



ISSN 2278 – 0211 (Online)

Risk Factors and Clinical Presentations of CNS Tuberculosis in a Population Attending a Tertiary Hospital

Basharat Mubeen

Senior Resident Pathologist, Skims, Soura, Jammu & Kashmir, India

Mohsin Ul Rasool

Senior Resident Pathologist, Skims Medical College, Jammu & Kashmir, India

Sajad Hamid

Lecturer Anatomy, Skims Medical College, Skims Medical College, Jammu & Kashmir, India

Sheefa Haq

Senior Resident Pathologist, Skims Soura, Jammu & Kashmir, India

Rumana Hameed

Pathology Department, Skims Soura, Jammu & Kashmir, India

Nayal Khursheed

Faculty Department of Neurology, Skims Soura, Jammu & Kashmir, India

Abstract:

Introduction: Tuberculosis is a granulomatous disease the incidence of which is on the rise due to new emerging contributing factors like The acquired immunodeficiency syndrome epidemic, emergence of multidrug-resistant strains, and immigration of people from endemic areas .

Aim: To study the risk factors and clinical presentations of CNS tuberculosis in a population attending a tertiary care hospital.

Material And Methods: The study was retrospective for a period of 8 years(May 2001 to May 2009) and prospective for a period of 2 years (May 2009 to May 2011).The clinical details of these patients were noted especially patient particulars, history(present,past & relevant),clinical features& investigations done. Various risk factors in these cases were studied Patients suffering from tubercular meningitis were excluded from this study.

Observations: Past history of tuberculosis was present in 23(25.55%) and family history of tuberculosis in 10(11.11%). In 44 cases (48.88%) no significant risk factor was noted. Chief symptoms of brain tuberculosis were convulsions (65.60%),headache(56.25%),fever(37.5%),vomiting(25%),visual impairment(9.3%) and weakness (25%).25% of patients were normal on clinical examination.Motor deficit was found in (37.5%),urinary incontinence(9.3%), ptosis(12.5%) and cranial nerve palsies in (18.75%) of cases.

Conclusion: Past history of tuberculosis was the major risk factor for development of CNS Tuberculosis.So the emphasis is proper management of every tuberculous patient so that future risk of CNS involvement is minimized.Convulsions and headache were the most common symptoms in brain tuberculosis.

Keywords: tuberculosis, headache, convulsion

1. Introduction

1.1. CNS Tuberculosis

Tuberculosis is a granulomatous disease caused by Mycobacterium tuberculosis a slow growing, gram-positive rod, which is resistant to acid decoloration when stained with aniline dyes. Its lipid wall contributes to the acid-fast quality, whereas its tuberculoproteins are associated with tissue hypersensitivity in the characteristic granulomatous reaction¹. Tuberculosis is endemic in developing countries, but even in the developed countries after an initial decline up to 1980s, the incidence of tuberculosis is on the rise. The acquired immunodeficiency syndrome epidemic, emergence of multidrug-resistant strains, and immigration of people from endemic areas are some of the factors contributing to this increase². According to the World Health Organization, there are approximately 9.2 million new cases of tuberculosis and 1.7 million deaths secondary to tuberculosis every year.³ According to the data of Revised National TB

Control Programme (RNTCP) in India, out of the total new TB cases in first two quarters of 2008, 18% were of extra-pulmonary TB. Since 2004, cases of extra-pulmonary TB have increased by 3% in 2008, as per RNTCP data. Out of these extra-pulmonary TB, 30% were of pleural effusion, 10% abdominal TB, 8% bone TB, 47% lymph node TB, 2% TB meningitis and 3% TB elsewhere in body except lungs. More than 11,000 people had died due to extra-pulmonary TB (2005-07) in India alone.

CNS tuberculosis is an uncommon manifestation & accounts for approximately 10-15% of all cases of tuberculosis, carries a high mortality and a distressing level of neurological morbidity, and disproportionately afflicts children and human immunodeficiency virus (HIV)-infected individuals⁴.

Infection of the CNS is one of the most devastating clinical manifestations of tuberculosis. In a large-scale epidemiological study of extrapulmonary tuberculosis in the United States, CNS involvement was noted in 5 to 10% of extrapulmonary tuberculosis cases⁵. In the largest prospective epidemiological study on CNS tuberculosis, the chance of developing CNS tuberculosis was 1.0% among 82,764 tuberculosis cases from 1970 to 2001 in a Canadian cohort⁶. Four major patterns of CNS tuberculosis are seen which include²:

- Tubercular meningitis (TBM)
- Tuberculomas in brain
- Tubercular brain abscess (TBA)
- Tuberculous encephalopathy
- Spinal tuberculosis and tuberculomas.

TBM is the most common form of CNS tuberculosis. Rich and McCordock⁷ demonstrated on autopsy that the majority of patients with TBM displayed a caseating focus in the brain parenchyma or meninges.

Tuberculomas are mass lesions and are rare in the developed countries but tuberculomas remain a common problem in tropical countries, where tuberculosis is rampant and represents the most frequent form of intracranial mass lesion^{8,9}. Tuberculomas may be single, but are more often multiple. Before the advent of chemotherapy for tuberculosis, tuberculomas accounted for 30% to 34% of all intracranial space-occupying lesions^{10,11}. These occur usually above the tentorium in adults and below it in children. The common sites of location are: the paracentral lobule, cerebellum, and the pontine tegmentum^{10,11,12}. Other less common sites are cavernous sinus, hypothalamus, sella, Meckel cave, cerebellopontine angle, and intraventricular area¹². Tuberculomas have to be differentiated from space-occupying lesions such as pyogenic abscess, toxoplasmosis, sarcoidosis, syphilitic gummas, and primary or metastatic malignant diseases. MRI may be a helpful tool in determining the correct diagnosis¹³.

There are 3 patterns of enhancement in intracranial tuberculomas that is solid-enhancing lesions, ring-enhancing lesions, and mixed-enhancing lesions¹⁴.

TBA are extremely rare. In a review by whitner¹⁵ only 57 published cases were seen. The criteria for diagnosis of tubercular abscesses are Pus within the brain, bacteriologic proof (presence of acid-fast bacilli/culture/ PCR) & histologic confirmation of abscess.

Computed tomographic scan shows hypodense lesions surrounded by enhanced ring. There may be associated edema. At times, it is difficult to differentiate tubercular abscess from the pyogenic abscess on the basis of clinical and radiologic findings. AFB should be demonstrated on Zeil-Nielsen stain for confirmation¹⁶.

Several risk factors for CNS tuberculosis have been identified. Both children and HIV-coinfected patients^{17,18} are at high risk for developing CNS tuberculosis. Other risk factors include malnutrition and recent measles in children¹⁹ and alcoholism, malignancies, and the use of immunosuppressive agents in adults^{20, 21, and 22}. Studies conducted in developed countries have also identified that foreign-born individuals (individuals born outside of developed countries) are overrepresented among CNS tuberculosis cases²³. Tuberculosis remains a worldwide burden, with a large majority of new active tuberculosis cases occurring in underdeveloped and developing countries²³. In 80% of new tuberculosis cases, demographic factors such as poverty, crowding, malnutrition, and a compromised immune system play a major role in the worldwide epidemic, while the remaining 20% of tuberculosis cases are associated with HIV in sub-Saharan Africa^{23,24}.

Tuberculosis is very common in our part of world. Though a lot of study has been done on this topic but regarding CNS tuberculosis we have only few prospective studies available. There is a desperate need for such a study in our part of country. This present study is planned with such a perspective in mind.

2. Materials and Methods

The study was conducted in Department of Pathology, Sheri Kashmir Institute of Medical Sciences. The study was retrospective for a period of 8 years (May 2001 to May 2009) and prospective for a period of 2 years (May 2009 to May 2011).

The clinical details of these patients were noted esp patient particulars, history (present, past & relevant), clinical features & investigations done. Blood and CSF PCR were done for detecting mycobacterium tuberculosis.

Patients suffering from tubercular meningitis were excluded from this study.

3. Observations

In the present series which included a retrospective study of 8 years and a prospective study of 2 years, a total no of 90 cases of CNS tuberculosis were analyzed.

3.1. Risk Factors

Various risk factors tuberculosis in these cases was studied. Past history of tuberculosis was present in 23(25.55%) and family history of tuberculosis in 10(11.11%). Extra-CNS tuberculosis was present in 7 cases (7.77%) out of which 4 had active lung tuberculosis.

6(6.66%) of our patients were diabetics. No case of immunosuppression /AIDS was present in our study. In 44 cases (48.88%) no significant risk factor was noted.

| Associated Risk Factor | No. of Patients | % Age of Patients |
|----------------------------|-----------------|-------------------|
| Past History | 23 | 25.55 |
| Family History | 10 | 11.11 |
| Diabetes | 6 | 6.66 |
| Extra-CNS Tuberculosis | 7 | 7.77 |
| No Significant Risk Factor | 44 | 48.88 |
| Total | 90 | 100 |

Table 1: Risk Factors of CNS Tuberculosis

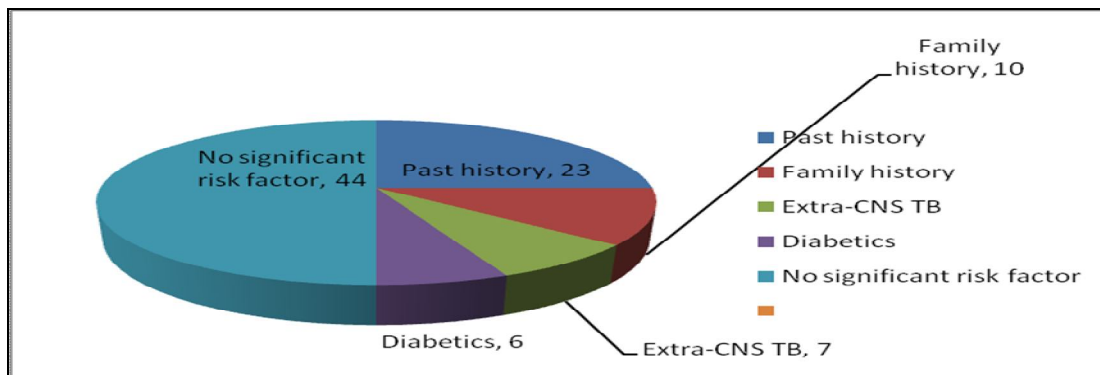


Figure 1: Risk factors

3.2. Signs and Symptoms (Brain Tuberculosis)

Chief symptoms brain tuberculosis was convulsions (65.60%), headache (56.25%), fever (37.5%), vomiting (25%), visual impairment (9.3%) and weakness (25%).

| Symptoms | No. of Patients | % Age of Patients |
|-------------------|-----------------|-------------------|
| Convulsions | 21 | 65.62 |
| Headache | 18 | 56.25 |
| Fever | 12 | 37.5 |
| Visual impairment | 3 | 9.3 |
| Vomitting | 8 | 25 |
| Weakness | 8 | 25 |
| Total | 32 | 100 |

Table 2: Symptoms of Brain Tuberculosis

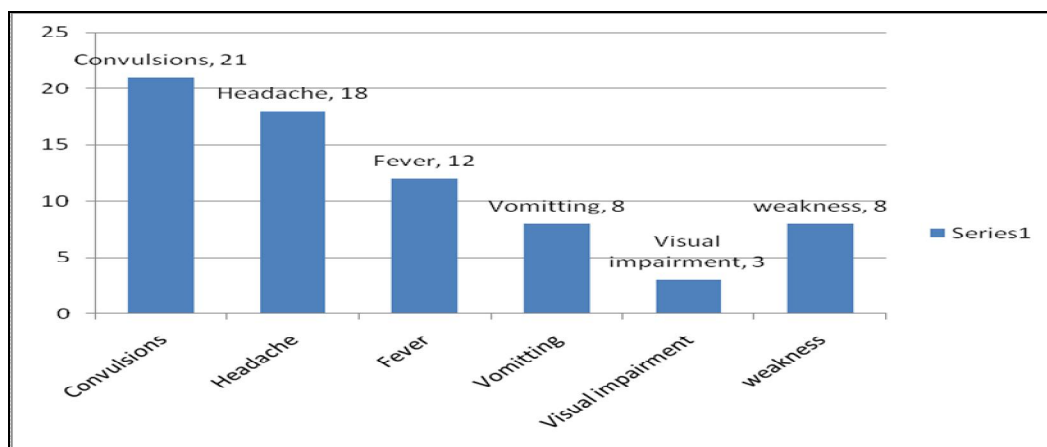


Figure 2: symptoms of brain tuberculosis

25% of patients were normal on clinical examination. Motor deficit was found in (37.5%), urinary incontinence(9.3%), ptosis (12.5%) and cranial nerve palsies in (18.75%) of cases.

| Clinical Examination Findings | No. of Patients | % Age of Patients |
|---------------------------------|-----------------|-------------------|
| Normal neurological examination | 8 | 25 |
| Motor deficit | 12 | 37.5 |
| Cranial nerve palsies | 6 | 18.75 |
| Ptosis | 4 | 12.5 |
| Urinary incontinence | 3 | 9.3 |
| Total | 32 | 100 |

Table 3: Clinical examination of Brain tuberculosis

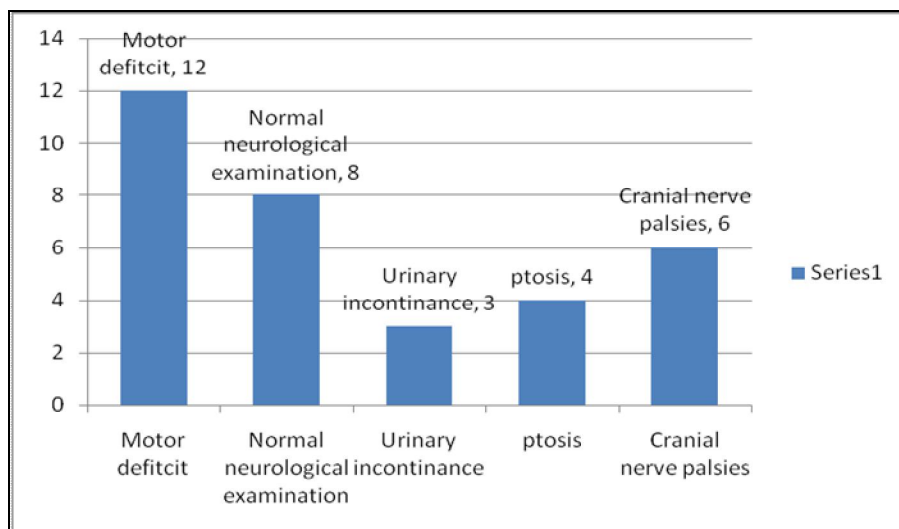


Figure 3: Clinical Examination of Brain Tuberculosis

4. Discussion

CNS tuberculosis is very common in developing countries with a high morbidity and mortality²³. Tuberculosis is endemic in developing countries, but even in the developed countries after an initial decline up to 1980s, the incidence of tuberculosis is on the rise. The acquired immunodeficiency syndrome epidemic, emergence of multidrug-resistant strains, and immigration of people from endemic areas are some of the factors contributing to this increase².

The diagnosis of CNS tuberculosis is based on clinical and laboratory findings. CT & MRI are very sensitive in preoperative diagnosis of tuberculosis¹¹ and have abated the need for routine histopathological diagnosis of tuberculosis.

4.1. Risk Factors

In our study past history of tuberculosis(25.55%) was a major risk factor followed by family history(11.11%),extra-CNS tuberculosis in (7.77%) and diabetics in (6.66%) of cases. No significant risk factor was present in 48.88% of cases.Neeru Vithalani etal²⁵ found most of the CNS lesions in children were part of either disseminated disease or military tuberculosis(34%) while only 21.8% accounted for isolated CNS disease, whereas in adults isolated CNS disease was present in 50% of cases. Matloob Azam²⁶ from Pakistan found family history of tuberculosis in 41% of cases. Ramdurg SR etal²⁷ found previous history of tubercular meningitis in 20% and old pulmonary tuberculosis in (6.66%) of cases.Martinez²⁸ found locus of extra-CNS tuberculosis in (62.5%) of cases with tuberculous pericardites in 12.5% of cases. In his study active pulmonary disease was found in 12.5% of cases. We did not find any case of HIV infection in our study which is in coherence with the study done by Cicek Bayinder²⁹.25% of patients in study done by Martinez²⁸ were HIV positive. L Cormican³⁰ found HIV positivity in 4.76% of cases. 20% of tuberculosis cases are associated with HIV positive infection in sub-saharan Africa^{23,24}. Tuberculosis is endemic in our part of world² and thus past history and family history were important risk factors in our study as was in other studies done in this geographic domain²⁷.Besides this, unlike west, people in the subcontinent tend to remain in joint families with close person to person contact contributing to strong family history of tuberculosis in our cases.

4.2. Clinical Presentation

In our study convulsions(65.60%) and headache(56.25%) were the most common symptoms followed by fever (37.5%),weakness (25%),vomiting(20%),visual impairment(9.3%).Convulsions were the predominant symptoms in studies done by Ravindra Kumar Garg etal³¹,EL Sayed MM etal³². Gulati found tuberculoma the commonest cause of seizures³³. In studies done by Martinez etal²⁸ headache was the most common symptom followed by focal neural deficit and seizures. Cicek Bayinder etal²⁹ found headache, fever, vomiting the most common symptoms similar to results shown by Lakatos B Prinz etal³³ In our study visual impairment was seen in 9.3% of cases which was in accordance with study done by EL Sayed MM etal³².

In our study on spinal tuberculosis stiff spine (89.65%), pain (79.33%), neural deficit (62%) were the most common symptoms followed by fever (17.24%). L.C.S HSU et al³⁴ also found pain & stiffness as the most dominant symptoms.

Halil Yanardag et al³⁵ found back pain and night sweats as the most common symptoms. Le Page et al³⁶ found neurological deficit in 74%. Mohammerreza Ehsaei³⁷ and L.F Owolabi³⁸ found neural deficit in 63.8% and 100% respectively. In neural deficit we found quadriplegia (1.7%), paraplegia (25.80%) and paraparesis (34.48%). Similarly Soon Mohn Chang et al³⁹ found paraplegia in 25% of cases. L Cornican et al³⁰ found neurological deficits in 100% of cases.

SUMMARY AND CONCLUSION:

The study was conducted in Department of Pathology, Sheri Kashmir Institute of Medical Sciences, Srinagar. The study was retrospective for a period of 8 years (May 2001 to May 2009) and prospective for a period of 2 years (May 2009 to May 2011).

The clinical details of these respective cases were taken from the records section of the Institute by screening the files of these patients.

In prospective study all proven cases of CNS tuberculosis were included in the study. Age was no bar for inclusion in the study. Patients with features of meningitis were excluded from the study. The study was undertaken with an aim to know the clinical profile of patients having CNS tuberculosis in a tertiary care hospital the conclusions drawn are summarized as:

- Past history of tuberculosis was the major risk factor for development of CNS Tuberculosis. So the emphasis is proper management of every tuberculous patient so that future risk of CNS involvement is minimized.
- Convulsions and headache were the most common symptoms in brain tuberculosis.

5. References

1. Gray F. Bacterial infections. *Brain Pathol.* 1997; 7:629–647.
2. Raza S, Sadaf A, Fecto F, et al. Patterns of tuberculosis in the central nervous system. *Infect Dis J Pak.* 2004; 13:99–104.
3. WHO Report 2008: Global tuberculosis control-
4. Berenguer, J., S. Moreno, F. Laguna, T. Vicente, M. Adrados, A. Ortega, J. Gonzalez-LaHoz, and E. Bouza. 1992. Tuberculous meningitis in patients infected with the human immunodeficiency virus. *N. Engl. J. Med.* 326:668-672.
5. Rieder, H. L., D. E. Snider, Jr., and G. M. Cauthen. 1990. Extrapulmonary tuberculosis in the United States. *Am. Rev. Respir. Dis.* 141:347-351.
6. Phipers, M., T. Harris, and C. Power. 2006. CNS tuberculosis: a longitudinal analysis of epidemiological and clinical features. *Int. J. Tuberc. Lung Dis.* 10:99-103
7. Rich AR, McCordock HA. The pathogenesis of tuberculous meningitis. *Bull Johns Hopkins Hospital.* 1933;52:5–37.
8. Dastur HM. Diagnosis and neurosurgical treatment of tuberculous disease of the CNS. *Neurosurg Rev.* 1983;6:111–117.
9. Parsons M, Pallis CA. Intradural spinal tuberculomas. *Neurology.* 1965; 15:1018.
10. Anderson JM, Macmillan J. Intracranial tuberculoma: an increasing problem in Britain. *J Neurol Neurosurg Psychiatry.* 1975; 38:194–201.
11. Arseni C. Two hundred and one cases of intracranial tuberculomas treated surgically. *J Neurol Neurosurg Psychiatry.* 1958; 21:308–301.
12. Yanardag H, Uygun S, Yumuk V, Cerebral tuberculosis mimicking intracranial tumour. *Singapore Med J.* 2005;46:731–733.
13. Oncul O, Baylan O, Mutlu H. Tuberculous meningitis with multiple intracranial tuberculomas mimicking neurocysticercosis, clinical and radiological findings. *Jpn J Infect.* 2005; 58:387–389.
14. Gupta RK, Kathuria MK, Pradhan S. Magnetization transfer MR imaging in CNS tuberculosos. *AJNR Am J Neuroradiol.* 1999; 20:867–875.
15. Whitner DR. Tuberculous brain abscess: report of a case and review of literature. *Arch Neurology.* 1978;35:148–153
16. Reichenthal E, Cohen ML, Schujman CB, I. Tuberculous brain abscess and its appearance on computerized tomography, case report. *J Neurosurg.* 1982; 56:597–600.
17. Dube, M. P., P. D. Holtom, and R. A. Larsen. 1992. Tuberculous meningitis in patients with and without human immunodeficiency virus infection. *Am. J. Med.* 93:520-524.
18. Rana, F. S., M. P. Hawken, C. Mwachari, S. M. Bhatt, F. Abdullah, L. W. Ng'ang'a, C. Power, W. A. Githui, J. D. Porter, and S. B. Lucas. 2000. Autopsy study of HIV-1-positive and HIV-1-negative adult medical patients in Nairobi, Kenya. *J. Acquir. Immune Defic. Syndr.* 24:23-29
19. Yaramis, A., F. Gurkan, M. Eleveli, M. Soker, K. Haspolat, G. Kirbas, and M. A. Tas. 1998. Central nervous system tuberculosis in children: a review of 214 cases. *Pediatrics* 102:E49.
20. Klein, N. C., B. Damsker, and S. Z. Hirschman. 1985. Mycobacterial meningitis. Retrospective analysis from 1970 to 1983. *Am. J. Med.* 79:29-34.
21. Ogawa, S. K., M. A. Smith, D. J. Brennessel, and F. D. Lowy. 1987. Tuberculous meningitis in an urban medical center. *Medicine (Baltimore)* 66:317-326.
22. Bidstrup, C., P. H. Andersen, P. Skinhoj, and A. B. Andersen. 2002. Tuberculous meningitis in a country with a low incidence of tuberculosis: still a serious disease and a diagnostic challenge. *Scand. J. Infect. Dis.* 34:811-814.

23. WHO. 2007. Global tuberculosis control: surveillance, planning, financing. WHO report 2007, WHO/HTM/TB/2007.376 ed. World Health Organization, Geneva, Switzerland
24. Waaler, H. T. 2002. Tuberculosis and poverty. *Int. J. Tuberc. Lung Dis.* 6:745-746.
25. Neeru Vithalani and PM udani. A study of 292 autopsy proved cases of tuberculosis, *Ind. J. Tub* vol xxix, No 2(48)
26. Matloob Azam, Nasera Bhatti; Intracranial tuberculomas and caries spine: an experience from children's hospital islamabad M Azam... - *J Ayub Med Coll*, 2004 - ayubmed.edu.pk
27. Ramdurg SR, Gupta DK, Suri A, Sharma BS; Spinal intramedullary tuberculosis; a series of 15 cases - *CI Neurosurgery* 2009 Feb, 11(2); 115-8
28. J T Martínez Lacasa, J Burillo, R Niubó, G Rufí, D Podzamczar, A Mariscal, R Reñé, F Fernández Nogués Cerebral tuberculoma. Report of 8 cases; *Medicina Clinica* (1991) Volume: 97, Issue: 6, Pages: 218-223 PubMed: 1943280
29. Cicek Bayinder, Ozgur Mete, Bilge Bilgic, prospective study of pathologically proven cases of CNS tuberculomas, march 2005.
30. L Cormican, R Hammal, J Messenger, and H J Milburn Current difficulties in the diagnosis and management of spinal tuberculosis *Postgrad Med J.* 2006 January; 82(963): 46-51.
31. Ravindra Kumar Garg*; diagnosis of intracranial tuberculoma; *Ind. J. Tub.*, 1996, 43, 35
32. El sayed MM Adeuja AO-Intracranial tuberculomas, the Hofuf Saudi Arabia experience; *Afr J Med Sci* 2006 Mar; 35(1): 21-7
33. Lakatos B, Prinz G, Sárvári C, Kamotsay K, Molnár P, Abrahám A, Budai J. [Central nervous system tuberculosis in adult patients]. *Orv Hetil.* 2011 Apr 10; 152(15): 588-96.
34. L C S Hsu, J C Y Leong, Tuberculosis of lower cervical spine, report of 40 cases. *The journal of bone and joint surgery* vol 66-B, no 1, jan 1984
35. Halil Yanardag M.D. B¹/₄lent Canbaz : Pott's Disease: The Clinical Features And Treatment Outcomes Of Eight Patients Of Spinal Tuberculosis; *The Internet Journal of Internal Medicine.* 2004 Volume 4 Number 2
36. Le Page L Feydy; Spinal tuberculosis: Longitudinal study with clinical, laboratorial & imaging outcomes: 2006 oct; 36(2); 124-91
37. Mohammadreza Ehsaei, MD.1, Fariborz Samini, MD.2, Gholamreza Bahadorkhan, MD.3 POTT'S Disease: a review of 58 cases, *Medical Journal of Islamic Republic of Iran*, vol 23, no 4, February 2010, p200-206
38. LF Owolabi, **MM Nagoda, AA Samaila, I Aliyu Spinal tuberculosis in adults: A study of 87 cases in Northwestern Nigeria *Neurology Asia* 2010; 15(3) : 239 – 244
39. Soon Mahn Chung, Nam Hyun Kim, Yong An Kim, Eung Shink Kam, Clinical studies of tuberculosis of spine; *Yonsei Medical Journal*: Vol 19, No 2, 1978