Clincial Research on Foot & Ankle

Chen et al, Clin Res Foot Ankle 2014, 2:2
http://dx.doi.org/10.4172/2329-910X.1000131

Review Article Open Access

Tuberculosis Arthritis: Epidemiology, Diagnosis, Treatment

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Received date: Dec 11 2013, **Accepted date:** Feb 27 2014, **Pub date:** March 5, 2014

Abstract

Tuberculosis (TB) arthritis accounts for approximately 1-3% of all cases of tuberculosis and for approximately 10-11% of extrapulmonary cases. TB arthritis primarily involves the large weight-bearing joints, in particular the hips, knees, and ankles, and occasionally involves smaller nonweight-bearing joints. The diagnosis of TB arthritis is often delayed due to lack of awareness, insidious onset, lack of characteristic early radiographic findings and often lack of constitutional or pulmonary involvement. Intense current and previous efforts into diagnostic, therapeutic, and preventive interventions have focused on pulmonary TB in adults, but TB arthritis has been relatively neglected. Additional research, understanding, and prevention of TB arthritis are urgently needed. In this article, we review the epidemiology, diagnosis, and principles of treatment of TB arthritis.

Keywords: Tuberculosis; Tuberculosis arthritis; Diagnosis; Treatment

Introduction

Musculoskeletal TB is a relatively rare extrapulmonary complication of Mycobacterium tuberculosis. Skeletal involvement is seen in 1% to 3% of patients with TB [1]. Among them, approximately one half of these affect the spine and the rest are extraspinal osteoarticular joint [2-7]. Poncet's disease or tubercular rheumatism is a nondestructive polyarthritis that occurs during acute TB infection in which neither evidence of direct mycobacterial involvement of the joints nor any other known cause of polyarthritis detected [8-11]. It is a different entity from tuberculosis arthritis (TB arthritis). TB arthritis is usually monoarticular and in which the organism can be isolated from the joint [10].

Osteoarticular TB occurs primarily by haematogenous spread from a primary focus like lung, kidney, lymph node, etc. or infrequently by contiguous spread from adjacent tissues of direct inoculation [8-13]. TB of joint may be due direct invasion of synovium, e.g. Poncet's arthritis [8-11]. It may also affect nonweight-bearing joint such as wrist, elbow, and small joints of hands. The mode of transmission is haematogenous from visceral foci such as the lung, kidneys, lymph node or other viscera [14-18].

Articular disease often starts as a synovitis progressing to periarticular demineralization, marginal erosions, and finally joint destruction [19,20]. The time period from synovitis to joint destruction can be rapid, particularly in weight-bearing joints. When tubercular arthritis complicated by secondary infection like Staphylococcus aureus presents, it results in accelerated joint destruction associated with severe systemic features [21,22]. Joint tissue necrosis secondary to other disease such as osteonecrotic joints, due to sickle cell disease and chondrocalcinosis may predispose to tubercular infection [23-26]. Before the advent of effective anti-TB chemotherapy, TB tenosynovitis and septic arthritis due to mycobacterial infections are now less common.

Patients generally have mild local and constitutional symptoms, frequently leading to significant delays in diagnosis. The diagnosis of tubercular arthritis is also frequently delayed due to its varied clinical presentation and often lack of constitutional features [6,27,28]. The delay in diagnosis and treatment may result in additional bone or joint destruction, especially in patients with either of those diseases with septic arthritis due to infection caused by mycobactrial species [6,29,30]. Therefore, it is important to understand the epidemiology, diagnosis and treatment of TB arthritis. In this study, we reviewed the epidemiology, diagnosis and treatment of TB arthritis.

Data Collection

We initially collected all of the articles that were published from January 1990 through October 2013, which described people who were affected by TB arthritis. These articles were obtained by searching MEDLINE (National Library of Medicine, Bethesda, Maryland, USA) using the key words "tuberculosis arthritis" or "osteoarticular tuberculosis". Articles that were not published in the English language, manuscripts without an abstract (which were assumed to not be original), and opinion articles were excluded from the review. After selecting the articles, the relevant information was extracted and classified according to TB arthritis epidemiology, TB arthritis diagnosis, TB arthritis management, the country of the first named author, the year of the publication, and the study design.

The searches were performed in July 2013 and August 2013. Using the search terms previously described, a total of 151 documents were retrieved from MEDLINE. After screening the articles, a total of 109 articles were considered to be relevant. The first authors were primarily from India, the United States, Turkey, Korea, Taiwan,

Germany and other countries. The country that produced the most original information was India, with 35% of the articles. After analyzing the abstracts, we found that 83% of the studies were case report, 10% were retrospective, and 7% referenced other designs.

Epidemiology

Tuberculosis (TB) remains a major health problem worldwide. In 2001 the World Health Organization (WHO) reported 2.4 million cases and approximately 2 billion people worldwide have latent TB infection [31,32]. During 2008, an estimated 9.4 million new TB cases were diagnosed, with most cases living in Africa and Asia [33], but no estimates of childhood TB were included. In a prospective community-based survey performed in an area of South Africa, children less than 13 years of age contributed 14% of the total TB disease burden, with an annual incidence of 408/100, 000 [34,35]. More recent estimates suggest that children less than 15 years of age contribute 10-20% of the disease burden in TB-endemic areas [36,37]. Tuberculosis is endemic in certain areas such as Asia, the Middle East, and Africa. The incidence of the disease in developed countries has been rising. Tuberculosis is most common in areas with crowding, poor sanitation, and malnutrition [31,32].

Skeletal involvement is seen in 1% to 3% of patients with TB and for approximately 10-11% of extrapulmonary cases [1]. Among them, approximately one half of these affect the spine and the rest are extraspinal osteoarticular joint [4-7]. The most common musculoskeletal sites are the spine, hip, and knee [38-41].

Diagnosis

There is usually long delay in diagnosis, due partly to the fact that it can mimic other disease due to its varied clinical presentation and radiographic appearance [42,43]. Early diagnosis of arthritis due to TB is essential to preserve the articular cartilage and joint space. Early diagnosis, specific and adequate treatment can be rewarding for maintaining good joint function. The diagnosis of TB small joint arthritis is often delayed due to lack of awareness, insidious in onset, lack of characteristic early radiographic findings and often lack of constitutional or pulmonary involvement. A high index of suspicion is necessary, especially in the context of persistent monoarthritis in a susceptible host. The immunocompromised individuals, elderly or children in close contact to TB or patient who under treatment with corticosteroid and/or immunosuppressive and biologic agent or history of trauma should undergo microbiological or histological tests for TB which remains the gold standard in the diagnosis of TB.

Clinical Presentation

TB arthritis is most commonly monoarticular and of insidious onset. It is commonly presented with chronic joint paint and only minimum sign of inflammation. Tubercular arthritis is characteristically monoarticular and most commonly affects the spine and weight-bearing joints such as the knee, hip, and ankle synovial type of TB arthritis is more commonly involved in the knee, hip, and ankle joint [12].

Most common symptom is local pain and swelling followed by restriction of movement of the affected area. There is wasting of the regional muscle and deformity may occur. Less commonly, painless cold abscess was the only clinical presentation. Involvement of multiple sites is seen in 5-30% cases of tubercular arthritis [44,45]. Reactivation of tubercular arthritis after treatment occurs in 17-34% of individuals. Reactivation most commonly occurs in hip joint [10,46,47].

Joints swelling and evidence of effusion, periarticular abscess and chronic sinus formation occur late. Multiple joint involvements has been reported [48-50]. Systemic symptoms of fever, weight loss, and night sweat may or may not be present during active TB arthritis. Less than 50% of individuals with tubercular arthritis have active pulmonary TB at the time of diagnosis [51,52]. Patients with TB may have hypersensitivity phenomena like erythema nodosum, episcleritis, uveitis and Poncet's arthritis.

Clinically, TB arthritis has been classified into 5 stages [53-58]. Stage I or the synovitis stage presents with soft tissue swelling, no bony lesion, localized osteoporosis, and outcome after treatment is excellent. Stage II is early arthritis with marginal erosions (one or more erosions or lytic lesion in the bone; discrete diminution of joints space). The outcome is good with only mild stiffness. Stage III is advanced arthritis with subperichondral cyst and loss of joint space. The outcome is fair with notable loss of motion. Stage IV is more advanced arthritis with joint destruction and no motion at the joint after treatment. Stage V is ankylosis of joint.

Bacteriology

A confirmation of acid fast bacillus (AFB) from any body fluid or tissue is the gold standard for the diagnosis of tuberculosis. Several studies have reported bacteriological positivity rates as high as 33% even for primary disease states, such as hilar adenopathy [59,60]. Therefore, every attempt must be made to bacteriologically prove the diagnosis in every case of suspected tuberculosis. Whatever method a clinician uses, he/she needs to collect at least two, preferably three, samples.

A Ziehl-Neelsen stain can reveal AFB only if the sample contains greater than 10,000 bacilli per mL. Different culture methods, such as Lowenstein-Jensen medium, radiometric (Bactec 12B liquid medium), and non-radiometric (Bactec MGIT 960 system), can be used for confirming diagnosis in the paucibacillary state [61,62]. The newer methods are capable of providing faster results and may be used if available. Mycobacterial culture assumes special significance in cases of suspected drug resistance [61,62].

Radiology

Radiographic features are usually noted 2 to 5 months after disease onset [6]. The classical triad of radiologic characteristics of TB arthritis is juxta articular osteoporosis, peripheral osseous erosion and gradual narrowing of intraarticular space [63-66]. In contrast to the Rheumatoid arthritis, the joints space is relatively preserved in early TB arthritis. In children, there may be enlargement of the epiphysis. Bone scan shows increased uptake, but bone scan finding are non-pathognomonic.

Imaging

Computerized tomography (CT) and magnetic resonance imaging (MRI) are helpful in defining the disease further [67]. MRI defines soft tissues better, while CT is good for bony lesions. The MRI features of tubercular arthritis include synovitis, effusion, central and peripheral erosions, active and chronic pannus, abscess, bone chips, and hypo-intense synovium. MRI is the investigation of choice to reveal both

extent and severity of damage [25]. An MRI is also nonspecific but evaluate the extent of the lesion better than X-rays. These imaging features in an appropriate clinical setting may help in the diagnosis of tubercular arthritis [65].

Tuberculin Skin Test

The Mantoux test is the recommended standard tuberculin skin test [TST]. Tuberculin is commercially available in 1, 2, and 5 Tuberculin Unit (TU) PPD (purified protein derivative, RT23 equivalent) forms [68-71]. For the test, it is important to raise a wheal of approximately 6 mm after the intra-dermal injection. The test is read 48-72 hours after an injection. Ballpoint or palpatory methods are used to read the induration. A prior Bacillus Calmette-Guérin (BCG) vaccine has influence on the PPD reaction depends on the following conditions, such as the intervals between BCG vaccination and TST, the age at vaccination [72,73]. If the prevalence of TB infection is high enough, the positive predictive value of TST would be higher [74]. If the patient returns for a reading beyond 72 hours but before the 7th post-injection day, a positive test can still be read. A repeat test may be needed if there is no induration and the wheals present beyond the stipulated time for reading. A repeat tuberculin test, when required, should preferably be performed on the other arm.

Interferon Gamma Release Assays (IGRAs)

In addition to the traditional TST, which is known to lack both sensitivity and specificity, blood-based assays have recently become available. These T-cell assays rely on the stimulation of host blood cells with M. tuberculosis-specific antigens and measure the production of interferon γ. Several studies have compared the two available commercial assays, T-Spot TB (Oxford Immunotec, UK) and Quantiferon-TB Gold (Cellestis, Australia), with the TST for both the detection of active disease and latent tuberculosis infection [75,76]. The T-cell assays have proven to be more specific than the TST but are currently unable to distinguish between active disease and latent tuberculosis infection [75,76]. Therefore, interpretation of the results remains dependent on the clinical context. Several studies have presented pediatric T-cell assay data; however, none have provided an assessment of age-related performance, and reservations remain regarding their performance in very young children and immunocompromised populations, such as those with HIV infection [77-79]. The costs and technical demands of IGRAs will most likely limit their wider use in resource-poor settings, where better tests are the most needed.

T-SPOT, Quantiferon-TB and TST have their good diagnostic values for chronic inflammatory arthritis, however, indeterminate results may complicate the use of them [80,81].

PCR Testing

Nucleic acid amplification tests using polymerase chain reaction (PCR) cannot differentiate living bacilli from dead bacilli. Thus, these tests continue to give positive results even after successful treatment. The PCR tests are positive in 95% to 100% of culture positive cases and in 50% to 60% of culture negative cases [82]. Over the past several decades, the diagnostic methods for M. tuberculosis have improved, and nucleic acid amplification techniques now allow rapid and sensitive detection in clinical setting [83].

Synovial Fluid Examination

Synovial fluid is usually nonhaemorrhagic and turbid with moderate elevation of white blood cell, ranging between10,000 and 20,000 cells/mL with predominance of polymorphonuclear leukocyte. Culture for M. tuberculosis is also to be planned. Joint fluid aspiration from the affected joint for standard/routine investigation and TB culture is recommended when possible for at-risk patients, even where previous cultures have been negative. Synovial fluid culture is positive in roughly 20-40% of cases [51]. PCR analysis in synovial fluid, tissue samples, bone marrow aspirate, and peripheral blood is faster and more specific, but less sensitive and less widely available [84,85].

Synovial Biopsy

The gold standard for diagnosis of tubercular arthritis is synovial biopsy, with positive results in 80% of cases [86,87]. It shows caseating granulomas, lymphocytes, and giant cells with caseation, which is very characteristic of tubercular arthritis.

Treatment

Splints may be used for a short time to relieve acute symptoms and for long time in specific cases of tuberculosis of joints to prevent deformities of infected extremities [40,88,89]. Operative treatment is usually limited and includes obtaining a biopsy and performing open or arthroscopic debridement, incision and drainage of abscess, and synovectomy [40]. A randomized trial performed primarily among ambulatory patients by the Medical Research Council Working Party on Tuberculosis of the Spine [90] demonstrated no additional benefit of surgical debridement or radical operation (resection of the spinal focus and bone grafting) in combination with chemotherapy compared with chemotherapy alone. In some circumstance, however, surgery appears to be beneficial and may be indicated. Such situations include failure to respond to chemotherapy with evidence of ongoing infection, the relief of cord compression in patients with persistent of recurrence of neurological deficits, or instability of the spine. Surgical procedures should be restricted to joints with severe cartilage destruction, joint deformity, large abscesses, multiple drug resistance or atypical mycobacteria [88-92].

The mainstay treatment of tuberculosis arthritis is appropriate anti-TB drug therapy (Table 1). Early antimicrobial therapy can result in near-complete resolution and preservation of function. In TB arthritis without pulmonary involvement, the risk of transmission to contacts is minimal and thus constitutes little threat to public health. Antimicrobial therapy in general should be of at least 12-18 months, but to be continued longer in children and immunocompromised hosts [12,14,19]. The basic principles that underlie the treatment of pulmonary tuberculosis also apply to extrapulmonary forms of the disease [63,93,94] (Table 2). Although many fewer treatment studies have examined treatment of extrpulmonary tuberculosis, compared with pulmonary disease, increasing evidence, including some randomized controlled trials, suggests the 6 to 9 months regimens (2 months of isoniazid (INH) and rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) followed by 4-7 months of INH and RIF is recommended as initial therapy unless the organisms are known or strongly suspected of being resistant to the first-line drugs. If PZA cannot be used in the initial phase, the continuation phase must be increased to 7 months, as describe for pulmonary tuberculosis. Several studies have examined treatment of bone and joint tuberculosis and have shown that 6-9-month regimens containing RIF are at least as

effective as 18-month regimens that do not contain RIF [90,95-99]. Myelopathy with or without functional impairment most often responds to chemotherapy. In two Medical Research Council studies conducted in Korea, 24 of 30 patients in one study [95] and 74 of 85 patients in an earlier study [100,101] had complete resolution of myelopathy or complete functional recovery when treated medically.

Category of treatment	Category of TB cases	Anti-TB drug regimens	
		Intensive phase	Continuation phase
Ⅰ	New Patient Regimen New smear-positive PTB Smear-negative PTB with extensive parenchymal involvement Severe forms of EPTB other than TB meningitis	2HRZE	4HR
Ⅱ	New Patient Regimen Smear-negative PTB without extensive parenchymal involvement Less severe forms of EPTB (e.g., TB cervical adenitis)	2HRZ	4HR
Ⅲ	New Patient Regimen TB meningitis	2HRZS[a]	4HR
Ⅳ	Retreatment regimen Previously treated smear-positive PTB (relapse, treatment after interruption or treatment failure) *If low risk for MDR-TB or risk unknown, continue with retreatment regimen* *If high risk for MDR-TB, use MDR-TB regimen below*	2HRZES/1HRZE	5HRE
Ⅴ	MDR Regimen MDR-TB	Individualized regimens	

Table 1: Treatment regimens for tuberculosis recommended by WHO [63]

Note: PTB: pulmonary tuberculosis; EPTB: extra-pulmonary tuberculosis; MDR-TB: ulti-drug resistant tuberculosis; HIV: human immunodeficiency virus; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; S: streptomycin.2HRZ 4HR: denotes a two-month intensive phase of daily isoniazid, rifampicin, and pyrazinamide followed by four-month continuation phase of daily isoniazid and rifampicin.

a: Other regimens are recommended for treatment of TB meningitis that includes replacing streptomycin with ethionamide and treating for 9-12 months.

Drug	Recommended dose per day	
	Adults: Dose and range (mg/kg body weight)	Children: Dose and range (mg/kg body weight)
Isoniazid	5 (4-6)	12 (10-15)
Rifampicin	10 (8-12)	15 (10-20)
Pyrazinamide	25 (20-30)	35 (30-40)
Ethambutol	15 (15-20)	20 (15-25)
Streptomycin	15 (12-18)	15 (12-18)

Table 2: Recommended doses of first line anti-tuberculosis drugs for adults [63,98]

Conclusions

TB is still an important public health problem in the world. TB arthritis accounts for approximately 1-3% of all cases of tuberculosis and for approximately 10-11% of extrapulmonary cases. Nonspinal skeletal TB is a rare and insidious in onset that is often difficult to diagnose. Early diagnosis, specific and adequate treatment can be rewarding for maintaining good joint function. The diagnosis of tubercular arthritis is largely clinical and required exclusions of other causes of mono/oligo and polyarthritis and high degree of suspicion. The mainstay of treatment is multidrug anti-TB therapy (for 12-18 months) and active-assisted nonweight-bearing exercises of the involved joint throughout the period of healing. Operative intervention (synovectomy and debridement) is required when the patient is not responding after 4-5 months of anti-TB therapy.

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