The Role of MRI in Differentiation of Bone Infarction and Osteomyelitis in Pediatric Patients with Sickle Cell Disease

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Abstract: Purpose: Trial to differentiate between bone infarction and osteomyelitis in pediatric patients with Sickle Cell Disease using MRI. **Patients and Methods:** Prospective study analyzed 48 pediatric cases of sickle cell disease with lower limb bone pain, tenderness or limping. , they were (26.male (54.2%) and 22 female (45.8%), their age ranged between 3 and 10 years with a mean of age 6.08±3.81 years. The imaging include Conventional radiography, Ultrasound +/- Doppler examination and MRI with and without contrast adminstration. **Results:** The detection of abnormality on MRI compared with plain x-ray and US was statistically significant (P value was 0.٠1 and 0.009 respectively). Infarction was the most common pathology detected among our studied group represented about 45.8% while infection represented 20.8 %. T1 with contrast and STIR were more sensitive in differentiating infection and infarction giving a high statistically significant difference p value (<0.001) for both sequences. MRI diagnosed 9 cases as equivocal, these cases were positive for infection in 5 cases and negative in 4 cases diagnosed as infarction at culture examination **Conclusion:** MRI is the most sensitive but not specific in detection abnormality in early bone marrow infection and infarction. It can differentiate infarction and osteomyelitis but early cases shows less specific finding making aspiration and tissue culture mandatory in equivocal MRI cases. Differentiating osteomyelitis from infarction in children with sickle cell disease remains a challenge for the pediatrician. *J Am Sci* 2017;13(2):77-85]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org. 11. doi:10.7537/marsjas130217.11.

Key Words: Sickle Cell Disease, bone marrow, magnetic resonance imaging, pediatric bone marrow disorders

1. Introduction:

Sickle cell disease (SCD) is a hereditary haemolytic anaemia caused by a point mutation in the gene responsible for the formation of normally functioning haemoglobin. This results in distortion of the shape of deoxygenated red cells and a reduced red cell life span giving rise to the main detrimental effect of haemolytic anaemia. Presence of unusually circulating cells result in impediment of micro-circulation, creating ischemia and localized infarction [(1).]

Acute condition results from painful vaso-occlusive crises (VOCs). The pain may include any organ. They are brought on by microvascular retardation with ensuing tissue ischemia [(2).]

Infarction is the primary complain of SCD, it might happen any place in the skeleton. in bony medullary cavities and epiphyses. " [(3).]

Osteomyelitis and septic joint arthritis are regular and serious complications of SCA [(4).]

The difference between osteomyelitites and infarction may be testing. The discoveries at radiograph are likewise nonspecific and at first frequently normal [(5).].

However, periosteal inflammation, osteopenia and sclerosis take 8 to 10 days to end up distinctly apparent and seen at both infarction and infection [(6).]

At MRI infarction and osteomyelitis may have a very similar appearance, showing areas of abnormal high signal intensity at T2WI and inversion recovery images and display contrast enhancement[(7).]. Thus, the difference at MRI may not be conceivable. Soft-tissue abnormal-ities were thought to demonstrate osteomyelitis. However the same soft-tissue abnormalities may seen in infarction [(8).]

In the intense stage, vaso-occlusive crises and osteomyelitis are indistinguishable. Both associated with an ascent in inflammation for example C-reactive protein and white cell number. The gold standard in diagnosis of osteomyelitis is a positive blood culture or joint suction, however, negative blood culture does not exclude the analysis of osteomyelitis [(9).]

The aim of this study was to detect the role of MRI in differentiation of bone infarction and osteomy-elitis in pediatric patients with sickle cell disease.

2. Patients and Methods:

2.1 Patients:

This prospective study included 48 patients with sickle cell disease. Their age ranged from 3 to 10 years old. They were referred from hematology unit of pediatric department of our Hospitals from November 2014 to December 2016. The inclusion criteria were

includes, patient with history of sickle cell disease complaining of bone pain, tenderness or limping with good renal functions. However, the exclusion criteria were including the patients unwilling to complete the study, patients with suspected unavailability throughout the study.

The study was approved by the local ethics committee of our institute, and a written consent from the parent was obtained to participate in the study.

All patients were subjected to physical examination, complete blood count, renal function tests and the following imaging:

2.2 Imaging modalities:

2.2.1. Plain Radiography:

Through the different fixed or portable X-ray apparatus, single or multiple views were done as:

A. Hip joint and upper femur, anteroposterior view: Equipme nts used were 24 x 30 cm detail or fast screen cassette, table bucky , stationary grid or grided cassette .The patient was supine with affected limb in the center of x – ray couch centering with vertical beam to the related joint at a point 2 and half cm distal along the perpendicular bisection of the line from the anterior superior iliac spine to the upper border of the symphysis pubic . Exposed on arrested respiration with optimum expsure factors and FFD. 102 cm

B. Knee joint and upper tibia, posteroanterior view as well as lateral view: In which, the epicondyles perpendicular to IR. Knee flexion of 20 to 30 degrees is usually preferred - this position relaxes muscles and shows maximum volume of the joint cavity.

2.2.2. Ultrasonography (US):

US was performed using Logiq E9 scanner (GE Healthcare, Wauwatosa, WI, USA) using a C1–10 MHz sector transducer. US examination was done at the area of interest and including Doppler evaluation if indicated.

2.2.3. Magnetic Resonance Imaging (MRI):

All MRI studies were done using Philips machine (01.5 Tesla). All patients were asked to get rid of any metallic subjects as well as they were asked about any contraindication to MRI examination (artificial heart valve, metallic stents or any prosthesis except that made of titanium). The parents were informed about the duration of the examination, the position of the patient and the importance of being motionless.

Patient were imaged in the supine position using surface coil for examining femur, tibia and ankle, while in examining the spine and pelvis, body phased array coil was used.

For children who cannot cooperate for study, sedation will be delivered by chloral hydrate (50 to 75 mg/kg) was given orally for 3 cases or by anesthesiologist in form of intravenous phenobarbitone (4-6mg/kg, maximum dose 200 mg) in 10 cases, these was given under complete observation using pulse oximetry.

The examination was done before contrast administration, a scout coronal T1-weighted view was obtained to verify the precise position of the patient and to act as a localizer for subsequent slices, then multiple pulse sequences were used to obtain axial images followed by coronal and/or sagittal images based on the location of the pathology encountered. In midline lesions (spine) sagittal planes were used while in laterally located lesions (any joint or limb) coronal images were more helpful.

The contrast media used were either Omniscan or Magnivist (Gadolinium (Diethelene Triamine Penta acidic acid (“Gd-DTPA’’)), it was administrated intravenously in a dose of 0.1 mmol/ kg body weight. T1-WIs was obtained immediately after the end of contrast injection.

The imaging protocol included sagittal and axial T1WI spin echo sequences (600/17/90/2 (TR/TE/ angle/NSA)), Sagittal, Coronal and Axial T2WIs (3446/ 130/90/3) sequences, STIR (1757/ 14/ 160/ 3TR/ TE/TI/NSA) sequences. GRE T1 (TR: variable/ TE: <30/flip angle: 70-110 degrees), GRE T2* (TR: variable/ TE: <30/flip angle: 5-20 degrees) PD (TR: >1000/TE: <30/flip angle: 90 degrees)

2.3. Statistical analysis:

All data were collected, tabulated and statistically analyzed using SPSS 19.0 for windows (SPSS Inc., Chicago, IL, USA) & Med Calc 13 for windows (MedCalc Software bvba, Ostend, Belgium).

Quantitative data were expressed as the mean ± SD & median (range), and qualitative data were expressed as absolute frequencies (number) & relative frequencies (percentage). Continuous variables were checked for normality by using Shapiro-Wilk test.

Mann Whitney U test was used to compare between two groups of non- distributed variables. Kraskall Wallis H test was used to compare between more than two groups of non-normally distributed variables. Percent of categorical variables were compared using Pearson’s Chi-square test or Fisher's exact test when was appropriate.

Validity MRI in differentiation between osteomylitis and infarction was calculated using diagnostic performance depend on sample 2x2 contingency tables generation using blood culture as reference (gold) standard.

The sensitivities, specificities, positive predictive values, negative predictive values, and accuracies, with their respective 95% confidence intervals were calculated.

All tests were two sided. P-value< 0.05 was considered statistically significant (S), p-value < 0.001 was considered highly statistically significant (HS), and p-value ≥ 0.05 was considered statistically insignificant (NS).

3. Results:

Our study included 48 pediatric patients with history of sickle cell disease, they were (26.male (54.2%) and 22 female (45.8%) with their age ranged between 3 and 10 years with a mean of age 6.08±3.81 years.

All patients (48 cases) presented with lower limb pain, 30 cases with limitation of movement, 18 cases by fever and 16 cases presented by localized tenderness.

The final diagnosis was made by culture examination from the soft tissue surrounding the lesion where 10 cases were positive for infection and 38 cases were negative.

Out of 48 examined patients Plain x-ray revealed abnormal findings in 14(29.2%) cases, ultrasound in and 15 (31.3%) and MRI examination in 36 (75%) cases, the detection of abnormality on MRI compared with plain radiography and US was statistically significant and Pvalue was 0.٠1 and 0.009 respectively **(table1).**

Using plain x-ray finding diagnosis of osteomylities was done in three (21%) cases and infarction in 6 (43%) cases, while in the other 5 (36%) cases the finding was equivocal in form of non specific lucency, periostitis and soft tissue swelling. Four of these cases were negative for infection at culture examination and diagnosed as bone infarction and one case was positive for infection.

Ultrasound findings in the form of periosteal elevation (9 cases) and fluid collection (15 cases) gave diagnosis of infection, On culture examination 10 cases was true positive for infection and the other 5 cases was false positive and diagnosed as infarction.

Depending on MRI finding infarction was the most common pathology detected among our studied group 22 cases represented about 45.8% while infection is the least common 5 cases represented 10.4 % of studied age group, the MRI finding was equivocal in 9 cases represented about 18.8 % (**Figure 1).**

Relation between final MRI diagnosis and different MRI sequences was reported in **(table 2):** where T1 with contrast and STIR were more sensitive in differentiating infection and infarction giving a high statistically significant difference p value <0.001 for both sequences.

Nine cases were equivocal on MRI all of these cases shows bone marrow edema, soft tissue edema, subperiosteal and surrounding soft tissue fluid collection with post contrast enhancement, culture evaluation of these cases was positive for infection in 5 cases and negative in 4 cases diagnosed as infarction.

Relation between culture result and MRI diagnosis shown in (**table 3)**

Table (1): Imaging evaluation of the studied sickle cell anemia patients.

Imaging evaluation	The studied Patients (N=48)	
	No.	%
X-ray		
Normal	34	70.8%
Abnormal	14	29.2%
US		
Normal	33	62.5%
Abnormal	15	31.5%
MRI		
Normal	12	25%
Abnormal	36	75%

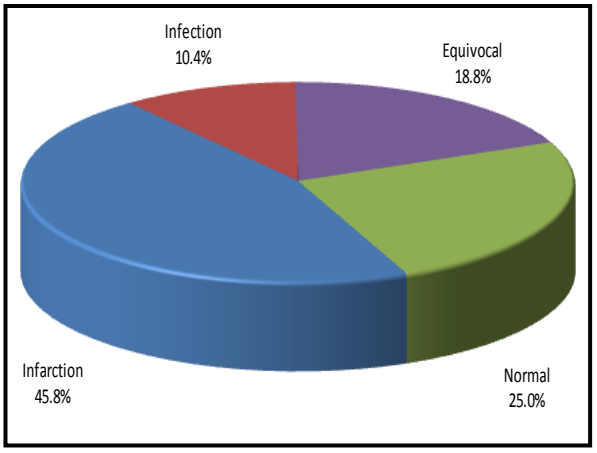


Figure (1): Pie charts for MRI diagnosis of the studied sickle cell anemia patients

Table (2): Relation between final MRI diagnosis and MRI sequences

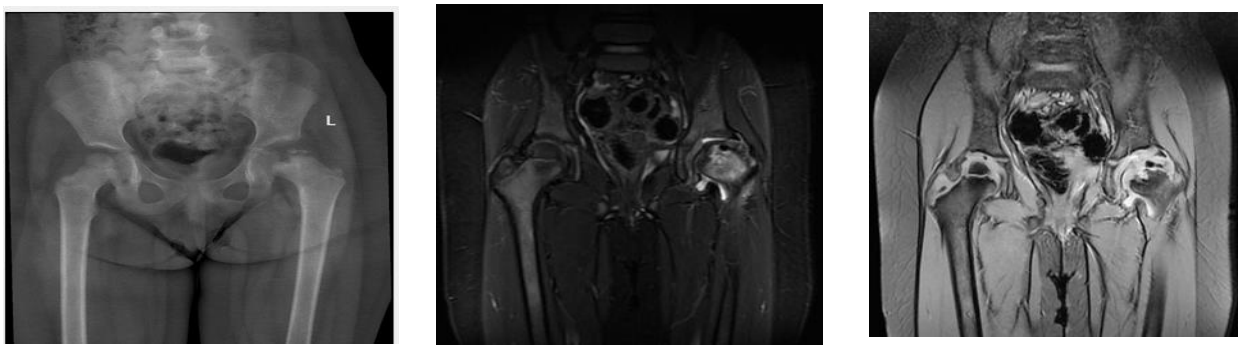
MRI findings	N	MRI diagnosis				Test‡	p-value (Sig.)
		Normal (N=12)	Infarction (N=22)	Infection (N=5)	Equivocal (N=9)		
T1 without contrast							
Normal	12	2 (58.3%)	1 (4.5%)	0 (0%)	0 (0%)	24.585	0.001 (S)
Abnormal	36	10 (41.7%)	21 (95.5%)	5 (100%)	9 (100%)		
T1 with contrast							
Normal	12	12 (50%)	0 (0%)	0 (0%)	0 (0%)	16.253	<0.001 (HS)
Abnormal	36	0 (50%)	22 (100%)	5 (100%)	9 (100%)		
T2							
Normal	12	6 (50%)	1 (4.5%)	0 (0%)	1 (11.1%)	13.127	0.004 (S)
Abnormal	36	6 (50%)	21 (95.5%)	5 (100%)	8 (88.9%)		
STIR							
Normal	12	11 (50%)	0 (0%)	0 (0%)	1 (11.1%)	13.127	<0.001 (HS)
Abnormal	36	1 (50%)	22 (100%)	5 (100%)	8 (88.9%)		

‡ Chi-square test. p-value < 0.05 is significant. Sig.: significance.

Table (3): Relation between culture result and MRI diagnosis.

MRI diagnosis	N	Negative culture (N=38)		Positive culture (N=10)		Test‡	p-value (Sig.)
		No.	%	No.	%		
■ Normal	12	12	31.6%	0	0%	34.526	<0.001 (HS)
■ Infarction	22	22	57.9%	0	0%		
■ Infection	5	0	0%	5	50%		
■ Equivocal	9	4	10.5%	5	50%		

‡ Chi-square test. p-value< 0.05 is significant. Sig.: significance.



(A) **(B)** **(C)**

Figure (2) A known case of sickle cell disease of 3 years old girl complaining of limping and limitation of left hip joint movement. **(A) Radiography of** both hip joints AP view showing flattened, sclerotic and fragmented left femoral capital epiphysis. (**B&C) MRI coronal STIR and coronal gradient respectively** showing the proximal left femoral epiphysis is flattened, sclerotic and fragmented associated with thick/hypertrophic articular cartilage. The proximal metaphysis shows irregularity with cyst/pseudocyst formation containing cartilage signal. Ipsilateral moderate joint effusion with contralateral incidentally finding mild right hip joint effusion.
Diagnosis: ***Stage IV Left femoral head Legg-calve-perthes disease.***

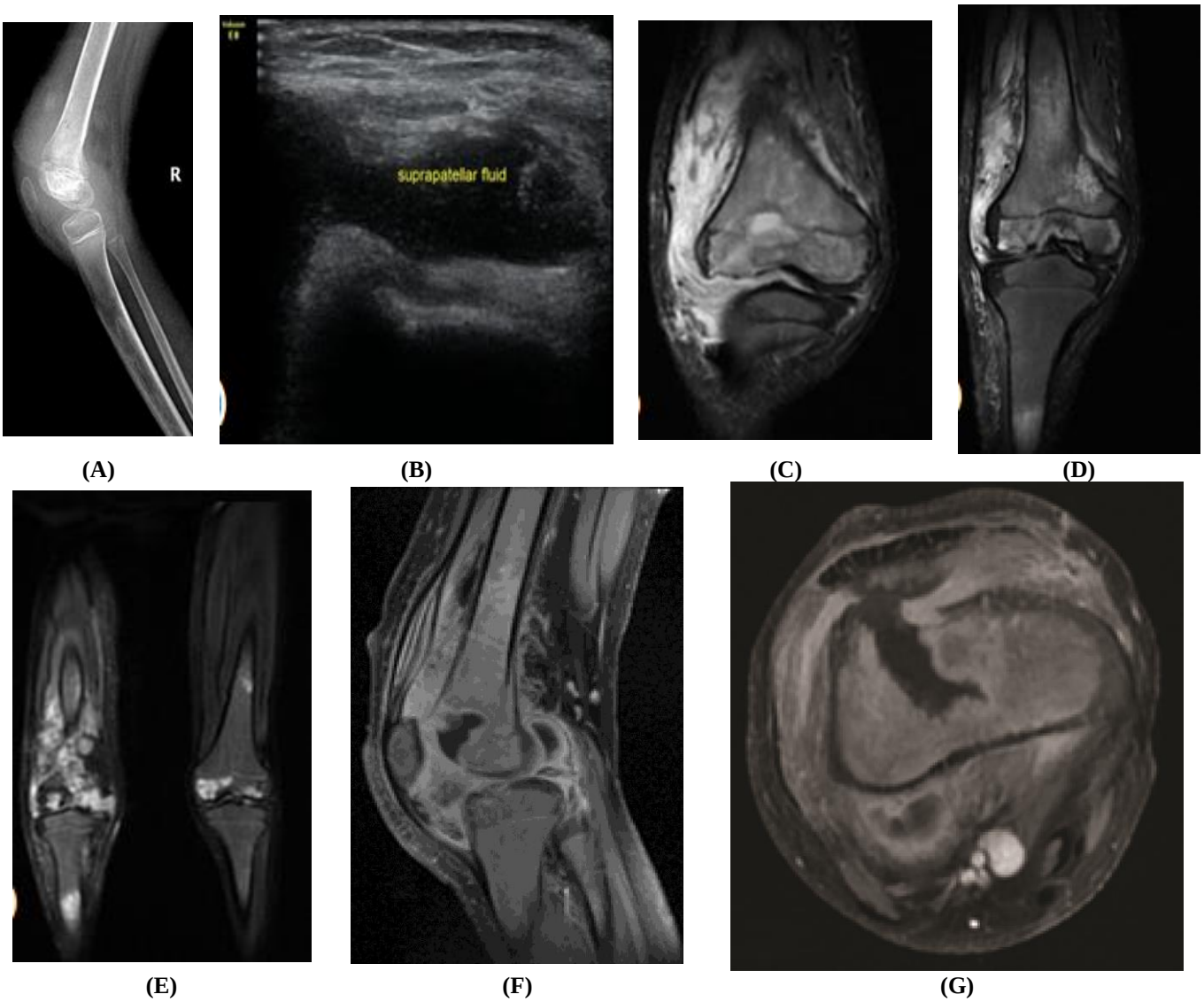
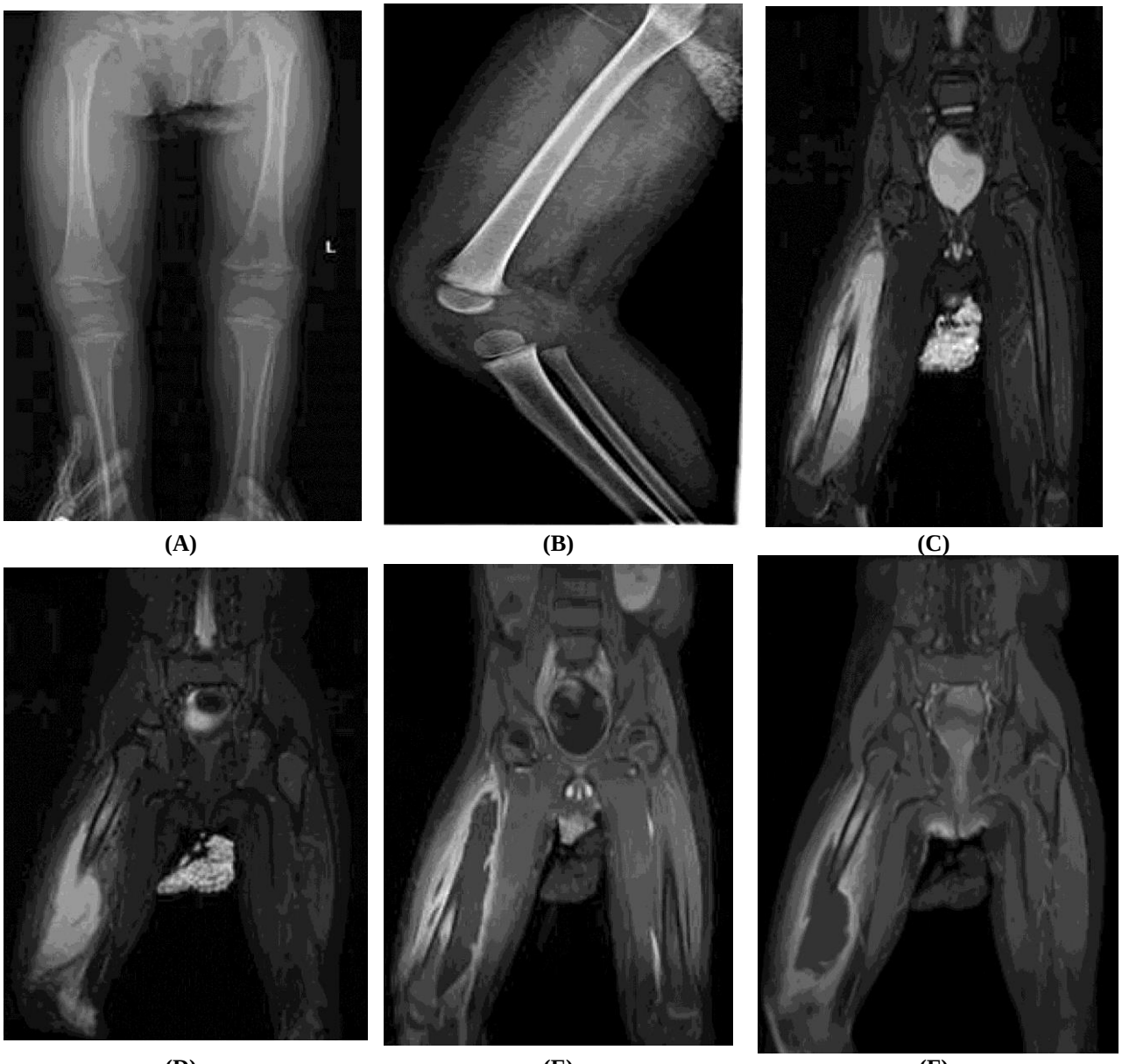


Figure (3) 6 years old girl with history of Sickle cell disease complain of right knee pain low grade fever by blood culture show increased inflammatory markers. **(A) Radiography of right knee joint** lateral view shows a small lytic lesion at the medial aspect of lateral femoral metaphysis near the growth plate with serpeginoues area of calcification as well as joint soft tissue swelling. (**B) High resolution US axial** view shows suprapatellal turbid effusion. **(C,D&E) MRI coronal STIR of right femur (F&G) Sagittal and axial right femur T1 fat suppression post IV contrast** show focal area of bone marrow low signal intensity lesion affecting the distal femoral metaphysis, and extending through the growth plate to the distal femoral epiphysis and reaching the knee joint space through fistulus tract formation associated with cortical defect. There is extensive intra and extra articular soft tissue edema involving the lower third of the thigh muscles.

Diagnosis: ***Right distal femur metaphysis/epiphysis Brodie's abscess associated extensive septic arthritis. Multiple bilateral bone marrow infarctions.***



(A) **(B)** **(C)**

(D) **(E)** **(F)**

Figure (4) A known case of ***Right femur osteomyelitis*** for 4 years old boy with sickle cell disease complaining of painful swelling right thigh tenderness and fever. **(A&B) Radiography of right femur AP and lateral views** show normal bone with soft tissue swelling. **MRI (C&D) Coronal STAIR demonstrate** diffuse abnormal heterogeneous medullary signal intensity at the right femoral diaphysis display high signal at STAIR, no evidence of cortical destruction. **(E&F) T1WI fat suppression without and with IV contrast respectively** showing abnormal heterogeneous medullary cavity enhancement. Large circumferential juxta-cortical fluid intensity about 15cm x5cmx5cm with thick irregular peripheral enhancement.

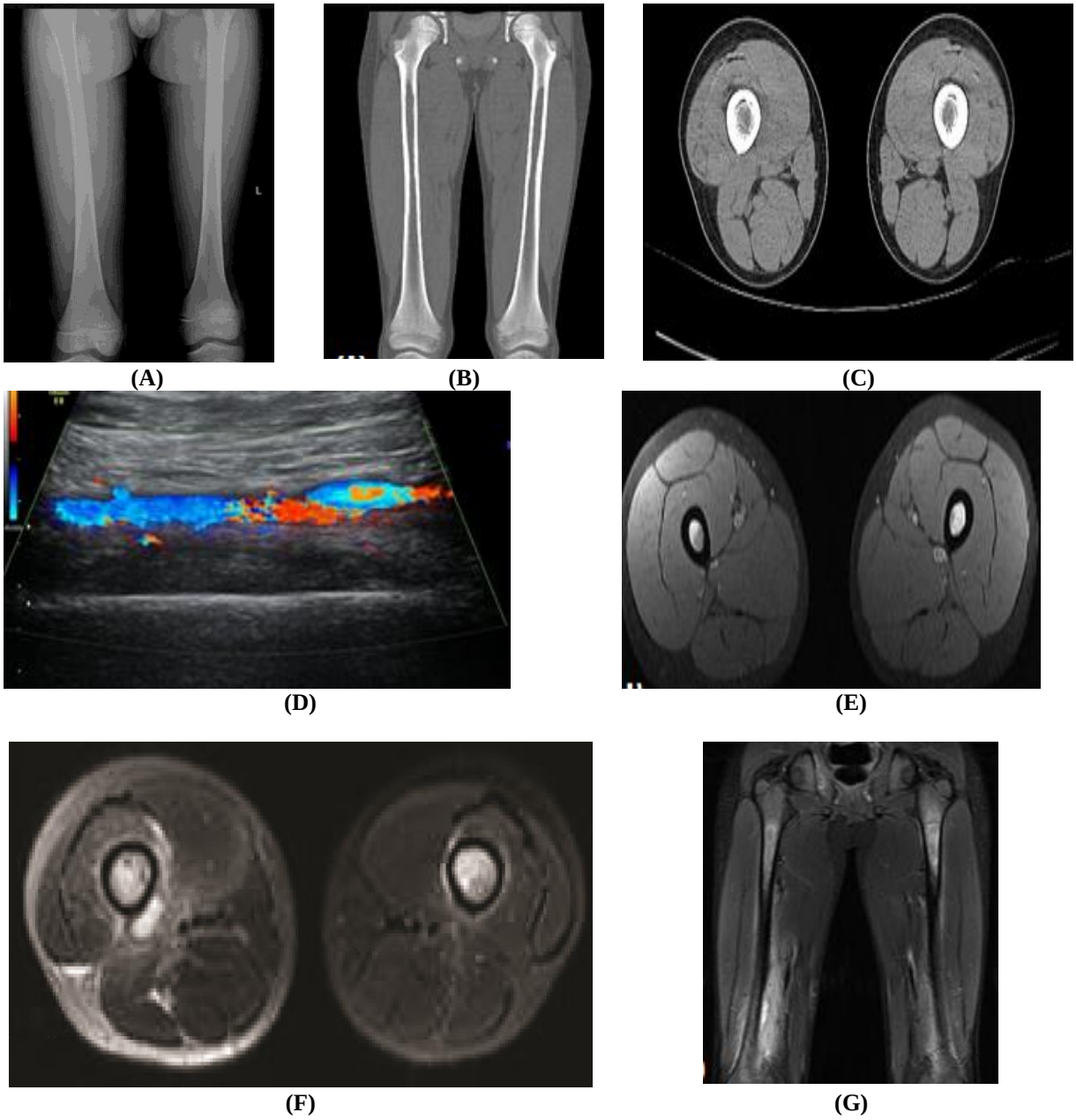
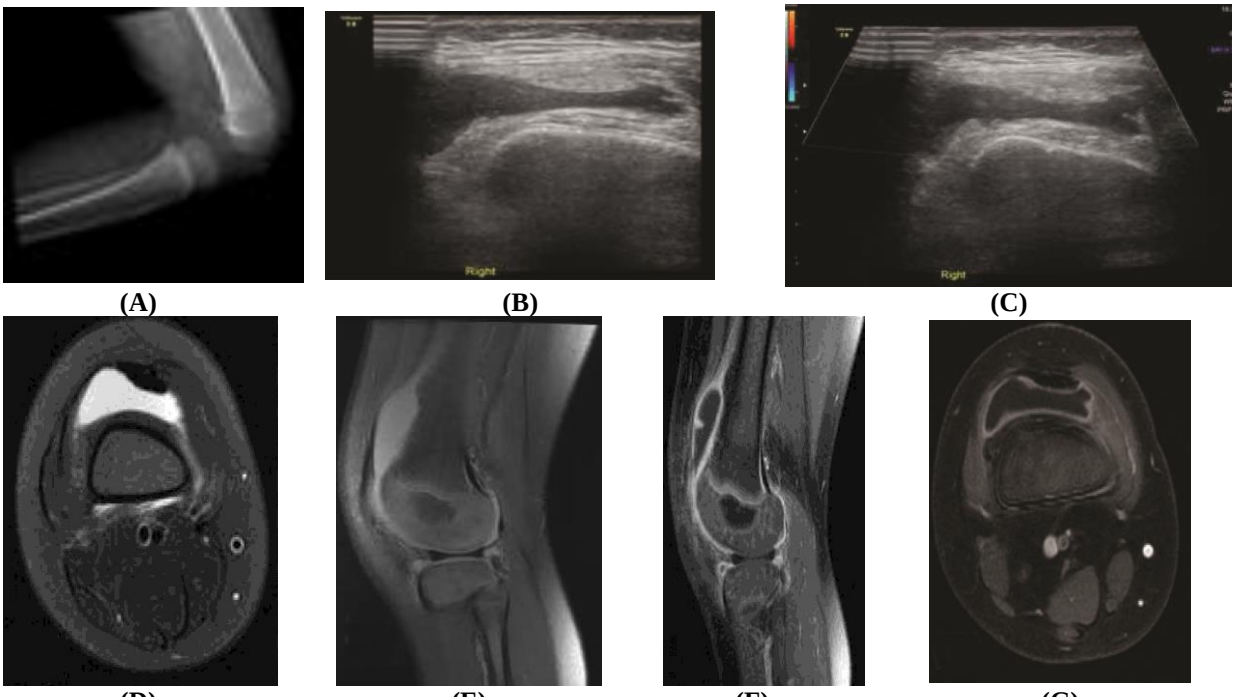


Figure (5) 10 years old boy complaining of bilateral thigh pain swelling and tenderness more at the right side. **(A) Radiography of both femurs AP view** shows no detectable abnormality. **(B&C) Coronal reformatted CT of both femur (bone window)and axial bone soft tissue window respectively** demonstrate no defined abnormality **(D) Colour Doppler high resolution US longitudinal view** show juxta-cortical thin layer of turbid collection with Juxta cortical circumferential soft tissue hyperemia. **(E) MRI axial STIR (F) Axial T1 fat suppression with IV contrast demonstrate & (G) Coronal STIR** demonstrate Diffuse bilateral femoral meta-diaphyseal abnormal heterogeneous bone marrow signal intensity predominantly high at STAIR and exhibit patchy contrast enhancement

Diagnosis: ***Bilateral femoral medullary infarction with small juxta-cortical collection confirmed by blood culture as aseptic.***



(A) **(B)** **(C)**

(D) **(E)** **(F)** **(G)**

Figure (6) 3 years old girl with history of sickle cell disease complaining of right Knee swelling fever and limitation of movement. (**A) Radiography of right knee joint lateral views show** no detectable abnormality.(**B&C) Gray scale and colour Doppler high resolution US axial** view respectively showing turbid suprapateller fluid collection without any flow vascularity.

(D) MRI axial T2WI (E) sagittal PD (F&G) Sagittal and axial T1 fat suppression post IV contrast respectively showing moderate amount of the right knee joint effusion seen mainly in the supra-patellar pouch. The post contrast image shows smooth synovial enhancement with no abnormal soft tissue abnormal enhancemen a part from reactional edema involving the surrounding knee joint muscles

Diagnosis: ***Right knee joint septic arthritis.***

4. Discussion:

Although recent advances in different diagnostic investigations, differentiating acute osteomlitis from bone infarction in sickle cells disease patients remains a clinical problem. Many imaging modalities have been employed for aiding in solving this issue. **(10)**

Kan et al. (11) reported that medullary bone infarcts are far more common than osteomyelitis in patients with sickle cell disease. In our studied patients the incidence of infarction was more common representing 26 cases (54%) and osteomylitis only detected in 20%.

Phatak et al(12) reported that ,in diagnosis of osteomyelitis ,X-Ray is useful as a first line to exclude trauma or tumor; But X-Ray are insensitive in early osteomyelitis detection that X-Ray is normal in osteomyelitis within the first 14 days of onset of infection and just 20% of cases bringing about radiographic variations from the norm following 2 weeks, in nearly similar result also in our study abnormality detected by X-ray in 14 cases only representing 29.2% of studied group.

Study done by **Pugmire et al.(13-16)** found that If the fluid-sensitive (e.g., STIR, T2-FS) images are ordinary in recent studies; IV gadolinium enhancement gives no extra demonstrative esteem. Be that as it may if the fluid-sensitive images are unusual, so IV gadolinium enhancement is of esteem in expanding the determination of an abscess (if exist) and in arranging the way to deal with abscess aspiration and drainage so MRI with IV contrast does not improve the affectability or specificity in determination osteomyelitis.

In accordance with previous literature, current study by MRI diagnosis T1 with contrast and STIR show abnormality at all cases represent 100 %. While T1 without contrast and T2 show abnormality at 21 cases represent 95.5%.

Almeida and Roberts(17) reported that determination of osteomyelitis in SCD rely upon clinical evaluation together with positive cultures from

blood or bone got by aspiration or biopsy, than upon any single imaging methodology. Bone pain in sickle cell disease is significantly more 50 times more likely because of a VOC than to osteomyelitis

At current study MRI has high sensitivity as all equivocal cases diagnosed by MRI as infarction show negative blood culture and that diagnosed as infection gave positive culture, thus blood culture and joint aspirate are the gold standard in diagnosis equivocal cases

5. Conclusion:

MRI is the most sensitive but not specific in detection abnormality in early bone marrow infection and infarction. It can differentiate infarction and osteomyelitis but early cases shows less specific finding making aspiration and tissue culture mandatory in equivocal MRI cases. Currently, we have limited reliable methods in the diagnostic process. We look forward to new technologies to help us in this challenging task.

References:

1. Lane P. Sickle cell disease. Pediatr Clin North Am 1996; 43:639-64.

2. Adebola E, Babatunde O, Shannon S, et al. Prevalence of Hypoxemia among Children with Sickle Cell Anemia during Steady State and Crises: A Cross-Sectional Study Niger J Clin Pract 16 (1), 91-95. Jan-Mar 2013.

3. Lonergan A, Col M, Cline S, et al. From the Archives of the AFIP Sickle Cell Anemia. RadioGraphics 2001; 21: 971–994.

4. Mehsen N, Barnetche T, Redonnet-Vernhet I, Guérin V, Bentaberry F, Gonnet-Gracia C, et al. Coagulopathies frequency in aseptic osteonecrosis patients. Joint Bone Spine 2009; 76(2): 166-9.

5. Umans K, Haramati W and Flusser B. The diagnostic role of gadolinium enhanced MRI in distinguishing between acute medullary bone infarct and osteomyelitis Magnetic Resonance Imaging 2000; 18: 255–262.

6. Khedr, Hassaan, Shabana et al. Musculoskeletal manifestations of sickle cell disease، diagnosis with whole body MRI: The Egyptian Journal of Radiology and Nuclear Medicine 2012; 43: 77–84.

7. Jain R, Sawhney S, Rizvi SG Acute bone crises in sickle cell disease: the T1 fat-saturated sequence in differentiation of acute bone infarcts from acute osteomyelitis. Clin Radiol 2008; 63: 59–70.

8. Cherry S, Greenhalgh M, Osipenko P, et al. The clinical effectiveness and cost-effectiveness of primary stroke prevention in children with sickle cell disease: a systematic review and economic evaluation. Health Technology Assessment programme 2012; 16(43).

9. Sawyer J and Kapoor M. The limping child: a systemic approach to diagnosis. Am. Fam. Physician 2009;79(3):215–224.

10. Inusa BP1, Oyewo A, Brokke F, Santhikumaran G, Jogeesvaran KH. Dilemma in differentiating between acute osteomyelitis and bone infarction in children with sickle cell disease: the role of ultrasound. PLoS One. 2013 6; 8(6):e65001.

11. Kan J, Hilmes M, Martus J, Yu C, et al. Value of MRI after recent diagnostic or surgical intervention in children with suspected osteomyelitis. Am J Roentgenol 2008; 191: 1595-600.

12. Phatak S, Kolwadkar P, Phatak M, et al. Pictorial essay: Radiographic skeletal changes in Sickle cell anemia. Indian J Radiol Imaging 2006; 16: 627-32.

13. Pugmire X, Shailam V and Gee S. Role of MRI in the diagnosis and treatment of osteomyelitis in pediatric patients :World J Radiol 2014; 6(8): 530-537.

14. Ejindu E, Hine B, Mashayekhi N, et al. Musculoskeletal Manifestations of Sickle Cell Disease: RadioGraphics 2007; 27: 1005–1021.

15. Berger E, Saunders N, Wang L, Friedman J. Sickle cell disease in children: differentiating osteomyelitis from vaso-occlusive crisis. Arch Pediatr Adolesc Med 2009;163: 251–255.

16. Malcius D, Jonkus M, Kuprionis G, Maleckas A, Monastyreckiene E, et al. The accuracy of different imaging techniques in diagnosis of acute hematogenous osteomyelitis. Medicina (Kaunas) 2009;45: 624–631.

17. Almeida and Roberts. Bone involvement in sickle cell disease. British Journal of Haematology 2005; 129: 482 –490.