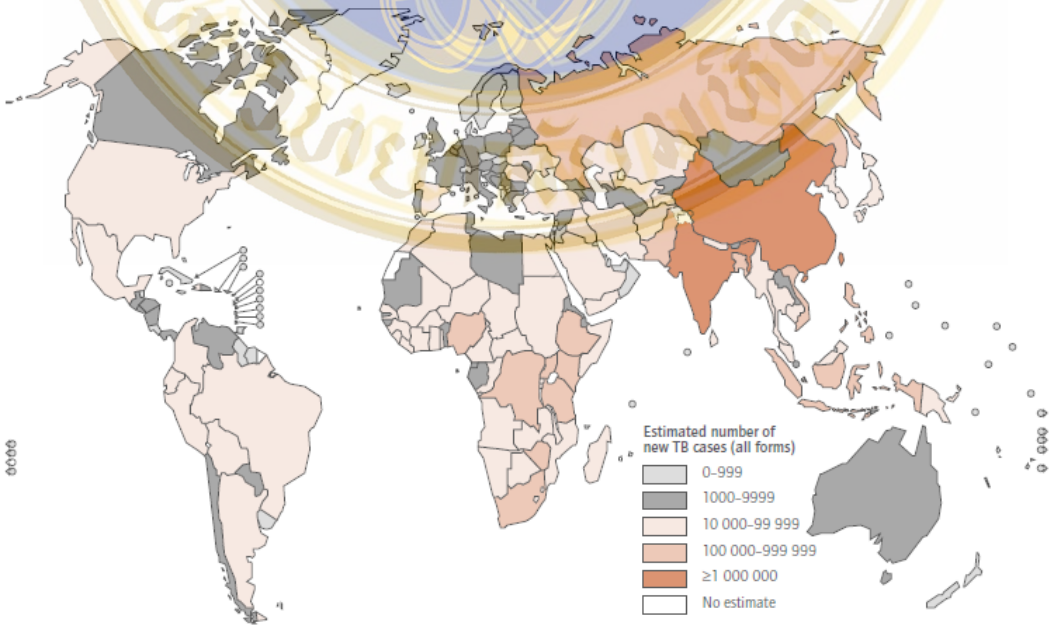

Figure 3.2 Estimated number of new TB cases, by country, 2007

Source: WHO Report, 2009

In Thailand, the tuberculosis prevalence (per 100,000 population) was actually declining between 1985 and 1989 from 150 to 80 (figure 3.3); but between 1990 and 2005 it did not decrease, rather it increased slightly (Thailand health profile 2005 – 2007).

Owing to the HIV/AIDS epidemic, tuberculosis is becoming a public health problem. In all upper Northern provinces, the TB-HIV co-infection rate has risen from 4.1% in 1991 to 15.1% in 2005. Overall, for the entire country for over 10 years, the co-infection prevalence has increased from 14.5% in 1989 to 28.7% in 2005 (Thailand health profile 2005 – 2007). Thailand is in the top 18th of the world high-burden countries of TB (WHO Report, 2009).

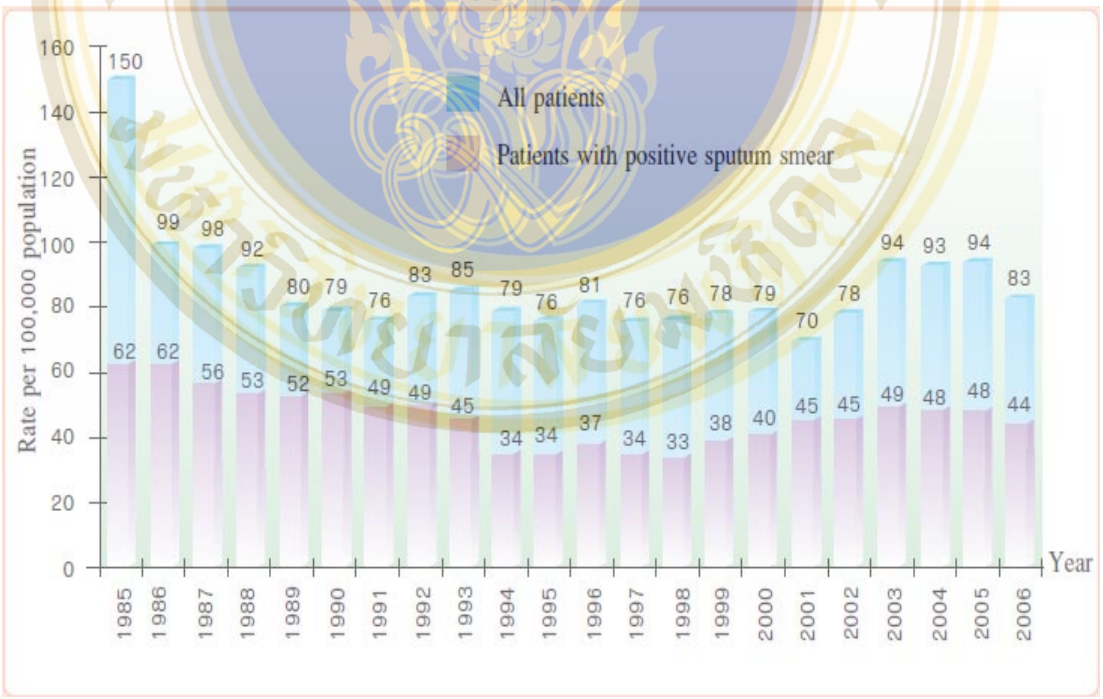

Figure 3.3 Rate of newly registered tuberculosis patients in Thailand, 1985–2006

Source: Thailand health profile, 2005 – 2007

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According to Farinha et al. (2000), although pulmonary TB tends to be the most common form of tuberculosis, the highest mortality and morbidity occurs with tuberculous meningitis (TBM), which develops in around 4% of children with tuberculosis (7 – 12% according to El Sahly et al., 2007 and 1 – 2% according to Starke, 1999).

The high incidence of tuberculosis in the Western Cape Province of South Africa has resulted in TBM being the most common type of bacterial meningitis admitted to the Tygerberg Children's Hospital (Springer et al., 2009). In the developing countries, 20–60% of the children dying of tuberculosis are known to have brain/meningeal involvement, in contrast to 5% or less in adults. Autopsy studies from the Indian subcontinent have revealed involvement of the CNS in 65% of patients with tuberculosis (Rafi et al., 2007).

Tuberculous meningitis (TBM) has its highest incidence in early childhood and, prior to the availability of anti-tuberculosis chemotherapy, was the commonest cause of tuberculosis-related death among young children (Styblo & Sutherland 1982).

TBM is the most severe complication of tuberculosis (Yorsangsukk et al., 2009) and frequently occurs in childhood, because 82% of the children in a cohort study in South Africa were <5 years of age (van Well et al., 2009). In a study in Turkey 77% of the children were younger than 5 years (Yaramis et al., 1998). In the same way, in a study by Berman et al. (1992), of the 238 cases confirmed in the period of 3 years (1985–1987), 25.2% were under 1 year, 51.7% under 2 years, and 79.8% under 5 years of age. TBM mostly occurs in the peak age of 6 months to 4 years (Nelson Textbook of Pediatrics, 2007). Boys and girls are equally affected by this disease (van Well et al., 2009).

In developed countries TBM is a rare disease but in developing countries it is still a serious cause of morbidity and mortality. Meanwhile, the incidence of TBM is directly related to the prevalence of tuberculous infection in a community, which in turn is dependent on the socio-economic conditions of the community. TBM is seen more in Africans than the other races of the world (El Sahly et al., 2007).

Although the incidence of tuberculosis is increasing, prevalence and mortality rates are declining (van Well et al., 2009). The mortality rate from TBM is

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30% and is increased in individuals who are also infected with HIV/AIDS at the same time (Yorsangsukkamol et al., 2009).

Most of the children affected by TBM have a family history of pulmonary TB. A study in South Africa revealed that 53% of their patients had contact with a household adult with proven pulmonary TB (van Well et al., 2009). While according to a study in London city, 47% patients had a history of recent or active TB occurring in a family member, whilst 42% had travelled recently (within the last 6 months) to a country where TB was endemic (Indian subcontinent, Africa, and Pacific Islands); 71% had either a family history or had travelled abroad. In the same way 16% had previously received BCG vaccination (Farinha et al., 2000).

BCG vaccine has shown consistently high efficacy against childhood tuberculous meningitis. Increasing in tuberculous meningitis cases were reported after BCG vaccination was discontinued in Sweden and the former Czechoslovakia (Trunz et al., 2006).

A study on children in Turkey showed that 66% of the patients had a family history of TB, 12% had a history of BCG vaccination, 29% had malnutrition, and 13% had a recent history of measles (Yaramis et al., 1998). Waecker and Connor reported that an adult source of contact was identified in 70% of cases of children with CNS TB (Waecker et al., 1990).

3.2 Pathogenesis

According to a very famous and reliable study of Rich et al., on the pathogenesis of TBM, this disease results from the haematogenous dissemination of Mycobacterium tuberculosis from primary pulmonary infection and the formation of small subpial and subependymal foci (Rich foci) in the brain and spinal cord (Rich et al., 1933).

Lymphohematogenous spread from a primary pulmonary focus leads to the development of a Rich focus in the brain. Rupturing of this caseous granuloma into the subarachnoid space causes 3 features responsible for the clinical manifestations of TBM:

1. Development of further tuberculomata.

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2. Basal inflammatory exudates that cause cranial nerve palsies and obstruct cerebrospinal fluid (CSF) pathways, resulting in hydrocephalus.

3. Obliterative vasculitis, which leads to infarctions.

Once the Rich focus has ruptured, a prodromal period of nonspecific symptoms, such as fever, vomiting, and behavioral changes, will develop. As the disease progresses, neck stiffness, loss of consciousness, motor deficits, and convulsions will follow (van Well et al., 2009).

In some individuals Rich foci rupture and release bacteria into the subarachnoid space causing meningitis. In others, foci enlarge to form tuberculomas without meningitis. The timing and frequency of these events in relation to primary pulmonary infection is dependent upon age and immune status. In children, dissemination usually occurs early and the risk of CNS tuberculosis is highest in the first year following infection (Thwaites et al., 2009).

Donald et al. (2005) suggested, particularly in childhood, that miliary tuberculosis is indeed directly involved in the pathogenesis of TBM in as much as that the overwhelming bacillaemia that accompanies miliary tuberculosis serves to increase the likelihood that a meningeal or sub-cortical Rich focus will be established, which may in its turn caseate and give rise to TBM.

3.3 Clinical manifestations

Clinical manifestations are very important for the diagnosis of TBM in children. To avoid the adverse outcome, clinical suspicion is very important in early diagnosis (Wani et al., 2008).

Clinical evaluation of the stage of TBM in patients is mostly according to the criteria of the Medical Research Council (BMRC criteria, 1948):

1. Stage I (Early stage): In this stage the patients have mainly non-specific symptoms, with little or no clinical signs of meningitis, with no paresis, in good general condition, and fully conscious.

2. Stage II (Medium stage): In this stage the patients are in a condition between those of stage I and stage III.

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3. Stage III (Advanced stage): In this stage the patients are obviously extremely ill, deeply stuporous or comatose, or with gross paresis.

On the other hand, van den Bos et al. (2004) have explained Medical Research Council staging, for the clinical evaluation of TBM patients, as follows:

1. Stage I: Children are fully conscious with nonspecific symptoms and no pareses.

2. Stage II: Children are stuporous and may have focal neurological signs or hemiparesis.

3. Stage III: Children are comatose or have complete hemiplegia or quadriplegia.

While van Well et al. (2009) have staged TBM using the modified criteria of the British Medical Research Council to determine the severity of TBM:

1. Stage I: TBM (Glasgow coma scale 15 with no focal neurologic signs).

2. Stage II: TBM (Glasgow coma scale 11–14 or Glasgow coma scale of 15 with focal neurologic deficit).

3. Stage III: TBM (Glasgow coma scale <11).

According to Farinha et al. (2000) in a study done in London, out of the 33 patients with TBM, 21 (64%) presented in stage III, 10 (30%) in stage II, and 2 (6%) in stage I (Farinha et al., 2000).

While a study in Turkey showed that a small percentage of patients were admitted in the first stage of disease (10%). The remaining 90% had a neurologic manifestation, with 56% of the children presented in the second stage and 34% in the third stage. The most common clinical manifestations were fever in 91%, vomiting in 87%, personality change in 63%, seizures in 62%, nuchal rigidity in 59%, and headaches in 58% of TBM patients (Yaramis et al., 1998).

According to van Well et al. (2009), the majority of patients on admission had poor weight gain, decreased level of consciousness, and any type of motor deficit. Meningeal irritation was present in 98% and signs of raised intracranial pressure in 23% of patients. Once TBM progresses to stage II and III of the disease, neck stiffness will almost always be present, as was the case in 98% of these studied patients.

Failure to thrive, loss of weight, irritability, poor appetite, sleep disturbance, vomiting and abdominal pain are often seen in young children (Curless

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and Mitchell, 1991). Patients with tuberculous meningitis (TBM) have been frequently observed to have excessive sleep during the day and frequent awakenings during night (Pardasani et al., 2008).

Seizures, both febrile and non-febrile, can be the presenting feature in children with focal neurological deficit, while the commonest being cranial nerve palsies and hemiplegia (Thwaites et al., 2009).

3.4 Diagnosis

Early diagnosis of TBM is important so that appropriate treatment can be instituted promptly to prevent poor clinical outcome and permanent neurological sequelae (Oztoprek et al., 2007). In the majority of patients, the diagnosis of TBM is usually made on the presenting clinical features and is supported by the findings on cerebrospinal fluid (CSF) examination, i.e. pleocytosis, elevated protein concentration, and reduced glucose concentration. The advent of Magnetic Resonance Imaging (MRI) has added an additional resource for the overall diagnosis of TBM (Sumi et al., 2002).

It can be difficult to diagnose CNS tuberculosis until the neurologic symptoms become severe. Unfortunately, the greater the delay in diagnosis and institution of adequate therapy, the less likely a full recovery will occur. Tuberculosis should be suspected in all children in whom meningitis develops with cranial nerve abnormalities, ventriculomegaly, or basilar meningeal enhancement on cranial imaging, even if the Mantoux tuberculin skin test is nonreactive or no family history of tuberculosis is reported. It should also be considered in children with any neurologic problems who have been exposed to adults at high risk of having tuberculous disease (Doerr et al., 1995).

According to van Well et al. (2009), a definite diagnosis of TBM is made when *Mycobacterium tuberculosis* is isolated from CSF. In all other cases, the diagnosis is “probable TBM” based on clinical signs of meningitis in the presence of characteristic CSF findings (macroscopically clear, pleocytosis, elevated protein, and reduced glucose). In addition, ≥ 2 of the following criteria have to be present:

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1. Recent poor weight gain (crossing of percentiles on Road to Health Card).
2. Household contact with sputum smear-positive tuberculosis.
3. Computed tomography (CT) scan compatible with TBM.
4. Chest radiography compatible with primary tuberculosis.
5. Positive tuberculin skin test.
6. Other clinical specimens positive for acid-fast bacilli.

(Road to Health Card is a record of immunizations and growth rate. It is given to mothers when their infant is born and is used to monitor the development of the child until he/she is five years old.)

The criteria used for the diagnosis of Tuberculous meningitis by Farinha et al., (2000) were the presence of increased lymphocytes (>10/mm^3) in the cerebrospinal fluid (CSF), with high protein (> 40 mg/dl) and low CSF/serum glucose ratios (< 0.6), plus one or more of the following:

1. Positive culture of CSF or other body fluids or tissues for *Mycobacterium tuberculosis*.

2. Positive microscopy for acid-fast bacilli (AFB) from CSF, gastric aspirate, sputum or sterile body tissue (ZN stain).

3. Positive Mantoux reaction (10 tuberculin Units >10 mm induration or >15 mm if the patient had received BCG in the past 5 years.

4. Epidemiological evidence of TB contact, e.g. close family member with active tuberculous disease.

5. Response to anti-tuberculous therapy.

In the same way, a study done in Western Cape Province of South Africa by van den Bos et al. (2004), TBM was diagnosed upon positive culture for *Mycobacterium tuberculosis* from one or more sources and an abnormal cerebrospinal fluid (CSF) combined with two or more of the following:

1. A positive Mantoux test (induration of ≥15 mm).

2. A chest radiograph compatible with primary TB (either a miliary picture or mediastinal adenopathy).

3. A cranial computerized tomography showing meningo-vascular basal enhancement, with or without hydrocephalus.

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4. Close household contact with an adult with sputum smear-positive pulmonary TB.

Isolation of *M. tuberculosis* from gastric aspirate, bronchial aspirate, sputum, or lymph node, combined with clinical suspicion of TBM, adds strongly to the diagnosis (van Well et al., 2009). BCG is more reliable and sensitive than the tuberculin test in the diagnosis of tuberculosis (Gocrnen et al., 1994).

A definitive diagnosis with the demonstration of the mycobacterium in the CNS is not always possible.

Recent poor weight gain is also a valuable clue to early diagnosis of pediatric TBM in areas where tuberculosis is endemic (Donald et al., 1985).

The definite diagnosis of TBM is difficult in all the patients, even in the modern hospitals of advanced countries. According to a study in London, delay in diagnosis occurred in a significant proportion of patients: more than 1 month in 50% of the TBM patients (Farinha et al., 2000).

Despite recent medical advances, the early diagnosis of TBM continues to be difficult, clinical manifestations and cerebrospinal fluid (CSF) abnormalities usually determine the initiation of empirical treatment (Chroda et al., in press. Corrected proof).

3.5 Laboratory investigations

In a study by Farinha et al. (2000), the mean peripheral leukocyte count was 11,700/mm^3 (range 4,300 – 23,300) with a mean of 65% neutrophils, 27% lymphocytes and 7% monocytes. Significant monocytosis (>1.0×10^9/L) occurred in only 23% of the TBM patients. The average erythrocyte sedimentation rate was 28 mm/hour (range 2–80 mm/hour).The mean sodium in the group of patients with tuberculous meningitis was 126 mmol/L (range was 118– 137 mmol/L). Hyponatremia (<135 mmol/l) was present in 79% of the patients.

Hyponatremia is thought to be due to the syndrome of inappropriate ADH secretion (SIADH) (Cotton et al., 1991). But later the possibility of inappropriate secretion of atrial natriuretic factor (ANP) was proposed as the mechanism most commonly involved (Narotam et al., 1994). The latter corresponds to a “cerebral salt

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wasting" syndrome and requires salt and fluid replacement rather than fluid restriction as treatment. Most of patients with hyponatraemia in the study of Farinha el al. (2000) had evidence of SIADH and were treated with fluid restriction, with good effect.

In a study in Turkey (Yaramis et al., 1998), only 10% of the TBM patients had a positive AFB smear in the CSF. Cultures of sputum and gastric aspirate tested positive in only 1% and 9% of the patients, respectively.

3.6 Tuberculin skin test (TST)

Mantaux test is the most common and reliable method for the tuberculin skin test in suspected TB patients. A positive tuberculin test can provide diagnostic support, but test results may be negative in patients with tuberculous meningitis (Donald et al 2004) or progressive tuberculous infection in any organs.

The tuberculin skin test and IGRAs (Interferon-gamma release assays) (using peripheral blood) may provide indication of previous tuberculosis infection and are probably most useful in young children, but results need to be interpreted cautiously as neither is sufficiently sensitive nor specific to diagnose active disease (Thwaites et al 2009).

The performance of the tuberculin skin test for the diagnosis of tuberculosis varies according to age, vaccination with BCG, nutritional status, HIV infection, and technique of administration (Joos et al., 2006).

Tuberculin skin test is done by intradermal injection of 5 tuberculin units. Test is read after 48–72 hours for the induration of reaction (van den Bos et al., 2004).

According to the WHO guidelines (2006), tuberculin skin test is regarded positive as follows:

1. ≥5 mm of induration, in high risk children (including HIV-infected children and severely malnourished children).

2. ≥10 mm of induration, in all other children (whether they have received a BCG vaccination or not).

Different studies have shown different percentage of positive tuberculin skin test in TBM infected children. The tuberculin skin test was positive in 60% (van Well et al., 2009) and 51% (Farinha et al., 2000) in the TBM patients. Rates of

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positive tuberculin skin test for children vary between 30 and 65% (Yaramis et al., 1998; van den Bos et al., 2004; Akhila et al., 2007; Donald et al., 1998).

However, individuals from high tuberculosis prevalence areas are more likely to have positive tuberculin skin tests with an unrelated illness (Kilpatrick et al., 1996).

3.7 Cerebrospinal fluid (CSF) analysis

Isolation of *M. tuberculosis* from CSF makes a definite diagnosis of TBM (van Well et al., 2009).

Examination of the cerebrospinal fluid is essential and typically reveals a leucocytosis (10 – 1000×10^3 cells/ml; mostly lymphocytes), raised protein (0.5 – 3.0 g/l), and CSF:plasma glucose <50%. The search for acid-fast bacilli (AFB) in CSF is crucial for the rapid diagnosis of TBM and can be seen in up to 80% of adult cases, but only 15-20% of children (Thwaites et al., 2009).

According to Donald et al. (2004), the typical CSF picture includes a low cell count (<300/mm^3) with a predominance of lymphocytes, a low glucose concentration (<2.2 mmol/L), and an elevated protein concentration (>0.8 g/L), but in 10 – 20% of cases, the glucose concentration may be normal and the protein concentration may be less than 0.8 g/L or even less than 0.45 g/L.

The study of van Well et al. (2009) showed that culture for *M. tuberculosis* from any type of origin was positive in 30%; in only 12% of patients was *M. tuberculosis* isolated from the CSF. The CSF results in these patients emphasize that the majority of patients with TBM will have a low, predominantly lymphocyte CSF pleocytosis in the presence of a raised protein level and reduced CSF/blood glucose ratio. These CSF findings, especially if culture negative, are highly suggestive of TBM in areas with a high prevalence rate of TB.

Yaramis et al. (1998) reported that approximately 80% of their CSF results were compatible with TBM (i.e., predominance of lymphocytes with elevated protein and reduced glucose concentrations).

The CSF findings (mean) for the 33 children with TBM in the study of Farinha et al. (2000) were as follows: opening CSF pressure recorded in 14 patients

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was 29 cm H_2O (range 17–50 cm H_2O); total cell count 157/mm^3 (range 20 – 620 cells/mm^3); lymphocytes 93% (range 68–100%); protein level 1.96 g/L (range 0.4 – 5 g/L); glucose level 0.4 mmol/L (range 0.2–4.1 mmol/L) and CSF/serum glucose ratio, recorded in 19 cases was 0.29 (range 0.02– 0.61). Amongst the 33 patients with TBM, CSF microscopy was positive for acid-fast bacilli (AFB) in 17 patients (51%), whilst CSF cultures were positive for *Mycobacterium tuberculosis* (*MTB*) in seven of these patients (21%).

Repeated lumbar punctures and CSF examination will increase diagnostic yield of TBM (Stewart et al., 1953; Kennedy et al., 1979). Positive CSF smear and culture is independently associated with large volumes (>6 ml) of CSF submitted for examination (Thwaites et al., 2004). As many as 11% of TBM patients are wrongly treated for bacterial meningitis on account of the results of the first lumbar puncture (Donald et al., 1990). CSF changes in TBM take long to normalize, and serial CSF findings may, therefore, retrospectively differentiate TBM from other types of meningitis where the CSF normalizes much quicker (Schoeman et al., 2001).

At present, the detection of *Mycobacterium tuberculosis* DNA in cerebrospinal fluid (CSF) using PCR has been widely used as more rapid, sensitive, and specific diagnostic method (Takahashi et al., 2007). According to Seth et al. (1996) PCR test along with the suggested clinical criteria, offers a rapid and fairly accurate diagnosis of TB. In their study, PCR test detected *M. tuberculosis* genomic DNA in the CSF of 85% of clinically suspected TBM cases. Shankar et al. (1991) compared polymerase chain reaction (PCR) in cerebrospinal fluid with conventional bacteriology and an enzyme-linked immunosorbent assay (ELISA) for cerebrospinal fluid antibodies in the diagnosis of tuberculous meningitis (TBM). The result showed that PCR was the most sensitive technique.

The COBAS AMPLICOR™ TB PCR test is a rapid and highly specific diagnostic test for TBM. However, there was a non-significant trend favoring slightly greater sensitivity using the manual AMPLICOR™ TB PCR test (Bonington et al., 2000). According to Bhigjee et al. (2007), targeting multiple sites of the TB genome using conventional PCR did not increase the number of positive cases. Real-time PCR method was more sensitive. However, all the current techniques are still too insensitive to confidently exclude the diagnosis on laboratory grounds.

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3.8 Chest X-Ray

Approximately 50% of patients with TBM have chest X-rays suggesting active or previous pulmonary tuberculosis (Thwaites et al., 2005). While Donald et al. (2004) suggested that a chest radiograph showed changes compatible with tuberculosis in 50 – 80% of cases. Chest radiographic findings, that are suggestive for TBM, include mediastinal lymphadenopathy, segmental infiltration and/or collapse, cavitation, or pleural effusion (van Well et al., 2009).

In a study by Farinha et al. (2000), the chest X-ray was abnormal in 15 patients (40%): nine patients had miliary shadow, four had mediastinal lymphadenopathy, three patients had evidence of consolidation, and one had a pleural effusion. While in a study in Turkey by Yaramis et al. (1998) has stated that abnormal chest radiography was noted in 187 patients (87%), with a variety of abnormalities including hilar adenopathy (34%), miliary pattern (20%), pneumonic infiltrate (18%), bronchopneumonic infiltrate (15%), and pleural effusion (1%).

3.9 Computerized tomography (CT) scan and magnetic resonance imaging (MRI)

Chest CT may provide more efficiency by detecting some abnormalities that had been missed by conventional X-ray. This is proved by the evidence of pulmonary tuberculosis which was found in 36/74 Turkish patients with TBM in whom chest X-ray was considered normal (Yaramis et al., 2007). Cerebrospinal MRI performed when TBM is suspected aids in its diagnosis and is also a useful means of monitoring the course of the disease under treatment (Abdelmalek et al., 2006). Cranial tomography and magnetic resonance imaging have revolutionized the diagnosis and management of tuberculous meningitis, but these studies may be normal early in the course of illness (Donald et al 2004). Changes of TBM to be recognized on imaging could be delayed for 4 to 6 weeks, thus negative results (Wani 2008).

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According to Tinsa et al. (2010), a contrast-enhanced cranial CT scan or MRI should form part of the initial assessment of any child with suspected central nervous system tuberculosis as well as in the follow-up.

The commonest cerebral CT features of TBM are hydrocephalus and basal contrast enhancing exudates. Both features are more common in children (nearly 80%) than adults (nearly 40%) (Ozates et al., 2000).

Magnetic resonance imaging has been shown to be superior to CT in demonstrating ischemia of the brain tissue in TBM, especially of the brainstem (Springer et al., 2009).

In a recent study in South Africa, van Well et al. (2009) stated that on CT images they scored hydrocephalus, periventricular lucency (white matter changes because of hydrocephalus), basal meningeal enhancement, infarctions, and tuberculomata. Limited air encephalography was used to determine the level of CSF obstruction by injecting 5 to 10 mL of air into the lumbar CSF space during lumbar puncture. Air demonstrated in the ventricular system on a skull radiograph is indicative of communicating hydrocephalus (CH), whereas air trapped at the basal cisterns without entering the ventricles proves noncommunicating hydrocephalus (NCH).

Farinha et al. (2000) revealed that amongst the 33 patients with TBM, 31 (94%) had hydrocephalus demonstrated on cranial CT scan on admission. 11 patients had evidence of cerebral infarction (low density areas), mainly in the basal ganglia. While in the study of Yaramis et al. (1998), cranial CT was performed for all patients and showed 172 patients (80%) with hydrocephalus, 26% with parenchymal disease, 15% with basilar meningitis, and only 2% with tuberculomas of the brain.

According to the recent guidelines of British Infection Society for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children (Thwaites et al., 2009), the brain of every patient with TBM should be imaged with contrast enhanced CT either before the start of treatment (as part of the diagnostic work-up), or within the first 48 h of treatment. Early brain CT can help diagnose TBM, and will provide important baseline information particularly when considering surgical interventions for hydrocephalus and prognosis of the patient.

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3.10 Neurological sequelae and Complications of TBM

Hydrocephalus is a common complication of TBM, occurring in 57% to 99% of patients. (Yaramis et al., 1998; Paganini et al., 2000; Lee et al., 2000; Doerr et al., 1995).

In a study conducted on children with TBM in Western Cape of South Africa by van Well et al. (2009), vision and hearing were classified as normal, impaired vision or hearing, and blindness or deafness. They divided neurologic outcome into 4 categories:

1. Normal, including normal motor function, intelligence, vision, and hearing.

2. Mild sequelae, including hemiparesis, mild intellectual impairment, and impaired vision and/or hearing.

3. Severe sequelae, including quadriparesis, severe intellectual impairment, blindness, and/or deafness.

4. Death.

Clinical outcome was defined as “good” in the case of mild neurologic sequelae or normal neurologic outcome and defined “poor” in the case of severe neurologic sequelae or death. Cranial nerve palsies occurred in 27% of children with TBM.

Vision was affected in 14% and hearing in 16% of the children with TBM. The deceased children died of cerebral herniation, infarction, cardiorespiratory arrest, shunt infection/obstruction, or pneumonia. All of their patients with stage I disease had normal neurologic outcome, and deaths did not occur in this group. In this study, only 16% of patients did not have sequelae, 71% had any type of sequelae, and 13% of the children died as a consequence of TBM. Associated with poor outcome in the univariate analyses were African ethnicity, young age, HIV coinfection, stage III TBM, absence of headache, absence of vomiting, convulsions, decreased consciousness, motor deficits, raised intracranial pressure, brainstem dysfunction, cranial nerve palsies, periventricular lucency, cerebral infarctions, and hydrocephalus (van Well et al., 2009).

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Ischemic complications are known to occur in tuberculous meningitis (TBM). They are usually seen in patients with TBM having a more severe disease. Diffusion weighted imaging (DWI) provides information regarding tissue ischemia at an early stage as compared to conventional MRI (Shukla et al., 2008).

The study of Sinha et al. (2010) revealed that vision impairment occurred in one-fourth of patients with tuberculous meningitis. Principal causes of vision loss were optochiasmatic arachnoiditis and optochiasmal tuberculoma. Impaired vision predicted death or severe disability.

According to the study by Farinha et al. (2000), the overall mortality in their group of patients was 13% (five deaths out of 38 patients). All patients died of complications associated with TBM. All five patients who died had been assessed on admission as being in Stage III of the MRC TBM classification of severity. Permanent neurological sequelae were observed in 14 patients (47%) out of 30 with CNS tuberculosis. 50% of their patients (19 of 38 patients) either died or developed permanent sequelae. None of the patients who received BCG had severe sequelae or died.

Yaramis et al. (1998) has stated that 49 patients (23%) of TBM died. 63% of deaths were of children age 5 years or younger.

Other studies in the literature showed normal outcome in 11% to 61%, sequelae in 13% to 75%, and death in 7% to 57% (Farinha et al., 2000; Yaramis et al., 1998; Paganini et al., 2000; Lee et al., 2000; Doerr et al., 1995; Girgis et al., 1998; Delage et al., 1979; Kumar et al., 2005).

With the exception of an increased incidence of intracerebral mass lesions in HIV infected individuals, HIV infection appears to have little impact on the findings and in-hospital mortality of tuberculous meningitis (Dube et al., 1992). In contrast, according to Katrak et al. (2000), clinical, radiological and pathological features of TBM in HIV-positive patients in an Indian sub-population are markedly different from those seen in HIV-negative patients and those reported in HIV-positive patients from Western regions. Patients co-infected with HIV had a more severe disease with a considerably worse outcome.

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3.11 Treatment

Cornerstones of TBM treatment are anti mycobacterial drugs, immunomodulation, and management of hydrocephalus and elevated intracranial pressure (van Well et al., 2009; Donald et al., 2004). Despite the availability of effective chemotherapeutic agents, the morbidity rates of central nervous system tuberculosis remain high (Topcu et al., 2002). About 30% of patients with tuberculous meningitis die despite anti-tuberculosis chemotherapy (Thwaites et al., 2002).

According to World Health Organization guidelines (2006), effective anti-microbial therapy for TBM must:

1. Treat the active infection by eliminating active bacilli, thus preventing neurological complications and death.

2. Prevent relapse by eliminating dormant bacilli.

3. Prevent the emergence of drug resistance, through combination therapy.

Irrespective of the results of individual tests, if tuberculous meningitis is seriously suspected, it is far better to begin treatment immediately and reconsider the diagnosis when the dust has settled (Donald et al 2004). According to Tung et al. (2002), if hyponatremia and hydrocephalus are detected, any ill infant presenting with a cerebrospinal fluid leukocyte count of less than 500 cells/mm^3 and lymphocyte predominance should be immediately treated with antituberculosis medication.

The outcome of treatment of patients with TBM is influenced by many factors, such as severity of the disease, effectiveness of antituberculous drugs, management of neurologic complications (particularly hydrocephalus), and appropriate use of general supportive measures (Molavi et al., 1985; Lorin et al., 1983). The study of Tan et al. (1999) on definitive non-HIV related TBM highlighted that complication of hydrocephalus during the course of the illness was a significant contributor to a poorer outcome. There was also a trend towards poorer prognosis in those who had advanced stage of disease at presentation. Delay prior to admission could perhaps be a more important factor than treatment delay in hospital in determining a poorer outcome.

Cerebrospinal fluid changes will still be evident 10 to 14 days after treatment begins and may increase despite treatment, so these assist in differentiating tuberculous meningitis from other bacterial meningitides (Donald et al 2004).

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Chemotherapy for TBM follows the model of short course chemotherapy for pulmonary tuberculosis – an intensive phase of treatment, followed by a continuation phase. But unlike pulmonary tuberculosis, the optimal drug regimen and duration of each phase are not clearly established. Isoniazid and rifampicin are the key components of the anti TB regimen (Thwaites et al., 2009).

Isoniazid penetrates the CSF freely and provides high drug level in CSF (Ellard et al., 1993; Kaojarern et al., 1991). Isoniazid has potent early bactericidal activity (Mitchison et al., 2000). Rifampicin penetrates the CSF less well (maximum concentrations around 30% of plasma), but the high mortality from rifampicin resistant TBM has confirmed its central role in the treatment of CNS disease (Thwaites et al., 2005). There is no conclusive evidence to demonstrate that pyrazinamide improves outcome of CNS tuberculosis, although it is well absorbed orally and achieves high concentrations in the CSF (Ellard et al., 1987; Donald et al., 1988).

Isonaizid, rifampicin and pyrazinamide are considered mandatory at the beginning of TBM treatment (Humphries, 1992). Some centers use all three drugs (isonaizid, rifampicin and pyrazinamide) for the duration of therapy (Thwaites et al., 2004).

There are no data from controlled trials to guide choice of the fourth drug in the treatment of central nervous system tuberculosis (Thwaites et al., 2009). Most authorities recommend either streptomycin or ethambutol, although neither penetrates the CSF well in the absence of inflammation (Ellard et al., 1993; Bobrowitz, 1972; Gundert-Remy et al., 1973), and both streptomycin and ethambutol can produce significant adverse reactions (Thwaites et al., 2009).

Streptomycin should not be given to those who have renal impairment and resistance is relatively common worldwide (WHO, 2008). Ethambutol-induced optic neuropathy is a concern, especially when treating comatose patients, although at the standard dose of 15-20 mg/kg the incidence is less than 3% (Donald et al., 2006).
Some centres, notably in South Africa, advocate ethionamide, which penetrates healthy and inflamed meninges (Donald et al., 1989), but it can cause severe nausea (Thwaites et al., 2009).

The fluoroquinolones may represent an effective fourth agent, although data concerning their CSF pharmacokinetics and safety during prolonged therapy are

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limited (Barsic et al., 1991; Berning et al., 2001; Alffenaar et al., 2008). Prolonged fluoroquinolone therapy is not advised for children (Mehlhorn and Brown, 2007).

The doses of anti-tuberculosis drugs for the treatment of CNS tuberculosis have conventionally followed those used for pulmonary tuberculosis (Thwaites et al., 2009). There is considerable experience of higher doses of INH (10-20 mg/kg to a maximum of 500 mg) in children (Donald et al., 1998). At standard doses isoniazid achieves CSF levels 10-15 times the minimum inhibitory concentration of susceptible M. tuberculosis (Kaojarern et al., 1991).

Rifampicin penetrates the CNS less well than isoniazid (Ellard et al., 1993) and high doses (20 mg/kg to a maximum of 600 mg) are reported to be well tolerated in children (Donald et al., 1998) and may increase the early bacterial kill (Diacon et al., 2007). Pyrazinamide crosses the bloodebrain barrier well and in children has been used at doses of 40 mg/kg to a maximum of 2 g. Once through the intensive phase of treatment, doses can be reduced to standard levels (Donald et al., 1998).

The increased risk of adverse events with higher doses of anti-tuberculosis drugs must be consideration for, unlike the treatment of pulmonary tuberculosis, interruptions in treatment are an independent risk factor for death from TBM (Thwaites et al., 2004).

In a study by van Well et al. (2009), all 554 of the children received antimycobacterial drugs. They used an intensive short-course regimen of daily isoniazid (20 mg/kg), rifampicin (20 mg/kg), pyrazinamide (40 mg/kg), and ethionamide (20 mg/kg) for 6 months. Wani et al. (2008) started the treatment with 4 drugs daily, that is, isoniazid 5 mg/kg (maximum 300 mg), rifampicin 10 mg/kg, pyrazinamide 25 mg/kg, and ethombutol 20 mg/kg or streptomycin 20 mg/kg (maximum 1 g) for 2 months; and isoniazid and rifampicin daily for 4 to 24 months depending upon the response. Yaramis et al. (1998) treated the TBM patients with a 12-month regimen, initially with Isoniazid, rifampin, and pyrazinamide or streptomycin, and changed to only two drugs (Isoniazid and rifampin) after 2 months of therapy.

A systematic review and meta-analysis concluded that six months of treatment were probably sufficient for TBM, provided the likelihood of drug resistance was low (van Loenhout-Rooyackers et al., 2001). However, most authorities

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recommend 12 months treatment, prompted by the uncertain influences of disease severity, CNS drug penetration, undetected drug resistance and patient compliance on response to therapy (Treatment of tuberculosis. MMWR, 2003; The National Collaborating Centre for Chronic Conditions, 2006).

According to the recent guidelines of British Infection Society for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children (Thwaites et al., 2009), anti-TB drugs for the treatment of TBM should be taken each day either individually or in combination form. Patients should be treated for a minimum of 12 months (Table 3.1).

3.1 Recommended treatment regimen for TBM caused by fully susceptible *M. tuberculosis*

Drug	Daily dose	Route	Duration
Isoniazid	10 – 20 mg/kg (max 500 mg)	Oral	12 months
Rifampicin	10 – 20 mg/kg (max 600 mg)	Oral	12 months
Pyrazinamide	30 – 35 mg/kg (max 2 g)	Oral	2 months
Ethambutol	15 – 20 mg/kg (max 1 g)	Oral	2 months

Source: Thwaites et al., 2009

3.12 Steroids

Corticosteroids have a long and checkered history in the treatment of TBM (Donald et al 2004). Adjunctive corticosteroid treatment of TBM has been recommended for more than 50 years, but there has been long-standing concern that corticosteroids reduce the penetration of anti-tuberculosis drugs into the CNS, cause gastro-intestinal bleeding, and might save lives but increase the number of disabled survivors (Thwaites et al., 2009).

Dexamethasone are useful as an adjunct in the treatment of tuberculous meningitis, especially in patients who have severe disease (Kumarvelu et al., 1994). Adjunctive dexamethasone increases survival from tuberculous meningitis, but the underlying mechanism is unclear. Dexamethasone may affect outcome from

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tuberculous meningitis by reducing hydrocephalus and preventing infarction (Thwaites et al., 2007).

Steroids have improved the outcome but have no effect on the occurrence of sequelae (Wani et al., 2008; van Well et al., 2009). Enhanced resolution of the basal exudate and improved survival rate were shown in CT scan to be associated with the use of corticosteroids in TBM (Schoeman et al., 1997).

In the study of van Well et al. (2009), prednisone (2 mg/kg/day) was given for the first month of treatment and then gradually discontinued over the next 2 weeks. Sixty-eight percent of the patients received corticosteroids. The absence of corticosteroids in TBM treatment was associated with fatal outcome in this study for all stages of disease. They found lower mortality with corticosteroids but not a better clinical outcome: the patients survived but with severe neurologic sequelae. Children who would otherwise die without corticosteroids will now survive with severe sequelae.

Wani et al. (2008) used dexamethasone along with anti-Tb therapy for first 4 weeks and tapered over a similar period (4 weeks) in stage II and III disease (89.47% of the patients). Yaramis et al. (1998) gave dexamethasone (0.3 to 0.5 mg/kg/day) to every patient in the first month of treatment for 3 – 4 weeks, and the dose was tapered over 7 to 10 days. Donald et al. (2004) used prednisone in young children for the first month of treatment at a dose of 2 – 4 mg/kg/day, up to a maximum of 60 mg, taking into account the fact that rifampin accelerates corticosteroid breakdown.

A recent Cochrane systematic review and meta-analysis of 7 randomized controlled trials involving 1140 participants (with 411 deaths) concluded that corticosteroids improved outcome in HIV-negative children and adults with TBM, but the benefit in HIV infected individuals remains uncertain (Prasad and Singh, 2008).

There are no data from controlled trials comparing different corticosteroid regimens; therefore choice of regimen should be based on those found to be effective in the published trials (Thwaites et al., 2009).

According to the recent guidelines of British Infection Society for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children (Thwaites et al., 2009), all patients with TBM should receive adjunctive corticosteroids regardless of disease severity at presentation. Children (≤14 years)

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should be given prednisolone 4 mg/kg/24 h (or equivalent dose dexamethasone: 0.6 mg/kg/24 h) for 4 weeks, followed by a reducing course over 4 weeks.

3.2 Corticosteroid regimens used in controlled trials associated with significant improvements in outcome

Trial	Girgis et al.	Schoeman et al.	Thwaites et al.	Thwaites et al.
Age of subjects	60% <14 years (median 8 years)	< 14 years	>14 years	>14 years
MRC Grade	All grades	Grade II & III	Grade I	Grade II & III
Drug	Dexamethasone	Prednisolone	Dexamethasone	Dexamethasone
Time	Dose/route	Dose/route	Dose/route	Dose/route
Week 1	12 mg/day IM (8 mg/day if <25kg)	4 mg/kg/day[b]	0.3 mg/kg/day IV	0.4 mg/kg/day IV
Week 2	12 mg/day IM (8 mg/day if <25kg)	4 mg/kg/day	0.2 mg/kg/day IV	0.3 mg/kg/day IV
Week 3	12 mg/day IM (8 mg/day if <25kg)	4 mg/kg/day	0.1 mg/kg/day oral	0.2 mg/kg/day IV
Week 4	Reducing over 3 weeks to stop[a]	4 mg/kg/day	3 mg total/day oral	0.1 mg/kg/day IV
Week 5		Reducing dose to stop[c]	Reducing by 1 mg each week over 2 weeks	4 mg total/day oral
Week 6				Reducing by 1 mg each week over 3 weeks

[a] Dexamethasone tapered to stop over 3 weeks: exact regimen not publishes.

[b] Route of administration not published.

[c] Prednisolone tapered to stop over unspecified time: regimen not published.

Source: Thwaites et al., 2009

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3.13 Surgical interventions

Elevated intracranial pressure can be life-threatening and caused poor clinical outcome. If the hydrocephalus is noncommunicating – a condition that can be demonstrated on air encephalography – a ventriculoperitoneal shunt should be placed immediately, which may lead to dramatic improvement. If the hydrocephalus is communicating, medical treatment with furosemide and acetazolamide will often normalize the intracranial pressure within one to two weeks. Patients who do not have a response to this treatment may undergo elective placement of a ventriculoperitoneal shunt (Donald et al., 2004).

Hydrocephalus is the commonest reason for neurosurgical referral in patients with TBM (Thwaites et al., 2009), but only one randomized controlled trial (Schoeman et al., 1991) has been published examining the management of this problem. In this trial 57 Children with communicating hydrocephalus were given anti-tuberculosis drugs and randomly allocated to intra-thecal hyaluronidase, or oral acetazolamide and frusemide, or no intervention. Intra-cranial pressure reduced significantly faster in the acetazolamide and frusemide group, although no effect on survival or disability was observed.

Communicating hydrocephalus (CH) is due to basal cistern block, while non-communicating hydrocephalus (NCH) is due to fourth ventricular outlet obstruction. In a study in South Africa, they treated NCH with a ventriculoperitoneal shunt (VPS) and CH with diuretics (50 mg/kg per day of acetazolamide and 1 mg/kg per day of furosemide). Majority of children with CH were treated with diuretics only (75%). Patients with CH not responding to diuretic treatment within a month (18%) received a VPS (van Well et al., 2009). While in the Turkish study (Yaramis et al., 1998) of 172 cases with hydrocephalus, 140 (81%) underwent surgical management.

According to Farinha et al. (2000), neurosurgical procedures were performed in 24 of 33 patients (73%) with TBM. These included the insertion of a Rickham reservoir (RR) alone in seven patients, ventriculo-peritoneal (VP) shunt in three, a combination of RR followed by a VP-shunt in eight, a RR followed by a ventriculo-atrial (VA) shunt in one, external ventricular drainage system insertion followed by a VP shunt in five patients.

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CH not responding to diuretics within 4 weeks is treated with a VPS (Schoeman et al., 1991). Most authorities suggest that early ventriculo-peritoneal shunting should be considered in all patients with non-communicating Hydrocephalus (Mathew et al., 1998; Kemaloglu et al., 2002). Early ventriculo-peritoneal shunting in children with significant hydrocephalus has been shown to reduce morbidity and mortality, and is a potentially favorable predictor of good outcome (Yamaris et al., 1998).

Response to external ventricular drainage has failed to predict those who benefit from early shunting (Mathew et al., 1998). Endoscopic third ventriculostomy can be considered as an ideal, safe, and long-lasting solution for hydrocephalus after chronic TBM. This is especially so if the patient has one or multiple episodes of shunt dysfunction (Jonathan and Rajshekhar, 2005). Endoscopic third ventriculostomy is advocated by some centres as an alternative to shunt surgery (Figaji et al., 2007; Jha et al., 2007; Jha DK et al., 2007).

According to the recent guidelines of British Infection Society for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children (Thwaites et al., 2009), hydrocephalus, tuberculous cerebral abscess, and vertebral tuberculosis with paraparesis are all indications for neurosurgical referral. Early ventriculo-peritoneal shunting should be considered in those with non-communicating hydrocephalus and in those with communicating hydrocephalus failing medical management. Communicating hydrocephalus may be treated initially with furosemide (40 mg/24 h in adults; 1 mg/kg/day in children) and acetazolamide (10-20 mg/kg/day in adults; 30-50 mg/kg/day in children) or repeated lumbar punctures. Urgent surgical decompression should be considered in all those with extra-dural lesions causing paraparesis.

3.14 Emperical treatment: when to start, when to stop?

Many patients with CNS tuberculosis require empirical therapy; inevitably, some will receive unnecessary treatment. Delayed anti-tuberculosis treatment of CNS tuberculosis is strongly associated with death and neurological sequelae. The low sensitivity of all currently available rapid diagnostic tests mean

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empirical therapy may need to be started in many patients with suspected CNS tuberculosis, although it is difficult to stop treatment once started. Therapeutic response (either lack of response or rapid recovery) should not be used to determine when to stop treatment. It is recommended that the safest approach is to give a complete course of treatment in all patients given empirical therapy unless an alternative diagnosis is made (Thwaites et al., 2009).

3.15 Treatment of drug resistant TBM

CNS tuberculosis caused by bacteria resistant to at least isoniazid and rifampicin [multi-drug resistance (MDR)] requires alternative therapy (Thwaites et al., 2005; Patel et al., 2004; Daikos et al., 2003).

The World Health Organization (WHO, 2006) recommends an injectable agent (e.g. amikacin, or capreomycin), ethionamide, pyrazinamide, and a fluoroquinolone (e.g. levofloxacin) for the initial phase of treatment of multi-drug resistant pulmonary tuberculosis. There are no equivalent recommendations for CNS tuberculosis.

According to the recent guidelines of British Infection Society for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children (Thwaites et al., 2009), the risk of drug resistance must be assessed individually for all patients with CNS tuberculosis. The presence of risk factors should prompt rapid susceptibility testing (by molecular and conventional methods) on diagnostic specimens and additional drugs must be strongly considered. Suspected isoniazid resistant disease (without rifampicin resistance) should be treated initially with conventional 4-drug first-line therapy. If low level resistance is proven, or the cultures are uninformative, they recommend 12 months treatment with rifampicin, isoniazid, and pyrazinamide, with ethambutol stopped after 2 months. If high level isoniazid resistance is proven, they recommend exchanging isoniazid for levofloxacin or moxifloxacin and treat for at least 12 months in combination with rifampicin and pyrazinamide; ethambutol can be stopped after 2 months. Patients with suspected or proven MDR CNS tuberculosis should be managed jointly with an MDR TB expert. They recommend initial therapy with at least a fluoroquinolone (either moxifloxacin or

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levofloxacin), pyrazinamide, ethionamide or prothionamide, and an injectable agent (amikacin or capreomycin), unless the susceptibility profile of the index case has shown resistance to any of these agents. Thereafter, treatment should be guided by national MDR experts, individual resistance profiles and the predicted CSF penetration of candidate drugs.

3.16 Complications of TBM treatment

Hepatic toxicity is the commonest serious drug-related event and is associated with old age, malnutrition, alcoholism, HIV infection, and chronic hepatitis B and C infections (Yew et al., 2006; Tostmann et al., 2008).

Drugs may need to be stopped or reduced to prevent hepatic failure, but it is uncertain when this should be done. Liver enzyme abnormalities may resolve spontaneously, but some authorities recommend stopping isoniazid, rifampicin, and pyrazinamide immediately if the serum transaminases rise above five times normal, or if the bilirubin rises (MMWR, 2003; British Thoracic Society, 1998). Others recommend stopping isoniazid alone if the transaminases rise above three times normal and stopping all drugs if serum albumin falls or the prothrombin time increases (Thompson et al., 1995).

According to the recent guidelines of British Infection Society for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children (Thwaites et al., 2009), new or worsening neurological signs in patients on treatment for CNS tuberculosis should prompt immediate imaging and neurosurgical review. Hyponatraemia should be considered as a cause of coma and seizures. Sodium should be corrected slowly, either by sodium and water replacement if the patient is hypovolemic, or by fluid restriction if they are euvolemic. Fluid restriction is generally not advised in young children, when the risks of dehydration may exceed the benefits of normalizing the serum sodium.

When drug-induced hepatitis occurs, the threshold for stopping rifampicin and isoniazid should be higher in those with CNS tuberculosis compared with pulmonary tuberculosis. If serum transaminases rise above five times normal, they recommend stopping pyrazinamide, continuing isoniazid, rifampicin, ethambutol, and

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performing daily liver function tests. If serum albumin falls, the prothrombin time rises, or the transaminases continue to rise, isoniazid and rifampicin should be withdrawn. Streptomycin and ethambutol should be given, and the addition of moxifloxacin or levofloxacin should be considered in those with severe disease (N.B. Moxifloxacin can cause hepatitis).

Rifampicin and isoniazid should be restarted immediately the liver function tests are normal. They recommend gradually increasing the dose of both drugs over 5-7 days, with regular (3x/week) liver function tests. Pyrazinamide should only be re-started once full dose rifampicin and isoniazid has been safely re-introduced and it must be given at a gradually increasing dose under close supervision (3x/week liver function tests). If pyrazinamide is not given or tolerated, ethambutol should be given throughout therapy, which should be extended to 18 months. Streptomycin can be stopped once the full dose of rifampicin and isoniazid are tolerated.

3.3 Suggested regimen for the reintroduction of anti-tuberculosis drugs following drug-induced hepatitis[a]

	Isoniazid		Rifampicin		Pyrazinamide
	Adult	Child	Adult	Child	
Day 1	150 mg	5 mg/kg	Omit	Omit	Omit
Day 2	150 mg	5 mg/kg	Omit	Omit	Omit
Day 3	300 mg	10 mg/kg	Omit	Omit	Omit
Day 4	300 mg	10 mg/kg	150 mg	5 mg/kg	Omit
Day 5	300 mg	10–20 mg/kg (max 500 mg)	300 mg	5 mg/kg	Omit
Day 6	300 mg	10–20 mg/kg (max 500 mg)	450 mg	10 mg/kg	Omit
Day 7	300 mg	10–20 mg/kg (max 500 mg)	450 mg (<50 kg) 600 mg (≥50 kg)	10–20 mg/kg (max 600 mg)	Consider gradual reintroduction if normal liver function after 14 days of full-dose rifampicin and isoniazid. If pyrazinamide not used, treat for 18 months

[a] If isoniazid, rifampicin, and pyrazinamide stopped because of drug-induced hepatitis, treat with ethambutol, streptomycin +/− moxifloxacin or levofloxacin until liver function normalises and isoniazid and rifampicin can be re-introduced. Note: moxifloxacin can cause hepatitis.

Source: Thwaites 2009

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CHAPTER IV
MATERIALS AND METHODS

4.1 Study design

This was a retrospective descriptive study. The medical records of patients admitted to Queen Sirikit National Institute of Child Health with clinical or laboratory based diagnosis of tuberculous meningitis were reviewed.

4.2 Location of the study

This study was conducted at Queen Sirikit National Institute of Child Health (QSNICH), Bangkok, Thailand.

4.3 Study period

The study was conducted from October 2009 to March 2010.

4.4 Data source

Medical records of tuberculous meningitis patients discharged from QSNICH during the 7-year period from January 1, 2003 until December 31, 2009.

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4.5 Population and sample

4.5.1 Study population

Thirty pediatric patients with tuberculous meningitis admitted to QSNICH from January 1, 2003 until December 31, 2009.

4.5.2 Inclusion criteria

1. Age ≤15 years (at the time of admission) both males and females.
2. Diagnosed as TBM using clinical data, such as abnormal CSF profile/abnormal neurological deficits which are compatible with TBM and evidence of TB infection.
3. Admitted to QSNICH from January 1, 2003 to December 31, 2009.

4.5.3 Exclusion criteria

1. Meningitis caused by viruses, protozoa, fungi or bacteria other than *Mycobacterium tuberculosis.*
2. Medical records are not available.

4.5.4 Sample size calculation

For this study we intend to only describe the characteristics of TBM patients. There is no comparison needed. TBM is a rare disease. Now-a-days the number of TBM cases is very less. Therefore, sample size calculation is not necessary.

We included all the TBM patients diagnosed during the 7-year period in QSNICH, which equal to 30 cases.

4.6 Statistical analysis

SPSS version 11.5 (SPSS Inc., Chicago, IL) was used. The data was analyzed by utilizing statistical test (Fisher's exact test) with a significant level at < 0.05.

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4.7 Research fund

Funding of this study was from The Faculty of Tropical Medicine, Mahidol University.

4.8 Ethics committee approval

Ethical approval of this study was obtained from 2 ethical committees, i.e. Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, and Ethics Committee of Queen Sirikit National Institute of Child Health. Both of the approvals were obtained in November, 2009.

4.9 Significance of the research

The results of this study would be helpful for increasing the awareness of the clinicians to diagnose the disease in its early stage and perform a close monitoring in patients with specific clinical manifestations or risk factors in order to provide early appropriate management to prevent the severity and therefore the sequelae of the disease.

4.10 Confidentiality

The name of the patients and any clues leading to the identification of the patients were not recorded in the case record form. The patient's hospital number and admission number were recorded in a different study log and then assigned a study code number which was a sequential number. The data was identified only by code number that could not be linked to any identifiable data. The person providing the medical records was a secondary person. He was not the doctor of the patients. There was a translator in QSNICH to help in data translation. The translator did/will not disclose any information of the patient files. He will keep the entire information secret, as in Appendix (Confidentiality agreement). This translation helped the investigator in

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filling case record form. The result was presented as overall data. No individual data was presented.

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CHAPTER V
RESULTS

A retrospective study of 30 pediatric patients with tuberculous meningitis, admitted at QSNICH from 2003 to 2009, was conducted.

5.1 Demographic data

Thirty TBM patients, who were admitted to QSNICH from 2003 to 2009, were studied. The number of TBM patients in each year from 2003 until 2009 was shown in figure 5.1. The number of patients admitted in 2003 was highest during the study period.

5.1 Numbers of TBM patients in each year from 2003-2009

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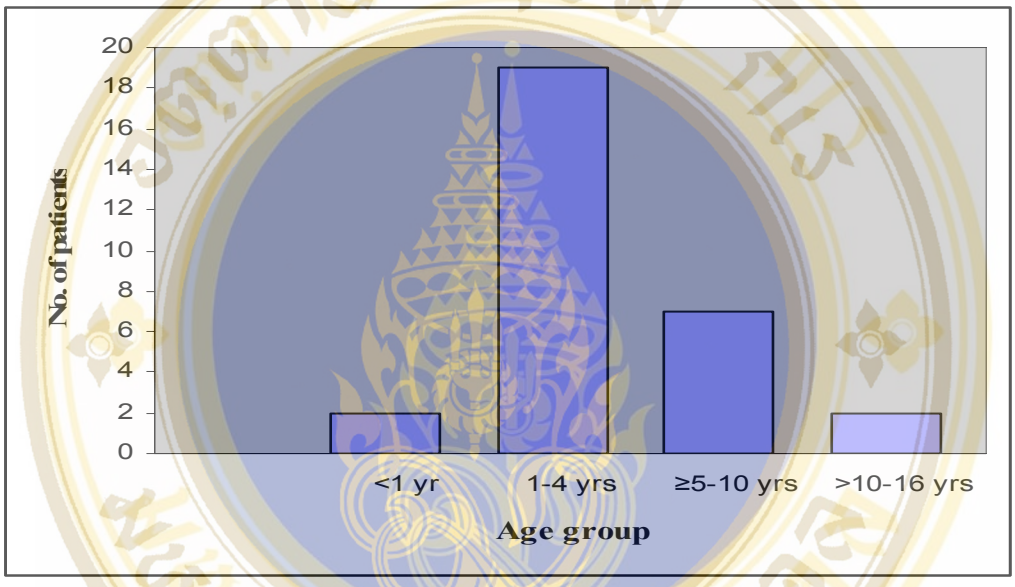
The patients were divided into 4 age groups. Age distribution of tuberculous meningitis patients was shown in figure 5.2. In this study 19 patients (63.33%) were in the age group of 1 – 4 years. Twenty one patients (70%) were less than 5 years of age.



5.2 Age distribution of tuberculous meningitis patients (n = 30)

The demographic data and underlying diseases of 30 TBM patients were shown in table 5.1. It showed that there was no significant difference between genders of the TBM patients. Both girls and boys had been almost equally (53.33% males and 46.67% females) affected. Eighteen patients (69.23%) had contact with sputum-smear positive pulmonary tuberculosis patients in their families. Twenty seven patients (96.43%) had a positive history of BCG vaccination. Sixty-seven percent of the patients had malnutrition. Forty percent of the patients were in stage I of the tuberculous meningitis. Forty percent of the patients had an underlying disease, like pneumonia, UTI, pulmonary tuberculosis, epilepsy, chronic otitis media, anemia, and septic arthritis.

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5.1 Demographic data and underlying diseases of 30 patients

Variable	Data, n (%)
Gender	
Male	16 (53.33)
Female	14 (46.67)
Age on admission	
Median (range)	2 yrs 4 mos (11 mos – 14 yrs 3 mos)
History of BCG vaccination (n = 28)	27 (96.43)
Breastfed (n = 16)	14 (87.50)
History of TB contact (n = 26)	18 (69.23)
Underlying disease	12 (40.00)
Immunosuppressive therapy (n = 26)	1 (3.85)
Nutritional status	
No malnutrition	10 (33.33)
First degree malnutrition	7 (23.33)
Second degree malnutrition	11 (36.67)
Third degree malnutrition	2 (6.67)
Chronic disease in family/household members	
No chronic disease	12 (40.00)
HIV/AIDS and pulmonary tuberculosis	1 (3.33)*
Pulmonary tuberculosis	16 (53.33)
Other chronic disease**	1 (3.33)
Type of place for living (n = 28)	
House	26 (92.86)
One room	1 (3.57)
Camp	1 (3.57)

*Father of this patient had both HIV/AIDS and pulmonary TB.

** One of the family members has cough and hemoptysis (sometimes), but not confirmed TB.

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Diagnosis and staging of TBM on admission were shown in table 5.2. On admission, 53.33% of the patients had another disease (Pulmonary TB, pneumonia, brain abscess, septicemia, typhoid fever, cerebral palsy or UTI) along with TBM. Final diagnosis of 76.67% of the patients was TBM, while final diagnosis of 23.33% of the patients was TBM plus another disease (Pulmonary TB, tuberculoma, septicemia or septic arthritis). The median of patients' stay in hospital was 36 days (range = 10 – 89 days).

5.2 Diagnosis and staging of TBM on admission (n = 30)

Variable	Data, n (%)
Admission diagnosis	
TBM	9 (30.00)
TBM + other disease*	16 (53.33)
Other disease**	5 (16.67)
Stage of TBM	
Stage I	12 (40.00)
Stage II	8 (26.67)
Stage III	10 (33.33)

* Pulmonary TB, pneumonia, brain abscess, septicemia, typhoid fever, cerebral palsy, and UTI.

** Pneumonia, encephalitis, and Supracellar and perineal mass.

More than half of the patients (63.33%) in this study were less than 5 years of age. Two (6.67%), 7 (23.33%), and 2 (7.67%) of the patients in this study were in the age group of < 1, ≥ 5 – 10, and > 10 – 16 years, respectively. All of the three deaths were less than 5 years of age.

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5.2 Clinical manifestations

Headache was asked from only 17 patients (56.67%) out of 30 TBM patients, because the others were too young to explain headache. Among these 17 patients, 9 (52.94%) had headache. Five patients (25%) had a history of weight loss in the previous 6 months. Abdominal complaints were present in 3 patients (10.00%). On admission, most of the patients (83.33%) had fever. Kernig's sign was positive in 2 patients (9.09%), while Brudzinski's sign was not positive in any patient. Papilledema and vomiting were present in 7 patients (29.17%) and 13 patients (43.33%), respectively. No patient came to the hospital in the state of coma. Photophobia was not present in any of the patients. Anterior fontanelle was examined in 10 patients (33.33%) and only one case (10%) demonstrated bulging of the anterior fontanelle.

Comparison of history, underlying disease, and clinical manifestations on admission among the patients in stage I, II, and III of TBM were shown in table 5.3. In stage I, fever, history of BCG vaccination, BCG scar, and headache were present in 91.67, 90.91, 83.33, and 75 % of the patients, respectively. In stage II, history of BCG vaccination, weakness, fever, and neck stiffness were present in 100, 100, 85.71, and 66.67 % of the patients, respectively. In stage III, history of BCG vaccination, history of TB contact, fever, and sustained clonus were present in 100, 85.71, 80, and 70 % of the patients, respectively.

5.3 Comparison of history, underlying disease, and clinical manifestations on admission among the patients in stage I (n = 12), II (n = 8), and III (n = 10) of TBM

Variable	Stage I n (%)	Stage II n (%)	Stage III n (%)	Total
History of TB contact	7/11 (63.64)	5/8 (62.5)	6/7 (85.71)	18 (69.23)
History of BCG vaccination	10/11 (90.91)	8/8 (100.00)	9/9 (100.00)	27 (96.43)
Underlying disease	6/12 (50.00)	2/8 (25.00)	5/8 (62.5)	12 (40.00)

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5.3 Comparison of history, underlying disease, and clinical manifestations on admission among the patients in stage I (n = 12), II (n = 8), and III (n = 10) of TBM (cont.)

Variable	Stage I n (%)	Stage II n (%)	Stage III n (%)	Total
Weakness	0/2 (0.00)	3/3 (100.00)	5/8 (62.5)	8/13 (61.54)
Headache	6/8 (75.00)	1/4 (25.00)	2/5 (40.00)	9/17 (52.94)
Anorexia	1/2 (50.00)	0/1 (0.00)	2/3 (66.67)	3/6 (50.00)
Vomiting	5/12 (41.67)	2/5 (40.00)	6/10 (60.00)	13/30 (43.33)
Weight loss within last 6 months	2/6 (33.33)	1/6 (16.67)	2/8 (25.00)	5/20 (25.00)
Cough	1/11 (9.09)	2/7 (28.57)	4/9 (44.44)	7/30 (23.33)
Fever (> 37.0 °C)*	11/12 (91.67)	6/7 (85.71)	8/10 (80.00)	25/30 (83.33)
Neck stiffness	6/11 (54.54)	4/6 (66.67)	6/10 (60.00)	16/30 (53.33)
BCG scar	5/6 (83.33)	2/5 (40.00)	2/6 (33.33)	9/17 (52.94)
Hydrocephalus	2/3 (66.67)	2/3 (66.67)	1/4 (25.00)	5/10 (50.00)
Sustained clonus	3/11 (27.27)	4/8 (50.00)	7/10 (70.00)	14/30 (46.67)
Seizures	4/10 (40.00)	4/7 (57.14)	4/8 (50.00)	12/30 (40.00)
Papilledema	3/11 (27.27)	1/5 (20.00)	3/8 (37.5)	7/24 (29.17)

* Axillary temperature was measured in every patient.

In table 5.4, clinical manifestations of the TBM patients on admission were compared in two age groups of < 5 and ≥ 5 years. In the age group of < 5 years of age, fever, neck stiffness, weakness, and sustained clonus were present in 85, 67, 67, and 55% of the patients, respectively. In the age group of ≥ 5 years of age, fever, headache, and vomiting were present in 89, 86, and 56% of the patients, respectively.

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5.4 Comparison of clinical manifestations of the TBM patients on admission, in two age groups of < 5 (n = 21) and ≥ 5 years (n = 9)

Symptom/sign	Age (< 5 years) n (%)	Age (≥ 5 years) n (%)	p-value
Weakness	6/9 (66.67)	2/4 (50.00)	1.000
Vomiting	8/18 (44.44)	5/9 (55.55)	0.443
Anorexia	2/5 (40.00)	1/1 (100)	1.000
Cough	7/18 (38.89)	0/9 (0.00)	0.071
Headache	3/10 (30.00)	6/7 (85.71)	0.050
Weight loss within last 6 months	2/14 (14.29)	3/6 (50.00)	0.131
Fever (> 37.0 °C)*	17/20 (85.00)	8/9 (88.89)	1.000
Neck stiffness	12/18 (66.67)	4/9 (44.44)	0.694
Sustained clonus	11/20 (55.00)	3/9 (33.33)	0.440
BCG scar	6/12 (50.00)	3/5 (60.00)	1.000
Seizures	9/18 (50.00)	3/7 (42.86)	0.704
Hydrocephalus	5/10 (50.00)	0/0 (0.00)	0.286
Papilledema	4/15 (26.67)	3/9 (33.33)	0.640

5.3 Laboratory investigations

Laboratory investigations of the complete blood count (CBC) of the patients on admission and during the therapy were shown in table 5.5. From the record of each patient, results of 5 CBC examinations (if present) were taken. First examination was taken as “on admission”, while the remaining 4 examinations were taken as “during the therapy” examinations. If a patient had more than 4 examinations during the therapy, only 4 of the examinations were taken (for example, if a patient had 8 CBC examinations, then the 2nd, 4th, 6th, and 8th examinations were taken). The purpose of finding the results of CBC examinations on admission and during the therapy was to find out whether there were significant differences between the results

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of CBC examinations on admission and during the therapy. These results did not show any significant difference between the two groups of results. On admission more than half of the patients had neutrophilia, anemia, and thrombocytosis, in 17 (56.67%), 16 (53.33%), and 17 (56.67%) patients, respectively. During the therapy, neutrophilia, anemia, and thrombocytosis were present in 16 (57.14%), 14 (50.00%), and 14 (51.85%) of the patients, respectively.

5.5 Laboratory examinations of the complete blood count (CBC) of the patients on admission and during the therapy

Variable	On admission (n = 30)	During the therapy (n = 28)
Total leukocyte count (/mm^3)		
Median (range)	12,595 (4,100 – 34,000)	10,800 (3,200 – 34,000)
Leukocytosis*, n (%)	7 (23.33)	7 (25.00)
Leukopenia*, n (%)	1 (3.33)	2 (7.14)
Neutrophils (%)		
Median (range)	69 (22 – 90)	69 (9 – 95)
Neutrophilia*, n(%)	17 (56.67)	16 (57.14)
Neutropenia*, n(%)	7 (23.33)	11 (39.29)
Lymphocytes (%)		
Median (range)	25.5 (5 – 73)	25.5 (5 – 74)
Lymphocytosis*, n(%)	10 (33.33)	12 (42.86)
Lymphocytopenia*, n(%)	14 (46.67)	14 (50.00)
Monocytes (%)		
Median (range)	5.5 (0 – 21)	4 (0 – 34)
Monocytosis*, n(%)	10 (33.33)	9 (32.14)
Monocytopenia*, n(%)	5 (16.67)	11 (39.29)
Eosinophils (%)		
Median (range)	0 (0 – 4)	0 (0 – 13)
Eosinophilia*, n(%)	2 (6.67)	3 (10.71)
Basophils (%)		
Median (range)	0 (0 – 6)	0 (0 – 6)
Basophilia*, n(%)	2 (6.67)	3 (10.71)
Hemoglobin (g/dl)		
Median (range)	11 (8 – 14)	11 (6 – 14)
Anemia*, n(%)	16 (53.33)	14 (50.00)
Platelet count (/mm^3)		n = 27
Median (range)	418,500 (17,000 – 1,063,000)	398,000 (17,000 – 1,063,000)
Thrombocytosis*, n(%)	17 (56.67)	14 (51.85)
Thrombocytopenia*, n(%)	1 (3.33)	1 (3.70)

* For cutoff values, please see appendix B

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Laboratory examination of the blood biochemistry of the patients on admission and during the therapy were shown in table 5.6. From the record of each patient, results of 5 blood biochemistry examinations (if present) were taken. First examination was taken as "on admission", while the remaining 4 examinations were taken as "during the therapy" examinations. If a patient had more than 4 examinations during the therapy, only 4 of the examinations were taken (for example, if a patient had 8 blood biochemistry examinations, then the 2nd, 4th, 6th, and 8th examinations were taken). On admission hyponatremia, acidosis, and hypokalemia were present in 22 (73.33%), 11 (36.67%), and 2 (6.67%) patients, respectively. While during the therapy hyponatremia, acidosis, and hypokalemia were present in 19 (70.37%), 16 (59.26%), and 5 (18.52%) patients, respectively. Out of 22 patients having hyponatremia on admission, 6 (27.27%), 8 (36.36%), and 8 (36.36%) of the patients were in stage I, II, and III of TBM (BMRC criteria), respectively. No patient had increased BUN, creatinine or alkaline phosphatase in the blood, on admission or during the therapy.

5.6 Laboratory examinations of the blood biochemistry of the patients

Variable	On admission	During the therapy
K (mmol/L)	n = 30	n = 27
Median (range)	4 (3 – 6)	4 (3 – 6)
Hypokalemia*, n(%)	2 (6.67)	5 (18.52)
Na (mmol/L)	n = 30	n = 27
Median (range)	133.5 (122 – 145)	135 (115 – 145)
Hyponatremia*, n(%)	22 (73.33)	19 (70.37)
Cl (mmol/L)	n = 30	n = 27
Median (range)	99 (91 – 115)	103 (82 – 115)
Hypochloremia*, n(%)	10 (33.33)	6 (22.22)
Hyperchloremia*, n(%)	2 (6.67)	9 (33.33)
HCO_3^- (mmol/L)	n = 30	n = 27
Median (range)	24 (13 – 38)	21 (8 – 38)
Acidosis*, n(%)	11 (36.67)	16 (59.26)
Alkalosis*, n(%)	2 (6.67)	3 (11.11)
Ca (mmol/L)	n = 18	
Median (range)	2 (1 – 3)	
Hypocalcemia*, n(%)	5 (27.78)	

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5.6 Laboratory examinations of the blood biochemistry of the patients (cont.)

Variable	On admission	During the therapy
Blood sugar (mg/dl)	n = 19	n = 21
Median (range)	110.5 (85 – 153)	102.5 (57 – 153)
Hypoglycemia*, n(%)	0 (0.00)	1 (4.76)
Total Bilirubin (mg/dl)	n = 19	n = 22
Median (range)	0.34 (0.12 – 1.58)	0.34 (0 – 2.33)
Hyperbilirubinemia*, n(%)	1 (5.26)	1 (4.54)
AST (U/L)	n = 19	n = 21
Median (range)	26 (14 – 94)	33 (12 – 124)
Increased AST*, n(%)	3 (15.79)	6 (28.57)
ALT (U/L)	n = 19	n = 21
Median (range)	14 (0 – 373)	24 (0 – 411)
Increased ALT*, n(%)	6 (31.58)	7 (33.33)

* For cutoff values, please see appendix B

CSF findings of the patients on first diagnosis and during the therapy were shown in table 5.7. From the record of each patient, results of 5 CSF examinations (if present) were taken. First examination was taken as "first diagnosis", while the remaining 4 examinations were taken as "during the therapy" examinations. If a patient had more than 4 examinations during the therapy, only 4 of the examinations were taken (for example, if a patient had 8 CSF examinations, then the 2nd, 4th, 6th, and 8th examinations were taken). On the first diagnosis, incresed opening pressure of CSF, increased closing pressure of CSF, and leukocytosis were seen in 19 (95.00%), 20 (95.24%), and 21 (91.30%) patients, respectively. While during the therapy, increased opening pressure of CSF, increased closing pressure of CSF, and leukocytosis were seen in 26 (92.86%), 25 (89.29%), and 24 (85.71%) patients, respectively.

On first diagnosis, the median percentages of polymorphonuclear cells and mononuclear cells in CSF were 9% and 85%, respectively. While during the therapy, the median percentages of PMN cells and mononuclear cells in CSF were 2.5% and 94.5%, respectively.

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5.7 CSF findings on first diagnosis and during the therapy

Variable	First diagnosis	During the therapy	p-value
Appearance	n = 30	n = 30	1.000
Colorless, n (%)	29 (96.67)	27 (90.00)	
Straw color, n (%)	1 (3.33)	1 (3.33)	
Red, n (%)	0 (0.00)	2 (6.67)	
Opening pressure (cmH_2O)	n = 20	n = 28	0.071
Median (range)	22 (6 – 58)	20 (3 – 58)	
Increased opening pressure*, n (%)	19 (95.00)	26 (92.86)	
Closing pressure (cmH_2O)	n = 21	n =28	0.876
Median (range)	15 (7 – 35)	14 (3 – 35)	
Increased closing pressure*, n (%)	20 (95.24)	25 (89.29)	
Total leukocyte count ($cells/mm^3$)	n = 23	n = 28	1.000
Median (range)	105 (0 – 1200)	65 (0 – 1340)	
Leukocytosis*, n (%)	21 (91.30)	24 (85.71)	
PMN (%)	n = 23	n = 28	0.696
Median (range)	9 (0 – 90)	2.5 (0 – 90)	
Mononuclear cells (%)	n = 23	n = 28	0.738
Median (range)	85 (0 – 100)	94.5 (0 – 100)	
Glucose (CSF/Blood) %	n = 27	n = 26	1.000
Median (range)	20 (2.7 – 64.94)	36.65 (1.54 – 84.15)	
Protein (mg/dl)	n = 29	n = 26	1.000
Median (range)	143 (7.2 – 444)	111.5 (7.2 – 448.7)	

* For cutoff values, please see appendix B

The CSF glucose as percentage of corresponding blood glucose and values of protein in CSF (on first diagnosis) were shown in table 5.8. Fourteen patients (51.85%) had the CSF glucose as percentage of corresponding blood glucose ≤ 20%.

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Fourteen patients (48.28%) had CSF protein values 151 - 450 mg/dl. No patient had CSF protein value more than 450 mg/dl.

5.8 CSF glucose as percentage of corresponding blood glucose and CSF protein on first diagnosis

CSF glucose as percentage of corresponding blood glucose (%)	Number	Percentage (%)	CSF Protein (mg/dl)	Number	Percentage (%)
≤ 20	14	51.85	Up to 50	4	13.79
21 – 40	5	18.52	51 – 100	5	17.24
41 – 60	6	22.22	101 – 150	6	20.69
61 – 80	2	7.41	151 - 450	14	48.28
> 80	0	0.00			
Total	**27**	**100.00**		**29**	**100.00**

Comparison of CSF analysis on first diagnosis among the patients of stage I, II, and III of TBM were shown in table 5.9. In stage I, all the patients had increased opening pressure and leukocytosis, while 88.89% of the patients had increased closing pressure. In stage II, all the patients had leukocytosis, while 83.33 and 62.5% of the patients had increased opening pressure and protein > 150 mg/dl, respectively. In stage

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III, all of the patients had increased opening pressure, increased closing pressure, and leukocytosis, while 50% of the patients had protein > 150 mg/dl.

5.9 Comparison of CSF analysis on first diagnosis among the patients of stage I, II, and III of TBM

Variable	Stage I (n = 12) n (%)	Stage II (n = 8) n (%)	Stage III (n = 10) n (%)
Increased opening pressure*, n (%)	8/8 (100)	5/6 (83.33)	6/6 (100.00)
Increased closing pressure*, n (%)	8/9 (88.89)	7/7 (100.00)	5/5 (100.00)
Leukocytosis*, n (%)	10/10 (100.00)	7/7 (100.00)	6/6 (100.00)
Glucose (CSF/Blood) ≤ 20%	7/12 (58.33)	2/6 (33.33)	5/9 (55.55)
Protein > 150 mg/dl	4/11 (36.36)	5/8 (62.5)	5/10 (50.00)

* For cutoff values, please see appendix B

Positive result on several important tests, which were done for the patients, were shown in table 5.10. Tuberculin skin test was done for 27 out of 30 patients. Nineteen patients (70.37%) had positive tuberculin skin test with induration ≥ 10 mm at 72 hours. Culture of CSF for *M. tuberculosis* was done for 14 patients but all were negative. Gastric wash was done for 19 patients but all were negative for *M. tuberculosis*. Diagnostic value from CSF examination showed more yield on PCR technique of 26.09% followed by acid fast stain of only 5.26%.

ESR was performed in only 6 cases and 5 in 6 cases (83.33%) had increased in value.

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5.10 Miscellaneous tests done for patients

Test	Number of positive result	Percentage (%)
Sputum microscopy for AFB	2/8	25.00
Tuberculin skin test (≥ 10mm)	19/27	70.37
PCR for *M. tuberculosis* (CSF)	6/23	26.09
Acid fast stain (CSF)	1/19	5.26
Culture for *M. tuberculosis* (CSF)	0/14	0.00
ESR		
Median (range)	43 (7 – 94)	
Increased ESR*	5/6	83.33

* For cutoff values, please see appendix B

5.4 Radiological examinations

Computerized tomography (CT) scans of the brain were done in all the 30 patients. CT scans could not demonstrate abnormality in 4 cases. Twenty-six patients (87%) had abnormal findings in the CT scans. Hydrocephalus was present in 22 patients (73.33%). Magnetic resonance imaging (MRI) was done only in one patient, with the result of hydrocephalus. This patient was in stage III of TBM on admission with the underlying diseases of pulmonary TB and pneumonia. This patient also had seizures, sustained clonus, and neurological sequelae (i.e. hemiplegia and blindness). CT scan findings were shown in table 5.11.

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5.11 Abnormal CT scan findings in 26 patients

Findings	Number	Percentage (%)
Hydrocephalus	22	84.61
Cerebral infarction	10	38.46
Cerebral edema	10	38.46
Basal arachnoiditis	8	30.77
Tuberculoma	7	26.92
Other abnormal findings*	9	34.61
More than one abnormal findings	20	76.92

* Other abnormal findings were mild degree of brain atrophy, prominent pituitary gland, Abnormal patchy enhancement at left side of tentorium and occipital cortex, small subdural collection of right frontal region, periventriculitis and cerebritis at left basal ganglion, and multiple brain abscesses.

Chest radiographies were done in 29 patients (96.67%). Seven patients had normal chest radiography, while 22 patients (75.86%) had abnormal chest radiography. Out of those 22 patients, 18 patients (81.82%) had infiltrations in their chest radiography, followed by hilar lymphadenopathy and atelectasis as shown in table 5.12. Fourteen patients (63.64%) had more than one abnormal finding in their chest radiography.

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5.12 Abnormal chest X-Ray findings in 22 patients

Chest radiograph findings	Number	Percentage (%)
Infiltration	18	81.82
Hilar lymphadenopathy	5	22.73
Atelectasis	5	22.73
Pleural effusion	1	4.54
Other abnormal findings*	6	27.27

* Other abnormal findings were mild widening of superior mediastinum, right blunt costophrenic abscess, deviation of heart and trachea to left side, and mass at right hilus.

5.5 Treatment

Doses of anti-tuberculous drugs used were shown in table 5.13.

5.13 Dosage of anti-TB drugs used

Drug	Median (mg/kg/day)	Range (mg/kg/day)
Isoniazid	10	7 – 13
Rifampicin	15	10 – 20
Pyrazinamide	25	20 – 35
Streptomycin	20	20 – 27
Ethambutol	20	15 – 27

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Second line anti-TB drugs were used in only 3 patients (10.00%). Only one patient (3.33%) had allergy to 3 anti-TB drugs (INH, rifampicin, and streptomycin). After starting anti-TB drugs INH, rifampicin, pyrazinamide, and streptomycin, this patient started generalized body rash. All the 4 drugs were stopped. Then one by one every drug was reintroduced, but reaction occurred to all 4 drugs, except pyrazinamide. So, for this patient pyrazinamide, ethambutol, and ofloxacin were started, which did not show any reaction. Corticosteroids, acetazolamide, anticonvulsants, and other antibiotics (other than anti-TB drugs) were used in 27 (90.00%), 28 (93.33%), 17 (56.67%), and 25 (83.33%) patients, respectively. Antibiotics other than anti-TB drugs were cefotaxime, ceftriaxone, meropenam, chloramphenicol, cloxacillin, ampicillin, co-amoxiclav, vancomycin, and ceftazidime. These antibiotics were used for concomitant diseases, like pneumonia, urinary tract infection (UTI), chronic otitis media, and septic arthritis. Ventriculo-peritoneal (VP) shunt was done for 9 patients (30.00%), but ventriculo-atrial (VA) shunt was not done for any patients. Treatment of TBM was shown in table 5.14.

5.14 Treatment of TBM (n = 30)

Variable	Number	Percentage (%)
Second line anti-TB drugs	3	10.00
Corticosteroids		
Dexamethasone*	1	3.33
Prednisolone	4	13.33
Dexamethasone followed by prednisolone	22	73.33
Acetazolamide	28	93.33
Anticonvulsants	17	56.67
Other antibiotics†	25	83.33
VP shunt	9	30.00

*This patient used only dexamethasone (because he died and used dexamethasone for 22 days before dead).

† Antibiotics other than anti-tuberculous drugs

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Anti-TB drugs regimens used for the treatment of TBM were shown in table 5.15. INH and rifampicin were used in 29 patients (96.67%), because one patient had allergy to INH and rifampicin. Twenty patients (66.67%) used the regimen of INH + rifampicin + pyrazinamide + streptomycin. One patient (3.33%) used the regimen of INH + rifampicin + pyrazinamide. This patient was alert, in stage I of TBM, had an underlying disease of pulmonary tuberculosis, and had already started anti-TB drugs (INH+RIF+PZA). The only second line drug used was ofloxacin in 3 patients (10.00%). The course and duration of anti-TB therapy used in TBM patients were shown in table 5.16.

5.15 Anti-TB drugs regimens used for the treatment of TBM (n = 30)

Anti-TB drugs regimen in intensive phase	Number	Percentage (%)
INH+RIF+PZA	1	3.33
INH+RIF+PZA+SM	20	66.67
INH+RIF+PZA+EMB	5	16.67
INH+RIF+PZA+SM+EMB	1	3.33
INH+RIF+SM+Ofloxacin	1	3.33
INH+RIF+EMB+Ofloxacin	1	3.33
PZA+EMB+Ofloxacin	1	3.33

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5.16 Course and duration of anti-TB therapy in TBM

Duration of therapy (months)	Number (n = 18*)	Percentage (%)
6	5	27.78
9	7	38.89
11	2	11.11
12	3	16.67
18	1	5.56

* Duration of therapy was recorded of only 18 patient because 3 patients died and 9 patients lost to follow up.

5.6 Outcome of the study

Mortality and morbidity rates observed during the study were shown in table 5.17. Overall 3 patients (10%) died out of the 30 TBM patients. Only one of them (33.33%) died due to TBM. Other 2 patient (66.67%) died due to other diseases (one due to severe bacterial pneumonia, while the other due to *Candida albicans* septicemia). Permanent sequelae were observed in 5 patients (16.67%), consisted of hearing loss (severe permanent sequelae) in 3 patients, quadriplegia (severe permanent sequelae) in one patient, and reduced vision (mild permanent sequelae) in one patient. Moderate permanent sequelae were not present in any patient.

All the 3 patients, who died, had CSF glucose as percentage of corresponding blood glucose < 40% and CSF protein 151 – 450 mg/dl.

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5.17 Mortality and morbidity rates observed

Variable	Number (n = 30)	Percentage (%)
Cured without sequelae	22	73.33
Mild permanent sequelae	1	3.33
Severe permanent sequelae	4	13.33
Deaths without severe sequelae	2	6.67
Death with severe sequelae	1	3.33

Concerning the neurological sequelae, most of the patients had hearing loss and blindness, in 6 patients (20%) and 5 patients (16.67%), respectively. Among 15 patients (50.00%) who had neurological sequelae, 10 patients (33.33%) had temporary sequelae while 5 (16.67%) had permanent sequelae. All neurological sequelae observed in the patients were shown in table 5.18.

5.18 Neurological sequelae observed in 15 patients

Sequelae	Number (n)	Percentage (%)
Temporary neurological sequelae	10*	33.33
Blindness	5	16.67
Hemiplegia	3	10.00
Hearing loss	3	10.00
Hemiparesis	2	6.67
Facial nerve palsy	2	6.67
Quadriplegia	1	3.33
Permanent neurological sequelae	5*	16.67
Hearing loss	3	10.00
Quadriplegia	1	3.33
Reduced vision	1	3.33

* Five patients (16.67%) had more than one neurological sequela

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Various stages of TBM (BMRC criteria) of the patients on admission versus permanent sequelae and deaths were shown in table 5.19. Twelve patients (40%) were fully conscious on admission. Permanent sequelae only occurred in patients who were in stage II or III of TBM on admission. But there was no relationship between death and the stage of TBM on admission (p-value = 1.000). The patient who was in stage I on admission and died, did not die due to TBM. Instead, he died due to *Candida albicans* septicemia. BMRC criteria were shown in appendix C.

5.19 Patients with various stages of TBM (BMRC criteria) on admission versus permanent sequelae and deaths

Stage of TBM	Number (%) (n = 30)	Permanent sequelae, n(%)	p-value	Death, n (%)	p-value
I	12 (40)	0 (0.00)	0.089	1 (33.33)	1.000
II	8 (26.67)	2 (40.00)		1 (33.33)	
III	10 (33.33)	3 (60.00)		1 (33.33)	

Nutritional status of the patients and its association with death were shown in table 5.20. Twenty patients (66.67%) had malnutrition at the time of admission. There was no association between the nutritional status of the patients and death (p-value = 1.000).

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5.20 Nutritional status of the patients and its association with death

Nutritional status	Number (n = 30)	Percentage (%)	Death (n)	Percentage (%)	p-value
Normal	10	33.33	1	33.33	1.000
First degree malnutrition	7	23.33	1	33.33	
Second degree malnutrition	11	36.67	1	33.33	
Third degree malnutrition	2	6.67	0	0.00	

Conscious level of the patients and its association with death was shown in table 5.21. Sixteen patients (53.33%) were having good consciousness on admission. On the other hand, no patient came to the hospital in the state of coma. It showed that majority of the patient were alert and having good consciousness on admission. There was no association between the conscious level of the patients and death because one dead case (33.33%) was in the group of patients who had good conscious level.

5.21 Conscious level of the patients on admission and its association with death

Conscious level	Number (n = 30)	Percentage (%)	Death (n)	Percentage (%)	p-value
Good conscious	16	53.33	1	33.33	0.515
Confused	3	10.00	0	0.00	
Somnolent	8	26.67	1	33.33	
Stuporous	3	10.00	1	33.33	

Treatment modalities and outcome of the TBM patients were shown in table 5.22. Although 27 (90.00%) patients used corticosteroids as adjuvant therapy, all the 3 deaths were in this group.

5.22 Treatment modalities and outcome (n = 30)

		Outcomes	
Treatments	**Number (%)**	**Improved, n (%)**	**Died, n (%)**
Anti-TB drugs alone	3 (10.00)	3 (100.00)	0 (0.00)
Anti-TB drugs + steroids (without VP shunt)	18 (60.00)	17 (94.44)	1 (5.56)
Anti-TB drugs + Steroids + VP shunt	9 (30.00)	7 (77.78)	2 (22.22)

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CHAPTER VI
DISCUSSION

6.1 Prevalence and epidemiology

In this study, 30 TBM patients were admitted to QSNICH during 9-year-period, from January, 2003 until December, 2009. But in a previous study conducted in the same hospital (previously called Children's Hospital) by Sunakorn et al. (1980) showed that in only 4 years (1960 – 1963), 221 patients of TBM were admitted to this hospital. This showed a significant decrease in the cases of TBM admitted to QSNICH in the recent years.

TBM frequently occurs in childhood, especially 6 months to 4 years of age (Nelson Textbook of Pediatrics, 2007). In a study conducted in Turkey, 77% of the children were younger than 5 years (Yaramis et al., 1998). In the same way, 79.8% of the children were under 5 years of age in the study of Berman et al. (1992) and 82% of the children in a cohort study in South Africa were <5 years of age (van Well et al., 2009). In a previous study, done in QSNICH, 70% of the children were < 3 years of age (Sunakorn et al., 1980).

In this study, 21 patients (70%) were less than 5 years of age. The results of this study were nearly the same, as explained in other studies (van Well et al., 2009; Yaramis et al., 1998; Berman et al., 1992).

Male and female were equally affected by this disease (van Well et al., 2009). This study also showed that there was no significant difference in the incidence of TBM in both gender.

Most of the children affected by TBM have a family history of pulmonary TB. A study in South Africa showed that 53% of their patients had contact with a household adult with proven pulmonary TB (van Well et al., 2009). According to a study in London, 47% patients had a history of recent or active TB occurring in a

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family member, whilst 42% had travelled recently (within the last 6 months) to a country where TB is endemic (Indian subcontinent, Africa, and Pacific Islands). Seventy one percent had either a family history or had travelled abroad. A study in Turkey showed that 66% of the patients had a family history of TB, while Waecker and Connor reported that an adult source of contact was identified in 70% of cases of children (Waecker et al., 1990). In this study 69.23% of the patients had contact with pulmonary tuberculosis patients in their families. This study gave nearly the same results as of other studies.

According to a study by Yaramis et al. (1998), only 12% of the children had a history of BCG vaccination, while only 16% had previously received BCG in a study by Farinha et al. (2000). In this study, 96.43% patients had a positive history of BCG vaccination. All the patients < 5 years of age had received BCG vaccination. This showed that, in contrast to other studies, most of the patients in this study (96.3%) had BCG vaccination. Though this showed a high coverage of BCG vaccination in EPI program in Thailand, but BCG vaccination could not protect from TBM in those who had TB contact in the family. This warrants further study on appropriate vaccination against tuberculous infection.

6.2 Clinical manifestations

In a study done in London (Farinha et al., 2000), 6% of the children presented in stage I, 30% in stage II, and 64% in stage III. A study in Turkey showed that 10%, 56%, and 34% of the TBM patients came in stage I, II, and III of the disease, respectively (Yaramis et al., 1998). In a previous study done in QSNICH (Sunakorn et al., 1980), 6.25%, 56.25%, and 37.5% of the patients presented in stage I, II, and III, respectively.

Forty percent of the children in this study were in Stage I, 26.67% in stage II, and 33.33% in stage III. It clearly showed that, in contrast to other 3 studies (van Well et al. 2009; Farinha et al., 2000; Yaramis et al., 1998), this study had more patients in stage I than in stage II or III. This early detection was may be due the fact that QSNICH is the biggest tertiary hospital for children in Thailand and also the presence of expert pediatricians.

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In the study of van Well et al. (2009), majority of patients on admission had poor weight gain, decreased level of consciousness, and any type of motor deficit. Yaramis et al. (1998) observed that the most common pre-admission clinical manifestations were fever reported in 91%, vomiting in 87%, personality change in 63%, seizures in 62%, nuchal rigidity in 59%, and headaches in 58% of TBM patients.

In this study, on admission, fever was present in 83.33%, weakness in 61.54%, neck stiffness in 53.33%, headache in 52.94%, vomiting in 43.33%, and seizures in 40% of the patients. In the age group of < 5 years of age, fever, neck stiffness, weakness, and sustained clonus were present in 85, 67, 67, and 55% of the patients, respectively. In the age group of ≥ 5 years of age, fever, headache, and vomiting were present in 89, 86, and 56% of the patients, respectively. In contrast to other study, the patients of this study had less vomiting and seizures. This was may be due to the reason that 40% of the patients in this study were in stage I of TBM.

6.3 Laboratory investigations

Tuberculin skin test was positive in 60% of the TBM patients in a study conducted in South Africa (van Well et al., 2009) and 51% in a study conducted in London (Farinha et al., 2000). Rates of positive tuberculin skin test for children varied between 30 and 65% in different studies (Yaramis et al., 1998; van den Bos et al., 2004; Akhila et al., 2007; Donald et al., 1998).

In this study, tuberculin skin test was positive in 70.37% of the patients, which was more than the previously mentioned studies.

In the study of Farinha et al. (2000), the mean peripheral leukocyte count was 11,700/mm^3 (range 4,300 – 23,300) with a mean of 65% neutrophils, 27% lymphocytes and 7% monocytes. Significant monocytosis (>1.0×10^9/L) occurred in only 23% patients.

In this study, most of the patients had neutrophilia, anemia, and thrombocytosis, in 56.67%, 53.33%, and 56.67% patients, respectively. Lymphocytopenia was present in 46.67% of the patients. We also observed that monocytosis was present in 33.33% of our patients which is higher than the previous report.

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ESR was performed in only 6 cases. However, 5 in 6 cases (83.33%) had increased ESR value. It shows that this is still a valuable test and suggestive or supportive for diagnosis.

Most of our patients (73.33%) had hyponatremia on admission. Median of blood sodium in our patients was 133.5 mmol/L and the range was 122 – 145 mmol/L. All the 3 patients who died had hyponatremia. Our results are nearly the same with the study by Farinha et al. (2000), which showed that hyponatremia was present in 79% of the patients. The mean sodium in the group of patients with tuberculous meningitis was 126 mmol/L (range was 118– 137 mmol/L).

Although in this study the number of patients decreased during the therapy (19 patients) than on admission (22 patients), but the number of patients having hypokalemia and acidosis increased during the therapy (5 patients having hypokalemia and 16 patients having acidosis) than on admission (2 patients having hypokalemia and 11 patients having acidosis). These differences were may be due to the fact that TBM patients usually do not give good response to anti-TB therapy in the first two weeks of therapy.

Typical examination of the cerebrospinal fluid reveals a leucocytosis (10 – 1000×10^3 cells/ml; mostly lymphocytes), raised protein (0.5 – 3.0 g/l), and CSF glucose as percentage of corresponding blood glucose < 50%. The search for acid-fast bacilli (AFB) in CSF is crucial for the rapid diagnosis of TBM and can be seen in up to 80% of adult cases, but only 15-20% of children (Thwaites et al., 2009).

The CSF findings (mean) for the 33 children with TBM in the study of Farinha et al. (2000) were as follows: opening CSF pressure recorded in 14 patients was 29 cm H_2O (range 17–50 cm H_2O); total cell count 157/mm^3 (range 20 – 620 cells/mm^3); lymphocytes 93% (range 68–100%); protein level 1.96 g/L (range 0.4 – 5 g/L); glucose level 0.4 mmol/L (range 0.2–4.1 mmol/L) and CSF/serum glucose ratio, recorded in 19 cases was 0.29 (range 0.02– 0.61). Amongst the 33 patients with TBM, CSF microscopy was positive for acid-fast bacilli (AFB) in 17 patients (51%), whilst CSF cultures were positive for *Mycobacterium tuberculosis* (*MTB*) in seven of these patients (21%). In the study of van Well et al. (2009), *M. tuberculosis* was isolated from the CSF of only 12% of patients.

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The results of this study were mostly according to the typical pattern of CSF. Leukocytes > 5 cells/mm^3, protein > 100 mg/dl, CSF glucose as percentage of corresponding blood glucose < 50%, and increased mononuclear cells were present in 91.30%, 68.96%, 77.78%, and 82.12% of the patients, respectively. Acid fast stain for *Mycobacterium tuberculosis* was positive in only 5.26% of patients, while PCR for *Mycobacterium tuberculosis* was positive in 26.09% of the patients. CSF culture for *Mycobacterium tuberculosis* was performed in 14 patients, but all were negative.

6.4 Radiological examinations

According to Thwaites et al. (2005) about 50% while according to Donald et al. (2004) 50 – 80% of patients with TBM have chest X-rays suggesting active or previous pulmonary tuberculosis.

In the study of Farinha et al. (2000) 40%, while in the study of Yaramis et al. (1998) 87% of the chest X-rays were abnormal. In our study 75.86% of the patients had abnormal chest X-rays.

According to Farinha et al. (2000), 94% of TBM children had hydrocephalus and 33.33% of the patients had evidence of cerebral infarction demonstrated on cranial CT scan on admission. While in the study of Yaramis et al. (1998), cranial CT showed 80% of the patients with hydrocephalus, 26% with parenchymal disease, and 15% with basilar meningitis.

In this study 86.67% of the patients had abnormal finding in the CT scan. Hydrocephalus, cerebral infarction, cerebral edema, and basal arachnoiditis were present in 73.33%, 33.33%, 33.33%, and 26.67% of the patients, respectively.

Only one patient who was demonstrated hydrocephalus by MRI because he was in a severe stage. This patient was in stage III of TBM on admission and had underlying diseases of pulmonary TB and pneumonia. This patient also had seizures, sustained clonus, and neurological sequelae (i.e. hemiplegia and blindness).

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6.5 Neurological sequelae and Complications of TBM

In the study of van Well et al. (2009), cranial nerve palsies occurred in 27%, vision was affected in 14%, and hearing in 16% of the children. Only 16% of patients did not have sequelae, 71% had any type of sequelae, and 13% of the children died as a consequence of TBM.

According to the study by Farinha et al. (2000), the overall mortality rate was 13%. All patients died of complications associated with TBM. All of the patients who died were in stage III on admission. Permanent neurological sequelae were observed in 47% of patients. None of the patients who received BCG had severe sequelae or died.

Yaramis et al. (1998) has stated that 23% of TBM patients died. Sixty-three percent of deaths were of children age 5 years or younger.

Other studies in the literature showed normal outcome in 11% to 61%, sequelae in 13% to 75%, and death in 7% to 57% (Farinha et al., 2000; Yaramis et al., 1998; Paganini et al., 2000; Lee et al., 2000; Doerr et al., 1995; Girgis et al., 1998; Delage et al., 1979; Kumar et al., 2005).

According to this study, 3 patients (10%) died; but only 1 patient (3.33%) died due to TBM. Other two patients did not die due to TBM, but instead died due to *Candida albicans* septicemia and severe bacterial pneumonia. All of the 3 dead patients had a history of BCG vaccination. Out of these 3 patients, one had BCG scar, one did not have BCG scar, and one had no available data about the presence of BCG scar. The patient who died due to TBM did not have available data about the presence of BCG scar. She had a history of contact with pulmonary TB patient (her grandmother) in her family. She had fever, vomiting, and severe clinical manifestations, like seizures, bulging anterior fontanelle, hydrocephalus, sustained clonus, and papilledema on admission.

Fifty percent of our patients had neurological sequelae. 33.33% of the patients had temporary while 16.67% had permanent sequelae. Among the neurological sequelae, most of the patients had hearing loss (20%) and blindness (16.67%).

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6.6 Treatment

In a study by van Well et al. (2009), they used an intensive short-course regimen of daily isoniazid (20 mg/kg), rifampicin (20 mg/kg), pyrazinamide (40 mg/kg), and ethionamide (20 mg/kg) for 6 months.

Wani et al. (2008) started the treatment with 4 drugs daily, i.e. isoniazid 5 mg/kg/day (maximum 300 mg/day), rifampicin 10 mg/kg/day, pyrazinamide 25 mg/kg/day, and ethambutol 20 mg/kg/day or streptomycin 20 mg/kg/day (maximum 1 g/day) for 2 months; and isoniazid and rifampicin daily for 4 to 24 months depending upon the response.

Yaramis et al. (1998) treated the TBM patients with a 12-month regimen, initially with isoniazid, rifampin, and pyrazinamide or streptomycin, and changed to only two drugs (isoniazid and rifampin) after 2 months of therapy.

In a study conducted in QSNICH by Sunakorn et al. (1980), all the patients were treated with anti-TB regimen of 6 months daily isoniazid (15 mg/kg/day), rifampicin (15 mg/kg/day), and ethambutol (15 mg/kg/day), with the addition of streptomycin (20 – 40 mg/kg/day) in the first 2 months.

According to this study, most of the patients used anti-TB drugs for 6 (27.78%) and 9 (38.89%) months. According to recent guidelines of British Infectious Society, anti-TB drugs should be given to TBM patients for a minimum of 12 months (Thwaites et al., 2009). American Academy of Pediatrics recommends using anti-TB drugs for 9 – 12 months in TBM patients (Red Book, 2009). But a systematic review and meta-analysis concluded that six months of treatment were probably sufficient for TBM, provided the likelihood of drug resistance was low (van Loenhout-Rooyackers et al., 2001).

In this study, isoniazid and rifampicin were used in 96.67% of the patients (one patient or 3.33% had allergy with isoniazid and rifampicin), while 66.67% patients used the regimen of isoniazid + rifampicin + pyrazinamide + streptomycin. But according to the recent guidelines of British Infectious Society, ethambutol is preferred over streptomycin as the fourth drug in the treatment of TBM (Thwaites et al., 2009).

The only second line drug used was ofloxacin in 10% of the patients. The highest doses of isoniazid, rifampicin, pyrazinamide, streptomycin, and ethambutol

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used for these patients were 13, 20, 35, 27, and 27 (mg/kg/day), respectively. In contrast to van Well et al. (2009), who used isoniazid in a higher dose of 20 mg/kg/day, the dose range of isoniazid in this study was between 7 and 13 mg/kg/day with very good results. This may show that increasing the dose of isoniazid can not decrease the rate of death or neurological sequelae in TBM patients.

Well et al. (2009), Wani et al. (2008), and Yaramis et al. (1998) used steroid in 68%, 89.47%, and 100% of the patients, respectively. In this study 90% of the patients received steroids. But according to the recent guidelines of British Infectious Society, all patients with TBM should receive adjunctive corticosteroids regardless of disease severity at presentation (Thwaites et al., 2009). In the same way, American Academy of Pediatrics also recommends to use adjunctive corticosteroids in children for the treatment of TBM (Red Book, 2009).

In the study of van Well et al. (2009), 18% of the patients received ventriculo-peritoneal shunt (VP shunt). While in the Turkish study (Yaramis et al., 1998) of 172 cases with hydrocephalus, 140 (81%) underwent surgical management. According to Farinha et al. (2000), neurosurgical procedures were performed in 73% of the patients, while in this study 30% of the patients received VP shunt. As UK and Turkey are more advanced than South Africa and Thailand, increased number of VP shunts done for TBM patients in these advanced countries may be due to the availability of more surgical facilities in the hospital.

All the 3 patients who died were using steroids as adjuvant therapy, while 2 out the 3 dead patients received VP shunt. This may not show the ineffectiveness of steroids, but may be confounded by severity. Because severe patients were likely to be treated with steroids and VP shunt.

In table 6.1 the study by Sunakorn et al. (1980) was compared with this study. The study by Sunakorn et al. was also done in Children's Hospital (old name of QSNICH). The number of patients in this study was more than the previous study (by Sunakorn et al. 1980). In contrast to the previous study, more patients were in stage I than in stage II in this study. Permanent sequelae were observed more in the previous study (56.25%) than in this study (16.67%). This may be due to the reason that more patients in this study were in stage I of TBM. The patients came earlier and the experienced doctor can detect the disease in early stage.

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6.1 Comparison of the study by Sunakorn et al. (1980) and this study

Variable	Sunakorn et al. (1980)	This study
Number of the patients	16	30
Age group	70% < 3years old	70% < 5 years old
Stage I, n(%)	1 (6.25)	12 (40)
Stage II, n(%)	9 (56.25)	8 (26.67)
Stage III, n(%)	6 (37.5)	10 (33.33)
Duration of therapy with anti-TB drugs	6 months	6 mos (27.78%) and 9 mos (38.89%)*
Anti-TB drug regimen(s) used	INH+RIF+EMB+SM	Different regimens
Second line anti-TB drugs used, n(%)	0 (0.00)	3 (10.00)
Permanent sequelae, n(%)	9 (56.25)	5 (16.67)
Permanent sequelae in stage I, n(%)	0 (0.00)	0 (0.00)
Permanent sequelae in stage II, n(%)	3 (33.33)	2 (40.00)
Permanent sequelae in stage III, n(%)	6 (66.67)	3 (60.00)
Mortality rate, n(%)	1 (6.25)	3 (10.00)**

* Some of the patients used anti-TB drugs for 11 mos (11.11%), 12 mos (16.67%), and 18 mos (5.56%).
** Only one patient (3.33%) died due to TBM. Other 2 patients died due to other diseases (one patient due to *Candida albicans* septicemia, while the other died due to severe bacterial pneumonia).

6.7 Limitations of the study

The main limitation of this study was its retrospective design. Information bias can not be avoided by using that design and by taking data from medical records. The other limitation of the study was the missing data, because it is an unavoidable part of a retrospective design study.

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CHAPTER VII
CONCLUSION

Thirty TBM patients who admitted to QSNICH during a period of 9 years (2003 – 2009) were retrospectively studied. A significant decrease in the cases of TBM admitted to QSNICH in the recent years was demonstrated.

Forty percent of the children were in Stage I, 26.67% in stage II, and 33.33% in stage III. Most of the patients came with fever (83%) and weakness (61%), followed by neck stiffness, headache, vomiting, and seizures in 53, 53, 43, and 40 percent of the patients, respectively. The patients in this study had less vomiting and seizures. Most of the patients (96%) had a positive history of BCG vaccination. Tuberculin skin test was positive in 70.37% of the patients.

The diagnostic criteria of TBM in this study were mostly according to the typical pattern of CSF analysis. Leukocytes > 5 cells/mm^3, protein > 100 mg/dl, and CSF glucose as percentage of corresponding blood glucose < 50% were present in 91, 69, and 78 percent of the patients, respectively. PCR technique is more valuable than AFB stain in detecting *M. tuberculosis* in CSF. PCR of CSF for *MTB* was positive in 26% of the patients, while AFB stain of CSF was positive in 5% of the patients. Culture of CSF for *M. tuberculosis* was negative in all the patients.

Ten percent of the patients died, but only 3% (one patient) died due to TBM. All of the dead patients had hyponatremia (one patient had moderate while 2 other patients had severe hyponatremia) and acidosis.

Survival rate of TBM in this study was 90% with 50% neurological sequelae, including 17% permanent sequelae.

Short duration of 6-month and 9-month of first line anti-TB drugs were prescribed in 28 and 39 percent of the TBM patients. Sixty-seven percent of the patients used the regimen of INH + rifampicin + pyrazinamide + streptomycin. Second

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line anti-TB drugs were used in only 3% of the patients. Ninety percent of the patients received steroids, while 30% of the patients received VP shunt.

The result of this study emphasizes the clinicians to diagnose TBM in its early stage using fever, a history of TB contact, abnormal CSF profile etc. and provide early appropriate management to prevent the severity and therefore the sequelae of the disease. However, more studies, especially prospective studies, are needed for better diagnosis and outcome of the treatment of TBM.

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APPENDICES

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APPENDIX A

CASE RECORD FORM (CRF)

Sample Number: _ _

Date of collection: _ _ / _ _ / _ _

By:

A Basic – Demographic Data

1 Date of admission (dd/mm/yy) : _ _ / _ _ / _ _

2 Date of discharge (dd/mm/yy) : _ _ / _ _ / _ _

3 Date of birth (dd/mm/yy) : _ _ / _ _ / _ _

4 Date of first diagnosis of TB meningitis (dd/mm/yy): _ _ / _ _ / _ _

5 Sex : □ M □ F

6 Weight : [_ _ . _] kg □NA

7 Height : [_ _ _] cm □NA

8 Referred from : □ Other hospital, specify: ----------

□ Clinic □ Home □ Others

9 Admission Diagnosis : □ ----------

□ ----------

10 Final Diagnosis : □ ----------

11 Stage of TBM on admission : □ I □ II □III □ NA

B History

1 Underlying disease(s) : □ HIV/AIDS □ Pulmonary TB

□ Others, specify: ----------

□ None □NA

2 Immunosuppressive therapy : □ Corticosteroids □ None

□ Others, specify: ---------- □NA

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3	History of BCG vaccination	:	□ Y	□ N	□NA
4	Breastfed (if age of the patient ≤ 2 years)	:	□ Y	□ N	□NA
5	Weight loss (within last 6 months)	:	□ Y	□ N	□NA
6	Presence of malnutrition	:	□ Y, 1st degree	□ Y, 2nd degree	
			□ Y, 3rd degree	□ N	□NA
7	Cough	:	□ Y	□ N	□NA
8	Headache	:	□ Y	□ N	□NA
9	Night sweat	:	□ Y	□ N	□NA
10	Vomiting	:	□ Y	□ N	□NA
11	Abdominal complaints	:	□ Y	□ N	□NA

C Family history:

1	Contact with sputum-smear-positive TB patient	:	□ Y	□ N	□NA
2	Mother's race	:	□ Thai	□ Non-Thai	
			□ Mixed		□NA
3	Father's race	:	□ Thai	□ Non-Thai	
			□ Mixed		□NA
4	Type of place for living	:	□ House	□ One room	□ Camp
			□ Other, specify: ----------		□ NA
5	Chronic diseases in family/household members	:	□ HIV/AIDS	□ Pulmonary TB	
			□ Chronic cough (COPD)	□ None	
			□Others, specify:----------		□NA

□ If present, specify the relationship: --------

D Clinical Manifestations (on admission)

1	Conscious level	:	□Good conscious □ Confused □ Delirious □ Somnolent □ Obtunded □Stuporous □ Comatose □NA
2	Glasgow Coma Scale	:	[_ _] score
3	Fever (>37.5°C)	:	□ Y □ N □NA

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4	Seizures	:	□ Y	□ N	□NA
5	Neck stiffness	:	□ Y	□ N	□NA
6	Kernig's sign	:	□ Pos	□ Neg	□NA
7	Brudzinski's sign	:	□ Pos	□ Neg	□NA
8	Bulging anterior fontanelle	:	□ Y	□ N	□NA
9	Hydrocephalus	:	□ Y	□ N	□NA
10	Sustained clonus	:	□ Y	□ N	□NA
11	BCG scar	:	□ Y	□ N	□NA
12	Photophobia	:	□ Y	□ N	□NA
13	Papilledema	:	□ Y	□ N	□NA
14	Weakness	:	□ Y	□ N	□NA
15	Anorexia	:	□ Y	□ N	□NA
16	Systolic BP (mmHg)	: Highest ……..		Lowest ……..	□NA
17	Diastolic BP (mmHg)	: Highest ……..		Lowest ……..	□NA
18	Heart Rate/Pulse (x/min)	: Highest ……..		Lowest ……..	□NA
19	Respiratory rate (x/min)	: Highest ……..		Lowest ……..	□NA
20	Body temperature (°C)	: Highest ……..		Lowest ……..	□NA
21	Body temperature	: □ Oral	□ Rectal	□Axillary	□NA

E Neurological sequelae observed in the patient

1	Motor disorders				
	Hemiparesis	:	□Y (Permanent)	□ Y (Temporary)	□ N □NA
	Hemiplegia	:	□Y (Permanent)	□ Y (Temporary)	□ N □NA
	Quadriplegia	:	□Y (Permanent)	□ Y (Temporary)	□ N □NA
2	Visual loss				
	Blindness	:	□Y (Permanent)	□ Y (Temporary)	□ N □NA
	Reduced vision	:	□Y (Permanent)	□ Y (Temporary)	□ N □NA
3	Hearing loss	:	□Y (Permanent)	□ Y (Temporary)	□ N □NA
4	Speech problems	:	□Y (Permanent)	□ Y (Temporary)	□ N □NA

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5 Facial nerve palsy : □Y (Permanent) □ Y (Temporary) □ N □NA

6 Mental retardation : □ Y □ N □NA

F Investigations:

F-1 Laboratory results (Blood/serum)

F-1A Complete Blood Count (CBC)

Date(dd/mm/yy)	_ _ / _ _ / _ _	_ _ / _ _ / _ _	_ _ / _ _ / _ _	_ _ / _ _ / _ _	_ _ / _ _ / _ _
Total leukocyte count (/mm^3)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Neutrophils (%)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Lymphocytes (%)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Monocytes (%)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Eosinophils (%)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Basophils (%)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Hemoglobin (g/dl)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Platelet count (/mm^3)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA

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F-1B Blood Biochemistry

Date(dd/mm/yy)	_ _/_ _/_ _	_ _/_ _/_ _	_ _/_ _/_ _	_ _/_ _/_ _	_ _/_ _/_ _
K (mmol/L)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Na (mmol/L)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Cl (mmol/L)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
HCO_3^- (mmol/L)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Ca (mmol/L)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Blood sugar (mg/dl)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
BUN (mg/dl)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Creatinine serum (mg/dl)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Total Bilirubin (mg/dl)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
AST (U/L)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
ALT (U/L)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
AP (U/L)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
GGT (U/L)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA

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F-1C Erythrocytes Sedimentation Rate (ESR)

Date(dd/mm/yy)	_ _ / _ _ / _ _	_ _ / _ _ / _ _	_ _ / _ _ / _ _	_ _ / _ _ / _ _	_ _ / _ _ / _ _
ESR (mm/hour)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA

F-2 Tuberculin test : □ Pos □ Neg □NA

F-3 RBC morphology : □ Normal □NA

□ Abnormal, define: ----------

F-4 CSF profiles

Date(dd/mm/yy)	_ _ / _ _ / _ _	_ _ / _ _ / _ _	_ _ / _ _ / _ _	_ _ / _ _ / _ _	_ _ / _ _ / _ _
Appearance	□ Colorless □ Turbid □Straw color □Brown □ Red □NA	□ Colorless □ Turbid □Straw color □Brown □ Red □NA	□ Colorless □ Turbid □Straw color □Brown □ Red □NA	□ Colorless □ Turbid □Straw color □Brown □ Red □NA	□ Colorless □ Turbid □Straw color □Brown □ Red □NA
Opening pressure (cmH_2O)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Closing pressure (cmH_2O)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Total white cells count (cells/µL)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
PMN (%)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Mononuclear cells (%)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA

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F-4 CSF profiles (cont.)

Date(dd/mm/yy)	_ _ / _ _ / _ _	_ _ / _ _ / _ _	_ _ / _ _ / _ _	_ _ / _ _ / _ _	_ _ / _ _ / _ _
RBC (cells/µL)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Glucose CSF/Blood (mg/dl)	[ ] / [ ] □NA	[ ] / [ ] □NA	[ ] / [ ] □NA	[ ] / [ ] □NA	[ ] / [ ] □NA
Pandy test	□Pos □ Neg □ NA	□Pos □ Neg □ NA	□Pos □ Neg □ NA	□Pos □ Neg □ NA	□Pos □ Neg □ NA
Protein (mg/dl)	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA	[ ] □NA
Acid fast stain	□Pos □ Neg □ NA	□Pos □ Neg □ NA	□Pos □ Neg □ NA	□Pos □ Neg □ NA	□Pos □ Neg □ NA
PCR for *M. tuberculosis*	□Pos □ Neg □ NA	□Pos □ Neg □ NA	□Pos □ Neg □ NA	□Pos □ Neg □ NA	□Pos □ Neg □ NA

F-5 Radiologic investigations

1 Abnormalities in Chest X ray : □ Y, describe:

PA: ----------

Lateral: ----------

□ N □NA

2 Abnormalities in CT scan **:** □ Hydrocephalus □Basilar arachnoiditis

□ Cerebral infarction □ Cerebral edema

□ Tuberculoma

□ Other, specify: ----------

□ Normal CT scan □NA

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3 Abnormalities in MRI : □ Hydrocephalus □Basilar arachnoiditis
□ Cerebral infarction □Cerebral edema
□Tuberculoma
□ Other, specify: ----------
□ Normal MRI □ NA

G Source(s) of culture for *M. tuberculosis*

Specimen	**CSF**	**GW**	**Sputum**	**BAL**
Request for C/S	□ Y □ N □NA	□ Y □ N □NA	□ Y □ N □NA	□ Y □ N □NA
Result	□Pos □ Neg □ NA	□Pos □ Neg □ NA	□Pos □ Neg □ NA	□Pos □ Neg □ NA

H Treatment

1 Anti TB drugs in intensive phase : □ INH, RIF, PZA □ INH, RIF, PZA, SM
: □ INH, RIF, PZA, EMB
□ Others, specify: ---------- □NA

2 Dosage of INH : □First dose: [ ] mg/kg □NA
□ Second dose (if first dose is changed): [ ]mg/kg

3 Dosage of RIF : □First dose: [ ] mg/kg □NA
□ Second dose (if first dose is changed): [ ] mg/kg

4 Dosage of PZA : □ First dose: [ ] mg/kg □NA
□ Second dose (if first dose is changed): [ ]mg/kg

5 Dosage of SM : □First dose: [ ] mg/kg □NA
□ Second dose (if first dose is changed):[ ] mg/kg

6 Dosage of EMB : □First dose: [ ] mg/kg □NA
□ Second dose (if first dose is changed): [ ]mg/kg

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7 Allergy to any anti-TB drug(s) : □ Y, specify: ----------

□ N □NA

8 Was the second line anti TB drugs used? : □ Y, specify (with dose): ----------

---

□ N □NA

9 Course of anti-TB therapy : □ 6 mos □ 9 mos □ 10 mos

: □ 12 mos □ More, specify: [_ _] mos

□ NA

10 Corticosteroids : □ Used, specify: ----------

Date of start: _ _ / _ _ / _ _

Date of discontinuation: _ _ / _ _ / _ _

□ Not used □NA

11 Acetazolamide : □ Used □ Not used □NA

12 Diuretics : □ Used, specify: ----------

□ Not used □NA

13 Anticonvulsants : □ Used, specify: ----------

□ Duration of usage: [ ] days

□ Not used □NA

14 Concomitant medication(s) : □ Used, specify: ----------

□ Not used □NA

15 Ventriculoperitoneal shunting : □ Y □ N □ NA

16 Ventriculoatrial shunting : □ Y □ N □ NA

I Outcome

1 Death : □ Y, define the cause: ----------

Date of death: __ __/__ __/__ __

□ N □NA

Was death directly related to TBM?

□Y □N □ NA

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2	Sequelae	:	□ Y, mild □ N	□ Y, moderate	□ Y, severe □ NA
3	Death and severe sequelae	:	□ N		□ NA
4	Complete recovery	:	□ Y	□ N	□ NA
5	Self discharged (against advice)	:	□ Y	□N	□ NA

Abbreviations:

- Y Yes
- N No
- M Male
- F Female
- Neg Negative
- Pos Positive
- NA Data Not Available
- CSF Cerebrospinal fluid
- GW Gastric washing
- BAL Broncho-alveolar lavage
- DLC Differential Leukocyte Count
- C/S Culture and sensitivity
- INH Isoniazid
- RIF Rifampicin
- PZA Pyrazinamide
- SM Streptomycin
- EMB Ethambutol
- PCR Polymerase chain reaction
- AFB Acid fast bacilli
- BUN Blood urea nitrogen
- BCG Bacillus Calmette-Guérin
- PMN Polymorphonuclear (leukocytes)

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- Mos Months
- Na Sodium
- Cl Chloride
- K Potassium
- Ca Calcium
- HCO_3^- Bicarbonate
- AST Aspartate aminotransferase
- ALT Alanine aminotransferase
- AP Alkaline phosphatase
- GGT γ-Glutamyltransferase

Comments:

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APPENDIX B
NORMAL VALUES FOR BLOOD AND CSF EXAMINATIONS

CBC (complete blood count)

Analyte	Normal value
Total leukocyte count (/mm^3)	
Birth	9,000 – 30,000
24 hours	9,400 – 34,000
1 month	5,000 – 19,500
1 – 3 years	6,000 – 17,500
4 – 7 years	5,500 – 15,500
8 – 13 years	4,500 – 13,500
Adult	4,500 – 11,000
Neutrophils (%)	
Bands	3 – 5
Segs	54 – 62
Lymphocytes (%)	25 – 33
Monocytes (%)	3 – 7
Eosinophils (%)	1 – 3
Basophils (%)	0 – 0.75
Hemoglobin (g/dl)	
1 – 3 days	14.5 – 22.5
2 months	9.0 – 14.0
6 – 12 years	11.5 – 15.5
12 – 18 years (male)	13.0 – 16.0
12 – 18 years (female)	12.0 – 16.0

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CBC (complete blood count) (cont.)

Analyte	Normal value
Platelet count (/mm^3)	
Newborn (after 1 week same as adult)	84,000 – 478,000
Adult	150,000 – 400,000

Source: Nelson Textbook of Pediatrics, 2007

Blood Biochemistry

Analyte	Normal value
K (mmol/L)	
< 2 months	3.0 – 7.0
2 – 12 months	3.5 – 6.0
> 12 months	3.5 – 5.0
Na (mmol/L)	
Newborn	134 – 146
Infant	139 – 146
Child	138 – 145
Thereafter	136 – 146
Cl (mmol/L)	
Newborn	97 – 110
Thereafter	98 – 106
HCO_3^-, venous (mmol/L)	22 – 29
Ca, ionized (mmol/L)	
Newborn, 3 – 24 hours	1.07 – 1.27
24 – 28 hours	1.00 – 1.17
Thereafter	1.12 – 1.23

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Blood Biochemistry (cont.)

Analyte	Normal value
Ca, total (mmol/L)	
Newborn, 3 – 24 hours	2.3 – 2.65
24 – 28 hours	1.75 – 3.00
4 – 7 days	2.25 – 2.73
Child	2.20 – 2.70
Thereafter	2.10 – 2.55
Blood sugar (mg/dl)	
1 day	40 – 60
>1 day	50 – 90
Child	60 – 100
Adult	70 – 105
BUN (mg/dl)	
Newborn	3 – 12
Infant or child	5 – 18
Thereafter	7 – 18
Creatinine (mg/dl)	
Newborn	0.3 – 1.0
Infant	0.2 – 0.4
Child	0.3 – 0.7
Adolescent	0.5 – 1.0
Adult (male)	0.6 – 1.2
Adult (female)	0.5 – 1.1
AST (U/L)	
0 – 5 days	35 – 140
1 – 9 years	15 – 55
10 – 19 years	5 – 45

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Blood Biochemistry (cont.)

Analyte	Normal value
ALT (U/L)	
0 – 5 days	6 – 50
1 – 19 years	5 – 45
Alkaline phosphatase (U/L)	
1 – 9 years	145 – 420
10 – 11 years	130 – 560
12 – 13 years (male)	200 – 495
12 – 13 years (female)	105 – 420
14 – 15 years (male)	130 – 525
14 – 15 years (female)	70 – 230
16 – 19 years (male)	65 – 260
16 – 19 years (female)	50 – 130

Source: Nelson Textbook of Pediatrics, 2007

Normal CSF values

Analyte or procedure	Normal value
Pressure (cm H_2O)	5 – 8
Leukocytes (/mm^3)	<5
Differential leukocyte count	≥75% lymphocytes
Protein (mg/dl)	20 – 45
Glucose (mg/dl)	>50 (or 75% serum glucose)

Source: Nelson Textbook of Pediatrics, 2007

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APPENDIX C
BMRC CRITERIA

BMRC (British Medical Research Council) criteria are used to determine the severity of TBM. These criteria were first introduced in 1947.

According to BMRC criteria, TBM patients are classified into 3 stages. According to Farinha et al. (2000), these stages are:

Stage I (early stage): In this stage patients are fully conscious and present with non-specific symptoms.

Stage II (intermediate stage): In this stage patients have minor neurological signs without marked alterations in consciousness, a condition between stage I and stage III.

Stage III (advanced stage): In this stage patients present with major neurological signs with marked alteration in consciousness or coma. (Farinha et al., 2000)

While van Well et al. (2009) have staged TBM using the modified criteria of the British Medical Research Council to determine the severity of TBM.

Stage I: TBM (Glasgow coma scale 15 with no focal neurologic signs).

Stage II: TBM (Glasgow coma scale 11–14 or Glasgow coma scale of 15 with focal neurologic deficit).

Stage III: TBM (Glasgow coma scale <11).

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APPENDIX D
STATEMENT ABOUT PUBLICATION

Publication of this study will follow rules of Faculty of Tropical Medicine Mahidol University, Faculty of Graduate Studies Mahidol University, and Queen Sirikit National Institute of Child Health, including all necessary official permissions.

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