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Research Article

Role of 3D gradient echo MRI sequence in early detection of hemosiderin in hemophilic joint

Doaa Abdelhakim Mahmoud Abdelrahman[1], Mohamed Farghaly Amin[1], Gehan Lotfy Abdel Elhakeem[2] and Ahmed Sayed Ibrahim Eissa [1]

[1] Department of Diagnostic Radiology, Faculty of medicine Minia university, Egypt.
[2] Department of Pediatric, Faculty of medicine Minia university, Egypt

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Abstract

Purpose of study: In hemophilic patients, Blood deposition within the joints (hemarthrosis) is the foremost cause of morbidity, this is because the affection of all joint components, this leads to inflammation and results in synovitis, osteochondral degeneration which eventually leads to hemophilic arthropathy. 3D Gradient echo MRI sequences are commercially available on most scanners including scanners with lower magnetic field strengths so they are commonly used in clinical practice. **The aim of this study** is to investigate the role of T1 3D FFE MRI sequence which is one of gradient echo MRI sequences for assessment of hemosiderin deposition in the joints of hemophilic patients. **Methods:** In this study we recruited 20 Hemophilic patients between august 2022 to April 2023who admitted to hematology unit by attacks of bleeding or for follow up. All patients underwent MRI for asymptomatic joint by conventional MRI sequences in addition to T1 3D FFE sequence (It has the name of SPGR in GE machine and the name of FLASH in siemens machine) correlation statical analysis was done between results of hemosiderin deposition by conventional sequences and by T1 3D FFE sequence. **Results:** T13D FFE MRI sequence can detect early hemosiderin deposition in hemophilic joint better than other conventional sequences and there is no significant correlation between hemosiderin deposition by conventional sequences and by 3DT1FFE sequence. (r was 0.51 and p value 0.05) **Conclusion:**3D T1 FFE is one of gradient MRI sequences has high capacity and efficiency to detect even subtle intra-articular hemosiderin and provides a potential sensitive method for the early diagnosis and prognosis of hemophilic arthropathy.

Key words: Hemophilia, Hemosiderin, 3D, MRI, joints

Abbreviations:

MRI: magnetic resonance imaging
GRE: gradient recalled echo
SPGR: spoiled gradient echo sequence
HA: Hemophilic arthropathy
FFE: fast field echo
PD: proton density
SWI: susceptibility weighted images

Introduction

Hemophilia is an X-linked bleeding disorder that affects about 25 out of every 100,000 live male births.(1) Coagulation factor VIII or IX deficiency or dysfunction, respectively (hemophilia A and hemophilia B), are responsible for the condition. (2)

Frequent joint bleeding, which frequently starts in childhood and causes debilitating arthropathy due to toxic iron depositions (i.e., hemosiderin) in synovium and cartilage, is a typical complaint among hemophilic patients. Osteochondral degradation and painful inflammatory synovial enlargement are common signs of iron-induced arthropathy. (1)

So it is crucial to develop a non-invasive biomarker sensitive to hemophilic arthropathy (HA) changes in the joint in order to maximize the effectiveness of expensive treatment regimens and to enhance disease progression monitoring.[3]

Pathophysiology of hemophilic arthropathy:
Hemosiderin causes synovium proliferation in the joint area, resulting in the development of various lytic enzymes that control chondrocyte death and a decrease in proteoglycan levels. This results in immediate joint "chemical" damage, which is an early stage of HA pathogenesis damage (first hit). [4]
To start a progressive process of synovial hypertrophy, synovitis, and synovial fibrosis, hemosiderin and iron deposition in the synovium release proinflammatory cytokines and tumor necrosis factor. Synovial macrophages carry these blood breakdown products into the articular cartilage, where they prevent the formation of proteoglycan. Reactive oxygen intermediates that are iron-catalyzed cause cartilage to progressively and irreversibly deteriorate. More cartilage damage results from the synovial inflammatory process being reactivated as a result of the cartilage injury. Immature cartilage is more vulnerable to blood-induced injury than mature cartilage.[2]

MRI of hemophilic arthropathy:
MRI depicts early alternations in joints, such as hemosiderin deposition and synovial hyper-trophy, and minor cartilage damage without joint-space reductions. MRI assessments of hemophilic arthropathy can have a considerable impact on hemophilia care. The findings may help determine which patients need early treatment and make it possible to predict their treatment response.[5]

Principals of GRE sequences:
3D GRE sequences categorized into dark fluid sequences (like spoiled gradient echo or FLASH) and bright fluid sequences (like double echo steady-state or DESS).[6]The basic principle of spoiled gradient recalled echo (SPGR), is it has relative T1-weighting. and dual-echo steady state (DESS) MRI, has a relative T2-weighting.[7] those pulse sequences are often generated using fat suppression or water excitation.[8]

Deoxyhemoglobin, ferritin, and hemosiderin are blood breakdown products that exhibit paramagnetic properties. During MR scanning, they interact with the local magnetic field, causing local field inhomogeneities and loss of MR signal. On T1 and T2 MR images, extracellular hemosiderin shows up as dark regions; this is known as the magnetic susceptibility effect.[2]

On GRE sequences, extracellular hemosiderin shows as a dark, black signal; however, there is a corresponding decrease of signal from the nearby structures, leading to what is known as the "blooming effect.". A subpar or impaired visualization of synovium on GRE sequences can occur as a result of the addition of black signal from normal structures to that of hemosiderin .[2]

Aim of the study
In this study, we investigate the role of using 3D T1FFE MRI sequence to characterize hemosiderin deposition as a sensitive method for HA in comparison with other conventional sequences.

Patients and Methods

Patients: This is a prospective cohort study conducted in Radio-diagnosis Department, Minya university hospital starting during august 2022 through April 2023 after ethical approval from the university ethical committee (approval number: 340:2022 approval date: 14 august 2022)

20 asymptomatic joints of 20 patients with their age ranged from 5-year-old to 18-year-old who admitted to hematology unit by attacks of bleeding or for follow up were examined by MRI. A written informed consent was taken from all the patients after full explanation of the technique and aim of the current study.
Inclusion criteria: This study included patients diagnosed with hemophilia A or B, their Age ranged from 5 to 16 years, every patient examined for one asymptomatic joint according to patient subjective assessment
Exclusion criteria: patients with co-morbidities cause osteoarthritic changes (ex: juvenile rheumatoid arthritis). - Patients with general cause contraindicate MRI ex: cochlear implant- Out of age range.

Methods:

MRI:

Technique of MRI examination:

- **Machine**: Philips, INGENIA (1.5T/digital stream) in the department of diagnostic radiology, minia university hospital
- **Position**: The patient lay supine on the table, Appropriate phased-array coils were used for the imaging of joint.
- **Contrast**: none
- **MRI protocol**: The following MRI pulse sequences obtained for all the patients:

Conventional MRI protocol include: T1WI, T2WI, STIR, PD WI

	T1WI	**T2WI**	**STIR**	**PDWI**	**PDSPIR**
plane	axial	axial	coronal	sagital	sagital
TR	475	3007	4253	2662	2500
TE	10	60	60	30	30
Flib angle	90	90	90	90	90

Additional 3DT1FFE sequence was used with the following parameters:
FOV: vary from 120 to 150 mm according to age of patient
Slice thickness 2.0/-1.0, **Gap**: -1 mm
TR 25 ms, **TE** 3.9 ms,
scanning time 2;32, SNR;1

Image interpretation:

Observation of hemosiderin in MRI was done by two expert radiologists (10 years' experience) blindly.

Considering inter reader observer ship agreement is the base standard for comparison.

Statical analysis:

Data was analyzed using statical package of social science (SPSS) version 22. Quantitate data were presented by mean and standard deviation also by minimum, maximum and range while qualitative data were presented by number and percentage

Person correlation test was used to show degree of association between scores. the probability of less than (0.05) was used as a cut off point for all significant test. Independent sample t teat was used to compare means of hemosiderin by conventional sequence and hemosiderin deposition by 3d T1 FFE sequence

Results

Table (1): Baseline characteristics of studied patients

Variable	**Value** **20 joints (100%)**
Age (years) (mean ± SD) Range	11.28± 3.9 (5-16)
Family history N (%) Positive Negative **Total**	 11 (55%) 9 (45%) **20 (100%)**
Type of Joint examined Knee Elbow Ankle **Total**	 15 (75%) 4 (20%) 1 (5%) **20 (100%)**

Age of children ranged from (5-16) years: mean was (11.28± 3.9) years. About 11 cases (55%) of cases had positive family history for hemophilia. Regarding type of joint examined, (75%) of joints was knee joint, (20%) were elbow joint and (5%) was ankle joint**.**

Table (II) Correlation between hemosiderin deposition by conventional sequence and hemosiderin deposition by 3d T1 FFE sequence among asymptomatic joints

	Hemosiderin deposition by conventional sequence	
	r	**P**
hemosiderin deposition by 3d T1 FFE sequence	0.51	0.05

Person correlation test was used

There was no significant correlation between hemosiderin deposition by conventional sequence and hemosiderin deposition by 3d T1 FFE sequence among asymptomatic joints so MRI by 3D T1FEE sequence can detect early and subtle hemosiderin deposition rather than conventional method**.**

Table (III) Comparison between hemosiderin deposition by conventional sequence and hemosiderin deposition by 3d T1 FFE sequence:

	hemosiderin by conventional sequence	**hemosiderin deposition by 3d T1 FFE sequence**	**P value**
Mean ± SD	1.26±0.89	1.97±1.2	0.008*

Hemosiderin deposition by 3d T1 FFE sequence was significantly higher than hemosiderin by conventional sequence**.**

In 9 joints both of them can detect hemosiderin **only** by 3DT1 FFE. In 7 joints: one of them consider amount of hemosiderin as minimal by conventional sequences, moderate by 3dT1FFE.The other consider amount of hemosiderin by conventional sequences ranging from minimal to mid, moderate to marked by 3d T1 FFE. In 4 joints: one of them can't detect hemosiderin by 3DT1 FFE, the other cant detects.

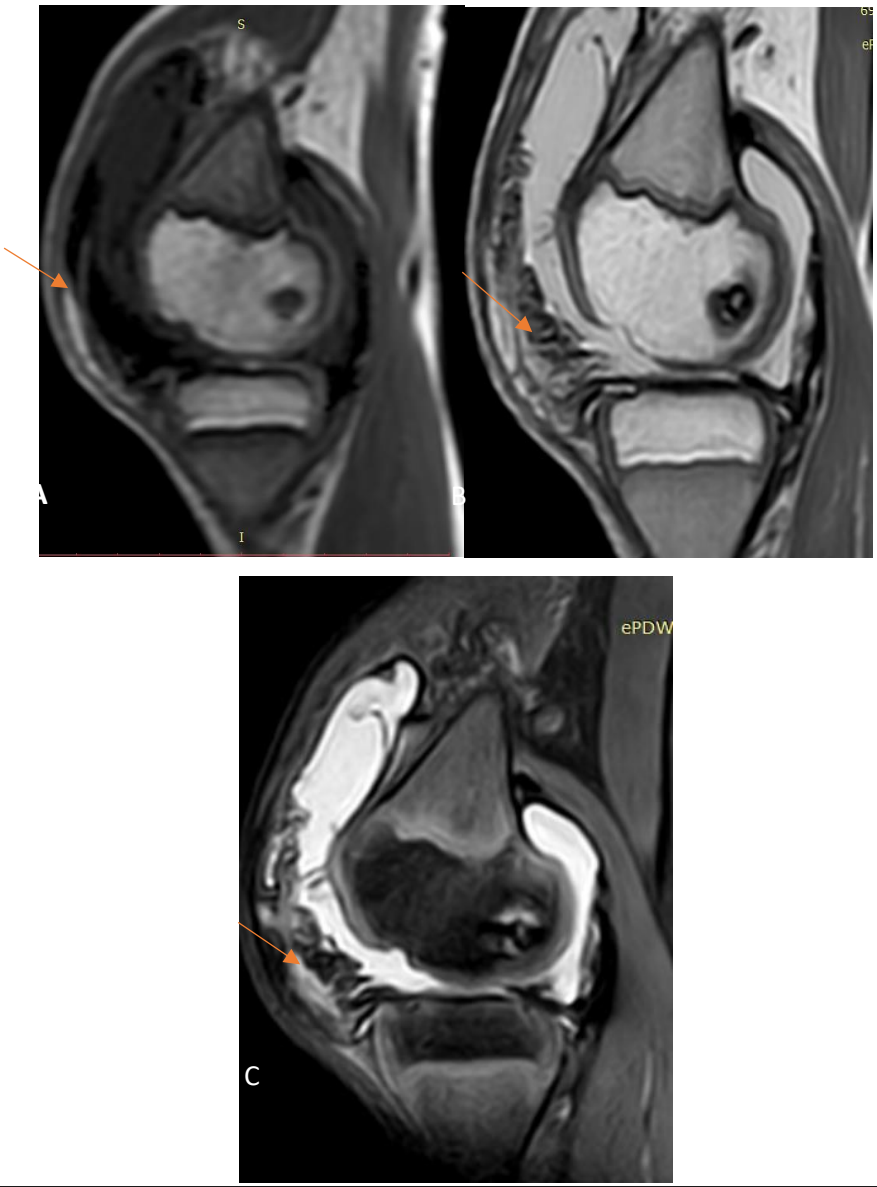
There is inter reader agreement to see hemosiderin by gradient sequence in 16 joints

Figure ligand

Figure ligand: 3 cases of hemophilic arthropathy show hemosiderin deposition better to be evaluated by T13DFFE sequence

Cases I:

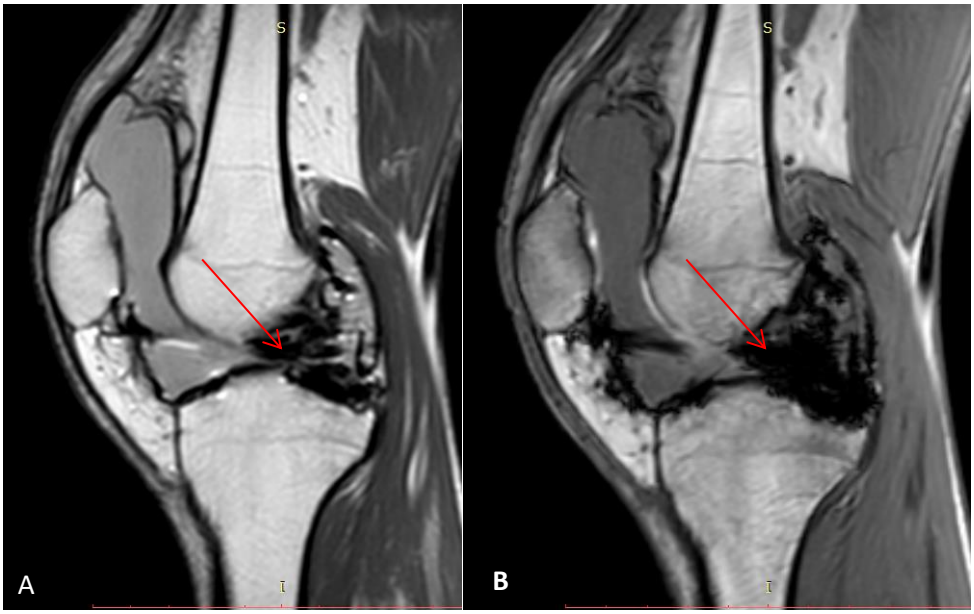
11 years old male known hemophilia A coming for routine screening. examination of left knee revealed:



Arrow show large amount of hemosiderin deposition in T13DFFE MRI sequence(A) which better demonstrated and well visualized in this sequence in comparsion with other conventional sequences as PD (B)and STIR MRI sequences (C)

Case II:

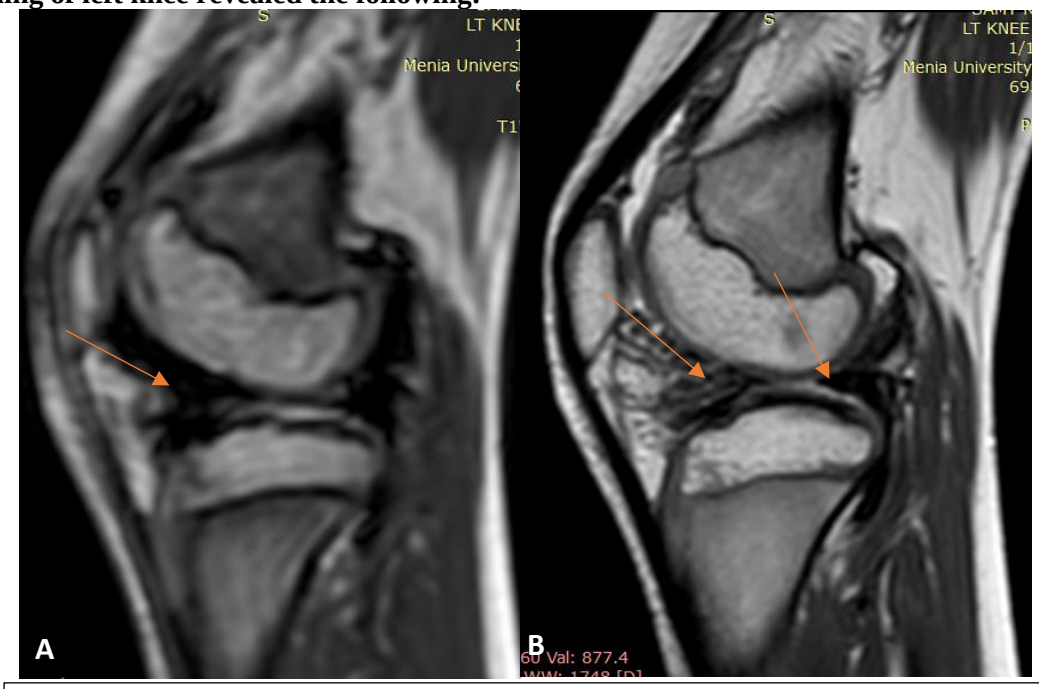
13 years old male patient known hemophilia A presented for follow up at hematology clinic. screening revealed the following:



A: sagittal T13D FFE MRI sequence (cartilage of bright signal) show moderate amount of hemosiderin deposition (red arrow) B: sagittal PD MRI sequence show minimal amount of hemosiderin deposition (red arow)

Case III:

10 years old male patient known hemophilia A presented for follow up at hematology clinic. screening of left knee revealed the following:



sagittal PD MRI sequence (A) show small amount of hemosiderin (orange arrow) in comparison with the same plane at T13DFFE sequence (B) (orange arrows)

Discussion

HA is a serious worry since it can lead to discomfort, disability, and a general decline in quality of life. Progression to HA can be significantly slowed down by early preventative treatment with clotting factor replacement to prevent the emergence of "target joints" (joints that undergo continuous bleeding over the course of six months) It has also been noted that large number percent of patients who have received prophylaxis since childhood nevertheless experience arthropathy. Asymptomatic bleeding and toxic iron buildup may accelerate joint degradation because, regrettably, the mechanism underlying HA is not well understood. Consequently, there is an urgent need for a sensitive, non-invasive biomarker for detection of early arthropathic affection as hemosiderin deposition.[3]

In our study we use T1 3D FFE sequence as an example for 3D gradient echo sequence as it is the available sequence on our MRI machine and it need no post processing reconstruction.
In our study knee joints were the commonest examined joints as it most commonly predicted to be affected considered a dependent joint during physical activities

Study group was between 5-16 years. Not more than 16 as We aim to detect early arthropathy in children. Not less than 5 years as the child will be so young to be cooperative and need of anesthesia during MRI examination
Out of 20 joints. 9 joint show minimal degree of hemosiderin deposition by 3DT1FFE sequence that not visualized by conventional sequences. 7joint had about moderate degree of hemosiderin deposition that can be visualized as a minimal amount by conventional sequences .4 joints shows no definite hemosiderin could be detected

Our study revealed that degree of hemosiderin deposition by 3d T1 FFE has no significant correlation with degree of hemosiderin deposition by conventional sequences so 3D T1 FFE can visualize early small amount of hemosiderin**.** Also, there is inter reader agreement that hemosiderin deposition by 3d T1 FFE sequence was significantly higher than hemosiderin by conventional sequence**.**

And This match other studies (3.12.8):
In the study of (Soliman, M., et al., 2017)[2] they mentioned GRE sequences has a high capacity to detect small amounts of intra-articular haemosiderin in the joint of patients with hemophilia.

In the study of (Prasetyo, M., et al., 2021) [9] they mentioned that The gradient-recalled echo (GRE) sequence MR is proved to be the best method to detect hemosiderin deposition.

In the study of (Pasta, G., et al., 2020) [10] they Mentioned that MRI imaging is a sensitive technique to visualize intra articular hemosiderin deposition especially when using T2* GRE sequences and using gradient echo (GRE) sequences can improve the visualization of hemosiderin
Other studies [3, 11, 12), (15] found there are other techniques for detection and quantification of iron deposition in joints of patients with hemophilia:

In the study of (Zhang, L., et al., 2022)[12] they revealed that susceptibility weighted images (SWI) has great potential to be used for detecting micro-hemosiderin deposition in hemophiliac arthropathies and developing preventative treatment plans. hemosiderin deposits were detected by the SWI sequence than the conventional sequence, indicating that the SWI sequence was more sensitive than the conventional sequence and could detect more joints with hemosiderin deposit in joints. SWI is based on T2-weighted gradient echo sequences and provides image contrast enhancement based on differences in magnetic susceptibility between different tissues while obtaining magnetic distance images and phase images. The SWI is sensitive to paramagnetic substances, especially iron in the form of hemosiderin and oxyhemoglobin

In the study of (Jang, H., et al., 2020)[3] they mentioned that Ultrashort echo time quantitative susceptibility mapping **(UTE-QSM)** method can identify hemosiderin accumulation in the joint and offers a potentially sensitive biomarker for hemophilic arthropathy diagnosis and prognosis. Maps of joint tissue vulnerability are produced in both

healthy participants and sick patients. While no localized regions with significant susceptibility were found in asymptomatic healthy volunteers, hemophilic patients' afflicted joints contained several locations with high susceptibility exceeding 1 ppm. Iron was found by histology in areas where UTE-QSM had revealed high susceptibility.

In the study of (von Drygalski, A., et al.,)[11] they strongly suggest that MRI T2* imaging can detect and quantity cartilage iron in the knee of patients with severe hemophilia also he mentioned iron not accumulate only in synovium but also in cartilage

Our study showed that blooming artifact of gradient sequence can obscure underlying synovium **and that match the study of** (Doria, A.S., et al., 2015) [13] they mentioned that blooming artifact of GRE is a limitation for visualization of other structures

Conclusion:

T1 3D FFE MRI sequence can detect even small amount of intra-articular hemosiderin and can be considered as a potential sensitive method for the early diagnosis of hemophilic arthropathy.

Limitations of study is Small number of populations**.** Long time of 3D T1 FFE sequence that allow examination of only one joint per each patient. No clinical correlations with patient MRI finding.

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