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Hemophilic arthropathy. A scoring system for magnetic resonance imaging

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Abstract The aim of this study was to define a system for scoring hemophilic arthropathy (HA) based on MR findings, providing for objective evaluation of the degree of joint involvement and evolution after on-demand administration of FVIII substitutional therapy or prophylactic treatment. A total of 133 MR examinations (89 basal and 44 during follow-up) were performed in 25 patients. Patients were divided in two groups depending on the therapy received and the length of time that the disease had been evolving at the start of the study. Group I was composed of 10 patients with secondary prophylaxis and group II was composed by 15 treated on demand. T1-weighted and T2*-weighted images performed on a 0.5-T unit were prospectively evaluated. The joint involvement was established on a scale of 0 (no abnormalities), I (minimal amount of hemosiderin), II (large amount of hemosiderin and isolated cartilaginous erosion), III (cartilage destruction, bone erosions, and subchondral cysts) to IV (large internal joint derangement, secondary osteoarthritis and/or ankylosis). At basal MR examination, patients of group I showed no abnormalities (n = 28, 75.6 %), grade I (n = 3), and grade II (n = 6) of HA. Patients of group II corresponded to MR grades III (n = 21) and IV (n = 11) of HA. The MR follow-up showed improvement in three joints of group I and worsening in 5 joints in group I and 2 joints in group II. Early signs of HA were detected in 10 joints with MR imaging but were underestimated on plain radiographs. Advanced degrees of HA were classified as severe under both imaging techniques. Magnetic resonance is the preferred imaging technique to assess HA. The earliest signs of joint damage, detected by MR, are overlooked by plain radiography. The MR scoring system can be used for evaluating HA. Follow-up MR should be performed to evaluate regression or worsening of the abnormalities, primarily in the case of patients with prophylaxis who usually suffer normal or early joint involvement not detected by other means.

Keywords MR imaging · Hemophilic arthropathy · Hemarthrosis · Synovial abnormalities

Introduction

Hemophilic arthropathy (HA) due to recurrent hemarthrosis is the most common musculoskeletal manifestation of hemophilia and one of the most disabling complications of this disease. Children with severe hemophilia suffer from recurrent and acute joint hemorrhage. Factor VIII or IX concentrate replacement infusions (treatment on demand) do not prevent HA [1]. Prophylactic treatment in patients with severe hemophilia

has been shown by several authors to be beneficial on the basis of radiological or orthopedic evidence [2]. The aim of this therapy is to keep the trough level of the deficient factor > 1 % to convert severe hemophilia into a milder form of the disorder. Nevertheless, while prophylaxis is generally considered to be the optimum form of treatment, the recommended starting age and dosage continue to be a matter of debate. Recent papers have stressed the importance of starting replacement therapy during the early years of life to minimize joint bleeding [2, 3, 4, 5].

A sensitive, non-invasive scoring system is therefore needed to optimize treatment, evaluate the cost-effectiveness of therapy, and to select the appropriate treatment option. Clinical assessment plays a minor role in evaluating the early phases of HA, because early clinical signs are often nonspecific and of little use in quantifying the degree of involvement. Conventional radiography has been used to evaluate HA and a scoring system based on plain radiographs has been used [6, 7]. This technique, however, primarily identifies bone lesions that appear in advanced HA, but does not detect early changes, such as synovial hypertrophy, or focal destruction of the joint cartilage. Sonography has been reported to be useful in the evaluation of synovial hypertrophy in the presence of joint effusion [8, 9, 10], but it does not provide a full evaluation of cartilage or bone involvement [9]. Intraosseous hemorrhage and subchondral cysts can be detected with CT, but the technique is of limited value in assessing cartilaginous or synovial lesions [10].

The improved soft tissue contrast afforded by MR imaging allows detailed evaluation of the hemophilic joint, rendering synovial and cartilaginous abnormalities visible. The ability to detect early stages of synovial or cartilage alterations with MR when conventional radiographs are still normal might help ascertain which patients need early treatment and monitor their response to therapy. Few publications discuss the potential of MR for HA evaluation [11, 12, 13, 14, 15, 16], and to our knowledge, no MR protocols or damage evaluation scoring systems have been devised to predict the progression of the disease or to monitor the results of prophylactic treatment.

The objective of our study was to assess the role of MR imaging in the delineation of synovial, cartilaginous, and osseous abnormalities, and to develop a semiquantitative system for assessing HA as support for therapeutic regimes in the early phases of arthropathy and for monitoring the response to therapy.

Patients and methods

We performed 133 MR examinations to evaluate HA abnormalities in 25 patients diagnosed for severe ($n = 20$) and moderate ($n = 5$) hemophilia in the Hemostasis and Coagulation Ward of our tertiary hospital.

Depending on patient age, bleeding history, and a physical examination, the patients had been submitted to secondary prophylaxis (group I) or on-demand treatment (group II).

Group I included 10 children with secondary prophylaxis that ranged in age from 3 to 10 years (mean age 6.7 ± 2.6 years). The basal examination consisted of MR studies on 37 appendicular skeletal joints, including 20 ankles, 11 knees, 4 elbows, and 2 hips. The MR examination was performed on joints in which there was a previous episode of acute hemarthrosis. Twenty-nine MR studies were performed on 17 joints over a 7-year follow-up period. The joints examined during follow-up were those joints in which some abnormality was found in the basal examination and joints presenting hemarthrosis during the follow-up period. During the first years of the study we only performed MR follow-up examination when some episode of hemarthrosis occurred; however, as the study evolved we started to perform MR follow-up each year in every joint which showed changes of HA in order to evaluate the evolution in a more standardized way.

Group II included 15 patients (10 severe and 5 moderate) who were being treated on demand. The patients ranged in ages from 12 to 42 years (mean age 27 ± 9.2 years). Basal MR imaging was performed on 52 joints (19 knees, 15 ankles, 10 elbows, 4 shoulders, and 4 hips). The joint imaged by MR were those with a clinical or radiographic history of hemarthrosis. Follow-up MR (15 MR examinations on 10 joints) were performed on joints with clinical evidence of worsening during the study period (7-year follow-up) or prior to considering surgical therapy.

Magnetic resonance examinations were performed using a 0.5-T system (Gyroscan T5). T1-weighted spin-echo (SE-T1; TR/TE = 535 ms/20 ms) and T2*-weighted gradient-echo (T2*-GE; TR/TE/flip angle = 735 ms/25 ms/20 °) sequences were obtained along two orthogonal planes in all cases and supplemented on occasion by a third plane. The MR examinations were performed with a surface coil of a shape and size adapted to the joint examined. The field of view, slice thickness, and interslice gap were also adapted to the size of the joint under examination, although the field of view was always under 180 mm and slice thickness less than 5 mm (with an interslice gap of 10 %). No contrast material was injected in any of the examinations.

Plain radiographic examinations were performed in anteroposterior and lateral projections and quantified according to the Pettersson scoring system (Table 1) as recommended by the World Federation of Hemophilia's Orthopedic Advisory Committee [6, 7]. To avoid unnecessary exposure to radiation, conventional radiography was not performed or repeated for this study: All the radiographs used for correlation to MR images were taken from patients' clinical histories and existing imaging films.

The MR images were prospectively evaluated by consensus between two radiologists. An evaluation form was used to assess the following findings: synovial hypertrophy with hemosiderin deposition; local or diffuse destruction of joint cartilage; narrowing of joint space; isolated or diffuse bone erosions; subchondral cysts; abnormal alignment; enlargement of the epiphysis; degenerative osteoarthritis; and hemophilic pseudotumor. Synovial hypertrophy with hemosiderin deposition was defined as the presence of abnormal intra-articular soft tissue which was hypointense on T1-weighted sequences and markedly hypointense on T2*-GE sequences. Additional MR findings, such as joint effusion, meniscal tears, and ligamentous lesions, were also reviewed.

Taken into account the physiopathology of joint abnormalities after articular bleeding episodes, we established a new classification of HA based exclusively on MR findings. The severity of the involvement was defined on a scale of 0–IV (Table 2): grade 0,

Table 1 Pettersson scoring system of radiological evaluation recommended by the orthopedic advisory of the World Federation of Hemophilia's Orthopedic Advisory Committee. Possible joint scoring: 0–13 points

Radiological abnormalities	Findings	Score (points)
Osteoporosis	Absent	0
	Present	1
Enlarged epiphysis	Absent	0
	Present	1
Irregular subchondral surface	Absent	0
	Partly involved	1
	Totally involved	2
Narrowing of joint space	Absent	0
	Joint space > 1 mm	1
	Joint space ≤1 mm	2
Subchondral cyst formation	Absent	0
	1 cyst	1
	> 1 cyst	2
Erosions of joint margins	Absent	0
	Present	1
Gross incongruence of articulating bone edges	Absent	0
	Slight	1
	Pronounced	2
Joint deformity (angulation and/or displacement between articulating bones)	Absent	0
	Slight	1
	Pronounced	2

Table 2 The MR findings and grade of hemophilic arthropathy

MR findings	MR grade
Normal	0
Slight synovial hypertrophy with hemosiderin in joint recess	I
Synovial hypertrophy with hemosiderin distributed all over the joint and isolated cartilaginous erosions	II
Diffuse cartilaginous destruction, loss of joint space, bone erosions and/or subchondral cysts	III
Severe joint derangement, secondary osteoarthritis and/or ankylosis	IV

when no abnormalities were detected on MR examination; grade I, when slight synovial hypertrophy and minimal amounts of hemosiderin were found in the joint recess (Fig. 1); grade II, when greater synovial hypertrophy were distributed all over the joint and only isolated local cartilage erosions could be seen (Fig. 2); grade III, when diffuse cartilage destruction and narrowing of the joint space, small areas of bone erosions and/or subchondral cysts were observed (Figs. 3, 4); and grade IV, when there was obvious internal joint derangement with cartilage destruction, large bone erosions, joint deformity (angulation and/or displacement between articulating bones), secondary osteoarthritis, or ankylosis (Figs. 5, 6).

The results of MR classification for each target joint were correlated to the Pettersson scoring system.

Table 3 The MR grade of involvement in basal and follow-up examinations

	MR studies (n = 133)			
	Group I (n = 66)		Group II (n = 67)	
MR grade	Basal (n = 37)	Follow-up (n = 29)	Basal (n = 52)	Follow-up (n = 15)
0	28	18	16	–
I	3	7	1	–
II	6	3	3	–
III	–	–	21	12
IV	–	1	11	3

Results

MR degree

Table 3 summarizes the MR classification of group-I and group-II joints based on examinations performed at the beginning of this study and during follow-up.

Group I

Synovial hypertrophy with hemosiderin deposits was the most frequent finding in group-I patients (24 joints, 36.36 %). When the basal MR examination was conducted, most group-I joints (28 of 37) showed no abnormalities and were classified as MR grade 0. The remaining 9 joints were classified as grade I (n = 3) or II (n = 6; Table 3). A total of 29 MR follow-up were performed on 7 patients (n = 17 joints) after prophylaxis was undertaken. In the MR follow-up, most group-I MR studies (18 of 29) were classified as MR grade 0. The remaining 11 MR studies were classified as grades I (n = 7), II (n = 3), or IV (n = 1). Three joints with grade I of HA at basal examination in which no more bleeding occurred were considered normal on follow-up MR examination

Group II

Bone erosion was the most frequent finding in group-II patients (40 joints, 59.7 %). Hemosiderin deposition, joint cartilage destruction, joint space narrowing, bone erosions, abnormal alignment, and subchondral cysts were likewise more common and severe in the joints of group II than group I. Meniscal tears, ligamentous lesions, and hemophilic pseudotumors were detected in group-II joints only.

Basal MR imaging of 16 joints performed in 5 patients with moderate hemophilia showed no abnormalities (MR grade 0). The 36 joints studied in the basal examination of 10 patients with severe hemophilia were

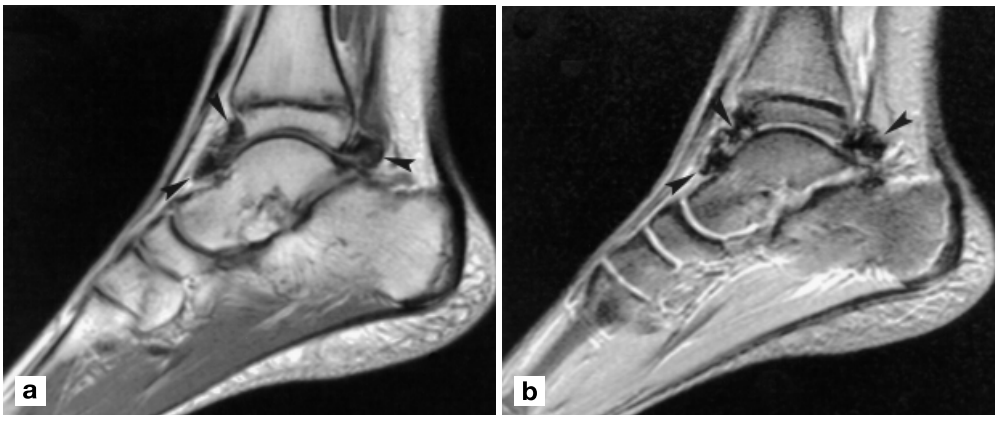


Fig. 1a, b Hemophilic arthropathy grade I in an 8-year-old patient. **a** Sagittal T1-weighted spin echo (SE) and **b** gradient echo (GE) T2*-weighted images of the left ankle show low signal intensity material in the anterior and posterior recess of the joint *(arrowheads)* due to hemosiderin deposition

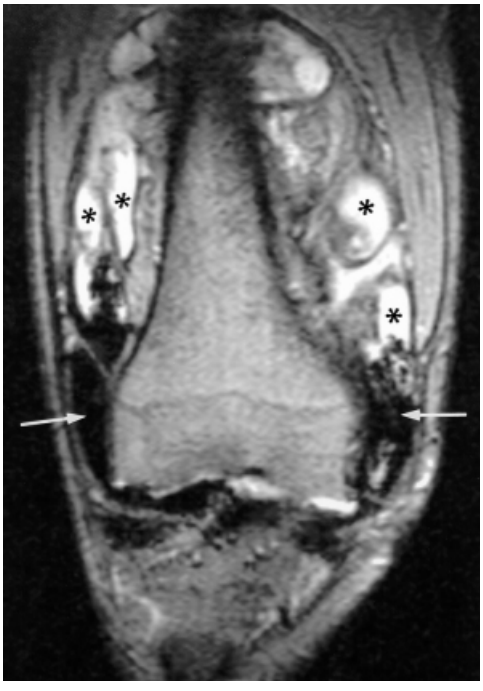


Fig. 2 Hemophilic arthropathy grade II in a 38-year-old patient. Coronal GE T2*-weighted image of the left knee demonstrates large amount of low signal intensity material *(arrows)* related to hypertrophic synovia with hemosiderin deposition associated with high signal intensity fluid *(asterisks)*

classified on the MR scale as grades I ($n = 1$), II ($n = 3$), III ($n = 21$), or IV ($n = 11$; Table 3).

Fifteen follow-up MR studies were performed on 10 joints in 5 patients with severe hemophilia. During follow-up all MR images were classified as grades III ($n = 12$) or IV ($n = 3$; Table 3).

Radiological vs MR score

The relationship between the degree of involvement based on plain radiography and MR findings in 31 group-I and 28 group-II joints is shown in Tables 4 and 5.

Plain radiographs underestimated the degree of HA in 7 group-I joints. In group-II patients the radiological score was 0 in 3 joints which were found to have abnormalities on MR imaging [grades I ($n = 1$) and II ($n = 2$)]. There were no significant differences between plain radiographic and MR image evaluation of hemophilic arthropathy.

Discussion

Grade 0 on the MR scale means a normal joint. Patients with prophylaxis were found to have mostly grade-0 joints, which remained normal during follow-up. Even in cases where bleeding had been clinically detected, the MR performed after resolution of acute hemarthrosis indicated that there were no morphological abnormalities.

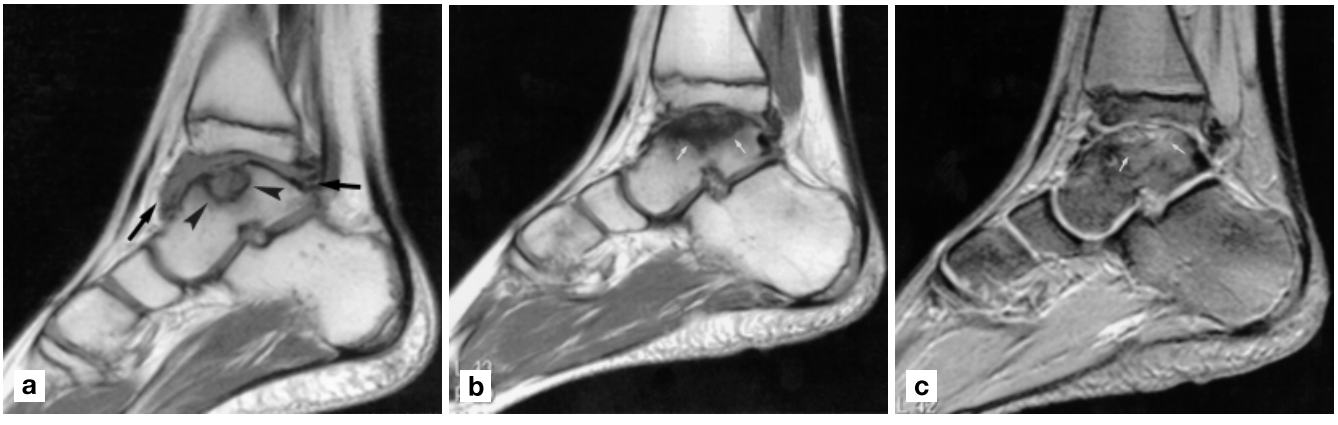
Grade-I involvement is characterized by the presence of slight amount of synovial hypertrophy in the synovial recesses without cartilaginous abnormalities. Hypertrophy of the synovia is the first morphological abnormality observed after two or three episodes of hemarthrosis in the same joint over a short period of time. We thought that the detection a grade I of HA is fundamental, because different degrees of synovial hypertrophy may evolve in a different way if no more joint bleeding occurs. An objective evaluation of the joint involvement in this early phase is essential for adequate follow-up of HA, mostly in patients submitted to prophylactic therapy. Previous studies suggest that when HA starts the arthropathy progresses even in the absence of further acute bleeding [17]. However, performing MR examinations we detected slight amounts

Fig. 3 Hemophilic arthropathy grade III in a 30-year-old patient. Sagittal SE T1-weighted image of the right knee shows marked destruction of joint cartilage and menisci, narrowed joint space and areas of bone erosions *(arrowheads)*

of hemosiderin on basal examinations which improve during follow-up in 3 joints of our series of patients submitted to prophylactic therapy. Although a larger series should be evaluated and a longer follow-up period is needed, these findings suggest that a return to normality or improvement is possible when slight synovial hypertrophy, such as in MR grade I, occurs. A possible explanation for the discrepancy between our findings and the previous studies about possible improvement in early phases of HA may be due to the fact that previous reports used radiological scores [18, 19, 20], which are less sensitive to earlier phases of arthropathy. In fact, in our series we had been unable to establish the presence of HA and the follow-up of abnormalities detected on MR in 6 joints if only conventional radiography had been evaluated. Our system to quantify synovial hypertrophy is semi-quantitative. This system, although subjective and imprecise, enabled us to compare synovial hypertrophy and hemosiderin deposition during follow-up, even when only small amounts of hemosiderin could be identified. The quantification of synovial hypertrophy can be performed in future studies with post-processing software that allows measurement of the volume of any tissue with manual delineation of the synovium or with automatic systems for recognition of different intensities. Whereas clinical and radiological scores did not correlate with either duration of disease or joint bleeding [21], quantification of synovial hypertrophy by an MR grading system could be helpful in evaluating the relationship between the number of hemarthrosis episodes and the degrees of joint involvement. Magnetic resonance imaging may not only have a potential role in follow-up of HA, but seems also useful in monitoring the therapy more objectively.

A joint is classified as grade-II HA when both synovial hypertrophy and local and isolated cartilaginous erosions can be identified. When joint bleeding continues to occur, synovial hypertrophy is found to increase progressively. Hypertrophied synovia are the cause of cartilaginous erosions and, as has been also demonstrated in other erosive arthropathies, in which synovial hypertrophy produces cartilaginous and bone erosions, the earlier the treatment is initiated the longer the joints resist destruction [22]. In HA, however, the optimum timing for synovectomy has yet to be established. Noninvasive assessment of the degree of synovial hypertrophy could be useful in the decision of perform a synovectomy; thus, the MR scoring system constitutes a

Fig. 4a–c Hemophilic arthropathy grade III in a 10-year-old patient. **a** Sagittal SE T1-weighted image of the left ankle demonstrates a subchondral hypointense cyst with a low signal intensity rim *(arrowhead)* correlated with reactive bone sclerosis on plain radiographs and associated hemosiderin deposits *(arrows)*. There is congruity without disruption of the subchondral plate. Two-year follow-up **b** sagittal SE T1-weighted and **c** GE T2*-weighted images show flattening and collapse of the talar articular surface *(small arrows)*



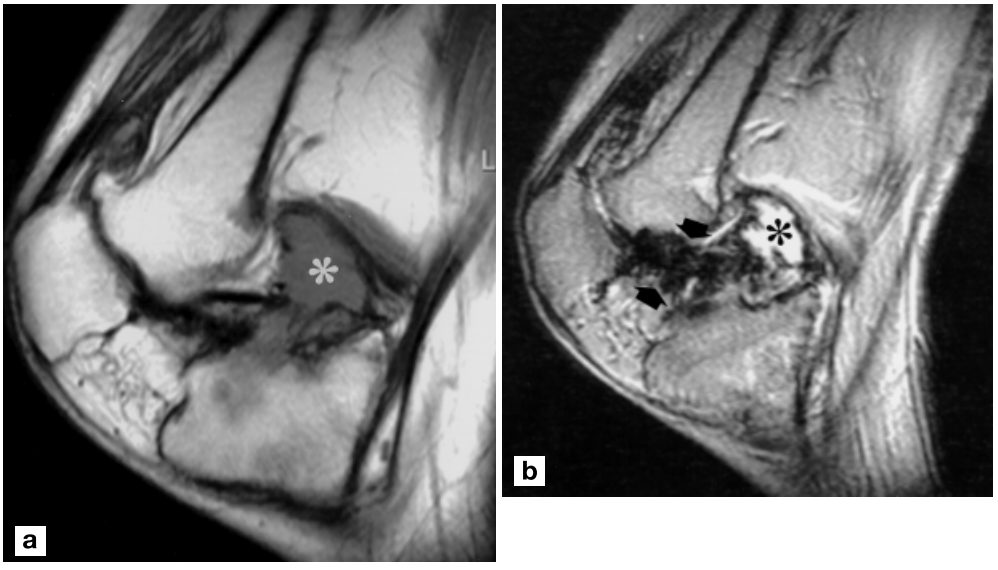


Fig. 5a, b Hemophilic arthropathy grade IV in a 40-year-old patient. **a** Sagittal SE T1-weighted and **b** GE T2*-weighted images show narrowed joint space with diffuse cartilage erosions, joint fluid *(asterisks)*, hemosiderin deposits *(arrows)*, joint deformity, and secondary osteoarthritis

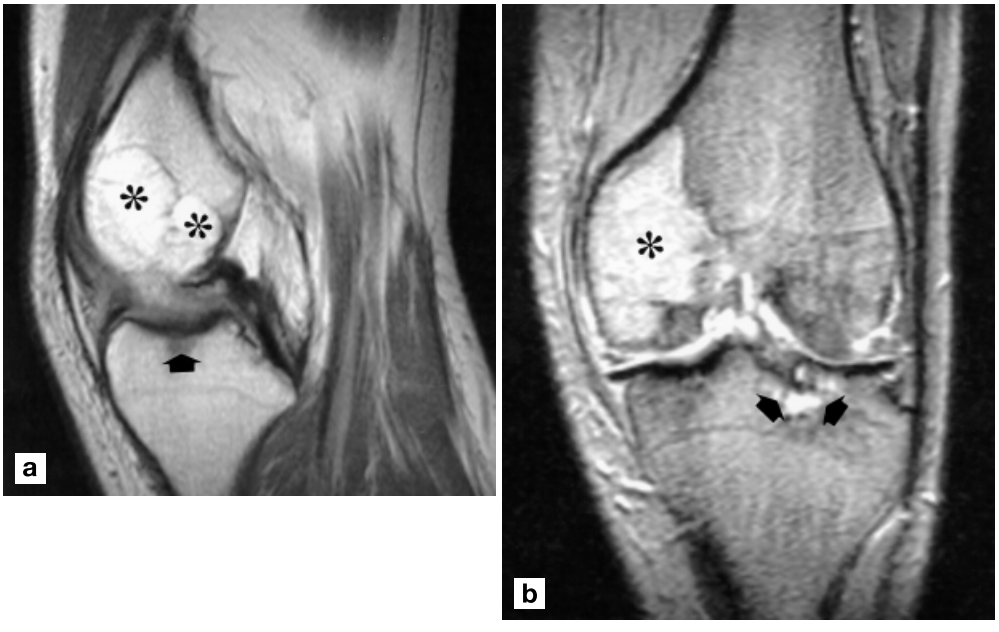


Fig. 6a, b Hemophilic arthropathy grade IV in a 36-year-old. **a** Sagittal SE T1-weighted and **b** coronal GE T2*-weighted images show a large multiloculated lesion in the medial condyle of the distal left femur with a signal intensity slightly higher than that of subcutaneous fat *(asterisks)* related to subacute blood. Narrowed joint space and bone erosions *(arrows)* are also seen

way to quantify synovial hypertrophy and early cartilaginous erosion.

Joints with MR grade-III HA are characterized by diffuse cartilaginous erosions and loss of joint space, isolated bone erosions, and subchondral cysts. This phase of HA can usually also be detected with plain radiography as loss of joint space, loss of subchondral bone white line, and subchondral cysts; however, whereas the evaluation of the extent of the disease is easier on MR imaging, plain radiographic findings may be subtle. Accurate diagnosis of this phase of involvement and clear differentiation from degree II is very important from a clinical point of view. In degree III of HA loss of joint congruency is irreversible and inevitably leads to osteoarthritis, so the prognosis is different and local therapy to prevent future damage is not the treatment of choice; hence, we feel that MR should be the standard technique used to evaluate the degree of involvement more precisely in this phase.

The MR grades II and III are differentiated on the basis of the assessment and degree of local isolated vs diffuse cartilaginous and bone erosions. There are some difficulties in establishing the differentiation between MR degrees II and III, because markedly hypointense

Table 4 Comparison between plain radiographic scores (Pettersson system) and MR grades of hemophilic arthropathy in 31 group-I joints

No. of joints	Pettersson score	MR grade
20	0	0
3	0	I
4	0	II
1	1	0
1	1	I
1	1	II
1	1	IV

Table 5 Comparison between plain radiographic scores (Pettersson system) and MR grades of hemophilic arthropathy in 28 group-II joints

No. of joints	Pettersson score	MR grade
4	0	0
1	0	I
2	0	II
5	2	III
5	6	III
2	6	IV
9	13	IV

synovia covering the cartilaginous surface render it very difficult to evaluate chondral integrity or incipient erosions. One of the limitations of this study is that there is lack of pathological correlation of our findings, making the exact differentiation between grades II and III difficult; however, future inclusion of MR sequences which are more sensitive in detecting early cartilaginous erosions [23] may allow this differentiation more precisely.

Internal joint derangement and secondary osteoarthritis is the final stage of HA, classified here as grade IV. In our series most of the joints classified on the MR imaging scale as grade IV did not generally appear to have large amounts of hemosiderin. Although a more continuous follow-up of patients would be necessary to establish the physiological developments leading to this observation, we believe that hypertrophied synovia can involute due to fibrosis, but once erosions appear the degenerative process evolves even if joint bleeding stops.

Other previously reported [10] associated abnormalities, such as joint effusion and periarticular soft tissues, were also visible in our series with different degrees of involvement in patients with on-demand and prophylactic therapy.

Intravenously administered paramagnetic contrast material has been used to better assess synovial inflammation and quantify the volume of synovial tissue; its use increases the sensitivity of MR imaging in establishing the degree of activity in some cases of inflammatory arthropathy [24]. Recently, Nägele et al. [25] studied 17 patients with HA of the knee, showing that enhanced MR provides better identification of synovial hypertrophy. We did not use contrast material in order to not increase the invasiveness of the tool, even though we believe that i.v. injection of gadolinium chelates might increase the MR sensitivity to differentiate grades I and II of HA and to quantify the degree of synovial hypertrophy, but that it probably would not afford any further information for grades 0, III, or IV.

Conclusion

In conclusion, MR imaging is useful in establishing the degree of involvement in HA. Based on the MR findings, we have defined a scoring system to quantify HA on a scale distinguishing from grades 0 (no abnormalities), I (minimal amount of hemosiderin), II (large amount of hemosiderin and isolated cartilaginous erosion), III (cartilage destruction, bone erosions, and subchondral cysts) to IV (large internal joint derangement, secondary osteoarthritis and/or ankylosis). This system is semiquantitative and therefore subjective with no clear delineation between different degrees of involvement; however, it is based on important hallmarks of the evolution of HA with implications for therapy. The evaluation of the degree of HA based on clinical and radiographic methods are also subjective, but none of them could detect early involvement.

This MR classification enables us to identify HA and to assess the effect of different systemic and local therapies. Magnetic resonance is the technique that allows a sensitive, non-invasive identification of HA in the earliest phases, and we think that it should be used to monitor the evolution of patients with prophylactic treatment.

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