Introduction
Tuberculosis (TB) is a major public-health problem with around 9 million new cases and 2 million deaths estimated to occur each year. About one-third of the world’s population has latent TB with a lifetime risk of TB disease of 10%. However, among those co-infected with HIV and latent TB infection, the risk for TB reactivation is 10% per year. Tuberculous meningitis is the most severe form of extra pulmonary tuberculosis. Its exact incidence and prevalence are not known in resource poor countries but in developed countries it ranges between 0 and 1 per 100,000 population. In South Africa, the incidence of TB in Western Cape province was 24 per 100,000 population among children aged 0 to 4 years for the period of 1985-1987. The high prevalence of HIV and TB in this region led to a rise in TB. In the Western Cape province, TB was the leading cause of meningitis among children below 13 years of age.

Diagnosis of TB is complicated because of its non-specific clinical presentation which may be acute, subacute or chronic. It may be febrile or afebrile. The signs and symptoms of stage 1 TB disease are non-specific and relate more to primary lung infection than neurological disease. TB mainly affects young children with the mean age ranging between 23 and 49 months. Diagnosis requires a high index of suspicion from the clinician. The Mantoux test is positive in only 30 to 50% and chest X-ray is normal in 20-50% of cases. Although radiological tests such as brain Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) are helpful, they may be normal in early stages and are not widely available in resource limited settings. Lumbar cerebrospinal fluid (CSF) is the most valuable test. The CSF proteins are elevated and may be markedly raised to 0.4 g/L.
to 5.0g/L secondary to hydrocephalus and spinal block. However, ventricular CSF may record normal chemistry and cells if drawn from a site proximal to the inflammation and obstruction. Leukocytes in CSF are increased to 10-500 cells/mm³, with majority having lymphocyte predominance. However, neutrophils may predominate initially which can confuse the picture. The gold standard in diagnosis of TBM is positive culture of Mycobacterium tuberculosis from CSF which has both a long turn around time and a low smear and mycobacteria culture positive rate except if 10 to 20ml of CSF are supplied to the laboratory.12 Newer tests like the GeneXpert with a quick turn around time have been found to have a high sensitivity on sputum even in children.13 However, studies show a reduced sensitivity of GeneXpert in CSF compared to sputum.14

Other tests that would support TBM diagnosis like sputum or gastric aspirates also have low culture yields.5 To standardize diagnosis, a consensus case definition using clinical presentation, laboratory and radiological findings was made to guide clinicians and researchers.15 Outcome of TBM is generally poor with mortality among children ranging between 13-69%9,16,17 Younger age, tonic posturing, papilloedema, focal neurological deficit and stage at presentation were found to affect the prognosis.16,17

Red Cross War memorial Children’s Hospital (RCWMCH) is a high TB and HIV burden setting with the prevalence of HIV and TB of 27.6% and 16.7% respectively among admitted patients on general paediatric wards.18 With this high prevalence, there was a need to document the diagnosis and treatment outcome of TBM in this hospital. We set out to describe our experiences in the presentation, diagnostic rigor, treatment and outcome of TBM at discharge from RCWMCH in the year 2009.

Methodology

This retrospective study was conducted at RCWMCH, a tertiary referral hospital affiliated to the University of Cape Town in South Africa. The study was approved by the Research ethics Committee of the University of Cape Town. The entry point was the hospital database which was used to generate a list of children who had been diagnosed with TBM from 1st January 2009 to 31st December 2009. The clinical notes of these patients were reviewed and relevant clinical data relating to the presentation, diagnosis, management and outcome of the children extracted using a pre-tested, pre-coded study tool.

We obtained the results of radiological examinations such as chest radiographs and brain CT scans or MRIs from the patient folders. Laboratory results were extracted from the National Health Laboratory Services electronic database. These included cerebrospinal fluid chemistry, microscopy, mycobacterial culture and antibiotic sensitivity, HIV test, sputum microscopy and mycobacterial culture results. The recently published consensus case definition of TBM was used to evaluate diagnostic certainty.15 This diagnostic criteria uses the clinical presentation and diagnostic tests to categorize TBM into Definitive, Probable, Possible and No TBM. Those who had a diagnosis of TBM in the folder but did not qualify according to the consensus case definition were excluded. Definite TBM was considered when Mycobacterium tuberculosis is isolated from CSF. Probable and Possible TBM were diagnosed according to consensus case definition for TBM for use in future clinical research.15 Probable TBM was considered when: 1) a patient presented with clinical features of meningitis and 2) suggestive CSF findings of TBM (total white cell count >5 cells×10⁶/L, protein >0.45 g/L and glucose <2.2 mmol/L), plus 3) one or more of the following: i) chest radiograph findings consistent with pulmonary TB, ii) an extra-meningeal specimen positive for AFB, iii) other evidence of extra-meningeal TB (e.g. abdominal ultrasound features) or iv) brain computed tomography (CT) evidence of TBM including one or more of the following: basal meningeal enhancement, hydrocephalus or infarctions. Possible TBM was diagnosed when: 1) a patient presented with clinical features of meningitis and either 2) four or more of the following were present i) a history of TB ii) a predominance of CSF lymphocytes (>50%), iii) illness duration of more than five days iv) CSF glucose <2.2 mmol/L, v) altered consciousness, vi) clear or yellow CSF with protein>1 g/L, vii) focal neurological signs, or 3) “markedly abnormal” CSF (excluding isolated hypoglycemia) with evidence of TB elsewhere.

For children who were transferred to other hospitals in Cape Town to complete their treatment, those hospitals were visited and their treatment outcomes at discharge recorded. The outcome of treatment variables were improvement with / without neurological sequelae, or death. Poor outcome was defined as death or neurological sequelae at discharge. The neurological sequelae were obtained from the doctors’ notes and it included physical neurological sequelae. The Mantoux skin test is regarded as reactive as defined
by guidelines of the World Health Organization: in high risk children (including HIV-infected children and severely malnourished children), >5 mm of induration, and in all other children (whether they have received a BCG vaccination or not), >10 mm of induration.19

TBM staging was undertaken using the modified criteria of the British Medical Research Council: 20 in which TBM Stage I is defined as (Glasgow Coma Scale (GCS) 15 with no focal neurologic signs), TBM stage II is (GCS 11–14 or GCS of 15 with focal neurologic deficit) and TBM stage III is (GCS <11).

Statistical Analysis
Data was entered anonymously into an excel spreadsheet. To assess the accuracy of the data entered, a random sample of the original forms was compared with a computer print-out. Data was analyzed using STATA statistical package (StataCorp, Version 11). Descriptive analysis using medians with inter-quartile ranges (IQR) are described for continuous variables that are not normally distributed while means and standard deviations (SD) are used for normally distributed data. For categorical variables, proportions are depicted as percentages of cases for which data is available. Data were tested for normality and the appropriate statistical test was used to test for strength of association.

Results
Of 22,943 children admitted to RCWMCH during the study period, we identified 40 children newly diagnosed with TBM; an incidence rate of 1.7 per 1000 admissions. The median age was 32 months (IQR 9-78.5) ranging from 6 weeks to 12 years. The male: female ratio was 1:1. Clinical features present at admission are summarized in table 1.

| Presentation                        | Frequency* | Percentage |
|-------------------------------------|------------|------------|
| History of Fever                    | 25/30      | 83%        |
| Temperature above 37.5°C            | 14/38      | 37%        |
| Altered level of consciousness      | 23/32      | 72%        |
| Convulsions                         | 12/16      | 75%        |
| Irritability                        | 11/13      | 85%        |
| Poor feeding                        | 17/20      | 85%        |
| TB contact                          | 15/32      | 47%        |
| Headache                            | 14/15#     | 93%        |
| Vomiting                            | 20/28      | 71%        |
| Cough                               | 13/16      | 81%        |
| Difficulty in breathing             | 7/26       | 26%        |
| Failure to thrive                   | 22/25      | 88%        |
| Meningism                           | 23/30      | 77%        |
| Bulging fontanelle                  | 4/8        | 50%        |
| Neurological deficits               | 21/34      | 62%        |
| Admission Fever Duration 1-7 days   | 14         | 74%        |
| (N=19)                              |            |            |
| 7-10 days                           | 5          | 26%        |

*The denominator varies according to available data. #Only those above 4 years

Common features included fever, vomiting, meningism, neurological deficits, altered level of consciousness and failure to thrive. Although 25/30 (83%) had a history of fever, 14/38 (37%) had a temperature of 37.5°C and above, one had 34.5°C and 23/38 (61%) had a normal temperature between 35 and 37.4°C at admission. Of the 32 with data on level of consciousness, only 18 had a record on the Glasgow coma scale. Of these 18, 9 had TBM stage 2 and 9 had TBM stage 3 according to the British Medical Research Council.20

According to the consensus case definition of TBM12, 6 (15%) had definitive TBM, 17 (42%), probable TBM and 18 (44%) possible TBM. Thirty-five patients (87%) were screened for HIV, of whom only 3 (10%) were infected. No patients were receiving antiretroviral therapy (ART) at the time of TBM diagnosis. In addition, two were HIV exposed but their HIV DNA/PCR test was negative. Only 20/40 had available records on immunization and they all had received BCG vaccination.

Table 2 summarizes the CSF results.
Table 2: Cerebrospinal Fluid Findings

| Results                        | Frequency* | Percentage |
|--------------------------------|------------|------------|
| CSF TB culture positive        | 6/22       | 27%        |
| AAFBs negative                | 22/22      | 100%       |
| Raised proteins concentration | 35/38      | 92%        |
| >0.4g/l                        | 38/39      | 97%        |
| Increased cell count >5cells/mm³ | 32/39   | 82%        |
| Neutrophil predominance        | 7/39       | 18%        |

*The denominator varies according to available data, # Only 22 had CSF culture and AAFB

The CSF protein concentration results were available in only 38 out of 40 children. Of these, 92% had raised protein concentration in CSF above 0.4g/l but 23 (62%) had markedly raised proteins above 1.0g/l. Ninety seven percent had above 5 cells /mm³ as shown in table 2 below. Cells were predominantly lymphocytes in 33 (83%). There were no results of blood glucose, but 33/38 (87%) had CSF glucose below 3.0 mmol/l.

Other tests done to make a diagnosis of tuberculosis including Mantoux test, chest X-rays, sputum smear and culture, and CT and MRI are summarized in table 3 below.

Of the 30 who had data on chest X-ray findings, abnormal findings were present in 24 (71%). Seventeen (57%) had findings suggestive of TB which included 5 (29%) with hilar or mediastinal lymphadenopathy, 4 (24%) with miliary picture, 4 (24%) with hilar adenopathy and reticulonodular infiltrates, 2 (12%) with lobar infiltrates, 1 (6%) with consolidation and perihilar infiltrates and 1 (6%) with consolidation and fine nodular opacities like miliary. Other abnormal chest X-ray findings included 3 with isolated right upper lobe consolidation, 3 with peri-hilar and hilar infiltrates and pneumonia and 1 with bronco pneumonic picture.

Management and Outcome:

All the children were treated with oral rifampicin, isoniazid, pyrazinamide and ethionamide which is the standard treatment in the country. They all received glucocorticosteroids; 36 (90%) received Prednisolone and 4/40 (10%) received Dexamethazone. Mannitol was administered to 6/40 (15%). They all received glucocorticosteroids; 36 (90%) received Prednisolone and 4/40 (10%) received Dexamethazone. Mannitol was administered to 6/40 (15%). TB treatment was started on day 1 of admission in 25/37 (67.5%), day 2 in 5/37 (13.5%) and day 3 in 7/37 (19%). Three of the patients had no clear records about the date of initiation of TB treatment. Surgery was performed on 10/40 (25%) – an extraventricular drain (EVD) alone was inserted in 3 children, 6 children received a ventriculo-peritoneal (VP) shunt alone and 1 child had both EVD and VP shunt. Six (15%) children with communicating hydrocephalus received serial lumbar punctures to reverse raised intracranial pressure. All 6 children had poor outcome.

Children with poor outcome of death and neurological sequelae had a statistically longer hospital stay with a median of 30 days, IQR 16-40 days while those with good outcome had a median of 5 days, IQR 2-17 days (Mann Whitney p<0.001). From RCWMCH, 2 went...
home, 2 died and 36 were referred to another hospital
to complete their treatment. Of this latter group, 21
were admitted to the local TB hospital, Brooklyn Chest
Hospital and 15 admitted to general hospitals in Cape
Town. Table 4 summarizes the outcome at final hospital
discharge.

| Outcome                                | Frequency | Percentage |
|----------------------------------------|-----------|------------|
| Improved without neurological sequelae. | 15/36     | 42%        |
| Improved with neurological sequelae     | 18/36     | 50%        |
| Died                                   | 3/36      | 8%         |

The outcome of 4 children could not be established
because they were transferred to other hospitals too early
and we did not find the data on outcome at discharge.

The trends noted with poor outcome were having
surgery; (8 versus 1), serial LPs, (6 versus none),
acetazolamine use (7 versus none) and longer mean
hospital stay. There was a strong association between
poor outcome (death and neurological sequelae) and
TB stage 3 on admission, Fischer’s exact test p<0.01.
There was no association found between poor outcome
and other presentations on admission. These included
HIV status, CSF white cell count, age, CSF chemistry
(protein and glucose), microscopy and culture.

The neurological sequelae experienced by the 18
children included hydrocephalus, (11), motor deficits
(11), cranial nerve palsies (9), deafness (2), epilepsy (1),
cortical blindness (1). Twelve of them suffered multiple
sequelae.

Discussion

TBM is a severe disease whose initial presentation in
children is like other common childhood illnesses
resulting in late diagnosis. Although it is usually
associated with poor outcome, our study found better
treatment outcome and several lessons that can be
drawn and applied.

We found a mean age of 48 months and only 11 were
infants under 1 year. This is comparable to what several
studies indicate that TB mainly affects young children
with the mean age ranging between 23 and 49 months.

All the 20 children with immunization records had
BCG vaccine which is not surprising because although
BCG is protective against TBM, studies show that those
who get TB after vaccination have a better treatment
outcome.

RCWMCH has a high HIV prevalence of 27.6% on
general paediatric wards but it was surprisingly low
at 9.7% among those with TBM. Previous studies
showed that HIV is a risk factor for central nervous
system TB. However, Gijs et al also found a low
HIV prevalence of 3.8% among children with TB in
Western cape province. This could be explained by the
high burden of TB in the region such that children are
infected regardless of their HIV status.

We found that TBM in these children presented mainly
with non specific common childhood diseases but
the data on duration was generally deficient. Of the
19 who had duration of fever, all were affected for
less than 10 days. Cough was acute in 8/15 (53%) of
children. Several studies have similar findings of short
duration of symptoms. More severe symptoms like
convulsions and impaired level of consciousness were
present in 12/16 (75%)% and 23/32 (72%) respectively.
These percentages seem high because many did not
have records and it can be hypothesized that the ones
without records most likely did not have the symptoms.
Paradoxically, failure to thrive was present among 22/25
(88%) despite the short duration of symptoms in the
majority. This is similar to Gitz et al’s study. We could
not determine missed opportunities of early treatment
because of the retrospective design. This has been
described by other studies.

Despite the difficulties of diagnosis of TBM, our study
demonstrated that almost all had a diagnosis made by
day 3 of admission. This is because of the high index
of suspicion and also the hospital had access to quick
laboratory and radiological tests which helped make a
quick diagnosis and also start treatment early.

Definite TBM was present in only 15% (Mycobacterium
tuberculosis isolated from CSF). TB culture positive
rates in CSF were lower in this study because only one
sample was used. Daniel et al found that culture positive
rates can go up from 53% on the first specimen to 83%
with the third specimen.

Outcome of treatment

Of the 36 children with available treatment outcome
at discharge from hospital, 15/36, (42%) improved
without neurological sequelae, 18/36, (50%) improved with neurological sequelae and 3/36, (8%) died. Our results were different from Gitz et al in another retrospective study on the outcome of paediatric TBM after 6 months of treatment which was conducted between January 1985 and April 2005 in South Africa. In their study, the clinical outcome of the 554 patients was as follows: normal (16%), mild sequelae (52%), severe sequelae (19%), and death (13%). Unfortunately, we did not grade the neurological sequelae due to the deficient data in our retrospective study. Outcome would also be different at the end of treatment compared to the time of hospital discharge when the neurological outcome is still evolving. The mortality in our study was 8% which is much lower than has been described in other studies where mortality ranges between 13% and 69% even in developed countries. The better outcome in this study may be because all the 37 with records on date of starting antiTB treatment (ATT) had started treatment within 3 days of admission. Early initiation of treatment has been established as the main prognostic factor that predicts disease lethality and sequelae. In addition, only 9 had TBM stage III basing on the GCS although 23 had impaired level of consciousness at admission. Stage III is associated with worse outcome. Availability of radiological tests like CT and MRI which were performed in 36/40 (90%) and were abnormal in 89% of cases further strengthened the diagnosis and then early treatment. Since TB prevalence is high in this region, TBM is always held in high suspicion and treatment was started early with good results.

In addition, the prevalence of HIV was low in the study. HIV was not associated with poor outcome probably because the numbers were very few. HIV co-infection has been associated with poor treatment outcome of TBM in children.

Like in other studies, we found that TBM stage III was associated with increased mortality. Our study was not powered to look for associations but those who had surgery, serial LPs, acetazolamine use and longer mean hospital stay had poor outcome of death and neurological sequelae. Similarly, longer hospital stay has been associated with poor outcome. Misra et al also found that hydrocephalus and shunt surgery were poor prognostic features. The strength of this descriptive study is that we used a retrospective chart review to attain data on a disease known to have very poor outcome and found better outcome than other studies. Our findings suggest that it is possible to reduce mortality and to improve outcome from TBM with rigorous diagnostics and early treatment initiation.

Limitations of our study included the retrospective design in which data recording was not standardized and as such some information was missing. In addition, we used the neurological sequelae recorded by the doctors in the folders which had missing data and could not therefore grade it. Another limitation was with our entry point which was the hospital records department. Some TBM diagnoses may have been missed out just as we found that some codes were in error.

Conclusions
We found that TBM mainly presented with acute non specific symptoms but the rigorous diagnostics helped make a quick diagnosis and start early treatment. Outcome of treatment at discharge was good with less than 10% mortality and half with neurological sequelae at discharge from hospital. Poor outcome was associated with TBM stage III disease.

Recommendations
We recommend a prospective study on the same topic so that the sequelae can be well documented. Since the presentation of TBM is non specific, clinicians in high TB endemic regions should have a high index of suspicion among all children with or without HIV infection. On suspicion of TBM, TB treatment should be started in the first 2 days of admission to improve the outcome.

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