Prevalence of autoimmune diseases in patients with sickle cell disease: a single center retrospective analysis

Sickle cell disease (SCD) affects millions of people throughout the world. SCD is caused by a mutation in the β-globin gene resulting in abnormal red blood cells and is characterized by chronic hemolytic anemia and painful vaso-occlusive crises. Patients with SCD may develop acute and chronic complications in several organs and have a limited life expectancy. In patients with SCD, the persistent hemolysis and ischemia-reperfusion injury due to recurrent vaso-occlusion, both resulting in increased oxidative stress, are the ingredients for a state of chronic inflammation. However endothelial damage is perpetuated by increased consumption of protective modulators such as protein C, protein S and nitric oxide.[1] This pro-inflammatory and pro-oxidative environment can be further maintained by activation of neutrophils, complement pathway and endothelial cells and a self-reinforcing cycle of cytokine production.[2] It is also known that infections occur more frequently in patients with SCD. Infections, interacting with an already activated immune system, are proposed as the so-called "second hit" in the cascade towards development of autoimmune diseases (AID).[3] The chronic inflammation together with genetic predisposition and environmental factors can potentially lead to an auto-inflammatory state and/or disease in SCD. A recent study showed a prevalence of AID of 1.3% in SCD patients between 7 and 17 years of age, which is lower than in the general African-American population.[4] However, only rheumatic diseases were included in this study, potentially explaining the lower prevalence. Furthermore, it is known that AID can also occur during adulthood. Our hypothesis is that due to the chronic inflammation, the prevalence of AID in patients with SCD is higher than that in the general population. Furthermore, we aimed to evaluate whether the occurrence of AID is associated with SCD-related complications, disease severity and treatment of SCD.

We performed a retrospective study at the Amsterdam University Medical Centers, Amsterdam, the Netherlands. All adults with SCD who visited our outpatient clinic between 2004 and 2021 were included in the study. Data (baseline characteristics, SCD complications and treatment) were extracted from the patients' electronic medical records. Laboratory values from the last visit at the outpatient clinic were also collected. The electronic records of all the patients included were searched for AID (*Online Supplementary Table S1*). The presence of autoantibodies and treatment (type) for the AID were also noted, if available. This study was performed according to institutional board requirements and the Declaration of Helsinki. Previously reported prevalences in the literature for the African-American population and estimated prevalence in the general Dutch population were used for matching to the general population without SCD. The patients' characteristics are described as medians with interquartile range (IQR) or count (percentage). The Mann-Whitney U test was used for the comparison of continuous variables and the χ^2 test (or Fisher exact test) for contingency tables. A *P* value of <0.05 was considered as statistically significant for all tests. Analyses were performed using SPSS Statistics version 26.0 (IBM Corporation, New York, NY, USA).

The patients' characteristics are summarized in Table 1. In total 338 patients were included. Thirty-six (10.7%) had been diagnosed with at least one AID. Fourteen different AID were diagnosed in these 36 patients (*Online Supplementary Table S1*). Age, sex and genotype of SCD were comparable between patients with or without AID. No differences in markers of inflammation or hemolysis were observed between patients with or without AID. The proportion of patients with retinopathy was higher in SCD patients with an AID than in those without AID (50% *vs*. 34%, respectively; *P*=0.002) (Table 2). The proliferative *versus* non-proliferative forms of retinopathy were similarly distributed between patients with and those without an AID. A trend towards a higher rate of microalbuminuria was found in patients with an AID compared to patients without an AID (39% *vs*. 23%; *P*=0.079). Other SCD complications and treatments were similar between the groups with or without AID. The most common AID in our cohort, with a prevalence of >1%, were hyperthyroidism or hypothyroidism (3%), sudden deafness (1.8%) and sarcoidosis (1.2%). Two patients were diagnosed with two different AID. One patient was known to have hypothyroidism and alopecia areata. Another patient had hyperthyroidism and sudden deafness. Table 3 lists the treatment strategies for all the patients with AID. In 24 patients, therapy was started for their AID. Local or systemic immunosuppressive treatment was started in 14 patients without complications.

In this study, we assessed the prevalence of AID in adult patients with SCD. At least one AID was observed in more than 10% of the patients. Based on previous reports on AID in the African-American population and the general Dutch population, a prevalence of 4.7% and 4.4%, respectively, could have been expected.[5] The prevalence of all the AID separately, except for alopecia areata (0.9% *vs*. 2.0%), appeared to be higher in this SCD cohort than in the general population.

In a previous study, the prevalence of AID in children with SCD was 1.3%.[4] Other reports have also described associations in patients with SCD and different AID.[6,7] The higher

Table 1. Characteristics of the cohort of sickle cell disease patients with or without autoimmune diseases.

	Total N=338	With AID N=36	Without AID N=302	*P*
Age in years, median (IQR)	33 (25-42)	32 (24-46)	33 (25-42)	0.903
Female, N (%)	171 (51)	20 (56)	151 (50)	0.529
BMI, kg/m^2, median (IQR)	22.5 (20.2-25.1)	23.6 (21.3-27.3)	22.4 (20.1-24.9)	0.070
Genotype, N (%)				0.212
HbSS	168 (50)	16 (44)	152 (50)	
HbSC	110 (33)	17 (47)	93 (31)	
HbSβ$^+$	31 (9)	1 (3)	30 (10)	
HbSβ^0	29 (8)	2 (6)	27 (9)	
Other[§]	6 (2)	0 (0)	6 (2)	
CRP,* mg/L, median (IQR)	3 (2-5)	2 (2-4)	3 (2-5)	0.173
ESR,* mm/hr, median (IQR)	7 (5-9)	8 (2-9)	6 (5-10)	0.857
Hemoglobin, g/dL, median (IQR)	10.0 (8.4-11.4)	10.3 (8.4-11.6)	9.8 (8.4-11.4)	0.462
Reticulocytes x 10^9/L, median (IQR)	168.7 (111.9-272.8)	159.9 (101.7-222.9)	169.9 (115.2-274.7)	0.475
Creatinine, μmol/L, median (IQR)	67 (55-82)	68 (58-86)	67 (55-81)	0.384
LDH, U/L, median (IQR)	322 (246-423)	295 (249-402)	324 (246-424)	0.420
Bilirubin total, μmol/L, median (IQR)	28 (16-50)	26 (16-45)	28 (16-51)	0.944
Ferritin, μg/L, median (IQR)	166 (81-376)	174 (100-289)	166 (79-394)	0.976
M/C ratio, mg/mmol, median (IQR)	1.16 (0.49-3.51)	1.46 (0.49-5.08)	1.15 (0.54-3.98)	0.901
Presence of autoantibodies,[#] N (%)	14 (4)	14 (39)	NA	NA

[§]Other consisted of HbSβ^{0}δ, HbSE and HbSD. *C-reactive protein and/or erythrocyte sedimentation rate were measured in 24 patients with and 150 patients without autoimmune diseases. [#]Autoantibodies included: anti-thyroid peroxidase, thyroid stimulating autoantibodies, anti-nuclear antibodies (anti-double-stranded deoxyribonucleic acid antibodies) and antiphospholipid antibodies. AID: autoimmune disease; IQR: interquartile range; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; M/C ratio: microalbuminuria/creatinine ratio; NA: not applicable.

prevalence in the current study might be explained by the higher average age of this cohort (median age of 33 years) since some AID are often diagnosed in adolescents or adulthood.[8] It is postulated that ongoing inflammation in patients with SCD may play a role in the increased risk of development of an AID. It has indeed been shown that chronic inflammation may promote a pro-inflammatory environment, in the end leading to autoimmune disorders.[9] Although we did not find differences in inflammatory markers (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) between patients with or without AID, these parameters were not measured systematically in our cohort and may be not sensitive enough to quantify the severity of the chronic inflammatory state associated with SCD. In fact, CRP is considered to be a more accurate reflection of the acute phase response and given the frequently observed discordance in ESR and CRP levels, their use as markers of chronic inflammation is still a matter of debate.[10] On the other hand, low-normal CRP levels were detectable in the majority of SCD patients, which is indicative of a low-grade inflammation in most patients. Another explanation for the elevated prevalence of AID in patients with SCD could be the high incidence of infections in these patients. Infections are thought to play a role in the development of AID, contributing to an abnormal immune response in which molecular mimicry, epitope spreading and bystander activation may play a role.[3] During life, SCD patients might encounter more infections which could contribute to the development of AID later on.

Higher proportions of retinopathy and microalbuminuria were seen in patients with AID, both of which are common forms of organ damage in SCD. Interestingly, retinopathy is most commonly seen in patients with HbSC, characterized by lower hemolysis and higher hemoglobin levels, while microalbuminuria is more frequently observed in HbSS patients and has been related to a high degree of hemolysis and lower hemoglobin levels.[11,12] The exact underlying mechanism for the association of these forms of organ damage with the prevalence of AID needs further evaluation. Nevertheless, recently, new single nucleotide polymorphisms in interleukin 6 have been associated with a higher likelihood of retinopathy in patients with HbSS, indicating the important role of inflammation in the development of this complication.[13] However, the exact contributions of infections, the adaptive and innate immune systems, environmental factors and genetic susceptibility to the development of organ damage in SCD and development of AID are still not fully understood.[14]

One of the limitations of our study is its retrospective design. However, most of the patients included in this study are regularly seen by a hematologist at an outpatient clinic and systematically checked for laboratory abnormalities

and several forms of SCD-related organ damage including regular ophthalmic and urine examinations, making it less likely that the higher incidences of retinopathy and microalbuminuria are due to more stringent examination in patients diagnosed with an AID. Another limitation is the relatively small sample size for a study on the prevalence of sometimes relatively rare forms of AID. Therefore, further research using International Classification of Diseases codes in large hospital databases is needed to validate our observation and to elucidate the precise role of inflammation preceding the development of AID in patients with SCD. Furthermore, relatively more common AID, such as eczema, psoriasis, vitiligo and asthma, were not consistently noted and/or reported by the hematologist, so these diseases were not taken into account in this analysis.

In conclusion, this is the first study showing an elevated prevalence of AID of more than 10% in adult patients with SCD. Based on these results, it is important to recognize symptoms which might help in earlier detection and treatment of AID.[15] Better understanding of the pathophysiology

Table 2. Complications of and treatment for sickle cell disease.

	Total N=338	With AID N=36	Without AID N=302	*P*
Complications, N (%)				
Frequent VOC	117 (35)	11 (31)	106 (35)	0.704
Stroke	22 (7)	5 (14)	17 (6)	0.157
History of ACS	98 (29)	11 (31)	87 (29)	0.922
Cholelithiasis	120 (36)	12 (33)	108 (36)	0.120
Microalbuminuria	82 (24)	14 (39)	68 (23)	0.079
Renal failure	23 (7)	3 (8)	20 (7)	0.753
Cutaneous ulcers	13 (4)	1 (3)	12 (4)	0.884
Elevated TRV	44 (13)	4 (11)	40 (13)	0.924
Retinopathy	122 (36)	18 (50)	104 (34)	0.002
Proliferative	33 (10)	5 (14)	28 (9)	
Non-proliferative	63 (19)	8 (22)	55 (18)	
Unspecified	27 (8)	5 (14)	22 (21)	
Osteonecrosis	62 (18)	7 (19)	55 (18)	0.928
Priapism	18 (5)	0 (0)	18 (6)	0.323
Treatment, N (%)				
Hydroxyurea	98 (29)	12 (33)	86 (29)	0.544
Chronic exchange transfusions	25 (7)	4 (11)	21 (7)	0.323
Iron overload	44 (13)	4 (11)	40 (13)	0.254
Chelation therapy	19 (6)	1 (3)	18 (6)	0.706

AID: autoimmune disease; VOC: vaso-occlusive crisis; ACS: acute chest syndrome. TRV: tricuspid regurgitation velocity.

Table 3. Treatment for autoimmune diseases in 36 affected patients among a cohort of 338 patients with sickle cell disease.

Autoimmune disease	N (%) of SCD patients with AID	Treatment (N of patients using therapy)
Myasthenia gravis	1 (0.3)	-
Multiple sclerosis	1 (0.3)	Glatiramer acetate
Sudden deafness	7 (2.1)	Corticosteroids (2)
Hyperthyroidism	5 (1.5)	Block and replacement therapy (3)
Hypothyroidism	5 (1.5)	Thyroid hormone supplementation (3); Radioactive iodine (1)
Diabetes mellitus type 1	2 (0.6)	Insulin (2)
Sarcoidosis	4 (1.2)	Corticosteroids (2)
Inflammatory bowel disease	2 (0.6)	Corticosteroids/anti-TNFα (1); Anti-TNFα (1)
Systemic lupus erythematosus	2 (0.6)	Hydroxychloroquine (2)
Mixed connective tissue disease	1 (0.3)	Corticosteroids, intravenous immunoglobulins, rituximab (1)
Henoch-Schönlein purpura	1 (0.3)	-
Antiphospholipid syndrome	3 (0.9)	Anticoagulants (3)
Mediterranean fever syndrome	1 (0.3)	Anti-interleukin 1 (1)
Alopecia areata	3 (0.9)	Local steroids (3)

One patient suffered from alopecia areata and hypothyroidism. Another patient had hyperthyroidism and sudden deafness. If not mentioned, no therapy was needed/started. SCD: sickle cell disease; AID: autoimmune disease; TNF: tumor necrosis factor.

of the development of AID in patients with SCD may help to design new interventions to downregulate this inflammatory cascade and to prevent the development of AID.

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https://doi.org/10.3324/haematol.2023.284552

Received: October 26, 2023.
Accepted: March 21, 2024.
Early view: March 28, 2024.

Disclosures

No conflicts of interest to disclose.

Contributions

MWT performed the research and analyzed the data. MWT, EN, CFJT, and BJB designed the research study and wrote the manuscript.

Data-sharing statement

Data can be obtained by contacting the corresponding author.

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