Measuring complications of sickle cell disease
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Summary and future perspectives
SUMMARY

Sickle cell disease (SCD) is an autosomal recessive inheritable disorder that predominantly affects the black population. In The Netherlands it mainly affects immigrants from Surinam and from Central and Western Africa. SCD is caused by a single nucleotide mutation (GAG for GTG) in the sixth codon of the gene encoding β-globin and is characterized by chronic haemolysis and vaso-occlusion throughout all organs.

SCD is a heterogeneous disorder leading to a variety of acute and chronic complications. Some patients experience only mild complications, whereas others suffer from severe life threatening complications.

This thesis describes the incidence and prevalence, mortality, presenting symptoms, the application of modern clinimetrics in measuring disease severity, cerebral blood flow measurement, and the implications on daily life of caretakers of children with SCD.

Chapter 1 is an introduction to SCD. Since this thesis mainly involves paediatric patients, the introduction starts with information about the incidence and prevalence of SCD disease in children in The Netherlands, followed by mortality and a pathophysiological description of the disorder. Subsequently, the morbidity and the consequences of chronic haemolysis and vaso-occlusion for various different end-organs are described. Finally, the current challenges in clinical management of patients with SCD are reviewed. The scope of this thesis is defined.

In Chapter 2 the prevalence and incidence of children with SCD in The Netherlands are estimated using the capture-recapture method. Also the proportion of children who have no access to the highest quality of care in relation to neonatal screening is evaluated. Cross-sectional survey of three data sources were used to estimate the prevalence and incidence of SCD in The Netherlands: the Dutch Paediatric Surveillance Unit, a survey among laboratories and a survey among Dutch paediatric practices. Children with SCD aged <18 years on January 1st 2003 and newly diagnosed children from January 1st 2003 onwards were included in the study.

The prevalence of children with SCD in 2003 was 1:5152 (95%CI 1:4513 - 1:6015). In the four years period thereafter, the yearly incidence was 1:2011 (95%CI 1:1743 - 1:2376). About 60% of the newly diagnosed SCD children were not reported by paediatricians. Nearly one third (27%) of the newly diagnosed cases were born outside The Netherlands and thus evaded neonatal screening.

This study demonstrates that prevalence and incidence of SCD in children in The Netherlands is higher than previously estimated and it demonstrates that not all children
receive comprehensive care. Most newly diagnosed children live in urban parts of the Netherlands, are of different ethnic backgrounds or are born in countries without a neonatal screening program. Furthermore, it is important to realise that a considerable number of children, who are at risk of serious infant morbidity, does not benefit from optimal care commencing at birth. One of the remaining questions is whether adjuvant screening programs should be initiated, e.g. programs directed at children that are adopted or children of immigrant families. Although neonatal screening on SCD is an important step towards improvement of quality of care, physicians and health planners should be aware of the current dichotomy in the care of these children with a serious chronic illness.

In Chapter 3 the presenting symptoms of SCD at diagnosis and the age at diagnosis are described. Over the past decades the prevalence of SCD in Europe has increased significantly due to immigration of families with SCD from many countries around the world. Still, many European physicians are not familiar with the presenting symptoms of this disease. As there is no neonatal screening program in most European countries, the diagnosis is usually made when medical care is sought for symptoms. Early recognition of the specific symptoms is important, because the prescription of adequate antibiotic prophylaxis combined with parental education, can reduce disease-related morbidity. In contrast, children detected by neonatal screening can start with penicillin prophylaxis at an early age, which decreases the complications of feared pneumococcal septicaemia that occurs in patients with SCD as a result of functional hyposplenism.

We evaluated the presenting symptoms and the age of diagnosis in 88 consecutive patients in the paediatric department of the Academic Medical Center in Amsterdam. The group comprised 67 patients with HbSS/HbS-β0-thalassaemia and 21 patients with HbSC/HbS-β+-thalassaemia, both groups diagnosed after the occurrence of symptoms. In the majority of the patients (72%) the diagnosis was based on SCD specific symptoms, such as painful crises, jaundice, anaemia and pneumococcal septicaemia/meningitis. Painful crisis was the most common presenting symptom. The median age at diagnosis in the total patient group was 25 months. However, in the group of children who were diagnosed by SCD specific symptoms (n=63) those with HbSS/HbS-β0-thalassaemia were diagnosed at a younger age (24 months) than those with HbSC/HbS-β+-thalassaemia (45 months).

An ongoing longitudinal study, including only patients diagnosed by neonatal screening, will give a more accurate estimate of the frequency of presenting symptoms in SCD such as dactylitis and painful crisis because bias will be minimal (i.e. reduced chance of fatalities before diagnosis in children diagnosed by neonatal screening). However, children diagnosed in the neonatal period will be less likely to present with pneumococcal infections.
**Summary and future perspectives**

**Chapter 4 and 5** discuss the application of modern clinimetrics to measure the severity of a complex disease. To increase our knowledge of the determinants of severity of SCD we need studies with a clear outcome. Knowledge of these determinants will help to unravel the pathophysiological mechanisms underlying the disease process, to identify novel targets for therapeutic or prophylactic interventions, and to improve patient care.

In **Chapter 4** we systematically review the literature to identify all indices used to classify SCD patients according to disease severity and we evaluate the content and methodological quality of these indices. A large number of studies, containing a composite severity index, was identified but none of these indices was fully validated. This is a major problem in SCD research due to the fact that there is no generally accepted index. To compare and to pool the results of different research groups, efforts should be made to reach international consensus on a definition of SCD severity. A severity index should contain a core set of items to measure this concept. The systematic review contributes to the development of a validated severity index by providing recommendations for its clinimetric prerequisites. It also contains generic lessons on the application of modern clinimetrics to the measurement of disease severity in any complex disorder.

**Chapter 5** describes the development and validation of a paediatric severity index for sickle cell patients. Since most children with SCD have not yet developed irreversible organ damage that occurs in adults such as pulmonary hypertension, retinopathy or cardiomyopathy, we developed a severity index incorporating items applicable to children. We defined the concept of severity as “the rate and extent of reversible and irreversible damage to organs related to SCD, resulting in impairments that require medical intervention”. The final index consists of 20 items, with 11 items concerning the cumulative lifetime incidence of organ damage (e.g. avascular bone necrosis, cerebral infarcts), four items concerning the number of recurrences of SCD-related complications over a period of two years (e.g. acute chest syndrome, painful crises) and five items concerning the outcome of laboratory tests (e.g. Hb).

Three different weighing systems to summarize the items were used (score A, B and C). First, all items were summed with an equal weight of 1, leading to score A. Secondly, acute life-threatening events and neurological complications were assigned more weight, receiving a score of 10, with all other items assigned a score of 1 (score B). Finally, items were weighted according to the severity of the different complications and the frequency of occurrence, ranging from 5-50 points (score C).

The index adequately differentiates between patient groups classified for severity by experts and by an existing index (Sickle Cell Disease Assessment Instrument: SCDAI). Moreover, the index differentiates between patients classified by genotype (HbSS/HbS-
\(\beta^0\)-thalassaemia versus HbSC/HbS-\(\beta^+\)-thalassaemia) or by the number of alpha-gene deletions. There was no significant correlation between the scores and current age and a weak correlation with an existing death risk score (1).

Score C, calculated with the most refined weighting system, i.e. differentiating between items according to severity and the frequency of occurrence of complications, discriminates best between the patient groups when classified by the experts, the SCDAI, genotype or alpha-gene deletions. Contrary to our expectation we did not find a higher severity score in older children. This lack of association between age and severity has also been observed by Cameron et al., who reported a lack of correlation between their severity index and age in a cross-sectional study (2). This should be interpreted as an indication of the heterogeneity in the clinical phenotype of SCD.

Further validation of this index is needed, e.g. in a large prospective cohort study of patients diagnosed early by neonatal screening. After further refinement and adaptation of this index, it may form a base from which international consensus can be reached on outcome assessment in studies of paediatric patients. It will be crucial to develop consensus on uniform outcome measures using widely accepted scales, since this enhances the comparability of results across studies and enables statistical pooling in future meta-analyses.

In Chapter 6 we evaluated cerebral blood flow (CBF) by Continuous Arterial Spin Labeling (CASL) at 3.0 Tesla MRI in children with SCD. Cerebral infarction is the most devastating complication of SCD, affecting approximately 30% of SCD patients by the age of 18 years (3-7). Most of these infarcts are not accompanied by focal neurological deficits and are therefore often called silent infarcts. In fact, this is a misnomer since they have been associated with diminished neurocognitive functioning and an increased risk of recurrent (overt) infarcts (8;9).

The theoretical concept behind cerebral infarction is as follows: in patients with anaemia adequate oxygenation of the brain tissue is presumably preserved by vasodilation of the cerebral vasculature. When reductions in arterial pressure arise or metabolic demands increase, there is limited reserve for further vasodilation to assure adequate oxygen supply to the brain. The ensuing ischemia predisposes to cerebral infarctions. Cerebral blood flow (CBF) and the Oxygen Extraction Fraction (i.e. the fraction of oxygen removed by the brain as the blood passes by) indicate the metabolic demands of the brain. Areas with a decreased CBF (compared to the opposite hemisphere) could be at risk of developing cerebral infarcts, as the metabolic demand of the brain can only be satisfied when the Oxygen Extraction Fraction increases.
We investigated CBF in 24 children with SCD and compared the CBF to 12 healthy children using CASL-MRI at 3.0 Tesla. Using this technique we could not confirm a higher CBF in SCD patients, but we did find hemispheric asymmetry in 58% of the patients compared to no asymmetry in the control subjects.

A longitudinal study should be performed to evaluate the clinical significance of this anatomical asymmetry in CBF in SCD children. CBF in combination with the Oxygen Extraction Fraction could be even more specific in predicting which children are at the highest risk of developing infarcts. Eventually the role of regular blood transfusions, hydroxyurea treatment and haematopoietic stem cell transplantation in patients with hemispheric asymmetry in CBF and thereby in the prevention of “silent” cerebral infarcts, should be evaluated in future studies.

Chapter 7 addresses the quality of life of caregivers of children with SCD. Taking care of children with chronic diseases is highly demanding and has practical and emotional consequences for the parents or other caregivers (10;11). Young children with a chronic condition are dependent on their caregivers for additional care and monitoring of their health. The quality of care they receive may be affected by the caregivers’ well-being. It is important to address the caregivers’ well-being and to identify the needs for additional support, both for the health and well-being of caregiver and child (12;13).

In this study we evaluated the quality of life of 54 caregivers of 60 children with SCD and of 28 controls from the same socio-economic status (SES) and ethnicity. To measure quality of life we used the TAAQoL questionnaire (14) for persons 16 years and older. Quality of life data of the SCD caregivers were also compared to the Dutch norm population (n=700).

Caregivers of SCD patients had a lower score on all QoL subscales compared to the Dutch norm population (P<0.005 on all subscales). These differences may be due to demographic differences, such as a lower SES and more single parenthood. Compared to the SES control group, caregivers of SCD patients had a lower QoL on the subscales depressive moods, daily activities, vitality, sleeping, happiness and cognitive functioning. Feelings of guilt, lack of sleep, limitations of daily activities due to caregiving of a chronically ill child could attribute to these lower scores.

Studying QoL in caregivers of chronically ill children is extremely important, since adequate functioning of the mother is important for the social, emotional and cognitive functioning of a child (15). In order to accomplish appropriate care, help from various health care providers is essential. Doctors and other health care workers should be aware of the emotional and functional needs of these caregivers. Improved support may be needed to ameliorate the QoL of SCD caregivers by decreasing caregiving burden.
Interventions aimed at helping parents to gain access to financial benefits, appropriate housing, stimulate employment of caregivers of chronically ill children, promoting good health of the caregivers and stress management might aid to reducing this burden.

FUTURE PERSPECTIVES

In the past decades life expectancy of patients with SCD has increased. Comprehensive care at specialised sickle cell clinics has further reduced morbidity and mortality. Moreover as a result of neonatal screening and early interventions there is a lower proportion of episodes of serious illness and hospital admissions (16). Because of these developments the median survival of patients with SCD has increased to over 50 years (17).

As a result of improved survival, doctors will be increasingly confronted with chronic complications that can lead to invalidity and a reduced quality of life. It is a challenge to detect patients at risk of severe progression of the disease and to discover new therapies that can decrease morbidity and mortality in this group.

The question remains which patients qualify for aggressive therapies such as haematopoietic stem cell transplantation and chronic blood transfusions. Ideally, an international consensus on a definition of SCD severity would help to select patients for therapeutic and prophylactic interventions. A severity index will also be helpful to unravel the pathophysiological mechanisms underlying the disease process. However, as SCD is a heterogeneous disease, an overall severity index for all age groups will be difficult to compose.

Detecting patients who are at risk of developing severe complications later in life is another aspect of intensive research. An important complication in children with SCD is cerebral infarction. Technologies should be explored to detect children at risk of silent infarcts. Hemispheric asymmetry could be an early indicator of inadequate oxygen supply to certain parts of the brain. In this thesis we have evaluated CASL-MRI, which is a relatively new technique to detect these asymmetries and this technique might be suitable for detecting children at risk of silent infarcts.

Overall, sickle cell disease is a complex, heterogeneous disease. As many aspects of SCD are still unexplored, the field of sickle cell disease research is extensive and challenging.
REFERENCES


