Sickle cell disease-related organ damage occurs irrespective of pain rate: implications for clinical practice

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ABSTRACT

In daily clinical practice, the frequency of painful crises (pain rate) is an important parameter of sickle cell disease severity. We assessed the prevalence of sickle cell disease-related organ damage and complications and their relation to pain rate. Organ damage and history of vaso-occlusive complications were obtained via systematic screening of consecutive patients and by chart review. In 104 adult sickle cell patients pain rate was related to a history of acute chest syndromes, avascular osteonecrosis, iron overload, priapism and cholelithiasis. However, major disease-related complications, such as microalbuminuria and pulmonary hypertension, were detected in 23% and 24% respectively of patients without painful crises in the study period underlining the importance of systematic screening for developing organ damage in sickle cell patients irrespective of pain rate.

Key words: sickle cell disease, organ damage, pain rate, systematic screening.

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Introduction

Sickle cell disease (SCD) is heterogeneous in its presentation, with differences in the rate and severity of complications even within a single genotype. Even patients with the most severe genotype, HbSS, may vary in their clinical presentation from being continuously admitted for the management of acute complications to rarely requiring medical care. Both vaso-occlusion and chronic hemolysis are major determinants of SCD-related organ damage.[1] With the increasing life expectancy of sickle cell patients in the Western world the effect of accumulating organ damage on the quality of life and life expectancy is becoming an important factor in managing SCD.[2] Early recognition of developing organ damage is imperative in order to institute specific therapeutics in a timely manner. However, a landmark autopsy study in sickle cell patients demonstrated a high prevalence of organ damage that often had not been recognized during life by treating phycisians.[2] Although the frequency of the painful sickle cell crisis, which is the hallmark SCD-related clinical complication, is considered a parameter of disease severity, most patients do not frequently experience painful crises that require medical care. Nonetheless, sickle cell patients generally have a significantly reduced life expectancy suggesting that clinically significant organ damage accumulates irrespective of the pain rate.[4] As the pain rate is considered an important parameter of SCD severity, we analyzed whether the prevalence of SCD-related manifestations is related to the frequency of painful crises.

Design and Methods

Patients

Adult sickle cell patients visiting the Department of Haematology of the Academic Medical Center (AMC) in Amsterdam were considered eligible. After obtaining written and informed consent, patients were screened for SCD-related manifestations from July 2005 until December 2006. This study was approved by the internal review board of the AMC and carried out in accordance with the principles of the Declaration of Helsinki.

The CURAMA study group is a collaborative effort studying sickle cell disease in the Netherlands Antilles and the Netherlands. Participating centers: The Red Cross Blood Bank Foundation, Curaçao, Netherlands Antilles; The Antillean Institute for Health Research, Curaçao, Netherlands Antilles, The Department of Internal Medicine, Slotervaart Hospital, Amsterdam, the Netherlands; the Department of Vascular Medicine and the Department of Hematology, Academic Medical Center, Amsterdam, the Netherlands; the Department of Hematology, Erasmus Medical Center, Rotterdam, the Netherlands; the Department of Pathology, Groningen University Hospital, the Netherlands; the Department of Internal Medicine, the Laboratory of Clinical Thrombosis and Hemostasis, and the Cardiovascular Research Institute, Academic Hospital Maastricht, the Netherlands.

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SCD related manifestations

SCD-related manifestations were assessed by systematic screening and medical record review and defined as follows: *microalbuminuria:* urinary creatinine (mmol/L) to urinary albumin (mg/L) ratio >3.5 (males)/>2.5 (females) confirmed with 24 hours urine collection with microalbuminuria >30 mg/24 hours.[5] *Renal failure:* creatinine clearance <100 mL/min (Cockcroft and Gault).[6,7] *Pulmonary hypertension* (PHT): tricuspid regurgitation jet flow velocity (TRV) ≥2.5 m/sec in rest detected by Doppler echocardiography. PHT was considered absent with no or only trace TRV.[8] *Retinopathy:* presence of at least mild non-proliferative retinopathy.[9] Perceptive hearing loss: loss of >20 dB with no other explanation than SCD.[10] *Cholelithiasis:* presence of gallstones (ultrasound) or previous cholecystectomy because of cholecystolithiasis. *Iron overload:* plasma ferritin level >1000 µmol/L (on at least three occasions during steady state) and a history of >20 transfused packed cells.[11] *Acute chest syndrome:* defined as previously described[12] occurring between January 2002-January 2007. *Symptomatic avascular osteonecrosis*: local pain and reduced function with documented osteonecrosis of the femoral or humeral head (hip or shoulder X-ray) or a history of surgical intervention for osteonecrosis. *Leg ulcers:* chronic ulcers of the ankle not otherwise explained. *Priapism*: spontaneous painful erection requiring hospital care. *Stroke*: history of stroke confirmed by magnetic resonance imaging or computerized tomography.

Pain rate

Pain rate was assessed by calculating the cumulative number of admissions for painful crises (defined as typical musculo-skeletal/abdominal pain not otherwise explained)[4] from January 2002 until January 2007 and categorizing patients into 3 groups: 0 crises/year, >0 and <1 crises/year or ≥1 crises/year. Painful crises not requiring medical care were excluded.

Laboratory parameters

All laboratory data were obtained during routine outpatient visits at least four weeks after the last acute disease-related complication or blood transfusion. Fetal hemoglobin percentage (HbF%) was determined by cation-exchange high performance liquid chromatography,[13] and α-thalassemia screening was performed with a multiplex PCR assay.[14]

Statistical analysis

The most severe SCD genotypes (HbSS and HbSβ^0-thalassemia) were grouped together, as were the relatively severe genotypes (HbSC and HbSβ$^+$-thalassemia). Continuous data are presented as medians with their corresponding interquartile range. Between group differences were tested with the Mann-Whitney U test. Categorical data are presented as percentages with between group differences or statistical dependence tested with Fishers' Exact Test. Bivariate correlations of ordinal data were tested by determining the Spearman correlation coefficient (rs). *p* values below 0.05 were considered statistically significant. SPSS 12.0.2 (SPSS Inc, Chicago, IL, USA) was used.

Table 1. Patients' characteristics.

	HbSS (n=59)/ Sb^0-thal (n=5)	*HbSC (n=29) /Sb$^+$-thal (n=11)*	*p**
N	64	40	
Age (year)	27 (21-41)	29 (24-38)	0.674
Female (%)	63	60	0.799
Bloodparameters			
Hemoglobin (g/dL)	90 (8.1-9.8)	11.3 (10.6-12.2)	<0.0001
Reticulocytes (%)	8.2 (5.9-10.9)	2.8 (2.2-3.8)	<0.001
Leukocytes (x10^9/L)	9.0 (7.2-11.7)	6.9 (5.9-8.9)	0.001
Fetal hemoglobin (%)	8.1 (3.8-14.6)	1.7 (1.0-3.2)	<0.001
Lactate dehydrogenase (U/L)	370 (291-518)	232 (190-262)	<0.001
Creatinine (µmol/L)	51 (42-57)	63 (53-78)	<0.001
Organ damage (%)			
Microalbuminuria	34	5	0.001
Renal failure	8	3	0.402
Pulmonary hypertension	32	12	0.047
Retinopathy	24	61	0.001
Perceptive hearing loss	14	14	1.000
Iron overload	17	0	0.006
Cholelithiasis	66	23	<0.001
Clinical complications (%)			
Avascular osteonecrosis	16	8	0.223
Leg ulcers	14	0	0.012
Acute chest syndrome	32	18	0.167
Number of crises/year:			0.472
none	27	38	
less than one	47	43	
one or more	27	20	
Stroke	11	0	0.042
Priapism (% of males)	21	6	0.206

*Results are medians (interquartile range). *Mann-Whitney-test or Two-sided Fisher-exact test.*

Results and Discussion

One hundred and ten adult sickle cell patients were eligible of whom 6 were excluded due to incomplete data collection (Table 1). Apart from retinopathy (which was more prevalent in HbSC/HbSβ$^+$-thalassemia patients), most manifestations of SCD were significantly more often present in HbSS/HbSβ^0-thalassemia patients. PHT was detected in 32% and 12% of the HbSS-HbSβ^0 and HbSC/HbSβ$^+$ respectively, with a median TRV of 2.60 (2.50-2.69) m/sec. None of these patients had severe PHT (TRV>3.0 m/sec.). Although significantly more patients with frequent sickle cell crises used hydroxyurea, no difference in SCD-related organ damage was observed between patients with or without hydroxyurea (*data not shown*).

Avascular osteonecrosis, a history of acute chest syndrome, priapism and cholelithiasis, as well as iron overload were significantly related to pain rate (Table 2). The association between iron overload and the pain rate is probably the result of liberal blood transfusions for treating painful crises prior to instituting evidence-based management protocols for SCD in the Netherlands.[15] Importantly, microalbuminuria and PHT were detected

Table 2. Prevalence of sickle cell related complications.

N. crises/year	*0*	*0-1*	*≥1*	*p**
N	32	47	25	
α-thalassemia (%)	27	37	50	0.132
Sex (%male)	34	43	36	0.851
Hydroxyurea use (%)	13	11	36	0.014
Organ damage (%)				
Microalbuminuria	23	21	25	0.906
Renal failure	3	9	4	0.819
Pulmonary hypertension	24	32	16	0.614
Retinopathy	43	39	35	0.602
Perceptive hearing loss	16	17	6	0.376
Iron overload	6	6	24	0.041
Cholelithiasis	32	48	75	0.002
Clinical complications (%)				
Avascular osteonecrosis	3	13	24	0.019
Leg ulcers	13	6	8	0.512
Acute chest syndrome	0	0	40	<0.001
Stroke	9	2	12	0.803
Priapism (% of males)	9	5	44	0.041
Genotype (%)				
HbSS/Sβ^0-thal	53	64	68	0.241
HbSC/Sβ$^+$-thal	47	36	32	

*Numbers are percentages. *p value based on Spearman rank test.*

in 23% and 24% respectively of patients without painful crises during the study period. Furthermore, PHT and microalbuminuria were detected in 23% and 10% respectively of patients with no painful crises in the last five years. These patients had no leg ulcers, episodes of priapism or acute chest syndrome in the last five years and appeared clinically well according to case history and physical examination. Such patients would probably have been misclassified as having mild SCD. These data indicate that several major disease related complications[6,10] are not related to pain rate and occur even in a significant number of patients that seem clinically well. This underlines the importance of systematic screening for SCD-related complications even in clinically mildly affected patients.

Several shortcomings of this study need to be addressed. Firstly, the history of acute painful crises was limited to the last five years and only painful crises for which patients were admitted were evaluated. Therefore, the conclusions may not be extrapolated for the number of painful crises experienced at home or before the evaluated five year period. Secondly, the retrospective nature of this study has probably resulted in a selection bias. Thirdly, since this study was performed in a tertiary teaching hospital, referral bias cannot be excluded. However, given the similar prevalence of most SCD-related disease manifestations in our cohort to that reported in literature[4,8,16-23] the study seems to be representative. The prevalence of renal failure may, however, be underestimated as supranormal proximal tubular function characteristic of SCD probably results in an overestimation of glomerular filtration.[24] Also, the prevalence of retinopathy in our study is higher than that of previous reports which is probably due to the inclusion of mild non-proliferative retinopathy.[25] Lastly, other forms of sickle cell-related organ damage, such as pulmonary, hepatic and neurocognitive organ damage, have not been analyzed in this study. Nonetheless, we feel that the aforementioned factors do not influence the main findings of our study.

In conclusion, clinically relevant forms of organ damage, such as PHT and micro-albuminuria, occur irrespective of the frequency of painful crises in adults with SCD. Systematic screening for and evaluation of organ damage in all sickle cell patients seems indicated since many of the sickle cell-related complications may otherwise go unnoticed, thereby delaying the institution of potential therapeutic measures.

Authorship and Disclosures

EJvB, JBS and BJB wrote the article, AvdG was involved in gathering patient data and MRMG gave methodological and statistical advice and was specifically involved in the echocardiographic evaluation of the patients. The authors reported no potential conflicts of interest.

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