Review Article

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Date received: 14/8/2018 Date accepted: 26/8/2018

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The craniovertebral junction (CVJ) is an anatomical complex formed by the basi occiput, lower 3rd of the clivus, foramen magnum and the upper two cervical vertebrae, along with the ligaments, vascular and nervous structures passing through these bony structures. Wide spectrum of developmental and acquired anomalies occurs at the CVJ. This is due to the complex developmental anatomy, the highly mobile junction of the upper cervical spine and the skull, and the complex transition between the spinal cord and the brain¹⁹. The resulting compression and destruction of the neuraxis as well as the vertebrobasilar tree leads to a constellation of symptoms and signs that often complicate the diagnosis of these disorders in children as well as in the adults.^{18,51,53}.

Spinal tuberculosis manifests in less than 1 % of patients with tuberculosis.⁷ Among the patients with tubercular spondylosis, CVJ tuberculosis is extremely rare consisting of just 0.3 to 1 % of cases.^{13,16,31} Tuberculosis at CVJ may cause AAD, secondary basilar impression⁷, epidural abscess and or granuloma leading to cervico medullary compression.¹²

The clinical profile of tubercular AAD ranges from nonspecific chronic clinical manifestations to marked neurological deficits. Delay in diagnosis may lead to irreversible neurological deficits and even death¹⁷. The diagnosis mainly depends up on clinicoradiological futures and confirmation by histopathological and bacteriological studies. Some times it may be difficult to differentiate it from pyogenic or fungal infection and neoplastic conditions like lymphoma or myeloma.^{22,55}. When treated adequately, tuberculosis is curable in almost all cases. Thus prompt diagnosis and timely intervention is the key to success in the management of this complex entity.

Tuberculosis (TB) of the vertebral column accounts for about 6% of extra pulmonary disease or approximately 5% of all diseases caused by Mycobacterium tuberculosis^{4,54}. In the spine, tuberculosis most commonly affects the thoraco lumbar region where as cervical tuberculosis is less common. Incidence of cervical TB ranges between Nepal Journal of Neurosciences 15:3-10, 2018

The Systemic Review of CV Junction Tuberculosis

5-15% of all cases of spinal TB^{2,15,25,34}. The tuberculosis of the atlanto axial region is the least common form of spinal tuberculosis. Tuli reported 1% of TB of craniovertebral junction where as Wang reported 0.3% incidence of CVJ TB.^{52,53,57}

The first case of CVJ tuberculosis was described by John Hilton and stressed the importance of rest for such patients.^{39,40} Since then lot of advances took place in the management and the journey came to the same conservative management. Tuli in 1975 proposed most appropriate guidelines and advocated the "*middle path regimen*" for the successful management of CVJ tuberculosis⁵². For the last two decades enormous amount of literature on CVJ tuberculosis is published from INDIA and many authors proposed excellent treatment guidelines.^{5,7,8,23,43,50,51,53} (Table 1)

Pathophysiological Mechanisms:

Cranio vertebral junction tuberculosis is a secondary infection beginning in either retropharyngeal space with secondary involvement of bone or rarely in the bone it self. With progression of the disease there is increasing ligamentous involvement with erosion of odontoid or C1 vertebra with a unstable articulation between the occiput and C1. If occipital condyles or C1 lateral masses are involved CVJ TB leads to AAD by two mechanisms such as osteomyelitis and destruction of the ligaments mainly the transverse and alar.^{33,40} Primary infection of the atlas or axis was rarely the cause of disease. Pandya described the possible mechanism of dislocation and pathological changes elucidated by autopsy studies and concluded that, there was involvement of the bone and ligaments by the disease process with destruction of the entire atlantoaxial ligaments.⁴⁰ Many authors have staged or graded the disease based on the pathological, radiological or clinicoradiological findings^{17,28,32} (Table 2).

Series	No of Pa- tients	Type of management	Ave. Grade	Mortality
Arora S ⁵ , 2011	26	Medical	N/A	NIL
ArunKumar MJ ⁶ ,2002	9	Surgical	Nurick's ³⁵ 3.4	NIL
Behari S ⁷ , 2003	25	Middle path regimen	2.5	NIL
Bhojraj S ⁸ ,2001	25	Middle path regimen	N/A	NIL
Chatterjee S ⁹ , 2015	23 (Paeds.)	Middle path regimen	2.3	NIL
Chaudhary K ¹⁰ , 2012	15	Middle path regimen	N/A	NIL
Gupta S K ²³ , 2006	51	Variable regimens according to different time periods	2.1	2
Qureshi M A ⁴² , 2013	15	Middle path regimen	N/A	NIL
Shukla D ⁴⁸ , 2005	24	Middle path regimen	N/A	NIL
Sinha S ⁵⁰ , 2003	18	Surgical N/A		1
TeegalaR ⁵¹ , 2008	71	Middle path regimen1.7NIL		NIL

Table 1: Compilation of different series and their management strategies

Neurological deficits following cord compression are multiple; they are not entirely related to the amount of soft tissue collection. These symptoms may present at various stages of the disease process. On the basis of magnetic resonance imaging (MRI), Pattison and Hoffman etal stated that 60% or more of the spinal cord compression results in neurological deficits.41,11,24 Al-Mulhim etal proposed that less than 50% narrowing of the cervical spine produces only mild to moderate deficits and that more than 75% narrowing causes severe neurological deficits.³ During the active phases of CVJ TB, however, predicting the neurological deficits on the basis of the extent of cervico-medullary compression may lead to a false sense of severity because the neurological deficits are the result of both the cervico-medullary compression and the instability. Likewise, during the stage of healing, the persistence of various grades of subluxation may not correspond to either neural recovery or the quality of mechanical stabilization achieved during the process of healing.³ This finding was apparent in the patients who improved from severe neurological deficits to near normal power on the ATT with immobilization of the neck, although their fixed AAD persisted.

Clinical Spectrum

Clinical presentations and radiological feature of CVJ TB have been extensively described in literature.^{47-51,53} Sub occipital pain being nearly ubiquitous.^{7,8,27,40,51} This

symptom along with the restricted neck movements, the tenderness over the upper cervical vertebrae and positive Hilton test (pain on application of pressure over the head and attempted rotation of the head over the neck) led most of the patients to be investigated. Though there is no statistically proven sex or age predilection of CVJ TB, many of the reported series had male predominance few with female predominance^{8,17,30,32}. Majority of the diseased patients in either 2nd or 3rd decade constituted 75% of the total. Other series have also reported adult predominance except Fang who has showed pediatric predominance.¹⁷ About 30-70% of patients with CVJ TB have been reported to present with neurological deficits.⁶ Neurological complications are more common and serious in cervical spine TB than in other vertebral TB. In the series of Hsu the incidence of cord compression was 42.5% compared with 15-30% over all incidence of compressive myelopathy seen in TB of the spine at other locations.²⁵ Early onset symptoms may be mild and non specific and there may be associated constitutional features such as malaise, nocturnal increase in body temperature, or weight loss^{17,20,27,31,33} Non specific neck pain and stiffness often lead to delayed diagnosis, sudden neurological deterioration and even death49. Instability of C1 and C2 can lead to acute compressions of the CV junction and sudden cardio respiratory arrest²⁷. Sinha *etal* reported that all the patients with CVJ tuberculosis presented initially with neck pain, neck stiffness with or without associated torticollis, leading to gradual quadriparesis and neurological deterioration.⁵⁰

CVJ tuberculosis

Author	Grade / Stage	Nature of clas- sification	1	2	3	4
Khandelwa l ²⁸	Stage	Radiological	Retropharyngeal abscess and no bony destruction.	Ligamentous de- struction with AAD, minimal bone destruction and retropharyn- geal mass.	Marked destruc- tion of bone, com- plete obliteration of anterior arch of C1 and eventually complete loss of the odontoid pro- cess, marked atlan- to axial as well as Occipito- Atlantal instability.	-
			Minor Deficits		Major Deficits	
Behari ⁷	Grade	Clinical	Only neck pain with out pyrami- dal tract involve- ment	Minor disability	Partially dependent for activities of dai- ly living	Totally de- pendent for activities of daily living
Krishnan ³⁰	Grade	Radiological	0: No displace- ment of the theca and no evidence of compression of the spinal cord.	1:Displacement of the theca with out any evidence of compression of the spinal cord.	2:Compression of the spinal cord with or with out degen- erative changes such as syrinx or myelomalacia.	-
Goel ¹⁸	Stage	Pathological	Unilateral in- volvement of the cancellous part of the facet of atlas	The disease pro- gresses to involve the atlantoaxial joint by destruc- tive necrosis and inflammation	The disease in- volves the contral- ateral atlantoaxial joint and other bones and joints in the region. Evi- dence of instability of the craniover- tebral junction is usually seen	
TeegalaR ⁵¹	A I - I M S C V J Grad- ing	Clinico radio- logical based on objective scoring system	Grade1: 3-5 com- posite score	Grade 2: 5-6	Grade3: 7-8	

Table 2: Summary of staging & grading of CVJ TB

Behari etal showed 72 % motor weakness and 48% of sensory impairment.⁷ Based on this grading, patients were divided into minor deficits, those who are having in grade I and grade II or severe deficits those who are in grade III or grade IV. They gave a surgical management protocol basing this disability grading. Minor deficits patients will be managed conservatively and severe deficits patients were primarily managed surgically.

For the first time, TeegalaR et al proposed All India Institute of Medical Sciences Craniovertebral junction tuberculosis grading system based on the clinicoradiological findings.⁵¹ The scoring was developed on restriction of neck movements, motor power and radiological parameters. A patient can attain a composite score of 3to 8. Patients are divided into Grade 1(score 3-4). Based on this grading system they proposed the management protocol. (Fig.1)

As reported by Dhammi and Raut, there are some unusual presentations of weakness in the form of hemiplegia or monoplegia in patients of CVJ TB.^{14,44} Though the exact mechanism of these unusual presentation are not known, It is believed that, if cervico medullary junction involvement extends slightly higher with involvement of one of the branches of the vertebral or lower basilar

Criteria	Description				
Essential	Radiological evidence of paravertebral collection with or without bone destruction and instability				
Supportive					
	1. Histopathological evidence of TB				
Major	2. Microbiological evidence of TB				
	3. Molecular diagnostic studies like Gene Expert				
Minor	1. Associated radiological evidence of pulmonary TB				
	2. Erythrocyte Sedimentation Rate (ESR) ≥50mm/1Hr				
	3. Positive Montoux test				
	4. Constitutional symptoms				
	Nocturnal increase in Temperature				
	• >10% weight loss in last 3 months				
	Loss of Appetite				
	5. Past of Tuberculosis				
	6. Clinicoradiological response to ATT				

Table 3. AIIMS diagnostic criteria of CVJ TB

artery causing medial medullary syndrome, sparing medial lemniscus. Thus the pyramids will be involved causing contra lateral hemi or monoparesis depending on the extent of pyramidal involvement. Theoretically all permutations and combinations can be explained by the site of lesion and decussation pattern of various fibers in the cervico medullary junction.

Torticollis, dysphagia, dysphonia, respiratory distress and sphincteric involvement are the other presenting features^{23,50,51}. Though sudden death has also been attributed to the unrecognized atlanto axial instability none of the other reported large series had such experience⁴⁰. The reported incidence of extra spinal tuberculosis in patients with CVJ tuberculosis ranged from 11 to 20%^{7,17,32,51}.

Imaging Studies & Diagnosis

Most often the diagnosis of CVJ TB was evident on the lateral plain radiographs of the CVJ⁵⁶. The combination of erosion of the atlas or axis, AAD and increased prevertebral soft tissue shadow was almost pathognomonic of CVJTB in the endemic area. Sometimes in plain radiographs of the CVJ in flexion and extension, the destruction of the anterior arch of the atlas and the Odontoid by the tubercular process leads to the loss of conventional radiological landmarks used to demonstrate AAD. In these circumstances, the diagnosis of AAD and its reducibility was made on the basis of the changes in the spinolaminar line. The plain film changes may lag behind the pathological alterations in the tuberculous spondylitis by up to 2to 6 months because the radiographic evidence of bone erosion appears only after 50% of the vertebra has been destroyed^{32,13,37}. The CT, MRI of the CVJ in the early phase of CVJ TB readily demonstrated bony fragmentation at the vertebral end plates and an associated obliteration of fat planes around the vertebral body in the early evolution of abscess²⁴ .The presence of multiloculations, calcified abscess with a thick enhancing irregular rim in the presence of vertebral body fragmentation is pathognomonic of TB and differentiates tuberculosis from other lesions at the CVJ, such as Rheumatoid arthritis, Brucellosis, Sarcoidosis, Fungal infection, Lymphoma or Chordoma⁴⁷. Latter conditions may produce a radiological appearance quite similar to that of CVJ TB except for the caseation necrosis leading to abscess formation that is commonly seen in CVJ TB^{1,45-47}. The use of CT provides additional details of the bony involvement, focal bone erosion or sclerosis¹². Jain studied CT scans of 30 consecutive patients and classified different types of bony lesions following tuberculosis into fragmentary, osteolytic, subperiosteal and localized with sclerotic lesions²⁶. He concluded that, the demonstration on CT of fragmentary type of bone destruction, especially if associated with a Para vertebral soft tissue mass is strongly suggestive of

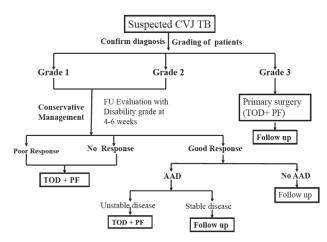


Figure 1: Flow chart showing AIIMS CVJ TB Management Protocol.

tuberculosis. Presence of calcification or bone fragments with in this mass add further support to the diagnosis³⁶. The use of MRI is the ideal diagnostic procedure to ascertain the presence and extent of compromise of the spinal canal and cord compression as well as to determine the size of the paraspinal abscess if present³⁰. Krishnan reviewed MRI and CT images of 29 patients and analyzed the extent of bony and soft tissue involvement if tuberculosis at the CVJ. Among 29 cases 19 patients had involvement of skull. The occipital condyles were involved in 48%, atlas in 72% and Dense in 62% of cases. TeegalaR etal reported 71 cases and showed the dense involvement in 86%, atlas in 67%, occipital condyles in 42%, C2 body in 24% and clivus in 15%⁵¹.

Krishnan et al reported soft tissue collection in the prevertebral space in 22, para vertebral in 27 and in epidural space in 25 out of 29 cases. Where as in AIIMS (All India Institute of Medical Sciences) series, radiological evidence of bone involvement was seen in 62 (87%) of 71 patients. Involvement of the odontoid process and anterior arch of the atlas was the most common pattern. Eightyfour percent of the patients had a soft tissue collection. In most cases, the epidural collection extended from the clivus to the C2 or C3 vertebra. A prevertebral collection was present in 80%, a paravertebral collection in 54%, and an epidural space collection in 37%. Thecal sac compression was seen in 22 cases (31%). Five patients had cord signal changes. AAD was present in 38 patients on initial presentation. Ill-defined landmarks at the CVJ precluded its identification in the remaining patients. Seven of 38 patients with AAD were Grade 3 and underwent surgery. 6 patients had residual AAD at follow-up with initial conservative treatment. Five of these patients had reducible AAD and underwent posterior fixation, and 1 patient had nonreducible AAD with a stable neurological condition. AAD resolved in 25 patients.

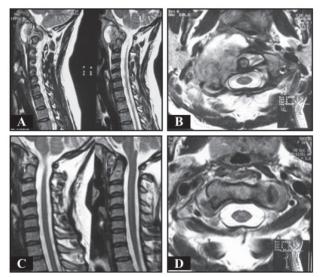


Figure 2: Showing the MRI of grade 2patient. A&B: pre treatment images of sagittal and axial images showing destruction of right atlanto axial joint and paraspinal collection causing the thecal sac compression. C&D: sagittal and axial images showing complete resolution of the disease with medical management.

The diagnosis of spinal tuberculosis has to be suspected on clinical parameters and confirm with radiological investigations predominantly MRI and should be confirmed with either microbiological pathological or molecular tests.⁵¹ Author has observed that in good number clinicians in individual practice tends to start the Anti Tubercular Treatment (ATT) based on clinicoradiological assessment. By this approach there can be inappropriate diagnosis in few percent of cases and may land up in drug resistance and unnecessary treatment of tubercular mimicking cases. To avoid this kind of problems, TeegalaR et al proposed the diagnostic criteria and the diagnosis of TB was established when a patient satisfies the essential criteria along with one major supportive criterion or at least 4 minor supportive criteria⁵¹. (Table3)

Management

The opinion in the literature regarding the management of CVJ TB has periodically undergone a pendular swing from absolute conservative to radical surgical extirpation^{23,26,16,17,27,32}. This inconsistency is mainly due to most of the reported cases being published either as case reports or parts of wider studies concerning tubercular afflictions of the skeletal system. Even in studies in which CVJ TB has been addressed specifically, the choice of intervention has depended largely on the preference of the surgeon and no clear guidelines have emerged. John Hilton first described a case of tubercular AAD and stressed

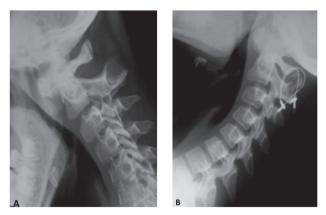


Figure 3 : Showing the residual AAD after the initial medical management.

the importance of rest for such patients^{39,40}. Grantham etal advocated Occipito- cervical orthodesis in cases of instability²¹. Tuli for the first time reported a large series of tubercular AAD and described his management by middle path regime⁵². He recommended bed rest, skull traction in extension and ATT. Fang etal proposed one stage anterior surgical debridement and fusion¹⁷. Lal etal proposed one stage posterior decompression and internal fixation with the use of a metal prosthesis with bone grafting followed by immobilization in a hard cervical collar³¹. Lifeso and Edwards etal recommended a two stage procedure -trans oral decompression (TOD) and posterior stabilization with an interval of two weeks with the patients neck being stabilized in a hallow vest^{16,32}.

Bhojraj etal managed 25 patients and Kotil managed 10 patients based on the extent of destruction at the CVJ. In the Behari et al., most of the patients with major deficits according to the disability status underwent early surgery^{7,8,29}. However, author found that, despite patients' moderate to severe disability, their motor weakness was not very significant. In authors series, 11% of patients with major disability had motor power greater than (MRC) Medical Research Council Grade 457,58. Once the acute illness settled, their performance status improved significantly. According to Behari et al., all patients partly dependent on others for their activities of daily living(ADL) constituted Grade 3 and underwent surgical intervention7. Author thinks that most of these patients could be followed instead of undergoing primary surgery. Conversely, Gupta et al. managed all patients, regardless of grade, conservatively with prolonged immobilization and an external fixator²³.TeegalaR et al have adopted a scoring system that incorporates both clinical and radiological data to assess the disease severity and appropriate mode of initial treatment⁵¹.(Table 2) This would help to avoid unnecessary

major surgery for a significant group of patients. At the same time, it is desirable to identify those patients who require surgical decompression and fixation to facilitate early rehabilitation and improve their quality of life.

It is noteworthy that all patients in this series were treated with the ATT regimen for 18 months, despite the lack of published evidence favoring this longer treatment over the World Health Organization 6- or 8-month regimens^{37,38}. This longer medical treatment duration was adopted according to Tuli's⁵³ recommendations for spinal TB. All the patients were managed with Philadelphia cervical collar support and ATT. There are no available studies proving the superiority of rigid external fixators over the Philadelphia cervical collar. None of the patients in this study required any kind of cumbersome, rigid external fixator such as halo traction and a sternal occipital mandibular immobilizer brace. The role of this kind of external fixator in achieving fusion rates and patient compliance, as compared with the Philadelphia collar, needs further evaluation. Patients with CVJ TB usually respond well to ATT. Hence, ATT and immobilization of the neck are often the only treatment necessary. Response to ATT presumably involves an enhanced fibrous reaction, which may obviate the need for additional operative stabilization. Yet its difficult to identify the factors responsible for residual AAD in the few patients who required posterior fixation despite the good response to medical treatment.

Based on large number series reported on the management of CVJ tuberculosis (Table 1), It is emphasized that, in dealing with such a complex problem, treatment needs to be based on early detection and protocol based management. These kinds of uniform guidelines across an endemic area will ensure good quality of treatment to these needy patients.

Conclusion

Tuberculosis though uncommon is one of the important causes of CVJ anomalies. Acute or sub acute onset of neck pain with restricted neck movements and features of progressive spinal cord compression in young adults or children should arouse the suspicion of a diagnosis of CVJ tuberculosis, which can be confirmed by imaging studies. Males are more commonly affected. MRI is the most useful investigation for the management. The vast majority of patients with CVJ TB respond well to ATT regardless of their initial grade (Fig 2). However there will be certain percentage of patients in severe neurological deficits with high-grade disability that needs primary surgery in the interest of avoiding long-term cumbersome, rigid external fixation. Few patients despite effective medical management had residual reducible AAD and requires posterior fixation as a delayed surgery (Fig 3).

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