Measuring complications of sickle cell disease
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Measuring disease severity in patients with sickle cell disease: a systematic review

Submitted

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ABSTRACT

Sickle cell disease (SCD) is a heterogeneous disease influenced by genetic and environmental factors. The aim of this study was to identify all indices used to measure disease severity in SCD and to evaluate their methodological foundations and utility for clinical research.

Studies containing a composite severity index to measure SCD severity were retrieved from MEDLINE up to October 2008 and from reference lists of relevant articles. Articles in which an index of sickle cell disease was used to distinguish patients according to their overall severity status were eligible for inclusion. The indices were analysed descriptively and their validity was assessed by modern clinimetric standards.

The full text of 118 articles was evaluated and 29 articles (28 in English), containing 30 indices, were included in the review. Of 30 identified indices, containing a total of 51 component items, 26 indices (87%) were not validated. In only five articles a definition of SCD severity was presented, and all definitions were different.

There is an urgent need for a comprehensive and rigorously validated instrument to measure disease severity in SCD. Such an instrument is essential for etiological research that will enable the construction of prognostic models.
INTRODUCTION

The heterogeneous phenotype in patients with sickle cell disease (SCD) is determined by the interaction of genetic and environmental factors, of which some have been identified (1-5). It is essential to know which determinants are associated with severe disease, so that prognostic models can be constructed. These prognostic models may help to identify patients who are at increased risk for a severe disease course before irreversible organ damage has occurred. These patients may benefit from early treatment with disease modifying therapies.

Unfortunately, prognostic models are not fully developed yet and more etiological research is needed. However, there is a critical barrier to the performance of etiological research in SCD as there is no established definition of “a severe phenotype”. This makes it difficult to define a valid outcome measure that can be quantified (6). As different investigators use different outcomes, it is very difficult to compare results across studies. Adverse outcomes like death and stroke have been used as outcomes in the past, but nowadays they are increasingly rare, especially in children. We require a contemporary definition of the severity of SCD (6).

Composite indices, capturing clinical events, laboratory tests and treatment data, have been used to measure overall disease severity. The content and methodological quality of these indices appears to be variable. We performed a systematic review to identify all existing severity indices for SCD and to evaluate the content and methodological quality of these indices.

A valid index in this field should distinguish patients according to their severity status, cumulative up to the time point when outcome is evaluated, covering all items that are apparently important, and demonstrate a high correlation with similar measurements of severity. The severity measured by such an index can then be used as an outcome measure in etiological research when determinants of “a severe phenotype” are studied.

METHODS

We searched Medline (1966-October 2008) combining the search term “exp anaemia, sickle cell/ [MeSH]” with “exp health status indicators/ [MeSH]” and with “severity OR severe OR clinical spectrum”. Reference lists were used to identify additional articles. The search was not limited by publication date or language. Two reviewers (XT and KF) independently reviewed all abstracts to establish eligibility.
Articles in which an index of SCD, capturing overall disease severity, was used to distinguish patients according to their current severity status were eligible for inclusion. An index was defined as a list of items to which numerical values were attached (e.g. CVA absent = 0, CVA present = 1). If a severity index was described in more than one article, we included the article in which most information on the development of the index was given.

Information on the type of study, the aim and description of the index, item definition and confounding, scoring and summarizing the items and the validity of the index was extracted independently in pairs by four reviewers (XT, HL, JH, KF) and discrepancies were resolved by discussion. Items were considered to be confounded when factors beyond the sickle cell disease process importantly influenced their occurrence. Reviewers assessed the clinimetric validity of the indices evaluating content validity, concurrent validity, construct validity and reproducibility (7), using established quality criteria (8).

Content validity, defined as the extent to which the disease severity was comprehensively sampled by the items (9), was considered adequate for indices that ensured a wide coverage of relevant items by examining the literature and consulting experts (8;10). Criterion validity was defined as the extent to which scores on a particular instrument relate to the “gold standard”, the best measurement instrument available (8). Since there is no “gold standard” for severity of SCD, we assessed whether the index demonstrated high agreement with another severity index that was used at the same time (concurrent validity) (7). Construct validity is the consistency of scores on a particular index with other measurements, based on hypotheses concerning the concepts that are being measured (7;11). E.g. in the case of SCD severity would be hypothesized to be associated with low haemoglobin levels or high LDH levels. Construct validity was considered adequate for indices for which < 25% of postulated hypotheses could be refuted (8).

The results of any reported tests for (intrarater, interrater and test-retest) reproducibility were recorded. Reproducibility was considered adequate when two measurements in time (between 1 and 4 weeks apart for test-retest reliability) showed high agreement (ICC > 0.8 for test-retest reliability and ICC > 0.7 for inter-observer reliability).

RESULTS

The Medline search yielded 1618 abstracts from which we selected 98 articles (Figure 1), as it was clear from the abstract that the article did not contain an index measuring severity in SCD disease in the remaining 1520 articles. Reference tracking resulted in 20 additional articles. After evaluation of the full text of these 118 articles, 29 articles (28
in English) were included in the review (Table 1). A frequently cited prognostic study by Miller did not meet our inclusion criteria, since this study used four separate events as proxies for severe sickle cell disease (death, stroke, 2 or more painful vaso-occlusive events/year and one or more acute chest syndromes/year). As the purpose of our review was to identify and evaluate composite severity indices that measure overall SCD severity, studies using separate events as an outcome were not eligible for inclusion (2).

Figure 1. Flow diagram of data extraction

Index types
In two articles the main objective of the study was to develop and evaluate a severity index for SCD (12;13). The other studies investigated the association between various determinants, e.g. laboratory values or geographic region of origin, and SCD severity. In those articles the severity indices were used as an outcome measure (Table 1). The concept that the severity index was intended to measure was defined by five authors (17%) (14-18) (Table 2) and only one article explicitly reported its measurement goal, which was classification of disease severity (13). None of the studies specified the target population for which the index was intended.

Items used in the indices
The five most frequently used items were painful vaso-occlusive crises (87% of the indices), central nervous system abnormalities, i.e. CVA, cerebral vasculopathy, seizures, encephalopathy (67% of the indices), aseptic/avascular necrosis of the bone (53% of the indices), acute chest syndrome (43% of the indices) and blood transfusions (40% of the indices). The characteristics of the included indices are given in Table 3 (see appendix page 105). The items were clearly defined in six indices (20%) (13;14;17-20).
Table 1. Description of the included studies: main objective and number of patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Main objective*</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson (21)</td>
<td>To evaluate the effect of persistence of significant amounts of HbF on the clinical severity of the manifestations of SCD</td>
<td>61</td>
</tr>
<tr>
<td>Steinberg (19)</td>
<td>A report of clinical and laboratory findings of patients with mild SCD</td>
<td>21</td>
</tr>
<tr>
<td>Hebbel (14)</td>
<td>To assess whether red cell adherence to endothelium is related to clinical manifestations of SCD</td>
<td>33</td>
</tr>
<tr>
<td>Cameron (12)</td>
<td>To compare the qualitative perception of severity in SCD with quantitative indices using objective criteria</td>
<td>24</td>
</tr>
<tr>
<td>Odenheimer (28)</td>
<td>To evaluate the relationship between haematological variables and disease severity</td>
<td>140</td>
</tr>
<tr>
<td>Roberts (29)</td>
<td>To examine HbF level and MCV in patients with HbSS from different regions of Saudi Arabia and to relate these findings to clinical and other haematological features</td>
<td>81</td>
</tr>
<tr>
<td>El-Hazmi (30)</td>
<td>To determine the features of SCD in children from the south-western region of Saudi Arabia, and to investigate the influence of other associated genetic abnormalities on the nature of SCD in this population</td>
<td>137</td>
</tr>
<tr>
<td>Phillips (15)</td>
<td>To correlate the frequency of painful events and the extent of end organ failure in SCD with rheologic properties of packed suspensions of sickle cells</td>
<td>16</td>
</tr>
<tr>
<td>Phillips (16)</td>
<td>To evaluate the relationship of plasma levels of tocopherol to disease severity in SCD</td>
<td>27</td>
</tr>
<tr>
<td>El-Hazmi (31)</td>
<td>To compare the populations with SCD of the eastern providence and the south-western providence of Saudi Arabia and to see if severity was different in the two populations and if a reason could be found for this</td>
<td>94</td>
</tr>
<tr>
<td>Hedo (32)</td>
<td>To correlate acute phase reactants with severity of homozygous SCD</td>
<td>73</td>
</tr>
<tr>
<td>Olatunji (33)</td>
<td>To compare clinical severity in patients with SCD having persistent hepatomegaly and those without hepatomegaly</td>
<td>80</td>
</tr>
<tr>
<td>Al-Momen (34)</td>
<td>To estimate vitamin B12 levels in patients with severe SCD</td>
<td>85</td>
</tr>
<tr>
<td>Houston (35)</td>
<td>To compare homocysteine levels in different subgroups of patients with SCD</td>
<td>99</td>
</tr>
<tr>
<td>Anyaegbu (36)</td>
<td>To study how the severity of SCD relates to neutrophil count and function</td>
<td>64</td>
</tr>
<tr>
<td>Moore (37)</td>
<td>To determine whether the measurement of HLA-1 heterodimers would offer further support for the presence of chronic inflammation in patients with SCD in steady state and after a recent crisis</td>
<td>50</td>
</tr>
<tr>
<td>Diop (38)</td>
<td>Evaluation of the clinical severity of sickle cell anaemia patients living in Senegal</td>
<td>60</td>
</tr>
<tr>
<td>Jardin (39)</td>
<td>To establish the clinical phenotype for Senegal, to link it to haplotype, level of Hbf and age</td>
<td>40</td>
</tr>
<tr>
<td>Grant (40)</td>
<td>To investigate depression and health care use in patients with SCD</td>
<td>43</td>
</tr>
<tr>
<td>Schnog (17)</td>
<td>To determine whether Duffy phenotype influences the severity of SCD</td>
<td>51</td>
</tr>
<tr>
<td>Lee (18)</td>
<td>To investigate whether CD36 expression on reticulocytes and red blood cells modulates the clinical course of SCD</td>
<td></td>
</tr>
<tr>
<td>Wali (41)</td>
<td>To correlate splenic function in Omani children with SCD to clinical severity and other parameters (haematological parameters, alpha-thalassaemia trait etc.)</td>
<td>72</td>
</tr>
</tbody>
</table>
Measuring disease severity: a systematic review

Table 1. (cont)

<table>
<thead>
<tr>
<th>Author</th>
<th>Main objective*</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inati (20)</td>
<td>To examine the correlation between the clinical manifestation of SCD and the beta-globin gene haplotypes</td>
<td>50</td>
</tr>
<tr>
<td>Day (13)</td>
<td>To develop and evaluate a SCD assessment instrument</td>
<td>3</td>
</tr>
<tr>
<td>Panepinto (42)</td>
<td>To determine the validity of child health questionnaire as a measure of health related quality of life (HRQL) in SCD by examining the relationship between HRQL and disease severity</td>
<td>95</td>
</tr>
<tr>
<td>Pearson (22)</td>
<td>To examine the associations among autonomic reactivity, clinical severity, family stressors and mental health symptoms in children with homozygous SCD</td>
<td>19</td>
</tr>
<tr>
<td>Oparinde (43)</td>
<td>To determine a possible role for hepatic enzymes as biochemical indices of severity</td>
<td>75</td>
</tr>
<tr>
<td>Sibenga (44)</td>
<td>To identify complementary and alternative therapies that are currently used by families for children with SCD and to investigate SCD families’ interest in complementary and alternative therapies</td>
<td>57</td>
</tr>
<tr>
<td>Afenyi-Annan (45)</td>
<td>To examine whether the Duffy-negative genotype leading to the Fy(a-b-) phenotype was associated with clinical disease severity and organ damage in patients with SCD</td>
<td>249</td>
</tr>
</tbody>
</table>

*As stated in the Introduction of the article.

Table 2. Concept of severity measured, as reported in 5 out of 29 articles

<table>
<thead>
<tr>
<th>Author</th>
<th>Concept of severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hebbel (14)</td>
<td>Clinical manifestations of SCD due to micro vascular occlusions</td>
</tr>
<tr>
<td>Phillips (15)</td>
<td>End organ failure score</td>
</tr>
<tr>
<td>Phillips (16)</td>
<td>Important vaso-occlusive manifestations</td>
</tr>
<tr>
<td>Schnog (17)</td>
<td>Vaso-occlusive score</td>
</tr>
<tr>
<td>Lee (18)</td>
<td>Complications of SCD classically related to vascular occlusions</td>
</tr>
</tbody>
</table>

Some items were only applicable to a proportion of the patient population (e.g. priapism, pregnancy terminating in live birth).

Many items were influenced by factors beyond the sickle cell disease process (confounded). Vaso-occlusive crises were generally scored when they led to hospitalisation and treatment with analgesics. Hospitalisation, however, may depend on many factors beyond the severity concept, such as physician experience and preference, family situation, coping skills and socio-economic background. Likewise, transfusion history reflects available resources and physician preferences.

The items were scored either as incidence during a certain time period (mostly one or two years) or as cumulative incidence over life time. In 19 of 24 (79%) indices that...
included diagnostic tests, it was unclear whether diagnostic tests (i.e. cardiac ultrasound, cerebral MRI) had been performed in all patients or only in those with clinical symptoms. For 8 of 11 (72%) indices that included the results of laboratory tests, it was not stated whether blood sampling had taken place in a stable clinical situation.

The number of items varied from three to 20 (21;22) per index. Taken together, the indices contained 51 items. In 11 indices (37%) all constituent items were contributing equally to the total sum score. In 19 indices (63%) items were scored differentially, by allocating more weight to specific items in comparison to others. However, the rationale for weighting of the items was not explained. Eight scores (27%) did not have an upper limit since their calculation incorporated the cumulative number of certain events e.g. transfusions or hospitalisations.

Validity
Four indices (13%) had been validated (12;13;22). Although these four indices performed well on specific validity criteria, none of the indices met all generally accepted validity criteria. Content validity was adequate for two indices, ensured by consultation of respectively five and 15 clinicians and scientists (13;22). Construct validity proved adequate for two indices when the scores of 24 patients were compared to a subjective ranking by four professionals (12). Reproducibility was tested for one index and proved adequate (12).

DISCUSSION
In this systematic review we found 30 composite severity indices for SCD, containing 51 different items ranging from haematological parameters to socio-economic consequences of the disease. The large number of indices reflects the lack of consensus on the concept of SCD severity and the best way to measure this concept. None of the indices was fully validated. For etiological research there is an urgent need for a comprehensive and rigorously validated instrument to measure disease severity in SCD that can be used as an outcome measure.

A definition of the concept of severity to be measured was lacking in most articles (n=25, 86%). A severity index needs readily identifiable and conceptually strong underpinnings (23). Although some might challenge a global severity concept, “most observers would share a ‘gut feeling’ about a severely affected patient”, as Serjeant states (24). As is evident from the results of this review, many researchers have tried to assemble a severity score that reflects this ‘gut feeling’. The lack of consensus on a definition of severity should be solved before an instrument that can measure it can be developed.
Selection of the items to be included in the index follows from the definition of the concept to be measured. For validity of the index, all relevant items reflecting the concept should be incorporated, and defined clearly. In 24 indices (80%) from this review the component items were not clearly defined, which leads to misclassification and imprecise measurements. Many of the items that are used in the indices of this review are confounded by factors beyond the severity of SCD, especially by health care interventions. Neonatal screening programs influence the average age at diagnosis, penicillin prophylaxis reduces the incidence of pneumococcal infections, blood transfusion schemes prevent CVAs, and the use of hydroxyurea decreases the incidence of vaso-occlusive pain crises. Items that are confounded will reduce the power of the index to distinguish patients from each other, and the influence of confounders should preferably be minimized. Since the influence of the health care system is substantial, this implies that scores obtained by a severity index should be used with great caution when comparing populations with different health care systems.

Any index will be subject to the effect of age because of floor/ceiling effects; items that are absent in the majority of patients from one age group may well serve to discriminate between patients in another age group. As patients grow older and progress from the neonatal period through childhood and adolescence into adulthood, they will all suffer from painful vaso-occlusive crises, but different complications occur. Before the age of 5 years spleen infarction, increased susceptibility to infection, acute splenic sequestration, dactylitis and vaso-occlusive crises, acute chest syndrome (ACS) and renal concentration deficits are the most striking features of SCD (25-27). In late adolescence and early adulthood, patients may experience leg ulceration and priapism, whereas kidney failure and irreversible organ damage of the lungs, eyes and other organs takes its toll in patients over the age of 30. This implies that a severity index may need to be targeted for age groups to perform/discriminate best.

In order to increase our understanding of SCD and develop prognostic models, we need to identify the determinants of a severe phenotype. Many research groups are working hard to find these determinants, using different outcome measures. It would be far more effective if results of these studies could be compared quantitatively and pooled. For this purpose, consensus on the concept of severity in SCD and an instrument or index to measure it is necessary. Efforts should be made to reach international consensus on a definition of SCD severity and a core set of items to measure this concept should be developed. As a starting point we propose to define the concept of severity as “the rate and extent of reversible and irreversible damage to organs brought on by the sickle cell disease process, resulting in impairment requiring medical intervention”. The index measuring this should contain well defined objectively measurable clinical variables, with minimal confounding by factors beyond the SCD process. Only the results of robust diagnostic tests, including laboratory tests, evaluating organ damage qualify to meet
these criteria. To capture the age-dynamics we propose to incorporate additional items concerning the frequency or “rate” of reversible symptoms in the index when it is used for paediatric patients.

This review reveals the urgent need to reach international consensus on a definition of SCD severity and a comprehensive and rigorously validated instrument to measure disease severity in SCD.
REFERENCES


