Tuberculous meningitis in HIV negative adult Sudanese patients: clinical presentation and out come of management

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Original Article

Abstract

Although TB most commonly involves the lungs, it can produce disease in nearly every organ system. Nervous system involvement is seen in up to 10% of patients with systemic tuberculosis. In countries with a high incidence of tuberculosis, like Sudan, tuberculous meningitis is typically a disease of young children and uncommon in adults.

Patients and Methods

In Sudan, there is paucity of information regarding the diagnosis and management of CNS tuberculosis. In this longitudinal hospital based study, we included 10 adult patients with tuberculous meningitis. The clinical presentation, laboratory findings including MRI and outcome of treatment were discussed.

Results

Fever, headache, nuchal rigidity and positive Kernig’s signs were found in all patients. Extraneural tuberculosis was found in 6 patients and CSF PCR for tuberculosis was positive in 7 out of 9 patients. Three patients died, 5 recovered with residual deficit and only 2 recovered completely.

Conclusions

Tuberculous meningitis is a serious condition and commonly overlooked especially in HIV negative patients. It is a great mimicker of various neurological conditions. The prognosis depends on the BMRC stage of disease.
Keywords: Tuberculosis, Tuberculous meningitis, Sudan.

Introduction
Tuberculosis is a major cause of morbidity and mortality throughout the world especially in the developing countries. The world health organization estimated that one third of the world’s population is infected with tuberculosis\(^{(1)}\). In 1999 eight million people developed tuberculosis world wide with 2.6 – 2.9 million deaths. The majority of cases occurred in Asia and Africa with increasing number in patients infected with HIV\(^{(2)}\).

Although TB most commonly involves the lungs, it can produce disease in nearly every organ system. Nervous system involvement is seen in up to 10% of patients with systemic tuberculosis\(^{(3)}\). Neurological tuberculosis may develop during primary infection or reactivate as a consequence of immunosuppression. In countries with a high incidence of tuberculosis, tuberculous meningitis is typically a disease of young children that develops 3-6 months after primary infection. In countries with a low incidence, it more commonly affects adults. It may follow primary infection, but more commonly due to reactivation of a dormant sub cortical or meningeal focus\(^{(4)}\). Tuberculomas, the parenchymal form of CNS tuberculosis, occur as single or multiple brain or spinal lesions and present with symptoms and signs of space-occupying lesions. Skeletal TB constitutes 35% of extra pulmonary disease with the spine affected 50-60% of the times\(^{(5)}\). Pott’s disease results from an infection of the bone by the Mycobacterium Tuberculosis bacteria via a combination of haematogenous route and lymphatic drainage. The organism may stay dormant in the skeletal system for an extended period of time before the disease can be detected\(^{(6)}\). Tubercular brain abscesses are very rare. Only 57 cases were reported in the world literature\(^{(7)}\).

The diagnosis of CNS tuberculosis still remains difficult in spite of the advent of the new imaging modalities like CT scan and MRI and the facility of DNA testing. A high index of suspicion is necessary for timely diagnosis and prompt initiation of therapy. AFB smears on CSF are positive in10-90% of patients; sensitivity can be improved if large volumes of CSF from multiple lumber punctures are centrifuged\(^{(8,9,10)}\).

CSF culture for meningitis tuberculosis is positive in 45-90% of cases\(^{(8,9,10)}\). CSF PCR for meningitis tuberculosis has a variable sensitivity and specificity, and therefore should not be used to exclude tuberculous meningitis\(^{(11)}\).

The emergence of drug-resistant strains of meningitis tuberculosis is a serious public health problem. Drug resistance has been reported in Sudan by Sharaf-Eldin et al in smear positive patients\(^{(12)}\). Fifty patients with persistent disease and amplifiable meningitis tuberculosis were included. Mutations were identified in the genes conferring resistance to INH (Kat G, 12%), RIF (rpoB, 8%), SM (r psl and rrs, 30%), EMB (embB, 4%) and 2 patients (4%) had mutations to both INH and RIF. Another study carried out in Khartoum, Gezira and camps for displaced people showed high incidence of drug resistance\(^{(13)}\).

In Sudan, there is paucity of information regarding the diagnosis and management of CNS tuberculosis. It remains a real diagnostic and management challenge.

There were no studies addressing the problem of tuberculosis of the nervous system in respect to clinical diagnosis, management, imaging characteristics, ZN staining, culture and PCR on CSF and other specimens.

This study is designed to address these problems.
Objectives
- To describe the different clinical presentations of tuberculous meningitis
- To assess the response to medical treatment
- To outline predictors of outcome

It is a prospective, hospital-based, longitudinal study.

Patients and methods
- The study was carried out in Shaab and Khartoum Teaching Hospitals, Khartoum, Sudan, during the period from February 2002 to November 2009.
- Ten adult patients (16 years or more) were included and eight patients excluded.
- Written consent of patients or relatives was taken.
- Full history, clinical examination, diagnosis and management of all patients were carried out by the investigators.
- About 10 ml of CSF was taken from each patient using standard methods for: cytology, biochemistry, gram and ZN staining and PCR testing for mycobacterium tuberculosis.
- Sputum and blood PCR testing for tuberculosis was carried on all patients.

DNA detection of Mycobacterium tuberculosis in biological samples.

Samples
Sputum and Cerebrospinal fluid. Samples were collected in sterile plain tubes and stored at 4 degree C or immediately processed.

Following the centrifugation of the samples at 2000rpm/15 minutes, suspend the pellets in lysis buffer using Cinnagen DNA extraction kit.

PCR amplification of MTB DNA
5 ul of extracted DNA was mixed with 20ul 1X PCR mixture, 0.3ul Taq-DNA polymerase using Cinnagen MTB PCR kit. The DNA was amplified using the following PCR cycles: 93 C for 60 sec; 72 C for 30 sec for one cycle, followed by 37 cycles of 93C for 20 sec; 72C for 30 sec and a final cycle of 93C for 20 sec; 72C for 120 second.

Analysis of results
10 ul of the PCR amplified DNA was electrophoresed in 2X agarose and stained with Ehtidium boride for detection of the 163 bp fragment specific for Mycobacterium tuberculosis.

Bacteriology
Biological samples were studied by microscopy using the following stains:
Gram stain, ZN stain

Inclusion criteria
Only patients with the diagnosis of definite or highly probable tuberculous meningitis were included, essentially as described and validated by Ahuja and colleagues.

Presence of fever and headache lasting more than 14 days, with or without vomiting, alteration of sensorium or focal deficit;
Presence of AFB on CSF smears stained with Ziehl-Neelsen (ZN) stain or culture (B1). And absence of other bacteria ad fungi, as well as malignant cells, in CSF (B2);
CSF pleocytosis with more than 10 cells/ml (more than 60% lymphocytes) (C1), and CSF concentrations of protein greater than 0.6 mg/ml (C2) and of glucose less than 60% of the corresponding blood level (C3).
Evidence of extraneural tuberculosis
We used PCR testing instead of culture of Mycobacterium tuberculosis.

Five groups were identified as different combinations of the above mentioned criteria:
- Definite tuberculous meningitis (A+B1+B2)
- Highly probable tuberculous meningitis (A+B2+C1+C2+C3+D)
- Probable tuberculous meningitis (A+B2+two of the criteria C1,C2,C3 or D)
- Possible tuberculous meningitis (A+B2+one of the criteria C1,C2,C3 or D)
- Other disease (absence of A or B2).

Group 1 and 11 patients were included (10 patients).
Group 111, 1V and V were excluded (8 patients).
Exclusion Criteria
- Children less than 16 years of age.
- Patients with the above criteria 111,1V and V.
- Patients with HIV.
- Patients with malignancy.
- Patients on immunosuppressant drugs.

Staging of tuberculous meningitis according to severity
Patients with tuberculous meningitis were classified into 3 stages according to severity, using the classification suggested by the British Medical Research Council (BMRC).

Stage I: Patients were conscious and had mainly non-specific symptoms, with or without signs of meningeal irritation, but no focal neurological signs. Diagnosis was established mainly on CSF findings.

Stage II: Patients were mentally confused and/or had neurological signs.

Stage III: Patients were comatose and had gross neurological signs.

Medical treatment
Consisted of the following drugs:
- Streptomycine (dose 10 mg/kg /day), or Ethambutol (25 mg/kg day)
- INH (5-10 mg/kg/day)
- Rifampicin (10 mg/kg/day)
- Pyrazinamide (35 mg/kg/day)
- Pyridoxine 40 mg/day)

After 2 months of treatment Streptomycin or Ethambutol and Pyrazinamide were stopped and Rifampicin, INH and pyridoxine continued for another 10 months.

All patients were supervised and side effects of drugs were looked for.

Monthly visual acuity and colour vision were checked for patients on Ethambutol, to monitor for toxic optic neuropathy.

Monthly hearing evaluation was conducted for patients on Streptomycin, to monitor for ototoxicity.

Monthly evaluation of liver enzymes were done for all patients (INH, Rifampicin and Pyrazinamide)

Neuroimaging studies were performed initially for all patients and then at about 3 months, 6 months and at the end of 12 months of treatment.

At the end of the 12 months course of treatment, the patients were evaluated clinically and by investigation to ensure complete resolution of disease activity.

Statistics: All necessary data were fed to IBM compatible computer, using SPSS statistical package for analysis.

Results
Demographic characteristics: (Table1)

Table 1: Demographic characteristics and Symptoms in 10 patients with tuberculous meningitis

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Duration of illness before treatment (d)</th>
<th>Symptoms</th>
<th>Fever</th>
<th>Headache</th>
<th>Neck stiffness</th>
<th>Double vision</th>
<th>Blurred vision</th>
<th>Seizures</th>
<th>Weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>39</td>
<td>120</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>2</td>
<td>M</td>
<td>54</td>
<td>60</td>
<td>+</td>
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<td>3</td>
<td>F</td>
<td>30</td>
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<td>+</td>
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<tr>
<td>4</td>
<td>F</td>
<td>50</td>
<td>60</td>
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<td>6</td>
<td>M</td>
<td>30</td>
<td>30</td>
<td>+</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>21</td>
<td>14</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>18</td>
<td>14</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>9</td>
<td>M</td>
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<td>14</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>10</td>
<td>F</td>
<td>21</td>
<td>14</td>
<td>+</td>
<td>+</td>
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</tr>
</tbody>
</table>

Ten adult patients with definite or highly probable tuberculous meningitis were studied (group1 and11). Five were males and five females. Their ages ranged between 18 to 54 years (mean age 27.6, median 23.5, +/- SD 11.5 years.

Six (60%) patients were students, two (20%) house wives, one (10%) medical doctor and one (10%) butcher.

Clinical Presentation: (Table 1 and 2)

Symptoms at presentation: (Table 1)

Duration of symptoms before presentation ranged between 5 and 120 days (mean 36.7 days).

All patients had fever, headache and neck stiffness (100%), and five (50%) had impaired vision and another five had double vision (50%). Two (20%) had seizure disorder and 4 (40%) had motor limb weakness.
Signs in the first 3 months of presentation: (Table 2, Figures 1 & 2).

Table 2: Neurological Signs in 10 patients with tuberculous meningitis

<table>
<thead>
<tr>
<th>Signs in the first 3 months of treatment</th>
<th>Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuchal rigidity</td>
<td>1, 2, 3, 4, 6, 7, 8, 9, 10</td>
<td>100%</td>
</tr>
<tr>
<td>Kernig’s sign</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9, 10</td>
<td>100%</td>
</tr>
<tr>
<td>Brudzinsk’s Sign</td>
<td>1, 3, 5, 6, 8</td>
<td>50%</td>
</tr>
<tr>
<td>Cranial nerve palsies</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9, 10</td>
<td>50%</td>
</tr>
<tr>
<td>Papilloedema</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9, 10</td>
<td>60%</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9, 10</td>
<td>10%</td>
</tr>
<tr>
<td>Motor weakness</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9, 10</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>1 (Military TB + R Supra clavicular LN abscess)</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>2 (Bilateral LN)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (L basal consolidation + minimal effusion)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (R Upper lobe consolidation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (Military tuberculous)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (R cervical LN abscess)</td>
<td></td>
</tr>
<tr>
<td>Extra neural TB</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9, 10</td>
<td>70%</td>
</tr>
</tbody>
</table>

Fig 1: For patient number 4
Showing evolution of disease within 5 weeks as shown on serial CT scans of the brain.
(essentially normal initial scan, followed by progressive meningeal enhancement and hydrocephalus and then the effect of medical treatment and shunting)

Initial CT scan of the brain Two weeks later

Five weeks later

Fig 2: For patient No 8
Fig 2(a): Showing abscess formation in right cervical lymph node six weeks following start of antituberculosis treatment

Fig 2(b): Showing bilateral LMN Facial and right 12th nerve palsies

Initial BMRC scale was one in 4 (40%) patients, 2 in 3 (30%) and 3 in 3 (30%).
Nuchal rigidity and a positive Kernig’s signs were found in all patients (100%).
Brudzinsk’s sign was positive in 5 (50%) patients. Cranial nerve palsy was reported in 7 (70%) patients, the commonest cranial nerves affected were the 6th nerve in 5 (50%) patients, the 3rd in 2 (20%), the 7th in 2 (20%), the 4th in one (10%), the 5th in one
(10%) and the 12th in one (10%). Papilledema was found in 6 (60%) patients and optic atrophy in one (10%). Motor weakness of limbs was found in 6 (60%) patients, (right hemiplegia in 3 (30%), quadriplegia in 2 (20%) and paraparesis in one (10%)).

Extraneural tuberculosis was found in 7 (70%) patients (five (50%) patients with some form of pulmonary tuberculosis, one (10%) patient with military tuberculosis and cervical tuberculous lymphadenopathy and one (10%) patient with isolated cervical lymphadenopathy.

Laboratory and imaging findings:
(Tables 3, 4 and 5)

Table 3: Investigations in 10 patients with tuberculous meningitis

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Tuberculin test</th>
<th>HR</th>
<th>WBC</th>
<th>ESR</th>
<th>HIV test</th>
<th>CSF</th>
<th>Spumum PCR</th>
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<tbody>
<tr>
<td>1</td>
<td>Negative</td>
<td>60</td>
<td>550</td>
<td>76</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>Negative</td>
<td>55</td>
<td>850</td>
<td>76</td>
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<td>3</td>
<td>Positive</td>
<td>60</td>
<td>1400</td>
<td>74</td>
<td>Negative</td>
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<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>Negative</td>
<td>60</td>
<td>250</td>
<td>76</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>Negative</td>
<td>60</td>
<td>250</td>
<td>76</td>
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<tr>
<td>6</td>
<td>Negative</td>
<td>15</td>
<td>600</td>
<td>30</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>7</td>
<td>Negative</td>
<td>15</td>
<td>600</td>
<td>30</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>8</td>
<td>Nodular</td>
<td>70</td>
<td>100</td>
<td>70</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>9</td>
<td>Nodular</td>
<td>70</td>
<td>100</td>
<td>70</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
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<tr>
<td>10</td>
<td>Nodular</td>
<td>70</td>
<td>100</td>
<td>70</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
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</tbody>
</table>

Table 4: CSF Findings in 10 patients with tuberculous meningitis:

<table>
<thead>
<tr>
<th>Protein (mg/dl)</th>
<th>Total WBC</th>
<th>Lymphocytes</th>
<th>% polymorphs</th>
<th>Sugar (mg/dl)</th>
<th>PCR</th>
<th>ZN staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>60</td>
<td>70</td>
<td>50</td>
<td>85</td>
<td>-</td>
<td>+</td>
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<tr>
<td>110</td>
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<td>60</td>
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<td>50</td>
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<td>82</td>
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<td>50</td>
<td>82</td>
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</tr>
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</table>

Table 5: MRI Findings of the Brain in 10 patients with tuberculous meningitis

<table>
<thead>
<tr>
<th>MRI Findings</th>
<th>Initial MRI</th>
<th>Follow up MRI (1-3 months)</th>
<th>MRI Findings at the end of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningeal enhancement</td>
<td>1,2,3,4,5,6,7,8,9,10</td>
<td>1,2,3,4,5,6,7,8,9,10</td>
<td>All Cleared</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>NAD</td>
<td>4, 6</td>
<td>4,6 (Shunted)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1 (Multiple)</td>
<td>1 (Increased in size)</td>
<td>1 (Resolved)</td>
</tr>
<tr>
<td></td>
<td>4 (Hypoplastic)</td>
<td>2 (R, posterior)</td>
<td>2 (Diast)</td>
</tr>
<tr>
<td></td>
<td>9 (Multiple)</td>
<td>9 (Increasing in No and size)</td>
<td>9 (Diast)</td>
</tr>
<tr>
<td>Infarctions</td>
<td>NAD</td>
<td>2 (Multiple Bilateral)</td>
<td>2 (Diast)</td>
</tr>
</tbody>
</table>
brain in 4 (40%) patients, hydrocephalus in 2 (20%) and cerebral infarction in one (10%).

MRI of the brain findings at the end of treatment: Meningeal enhancement cleared in all patients who were alive, 2 (20%) patients shunted for hydrocephalus and tuberculomata resolved in the remaining 2 alive patients.

Outcome of treatment: (Table 6)

Table 6: Outcome of treatment in 10 patients with tuberculous meningitis

<table>
<thead>
<tr>
<th>Patient</th>
<th>BMRC</th>
<th>Initial Neurological signs</th>
<th>New signs while on treatment</th>
<th>Neurological signs after completion of treatment</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>BE 6°, Siznors</td>
<td>R posineuritic, hydromyelia</td>
<td>NAD</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>Bilateral 6°</td>
<td>R posineuritic, hydromyelia</td>
<td>NAD</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>R 6th</td>
<td>R posineuritic, hydromyelia</td>
<td>NAD</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>L 6th</td>
<td>R posineuritic, hydromyelia</td>
<td>NAD</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>Papilledema, paraparesis</td>
<td>Appearance of cerebral edema</td>
<td>NAD</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>L 6th, Bil optic atrophy</td>
<td>Appearance of cerebral edema</td>
<td>NAD</td>
<td>Died</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>Bil 6th, R, optic atrophy</td>
<td>Appearance of LEK abscesses</td>
<td>NAD</td>
<td>Died</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>R 6°, R, L 6°, R, L 6°, R,</td>
<td>Appearance of LEK abscesses</td>
<td>NAD</td>
<td>Died</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>NAD</td>
<td>NAD</td>
<td>NAD</td>
<td>Died</td>
</tr>
</tbody>
</table>

Development of new signs after starting treatment: Eight (80%) patients developed new signs or showed increase in size of the existing lesions.

Outcome at the end of treatment: Two (20%) patients recovered completely, 3 (30%) died and 5 (50%) recovered with residual deficit. The brunt of deficit was on the cranial nerves (bilateral optic atrophy in 4 (40%) patients, bilateral 7th and right 12 in one patient and paraparesis in one (10%).

Discussion

Tuberculous meningitis is still the most serious form of tuberculosis and carries a high mortality and morbidity. In endemic areas TBM is a disease of early childhood[17], where as in non-endemic areas TBM is a disease of adulthood. Risk factors for the last group were HIV infection, age, alcoholism, diabetes mellitus, malignancy and use of corticosteroids.[18, 19, 20, 21].

Uncertainty dominates all aspects of tuberculous meningitis (TBM). The variable history and clinical presentations contribute much to the delay in diagnosis and management and hence the outcome. The conventional diagnostic tools are usually unreliable and lack sensitivity and specificity. Ziehl-Neelsen staining lacks sensitivity and culture results are often negative and give much uncertainty and undue delay to the diagnosis and treatment.

Tuberculin testing is of limited value, especially in endemic areas like Sudan. Early studies found 22% of those with TBM were negative to 100 units PPD[22]. A recent study demonstrated cumulative reactivity with 10–100 units PPD to be 75 %[23]. Some studies suggest that tuberculin testing may be more useful in children, with 86% having greater than 15 mm of induration with 5 units purified protein derivative (PPD)[24]. In our series, it was negative in 2 out of the 9 tested patients (22.2%).

The new rapid diagnostic methods, like Polymerase Chain Reaction (PCR) are not readily available in developing countries where the burden of disease. PCR offers a rapid and fairly accurate diagnosis of tuberculous meningitis[25,26]. Although specificity and sensitivity as high as 100% have been reported, until there is advancement in PCR technique, this test alone is insufficient as a single diagnostic test for tuberculosis[27, 28].

In this study, a positive PCR for M tuberculosis was obtained in 7 (77.8%) out of 9 patients.

Classic presenting features of TBM are not uncommon and high index of suspicion is required. Almost all the available series of TBM reported in the literature stress the importance of early diagnosis and the prompt institution of chemotherapy[29-34]. Delay in
treatment either result in death, or substantial neurological morbidity\(^{(35)}\).

The nature of neurological complications that can occur can be predicted from an understanding of the pathogenesis of TBM. Adhesions can result in cranial nerve palsies (Especially II, III, IV, VI, VII, and VIII), constriction of the internal carotid resulting in stroke, and obstruction of CSF flow leading to raised intracranial pressure, reduced conscious level, and hydrocephalus.

Diagnosis is dependent on lumbar puncture and CSF examination. Abnormalities in the CSF depends on a tuberculin reaction within the subarachnoid space. Those with depressed cell mediated immunity may have atypical findings in the CSF.

Lymphocytosis of between 100 and 1000 cells/mm\(^3\) is more usual, although in the first 10 days polymorphonuclear leucocytes may predominate\(^{(36)}\). A raised CSF protein occurs in the majority, and CSF glucose will be reduced in 70\%\(^{(30, 36)}\).

The advent of CT and MRI has provided insight into disease progression, and gives prognostic and diagnostic information\(^{(37, 38)}\). Both CT and MRI of the brain will disclose hydrocephalus, basilar meningeal thickening, infarcts, oedema, and tuberculomas. The incidence of hydrocephalus is greater in the young, and increases with duration of the illness. In children hydrocephalus is almost always present after 6 weeks of illness\(^{(37)}\). Infarcts are seen on CT in 28\%, with 83\% occurring in the middle cerebral artery territory\(^{(39)}\). The basal ganglia are the most commonly affected region.

Magnetic resonance imaging has increased sensitivity in detecting the distribution of meningeal inflammatory exudates and other lesions\(^{(39)}\).

Important mimickers include cryptococcal meningitis, cytomegalovirus encephalitis, sarcoidosis, meningeal metastases, and lymphoma.

Before the introduction of chemotherapy TBM was almost universally fatal. Cases of transient self limiting TBM are reported in the literature\(^{(40)}\), but these are exceptional.

Generally, the consensus is to combine isoniazid, rifampicin, and pyrazinamide as initial treatment. The addition of the fourth drug is left to local choice and experience, with little evidence to support the use of one over the other.

There is conflicting evidence for the duration of treatment. The current United Kingdom guidelines recommend 12 months in uncomplicated cases of TBM (including cerebral tuberculoma without meningitis), extending to 18 months should pyrazinamide be omitted\(^{(41)}\).

The rationale behind the use of adjuvant corticosteroids lies in reducing the harmful effects of inflammation as the antibiotics kill the organisms. Corticosteroids do not seem to reduce the proinflammatory cytokines found in the CSF of those with TBM\(^{(42)}\). Although the mechanism remains obscure, clinical trials suggest that corticosteroids have a beneficial effect in some groups of patients and a consensus has emerged that adjuvant corticosteroids should be used in those presenting with MRC stage II or III TBM\(^{(41, 43, 44)}\).

Neurological deterioration occurring in a patient under treatment for TBM may have various causes, and requires urgent radiological assessment. Rising intracranial pressure requires active management. Hydrocephalus is a common complication that may lead to permanent neurological damage or death if left untreated. Prompt assessment by CT is of value in both diagnosis and management\(^{(36)}\).

Development of new neurological signs during anti tuberculou s therapy was also observed. It could be a paradoxical reaction and unlikely due to ineffective or inappropriate agents as most of the newly developed complications resolved with
continued treatment. Paradoxical reaction during effective antituberculous treatment is well known phenomenon\(^{(45,46,47)}\). It may be due to complex interaction between the host immunity and the M tuberculosis and usually subsides with continued anti TB treatment or addition of corticosteroids\(^{(45,46,47)}\).

Case fatality rate in our series was (30%) and is comparable to many studies world wide\(^{(48,49)}\). The case fatality of tuberculous meningitis is one of the highest in neuroinfections and hence, high index of suspicion and empirical initiation of prompt treatment pending the results of investigation is crucial.

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