Risk factors and impact of orthopaedic monitoring on the outcome of avascular necrosis of the femoral head in adults with sickle cell disease: 215 patients case study with control group

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KEYWORDS
Osteonecrosis; Femoral head; Sickle cell disease; Risk factors

Summary
Introduction: Sickle cell disease is a public health problem. The WHO has recommended that global management be implemented to reduce mortality and morbidity. Since no comprehensive care programme for bone and joint complications exists, the Caribbean Sickle Cell Disease Center added orthopaedic consultation to screen for and monitor these complications in 1992.

Hypothesis: Comprehensive medical and surgical care of patients with sickle cell disease will reduce the complications and disability associated with this disease.

Populations and methods: Two populations were compared to evaluate the impact of comprehensive disease management on the occurrence of avascular necrosis (AVN) of the femoral head (femoral head AVN). The case-control series, [E-1994], included 115 patients (58 SS and 57 S) without orthopaedic monitoring and was evaluated retrospectively. The other patient series, [E-2008], included 215 patients (94 SS and 121 SC) with systematic orthopaedic care and was followed prospectively. Age, gender, duration of follow-up, haemoglobin levels, genotype, pain before treatment, associated humerus AVN and leg ulcers were analysed.
Introduction

Sickle cell disease (SS homozygote and SC double heterozygote, Punjab SD, Sβ thalassemia) is a significant public health problem in Africa, the Mediterranean and the West Indies, which now has spread throughout the world [1]. In Europe, in addition to thalassemia, the S gene has been detected in African and West Indian immigrant populations at a frequency of 2.4% in Brussels, 2.1% in London and 2.4% in Paris [2–6]. Paradoxically, in Northern European countries, haemoglobin diseases (thalassemia and sickle cell disease) are considered to be rare genetic diseases, but they have become a public health concern [7]. Migration explains the presence of the S gene in various regions of the world (Table 1). This hereditary haemoglobin disease was declared as a public health priority in 1990 by Guadeloupe, in 2005 by the Union of African States, in 2006 by the WHO and in 2005 (E-1994), 2006 by the WHO and in 2005 (E-2008) (Table 1).

### Table 1

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<tr>
<th>Region</th>
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<tbody>
<tr>
<td>Cuba</td>
<td>5</td>
<td>Saudi Arabia</td>
<td>5–25</td>
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<tr>
<td>Puerto Rico</td>
<td>5</td>
<td>Greece</td>
<td>8–27</td>
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<td>Jamaica</td>
<td>10</td>
<td>Brazil</td>
<td>7–10</td>
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<tr>
<td>Italy (south)</td>
<td>10</td>
<td>India</td>
<td>9–38</td>
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<tr>
<td>Venezuela</td>
<td>11</td>
<td>Caribbean Islands</td>
<td>10–12</td>
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<tr>
<td>Curacao</td>
<td>12</td>
<td>Panama</td>
<td>12–14</td>
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<tr>
<td>Surinam</td>
<td>15</td>
<td>Africa</td>
<td>15–40</td>
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Management of sickle cell disease is challenging. Clinical symptoms can be severe in some patients and limited in others. Recommended management consists of:

- **primary prevention:** use of targeted information to reduce the number of births to parents who are carriers;
- **secondary prevention:** anticipate and reduce the occurrence of complications by screening new-borns and monitoring them after birth (evaluation of time without clinical symptoms or baseline, antibacterial prophylaxis, vaccination, patient and parent education);
- **tertiary prevention:** screening and treatment of complications [8–11].

Bone and joint complications are common in sickle cell disease (bone infarction, bone infection, necrosis) in about 31% of patients. Bone infection is the most common complication, especially in African countries [12]. Among potential aseptic joint complications, the most common and the most disabling is avascular necrosis of the femoral head (femoral head AVN). Management is difficult [13–16].

Since 1984, the systematic screening of new-borns and early medical care of children with sickle cell disease have resulted in very few bone and joint infections in Guadeloupe. However management of aseptic necrosis has not yet been set out in a systematic manner [17]. In 1992, the Caribbean Sickle Cell Disease Centre in Guadeloupe invited us to develop a comprehensive management programme for hip necrosis that included the following elements [18–23]:

- prevention of humerus and femoral head avascular necrosis through patient education about the early signs of hip or shoulder involvement;
- clinical examination after every vaso-occlusive crisis or child-birth episode and resting a hip that is painful (pain medication, use of crutches and canes to unload painful hip);
- prevention of sequela through conservative surgical treatment (drilling, osteotomy).

We performed a descriptive, comparative study to assess the risk factors for femoral head AVN and evaluate the effectiveness of a comprehensive management programme (medical and orthopaedic) on the occurrence of femoral head AVN in patients with sickle cell disease. The study comprised two series of patients with sickle cell disease who were at least 16 years of age. The first series, [E-1994], included patients identified as having sickle cell disease starting in 1984 at the Pointe-à-Pitre Hospital, before the Caribbean Sickle Cell Disease Centre opened. These patients were not monitored regularly, thus their data were collected retrospectively. The second series, [E-2008], included all the patients with sickle cell disease who were identified at the Caribbean Sickle Cell Disease Centre between 1995 and 2008, provided informed consent and did not have
Patients and methods

Patients

The [E-1994] series included 115 patients (58 SS and 57 SC; 42 men and 73 women). The [E-2008] series included 215 patients (94 SS and 121 SC; 85 men and 130 women) who were monitored regularly. The minimum age for inclusion into either series was 16 years. The evaluations consisted of:

- clinical examination of the hip and other joints at each visit by doctors familiar with sickle cell disease management; radiographs of the hips and shoulders at the first visit with an orthopaedic surgeon monitoring patients every year;
- consultation after each crisis and bone imaging (radiographs and MRI when humeral head or femoral head AVN suspected);
- joint unloading and anti-inflammatory medication in cases of hip pain; d) parent, adolescent (not evaluated here) and patient education to encourage them to mention any persistent hip pain.

Diagnosis of femoral head avascular necrosis

The diagnosis of femoral head AVN was based on data in medical records, clinical examination, hip and shoulder radiographs performed on the [E-1994] and [E-2008] series, and bone and joint evaluations of the hip. Radiographs and Tec-99 bone scans were performed annually or when the patient presented with symptoms. CT scan or magnetic resonance imaging (MRI) was requested following an abnormal bone scan or cases of persistent pain to assist in making a diagnosis of femoral head AVN [18,24]. Other joints (shoulder, knee, ankle, lumbar spine) were evaluated and imaging modalities requested in cases of presenting symptoms, pain, and reduced range of motion [18,25–28].

Variables evaluated

Data were collected from all the patient in both series for the following variables: patient age at first visit, age at diagnosis of femoral head AVN, duration of monitoring, haemoglobin levels (Hb), femoral head AVN and haemoglobin levels, genotype, gender, pain before treatment, bilateral cases, femoral head AVN and shoulder involvement, femoral head AVN and leg ulcers.

Statistical analysis

Average values were compared according to Schwartz [29],

$$e = \frac{(M_A - M_B)}{(S_A^2/N_A + S_B^2/N_B)^{1/2}}$$

where $S_A^2$ and $S_B^2$ represent the estimated variances (difference is significant if $e \geq 1.96$). The Chi² test was used to verify the relationship between two characteristics in the two populations being studied. The $P$-value was derived from the software Excel™ ($P < 0.05$ was a significant difference). An odds ratio (OR) was calculated to measure the relationship between qualitative variables (pain, laterality, combination with leg ulcers).

Results

Characteristics of the two patient populations

The age, gender and genotype distribution were the same for the two series (Fig. 1, Table 2). When all the genotypes were pooled together, the average age when femoral head AVN was diagnosed was 35.3 ± 1.4 for patients in the [E-1994] series and 29.5 ± 3.4 (n = 31) for patients in the [E-2008] series; this difference was not significant ($P = 0.6$, Table 2).

For the [E-1994] series, the average haemoglobin level was 8.9 ± 0.9 g/dL in SS patients and 11.4 ± 0.4 g/dL in SC patients ($P < 0.001$). For the [E-2008] series, it was 8.3 ± 0.3 g/dL in SS patients and 11.4 ± 0.3 g/dL in SC patients ($P < 0.001$). If the SS and SC groups are compared over both time periods, only the SS group had different haemoglobin levels ($P = 0.03$, Table 2).

Patients in the [E-1994] series were followed for an average of 8.7 ± 0.6 years ($n = 115$) and patients in the [E-2008] series were followed for 11.3 ± 0.7 years ($n = 215$). There was a significant difference between the [E-1994] and [E-2008] series ($P < 0.01$; Table 2). When all the genotypes were pooled together, the frequency of femoral head AVN was 36.5% (42/115) for the [E-1994] series versus 14.4% (31/215) for the [E-2008] series ($P < 0.001$; Table 3).

The average haemoglobin levels were higher in patients who developed femoral head AVN in the [E-1994] and [E-2008] periods ($P < 0.001$). There were no significant differences in haemoglobin levels in the [E-1994] and [E-2008] periods (Table 3). Genotype (SS or SC) did not affect the frequency of femoral head AVN occurrence in either period (Table 3). Femoral head AVN occurred less often in women than men in the [E-1994] series ($P = 0.01$). In the [E-2008] series, AVN occurred as often in women as in men ($P = 0.9$; Table 3).

Pain related to femoral head AVN was present in 50% of patients, both SS and SC, in the [E-1994] series. In the [E-2008] series, pain was present in 42% of cases, but not in 98% of cases. There were no differences between the two periods...

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<tr>
<td></td>
<td>n = 115</td>
<td>n = 215</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>42 (36.5%)</td>
<td>85 (39.5%)</td>
<td>n/s</td>
</tr>
<tr>
<td>Women</td>
<td>73 (63.5%)</td>
<td>130 (60.5%)</td>
<td>n/s</td>
</tr>
<tr>
<td>SS genotype</td>
<td>58 (50.4%)</td>
<td>94 (43.7%)</td>
<td>n/s</td>
</tr>
<tr>
<td>SC genotype</td>
<td>57 (49.6%)</td>
<td>121 (56.3%)</td>
<td>n/s</td>
</tr>
<tr>
<td>Patient age when disease management started (years)</td>
<td>30.4 ± 2.1</td>
<td>29.5 ± 1.36</td>
<td>n/s</td>
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<tr>
<td>Age when femoral head AVN diagnosis was made (years)</td>
<td>35.3 ± 1.4</td>
<td>29.5 ± 3.4</td>
<td>n/s</td>
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<tr>
<td>Average haemoglobin levels (g/dL)</td>
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<tr>
<td>SS genotype</td>
<td>8.9 ± 0.9</td>
<td>8.3 ± 0.3</td>
<td>n/s</td>
</tr>
<tr>
<td>SC genotype</td>
<td>11.4 ± 0.4</td>
<td>11.4 ± 0.3</td>
<td>n/s</td>
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<tr>
<td>P</td>
<td>0.001</td>
<td>0.001 (SS vs SC)</td>
<td>n/s</td>
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<tr>
<td>Follow-up period (years)</td>
<td>8.7 ± 0.6</td>
<td>11.3 ± 0.7</td>
<td>P &lt; 0.01</td>
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(P = 0.5) (Table 3). When femoral head AVN was present, it happened bilaterally more often in the [E-1994] series (P = 0.005) than in the [E-2008] series (P = 0.1; Table 3).

When the combination of femoral head AVN and shoulder involvement was assessed in both populations, we found that shoulder involvement was significantly associated with femoral head AVN (P = 0.01) (Table 3). In the [E-1994] series where the patients were not monitored, 85.7% of patients with femoral head AVN also had leg ulcers (P = 0.0001); this combination was present in only 16.1% of patients in the [E-2008] series (P = 0.0002) (Table 3). Significantly, fewer patients in the [E-2008] series presented with leg ulcers (Table 3).

Discussion

The two series were directly comparable because of similar population characteristics (age, gender and genotype). Both series had patients above 16 years of age. Femoral head AVN secondary to sickle cell disease occurs in younger patients than primary or idiopathic femoral head AVN (appears at an average age of 45 years) [28,30–33]. Treatment of advanced femoral head AVN by arthroplasty is difficult and costly, especially in Africa and developing countries [21,34–37]. There was a significant difference in the duration of monitoring between the two series (8.7 ± 0.6 years for [E-1994] and 11.3 ± 0.7 years for [E-2008]). Although the study was not randomized, the make-up of a control group from the same population and the lengthy follow-up with the prospective group in theory limits the bias that could hinder interpretation of the results (lost to follow-up, incomplete records).

Blood viscosity depends on haematocrit, plasma viscosity (carrying phase) and rheological properties of the red blood cells [38–41]. Elevated haemoglobin or haematocrit levels in combination with rheological problems lead to sickling and vaso-obclusion, especially in the femoral head sinusoids. In our study, there was a relationship between elevated haemoglobin levels and femoral head AVN, which suggests that vaso-occlusion and increased viscosity are determining factors for femoral head AVN [42].

The frequency of femoral head AVN as a function of genotype and gender has been debated, and varied by series in this study. The study by Hernigou et al. [21] with 131 patients (101 SS and 30 SC) suggested that it was more common in SS homozygotes (42%) than SC double heterozygotes (20%); it was also more common in women than in men. Other studies have reported a higher occurrence in SC than SS genotypes. This no longer holds true today; the average lifespan is similar in both groups because of improved disease management. Gender and genotype were not risk factors for femoral head AVN, that should be sought in all patients [14,23,28].

In contrast to idiopathic necrosis, asymptomatic forms of femoral head AVN were seen that could appear normal for a long period of time. The weak relationship between symptoms and necrosis before treatment can be explained by episodes of latent sickling, with little pain, that cause bone infarction in the femoral head (sclerosis often seen by chance during the treatment of symptomatic femoral head AVN on the contralateral side) [24,43]. The lack of pain documented in this study suggests that femoral head AVN could progress with or without symptoms. Surgical treatment is not justified in these cases of asymptomatic necrosis, but these cases should be monitored clinically [18,43]. Necrosis in the hip can be unilateral or bilateral. Bilateral cases occurred in 54% of patients in the study by Milner et al. [23]. In our study, bilateral cases were more frequently observed in the [E-1994] series, which can be explained by the lack of medical monitoring in the [E-1994] period. Targeted evaluations and appropriate care should be performed on the healthy contralateral hip [43].

Involvement of the epiphysis of multiple joints and bones of an individual has been reported, with humeral head AVN being the most common [18,21,27,28,44–46]. Milner et al. [46] reported this in more than 50% of their patients. In our study, the shoulder was involved more often in the [E-2008] series than in the [E-1994] series (P = 0.01), which is
Table 3 Results of comparison between the two groups: [E-1994] without monitoring and [E-2008] with monitoring.

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<tr>
<td>Femoral head AVN occurrence rate</td>
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</tr>
<tr>
<td>n = 115</td>
<td>42/115 (36.5%)</td>
<td>31/215 (14.4%)</td>
<td>P &lt; 0.001</td>
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<tr>
<td>Hb levels (g/dL) as a function of femoral head AVN</td>
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<tr>
<td>Femoral head AVN +</td>
<td>11.3 ± 0.5</td>
<td>11.1 ± 0.5</td>
<td>n/s</td>
<td></td>
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<tr>
<td>Femoral head AVN</td>
<td>9.5 ± 0.5</td>
<td>10.1 ± 0.3</td>
<td>n/s</td>
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<tr>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
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<tr>
<td>Frequency relative to genotype</td>
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<tr>
<td>Femoral head AVN +</td>
<td>21 (50%)</td>
<td>14 (45.2%)</td>
<td>n/s</td>
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<tr>
<td>SC</td>
<td>21 (50%)</td>
<td>17 (54.8%)</td>
<td>n/s</td>
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<tr>
<td>P = 1</td>
<td>P = 0.6</td>
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<tr>
<td>Frequency of femoral head AVN relative to gender (M/F)</td>
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<tr>
<td>Men</td>
<td>21/42 (50.0%)</td>
<td>12/85 (14.1%)</td>
<td>P &lt; 0.001</td>
<td></td>
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<tr>
<td>Women</td>
<td>21/73 (28.8%)</td>
<td>19/130 (14.6%)</td>
<td>P &lt; 0.001</td>
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<tr>
<td>P = 0.01</td>
<td>n/s</td>
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<tr>
<td>Pain associated with femoral head AVN before treatment</td>
<td></td>
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<tr>
<td>Hip pain</td>
<td>21/42 (50%)</td>
<td>13/31 (42%)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>21/42 (50%)</td>
<td>18/31 (58%)</td>
<td>n/s</td>
<td></td>
</tr>
<tr>
<td>P = 0.01</td>
<td>n/s</td>
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<tr>
<td>Femoral head AVN laterality</td>
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<tr>
<td>Unilateral</td>
<td>12/42 (28%)</td>
<td>11/31 (55.5%)</td>
<td>n/s</td>
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<tr>
<td>Bilateral</td>
<td>30/42 (72%)</td>
<td>20/31 (64.5%)</td>
<td>n/s</td>
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<tr>
<td>P = 0.005</td>
<td>n/s</td>
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<tr>
<td>Femoral head AVN and shoulder involvement</td>
<td></td>
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<td></td>
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<tr>
<td>Association +</td>
<td>16/42 (38.1%)</td>
<td>21/31 (67.7%)</td>
<td>P = 0.01</td>
<td></td>
</tr>
<tr>
<td>Association —</td>
<td>26/42 (61.9%)</td>
<td>10/31 (32.3%)</td>
<td>P = 0.05</td>
<td></td>
</tr>
<tr>
<td>n/s</td>
<td>n/s</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Femoral head AVN and leg ulcers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcer +</td>
<td>36/42 (85.7%)</td>
<td>5/31 (16.1%)</td>
<td>32.2</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Ulcer —</td>
<td>6/42 (14.3%)</td>
<td>26/31 (83.9%)</td>
<td>P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td>P &lt; 0.0002</td>
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attributed to the systematic monitoring during the prospective study. The epiphysis is involved because vaso-occlusion occurs in the terminal circulation, which is similar in the humerus and femoral head [46–48]. Symptoms are vague in the initial stages (pain, loss of function) [25,46]. When femoral head AVN is present, the possibility of humeral head AVN should be systematically assessed [25,28,45,46,48]. Necrosis has been identified in knees, talus and elbows [27,49].

Starting at 10 years of age, 10 to 20% of patients will develop leg ulcers at one point in their lifetime [50–53]. In both series, we found that femoral head AVN was significantly associated with leg ulcers. Leg ulcers are considered to be an associated factor in the appearance of femoral head AVN [18,50–53].

The reported frequency of femoral head AVN secondary to sickle cell disease varies between 8 and 40%. In adults, the frequency is about 40% [21,39]. This is similar to the frequency observed in [E-1994], our non-monitored population. Data from the prospective study with [E-2008] allowed the prevalence of femoral head AVN of 14.4% to be calculated from a regularly monitored population. This frequency is clearly lower than published values. The [E-2008] series patients had better, earlier medical care, particularly for vaso-occlusive crises (hydration, pain medication, oxygen therapy, anaemia treatment) that reduced the risk of vaso-occlusion in bone tissue. The reduced risk of femoral head AVN could be attributed to the parallel conservative orthopaedic treatment in our study (bone and joint monitoring after every vaso-occlusive crisis, special monitoring during adolescence or after pregnancy, early unloading of a painful hip). By comparing the [E-1994] and [E-2008] series, the frequency of femoral had AVN went from 36.5% to 14.4% (P < 0.0001). Medical treatment to stop sickle cell disease crises on one hand and conservative orthopaedic treatment with joint unloading on the other hand, could explain this significant reduction in femoral head AVN in our [E-2008] series. This observation should be confirmed with a randomized study to avoid any biases that exist with a case-control study where only one arm was followed prospectively.

Conclusion

Before the Caribbean Sickle Cell Disease Centre in Guadeloupe was created, a sickle cell disease patient was
considered “at risk” because of the lack of medical monitoring. The life expectancy of these patients has improved because of systematic screening in new-borns and early medical management (prophylaxis using long-term antibiotic treatment, vaccination, regular monitoring, improvements in hygiene, use of drug treatments such as hydroxyurea).

A relationship was found between elevated haemoglobin levels and femoral head AVN, which suggests that high blood viscosity, hypoxia and vaso-occlusion all have a role in its appearance. The risk factors for femoral head AVN identified in our study (elevated Hb, presence of leg ulcers, shoulder involvement) can be added to those reported in the literature: low HbF levels, association with α-thalassemia trait, low mean corpuscular volume, proliferative retinopathy. By defining these factors, patients with a risk of femoral head AVN can be identified earlier, which ensures a better follow-up. A comparison of the two series showed that comprehensive care (medical and orthopaedic) was beneficial to patients in the [E-2008] series. This monitoring includes appropriate medical treatment for vaso-occlusive crises and conservative orthopaedic treatment for hip pain, and can explain the reduced occurrence of femoral head AVN.

The Caribbean Sickle Cell Disease Centre protocol can be used for tertiary prevention of bone and joint complications:

- appropriate medical treatment and prevention to reduce vaso-occlusive crises;
- patient education on the presenting symptoms in the hip and other joints;
- clinical examination of bones and joints performed annually and after every vaso-occlusive crisis;
- special monitoring during adolescence and after a pregnancy;
- early, orthopaedic or conservative surgical (drilling, osteotomy) management when necrosis is present, to reduce the disabling complications of femoral head AVN.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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