Review Article

Management of tuberculosis of the central nervous system: Our experience

P.N. TANDON

> 'From both thy nostril, from both eyes,
> From thy ears and from thy chin.
> Forth from thy brain and tongue I root
> Consumption seated in thy head.
> Forth from the neck and from the nape
> From dorsal vertebrae and space,
> From arms and shoulder blade I root
> Consumption seated in thine arm.'
>
> —Hymn from *Rigveda* (8.v.x.i.63,1–6)

Tuberculosis of the central nervous system (CNS) is the most serious complication of this disease of antiquity. Recorded evidence of tuberculosis is available from all over the world, from prehistoric times including *Rigveda*, *Yajurveda*, Old Testament, Egyptian mummies, Neolithic era in Germany, pre-columbian America, Nazca culture in Peru among others.[1–5] The disease affecting the CNS, which obviously was tuberculous meningitis (TBM), was described by Galen as Phrenitis—a term continued to be used till AD 18th century.[6] It is claimed that the term meningitis was first used by the French army surgeon Francois Herpin in 1803. Charles Morehead working in Bombay (presently Mumbai; 1847–48) described the autopsy findings in a number of children with meningitis which was undoubtedly tuberculous in nature. This was before Robert Koch in 1882 isolated *Mycobacterium tuberculosis*.[7] (For more details of the history see references 8–10.) Unfortunately, the disease continues to be rampant in many parts of the world including India. It is estimated that today approximately 2 billion people are infected with *Mycobacterium tuberculosis* and the disease killed 1.7 million in 2006, approximately 4500 each day (WHO, 2008 tuberculosis facts. Available at *www.who.int/tb/publications/2008/factsheet_april08.pdf* accessed on 1 Mar 2018).

In spite of having been personally misdiagnosed to be suffering from TBM and having worked as a thoracic surgeon in a tuberculosis hospital, CNS tuberculosis was only of theoretical interest to me. During my 4 years' training in Neurosciences at Oslo, Norway and Montreal, Canada, I had seen only one patient with a calcified tuberculoma of the brain. So, for all practical purposes, I was not trained to deal with patients affected with diverse manifestations of this disease encountered in India. Yet soon after beginning my career as a Neurosurgeon in Lucknow, it became obvious that CNS tuberculosis, mimicking a host of neurological disorders, was a major entity in the country needing attention. This experience not only helped me in collecting some data on a variety of tuberculous lesions affecting CNS but aroused my curiosity to learn more about the disease. This resulted in an extensive review of the literature, both from India and abroad (this has been summarized by me in several reviews on the subject.[8–10] This was confirmed by a review of the literature at other centres (Vellore, Madras [now Chennai], Bombay, Calcutta [now Kolkata]) and discussions with colleagues.[11–22] A similar experience was recorded by colleagues from other developing countries—Thailand, Nigeria, Uganda, Rhodesia (now Zimbabwe), Senegal, South Africa.[23] Even though the incidence of this disease had reduced markedly in the West, some important studies were also reported from there.[24–26] It became obvious that practically all aspects of CNS tuberculosis needed to be studied afresh, especially because the knowledge in the 1950s and 1960s was inadequate to resolve the problems faced by us. Several groups in the country were engaged in the task. Our studies were primarily concerned with improving the diagnosis and therapy, in particular those relevant for neurosurgeons.

In the early years, our studies were restricted to carefully recording the protean clinical manifestations of the disease as seen in India. It became obvious that the disease seen by us was distinct from the standard descriptions in textbooks, which made its diagnosis difficult. Commonly believed to be a disease of childhood, we encountered it in all ages. The prevalent practice of administering 'streptomycin–penicillin' for all febrile illnesses, modified not only the clinical picture but also findings of the cerebrospinal fluid (CSF). The difficulty of isolating tubercle bacilli from the CSF, a common feature of most studies reported from India, added to the problems of establishing a fool-proof diagnosis. In any case, neurologists and neurosurgeons had to deal with sequelae of the acute phase of the disease.[23] The following review thus deals primarily with our studies on management issues related to CNS tuberculosis, a subject on which, we believe, we made some important contributions. Pott's disease of the spine and diseases affecting the spinal cord are not discussed owing to limitations of space, even though these have been documented in a number of our publications.[8,9,27,28]

Based on our clinico-pathological studies, the most important unanswered question appeared to be the pathogenic basis of the diverse lesions affecting the CNS. While some patients have diffuse meningitis, others predominantly chronic basal meningitis and yet others a single solid tuberculoma while some others have a cluster of multiple small lesions or a tubercular abscess or a cystic lesion. A search of the literature not only failed to provide an answer[29] but the subject was not even discussed.

Professor Emeritus, Department of Neurosurgery, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India; President, National Brain Research Society, Manesar, Haryana, India

EXPERIMENTAL TUBERCULOSIS OF THE CNS

While continuing our clinical studies, it was decided to attempt to develop an experimental animal model of CNS tuberculosis. Detailed discussions with Professor Baldev Singh and with the active support of Colonel Kalra, Professor of Microbiology, it was decided to modify the immune status of Rhesus monkeys before challenging them with a known pathogen, i.e. *Mtb* using intracardiac, intracisternal and intraparenchymal injection. We succeeded in establishing a variety of lesions mimicking human disease.[30]

There is enough clinical and experimental evidence to indicate that meningitis is the result of discharge of tubercle bacilli into the CSF from a caseous focus (Rich Focus) in the brain or the meninges, and not a consequence of primary haematogenous spread. In contrast, a parenchymatous tubercle is due to direct haematogenous spread to the brain.

We observed that in monkeys challenged with intracisternal injection of live human tubercle bacilli, the type of lesion depends upon the state of immunity or allergy at the time of the insult. In unimmunized tuberculin-negative monkeys such a challenge resulted in diffuse meningitis, while in BCG-vaccinated animals, the meningitis was restricted to the site of injection. Tuberculin-induced hypersensitivity resulted in a marked reaction, with greater necrosis and marked oedema of the brain akin to tuberculous encephalopathy reported by Dastur and Udani[17] in children.

We demonstrated that the nature of the lesion depends upon the number of bacilli, their virulence and their site of deposition on the one hand and the state of immunity and allergy of the host on the other. It is important to realize that such a statement fails to provide a precise answer about the pathogenic mechanism.[31]

It may be mentioned that till today no other animal model of CNS tuberculosis has been developed. The untimely demise of Colonel Kalra prevented us from enlarging the scope of our study.[32] This study was done with the financial support of only a few thousand rupees from the Indian Council of Medical Research (ICMR). The other experimental studies which elucidated some aspects of pathogenesis of tuberculous infection of the CNS were with other colleagues.[33,34]

TUBERCULOUS MENINGITIS

TBM is the most common manifestation of CNS tuberculosis and is the most difficult to manage. Our accumulating experience resulted in a series of invited reviews by international books such as *Tropical neurology* edited by J.D. Spillane[8] and the encyclopaedic *Handbook of clinical neurology* (43 volumes) edited by P.J. Vinken and G.W. Bruyn.[9] Without elaborating these studies, resulting in these state-of-art reviews, which highlighted the protean clinical presentations, quite different from the standard textbook descriptions; atypical CSF findings; difficulty of isolating the tubercle bacilli; the variety of secondary complications, a series of studies were carried out to resolve the vexed issue of difficulty in diagnosis. In addition to those mentioned earlier, important contributions have been made over the years on the subject by our colleagues from the Departments of Neurology, Microbiology and Biotechnology. Ahuja *et al*.,[35] Paharaj *et al*.,[36] and Goyal *et al*.,[37] proposed a scheme of diagnostic criteria for tuberculous meningitis and their validation. Behari *et al*.,[38] Seth *et al*.[40] and Singh *et al*.[46] recorded their experience with polymerase chain reaction (PCR). Jaya Tyagi and her group made important contributions on the subject using sophisticated molecular approaches.[42,43] Mention must also be made of studies done by our radiology colleagues,[44] which not only helped in the diagnosis of meningitis (not necessarily its aetiology), but also its severity, associated pathologies such as hydrocephalus, tuberculomas and infarcts which helped in comprehensive management and prognosis of the disease. Notwithstanding, the recommendations by WHO (2014), favouring the use of Xpert Mtb/RIF as the initial diagnostic test, it is fair to say that the problem of early, rapid and reliable diagnosis remains unresolved.

To resolve the controversial issue regarding therapeutic use of corticosteroids along with chemotherapy, Prasad and colleagues did a randomized controlled trial,[45] a meta-analysis[46] and a Cochrane review.[47]

An important contribution in the field is the publication of 'Guidelines for the management of CNS tuberculosis' under the chairmanship of Professor S.K. Sharma.[48]

This write-up is primarily restricted to systematic investigations of sequelae of TBM requiring neurosurgical intervention, i.e. post-meningitic hydrocephalus and spinal arachnoiditis. These are the obvious consequences of the organizing basal exudates, a characteristic feature of this disease.

TUBERCULOUS SPINAL ARACHNOIDITIS

One of the first studies on CNS tuberculosis done by us in Lucknow was an aetiological survey of paraplegia. Among the 266 patients admitted to the medical and neurosurgical services, 48 (18%) were due to tubercular lesions—41 Pott's disease, 5 spinal arachnoiditis, one each tuberculous myelitis and intradural granuloma.[27] Pott's disease which has been described in detail in our publications,[8,9] where we outlined the indications for surgical treatment, its diverse presentations will not be discussed here. However, post-meningitic spinal arachnoiditis deserves special mention since we developed a therapeutic strategy, not reported hitherto even though Dastur and Wadia[48,49] had described its pathology and clinical features in details. We observed this syndrome to develop in three different stages of TBM—during the active phase of meningitis; at a variable time after the signs and symptoms of meningitis have regressed following antitubercular therapy and in an occasional patient where the brunt of disease from the beginning falls on the spinal cord, the cerebral involvement being minimal. We established that use of intrathecal cortico-steroids along with systemic antitubercular chemotherapy produced remarkable remission of the signs and symptoms in selected cases.[9,28,51]

POST-MENINGITIC HYDROCEPHALUS

This is one of the commonest complications—rather an accompaniment—of TBM. According to Mullener,[6] in the 18th century, CNS tuberculosis was primarily identified as 'Dropsy in the brain' or 'febris hydrocephalica'. The credit for recognizing the role of meningitis as the cause of hydrocephalus goes to Odier,[6] although the term meningitis was used for the first time by Herpin only in 1803.[52] Before the introduction of CT/MRI in the late 1970s and early 1980s, the only diagnostic procedure available to assess the CSF pathways were PEG/VEG, myelography. These investigations often provided misleading or inadequate information as to the cause of the hydrocephalus resulting in unsuccessful therapy.[30,53,54] In those early days the ventricular diversion shunts (Pudenz or Holter) required for surgical relief of this condition were not available in India. Based on our experience with use of hydrocortisone in cases of post-meningitic spinal arachnoiditis mentioned earlier, we attempted its intraventricular use along with standard medical treatment in a series of children with post-meningitic hydrocephalus without any success. We realized that

it was necessary to have more precise knowledge of the CSF pathways to plan a rational surgical approach. It was only in 1969 that we managed to persuade the Bhabha Atomic Research Centre (BARC) to provide us radio-iodine (131-I) labelled human serum albumin (RISHA) to enable us to study the CSF dynamics in these patients.[31,32] Isotope scanning of CSF pathways revealed abnormalities of the pathways and/or flow dynamics in two-thirds of patients with tuberculous meningitis. It established the precise cause of raised intracranial pressure and hydrocephalus in all such patients. The site of obstruction in CSF pathways could be single or multiple. The study provided information, for the first time, to enable evidence-based rational therapy.[32] This was the first comprehensive investigation of CSF pathways in patients with TBM in the world. Thanks to Professor Purushotam Upadhyaya, our paediatric surgeon's innovative efforts, we soon were able to get his indigenously manufactured shunt assembly to treat these patients. He and his group later published their experience with this shunt.[55]

INTRACRANIAL TUBERCULOMAS (ICtm)

As mentioned earlier, by the time I started my neurosurgery career in Lucknow in 1961, reports from Bombay, Madras and Vellore had established that tuberculoma was one of the most common intracranial space-occupying lesions (ICSOLs) in India—as high as 30.5% of all ICSOLs in Bombay[56,57] and 20% at Madras.[22,58,59] This was before the era of CT scans. Hence, it was difficult to be sure of the diagnosis preoperatively. Dastur and Desai[19] had highlighted this problem on the basis of a comparative study of 107 cases each of brain tuberculomas and gliomas.

By 1977, when we had operated upon 1029 ICSOLs at AIIMS, the incidence of tuberculomas was only 4.2%, the lowest from any centre in India, even when the incidence of pulmonary tuberculosis and TBM remained quite high.[60] This trend continued even when we had operated upon over 2000 ICSOLs. Even among children we reported an incidence of only 9.1%,[61] compared to over 30% from Madras and Bombay.[56,62,63] Similarly Kak[64] from Chandigarh reported a relatively lower incidence (8%) than seen by us in Delhi, and Bagchi[65] reported an incidence of 8% from Calcutta. The reason for this regional difference in the incidence by ICtm is still not clear. By the mid-1990s the incidence of ICtm had started to decrease all over India. Radiologically, cases of ICtm presented in diverse forms—single small or nodular, large, single or multiple, plaque-like, as cluster of grapes,[8] cystic or as an abscess,[66] in the basal ganglia and thalamus,[67] anterior pituitary,[68] and in the brainstem.[69] In the earlier years, the standard treatment of ICtm was surgical excision which was safe under cover of antitubercular therapy.[8] There were stray reports of single cases of tuberculoma resolving on medical treatment. On the other hand, there were reports of tuberculoma appearing in patients on antitubercular therapy for TBM.[70,71] However, with the availability of the first CT scan in India in 1978 at AIIMS, we decided to study the possibility of non-invasive diagnosis of these lesions.[72] Once reasonably certain of the CT diagnosis, it was considered ethically and scientifically justified to prospectively study the effect of medical therapy with or without corticosteroids instead of surgery. A series of 50 patients, whose life or vision was not threatened by associated raised intracranial pressure were put on standard antitubercular therapy.[73] Most small- and medium-sized lesions resolved completely. Central liquefaction requiring surgical evacuation was observed in one patient with brainstem tuberculoma.[74] Only 3 patients failed to respond to treatment and one person died. Although it was not a randomized controlled trial, it provided unequivocal evidence that antitubercular therapy alone would cure most, it not all, cases of ICtm.

In 1989, we reported our experience with ICtm at the World Congress of Neurology, confirming the value of antitubercular therapy alone.[75] This regimen has now been generally adopted as the first and in most cases the only treatment of choice, making surgical therapy almost unnecessary.[10] Interesting data, based on a DM Thesis, on CNS tuberculosis (2007–2017), have been recently provided by Tripathi (personal communication, M. Tripathi, 2018)—of 125 patients with ICtm only 12 required surgery. This finds confirmation in the current surgical pathology data provided by Sarkar (personal communication, C. Sarkar, 2017). Between 2012 and 2016, among the 18 827 CNS 'tumours' submitted to biopsy there were only 95 tubercular lesions—50 intracranial and 45 spinal. Thus, barring a few exceptions, the standard treatment for ICtm now is medical therapy and not surgery.

DISCUSSION

Tubercle bacillus, one of the most ubiquitous pathogens, in existence since antiquity, which is able to afflict practically all parts of the body, produces its most devasting effects when it involves the CNS. Its protean manifestations, and ability to survive in a dormant state in the body for a long duration results in diverse pathologies, make its diagnosis and management a Herculean task. Its high prevalence affecting the CNS inevitably aroused interest of both clinical and basic scientists in India. We soon discovered that the existing textbook descriptions of its clinical manifestations, methods of diagnosis and problems of management were inadequate to meet its challenges. Obviously, 'tuberculosis had not read the books' and 'the books failed to keep up' with its 'devious ways of evading its eradication'. Thus, we ended up re-exploring practically all aspects of neurotuberculosis—its pathology, pathogenesis, clinical manifestations, diagnosis and management of diverse syndromes had to be redefined and elaborated and new strategies for treatment evaluated. In this brief write-up, I have attempted to summarize our efforts in this direction. While no revolutionary discoveries were made, we had the satisfaction of adding some valuable new information and improving the management of our patients. Thus, we were able to develop an experimental model of the disease in Rhesus monkeys, and were pioneers in studying its diverse effects on CSF pathways and flow dynamics, and were among the first to describe its image morphology on CT. But the most gratifying part of our efforts was to revolutionize the treatment of ICtm, virtually eliminating the need for surgery for the vast majority of such patients. That these contributions were globally recognized is evidenced by being invited to contribute to the most prestigious textbooks of neurology and operative neurosurgery.[8,9,76–78] Our studies were abstracted in *Infectious Disease Abstracts* and quoted in a textbook on CSF in diseases of the nervous system.[79] In his book, Kocen commented, 'In more recent years, the major contributions on both the pathology and the varied clinical manifestations of tuberculosis of the brain and spinal cord have come from India, in particular from Dastur, Tandon and Wadia.'[79]

CLOSING REMARKS

The above account summarizes the research contributions of AIIMS in the field of CNS tuberculosis. It reflects to a large extent those areas in which I was personally involved. It is also biased in highlighting the contributions of the department of neurosurgery because of my greater familiarity with it. A brief mention has been made of the contributions by other departments, especially

neurology, neuroradiology and neuropathology on related subjects. It certainly is not a comprehensive review, but hopefully it will show how efforts were made, on a continuing basis, to resolve some of the clinically relevant, ill-understood management issues. It also reflects the advantages of timely use of emerging techniques and technologies especially those in the field of neuroimaging and molecular biology. These helped to refine our management strategies, resulting in evidence-based improvement in outcomes. It helped in radically modifying the therapy of ICtm.

REFERENCES

1 Morse D. Prehistoric tuberculosis in America. *Am Rev Respir Dis* 1961;**83:**489–504.
2 Morse D, Brothwell DR, Ucko PJ. Tuberculosis in ancient Egypt. *Am Rev Respir Dis* 1964;**90:**524–41.
3 Smith E, Dawson WR. *Egyptian mummies*. London:George Allen and Unwin; 1924.
4 Allison MJ, Mendoza D, Pezzia A. Documentation of a case of tuberculosis in Pre-Columbian America. *Am Rev Respir Dis* 1973;**107:**985–91.
5 Chalke HD. Some historical aspects of tuberculosis. *Public Health* 1959;**74:**83–95.
6 Mullener E-R. Six Geneva physicians on meningitis. *J History Med Allied Sci* 1965;**20:**1–26.
7 Koch R. [Die Aetiologie der Tuberculose]. *Berl Klin Wochenschrift* 1882;**19:** 221–30.
8 Tandon PN, Pathak SN. Tuberculosis of the nervous system. In: Spillane JE. *Tropical neurology*. London:Oxford University Press; 1973:37–62.
9 Tandon PN. Tuberculous meningitis (cranial and spinal). In: Vinken PJ, Bruyn GW (eds). *Handbook of clinical neurology*. Volume 33. Amsterdam:North Holland Publishers; 1978:195–262.
10 Tandon PN. Nervous system tuberculomas and their treatment. *Neurol Infn Epid* 1996;**1:**109–17.
11 Khatua SP. Tuberculous meningitis in children; analysis of 231 cases. *J Indian Med Assoc* 1961;**37:**332–7.
12 Manchanda SS, Lal H. Tuberculous meningitis in children—a problem unsolved in India. *Indian Pediatr* 1966;**3:**167–76.
13 Prasad S. Etio-epidemiology of tuberculous meningitis in children. *Indian J Child Health* 1963;**12:**110–16.
14 Sheth SC. Extrapulmonary tuberculosis, incidence, diagnosis and management. *J Indian Med Assoc* 1961;**37:**443–6.
15 Udani PM. Incidence of tuberculosis in children. *Indian J Child Health* 1961;**10:** 515–24b.
16 Dastur DK, Udani PM. Pathology and pathogenesis of tuberculous encephalopathy. In: Proceedings V International Congress of Neuropathology. *Excerpta Medica* 1965:1006.
17 Dastur DK, Udani PM. The pathology and pathogenesis of tuberculous encephalopathy. *Acta Neuropathol* 1966;**6:**311–26.
18 Udani PM, Parekh UC, Dastur DK. Neurological and related syndromes in CNS tuberculosis. Clinical features and pathogenesis. *J Neurol Sci* 1971;**14:**341–57.
19 Dastur HM, Desai AD. A comparative study of brain tuberculomas and gliomas based upon 107 case records of each. *Brain* 1965;**88:**375–96.
20 Ramamurthi B: Tuberculomas of the brain. *Indian J. Surg* 1956;**18:**452.
21 Ramamurthi B: Treatment of tuberculomas of the brain in children. *Indian J. Child Health* 1960;**9:**193.
22 Mathai KV, Chandy J. Tuberculous infections of the nervous system. *Clin Neurosurg* 1966;**14:**145–77. PubMed PMID: 5992186.
23 Tandon PN, Tandon HD: Tuberculus meningitis: A continuing challenge. *J All India Inst Med Sci* 1975;**1:**99–112.
24 Lorber J. Treatment of tuberculous meningitis. *Br Med J* 1960;**1:**1309–12.
25 Smith HV. Tuberculous meningitis. *Int. J. Neurol* 1963;**4:**134.
26 Falk A. U.S. Veterans administration-armed forces cooperative study on the chemotherapy of tuberculosis.13. Tuberculous meningitis in adults, with special reference to survival, neurologic residuals, and work status. *Am Rev Respir Dis* 1965;**91:**823–31.
27 Misra RN, Tandon PN, Lahiri AK: Etiological survey of paraplegia. *Neurol India* 1964;**12:**50–53.
28 Tandon PN. Spinal tuberculosis. In: Ramamurthi B, Tandon PN (eds). *Textbook of neurosurgery*. New Delhi:National Book Trust; 1980:713–25.
29 Rich AR. *The pathogenesis of tuberculosis*. Springfield, Illinois:Charles C. Thomas; 1951.
30 Tandon PN, Singh B, Mohapatra LN, Kumar M, Das S. Experimental tuberculosis of the central nervous system. *Neurol India* 1970;**18:**81–5.
31 Tandon PN, Rao MAP, Pathak SN, Dar J. RISHA cistemography in the management of tuberculous meningitis. In: Kapila CC, Dastur DK, Singh B, Tandon PN (eds). *Tuberculosis of the nervous system*. New Delhi:Indian Academy of Medical Sciences; 1972:55–7.
32 Tandon PN, Rao MAP, Pathak SN, *et al*. Radio-isotope scanning of the cerebrospinal fluid pathways in tuberculous meningitis. *J. Neurol Sci* 1975;**25:**401–13.
33 Mehbooullah, Shriniwas, Bhuwala RA *et al*. Fate of Mycobacterium tuberculosis in BCG vaccinated and normal guinea pigs. *Neurol India* 1982;**30:**232–8.
34 Shriniwas, Mahboobullah, Bhujwala RA, Pal D, Kiran U, Tandon PN. Fate of Mycobacterium tuberculosis and M. scrofulaceum in guinea pigs after intracisternal inoculation. *Indian J Med Res* 1983;**78:**751–5.
35 Ahuja GK, Mohan KK, Prasad K, Behari M. Diagnostic criteria for tuberculous meningitis and their validation. *Tuber Lung Dis* 1994;**75:**149–52.
36 Praharaj SS, Sharma MC, Prasad K, Misra NK, Mahapatra AK. Unilateral meningeal thickening: A rare presentation of tuberculous meningitis. *Clin Neurol Neurosurg* 1997;**99:**60–2.
37 Goyal M, Sharma A, Mishra NK, Gaikwad SB, Sharma MC. Imaging appearance of pachymeningeal tuberculosis. *AJR Am J Roentgenol*. 1997;**169:**1421–4.
38 Behari M, Raj M, Ahuja GK, Shrinivas. Soluble antigen fluorescent antibody test in the serodiagnosis of tuberculous meningitis. *J Assoc Physicians India*. 1989;**37:** 499–501.
39 Shankar P, Manjunath N, Mohan KK, Prasad K, Behari M, Shriniwas, Ahuja GK. Rapid diagnosis of tuberculous meningitis by polymerase chain reaction. *Lancet* 1991;**337:**5–7.
40 Seth P, Ahuja GK, Bhanu NV, Behari M, Bhowmik S, Broor S, *et al*. Evaluation of polymerase chain reaction for rapid diagnosis of clinically suspected tuberculous meningitis. *Tuber Lung Dis* 1996;**77:**353–7.
41 Singh KK, Nair MD, Radhakrishnan K, Tyagi JS. Utility of PCR assay in diagnosis of en-plaque tuberculoma of the brain. *J Clin Microbiol* 1999;**37:**467–70.
42 Haldar S, Sharma N, Gupta VK, Tyagi JS. Efficient diagnosis of tuberculous meningitis by detection of Mycobacterium tuberculosis DNA in cerebrospinal fluid filtrates using PCR. *J Med Microbiol* 2009;**58:**616–24.
43 Haldar S, Sankhyan N, Sharma N, Bansal A, Jain V, Gupta VK, *et al*. Detection of Mycobacterium tuberculosis GlcB or HspX Antigens or devR DNA impacts the rapid diagnosis of tuberculous meningitis in children. *PLoS One* 2012;**7:**e44630.
44 Bhargava S, Gupta AK, Tandon PN. Tuberculous meningitis—a CT study. *Br J Radiol* 1982;**55:**189–96.
45 Kumarvelu S, Prasad K, Khosla A, Behari M, Ahuja GK. Randomized controlled trial of dexamethasone in tuberculous meningitis. *Tuber Lung Dis* 1994;**75:**203–7.
46 Prasad K, Menon GR. Corticosteroid adjunctive treatment in tuberculous meningitis. A meta-analytic study. *J Clin Epidemiol* 1999;**52** (Suppl 1):19S.
47 Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev* 2008;(1):CD002244. Update in: *Cochrane Database Syst Rev* 2016;**4:**CD002244.
48 Sharma SK, Ryan H, Khaparde S, Sachdeva KS, Singh AD, Mohan A, *et al*. Index-TB guidelines: Guidelines on extrapulmonary tuberculosis for India. *Indian J Med Res* 2017;**145:**448–463.
49 Wadia NH, Dastur DK. Spinal meningitides with radiculo-myelopathy. 1. Clinical and radiological features. *J Neurol Sci* 1969;**8:**239–60.
50 Dastur D, Wadia NH. Spinal meningitides with radiculo-myelopathy. 2. Pathology and pathogenesis. *J Neurol Sci* 1969;**8:**261–97.
51 Tandon PN, Misra RN, Singh B: Post-meningitis spinal arachnoiditis: *Bull All India Inst. Med. Sci* 1968;**2:**88–96.
52 Tandon PN, Pande A. Tuberculosis of the central nervous system. In: Tandon PN, Ramamuthi B (eds). *Textbook of neurosurgery*. 3rd ed. New Delhi: Jaypee Brothers Medical Publishers; 2012:725–41.
53 Lall BN, Tandon PN, Ghosh SK. Positive contrast ventriculography. *Indian J Radiol* 1964;**18:**23–5.
54 Ghosh SK, Banerji AK, Haldar RK, Tandon PN. Positive contrast ventriculography. Some aspects of pitfalls in techniques and interpretation. *Indian J Radiol* 1970;**24:** 114–18.
55 Upadhyaya P, Bhargava S, Sundaram KR, Mitra DK, George J, Singh DC. Hydrocephalus caused by tuberculous meningitis: Clinical picture, CT findings and results of shunt surgery. *Z Kinderchir* 1983;**38** Suppl 2:76–9.
56 Lalitha VS, Dastur DK. Tuberculosis of central nervous system –Brain tuberculomas vis-à-vis intracranial space occupying lesions 1953–1978. *Neurol India* 1980;**28:** 202–6.
57 Dastur HM. A tuberculoma review with some personal experiences. I. Brain. *Neurol India* 1972 Sep;**20:**111–26.
58 Ramamurthi B. Batrajan: Treatment of tuberculomas of the brain in children. *Indian J. Child Health* 1960;3:193.
59 Ramamurthi B, Varadarajan MG. Diagnosis of tuberculomas of the brain. Clinical and radiological correlation. *J Neurosurg* 1961;**18:**1–7.
60 Tandon PN. Travails of neurosurgery in developing countries. *Int Neurol Madras Pros*. 1977;**7:**79–89.
61 Misra BK, Tandon PN, Banerji AK, Bhatia R. Intracranial tumours of infancy, childhood and adolescence. *Indian J Cancer* 1984;**21:**63–7.
62 *Ramamurthi: Twenty years* (Institute of Neurology, Madras). Madras:Manickan Press; 1970:35.
63 Bhagwati SN. Intracranial tuberculomas. *Neurol India* 1986;**34:**161–3.
64 Kak VK. Neurosurgery. In: Pandya SK (ed). *Neurosciences in India: Retrospect and prospect*. New Delhi:The Neurological Society of India and CSIR; 1989:593.
65 Bagchi A. The intracranial tuberculomas. *J Indian Med Assoc*. 1961;**37:**429–33.
66 Sandhyamani S, Roy S, Bhatia R. Tuberculous brain abscess. Acta Neurochir (Wien) 1981;**59:**247–56.
67 Bhatia R, Tandon P, Misra NK. Inflammatory lesions of the basal ganglia and thalamus: review of twenty-one cases. *Neurosurgery* 1986;**19:**983–8.

68 Chowdhry C, Mehta VS, Roy S. Tuberculomas of the anterior pituitary. A case report. *Neurol India* 1986;**34:**4.
69 Verma A, Tandon PN, Maheshwari MC. Trismus caused by paradoxical activity of jaw-closing muscles in brain stem tuberculoma. *Oral Surg Oral Med Oral Pathol* 1988;**65:**675–8.
70 Pauranik A, Behari M, Maheshwari MC. Appearance of tuberculoma during treatment of tuberculous meningitis. *Jpn J Med* 1987;**26:**332–4.
71 Borah NC, Maheshwari MC, Mishra NK, Goulatia RK. Appearance of tuberculoma during the course of TB meningitis. *J Neurol* 1984;**231:**269–70.
72 Bhargava S, Tandon PN. CNS tuberculosis: Lessons learnt from CT studies. *Neurol India* 1980;**28:**207–12.
73 Tandon PN, Bhargava S. Effect of medical treatment on intracranial tuberculomas—a CT study. *Tubercle* 1985;**66:**85–97.
74 Pandya SK, Desai AD, Dastur HM. Caseative liquefaction within brain stem tuberculomas under drug therapy. *Neurol India* 1982;**30:**121.
75 Tandon PN. Intracranial tuberculoma: Unsolved problems. In: Chopra JS (ed). *Advances in neurology*. Amsterdam:Elsevier Science (Biomedical Division); 1990: 299–308.
76 Tandon PN, Bhatia R, Bhargava S. Tuberculous meningitis. In: Harris AA (ed). *Handbook of clinical neurology*. Volume 8. Amsterdam:Elsevier Science; 1988: 195–266.
77 Bhatia R, Tandon PN. Surgical management of tuberculosis, cysticercosis and fungal infections of the nervous system. Indications, methods and results. In: Schmidek HH, Sweet WH (eds). *Operative neurosurgical techniques*. 2nd ed. Volume 1. New York:Grune & Stratton; 1978:79–91.
78 Patir R, Bhatia R, Tandon PN. Surgical treatment of tuberculous infections of the nervous system. In: Schmidek HH, Roberts DW (eds). *Schmidek and Sweet's operative neurosurgical techniques: Indications, methods, and results*. 5th ed. Philadelphia, PA:Saunders/Elsevier; 2006:1617–31.
79 Kocen R. Tuberculosis of the nervous system. In: Kennedy PGE, Johnson RT (eds). *Infections of the nervous system*. London:Butterworths; 1987.