

## Review Article

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# Atopic dermatitis in sickle cell children

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## ABSTRACT

Sickle cell disease is an autosomal recessive disease characterized by recurrent vaso-occlusive events. Despite the genetic basis of its pathophysiology, recent researchers stated that it is an inflammatory immune-mediated disease where inflammation plays a crucial role in the initiation of adherence between sickle cells and vascular endothelial cells. Allergic, as well as infectious, inflammation is proposed to contribute to the initiation of vaso-occlusive events. Although several researchers reported an association between sickle cell disease and atopic conditions such as bronchial asthma and allergic rhino-conjunctivitis, few cases have reported an association between sickle cell disease and atopic dermatitis. Atopy was reported to be considerably linked to sickle cell disease for several reasons. Firstly, patients with sickle cell disease have higher IgE levels than the general population. Secondly, the mechanism of activation of molecular adhesion between endothelial and blood cells are similar between both sickle cell disease and atopic disease. Thirdly, the cytokines produced from platelet activation are the same cytokines that stimulate allergic inflammation in atopic diseases and promote adherence of sickle cells and endothelium in sickle cell disease. Lastly, sickle cell disease was reported to be associated with other atopic diseases.

**Keywords:** Atopic dermatitis, Sickle cell, Anemia, Atopy, Eczema, Pediatric, Children

## INTRODUCTION

Sickle cell disease (SCD) is a genetic autosomal recessive disease that results from the existence of a mutated type of hemoglobin (hemoglobin S) and presents during early childhood with vaso-occlusive crises. Individuals who carry the sickle cell genes in homozygous forms present with sickle cell disease (SCD), whilst those who carry a single copy of the gene (heterozygous) are sickle cell carriers. Clinically, patients with sickle cell disease present with manifestation of vascular occlusive phenomenon.<sup>1-3</sup> Following hypoxia, dehydration, or change in body temperature, patients with sickle cell

disease (SCD) experience vaso-occlusive manifestations including acute pains, bone pain, chronic hemolytic anemia, splenic sequestration or infarction, recurrent infection, growth retardation, dactylitis, dyspnea, acute chest syndrome, avascular necrosis of femur head, recurrent cerebrovascular stroke, recurrent thrombotic events, retinal hemorrhage, cardiac chamber dilatation, cholelithiasis, priapism, renal involvement, and lower extremity ulcers.<sup>4</sup>

Atopic dermatitis, on the other hand, is a chronic immune-mediated skin disease that is characterized with recurrent relapses of pruritis, xerosis, itching, hand or

foot dermatitis, ichthyosis, cheilitis, palmar hyperlinearity, or keratosis pilaris that start at early age of childhood in patients with family history of atopy such as atopic conjunctivitis, atopic rhinitis, or bronchial asthma.<sup>5</sup> Atopic dermatitis is a cell-mediated immune disease characterized by increased levels of T-helper type 2 (Th2) cells as well as interleukin (IL) levels, particularly IL-3, IL-4, and IL-5.<sup>6</sup> This review aims at addressing the potential association between atopic dermatitis and sickle cell disease.

## **PATOPHYSIOLOGY OF SICKLE CELL DISEASE**

The widely accepted pathophysiology of sickle cell disease is related to the altered physical properties of the mutated hemoglobin S. Under deoxygenated situations, hemoglobin S changes its physical characters, solubility, viscosity, stability, and morphology. It forms polymers and crystals in a gelatin-like substance that sickle repetitively leading to membrane damage, altered cell membrane permeability to  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Ca}^{++}$ , and subsequent alteration of cytoskeleton proteins. Additionally, the structure of the lipid bilayer of the cell membrane changes and the membrane becomes more rigid. This contributes to thrombosis and vaso-occlusive phenomena. Furthermore, the cells that carry hemoglobin S express on its surface very late antigen-4 (VLA-4) that interacts with molecules on the endothelial lining of blood vessels such as vascular cell adhesive molecule-1 (VCAM-1). Deformable cells adhere to vascular endothelium 10 times more than normal cells. Leucocytes, particularly neutrophils, also share by expressing adhesive molecules.<sup>1,7,8</sup>

## **IMMUNOLOGY OF SICKLE CELL DISEASE**

Whilst the susceptibility of patients with sickle cell disease to recurrent infection has been long attributed to immunological alteration following splenic dysfunction, recent evidence suggests that sickle cell disease is an inflammatory disease with a persistent low-grade inflammation that is responsible for initiation of the vaso-occlusive crisis.<sup>9-11</sup> Researchers found that patients with sickle cell disease have high levels of acute phase reactants, serum amyloid A, C-reactive protein and orosomucoid during disease remissions and significantly higher levels during relapses.<sup>12</sup> The inflammation encountered in patients with sickle cell disease activate vascular endothelium and enhance expression of adhesion molecules that interact with the deformed red blood cells leading to vascular occlusive events.<sup>10</sup> Moore et al, in their review, suggested that the inflammatory reaction that promotes adhesion between sickle cells and vascular endothelium can be allergic or infectious inflammation.<sup>10</sup> The postulation of the allergic inflammation theory was proposed based on the demonstration of similar mechanisms of activation of endothelium and expression of adhesion molecules after immunoglobulin E (IgE)

activation in patients with bronchial asthma and atopic dermatitis.<sup>13,14</sup>

## **SICKLE CELL DISEASE AND ATOPY**

During the past few decades, evidence from literature studies supported the existence of an association between sickle cell disease and atopy. Firstly, significantly elevated levels of IgE were reported among patients with sickle cell disease in different researches, and the levels of IgG and IgA were also high.<sup>15,16</sup> Secondly, the mechanism of activation of endothelium and increasing the expression and activity of adhesion molecules is encountered in other atopic diseases such as bronchial asthma and atopic dermatitis.<sup>13,14</sup> Thirdly, the cytokine profile produced by activated T helper cells lead to allergic inflammation as well as upregulation of VCAM-1 molecular expression on endothelial lining which will consequently recruit leucocytes to the site of inflammation.<sup>17</sup> Lastly, the association between sickle cell disease and atopic diseases reported from the literature, as well as the increased severity, morbidity, and mortality with exacerbations of atopic diseases support the postulation that allergic inflammation plays a crucial role in the pathophysiology of sickle cell disease.<sup>10</sup> For instance, several researches reported cases with sickle disease associated with bronchial asthma.<sup>16,18-20</sup> They have reported that exacerbations of bronchial asthma were associated more severe symptoms of sickle cell disease and higher mortality rates, which support the theory of allergic inflammation nature of activation of endothelial molecular adhesion molecules and subsequent cascade of vaso-occlusive phenomena. Sickle cell disease in one study was found to be associated with asthma (aOR=1.46), bronchitis (aOR=1.71), and eczema (aOR=1.74). Cases of IgA nephropathy was also reported to be associated with sickle cell disease.<sup>21,22</sup>

## **SICKLE CELL DISEASE AND ATOPIC DERMATITIS**

As aforementioned, sickle cell disease seems to be considerably associated with atopy and atopic diseases. Few studies from the literature have reported cases with sickle cell disease and atopic dermatitis. Data from the FDA reported five cases during the period 2010 to 2011 who had eczema and sickle cell disease. Females constituted the vast majority of those patients (80%), whilst men constituted only 20%. One of them had another co-existing atopic disease (bronchial asthma).<sup>23</sup> Similarly, a cohort study conducted in Florida on children with sickle cell disease stated that – by multiple logistic Regression analysis– sickle cell disease was significantly associated to eczema (aOR= 1.74, 1.23–2.46).<sup>21</sup>

In atopic dermatitis, blood thrombospondin levels are elevated specifically with disease activity.<sup>24</sup> These thrombospondins are thought to promote adherence between sickle cells and vascular endothelium through modulating antigens expressed on sickle cell surface such

as VLA-4, CD36, and GPIb/IIIa. Thrombospondins are produced by the activated platelets when an allergen binds to the platelet Fc-II- associated IgE.<sup>10</sup>

## CONCLUSION

The genetic basis of sickle cell disease is not the only pathophysiologic mechanism encountered, growing evidence suggests that an inflammatory immune-mediated pathology plays a crucial role as well. Inflammation is thought to promote adherence between sickle cells and vascular endothelial cells. Allergic, as well as infectious, inflammation is proposed to contribute to the initiation of vaso-occlusive events. Although several researchers reported an association between sickle cell disease and atopic conditions such as bronchial asthma and allergic rhino-conjunctivitis, few cases were found that reported an association between sickle cell disease and atopic dermatitis. Atopy was reported to be considerably linked to sickle cell disease for several reasons. Firstly, patients with sickle cell disease have higher IgE levels than the general population. Secondly, the mechanisms of activation of molecular adhesion between endothelial and blood cells are similar between both sickle cell disease and atopic disease. Thirdly, the cytokines produced from platelet activation are the same cytokines that stimulate allergic inflammation in atopic diseases and promote adherence of sickle cells and endothelium in sickle cell disease. Lastly, sickle cell disease was reported to be associated with other atopic diseases.

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