Cytokine 56 (2011) 471–476

Contents lists available at SciVerse ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/issn/10434666

Increased concentrations of IL-18 and uric acid in sickle cell anemia: Contribution of hemolysis, endothelial activation and the inflammasome

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ARTICLE INFO

Article history:
Received 26 April 2011
Received in revised form 12 July 2011
Accepted 1 August 2011
Available online 26 August 2011

Keywords:
Sickle cell anemia
Cytokine
Inflammation

ABSTRACT

Sickle cell anemia (SCA) is a common, severe monogenetic disorder characterized by chronic hemolysis, frequent infections, a chronic inflammatory state and recurrent occlusions of the microcirculation, resulting in painful crises, organ damage and premature death. This study evaluated associations between serum levels of IL-18, uric acid, hemolytic markers, and inflammatory molecules in SCA patients. A cross-sectional study was performed including 45 SCA patients (median age of 20.5 years) without general symptoms and who had not undergone blood transfusions. Inclusion criteria for the steady-state SCA patients were the absence of hospitalization and the absence of infections. Interleukin-18 and uric acid levels were correlated closely with markers of hemolysis, endothelial dysfunction and others cytokines levels. These findings suggest probable influences of IL-18 and uric acid in the pathophysiology of vascular occlusion in SCA. Additional studies should be performed to characterize similar prognosis markers and possible therapeutic targets.

1. Introduction

Sickle cell anemia (SCA) is an inherited recessive autosomal disorder characterized by clinical heterogeneity that may be supported by a harmful environment, ethnicity, social, and economic factors and genetic markers secondary to epigenetic phenomenon. These genetic factors include an association between SCA and the β-S-globin gene cluster haplotypes, the presence of alpha-thalassemia and the well-known prognostic marker, the fetal hemoglobin concentration [1]. Vaso-occlusive episodes (VOE) in SCA are complex processes governed by many factors involving interactions among sickled red blood cells (RBC), endothelial cells, leukocytes, platelets, coagulation factors, and plasma proteins. The chronic inflammatory state that is characteristic of SCA patients [2] has been associated with high expression levels of adhesion molecules and soluble mediators by the vascular endothelium as a consequence of endothelial cell damage and activation, resulting in increased expression of surface molecules on endothelial cells, RBC, platelets and leukocytes and an increase in inflammatory cytokines and molecules [3].

The interleukin-18 is a pro-inflammatory cytokine that induces the release of TNF-alpha, IL-1, chemokines such as IL-8, cell adhesion molecules, and the decrease nitric oxide (NO) synthesis [4,5]. Previous studies have not indicated a role for IL-18 in SCA patients, but this cytokine is known to have a strong association with inflammatory events [6–9]. Increases in circulating levels of IL-18 have been described during a severe sepsis state [10], suggesting a role for this cytokine in host defense through leukocyte activation and in potential host damage due to tissue lesions [11,12].

The active form of IL-18 depends on the activation of the caspase-1 cascade. Caspase-1 leads to the cleavage of the pro-form of IL-18 into a functional cytokine. The activation of caspase-1 depends on a cytosolic multiprotein complex called the inflammasome. Two inflammasomes have been described thus far: the NALP1 and NALP3 inflammasomes. The NALP3 inflammasome is composed of NALP3 (NACHT, LRR and pyrin domain), the adaptor protein ASC (apoptosis-associated speck-like protein containing a caspase-recruitment domain), and caspase-1, and the NALP1 inflammasome additionally contains caspase-5. The recognition of danger signals, such as pathogen-associated molecular patterns, ATP and uric acid leads to oligomerization of NALP3 and association of the inflammasome components, inducing the proteolytic cleavage of procaspase-1 into its active form. The caspase-1 can then process pro-IL-18 into IL-18 [13].

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doi:10.1016/j.cyto.2011.08.013

Platt [3] has described a state of chronic inflammation in the pathogenesis of SCA, and emphasized an important role of leukocytes in this process. Based on the strong evidence for the importance of inflammatory molecules in SCA and the lack of studies addressing the influence of IL-18 and uric acid, we have undertaken this study. Here we explore the association of serum levels of IL-18 and uric acid, hemolytic markers and inflammatory molecules in a group of Brazilian SCA patients in order to examine the role of the inflammasome in the inflammatory environment frequently described in this disease.

2. Materials and methods

2.1. Study subjects

We performed a cross-sectional study composed of 45 SCA patients (21 men and 24 women; mean age of 20.50 ± 13.99 years) that were diagnosed according to their hemoglobin profile as having hemoglobin S (HbS) homozygous state (HbSS). Patients are routinely follow-up at the Outpatient Clinic of the Hematology and Hemotherapy Foundation – (HEMOBA) in Bahia, a Northeast Brazilian state with the highest incidence of sickle cell disease (SCD) in Brazil. All patients were in steady-state, which was characterized by an absence of blood transfusion in a period of four month prior to blood sampling. Inclusion criteria for steady-state SCA patients were characterized as a period of three months without any acute events, absence of general symptoms, hospitalization, or infections.

None of patients had taken antibiotics or corticosteroids prior to blood sampling that was withdrawn during a regular clinical visit. The medical history data of the SCA patients were search from patients' records.

Analyses of interleukin, arginase and soluble adhesion molecules were developed in a group of controls individuals, and also in controls pattern from the fabricant.

The control group consisted of 45 individuals who attended the clinical laboratory of the Pharmacy College of the Federal University of Bahia (UFBA), and these individuals were age- and sex-matched with the SCA patients group. The control individuals had normal hemoglobin profiles and lacked a history of anemia, inflammatory conditions, and hematological diseases.

The study was approved by the Oswaldo Cruz Research Foundation's Human Research Board and was in accordance with Declaration of Helsinki of 1975 as revised in 2000, and all subjects or responsible officials filled out a written informed consent form.

2.2. Hematologic analysis

Hematological analysis was performed using an electronic cell counter (Coulter Counter T890, Brea, CA, USA). The HbS presence was identified by the solubility test, the sickle hemoglobin test and by the analyses of hemoglobin profile by high-performance liquid chromatography (HPLC) (Bio-Rad Variant, CA, USA), which assays were run with controls samples from patients previously diagnosed and controls from a kit of hemoglobin pattern supplied by manufacturers, following their recommendations. The HPLC analysis of sample with S hemoglobin is confirmed by the retention time that is 4.30–4.70 min and it is in accord to the control pattern. Also, the HbS presence was confirmed by running electrophoresis at alkaline pH, and acid pH. The fetal hemoglobin concentration also has been confirmed by the Betke biochemical method followed spectrophotometer measurement.

2.3. Serum measurement of soluble adhesion molecules (sICAM-1 and sVCAM-1)

The serum soluble intercellular adhesion molecule (sICAM-1) and soluble vascular adhesion molecule (sVCAM-1) levels of the SCA patients were measured using a human DuoSet ELISA Kit (R&D, Minneapolis, MN, USA).

2.4. Biochemical analyses

Serum concentrations of lipid molecules, hemolytic markers, hepatic function markers, C-reactive protein, and uric acid of all of the patients were determined using commercially available kits (Flexor 80, Netherlands).

2.5. Cytokines and serum arginase level measurements

Interleukin-10, IL-17 and IL-18 were measured using Cytokine ELISA OptEIA kits (BD Pharmingen, San Diego, CA, USA; eBioscience, San Diego, CA, USA). Arginase levels were measured using a Human Arginase I ELISA Kit (Cell Science, Canton, MA, USA) according to the manufacturer's recommendations.

2.6. Statistical analysis

Baseline characteristics are summarized as means and proportions of selected variables. The distribution of quantitative variables was determined using the Kolmogorov–Smirnov test. Mean values of quantitative variables between groups were compared using an unpaired *t*-test for data distributed normally and a Mann–Whitney test for non-normal data. Bivariate correlation analyses were carried out to determine correlations between pairs of variables using Pearson's and Spearman's rank correlation (R). All tests were considered significant if p values were less than 0.05. Data analyses were performed using the STATA 10 (StataCorp, Texas, USA) and GraphPad Prism 5 (Graphpad Software, San Diego, CA) software packages.

3. Results

3.1. Medical history

The most common clinical complications in the SCA patients were the occurrence of a painful crisis, 41/43 (98.3%); followed by infection, 25/43 (58.1%); pneumonia, 16/43 (37.2%); leg ulcer, 8/43 (18.6%); cholelithiasis, 8/43 (18.6%); splenic sequestration, 7/43 (16.3%); priapism, 3/21 (14.3%); splenectomy, 6/43 (14.0%); acute chest syndrome, 6/43 (14.0%); hepatomegaly, 6/43 (14.0%); osteomyelitis, 3/43 (7.0%); dactylitis, 3/43 (7.0%); avascular necrosis, 2/43 (4.7%); retinopathy, 1/43 (2.3%); stroke, 1/43 (2.3%), and aplastic crisis, 1/43 (2.3%). The laboratory profile of these patients is shown in Table 1.

3.2. Cytokines, biochemical and soluble adhesion molecule concentration among sickle cell anemia patients and individuals from a control group

Cytokines, arginase, uric acid, and soluble adhesion molecule serum levels on SCA patients and individuals from a healthy group are shown in Table 2.

3.3. IL-18 and uric acid

IL-18 was positively associated with the serum concentration of uric acid ($p = 0.042$; $r = 0.361$) (Fig. 1).

3.4. IL-18 and hemolytic markers

IL-18 was positively associated with lactate dehydrogenase (LDH) ($p = 0.001$; $r = 0.547$) (Fig. 2A). Nine patients had IL-18

Table 1
Baseline characteristics of the steady-state sickle cell anemia patients.

Characteristics	Patients	
	N	Mean ± SD
Age (Years)	45	20.49 ± 13.99
Gender		
Male	21	
Female	24	–
Hemoglobin profile		
S	45	86.30 ± 9.47
Fetal	45	6.85 ± 3.89
Hemolysis		
RBC ($\times 10^6$/mm^3)	45	2.72 ± 0.68
Hemoglobin (g/dL)	45	8.09 ± 1.60
Hematocrit (%)	45	24.42 ± 5.20
Mean cell volume (fL)	45	91.06 ± 9.02
Mean cell hemoglobin (pg)	45	30.16 ± 3.69
Reticulocyte count (%)	45	7.16 ± 3.69
Erythroid precursors	45	1.27 ± 5.84
Leukocytes		
WBC ($\times 10^9$/L)	45	11.87 ± 3.62
Neutrophil ($\times 10^9$/L)	45	5.75 ± 1.53
Lymphocyte ($\times 10^9$/L)	45	4.71 ± 1.34
Monocyte ($\times 10^9$/L)	45	0.55 ± 0.40
Platelets		
Platelet Count ($\times 10^9$/L)	45	373.24 ± 183.40
Markers of lipid metabolism and inflammation		
Total cholesterol (mg/dL)	45	158.53 ± 43.18
HDL cholesterol (mg/dL)	45	42.93 ± 9.84
LDL cholesterol (mg/dL)	45	87.48 ± 47.39
VLDL cholesterol (mg/dL)	45	28.12 ± 16.19
Triglycerides (mg/dL)	45	140.60 ± 80.99
Uric acid (mg/dL)	45	4.40 ± 2.02
C-reactive protein (mg/L)	45	11.73 ± 25.39
Markers of hepatic dysfunction and hemolysis		
Aspartate aminotransferase (U/L)	45	32.78 ± 14.84
Alanine aminotransferase (U/L)	45	7.29 ± 4.73
Total bilirubin (mg/dL)	45	1.89 ± 1.10
Direct bilirubin (mg/dL)	45	0.58 ± 0.24
Indirect bilirubin (mg/dL)	45	1.31 ± 0.95
Lactate dehydrogenase(U/L)	45	720.98 ± 257.09

RBC, Red Blood Cell; WBC, White Blood Cell; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; VLDL-C, Very Low-Density Lipoprotein Cholesterol.

Table 2
Cytokines, hemolytic marker and soluble adhesions molecule between 45 sickle cell anemia patients and 45 individuals from a healthy group and controls patterns.

	Patients		Healthy group		*P* value*
	Median	SD	Median	SD	
Cytokine					
IL-10 (pg/mL)	8.87	1.52	9.90	3.22	0.248
IL-17 (pg/mL)	4.58	8.86	2.52	5.14	0.011
IL-18 (pg/mL)	3142.08	1374.81	393.4[a]	339.3[a]	–
Hemolytic marker					
Arginase (ng/mL)	25.77	17.97	14.70	5.36	0.005
Soluble adhesion molecule					
ICAM-1 (ng/mL)	411.66	102.81	237.59	66.18	0.0001
VCAM-1 (ng/mL)	756.39	383.80	263.62	75.42	0.0001

SD, Standard Deviation; ICAM-1, Intercellular Adhesion Molecule; VCAM-1, Vascular Adhesion Molecule.
* Mann–Whitney test.
[a] Controls pattern provided by the manufacturer.

values greater than the 75th percentile with high serum concentrations of LDH and indirect bilirubin; eight patients had IL-18 values less than the 25th percentile with low serum concentrations of LDH and indirect bilirubin (Fig. 2B and 2C). The serum concentration of IL-18 was positively associated with the percentage of erythroid precursors ($p = 0.022$; $r = 0.396$) (Fig. 2D).

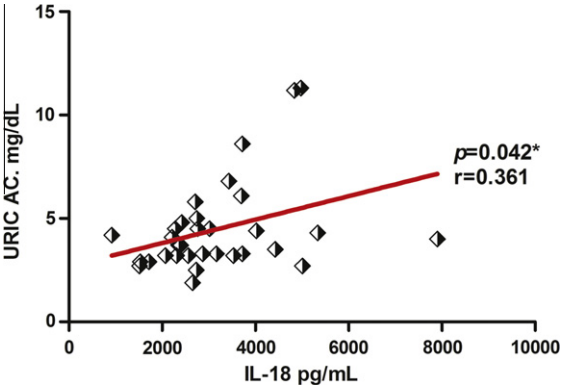

Fig. 1. IL-18 and uric acid. Serum levels of IL-18 are positively correlated with uric acid levels. Spearman's*, $P < 0.05$.

3.5. Uric acid and hemolytic markers

Uric acid was positively associated with total bilirubin ($p = 0.030$; $r = 0.338$) (Fig. 3A) and indirect bilirubin ($p = 0.028$; $r = 0.331$) (Fig. 3B). Eleven patients had uric acid values greater than the 75th percentile with a high serum concentration of arginase and indirect bilirubin; twelve patients had uric acid values less than the 25th percentile with low serum concentrations of arginase and indirect bilirubin (Fig. 3C and D).

3.6. Uric acid, soluble adhesion molecules and lipids

Uric acid was positively associated with sVCAM-1 ($p = 0.030$; $r = 0.327$) (Fig. 4A). Eleven patients had uric acid values greater than the 75th percentile with high serum concentrations of sVCAM-1 and low serum concentrations of low-density lipoprotein cholesterol (LDL-C), 12 patients had uric acid values less than the 25th percentile with low serum concentrations of sVCAM-1 and high serum concentrations of LDL-C (Fig. 4B and C).

3.7. Uric acid and cytokines

Uric acid was positively associated with the serum concentration of IL-10 ($p = 0.030$; $r = 0.352$) (Fig. 5A). Eleven patients had uric acid values greater than the 75th percentile with high serum concentrations of IL-17; 12 patients had uric acid values less than the 25th percentile with low serum concentrations of IL-17 (Fig. 5B).

4. Discussion

The defect in vascular homeostasis in SCA is caused by endothelial activation, cell interaction, inflammatory molecules and the influence of coagulation factors, resulting in vascular occlusion and the clinical phenotype characteristic of patients [2,14]. These clinical aspects are correlated with the expression of cytokines profiles, such that the disruption of the cytokine balance should precipitate the occlusive events by inducing endothelial cell activation [15]. Our study examined the possible participation of IL-18 and uric acid in vascular events and their association with cytokines, hemolytic markers and lipid markers, implicating the inflammasome in SCA patients.

We first demonstrated a positive association between IL-18 and uric acid in the group of SCA patients. This result may indicate the participation of the inflammasome pathway [16] in the inflammatory events occurring in SCA patients, with the participation of uric acid being the final product of cellular catabolism of purine and monosodium urate crystals in their active form [17]. These compounds have previously been indicated as danger signals that

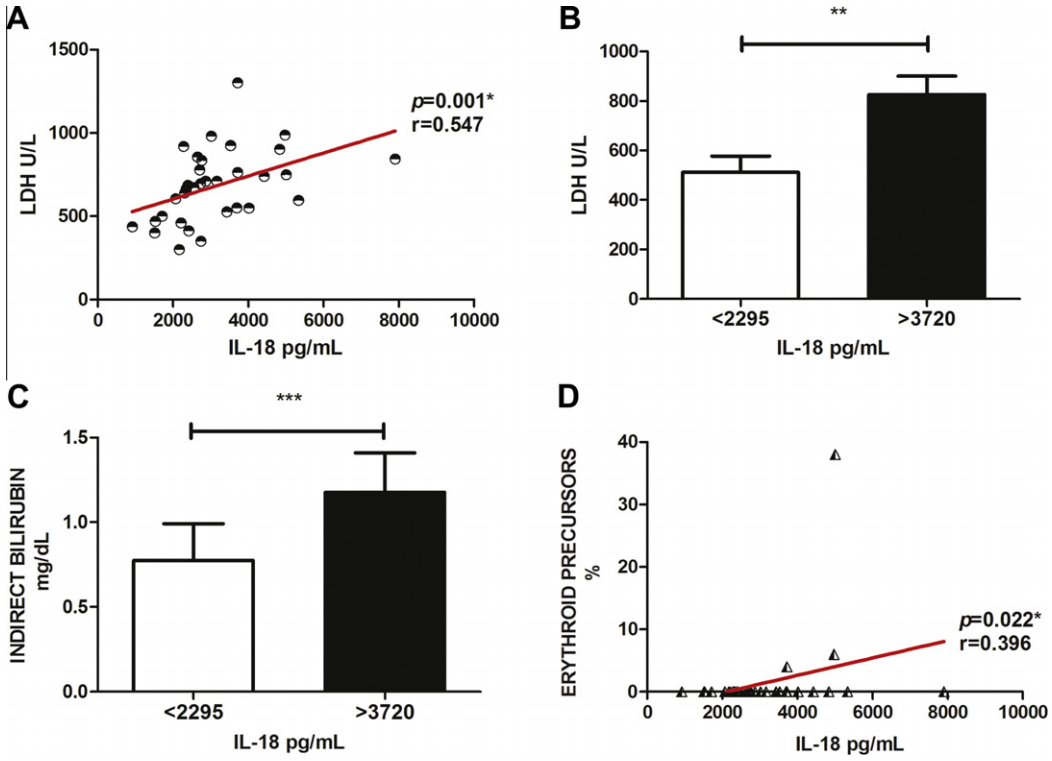

Fig. 2. Hemolitic markers and serum levels of IL-18 in SCA patients. (A) Positive correlation between serum levels of IL-18 and LDH. (B) Increased serum levels of LDH are associated with high serum levels of IL-18. (C) Increased serum levels of indirect bilirubin are associated with high serum levels of IL-18. (D) Positive correlation between serum levels of IL-18 and erythroid precursors. Spearman's*, $P < 0.05$; Test-T**, $P < 0.05$; Mann–Whitney Test***, $P < 0.05$.

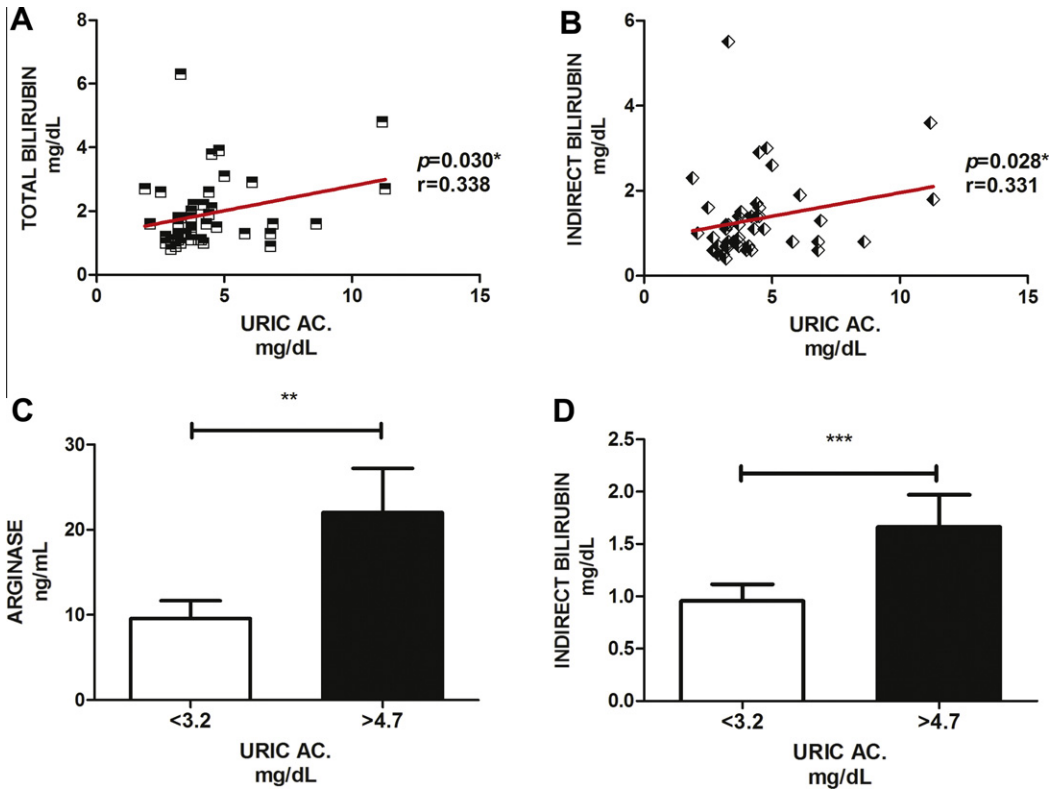

Fig. 3. Hemolitic markers and serum levels of uric acid. (A and B) Positive correlation between serum levels of bilirubins and uric acid. (C) Increased serum levels of arginase are associated with high serum levels of uric acid. (D) Increased serum levels of indirect bilirubin are associated with high serum levels of uric acid. Spearman's*, $P < 0.05$; Test-T**, $P < 0.05$; Mann–Whitney Test***, $P < 0.05$.

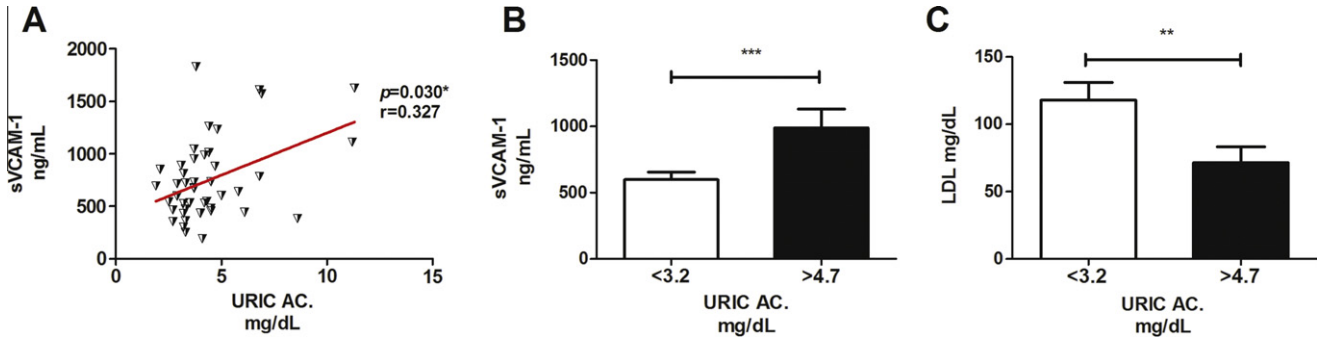

Fig. 4. Soluble adhesion molecules, lipids and uric acid. (A) Positive correlation between serum levels of sVCAM-1 and uric acid. (B) Increased serum levels of sVCAM-1 are associated with high serum levels of uric acid. (C) Decreased serum levels of LDL-C are associated with high serum levels of uric acid. Spearman's*, $P < 0.05$; Test-T**, $P < 0.05$; Mann–Whitney Test***, $P < 0.05$.

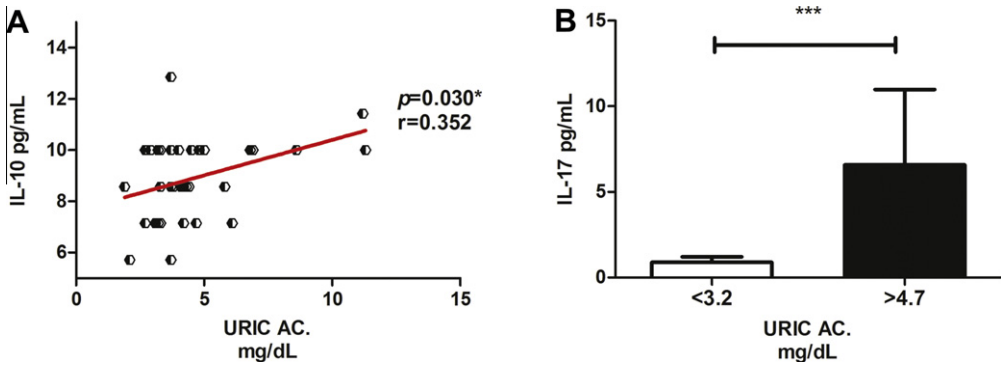

Fig. 5. Cytokines and uric acid. (A) Positive correlation between serum levels of IL-10 and uric acid. (B) Increased serum levels of IL-17 are associated with high serum levels of uric acid. Spearman's*, $P < 0.05$; Mann–Whitney Test***, $P < 0.05$.

activate the NALP3 inflammasome, mediating caspase-1 activation and the production of IL-1 beta and IL-18 [18]. Therefore, this pathway should have a role in the pro-inflammatory cytokines that participate in the clinical profile of SCA patients.

The IL-18 is a pleiotropic cytokine related to innate immune defense [19], inducing acute inflammation and promoting neutrophil accumulation [20]. These functions may also be possible influences of IL-18 on the well-described vascular events in SCA. In this study, we demonstrate a positive association between IL-18 and hemolytic markers such as LDH. The measurement of this enzyme in SCA patients has been characterized by Taylor et al. [21] to predict disease survivors. High serum levels of LDH represent an increased risk of early mortality. Thus, increased serum levels of LDH together high serum levels of a pro-inflammatory cytokine like IL-18 could be considered possible risk factors, and patients presenting these indicators likely will have a poor prognosis; this hypothesis that should be confirmed by a clinical prospective study.

In addition, not only is uric acid a marker of catabolic rate, but some authors suggest that increased serum levels of uric acid may promote arteriolosclerosis [22], atherosclerosis [23] and organ damage [24], perhaps by exerting a deleterious effect on endothelial cell function [25]. Uric acid can act as a pro-oxidant, particularly at high concentrations, and thus may be a marker of oxidative stress; it may also have a therapeutic role as an antioxidant [26]. These observations illustrate a potential negative contribution for high serum concentrations of uric acid in SCA. Our results confirm this assertion as we show an association between increased serum concentrations of uric acid and sVCAM-1 (an endothelial activation marker) and classical markers of a chronic hemolytic state such as bilirubin and arginase [27].

The negative influence of uric acid may be associated with the activation of the inflammasome complex and other oxidative mechanisms. Ruggiero et al. [28] have observed a progressive linear increase of uric acid that is positively associated with pro-inflammatory and anti-inflammatory cytokines. Pfeffer et al. [29] and Terada et al. [30] have described the influence of TNF-alpha, IL-1, IL-6 and oxygen tension on *xanthine oxidoreductease* (*XO*) gene transcription, which lead to a simultaneous increase in uric acid and free radical production, resulting in endothelial dysfunction [31]. In our study, we observed a positive correlation between high serum concentrations of uric acid and IL-10, IL-17, and IL-18 levels. Our hypothesis is that the profile of chronic hypoxia and inflammation presented by SCA patients results in the up-regulation of the XO, a key metabolic enzyme in the purine pathway. These findings also suggest that uric acid levels indirectly reflect a pro-inflammatory state, hypoxia and the presence of free radicals.

Further, the participation of uric acid in oxidative metabolism has been characterized by Patterson et al. [32], who demonstrated that uric acid protects native low-density lipoprotein cholesterol (LDL-C) against oxidation by transition metal ions, but accelerates the oxidation of mildly oxidized LDL-C. This shows the strong influence of uric acid on complex mechanisms related to oxidative stress and endothelial activation. Our results demonstrate a possible association between LDL-C and uric acid, in which patients with low concentrations of LDL-C presented increased concentrations of uric acid. The low levels of LDL-C in SCA patients [33,34] may reflect a down-regulation of cholesterol biosynthesis [35], an increase plasma volume having a dilution effects on plasma constituents [36] or a significant increase in cholesterol utilization during this hemolytic anemia [37]. The combination of these possibilities illustrates that low serum levels of LDL-C and increases in the uric acid concentration may reflect a worse level of hemolytic anemia, a virtual absence of atherosclerosis, and consequently a severe clinical version of SCA.

5. Conclusion

We conclude that both the inflammasome and molecules such as IL-18 and uric acid are involved in vascular occlusion in SCA and that molecules are strongly associated with classical hemolytic and endothelial activation markers, illustrating the important role of this complex event in SCA.

On the basis of our results, additional studies are warranted to determine whether these molecules have utility as easily assessable markers for assessing the relative risk of vascular events and possible therapeutic targets in SCA patients.

Conflict of interest disclosure

The authors declare no competing financial interests.

Authorship

BAVC and WVB designed and performed experiments, analyzed data and co-wrote the manuscript; ADZ was involved in the clinical monitoring of patients; MGR contributed intellectually; and MSG idealized the project, contributed intellectually, analyzed data and co-wrote the manuscript.

Acknowledgments

This work was supported by grants from the Brazilian National Council of Research (CNPq) (3065427/2007-5 and 484457/2007-1) (M.S.G.); the Foundation of Research and Extension of Bahia (FAPESB) (1431040053063 and 9073/2007) (M.S.G.); and MCD/CNPq/MS-SCTIE-DECIT (409800/2006-6), (M.S.G.). The sponsors of this study are public or nonprofit organizations that support science in general. They had no role in gathering, analyzing or interpreting the data.

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