Multifocal Joint Osteonecrosis in Sickle Cell Disease

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Abstract: The purpose of this study was to evaluate the frequency of multifocal osteonecrosis in patients with sickle cell disease. Between 1980 and 1989, 200 patients with sickle cell disease were treated in our institution for osteonecrosis. The patient population consisted of 102 males and 88 females with a mean age of twenty-six years at the time of presentation (range, eighteen to thirty-five years) and was followed until the year 2005. This cohort of patients was follow-up during average 15 years (until the year 2005). Multifocal osteonecrosis was defined as a disease of 3 or more anatomic sites. At the time of presentation, 49 patients were identified as having multifocal osteonecrosis. At the most recent follow-up, 87 patients had multifocal osteonecrosis. So at the last follow up among these eighty-seven patients, the occurrence of osteonecrosis was 158 lesions of the proximal femur associated with 151 proximal humerus osteonecroses, thirty-three lateral femoral condyle osteonecroses, twenty-eight distal femoral metaphysis osteonecroses, twenty-seven medial femoral condyle osteonecroses, twenty-three tibial plateau osteonecroses, twenty-one upper tibial metaphysis osteonecroses and forteen ankle osteonecroses. The total number of osteonecrosis was 455 in these 87 patients. The epiphyseal lesions were more frequent than the metadiaphyseal lesions excepted in the proximal tibia (Table **3**). In conclusion, in patients with sickle cell disease, the risk of multifocal osteonecrosis is very high. In patients with hip osteonecrosis, the other joints should be evaluated with radiograph and MRI if the joint is symptomatic. In patients with osteonecrosis of the knee, shoulder or ankle, the patients' hip should be evaluated by radiographs or MRI, regardless of whether the hip is symptomatic.

INTRODUCTION

Sickle cell disease is an important cause of osteonecrosis affecting persons in Africa, in the United States of America, in the Indian Subcontinent, in the Persian Gulf and in the Mediterranean countries. Osteonecrosis affects the hip most commonly [1, 2] but may also affects other sites [3] including the knee, shoulder, ankle, spine and other joints. When the disease extents to several joints, the effects on the patients are magnified. There have been only a few case reports concerning multifocal osteonecrosis [4, 5] and these studies have included a very small number of patients with sickle cell disease. However in the experience of the authors, sickle cell disease is a frequent comorbidity associated with multifocal osteonecrosis. The purpose of this study was to review the incidence of multifocal osteonecrosis in this disease, the distribution of the joints concerned by multifocal osteonecrosis and the clinical consequences in the long term (average fifteen years of follow up) of multifocal osteonecrosis in these patients with sickle cell disease.

To be considered as a multifocal osteonecrosis an involvement of three separates sites was necessary. For example a patient with osteonecrosis of one hip, one knee, and one shoulder would meet the criteria; a patient with three osteonecroses but not three separate sites involved would not be considered as multifocal osteonecrosis (example two hips and one knee).

200 patients homozygous for hemoglobin S (SS genotype) but also with the double heterozygous hemoglobinopathies (hemoglobin SC genotype and hemoglobin SBeta thalassemia) were included in the study. A diagnosis based on a hemoglobin analysis was done at our hospital for each patient. One thousand and six hundred joints (400 hips, knees, shoulders and ankles) were studied in these 200 adult patients with sickle cell disease. These 200 patients were initially evaluated between 1980 and 1989 and were followed every year until year 2005 for a minimum of ten years and a mean of fifteen years (maximum twenty years).

MATERIAL AND METHODS

Actually, more than 1500 patients are treated at our institution for sickle cell disease. Among this population of patients homozygous for hemoglobin S (SS genotype) and also those with the double heterozygous hemoglobinopathies (hemoglobin SC genotype and hemoglobin Sβ thalassemia) 200 were included in the study and initially evaluated at the time of presentation between 1980 and 1989. The patient population consisted of 102 males and 88 females with a mean age of twenty-six years at the time of presentation (range, eighteen to thirty-five years) and was followed until

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the year 2005. These patients were treated for at least one osteonecrosis site.

MRI of hips, shoulders, knees, ankles were obtained at the entry of the study for all the patients. Patients were followed prospectively every year with a radiograph if a joint became symptomatic. In absence of evidence of osteonecrosis on radiographs of a symptomatic joint, patients had an MRI performed. When osteonecrosis was present on a joint, the patients had an MRI performed on the contralateral joint in absence of radiological evidence of osteonecrosis as the contralateral side. The average duration of follow-up after inclusion of the patient in the study was fifteen years (range ten to twenty).

According to the number of MRI performed in this study, MRI examinations were limited and performed as screening techniques in many joints of these patients. This limited examination consisted of T1 weighed images with the following parameters: 450-600/10-15 (repetition time msec echo time msec); 5 mm thickness, 2 mm intersection gap, 38 cm field of view, 256 x 256 matrix. In case of osteonecrosis, the full examination consisted of additional imaging sequences: fast spin echo T2 weighed images with fat suppression.

The diagnosis of osteonecrosis was done on MRI or radiographs. Radiological signs of osteonecrosis in epiphysis were sclerotic or cystic changes, crescent line, and collapse. In the metadiaphyseal area, demarcating sclerosis was considered as a radiologic sign of infarct. Because fatty marrow or mixed marrow can be found in the epiphysis of patients with sickle cell disease the diagnosis on MR imaging was only based on bandlike abnormal signals [bandlike hypointense zones on T1 weighted images and matching hyperintense zones on short tau inversion (STIR images)].

Sites of osteonecrosis were found in the proximal femoral epiphysis, in the proximal humeral epiphysis, in the distal femoral epiphysis, in the proximal tibial epiphysis, in the distal tibial epiphysis and in the talus. In the knee joint each femoral condyle and tibial plateau was considered as a different site of osteonecrosis. The means for example that one knee could have four epiphyseal osteonecroses sites but was considered as only one anatomical site.

Osteonecrosis was found in two areas: epiphyseal areas in contact or not with cartilage and meta diaphyseal areas not in contact with endosteum. This means that one knee could have two metadiaphyseal osteonecroses and four epiphyseal osteonecroses.

RESULTS

1. Prevalence of Multifocal Osteonecrosis

1.1. At Presentation

Of the 200 patients, forty-one (20 per cent) were found to have multifocal osteonecrosis at study entry. These forty-one patients identified as having multifocal osteonecrosis at presentation were associated at twenty other patients with osteonecrosis in only one or two separate sites. So multifocal osteonecrosis represented 67 per cent of patients with osteonecrosis at presentation (forty-one among sixty-one).

The sixty-one patients with at least one site osteonecrosis had disease of the hip at presentation: forty-two who had disease of the hip were homozygous for hemoglobin S, fourteen had hemoglobin S/hemoglobin C, and five had hemoglobin S/B thalassemia.

Because 130 of 200 patients in the over-all group were homozygous for hemoglobin S, the prevalence of disease of the hip in this group at entry of the study was forty-two of 130 (32 per cent), fourteen of fifty-five (26 per cent) in the patients who had hemoglobin S/ hemoglobin C and five of fifteen (33 per cent) in the patients with hemoglobin S/B thalassemia.

The prevalence of multifocal osteonecrosis in these patients was respectively for the different hemoglobin disease 22 per cent (twenty-eight of 130), 16 per cent (nine of fifty-five) and 26 per cent (four of fifteen) at entry of the study.

One hundred and forty-nine bony lesions were identified at presentation among the forty-one patients with multifocal osteonecrosis (average 3.6 osteonecrosis per patient). All the patients had hip involvement. Other sites involved included the shoulder in thirty-seven patients, the knee in eleven patients, and the ankle in three patients. Bilaterality (as confirmed by radiographs or MRI) was common including 70 per cent of the hips, 62 per cent of the shoulders, and 45 per cent of the knees (Table **1**).

1.2. At the Most Recent Follow-Up

Of the 200 patients followed for an average of fifteen years (minimum ten years, maximum twenty years), eighty-seven patients had multifocal osteonecrosis at the last follow up. All the twenty patients that had osteonecrosis at one or two sites at presentation had a multifocal osteonecrosis at the most recent follow-up. Twenty-six other patients developed multifocal osteonecrosis during the period study. The time between diagnosis on the first site and diagnosis of

Table 1. Osteonecrosis Involvement at Presentation (Epiphyseal and Metadiaphyseal Lesions)

	Total Number of Osteonecrosis Percentage of Sites with Osteonecrosis n, (%)	Number of Patients with Bilateral Lesions n, (%)	Total Number of Patients n, (%)
Hip	70 (47%)	29 (70%)	41 (100%)
Shoulder	60 (40%)	23 (62%)	37 (90%)
Knee	14 (9%)	5 (45%)	11 (27%)
Ankle	5 (3%)	1 (33%)	3 (7%)
Total	**149**	**29 (70%)**	**41 (100%)**

osteonecrosis on the second site was within two years for 50 per cent of the patients; and 25 per cent of the patient developed avascular necrosis in the third site within four years after the diagnosis at the second site. These eighty-seven patients identified as having multifocal osteonecrosis at the most recent follow up were associated with forty-nine other patients with osteonecrosis in only one or two separate sites. So multifocal osteonecrosis represented 64 per cent of the patients with osteonecrosis at most recent follow up (eighty-seven among 136 patients).

Among the eighty-seven patients with 158 osteonecroses at the proximal part of the femur at the most recent follow-up, the most common site besides the hip was the proximal humerus (eighty-one patients, i.e. 93 per cent), followed by the lateral femoral condyle (twenty-five patients, i.e. 29 per cent), the distal femoral metaphysis (twenty-one patients, i.e. 24 per cent), the medial femoral condyle (nineteen patients, i.e. 21 per cent), the upper tibial metaphysis (sixteen patients, i.e. 18 per cent), and others (Table **2**).

So at the last follow up (mean 15 years, rage 10 to 20 years) among these eighty-seven patients, the occurrence of osteonecrosis was 158 lesions of the proximal femur associated with 151 proximal humerus osteonecroses, thirty-three lateral femoral condyle osteonecroses, twenty-eight distal femoral metaphysis osteonecroses, twenty-seven medial femoral condyle osteonecroses, twenty-three tibial plateau osteonecroses, twenty-one upper tibial metaphysis osteonecroses and forteen ankle osteonecroses. The total number of osteonecrosis was 455 in these 87 patients. The epiphyseal lesions were more frequent than the metadiaphyseal lesions excepted in the proximal tibia (Table **3**).

2. Incidence of Multifocal Osteonecrosis in the Population of this Series

At the time of presentation forty-one patients had the diagnosis of multifocal osteonecrosis. At the last follow-up eighty-seven patients had multifocal osteonecrosis. So of the 200 patients followed for average 3000 patients-years, forty-six (23 per cent) had developed multifocal osteonecrosis during the period study (1.5 case per 100 patients-year). Multifocal osteonecrosis was greatest in the groups with the SS genotype (43 per cent, i.e. 37 among eighty-seven) followed by those with the hemoglobin SC genotype (38 per cent, i.e. 33 among eighty-seven) and patients with the $S\beta^{+}$ thalassemia genotype (19 per cent, i.e. 17 among eighty-seven). Because the age distribution of patients differed by genotype, age calculated prevalence rate of multifocal osteonecrosis were calculated. Pair wise tests of the incidence of multifocal osteonecrosis according to the genotype revealed that the age-adjusted rates in patients with the hemoglobin SS genotype differed from that in patients with the hemoglobin SC genotype ($p < 0.01$). To determine whether there was an age specific difference in the incidence of multifocal osteonecrosis according to genotype, we studied two age groups of interest: patients who were between eighteen and thirty years old and these who were thirty years old or older. We found that in the older age group the incidence of multifocal osteonecrosis (2.8 cases per 100 patients-years) was highest among patients with the SC genotype. The incidence of multifocal osteonecrosis was higher among patients with the S.S. genotype in the younger age group (3.6 cases per 100 patients-years).

Hip symptoms (with or without multiple joint pain) was the most common presentation (thirty-six patients, 87 per cent). The shoulder was the only presenting symptomatic joint in three patients and the knee the only presenting symptomatic joint in two patients. Of the fifty-five joints or bone sites in which symptoms initially presented, there was forty-five hips (81 per cent of presenting joints), eight shoulders (15 per cent of presenting joints), two knees, (47 per cent). Almost 35 per cent of the hips (twenty-five hips), 86 per cent of the shoulders (fifty-two shoulders) and 85 per cent of the knees (twelve knees) in which osteonecrosis was present at presentation had no pain or limitation of motion at the time of diagnosis. However, all these joints or bone sites became painful later and all the joints involved had limitation of motion at the most recent follow up.

DISCUSSION

Previous reports concerning multifocal osteonecrosis have been limited to case reports or to osteonecrosis associated with other risk factors. In our study with sickle cell disease we found mean 5.2 sites involved by osteonecrosis at the most recent follow-up. The hips were involved in all the patients with multifocal osteonecrosis and there was a bilateral predominance of all sites.

Multifocal disease was found to occur in at least 64 per cent of patients as having at least one osteonecrosis. The high incidence of osteonecrosis is this series was related to the routine use of MRI. There is a risk of underestimation of patients with multifocal osteonecrosis since patients may have silent lesions not identified in absence of radiographs or MRI. This is especially true in sickle cell disease because all the osteonecrosis do not occur at the same time and all joints do not become symptomatic at the same time. In this series

Table 2. Osteonecrosis Involvement at the Last Follow-Up (Epiphyseal and Metadiaphyseal Lesions)

	Total Number of Osteonecrosis Percentage of Sites with Osteonecrosis n, (%)	Number of Patients with Bilateral Lesions n, (%)	Total Number of Patients n, (%)
Hip	158 (35%)	75 (86%)	87 (100%)
Shoulder	151 (33%)	71 (88%)	81 (93%)
Knee	132 (29%)	18 (60%)	30 (34%)
Ankle	14 (3%)	4 (66%)	6 (7%)
Total	**455**	**77 (89%)**	**87 (100%)**

Table 3. Repartition Between Epiphyseal and Metadiaphyseal Ostéonécroses at the Last Follow-Up

	Epiphyseal Osteonecrosis n, (%)	Metadiaphyseal Osteonecrosis n, (%)
Proximal femur 158 lesions	136 (86%)	22 (14 %)
Proximal humerus 151 lesions	133 (88%)	18 (12%)
Distal femur 88 lesions	0 (68%)	28 (32%)
Proximal tibia 44 lesions	23 (52%)	21 (48%)
Distal tibial and talus 14 lesions	9 (64%)	5 (36%)

of 136 patients with at least one osteonecrosis, 60 per cent of the patients with osteonecrosis of the hip had multifocal osteonecrosis, but 90 per cent of the patients with osteonecrosis of the shoulder and 95 per cent of the patients with osteonecrosis of the knee had multifocal osteonecrosis at the most recent follow-up. This study emphasizes the need to screen other joints in patients with osteonecrosis of the knee, shoulder because the risk of multifocal osteonecrosis in these patients. If a patient complains of pain in other joints and if plain radiographs appear normal, MRI is indicated to assess osteonecrosis.

The authors acknowledge that some areas of osteonecrosis may have been missed. Even if hips, shoulders and ankles of the patients were evaluated with MRI, other asymtomatic joints may not have evaluated and therefore unidentified lesions in other sites may be present.

Total body scintigraphic bone scans may be an effective mean of screening for multifocal osteonecrosis in other etiologies. However in sickle cell disease scintigraphic bone scans may not be the best diagnostic modality in these patients because the hematological disease. Previous reports [6-8] have shown increased isotope uptake in peripheral extremities, consistent with marrow expansion in all patients with sickle cell disease who were examined by using Tc-99m sulfur colloid. The areas of marrow infarction could not be differentiated.

With the possible exception of patients with uncommon genotype, we can consider that this sample of 200 patients is representative of the population of patients with sickle cell disease. We found in this study a very high incidence of osteonecrosis in sickle cell disease. This may be explained by the age of our patients, (particularly with an increase of the rate of osteonecrosis in older patients with the hemoglobin SC genotype) and by the fact that our patients had MRI performed on many joints. This study revealed also that patients with sickle cell disease are at highest risk for multifocal osteonecrosis. Because about 50 per cent of the patients developed avascular necrosis at the second site within two years after diagnosis of avascular necrosis at the first site and because 25 per cent of the patients developed avascular necrosis at the third site within four years after the diagnosis at the second site, it may be necessary to screen the patients at six months or one year intervals. Because avascular necrosis was found to occur as frequently in the humeral heads as in the hip at the most recent follow-up, the shoulders should be imaged also frequently.

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