Avascular necrosis of the femoral head among children and adolescents with sickle cell disease in Greece

Hemoglobinopathies are very common in Greece, the incidence of β-thalassemia trait being 8% and that of sickle cell trait ranging from 1 to 32% in various districts.[1] In Greek populations, sickle cell disease (SCD) is mainly represented by S-β thalassemia.

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Sickle cell disease (SCD) is a well recognized cause of avascular necrosis (AVN) of the femoral head, a complication that is chronic, painful and potentially disabling.[2] We report the outcome of 7 young SCD patients attending our unit who presented with femoral AVN. The mean age at the time of diagnosis was 11.14±3.8 years, the range from 7 to 18 years (Table 1). Overall, 13 hips were affected and in 11 cases symptoms indicating AVN were present; AVN was diagnosed in the 2 asymptomatic hips during laboratory examination of the contralateral symptomatic hip. In all but one patient both hips were involved. Besides the underlying disease, no additional predisposing factors such as alcohol abuse or intake of steroids were present. The diagnosis was confirmed radiographically (using X-ray and/or magnetic resonance imaging) and classified according to a modified Marcus-Ennecking grading system.[3]

With regards to treatment, subtrochanteric varus osteotomy was performed in 9 out of the 13 hips. The technique of osteotomy has been well established in the treatment of femoral AVN associated with various conditions such as Legg-Calvé-Perthes disease and has given satisfactory results when performed by experienced surgeons providing a new articular surface, achieving core decompression, allowing for revascularization and permitting conversion to arthroplasty if later necessary.[4,5] The remaining 4 hips were treated conservatively, the management consisting of a 6-month limited weight-bearing regime with bed rest and use of crutches, as well as non-steroid analgesic medication. Patients were followed up for a mean period of 6 years (range 2-10 years).

Of the 9 hips treated surgically, a clinical improvement was noted in 8. This was indicated subjectively by pain relief, increase of joint motion and enhancement of walking, and objectively by improvement of the Harris hip score.[6] Radiographic improvement was also observed (Figure 1), with the exception of one hip which remained stable despite mitigation of symptoms. In no case did complications arise at surgery. During follow-up, fracture of the femoral shaft complicated one case.

With regards to the 4 hips managed with conservative treatment, 2 were in the same patient who had presented with mild unilateral symptoms, was diagnosed early and closely followed for 10 years remaining free of symptoms and presenting no radiographic deterioration. The 3rd hip was recently diagnosed as stage 1 AVN, was asymptomatic and remained clinically and radiographically stable, while the 4th hip with AVN was in a patient who repeatedly refused to undergo surgery, later developed osteomyelitis and deteriorated both clinically and radiographically.

Although SCD is the commonest cause of femoral osteonecrosis in children,[7] data regarding this complication are limited. It usually develops in late adolescence or early adulthood, although its onset can be in childhood, in concert with the mean age of diagnosis in our group of patients.[2] Its overall prevalence varies in different reports from 2.9% to 41%, with predisposing factors being a high hematocrit and frequent vaso-occlusive crises, as was the case in our cohort.[8,9] Although it has been suggested that $S\beta^+$ patients develop AVN less frequently and later in life than those with the $S\beta^0$ genotype 7, in our study group 4 out of 7 patients were $S\beta^+$, this being the commonest genotype in the Greek SCD population.

Many alternative options have been advocated regarding the treatment of osteonecrosis in SCD patients, but results have not been ideal. The efficacy of conservative treatment, usually considered in the early stages of the disease, is not always satisfactory even when adopted before deformity of femoral head occurs.[2] Surgery is favored in most cases when symptoms are present.[3] Arthroplasty has been considered the main treatment, although more conservative surgical techniques have been reported, including core decompression, intertrochanteric osteotomy, cement injection and use of bone grafts or vascularized fibular grafts.[3,9,10] None is consistently considered a satisfactory approach, while complications such as sepsis, intra-operative fracture, femoral perforation and loosening of components remain.[3,7,10]

It is obvious that femoral head AVN is a severe complication resulting in chronic pain and further deterioration of quality of life in SCD patients. No completely satisfactory cure is currently available for this potentially crippling condition, although with treatment symptoms can be minimized. Magnetic resonance imaging permits early diagnosis, even when symptoms are not present or lesions are not demonstrable on plain radiographs, enabling

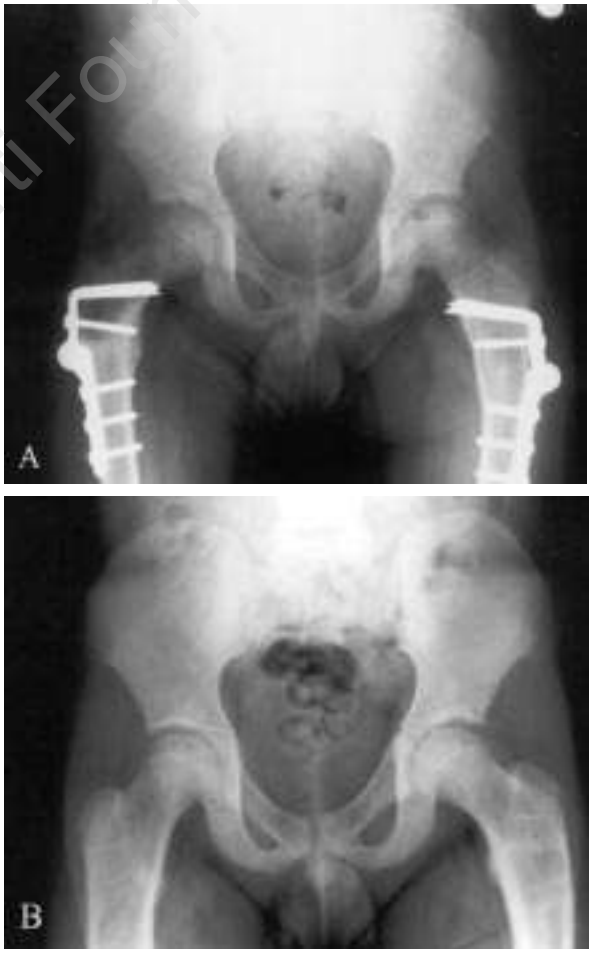

Figure 1. X-ray of patient # 4 performed 6 months (1a) and 8 years (1b) post-operatively, both hips presenting a stage 4 to stage 2 improvement.

Table 1. Clinical data regarding the 13 hips with AVN.

Patient #.	Hip R	Hip L	Age (yr)	Sex	Genotype	Ht (%)	Stage *(b) x-ray	Stage *(b) MRI	Treatment	Stage *(a) x-ray	Stage *(a) MRI	Follow-up
1.	+		11	F	SS	25	4	–	**S	2	–	Improved
		+	11				4	–	S	2	–	Improved
2.	+		7	M	$S\beta^0$	26	3	–	S	2	2	Improved
3.	+		12	F	$S\beta^+$	29	5	–	S	3	3	Improved
		+	12				2	–	**C	3	3	Deteriorated
4.	+		7	M	$S\beta^0$	27	4	–	S	2	–	Improved
		+	7				4	–	S	2	–	Improved
5.	+		18	M	Sβ+	28	5	–	S	4	4	Stable
		+	18				3	–	S	2	2	Improved
6.	+		13	M	$S\beta^+$	30	2	2	S	2	2	Improved
		+	18				normal	1	C	normal	1	Stable
7.	+		10	F	$S\beta^+$	28	2	2	C	2	2	Improved
		+	10				normal	1	C	normal	1	Stable

**b = before treatment, *a = after treatment, **S = surgical treatment, **C = conservative treatment.*

prompt identification of the disease and initiation of earlier treatment regimens, in order to achieve a better outcome.

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HLA-DRB1*15 and pediatric aplastic anemia

We report a positive association between HLA-DRB1*15 (p = 0.0002) in Turkish patients with pediatric severe aplastic anemia (SAA) and a paradoxically favorable influence of the susceptibility marker on the clinical response to immunosuppressive therapy. These findings point to an immune mechanism mediated by DRB1*15 in SAA which confers responsiveness to treatment.

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Severe aplastic anemia (SAA) is a hematologic disorder characterized by peripheral blood cytopenias and reduced bone marrow cellularity in the absence of an underlying myeloproliferative disorder or malignancy. Most cases are described as idiopathic. Immune mechanisms have been considered in the pathogenesis of SAA and an HLA-DR-restricted immune reaction against hematopoietic cells has been reported.[1] Immunogenetic studies in different populations have identified an association between SAA and the serologically detected HLA-DR2 antigen or its molecular correspondents, DRB1*15/ *1501.[2-4] DRB1*1501 has also been reported to be closely associated with a favorable response to cyclosporin-A (CSA) therapy in patients with SAA.[5]

We examined the HLA-DRB1 locus in 33 Turkish pediatric SAA patients diagnosed and treated in Istanbul between 1992 and 2000. All patients with SAA had the following laboratory findings: hemoglobin < 100 g/L, hematocrit ≤ 30%, platelet count ≤ 50×10^9/L, white blood cell count ≤ 3.5×10^9/L and granulocytes ≤ 1.5×10^9/L. Bone marrow biopsy and aspirations showed decreased cellularity and the absence of significant fibrosis or neoplastic infiltration in all cases. Seventeen patients who did not have an HLA-matched donor received high dose methyl-