

# Isolated brain stem tuberculoma presenting with “one and a half syndrome”

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## ABSTRACT

In this report, we describe a patient with left conjugate gaze palsy and internuclear ophthalmoplegia on the opposite gaze (one-and-a-half-syndrome [1½ syndrome]). Magnetic resonance imaging of the brain showed nodular enhancing brain stem lesions. After excluding other potential diseases, tuberculoma was thought to be the underlying etiology. Recovery was achieved 8 weeks after initiation of anti-tuberculous (anti-TB) therapy. The isolated nature of the tuberculoma and the association with this rare syndrome is highlighted.

Saudi Med J 2006; Vol. 27 (9): 1407-1411

Brain stem tuberculomas are most often seen in patients with tuberculous meningitis (TBM), or those with multiple tuberculomas of the brain. Isolated tuberculomas presenting as mass lesions in the brain stem without evidence of tuberculous involvement of any other system, or other parts of the central nervous system (CNS), are distinctly rare.<sup>1</sup> The objective of this report is to increase awareness of physicians to such a rare entity and to consider brain stem tuberculosis (TB) as one of the important differential diagnoses of brain stem space-occupying lesions (SOL).

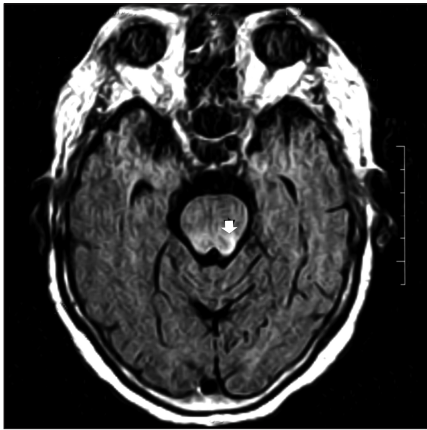
**Case Report.** A 73-year-old diabetic and hypertensive Saudi woman, with no previous or concurrent history of tuberculosis presented to the emergency department with repeated falls due to progressive bilateral eyelid droop over several weeks. There was no loss of consciousness, seizures or unusual movements. Her past medical history was remarkable for thyroidectomy (Hashimoto's

thyroiditis). She had no known exposure to persons with TB. On examination, she was conscious, partially confused with a temperature of 38.2°C. There were no signs of meningeal irritation. Cranial nerve examination revealed complete bilateral ptosis with preservation of pupil size in both eyes. The right eye was deviated outward in primary gaze (paralytic pontine exotropia). She was unable to move both eyes horizontally to the left, with failure of adduction of the left eye with nystagmus of the right eye on right horizontal gaze (internuclear ophthalmoplegia [INO]). She had extrapyramidal signs on the right upper and lower limbs; however, her tone, power and planter responses were normal. Reflexes were diminished. Funduscopic examination revealed no papilledema. The laboratory tests: leucocytosis of  $25.8 \times 10^9/l$  with neutrophilia of  $22.9 \times 10^9/l$ , hemoglobin of 13.5 g/dl, platelets of  $250 \times 10^9/l$ . Renal and liver function tests were normal. Thyroid stimulating hormone 35.6 (0.27-4.2 mIU/l), free throxine 7.6 (12-22 pmol/l). Erythrocyte

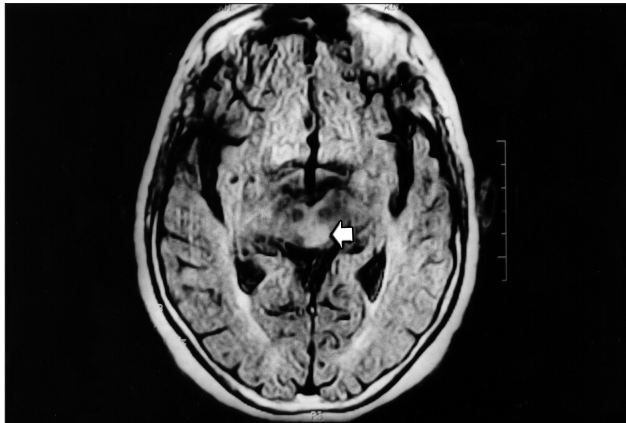
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Received 31st October 2005. Accepted for publication in final form 20th March 2006.

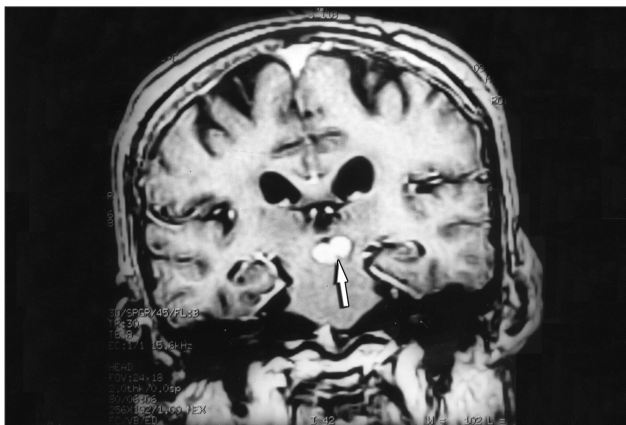
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**Figure 1** - Magnetic resonance imaging: Axial FLAIR sequence showing a diffuse intraaxial hyperintensity in the pontine isthmus crossing the midline more on the left side (arrow) with involvement of the medial longitudinal fascicles (MLF) and peri-aqueductal region.

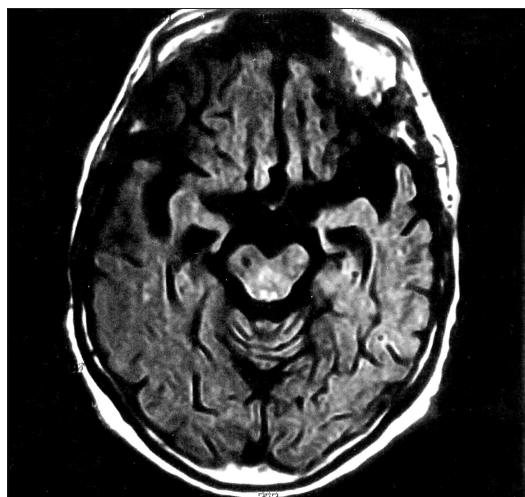


**Figure 2** - Magnetic resonance imaging: Axial FLAIR sequence at the level of the cerebral peduncles showing a diffuse intraaxial hyperintensity more on the left side (arrow).



**Figure 3** - Magnetic resonance imaging: Post contrast Coronal T1 showing 2 conglomerate enhancing nodular lesions at the level of the cerebral peduncles (long arrow).

sedimentation rate 46 mm/hr and C-reactive protein 51 mg/l. Brucella antibodies were not detected. A blood culture set was obtained, and she was started on ceftriaxone intravenously at a dose of 2 g every 12 hours, which was subsequently discontinued, due to the absence of meningitis. Cerebrospinal fluid analysis, revealed a clear fluid with leukocyte count of 4/mm<sup>3</sup>, red cells of 99/mm<sup>3</sup>, protein of 0.99 g/l and CSF glucose more than 50% that of serum. Direct examination and culture of CSF were negative for acid fast bacilli (AFB), fungal, and bacterial pathogens. Antinuclear antibody and rheumatoid factor were negative. Human immunodeficiency virus (HIV) and Mantoux tuberculin skin tests (5 tuberculin units) were negative. Chest radiograph was normal. Axial fluid attenuation inversion recovery (FLAIR) MRI at baseline in December 2004 (**Figures 1 & 2**) showed intra-axial hyper-intense lesions at the level of pontine isthmus and cerebral peduncle with surrounding peri-lesional edema suggestive of inflammatory process, possibly tuberculoma. There was no enhancement of basal meninges and no hydrocephalus. An old left thalamic and basal ganglia infarct was also demonstrated. Coronal MRI of the brain stem showed conglomerate enhancing nodular lesions at the level of the cerebral peduncles (**Figure 3**). Bilateral internal carotid angiogram, showed generalized atherosclerotic changes with no evidence of vascular occlusive lesion or vasculitis. Vertebral artery angiogram, showed similar atherosclerotic changes in the cranial portion of both vertebral arteries. Computed tomography of chest, abdomen and pelvis did not reveal any evidence of malignancy. She was started on rifampicin 600 mg, isoniazid 300 mg, ethambutol 1.2 g, and pyrazinamide 2 g orally once daily for 2 months, followed by rifampicin and isoniazid for a total of 9 months. Magnetic resonance imaging, one month after the start of anti-TB therapy, showed interval progression and ballooning of midbrain, and pontine lesions. The CSF analysis at that point, showed a leukocyte count of 46/mm<sup>3</sup>, red cells of 2480/mm<sup>3</sup>, protein of 0.76 g/l and glucose of 5.9 mmol/l. Direct examination and culture of CSF for AFB, fungal, and bacterial pathogens were negative. Cerebrospinal fluid, polymerase chain reaction (PCR) for TB, was carried out later at another center and it was negative. Dexamethasone at a dose of 4 mg every 6 hours was started for a presumed paradoxical expansion of the CNS tuberculomas on anti-TB therapy. At 8 weeks, this was discontinued, and her ptosis then improved approximately 70% in the left eye and 60% in the right eye. Left conjugate gaze improved remarkably, but the INO on the right gaze persisted. Follow up brain MRI, 8 and 12 weeks after starting anti-TB therapy showed interval



**Figure 4** - Axial FLAIR sequence at the level of cerebral peduncles showing interval regression in the magnitude and severity of the diffuse hyperintensity (noted in Figure 2) with minimal residual changes.

regression of pontine and midbrain lesions with resolution of the peri-lesional edema. She continued to do well on further follow up, and after 9 months of therapy, she showed complete reversal of the clinical syndrome, and significant resolution of the brain stem abnormalities on magnetic resonance imaging (**Figure 4**).

**Discussion.** Central nervous system tuberculosis (CNS-TB), is the most serious form of extrapulmonary tuberculosis. It may occur in approximately 10% of immunocompetent subjects.<sup>1</sup> In developing countries, the incidence of brain tuberculoma constitutes 5-40% of intracranial SOL.<sup>2</sup> In a study in Saudi Arabia, CNS tuberculoma constituted 10-15% of all SOL.<sup>3</sup> The pattern of nervous system TB varies from TBM, tuberculoma, TB abscess, and spondylitis. Bahemuka et al<sup>4</sup> described the pattern of CNS-TB in 121 consecutive patients with infection of the nervous system in Riyadh, Saudi Arabia, and found that brain tuberculomas, and TB brain abscesses constituted 35.9% (14 out of 39 patients with CNS-TB), while TBM and spinal TB were seen in 28.2% (11/39), and 35.9% (14/39) of cases respectively. This pattern is different from that described in the literature, where meningitis occurred more often.<sup>5</sup> The CNS tuberculoma presents with seizures, mental state abnormality, gaze disturbance, monoplegias, hemiplegias or cranial nerve palsies, frequently the second, third, fourth, sixth and seventh nerves. In less common forms of tuberculomas of the basal ganglia, brain stem

and cerebellum, differentiation from primary or secondary neoplasia is problematic, particularly in adults.<sup>6</sup> Isolated brain stem tuberculoma, is the least common accounting for 2.5-8% of all intracranial tuberculomas.<sup>7</sup> The differential diagnosis of brain stem SOL includes pyogenic, fungal, parasitic, spirochetal brain abscesses, neurobrucellosis and tuberculosis. Primary CNS malignancy, such as, gliomas, astrocytomas, meningiomas, lymphoma and secondary malignancies from breast, lung, and melanomas may mimic tuberculoma. Neurosarcoidosis and vascular malformations, are among the other non-infectious etiologies of brain stem SOL. The differentiation between tuberculoma and brain tumor is never absolute, clinically or radiologically. Brain stem tuberculomas, are most often seen in patients with TBM or multiple tuberculomas of the brain. Isolated tuberculomas presenting as mass lesions in the brain stem without evidence of tuberculous involvement of any other system or other parts of the CNS, are distinctly rare.<sup>8</sup> Recent development in MRI, have defined groups of appearances in which the probability of the diagnosis of parenchymal tuberculoma is extremely high particularly in areas where TB is endemic. The FLAIR acquisitions are helpful in cases, where meningeal disease is suspected.<sup>9</sup> The role of biopsy is controversial. The advantage of tissue diagnosis is the possibility to reach a definite diagnosis, culture of *Mycobacterium tuberculosis*, and hence, proper selection of drugs for resistant strains, easier interpretation of paradoxical reactions, and early exclusion of more serious conditions.<sup>5</sup> However, biopsy is expensive, can be complicated by dissemination of TB infection in the CNS and residual neurological deficit.<sup>10</sup> In addition, biopsy is not always diagnostic, as the pathologic diagnosis is not absolute, evidence of AFB is not commonly found, caseating granulomatous lesions if reported may be the only evidence of mycobacterial infection and growth of *Mycobacterium tuberculosis* from CSF can take up to 8 weeks.<sup>11</sup> Fisher<sup>12</sup> in 1967 coined the term "1½ syndrome" for a paralysis of eye movements in which one eye lies centrally and fails completely to move horizontally, while the other eye lies in an abducted position and cannot be adducted past the midline. The etiology of this syndrome is unilateral pontine tegmental lesion, affecting the paramedian pontine reticular formation (PPRF) or 6th nerve nucleus causing ipsilateral conjugate gaze palsy. It can also involve the adjacent medial longitudinal fasciculus; causing loss of adduction of the ipsilateral eye on conjugate gaze to the opposite side, namely, one and half components of normal conjugate gaze

**Table 1** - Reported cases of brain stem tuberculoma presenting with “1½ syndrome”.

Author	Year	Age/gender	CNS site	Other diseases	Biopsy	CSF	Outcome
Talamus <sup>13</sup>	1989	53M	P	PI effusion	N	Normal	Died
Minager <sup>14</sup>	2000	27M	P	AIDS, IVDU, TBM	N	Abnormal	CR
Vimla <sup>15</sup>	2004	12F	P/MB	NONE	N	Normal	CR
Enani	2006	73F	P/MB	DM, HTN	N	Normal	CR

CNS – central nervous system, CSF – cerebrospinal fluid, P - pons, PI –pleural, N – not done, IVDU – intravenous drug user, TBM – tuberculosis meningitis, CR - complete recovery, MB – midbrain, DM – diabetes mellitus, HTN - hypertension, AIDS - acquired immunodeficiency syndrome.

is lost. Tuberculosis is rarely the underlying cause of this syndrome. This association had been reported only 3 times in the literature.<sup>13,14,15</sup> (Table 1). Vimla et al<sup>15</sup> reported a 12 year old patient, who presented with isolated “1½ syndrome”, MRI showed conglomerate lesions in pons and midbrain with an intermediate signal rim surrounding the lesion. Empirical treatment with anti-TB drugs resulted in complete restoration of ocular motility with resolution of lesions on follow up MRI at 6 months. This was similar to our patient as in both cases, the brain stem was the only site for the presumed tuberculoma, and biopsy was not performed taking the epidemiological settings for TB in consideration, and due to the concern of residual neurological deficits on sampling a deep brain structure. Foyaca-Sibat and Ibanez-Valdes,<sup>16</sup> described a series of 19 patients with “1½ syndrome” and provided a novel classification. In their series, the most common causes were hemorrhagic stroke, subarachnoid hemorrhage, and demyelinating diseases. Basilar artery aneurysm, secondary to HIV-associated vasculitis was reported in one patient with the classical “1½ syndrome” Type 1. Three other AIDS patients with atypical forms of the syndrome were also reported. One with concomitant cryptococcal meningitis, another with neurocysticercosis, and the third with cerebral tuberculoma/cavernous sinus syndrome. There was no brain stem involvement in the last patient. Our patient’s presentation was rather unique. She had no TB involvement elsewhere. The complete bilateral ptosis was explained by the midbrain lesion involving the 3rd nerve nuclei and the pontine lesion predominantly on the left side, involved the left PPRF causing conjugate gaze palsy. Another unusual feature, was the development of biochemical but not clinical TBM one month after treatment coinciding with the paradoxical response. Although the diagnosis of brain stem TB was presumptive, and the expansion of the lesion on anti-

TB treatment was worrisome, the response to short course of corticosteroids and the progressive clinical improvement on continuation of anti-TB drugs after steroid withdrawal, supported by radiological resolution, made the diagnosis appropriate.

In conclusion, although isolated brain stem tuberculoma is extremely rare, it should be seriously considered in the differential diagnosis of brain stem SOL. The diagnosis of brain stem tuberculoma, is difficult without tissue confirmation. However, in endemic regions proper integration of clinical and radiological data with the response to anti-TB therapy makes the diagnosis almost certain.

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