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

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Disclosures

No conflicts of interest to declare.

Contribution

MWT performed the research;

MWT;EN;CT;BB designed the research study;

MWT analysed the data;

MWT;EN;CT;BB wrote the manuscript.

Data-sharing statement

Data can be obtained by contacting the corresponding author.

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-occlusions, 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.(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 autoimmune diseases (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 compared to 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 that visited our outpatient clinic between 2004 and 2021 were included in the study. Data (baseline characteristics, SCD and complications and treatment) were

extracted from the from electronic medical records. Laboratory values were also collected from the last visit at the outpatient clinic. The autoimmune diseases were searched for in the electronic patient records of all included patients (Supplementary table 1). The presence of autoantibodies and treatment (type) for the AID were also noted, if avaiable. This study was performed according to the institutional board and the Declaration of Helsinki. Previously reported prevalences from literature in the African-American population and estimated prevalence in the general Dutch population were used as matching general population without SCD. Patient characteristics are described as medians with interquartile range (IQR) or count (percentage). The Mann-Whitney U test was used for comparing continuous variables and the Chi-square test (or the Fisher exact) for contingency tables. A P value of <0.05 was considered as statistically significant for all testing. Analyses were performed using SPSS Statistics version 26.0 (IBM Corporation, New York, USA).

Patient 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 AIDs were diagnosed in these 36 patients (Supplementary table 1). 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 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 AIDs. The most common AIDs 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 AIDs. One patient was known with hypothyroidism and alopecia areata. Another patient had

hyperthyroidism and sudden deafness. In table 3, the treatment strategies are listed 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 the AIDs in adult patients with SCD. In more than 10% of the patients at least one AID was observed. Based on previous reports on AID in the African-American population and the general Dutch population, a prevalence of respectively 4.7% and 4.4% may be expected.(5) The prevalence of all the AIDs separately, except for alopecia areata (0.9% vs 2.0%), appeared to be higher in this SCD cohort compared to the general population.

In a previous study, a prevalence of 1.3% in children with SCD was reported.(4) Other reports have also observed associations in patients with SCD and different AIDs.(6, 7) The higher prevalence in the current study might be explained by the higher average age of this cohort (median age of 33 years) since some AIDs 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 measures were not tested 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 indicating a low grade inflammation in the majority of patients. Another explanation for the elevated prevalence of AID in patients with SCD could be the elevated incidence of infections in these patients. Infections are thought to play a role in the development of

autoimmune diseases, 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 AIDs later on. In patients with AIDs, higher proportions of retinopathy and microalbuminuria were seen, 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 with high grade 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 as 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, adaptive and innate immune system, environmental factors and genetic susceptibility in the development of organ damage in SCD and development of AID remain not fully understood.(14) One of the limitations of our study is the retrospective design. However, most of the patients included in this study are regularly seen by a hematologist at the outpatient clinic and systematically checked on laboratory abnormalities and several forms of SCD related organ damage including regular ophthalmic and urine examination making it less likely that the higher incidence 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 ICD 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, the relatively more common AIDs i.e. eczema, psoriasis, vitiligo or asthma, were not consequently noted and/or reported by the hematologist. So these disease were not taken into this analysis.

In conclusion, this is the first study showing an elevated prevalence of AIDs 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 AIDs.(15) Better understanding of the pathophysiology of the development of AID in patients with SCD may help to design new interventions in downregulating of this inflammatory cascade and to prevent development of AIDs.

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Table 1. Patient characteristics of the cohort with or without autoimmune disease

	Total (n=338)	AID+ (n=36)	AID- (n=302)	P
Age (years)	33 (25-42)	32 (24-46)	33 (25-42)	0.903
Female	171 (51)	20 (56)	151 (50)	0.529
BMI (kg/m^2)	22,5 (20,2-25,1)	23,6 (21,3-27,3)	22,4 (20,1-24,9)	0.070
Genotype: HbSS HbSC $HbS\beta^+$ $HbS\beta^0$ Other	 168 (50) 110 (33) 31 (9) 29 (8) 6 (2)	 16 (44) 17 (47) 1 (3) 2 (6) 0 (0)	 152 (50) 93 (31) 30 (10) 27 (9) 6 (2)	 0.212
CRP (mg/L)*	3 (2-5)	2 (2-4)	3 (2-5)	0.173
ESR (mm/Hr)	7 (5-9)	8 (2-9)	6 (5-10)	0.857
Hemoglobin (g/dL)	10.0 (8.4-11.4)	10.3 (8.4-11.6)	9.8 (8.4-11.4)	0.462
Reticulocytes (10E9/L)	168.7 (111.9-272.8)	159.9 (101.7-222.9)	169.9 (115.2-274.7)	0.475
Creatinine (µmol/L)	67 (55-82)	68 (58-86)	67 (55-81)	0.384
LDH (U/L)	322 (246-423)	295 (249-402)	324 (246-424)	0.420
Bilirubin total	28 (16-50)	26 (16-45)	28 (16-51)	0.944
Ferritin (µg/L)	166 (81-376)	174 (100-289)	166 (79-394)	0.976
M/C ratio (mg/mmol)	1.16 (0.49-3.51)	1.46 (0.49-5.08)	1.15 (0.54-3.98)	0.901
Presence of autoantibodies#	14 (4)	14 (39)	NA	NA

Data presented as the median (interquartile range) or number (percentage) unless otherwise indicated. Other consists HbsBeta0delta, HbSE and HbSD. AID: autoimmune disease. BMI: body mass index. CRP: C-reactive protein. ESR: erythrocyte sedimentation rate. LDH: lactate dehydrogenase. M/C ratio: microalbuminuria/creatinine ratio. NA: not applicable. * CRP and/or ESR were measured in 24 patients with AID and 150 patients without AID. # Autoantibodies including: anti-thyroid peroxidase, thyroid stimulating autoantibodies, antinuclear antibodies (anti-double-stranded deoxyribonucleic acid antibodies) and antiphospholipid antibodies.

Table 2. Patients with the complications of sickle cell disease and treatment

	Total (n=338)	AID+ (n=36)	AID- (n=302)	P
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: Proliferative Non-proliferative Unspecified	122 (36) 33 (10) 63 (19) 27 (8)	18 (50) 5 (14) 8 (22) 5 (14)	104 (34) 28 (9) 55 (18) 22 (21)	0.002
Osteonecrosis	62 (18)	7 (19)	55 (18)	0.928
Priapism	18 (5)	0 (0)	18 (6)	0.323
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

Data presented as the median (interquartile range) or number (percentage) unless otherwise indicated. AID: autoimmune disease. VOC: vaso-occlusive crisis. ACS: acute chest syndrome. TRV: tricuspid regurgitation velocity.

Table 3. Treatment for autoimmune diseases

Autoimmune disease	**N=36**	**Treatment (number of patients using therapy)**
Myasthenia Gravis	1 (0.3)	-
Multiple Sclerosis	1 (0.3)	Glatiramer acetate
Sudden Deafness	7 (2.1)	Corticosteroids (n=2)
Hyperthyroidism	5 (1.5)	Block and replace therapy (n=3)
Hypothyroidism	5 (1.5)	Thyroid hormone suppletion (n=3) Radioactive jodine therapy (n=1)
Diabetes Mellitus type 1	2 (0.6)	Insulin therapy (n=2)
Sarcoidosis	4 (1.2)	Corticosteroids (n=2)
Inflammatory Bowel Disease	2 (0.6)	Corticosteroids/anti-tumor necrosis factor α (n=1); Anti-tumor necrosis factor α (n=1)
Systemic Lupus Erythematosus	2 (0.6)	Hydroxychloroquine (n=2)
Mixed Connective Tissue Disease	1 (0.3)	Corticosteroids, intravenous immuun globulins, rituximab (n=1)
Henoch Schönlein Purpura	1 (0.3)	-
Antiphospholipid Syndrome	3 (0.9)	Anticoagulant treatment (n=3)
Mediterranean Fever Syndrome	1 (0.3)	Anti-interleukin 1 (n=1)
Alopecia areata	3 (0.9)	Local steroids (n=3)

One patient suffered from alopecia areata and hypothyroidism. Another patient had hyperthyroidism and sudden deafness. If not mentioned, no therapy was needed/started.

Supplementary data

Supplementary table 1. Prevalence of autoimmune diseases, respectively in the cohort and in the literature

	Cohort (n=338)	**Control from literature (%)**
Autoimmune disease	**38 (10.7)**	**4.7**
Sudden Deafness(1)	7 (2.1)	0.005-0.02
Hyperthyroidism(2)	5 (1.5)	0.90
Hypothyroidism(3)	5 (1.5)	0.42
Sarcoidosis(4)	4 (1.2)	0.14
Alopecia areata	3 (0.9)	2.0
Antiphospholipid Syndrome(5)	3 (0.9)	0.05
Diabetes Mellitus type 1(6)	2 (0.6)	0.48
Inflammatory Bowel Disease(7)	2 (0.6)	0.096-0.32
Systemic Lupus Erythematosus(8)	2 (0.6)	0.22
Fever Syndrome(9)	1 (0.3)	0.001
Henoch Schönlein Purpura(10)	1 (0.3)	0.02
Myasthenia Gravis(11)	1 (0.3)	0.008
Mixed Connective Tissue Disease(12)	1 (0.3)	0.002
Multiple Sclerosis(13)	1 (0.3)	0.01

Data presented as number (percentage). The prevalence's, which has been shown in literature, are listed in percentages.

No cases were found for Guillain-Barré syndrome, granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, anti-glomerular basement membrane disease, autoimmune hepatitis, primary biliary cholangitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Behçet's disease, polyarteritis nodosa, Henoch Schonlein purpura, antiphospholipid syndrome, dermato-/polymyositis, scleroderma, pernicious anemia, autoimmune hemolytic anemia, immune mediated thrombocytopenic purpura and aplastic anemia.

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