Screening of Hip Osteonecrosis in Patients with Sickle Cell Disease and its Association with Hematological Parameters

Thesis

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By

Aida Muhammad Ali Abdo

M.B, B.Ch, 2011 – Aden University – Yemen

Supervised by

Prof. Dr. Mohsen Saleh El-Alfy

Professor of Pediatrics

Faculty of Medicine - Ain Shams University

Ass. Prof. Dr. Iman Ahmed Ragab

Ass. Professor of Pediatrics

Faculty of Medicine - Ain Shams University

Ass. Prof. Dr. Shaymaa Abdel-Sattar

Ass. Professor of Radiodiagnosis

Faculty of Medicine - Ain Shams University

Faculty of Medicine

Ain Shams University

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List of Abbreviations

Abb.	Full term
AVN	Avascular necrosis
ACS	Acute chest syndrome
BMI	Body Mass Index
CBC	Complete Blood Count
CT	Computerize Tomography
DNA	Deoxyribonucleic acid
Hct	Hematocrit
HPLC	High Performance Liquid Chromatography
Ht	Height
IgG	Immunoglobulin G
LDH	Lactate dehydrogenase
MCH	Mean Corpusculare Hemoglubine
MCV	Mean Corpusculare Volume
MRI	Magnetic Resonance Imaging
ON	Osteonecrosis
ONFH	Osteonecrosis of femoral head
PCR	Polymerase chain reaction
RBCs	Red Blood Cells
Retics	Reticulocytes
THR	Total hip arthroplasty
SCD	Sickle cell disease
SDS	Standard deviation score
Wt	Weight
α	Alpha
β	Beta
γ	Gamma

INTRODUCTION

Sickle cell disease (SCD) is the most common inherited blood disease, with a worldwide distribution. The disease is characterized by vaso-occlusive crises due to the shape of the red blood cells consequent to the polymerization of one type of hemoglobin, called hemoglobin S, hemolytic anemia and increased susceptibility to infections ***(Wang et al., 2009).***

Osteonecrosis (or ischemic necrosis) is a frequent complication in SCD with painful and debilitating features. In areas of high prevalence of SCD, especially in tropical regions, SCD is a major cause of osteonecrosis of the femoral head ***(Mukisi et al., 2011).*** It is usually an insidious and progressive disorder, affecting mainly the hip (femoral head) and shoulder (humeral head). Approximately 50% of SCD patients have evidence of complications after the age of 30 years old. In children, SCD is the leading cause of osteonecrosis, with a prevalence of 3% before 15 years of age and an incidence of two cases per 100 patients/year ***(Naoum et al., 2004).***

The commonest presentation of AVN of the hip includes pain, limitation of movements, and limp. Plain x-ray features of AVN are attenuation of the epiphysis, lucent areas, flattening or collapse of articular surfaces, sclerosis, and joint space narrowing. However, these signs are only seen in advanced disease. Magnetic resonance imaging (MRI) is a useful tool for detecting and grading early changes ***(Rees et al., 2010).***

Identification of risk factors and early screening would help in placement of appropriate measures to prevent osteonecrosis in high risk patients. This is very important because most patients with osteonecrosis present in advanced stages, when the only treatment option is total hip replacement. Furthermore, it has been shown that the natural history of asymptomatic osteonecrosis of the femoral head in adults with sickle cell disease is progression to collapse ***(Akinyoola et al., 2009).***

AIM OF THE STUDY

- To screen for hip osteonecrosis in children with sickle cell disease by:
  - Musculoskeletal assessment of movement of hip joints.
  - Conventional plain X-ray for hip joints.
  - MRI for hip joints.
- To study the association between MR findings with disease status and hematologic parameters.

Chapter 1

SICKLE CELL DISEASE: PATHOGENESIS AND COMPLICATIONS

Sickle cell disease (SCD) is a hereditary disorder of abnormality in the oxygen-carrying haemoglobin molecule in red blood cells (RBC). It is inherited as an autosomal recessive disorder. Morphological expression depends on the acquisition of two abnormal allelomorphic genes related to haemoglobin formation. SCD occurs when a person inherits two abnormal copies of the haemoglobin gene, whereas a person with a single abnormal copy is said to have the 'sickle-cell trait' and they usually do not experience symptoms. It has no sexual predominance and is a lifelong disease ***(Raju et al., 2015).***

The global distribution of Hb S is indicative of two factors: selection for carriers through their survival advantage in malaria-endemic regions and subsequent migration. Four region-specific African haplotypes (the Senegal, Benin, Bantu, and Cameroon haplotypes) and one Asian haplotype (the Arab-India haplotype) have been defined, providing support for the hypothesis that the mutation-causing Hb S has occurred, and been locally amplified, on at least two, and possibly several, separate occasions ***(Hernigou, 2014).***

Although the molecular abnormality leading to the sickle gene is the same in all haplotypes, there is a wide variation in

the clinical manifestations and severity of the associated disease. The clinical phenotype of SCD is said to be multigenic ***(Chui and Dover, 2001).*** The sickle genotype (Table 1), beta globin haplotype, and other genes, unlinked to the beta globin locus, participate in the relevant pathological events that lead to modification of the phenotypic expression of the sickle gene ***(Chui and Dover, 2001).*** Among the genetic factors that have been associated with milder disease phenotype are alpha-thalassemia and high levels of fetal hemoglobin ***(Stuart and Nagel, 2004),*** both are more commonly observed in SCD prevalent in the Eastern part of Saudi Arabia ***(El-Hazmi et al., 1999).*** Environmental factors such as infections, nutrition, and socioeconomic status may also influence the course of the disease and the rate of survival.

Table (1): Comparison between SCD genotypes ***(Jastaniah, 2011).***

SCD genotype	Definition	Clinical severity
HbSS disease or sickle cell anemia	Homozygote for the βS globin gene	Usually severe or moderately severe phenotype
HbS/βo thalassemia	Severe double heterozygote for HbS and βo thalassemia	Usually indistinguishable from sickle cell anemia phenotypically
HbSC disease	Double heterozygosity for HbS and HbC	Intermediate clinical severity
HbS/β+ thalassemia	Double heterozygosity for HbS and β+ thalassemia	Mild to moderate severity, but variable in different ethnic groups
HbS/HPFH	HbS and hereditary persistence of fetal Hb	Very mild phenotype or symptom free as a result of high Hb F
HbS/HbE syndrome	Double heterozygosity for HbS and HbE	Very rare and generally very mild clinical course
Other rare combinations	HbS/HbD Los Angeles, HbS/HbO Arab, G-Philadelphia	Rare combinations with variable clinical course

Comparison of genotypes

The frequency and severity of clinical complications varies between the genotypes; SS disease and sickle cell-β0 thalassemia are most severe clinically and hematologically. Sickle cell-β+thalassemia presents a very wide clinical spectrum depending on the molecular mutation for the β-thalassemia gene and the amount of HbA produced. In people of West African origin, the sickle cell-β+thalassemia gene is associated with a mild reduction of normal β-chain synthesis, HbA levels of 15%–25%, and generally a mild clinical course. SC disease is generally mild but more prone to proliferative sickle retinopathy ***(Graham, 2013).***

Pathophysiology:

Under deoxygenation, HbS polymerizes, leading to initial reversible structural changes. It ultimately leads to permanent membrane damage after repeated deformation. Infection, physical exercises, acidosis, cold, and dehydration are other conditions that predispose HbS to polymerization. Following deoxygenation, HbS become fragile with marked decreased solubility and elasticity. These abnormal sickle cells fail to return to normal shape when there is a restoration of oxygen tension ***(Raju et al, 2015).***

Red cells high containing levels of sickle haemoglobin contribute to the pathophysiological development of sickle cell anaemia in three ways ***(Platt, 2008).*** Firstly, the loss of