Osteoarticular tuberculosis in children. A fast reappearing disease diagnosed by $^{18}$F-FDG PET/CT and other modalities. The cover page of Nicholas Andry booklet L' Orthopedie

Abstract
Osteoarticular tuberculosis (OAT) is not uncommon in children. Early diagnosis and treatment are essential to avoid ultimately long-term disabilities. Nicolas Andry (1658-1742) gave for the first time the name of the specialty of Orthopedics (L’Orthopédie) and its symbol of the crooked tree, in a paper in which he suggested how to avoid and to treat rachitis in children. We review the correlative-imaging findings and provide insights regarding the strengths and limitations of the conventional imaging modalities and those of nuclear medicine for the diagnosis of OAT and its differential diagnosis from other diseases.

Introduction

Tuberculosis (TB) was endemic in animals from the Paleolithic Age, about 2-3 million years ago, long before affecting humans [1, 2]. Other researchers reported that TB in men was present at the Middle Neolithic Age, 6,500 years ago [3]. Nicolas Andry (1658-1742) gave for the first time the name of Orthopedics (L’Orthopédie) as a new specialty and its symbol of the crooked tree (Figure 1). In his paper he suggested how to avoid and to treat rachitis in children [4]. The disease is due to Koch’s bacillus or mycobacterium of tuberculosis and can be transmitted even by air quite easily [5]. Children present a much greater risk than adults, often through exposure to adults infected with the bacillus [6].

Figure 1. Nicholas Andry (1658-1742) gave orthopaedics its name and the symbol of the crooked tree.
and emergence of multidrug-resistant (MDR) strains of mycobacterium TB. According to WHO (2016), an estimated 1 million children became ill with TB and 250000 children died of TB, including children with HIV associated with the disease.

Extrapulmonary tuberculosis (EPTB) is common in children and its clinical presentation varies with age. Around 20% of all mycobacterial infections in children are EPTB [11], including osteoarticular TB. Osteoarticular TB has an equal incidence between the sexes [12]. Bone and joint involvement is considered the third most common type of EPTB following thoracic and lymph node TB [1, 6].

The most common manifestations of osteoarticular TB in children are spondylitis, arthritis and osteomyelitis. Spinal TB, known as ‘Pott’s Disease’, is one of the most common osteoarticular TB, accounting for about 50% of skeletal TB cases which most likely occurs in the thoracic vertebrae causing rachitis [13-16]. The Rajasekaran study (1998) [17] found that the number of segments involved in pediatric spinal TB was 1.9 times more than that of adults. Pediatric vertebrae are more likely to be damaged than adult vertebrae because they consist primarily of cartilage. Spinal TB causes destruction of vertebral bodies leading to typical spinal deformity and possibly paralysis. If rachitis is left untreated, kyphosis is formed which will continue to grow as the child grows up [17, 18]. Deformity may be further aggravated in time even after TB is cured [19]. This deformity affects not only the spine, but also the cardiopulmonary function and may cause spinal cord compression. Approximately 20% of patients with spinal TB undergo surgery [13]. Early diagnosis and appropriate therapy are crucial for the successful treatment of this disease [2, 19].

**Imaging methods**

It is difficult to get samples from the lesion of bones for histopathologic examination especially in children who usually show poor compliance [14]. Diagnosis is often clinically suspected.

In a study by Su-Ting Chen et al. (2015) [14], 108 out of 113 patients with osteoarticular TB were empirically diagnosed by imaging modalities. The existing imaging modalities are as ultrasound, X-rays, computed tomography, magnetic resonance imaging (MRI) and nuclear medicine techniques. Nuclear medicine techniques include single photon emission tomography (SPET) and fluorine-18-fluoro deoxy glucose positron emission tomography/ computed tomography (18F-FDG PET/CT) and 18F-sodium fluoride PET/CT (18F-NaF PET/CT) and play an important role in diagnosing and evaluating the severity and therapeutic response of osteoarticular TB.

**Conventional imaging**

X-rays radiographs remains the initial modality for mass screening purposes. The most frequent radiological findings in osteoarticular TB are: bone destruction, cold abscesses and hypertrophic articular membrane [6]. Furthermore, narrowing of the intervertebral space (Figure 2) and the degree of kyphosis (Figure 3). In practice, distinguishing TB spondylitis from pyogenic spondylitis on plain radiographs is usually not possible. The earliest sign diagnosed by X-rays may be demineralization of the endplates of the vertebrae with resorption and loss of 30% of bone mineral [7]. With further progression of the disease, radiographs will show progressive vertebral collapse with anterior wedging and varying degrees of kyphosis [7, 20, 21]. Rajasekaran et al. (2001) [22] found that some additional signs appeared during the course of the spinal TB on the radiographs, like dislocation of the facet joints (Figure 2A), posterior retropulsion of the infected vertebral segments (Figure 2B), lateral translation of the vertebral column in the anteroposterior view (Figure 2C) and toppling of the superior vertebra (Figure 2D). These signs occur in the early stages of the disease, even in the active period. One can assess the risk of kyphosis in children through the features presented on the X-rays films. The presence of two or more signs is a reliable predictor of patient’s spine deformity. For deformities exceeding 30 or even 60 degrees surgery is recommended in these cases [22]. Paravertebral abscess can be seen in the late stage of the disease on X-rays plain films [2]. The anterior type of the vertebrae is more common in the pediatric spinal TB and in such cases a globular or fusiform radiodense shadow is visible on plain radiographs. Long standing abscesses may produce a scalloped appearance called “the aneurysmal phenomenon”, which is due to concave erosions around the anterior margins of the vertebral bodies.
Figure 4. A 10 years old boy with spine tuberculosis. Preoperative radiological showed destructive segments located at T11-T12 vertebrae, with a kyphosis.

Peri-articular osteoporosis, peripherally located osseous erosion, and progressive decrease in the joint space suggest the diagnosis of tuberculous arthritis and are popularly referred to as the ‘Phemister triad’. The joint space gradually decreases as the disease progresses. However, the destruction of cartilage may not be noted on X-rays plain films.

Tuberculous osteomyelitis is most often involved in the skull vault, hands, feet and ribs [23]. The multiple sites involved are often seen in children, but are more limited to single bones in adults. On radiographs, soft-tissue swelling and osteoporosis are seen in all forms of tuberculous osteomyelitis. These lesions have different imaging findings: cystic, focal erosions, infiltrative and dactylitis and the cystic manifestation in children are more than that in adults, showing radiolucent prototype or oval lesions, with visible marginal sclerosis in some cases. Sometimes the expansion of the bones and honeycombs will be seen (Figure 5). These cystic lesions may cross the epiphyseal plate to involve epiphysis. The radiographs show that these lesions appear as cyst-like cavities with enlarged diaphyses. However, the relatively low resolution of X-rays plain films, overlapping tissues and organs and image artifacts, may diminish the diagnostic value of the image showed. Therefore, other imaging examinations should be supplemented.

Compared with plain radiographs, CT provides better details of irregular lytic and sclerotic lesions, disc collapse and disruption of bone circumference (Figure 6B, C) and also better define the shape and possible calcification of soft tissue abscesses (Figure 6A) [7, 24]. Furthermore, CT can better show Pott’s disease by identifying sequestrums, perilesional sclerosis and epidural or soft tissue abscesses [24], especially in areas that are difficult to assess on radiographs such as posterior lesions [25]. Patterns of bone destruction (fragmentary, sclerotic, osteolytic, and subperiosteal) can also be well observed on CT [7, 24]. Patients with suspected lung or abdominal TB often undergo CT examinations and thus detect clinically unsuspected, skeletal TB [24]. In addition, CT is ideal for guiding a percutaneous diagnostic biopsy. It has been reported that CT in cases of spinal infections can diagnose TB in 77% [7, 24, 26-28]. However, the role of CT in defining the epidural space distention due to the disease and its effect on the neural structure is less accurate. The CT findings related to soft tissue masses, the intervertebral discs and spinal cord were not as accurate as those of MRI [24].

Figure 5. A 3 years old boy with phalangeal TB. Palm radiograph shows cystic low-density shadow in the bone marrow cavity of the middle phalanx of the index finger (arrow).

Figure 6. Transaxial CT imaging of patients with known osteoarticular TB. A, A 17 years old boy with cold abscess. Axial CT finds calcification of the right psoas major abscess (arrow). B, A 6 years old girl with TB. The eroded T11 vertebra and paravertebral abscess is seen on the CT image (arrow). C, A 10 years old boy with TB involving the right acetabulum. The axial CT image showed irregular lytic lesions and sclerosis (arrow).

Figure 7. A 6 years old girl with spine TB. Images from MRI (T1, A-B and T2, C-D) showing destructive segments located at T10-T11 vertebrae and showing paravertebral collection extending from T7-T11 (arrow).

Magnetic resonance imaging can give us useful images without any ionizing radiation to patients, which is important in children and can evaluate bone marrow soft tissue involvement at the early stage of the disease. Vertebral collapse and paravertebral and epidural abscess, as well as the varying degrees of epidural compression, are best evaluated using MRI (Figures 7, 8). Magnetic resonance imaging is the
most sensitive for early diagnosis and follow-up of spinal TB [29]. The earliest sign for TB is marrow edema, which is seen as a hyperintense signal on T2 and short-tau inversion recovery (STIR) images. Changes in spinal TB are detected 4-6 months earlier by MRI than by conventional methods [30]. These changes include the destruction of the vertebrae and the relative preservation of the intervertebral disc [2, 25, 31]. Chandrasekhar et al. (2013) [32] have suggested a novel MRI scoring system that tests eight parameters including T1 hypointensity, T2 hyperintensity, disc involvement, epiphyseal involvement, pedicle involvement, paraspinal extension, anterior subligamentous extension and no sinus process involvement, and it was noted that score ≥6 favored a tuberculotic pathology. Sureka et al. (2013) [33] reported that in MRI the involvement of the costovertebral joints and the posterior elements with intact low-signal cortical outline, suggested the possibility of spinal TB. Children with TB spondylitis more frequently than adults, showed in the intervertebral disc hypointense signal on T2-W images [34]. As the disease progresses, MRI shows loss of definition of the endplates and the adjacent vertebral bodies, with hypointense signal on T1 and hyperintense signal on T2 and STIR images. Spinal deformity can occur several months to years after the lesions heal, and glial cell proliferation, severe cord atrophy, syringohydromyelia and peridural contractile scars can be detected by MRI [35].

Magnetic resonance imaging in TB arthritis or osteomyelitis, often shows marrow changes, synovitis, joint effusion, pannus, tenosynovitis, bursitis, periarticular inflammation, cartilage and bone erosion (Figure 9). Gradient-echo sequence plays an important role in the evaluation of cartilage involvement [30]. These changes are usually hypointense signal in T1-W sequence and hyperintense signal in T2-W sequence. However, the imaging findings of TB arthritis are nonspecific on MRI. Suppurative and juvenile idiopathic arthritis may have similar characteristics.

Ultrasonography can detect soft-tissue extension of the skeletal lesions and is widely used in guided needle aspiration or biopsy for early histopathological diagnosis [9, 25]. Unenhanced MRI does not necessarily differentiate synovial thickening from effusion, but an ultrasound can help to differentiate them, with the former being anechoic and the latter being hypoechogenic. In experienced hands, bone destruction (hyperechoic cortical with irregular bone destruction), abscess (the turbid liquid in and around the area of bone destruction), sequestrum formation (patchy and punctate strong echo), joint effusion (echo-free zone around the joint), soft-tissue swelling (muscles around the lesions with echo reduction), periosteal elevation (continuous echo on the surface of the cortical bone), destruction of epiphysis and epiphyseal cartilage (normal hypoechogenic to echoless epiphyseal cartilage with blur boundaries and increased echo) and blood flow signals can be seen on ultrasound images of children with osteoarticular TB. Ultrasound with high-frequency transducers can provide invaluable information about the synovium, tendon sheaths, and bursal spaces [21, 25]. However, it is difficult to diagnose bone and joint TB only by ultrasonography.

**Figure 8.** A 10 years old boy with spine TB. Sagittal T2-weighted MRI images showed epidural and paravertebral abscess formation, and spinal cord compression (arrow).

**Figure 9.** A 17 years old boy with tibia TB. Magnetic resonance imaging shows a tubercle in the metaphysis of the left tibia, involving the epiphysis, which is about 1.3cm×2.0cm in its largest dimension (arrow).

**Nuclear medicine imaging**

Nuclear medicine imaging technology allows for the most accurate correlation of anatomical and metabolic information, enabling the fusion of anatomical and functional images. Fusion imaging contributes to early detection and evaluation of diseases involvement. Anatomical imaging can evaluate the structural changes associated with infection while functional imaging can demonstrate early functional impairment secondary to infectious process. Single photon emission computed tomography/CT, PET/CT as emission computed tomography (ECT) contribute to early diagnosis and treatment response evaluation of osteoarticular TB [36].

Single photon emission tomography-bone-targeting radiopharmaceuticals are analogs of calcium, hydroxy groups or phosphates. The most commonly used radiopharmaceuticals are 99mTc-labeled diphosphonates for imaging osteoblastic activity, such as methylene diphosphonate (MDP) [37]. Compared with planar 99mTc-MDP whole-body bone scintigraphy, SPET/CT imaging allows three-dimensional localization of tracer activity to bone lesions (Figure 10) and is useful for differentiating soft tissue from bone infections, for assessing sites of suspicious bone infection with structural alterations and can observe the extent of the lesion at...
complex anatomical sites [37]. In addition, the early and delayed 99m-Tc-MDP SPET/CT imaging can differentiate other disease like rheumatoid arthritis and osteoarthritis [38]. Other radiopharmaceuticals used for the diagnosis of skeletal infections are 99m-Tc-PYP, 99m-Tc-HMDP and 99m-Tc-HEDP. A study [39] suggested that SPET/CT with 99m-Tc-EDDA-HYNIC-TOC or 111-In-DTPA-octreotide can differentiate bone TB from systemic granulomatous infections but not from other bacterial infections.

Ethambutol is one of the first-line treatments for TB. Karamalharda et al. (2018) [40] showed that 99m-Tc-ethambutol is a useful radiopharmaceutical to detect and localize both intra- and extra-pulmonary TB with minimal or no side-effects while is safe to be performed even in pediatric patients.

**Figure 10.** Single photon emission tomography/CT imaging (with 99m-Tc-MDP) of patients with osteoarticular TB. A-G, A 17 years old boy with spinal and elbow TB. The anterior maximum intensity projection images (A) showed abnormal activity at the L2-L5 vertebrae and the right elbow joint. (B, C and D) CT images showed bone destruction in these sites. The SPET/CT (E) and 3D SPET (F and G) images not only showed the metabolic status of the lesions, but also determined the location of the lesions more clearly and intuitively.

Children who use SPET/CT have lagged behind adults for fear that CT components may increase the dose of radiation burden in children [41]. Therefore, SPET/CT scans should be tailored to every child examined to ensure compliance with the ALARA (as low as reasonably achievable) principle for radiation protection.

Fluorine-18-FDG PET/CT shows superior image resolution [42,43]. Recent advances in PET imaging systems have increased the ability to visualize and quantify small concentrations of PET tracers for patients thus using low-dose radiation [44]. Since TB in children involves the extremities more often than in adults and also more extensive disease, whole-body imaging is essential in suspected TB cases [2, 21, 45, 46]. It can also assess and stage pulmonary and extrapulmonary TB simultaneously, saving time and cost [47, 48]. Albano et al. (2017) [49] reported that 18F-FDG PET/CT revealed incidentally unilateral TB sacroiliitis. Furthermore, 18F-FDG PET/CT can differentiate active from latent TB [50-52], with high sensitivity while high image quality negative studies largely exclude active disease. A recent study found that 18F-FDG PET/CT was superior to MRI in differentiating TB and supplicative spondylodiscitis [52, 53]. The SUV level of 18F-FDG PET in TB spondylodiscitis was higher than that in pyogenic spondylodiscitis [54]. However, some scholars still do not believe that 18F-FDG PET/CT is ability to clearly distinguish granulomatous disease from other diseases, such as bone metastases or suppurative osteomyelitis, based on standardized uptake values (SUVmax) [52, 55]. Dual-time-point imaging (DTPI) has been used to distinguish benign from malignant processes. Although some reports indicate that DTPI may help identify TB [56], its value remains controversial [52]. In recent years, three-dimensional reconstruction technology has also been gradually applied to nuclear medicine imaging. 3D PET/CT and 3D SPET/CT images are helpful in locating lesions even by complex anatomic sites [57].

In addition, 18F-FDG PET/CT has been used for the guidance of biopsy, the development of surgical plan, and the evaluation of follow-up [51, 54, 58, 59]. One of the main advantages of PET is its ability to semi-quantify 18F-FDG uptake and assesses the early response to treatment in EPTB and especially in TB abscesses while the radiologic characteristics may remain unchanged [47, 50, 52, 60-62]. During one month follow-up, Bassetti et al. (2017) [54] showed an average reduction of 48% in SUV of tuberculous spondylodiscitis after antituberculosis treatment. In developing countries, TB multidrug-resistant (MDR) and extensively drug-resistant (XDR-TB) often need monitoring therapy.

Some studies [58, 63] have demonstrated that the size of some bacillus-negative tuberculomas may remain unchanged or even increase during anti-TB treatment. Fluorine-18-FDG PET/CT imaging can be useful in this situation. If the lesion activity increases, the tuberculoma is likely to be active and the previous treatment protocol should be discontinued and changed, and surgery should be performed if necessary. If the lesion is significantly reduced or there is residual faint activity, current treatment should be continued [63, 64].

In general, after 3 to 9 months of continuous treatment, 18F-FDG PET/CT may show an objective response to the treatment [52]. In addition, 18F-FDG PET/CT was proposed as a surrogate end point for new drug trials and a marker of disease status in patients with HIV and TB co-infections [5, 52]. Future developments in nuclear medicine in the diagnosis of bone and joint TB may include anti-TB-related tracers and improvements in the semi-quantification of osteoarticular TB lesions [52].

**Sodium fluoride labeled with fluorine-18 PET/CT**

In 1962, Blau first proposed 18F-NaF as a bone scanning agent, yet its clinical use was restricted by the fact that gamma camera scanners were unavailable at that time. In the late 1990s, with the advent of the hybrid PET/CT camera, the interest in using 18F-NaF was rekindled [65]. Sodium fluoride labeled with fluorine-18 is an excellent bone-seeking agent, which binds to the bone at the site of bone formation or remodeling [66]. The bone uptake of 18F-NaF was twice as much as that of 99mTc-MDP, and was removed more rapidly by soft tissues, thus shortening the examination time and increasing bone-background ratio of 18F ions, thus improving accuracy of bone lesions detection [67]. The favorable kinetics of 18F-NaF make it an accurate imaging
agent for bone blood flow and metabolism. The superior image contrast and high spatial resolution of $^{18}$F-NaF PET/CT provide greater anatomic localization of osseous lesions and have been used in various types of bone disorders, including bone and joint TB (Figure 11). Several other studies [68, 69] has shown that $^{18}$F-NaF PET/CT have a higher negative predictive value compared with $^{99m}$Tc-MDP SPET and planar $^{99m}$Tc-MDP. In the process of inflammation, the early-phase images of $^{18}$F-NaF PET/CT demonstrated that the uptake of the radioactive tracer increased, as also the information obtained from the perfusion and blood pool phase of the three-phase bone scan, suggesting that $^{18}$F-NaF PET/CT early-phase scan may replace three-phase bone scan [70, 71]. Beyond that, $^{18}$F-NaF PET/CT scans have the ability to evaluate semi-quantitative parameters such as SUV and has the potential for monitoring treatment response in patients with bone TB.

![Figure 11](image-url)

**Figure 11.** Fluorine-18-NaF PET/CT imaging of patients with spine TB. (A) A 17 years old girl with spine TB. Maximum intensity projection image showed increased $^{18}$F-NaF uptake in T12-L1 vertebrae. (B, C and D) The axial images of PET/CT demonstrated that the bone structure was disordered with some osteolytic bony destruction and abnormal activity. Maximum standardized uptake value (SUV(max)) was 24.5.

Sodium fluoride labeled with fluorine-18 is administered in smaller doses, so that the total actual radiation absorbed dose was almost comparable with that of $^{99m}$Tc-labeled conventional bone imaging agents. In addition, $^{18}$F-NaF has a low affinity to proteins, fast clearance from blood and excellent extraction from bones which make $^{18}$F-NaF an excellent bone imaging agent [72].

It is also important to recognize the limitations of $^{18}$F-NaF PET/CT, including high cost and that it is non-specific for the diagnosis of tuberculous osteoarthropathy [73] because tumors, traumas and other bone malformations such as fibrous dysplasia and Paget’s disease. On the other hand, PET/CT imaging, although quite useful to diagnose osteoarthritic TB [74] is also expensive.

**In conclusion,** pediatric osteoarticular TB remains a diagnostic problem in our days. Early diagnosis and treatment are essential to avoid skeletal deformities and ultimately long-term functional disabilities [75, 76]. Radiography can be used as initial screening. Computed tomography provides detailed views of skeletal lesions, more effectively defining the calcification of soft tissue abscesses. Magnetic resonance imaging is the best modality for evaluating TB spondylitis. It helps to determine the presence of epidural components and cord compression. Ultrasonography is usually helpful in identifying abscesses, joint effusions and is widely used in guiding needle aspiration. Nuclear medicine techniques play an important role in the detection of TB lesions, disease activity and disease stage, disease complications identification of dynamic and latent disease and of potential biopsy targets [77].

**Bibliography**


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States: Old Greek coins made of any kind of material. Its value was 2 drachmae. a) Head of the Sun in gold, 375b.C, found in Rhodes, b) Iraklis wrestling with a lion, 350-330b.C, found in the city of Iraklea, Italy