International Journal of Neurology and Neurosurgery
January - June 2012, Volume 4 Number 1

Clinical risk Factors affecting the Outcome of Cranial Tuberculosis

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Abstract

Objective: *To discover the clinical risk factors that may affect the outcome, over a 6-year period of CTB at King Abdul Aziz University Hospital (KAUH), Jeddah,*

Design: *Retrospective study From January 2005 to December 2010.*

Results: *A total of 78 cases were reviewed. 34 (43.59%) males and 44 (56.41%) females. Factors that may lead to poor prognosis were: old age (p<.047), headache (p<.025), history of weakness (p<.005), classic TB symptoms (p<.001), history of contact with a TB patient (p<.006), HIV (p<.001), elevated ESR (p<.001) and altered mental status (p<.001).*

Conclusion: *CTB presentation is usually with headache. Clinical risk factors are: headache, weakness, ESR and others. Patients with those risk factors should receive full medical treatment.*

Keywords: *Tuberculoma, Meningitis, Tuberculosis, Saudi Arabia, Jeddah*

Introduction

Cranial Tuberculosis (CTB) is a potentially fatal disease if untreated properly[1]. CTB is a very critical disease in terms of fatal outcome and permanent deficits, requiring rapid diagnosis and treatment. Prediction of prognosis of CTB is difficult because of the protracted course, diversity of underlying pathological mechanisms, variation of host immunity, and virulence of *M tuberculosis*. Prognosis is related directly to the clinical stage at diagnosis[2,3].

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(Received on 07.12.2011, accepted on 21.01.2012)

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Tuberculomas account for 0.9% of intracranial masses in TB-endemic areas[4].

The WHO's 2003 publication *Tuberculosis: Advocacy Report* stated that 8 million new cases of TB are reported annually and 2 million deaths occur each year[5].

It has been reported that out of all extra-pulmonary TB patients, 4.7 % can develop CTB. TB is the seventh leading cause of death and disability worldwide. In 1997, TB meningitis (TBM) was the fifth most common form of extra-pulmonary TB. TBM accounted for 5.2% of all cases of exclusively extra-pulmonary disease and 0.7% of all reported cases of TB[6].

Currently, more than 2 billion people (i.e., one third of the world's population) are infected with tuberculosis (TB), of which approximately 10% will develop clinical disease. The incidence of central nervous system (CNS) TB is related to the prevalence of TB in the community, and it is still the most common type of chronic CNS infection in developing countries.

In Saudi Arabia, the estimated percentage of CTB is 4.4% of all the extra-pulmonary tuberculosis[7]. Tuberculous meningitis represents around 6.3% of all TB patients[8].

Mycobacterium tuberculosis bacilli enter the host by droplet inhalation. Localized infection escalates within the lungs, with dissemination to the regional lymph nodes. In persons who develop TBM, bacilli seed to the meninges or brain parenchyma, resulting in the formation of small subpial or subependymal foci of metastatic caseous lesions, termed Rich foci.

The second step in the development of TBM is an increase in size of a Rich focus until it ruptures into the subarachnoid space. The location of the expanding tubercle (ie, Rich focus) determines the type of CNS involvement. Tubercles rupturing into the subarachnoid space cause meningitis.

Studies for the risk factors that affect the outcome of CTB in this region of the world are limited. The pattern of clinical manifestations and outcome of CTB are not well defined. The aim of this study is to describe the pattern of CTB at King Abdulaziz University Hospital (KAUH) and to find out the clinical risk factors that can affect the outcome of the treatment in CTB patients.

Population and method

From January 2005 to December 2010, medical files of patients with a diagnosis of cranial tuberculosis (CTB) were retrospectively reviewed. The CTB included both brain tuberculoma and tuberculous meningitis (TBM). Only those with characteristic pathologic findings and/ or radiological features (on MRI) suggestive of CTB were enrolled. Demographic data and clinical manifestations were reviewed and analyzed. The outcome was recorded.

Pathology specimen

The pathologic diagnosis included 78 CTB. The diagnosis was determined with specimens removed at surgical resection (intra-cranially) or biopsy and/or radiological findings suggestive of CTB. The specimens were reviewed by general pathologists at KAUH. The specimens were obtained from both enhanced and non-enhanced areas of each tumor with reference to three-dimensional contrast material–enhanced MR images by using a neuro-navigational system (BrainLab Vector Vision neuronavigation system, germany) during surgery or biopsy. Routine histo-pathological tests were done (hematoxylin and eosin) and special immune-histochemistry studies (e.g. cytokeratins and EMA) for all patients.

All the specimens were sent to the microbiology studies and the diagnoses were confirmed using Ziehl- Neelson stain for acid fast bacilli, Polymerase chain reaction (PCR) for tuberculosis and TB cultures.

Postoperative treatment

After diagnosis with CTB, patients subsequently received anti-tuberculous chemotherapy according to the following protocol: isoniazid (INH)(5 mg/kg), rifampin (RIF)(10mg/kg), pyrazinamide (PZA) (15-30 mg/kg), streptomycin (SM) (15mg/kg),ethambutol(Eth)(15mg/kg)and pyridoxine. Corticosteroid was given to all patients in tapering doses over 10 days. INH, RIF, Eth ± PZA were given for all adult patients. INH, RIF, SM ± PZA were given for all pediatric patients. The anti-TB medication duration of treatment varies (6 – 24 months) according to the infectious diseases (ID) team.

Patients presented with hydrocephalus, had ventriculo-peritoneal shunting inserted.

All the patients were evaluated at monthly outpatient examinations by both neurosurgery and ID services.

The remission was defined by disappearance of the tissue changes from the brain MRI images done in the post operative period six monthly.

Statistical analysis

All collected data were processed using SPSS 16 software (SPSS Inc., Chicago Illinois). The data were summarized as the mean ± standard deviation unless otherwise indicated. Univariate analysis of pooled data was performed with the Student t test for continuous parametric and Mann-Whitney test for nonparametric variables, and the X^2 test (or Fisher exact test) for categorical variables. The correlation was made between the age, clinical presentation, treatment and the outcome using Spearman correlation test

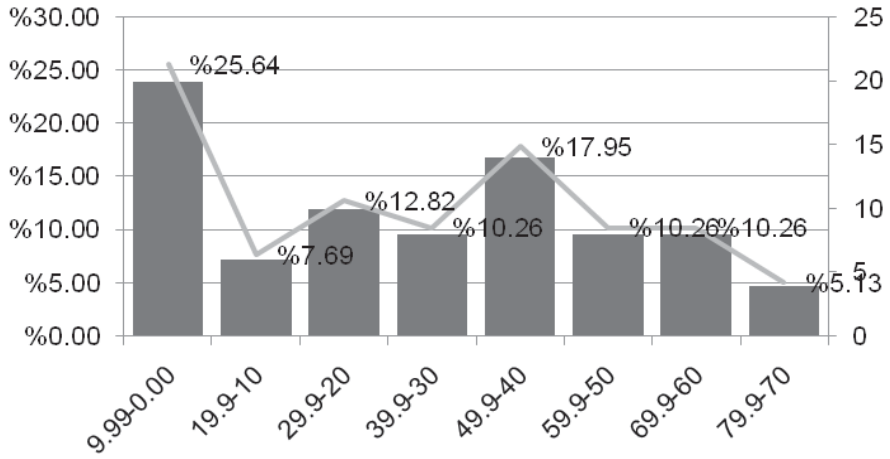
Differences with $p<0.05$ were considered significant.

The ethics committee of King AbdulAziz university Hospital, Jeddah, Saudi Arabia approved this retrospective study without requiring patients' consent.

Results

Age: the mean of age was 33±23.5 (1-95) years (figure1)

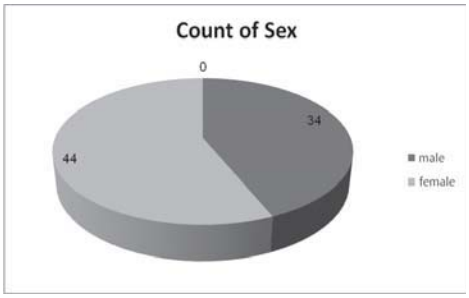
Fig 1. Histogram of the patients' count and percentage of different age groups



Sex

The gender analysis showed that there were 34(43.59%) males and 44(56.41%) females. The male to female ratio was 1:1.3 (Figure 2)

Fig 2. Pie diagram representing the number and percentage of the patients' gender



Race

The analysis of the patients' race showed the following: Arab 23 (29.29%), African 45(57.69%), Central Asian 8(10.26%) and East Asian 2(2.56%). There was a significant inter-racial difference chi square value 56.46 p <0.0001.

Presenting symptoms

• Duration of symptoms: The average duration of symptoms is 1.4 ± 1.7 months.

• Co-existence of lung TB: 18(23.08%) of patients' had lung TB.

• The most common location for CTB was the meninges 51 (43.97%) followed by multiple locations 38 (32.76%). (Table 1)

Table 1. The number and percentage of the TB involvement in different locations

TB location	N	%
Meninges	51	43.97%
Frontal	25	21.55%
Parietal	10	8.62%
Temporal	12	10.34%
Occipital	10	8.62%
Posterior Fossa	8	6.90%
Total	116	100.00%
Multiple	38	32.76%

• 12(17.95%) patients had a positive contact history with TB patients.

• 22(28.21%) patients presented with classic history of TB (fever, night sweat and weight loss).

• The most common complaint in the history was headache 60(76.92%) followed by weakness 36(38.46%).

Clinical signs

The most common physical examination finding was motor weakness 36(46.15%) followed by abnormal cranial nerve 20(25.64%). (Table 2)

Table 2. Number and percentage of different clinical features of BTB upon presentation

Clinical feature	*N*	%
Headache	60	76.92%
Numbness	14	17.95%
Seizure	30	38.46%
Vision problem	14	17.95%
Weakness	36	46.15%
abnormal CN	20	25.64%
weakness PX	36	46.15%
Abnormal sensation	14	17.95%
Cerebellar abnormality	6	7.69%

CN: cranial nerves, PX: physical examination

• 40(51.28%) of patients presented with abnormal mental status. Of those; 32(80%) presented with confusion, 6(15%) presented with coma and 2 (5%) of patients were obtunded.

• 36 (46.15%) of patients found to have motor weakness of different power grades. (Table 3)

Table 3. The number and percentage of the motor power according to the presenting grade in CTB

Grade	*N*	%
0	16	44.44%
1	4	11.11%
2	2	5.56%
3	8	22.22%
4	6	16.67%
Total	**36**	**100.00%**

0=no contraction, 1=some contraction but no movement "flickers", 2= movement without gravity, 3= movement against gravity without resistance, 4= movement against partial resistance, 5= movement against full resistance

Tests and Surgical interventions

• 6(7.69%) patients had a positive PPD test.

• 26(33.3%) patients had an evidence of dilated ventricles on the MRI study.

The surgical intervention was needed as the following:

1. Biopsy: the number of patients had biopsy 14(17.95%).

2. Ventriculo-Peritoneal shunts were inserted in 9(11.53%).

3. Surgical resection through craniotomy 18(23.08%).

Anti-TB chemotherapy

76(97.44%) of patients received anti TB medications. 10(12.82%) of patients had a relapse after treatment. 66(84.62%) of patients were compliant with medical treatment.

Table 4. Different factors with outcome correlation significance

Risk Factor	Correlation	P Value
Sex	0.154	0.177
Age	0.226	0.047
Race	0.099	0.39
Headache	0.253	0.025
Seizure	0.196	0.086
Classic symptoms	0.21	0.001
Duration of symptoms	0.73	0.001
History of weakness	0.312	0.005
History of contact	0.306	0.006
Vision problem	0.187	0.1
Ms abnormality	0.444	0.001
CN abnormality	0.117	0.308
PPD	0.12	0.297
ESR	0.80	0.002
HIV	0.18	0.031
Hydrocephalus	0.104	0.365
Lung TB	0.072	0.533
Posterior fossa	0.174	0.135
Temporal	0.034	0.767
Occipital	0.018	0.876
Parietal	0.132	0.25
Frontal	0.183	0.112
Meninges	0.081	0.483
Anti TB	0.59	0.05

Outcome

54(69.23%) of patients recovered completely. 16(20.51%)of patients were left with permanent disability and 8(10.25%) patients died.

Five year survival rate was 90%.

Risk factors

Clinical features

Age was a risk factor that affected the outcome r (.22) 78 p<.047. Where patients younger than 31.4 years of age had a better outcome than older patients.

Symptoms

• Headache: patients presented with headache showed worse outcome than other patients r (.25) 78 p<.025 .

• History of weakness: patients presented with history of weakness had a worse outcome than other patients r (.32) 78 p<.005.

• Classic symptoms: classic symptoms (fever, night sweat and weight loss) showed to be a risk factor that affected the outcome negatively. r(. 21)78 p<.001.

• History of contact with a TB patient was a risk factor r (.306) 78 p< .006. Where patients who had a contact with another TB patient had a worse outcome than other patients.

• Seizure was not a risk factor for poor outcome r(.18)78 p<.08.

Physical examination

Mental status abnormality: patients presented with altered mental status had a worse outcome than other patients r (.44) 78 p<.001.

Investigations

HIV positive patients had a worse prognosis than HIV negative patients r (.36) 78 p<.001.

ESR: elevated ESR value was a risk factor for poor outcome where patients with ESR > 39.8 had a worse outcome than other patients r (.80) 78 p< .001 (Table4)

Treatment

Anti TB therapy (ATT); the duration of the ATT medications was a significant factor that affected the outcome R^2 =.28, F (1, 40) = 15.84, p < .0001. Patients received ATT medication less than 13.1 moths had a worse prognosis than other patients.

Surgery: surgery did not affect the outcome craniotomy p<.18. However, the sub-group analysis for hydrocephalus showed a significant benefit of inserting a V-P shunt on the outcome p<.001.

Seizure: the Mann-Whitney test between the seizure presentation and poor outcome showed insignificant correlation with P<.15.

Posterior fossa location the Mann-Whitney test between the location of posterior fossa and poor outcome showed insignificant correlation with P<.08.

Race: The patients' race did not affect the outcome. However, it appeared that race can affect the relapse rate, where relapse occurred more frequently in Africans and Arabs R (68) =0.104 p<0.012.

Discussion

Despite great advances in immunology, microbiology, and drug development, TB remains among the great public health challenges. Poverty; lack of functioning public health infrastructure; lack of funding to support basic research aimed at developing new drugs, diagnostics, and vaccines; and the co-epidemic of HIV continue to fuel the ongoing epidemic of TB.

Cranial tuberculosis is a potentially fatal disease with permanent disabilities. The reported outcome varies between centers. Moreover, the best treatment regimen is still not standardized[9]. In this article the author focuses on the clinical risk factors and treatment modalities that affect the CTB. By knowing such factors the treating physician/ surgeon can predict the outcome at the presentation time.

A close study was done in Taiwan[10]. In the current study, the mean age of involvement is 33 years with slight female predominance distributions; this differs from Hsu et al. where the reported age was 54 year with male predominance. However, this finding has been reported before from the Middle East [7,8,11]. The current study confirms it in CTB. The young age involvement in the current article can be related to the general age distribution of the population of Saudi Arabia with large young population, so the infectious disease involvement as well can affect this age group. However, this finding needs further studies to find out the reason(s).

There is a significant interracial difference in term of involvement with CTB; this can be related to the socioeconomic status of the patients and the poor home status of the communities involved with CTB. That is a common tradition to live in crowded houses with poor ventilation system.

The clinical presentation (headache and motor weakness) are non-specific for CTB, moreover, history of contact with a TB patient can be of help the diagnosis only in 18% of patients. In addition, the classic history of TB

(weight loss, fever and night sweet) occurs in only 28% of cases. The tuberculin skin test is positive in 7% of patients. That means, in TB endemic areas, all of the mentioned features are not specific for CTB diagnoses, so the neuro-imaging namely brain MRI is essential for the diagnosis process of the patients and if there is a doubt, lesion's biopsy is indicated for confirmation.

The survival rate in this study is 70(90%) is close to the Kelly et al study where they reported a mortality of 16%[12]. This information has to be disclosed to the patient with CTB upon presentation.

The coexistence of active pulmonary TB with CTB is 23%. That is slightly different than another study done in Turkey where the reported percentage was around 36%[13].

The factors affecting the outcome of CTB are age > 31.4 years, headache and weakness classic symptoms ($p<0.001$), contact history with TB patients ($p<0.017$), ESR > 39 and duration of symptoms > 1.4 months. Patients with these risk factors should receive full medical treatment for at least thirteen month.

This study shows that craniotomy does not affect the outcome of CTB, this finding was supported by previous study[4]. However, in presence of hydrocephalus and sings of increased intracranial pressure V-P shunting is beneficial. This finding is in line with other article that showed the same result[14]. Keeping in mind that liberal use of shunting is associated with high failure rate[15], Overall, the strict use of surgery to relieve the intracranial pressure is recommended.

To increase the strength of this article a larger number of patients is needed, as well as a prospective design.

Overall, the current study discovered part of the risk factors (clinical only). Other factors including genetic, microbiologic and immunologic need further studying.

Conclusion

Factors affecting the outcome of CTB are age > 31.4 years, headache and weakness classic TB symptoms, contact history with TB patients, elevated ESR and duration of symptoms > 1.4 months. Patients with these risk factors should receive full medical treatment for at least thirteen month.

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