Sickle cell disease, pathophysiology and clinical complications
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Sickle cell disease related organ damage occurs irrespective of pain rate; Implications for clinical practice

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on behalf of the CURAMA study group.

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Abstract

In daily clinical practice, the frequency of painful crises (pain rate) is considered an important parameter of sickle cell disease (SCD) severity. We assessed the prevalence of SCD-related organ damage and complications and their relation to pain rate. Organ damage and the 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 and were not related to pain rate. The occurrence of several major SCD related disease manifestations is not related to painful crisis frequency underscoring the importance of systematic screening for developing organ damage in sickle cell patients irrespective of pain rate.
Introduction

Sickle cell disease (SCD) is heterogeneous in its presentation, with differences in the rate and severity of complications not only between different genotypes but within a single genotype as well. 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 haemolysis 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 not recognized during life by treating physicians.\(^3\) 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, in general sickle cell patients 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.
Chapter 3

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 as defined below. 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.

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 hour urine collection with microalbuminuria >30 mg/24 hours. Renal failure: creatinine clearance <100 ml/min (Cockcroft and Gault). Pulmonary hypertension (PHT): tricuspid regurgitation jet flow velocity (TRV) ≥2.5 m/s in rest detected by Doppler echocardiography. PHT was considered absent with no or only trace TRV. Retinopathy: presence of at least mild non-proliferative retinopathy. Perceptive hearing loss: loss of >20 dB with no other explanation than SCD. Cholecystolithiasis: 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. Acute chest syndrome (ACS): defined as previously described occurring between January 2002-January 2007. Symptomatic avascular osteonecrosis: local pain and reduced function 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) from January 2002 until January 2007 and categorizing patients into three groups: no crises, less than one crisis, or one or more crises a year (on average). Painful crises not requiring medical care were excluded.
Sickle cell disease related organ damage occurs irrespective of pain rate

**Laboratory parameters**
All laboratory data were obtained during routine outpatient visits at least 4 weeks after the last acute disease related complication or blood transfusion. Foetal haemoglobin percentage (HbF%) was determined by cation-exchange high performance liquid chromatography\(^\text{13}\), and \(\alpha\)-thalassaemia screening was performed with a multiplex PCR assay.\(^\text{14}\)

**Statistical analysis**
The most severe SCD genotypes (HbSS and HbS\(\beta\)\(^-\)-thalassaemia) were grouped together, as were the relatively genotypes (HbSC and HbS\(\beta\)\(^+\)-thalassaemia). Continuous data are presented as medians with their corresponding interquartile range (IQR). 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 (\(r_s\)). P-values below 0.05 were considered statistically significant. SPSS 12.0.2 (SPSS Inc, Chicago, IL) was employed.
Chapter 3

Results and Discussion

One hundred and ten adult sickle cell patients were eligible of whom 6 were excluded due to incomplete data collection, leaving 104 included sickle cell patients (see Table 1).

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<td>N</td>
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<tr>
<td>Age (year)</td>
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<tr>
<td>Female (%)</td>
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<tr>
<td>Blood parameters</td>
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<tr>
<td>Haemoglobin (g/dL)</td>
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<tr>
<td>Reticulocytes (%)</td>
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<tr>
<td>Leucocytes (×10^9/L)</td>
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<tr>
<td>Fetal Haemoglobin (%)</td>
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<tr>
<td>Lactate Dehydrogenase (U/L)</td>
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<tr>
<td>Creatinine (umol/L)</td>
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<tr>
<td>Organ damage (%)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
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<tr>
<td>Renal failure</td>
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<tr>
<td>Pulmonary hypertension</td>
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<tr>
<td>Retinopathy</td>
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<tr>
<td>Perceptive hearing loss</td>
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<tr>
<td>Iron overload</td>
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<tr>
<td>Cholelithiasis</td>
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<tr>
<td>Clinical complications (%)</td>
</tr>
<tr>
<td>Avascular osteonecrosis</td>
</tr>
<tr>
<td>Leg ulcers</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
</tr>
<tr>
<td>Number of crises /year:</td>
</tr>
<tr>
<td>- none</td>
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<tr>
<td>- less than one</td>
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<tr>
<td>- one or more</td>
</tr>
<tr>
<td>Stroke</td>
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<tr>
<td>Priapism (% of males)</td>
</tr>
</tbody>
</table>

Results are medians (interquartile range). *Mann-Whitney-test or Two-sided Fisher-exact test.
Sickle cell disease related organ damage occurs irrespective of pain rate

Apart from retinopathy (which was more prevalent in HbSC/HbSβ⁺-thalassaemia patients), most manifestations of SCD were significantly more often present in HbSS/HbSβ⁰-thalassaemia patients. PHT was detected in 32% and 12% of the HbSS-HbSβ⁰ and HbSC/HbSβ⁺ respectively, with a median TRV of 2.60 (2.50-2.69) m/s. None of these patients had severe PHT (TRV>3.0 m/s). 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 ACS, 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 likely the result of liberal blood transfusions for treating painful crises prior to instituting evidence based management protocols for SCD in the Netherlands. Importantly, microalbuminuria and PHT were detected 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 did not have leg ulcers, episodes of priapism or ACS in the last 5 years and appeared clinically well based upon history taking and physical examination. Such patients would likely have been misclassified as having mild SCD. These data indicate that several major disease related complications are not related to pain rate and occur even in a significant number of patients that seem clinically well, underscoring 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 5 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 5 year period. Secondly, selection bias has likely occurred given the retrospective nature of this study. 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 it seems representative. The prevalence of renal failure may, however, be underestimated as the characteristic supranormal proximal tubular function characteristic of SCD likely results in an overestimation of glomerular filtration. Also, the prevalence of retinopathy in our study is higher as compared to previous reports which is likely due to the inclusion of mild non-proliferative retinopathy. Lastly, other forms of sickle cell related organ damage such as pulmonary, hepatic and neurocognitive organ damage have not been analysed 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.

### Table 2. Prevalence of sickle cell related complications.

<table>
<thead>
<tr>
<th></th>
<th>No. of crises/year</th>
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<tr>
<td></td>
<td>0</td>
<td>0.1</td>
<td>≥1</td>
</tr>
<tr>
<td>N</td>
<td>32</td>
<td>47</td>
<td>25</td>
</tr>
<tr>
<td>Alpha-thalassaemia (%)</td>
<td>27</td>
<td>37</td>
<td>50</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>34</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>Hydroxyurea use (%)</td>
<td>13</td>
<td>11</td>
<td>36</td>
</tr>
</tbody>
</table>

**Organ damage (%)**
- Microalbuminuria: 23, 21, 25 | 0.906
- Retinal 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-thal: 53, 64, 68 | 0.241
- HbSC/Sβ-thal: 47, 36, 32 | 0.241

Numbers are percentages. *P*-value based on Spearman rank test.
Sickle cell disease related organ damage occurs irrespective of pain rate

Reference List


Sickle cell disease related organ damage occurs irrespective of pain rate.