

Five benign myoskeletal diseases in paediatrics and the role of Nuclear Medicine. Do they differ from those in adults?

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Hell J Nucl Med 2013; 16(1): 2-8

Epub ahead of print: 26-03-2013

Published on line: 10 April 2013

Abstract

In this paper we discuss trauma, osteomyelitis, fibrous dysplasia, Legg-Calvé-Perthes disease and osteopetrosis in children. Pathophysiology, incidence, clinical signs, diagnosis and specific treatment of these diseases are described. We have focused on diagnostic imaging techniques which can be applied in children: X-rays, magnetic resonance imaging bone scintigraphy with technetium-99m-methylene diphosphonate (^{99m}Tc-MDP) and positron emission tomography (PET) with fluorine-18 fluorodesoxyglucose (¹⁸F-FDG) and fluorine-18 fluoro sodium fluoride (¹⁸F-NaF). *In conclusion*, bone scintigraphy with ^{99m}Tc-MDP and better with PET (¹⁸F-FDG and ¹⁸F-NaF) can support diagnosis of most of these myoskeletal diseases in children. Radiology is usually applied for local lesions examinations. Magnetic resonance imaging can be used in specific cases in periosteal and bone marrow lesions and CT may be avoided due to its radiation burden, in children.

Introduction

We often discuss myoskeletal diseases in adults. In our days diseases in children become more important due to population increase and the fact that children are a sensitive group of our population. In this paper we focus on special signs, diagnosis and treatment of five of these diseases in children that deserve early diagnosis and early therapeutic response. The most often diagnosed benign bone disease in children is osteochondroma or exostosis, which we do not discuss here, because its diagnosis is clinical, usually has no symptoms and also need no treatment. On the contrary, osteopetrosis is the most rare benign bone disease in children but is discussed because it has a very interesting evolution and thus, early diagnosis is important. Traumas and osteomyelitis are often diagnosed myoskeletal

diseases and nuclear medicine diagnostic procedures are worth mentioning. The other two diseases, fibrous dysplasia and Legg-Calvé-Perthes disease are rather rare but the role of nuclear medicine is worth discussing. All five diseases described in children in this paper have a distinct clinical image as well as a specific pathogenesis and treatment. Four of these diseases do not differ in general terms from those

Table 1. Dosimetry for ¹⁸F-NaF-PET and ^{99m}Tc-MDP examinations [1]

Weight patients (kg)	Administered dose (MBq)	Effective dose (mSv)
¹⁸ F-NaF		
5	11	3.8
10	22	3.2
^{99m} Tc-MDP		
5	37	3.4
10	74	3.1

Table 2. Radiation doses from radiopharmaceuticals used in PET scan in children, as compared to adults [2]

Age (y)/mass (kg)	1/9.7	5/19.8	10/33.2	15/56.8	Adult/70
For ¹⁸ F-FDG*					
Administered activity (MBq)	51.3	105.0	176.0	301.0	370.0
Urine bladder wall(mGy)	73.2	79.3	86.6	99.7	95.7
Effective dose (mSv)	8.0	8.3	8.4	9.2	9.0
For ¹⁸ F-NaF*					
Administered activity (MBq)	20.7	41.8	70.3	120.0	148.0
Urine bladder wall (mGy)	27.9	30.2	33.0	37.9	36.5
Effective dose (mSv)	3.0	3.1	3.2	3.5	3.4

*Estimates based on ICRP publication 80 [2]. For each radiopharmaceutical, weight-based administered activity is given in MBq. Also listed are dose to critical organ (organ receiving highest dose) in mGy and effective dose in mSv.

in adults. The only exemption is osteopetrosis, which sometimes is very grave and even lethal in infants. On the other hand, all these diseases have a higher prevalence in children than in adults. Tables 1-4 indicate and compare the radiation burden to children by various imaging techniques.

Trauma

Radiological skeletal survey remains the initial imaging modality of choice for the evaluation of bone traumas that may

cause fractures in children [1]. The preferred imaging techniques that yield optimal diagnostic information in traumas will be discussed [4, 5]. Fractures not apparent in routine radiographs may be readily detected with CT, MRI, or radionuclide bone scanning. By MRI we can well detect the disruption of the cortex and of the medullary fat [6].

The use of bone scintigraphy with ^{99m}Tc-MDP in bone traumas has played a secondary role being reserved for selected cases in which radiographic findings are inconclusive [6].

Bone scan is also useful when the child is not able to localize the exact site of pain or trauma and the X-rays are unable to detect an occult lesion. In children, attention should be given to the activity of the growth plate. If the fracture line disrupts metaphysis, reduction in the growth plate activity may be seen on that side and may signal reduction of normal bone growth.

Bone scan is also useful for evaluation of the abused child (Fig. 1) [7]. Shear injuries may result in periosteal retraction along the bones as described in athletes' injuries, where X-rays are non diagnostic. The "toddler's fracture" causes spirally increased tracer uptake along the shaft of the tibia. Direct bone or periosteum trauma causes almost immediate bone reaction, which results in pathologically increased accumulation of bisphosphonates as early as 24-48h after injury. Increased accumulation of the radiotracer focally or diffusely can be well defined. In areas of a previous fracture or a biopsy or of a previous injury increased accumulation of the tracer can be detected several years later.

Table 3. Radiation doses to children by age from diagnostic radiography and computed tomography [3]

Type of examination	Dose-quantity 1	5 years	10 years	Adults
<i>Radiography</i>				
Skull AP	ESD (mGy)	1.25	-	2.3
Skull LAT	» »	0.58	-	1.2
Chest PA	» »	0.11	0.07	0.15
Abdomen AP	» »	0.59	0.86	4.7
Pelvis AP		0.51	0.65	3.6
<i>Computed Tomography</i>				
Brain	ED (mSv)	1.9	2.0	1.9
Facial bone/Sinuses	» »	0.5	0.5	0.9
Chest	» »	2.5	3.0	5.9
Entire Abdomen	» »	5.4	5.8	10.4
Spine	» »	8	7.6	10.1

AP: anterior-posterior; LAT: lateral; PA: posterior-anterior; ESD: entrance surface dose ; ED: effective dose; Dose-quantity1: different dosimetric quantities have been used to quantify radiation dose to patients depending on modality [3].

Table 4. Estimated organ and effective doses in mSv for pediatric CT [2]

Organ	Age			
	9 mo (M)	4 y (F)	11 y (M)	14 y (M)
Bone marrow	6.02	6.64	7.33	7.62
Lungs	15.95	14.75	12.74	13.04
Stomach	15.62	14.13	12.71	10.73
Muscle	8.20	7.68	5.93	5.40
Breast		10.67		
Gonads	12.66	14.39	8.15	7.83
Effective dose	12.41	12.80	9.88	9.24
Age*	12 mo	5 y	10 y	
CTADI*	11.11	10.20	9.19	

M: male; F: female; CTADI: CT anthropomorphic dose index; * Ages and CT anthropomorphic dose index values for similar acquisition from Fahey et al. [2], included for comparison. Radiation organ doses (in mGy) and effective doses (in mSv) from CAP CT, 120kVp, 100mAs, 12mm beam thickness, and 1:1 pitch based on the set of computerized pediatric phantoms of the University of Florida [2].



Figure 1. Child abuse in a 2-month-old boy as detected with ¹⁸F-NaF-PET. Maximum intensity projection image demonstrates multiple rib fractures (arrows and arrowheads) [40].

Fluorine-18 labeled sodium fluoride ($^{18}\text{F-NaF}$) PET has greater sensitivity in the overall detection of fractures related to child abuse, than the baseline skeletal $^{99\text{m}}\text{Tc-MDP}$ scintigraphy [1].

In some cases, surgery is recommended as *initial treatment*, but most often surgery is used when other treatments fail to relieve symptoms [8]. Rehabilitation is often necessary during primary treatment and in the follow-up period after surgery.

Osteomyelitis

Osteomyelitis (OM) is an inflammation of the bone and bone marrow, usually caused by bacterial infections and occasionally by fungi, viruses or parasites [9]. Osteomyelitis may cause growth changes or pathological fractures [10, 11]. Haematogenous multifocal OM in children may be dangerous because sepsis may develop quickly if not early treated [12] (Fig. 2.3).

The most common offending organism in OM is staphylococcus aureus. Acute hematogenous OM typically affects children being at a period of rapid growth and bone elongation. The predilection areas for the process of infection are long bone metaphyses of the femur and tibia. The infection does not often cross metaphysis due to the growth plate barrier and does not commonly affect the nearby joints. The metaphyseal blood supply is such that the vessels make a hairpin turn and blood flow slows, allowing microorganisms to take hold [13]. Another common site of infection is discitis.

The total annual incidence rate of OM is 13 per 100,000, 8 acute and 5 subacute OM per 100,000) [14]. Studies from Scotland have shown a decline in the incidence of OM from 8.7 in 1970 to 2.9 in 1997 per 100,000 with more subacute

cases and fewer long bones involved [15]. On the contrary, a Lithuanian study has shown a rise in the total annual incidence of OM from 11.5 in 1982 to 14.3 in 2003 per 100,000 population [16]. The incidence of vertebral OM in children as reported by the National Patient Registries of France is less than 0.5 per 100,000 children [17].

The *three phase bone scan of the skeleton* is indicated as the initial diagnostic method for all children with suspected OM, given that the positive scintigraphic findings of increased accumulation of $^{99\text{m}}\text{Tc-MDP}$ in the affected bone can be detected as early as 24h after the emergence of symptoms. Specific scintigraphic findings enable prompt diagnosis and treatment before any serious bone tissue destruction occurs. The three phase bone scan shows increased accumulation of bisphosphonates in all three phases. The flow phase and the blood pool phase increase the specificity of scintigraphic findings in OM, showing hyperemia and inflammatory reaction. Increased accumulation of the tracer in the affected bone localizes infection [4]. Sometimes on scintigraphy instead of increased tracer uptake in the delayed phase, there may be either reduced tracer uptake due to infarction of the bone or a photopenic area due to osteolysis and/or abscess.

Besides the above, *indium-111 oxine ($^{111}\text{In-oxine}$) and technetium-99m ($^{99\text{m}}\text{Tc}$) in vitro labeled autologous leukocytes* may be used in children for a more specific investigation. An overall sensitivity of 88% and specificity of 91% for this technique are reported for the diagnosis of OM [18].

These studies are especially useful to exclude infection in a previously traumatic bone. Nevertheless, false positive scans for infection have been reported, related to acute fractures [19]. Delay in the administration of the labeled leukocytes may cause false negative results due to decreased leukocyte viability.



Figure 2. The initial bone scan of a 3 years old boy with clinically diagnosed OM showing increased tracer uptake to the middle and lower third of the right femur (left). Following treatment by antibiotics OM was improved (middle) and treated (right image).

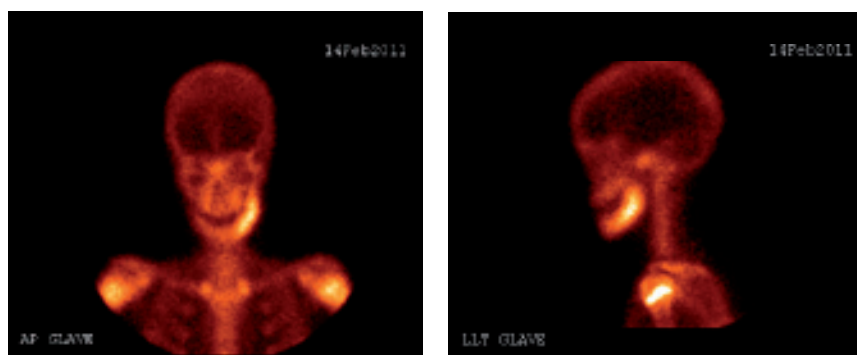


Figure 3. A 14 years old boy with a history of tooth extraction two years before. Osteomyelitis involving the left side of the mandible. Bone scan of the skull: anterior and left lateral views.

In cases where the scintigraphy with bisphosphonates is negative, there is no need to continue with radiolabeled leukocytes, since a negative bone scan basically rules out osteomyelitis.

It has been reported that *labeled leukocytes with ^{99m}Tc-HM-PAO* have an accuracy similar to that of ¹¹¹In-oxine labeled leukocytes as regards the diagnosis of OM. The ^{99m}Tc-HM-PAO labeled leukocytes have the advantage of providing same day results and of giving a much lower radiation dose than that of the ¹¹¹In-oxine. The main advantage of ¹¹¹In-oxine over ^{99m}Tc-HM-PAO labeled leukocytes is its higher labeling efficiency and less efflux of radioactivity from the labeled leukocytes [20].

When there is less or no bone marrow activity on the ^{99m}Tc-SC scan, in areas with intense accumulation of leukocytes, infection is probable [21].

In general, *X-rays* do not show any significant abnormality at the early stage of OM. Findings of MRI in acute OM may be non-specific. Imaging by single photon emission tomography (SPET) of acute OM can localize the exact site of the tracer uptake, while often the corresponding CT images show no obvious change at the early stage. The ¹⁸F-FDG PET scan may provide high-resolution tomographic images. With time, CT images may show lytic areas and also cortical erosion and areas of air in the bone and may be more informative than MRI [22, 23].

Many cases, OM in children can be *effectively treated* with antibiotics and pain medications. Biopsy can indicate the choice of the best antibiotic. Sometimes, surgery may be necessary as when there is an abscess or damaged soft tissue or bone that needs to be removed.

Fibrous dysplasia

Fibrous dysplasia (FD) is a benign congenital bone disorder characterized by areas of anomalous bone formed in mesenchyme, which can be found in one or several bones. On histology, fibrocellular matrix of immature collagen contains small irregularly shaped trabeculae of immature, inadequately mineralized bone [24]. Fibrous dysplasia is found predominantly in children and young adults, with 75% of patients presenting before the age of 30 years (highest incidence between 3 and 15 years). Fibrous dysplasia is not rare although its true incidence and prevalence is difficult to estimate. It has been reported that FD represents approximately 5% to 7% of all benign bone tumors [25].

Fibrous dysplasia can affect any bone and can be divided into four subtypes: monoostotic (Fig. 4), polyostotic, craniofacial and cherubism (mandible and maxilla alone) [26].

The majority, 70%-80% of cases with FD are monoostotic [24]. About 10% of the polyostotic cases coexist with some endocrine-related conditions, like: precocious puberty, thyroid gland disease or areas of increased skin pigmentation. Mild cases usually cause no signs or symptoms. More serious cases of FD may result in bone pain and deformities.

X-rays in FD show radiolucent lytic medullary lesions with some sclerosis and expansion of the bones [13]. Computed tomography in 56% of the cases, shows ground-glass opacities, in 23% homogeneously sclerotic lesions, and in 21% cystic lesions [27]. Expansion of the bone with intact overlying bone and endo steal scalloping may also be seen [24].

Magnetic resonance imaging is not particularly useful in differentiating FD from other diseases as there is marked variability in the appearance of bone lesions, which often

resemble tumour or other more aggressive lesions [27].

Typical skeletal scintigraphic findings in FD, with ^{99m}Tc-MDP are: intensive accumulation of the radiopharmaceutical, especially in the bones of the skull in monoostotic FD, and in the lower extremity bones in cases of polyostotic FD. In the three phase bone scan of the affected areas, there is no asymmetry, nor relative hyperemia, findings that might exclude the infectious etiology of these lesions. It seems that the potentially operable symptomatic lesions may be more accurately evaluated with the dual-phase ^{99m}Tc methoxyisobutyl isonitrile (*^{99m}Tc-MIBI*) scintigraphy as compared with ^{99m}Tc-MDP and guide surgical treatment [28].

Treatment focuses on relieving signs and symptoms. Adequate pain management is required to maintain functional status and the quality of life [29]. Children with polyostotic FD require aggressive and innovative intervention, in order to avoid severe skeletal deformities. Bone grafting is seldom indicated. The use of intramedullary internal fixation devices is preferred over plate and screw devices, whenever possible. The management of each patient must be individualized. Patients and their parents must be prepared for multiple episodes of reconstructive surgery throughout the years to follow [30].

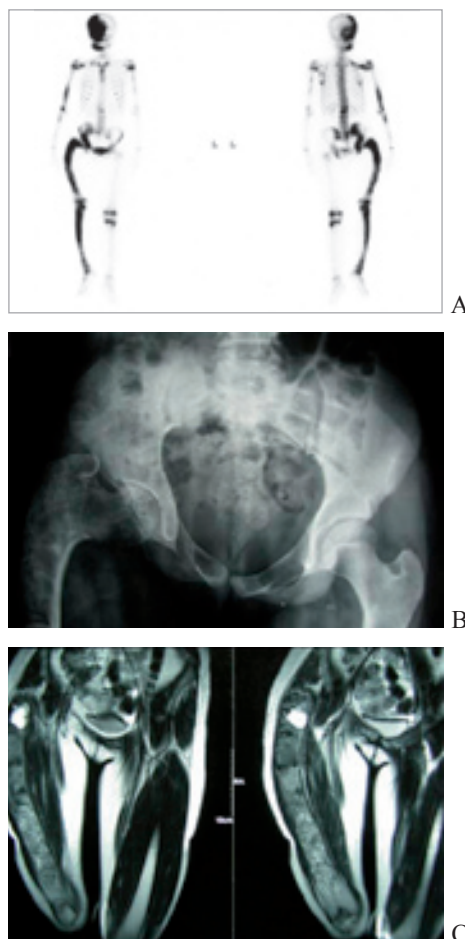


Figure 4. Polyostotic fibrous dysplasia. A. Bone scan. B. Radiography (femur). C. MRI (femur) [41].

Legg-Calvé-Perthes disease

Legg-Calvé-Perthes disease (LCPD) is an idiopathic avascular necrosis of the growing femoral epiphysis, which if untreated, can result in deformity and decreased containment of the femoral head in the acetabulum [13].

Emergence of the disease is slow, manifested by pain and limited extremity movement due to vascular changes and ischemia. Ischemia leads to tissue and bone marrow necrosis, but without affecting the epiphyseal plate. Legg-CPD is one of the most common hip disorders in young children, occurring in approximately 5.5 of 100,000 children per year. A lifetime risk of developing the disease is about 1 per 1200 individuals. Male to female ratio of occurrence is 3-5:1. Most cases of LCPD have presented themselves by the age of 14 years [31].

Early diagnosis and prompt treatment impedes progression and shortens the necessary time for treatment. At the early stage, X-rays may show in the femoral head increased cartilage and subchondrial fissure fracture or may not be diagnostic, while bone scintigraphy will show photopenia in the epiphysis. At the intermediate stage of the disease, fragmented femoral epiphysis can be found and later flattened and distorted femoral head is a typical finding.

T-1 weighted MRI demonstrates loss of normal high-signal marrow of the epiphysis. Later metaphyseal cysts are found on T-2 WI MRI [13].

A typical finding on the ^{99m}Tc-MDP bone scan at the early stage of the disease is the absence of accumulation of the tracer in the femoral head segment (cold defect). Pinhole collimator views are ideal and may often reveal defects, not seen even on the SPET scans [32]. Unfortunately, often, patients are referred for a scan few months after diagnosis. By that time X-rays will also be diagnostic showing pathologic changes in the femoral head (Fig. 5). Bone scan is valuable at this stage because it shows the degree of revascularization of the femoral head, which indicates prognosis and future management. If a stripe of increased activity is seen lateral to the photopenic defect in the head of the bone, this indicates revascularization through superior capsular arteries and predicts favorable prognosis. If revascularization occurs through collateral circulation or through metaphyseal arteries, increased tracer uptake will be seen in the adjoining metaphysis.

In advanced cases of avascular necrosis, at areas of bone remodeling, femoral head may be distorted with increased ^{99m}Tc-MDP accumulation. Often, secondary arthritic changes may also develop causing increased tracer uptake in the acetabulum.

Bone marrow imaging with ^{99m}Tc-sulphur colloid has also been used to evaluate the vascular supply of the femoral head and neck. In general, the absence of radiocolloid uptake in the femoral neck indicates vascular impairment, while its presence indicates intact blood supply [4].

The goal of treatment is to avoid severe degenerative arthritis. There is no clear consensus on nonoperative or operative treatment protocols for pediatric patients presenting with LCPD. A meta-analysis of 23 studies with 1232 patients suggested that operative treatment is more likely to yield a spherical congruent femoral head than nonoperative treatment among patients 6 years of age or older. Among patients younger than 6 years, operative and nonoperative methods have the same likelihood to yield a satisfactory outcome. Among these patients, pelvic procedures were more likely to result in a good radiographic outcome than femoral procedures [32]. The use of zoledronic acid has also been investigated [33].

Osteopetrosis

Osteopetrosis (OP) is a heterogeneous group of hereditary diseases of bone resorption by osteoclasts, manifested by increased bone mass and bone density. The osteoclasts activity impedes bone remodeling process, and seriously damages bone formation and structure. The overall incidence of OP is estimated to be only 1 case per 100,000-500,000 population [34-36].

There are three distinct types of OP: the infantile, or "malignant", or "lethal" form, the autosomal recessive, or "intermediate" form, and the autosomal dominant form [37]. Children affected by more serious forms of the disease, aside from bone deformities may also suffer from central nervous system disorders [38]. The disease may result in death usually at the first years of life, due to recurrent infections [39]. Bones become brittle [43], especially in the autosomal dominant type of the disease. On the other hand, patients may be asymptomatic and bone scan can be the first diagnostic approach.

The typical radiological image of OP is generalized osteosclerosis and the formation of bone-in-bone. Bones may be uniformly sclerotic, but alternating sclerotic and lucent bands may also be noted in the iliac wings and at the epiphysis of long bones. In children there is gradual obliteration of the medullary cavity, and pancytopenia (malignant OP). Because OP encompasses an heterogeneous group of disorders, findings differ according to the type of OP [28]. Radiographs may show evidence of fractures or of osteomyelitis.

Bone scintigraphy with bisphosphonates shows bone deformities and sites of old and new fractures. Sometimes bone scan shows diffusely increased tracer uptake like a superscan (Fig. 6). It is recommended to repeat the bone scan

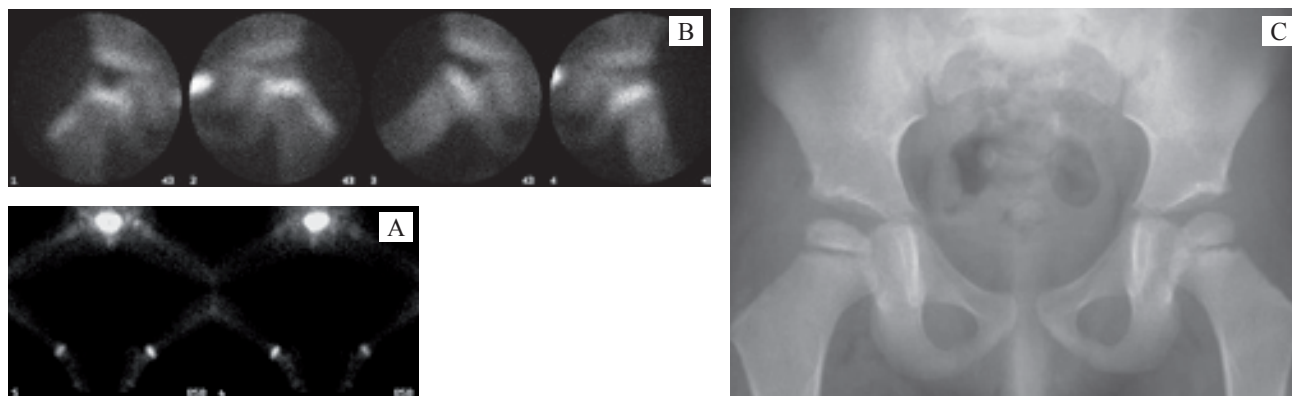


Figure 5. A 4 years old boy with a history of two weeks of non-specific right lower extremity pain with limping. Static images of the hips. A. Immediate frog leg view. B. Anterior delayed pinhole view with decreased tracer accumulation in the region of the femoral head. This finding is most consistent with LCPD of the femoral head. C. A plain radiograph of the pelvis, shows slightly sclerotic right femoral capital epiphysis smaller than the left one, consistent with the scintigraphic data [42].

during the follow-up period, since new asymptomatic bone fractures may be diagnosed.

Infantile OP warrants treatment because of the adverse outcome associated with the disease [33]. Vitamin D₃ (calciferol) appears to help by stimulating dormant osteoclasts and thus bone resorption. Treatment with gamma interferon has offered long-term benefits, by improving white blood cells function and decreasing the incidence of new infections. Erythropoietin can be used to correct anemia. Corticosteroids have also been used to treat anemia, as well as to stimulate bone resorption. In pediatric OP, surgical treatment of fractures may be necessary [32].

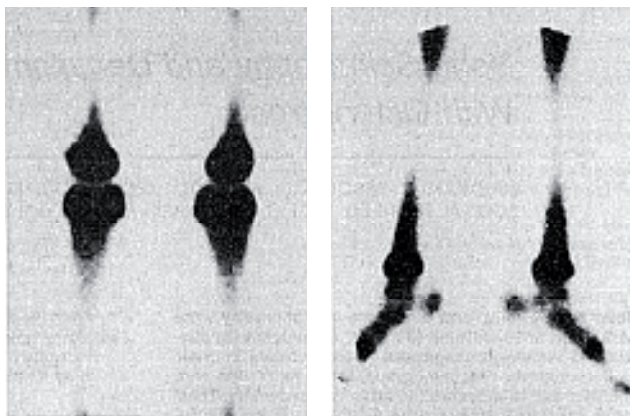


Figure 6. Bone scintigraphic features in a child with clinical diagnosis of osteopetrosis: intense tracer activity in the femoral, tibial and humeral bones [42].

In conclusion, bone scintigraphy with ^{99m}Tc-MDP and better with PET (¹⁸F-FDG and ¹⁸F-NaF) can support diagnosis in all five benign myoskeletal diseases described in children. Radiology is used for more advanced stages of these diseases and for studying specific in situ sites of the body. Magnetic RI is specific for periosteal and bone marrow lesions while CT better be avoided in children.

The authors declare that they have no conflicts of interest.

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