Measuring complications of sickle cell disease
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Introduction
Prevalence and incidence of children with sickle cell disease

Sickle cell disease (SCD) is a hereditary autosomal recessive disorder of haemoglobin resulting in chronic anaemia and vaso-occlusion and mainly affects the black population.

In Western Europe 0.02% of the children born are affected by SCD (1). Worldwide this number reaches up to 0.2% of the newborns with the highest incidence (1.7%) in Western Africa (1). In the United Kingdom the estimated number of SCD patients is approximately 12000 (2) and it is presently the most common genetic disorder. At this moment the exact incidence and prevalence of SCD in the Netherlands is unknown. Assuming that 0.02% of the 200,000 babies that are born in the Netherlands yearly would be affected by SCD, 40 children with SCD would be born in this country every year. In the past decades the black population in The Netherlands has increased due to immigration from Western Africa, Surinam and the Dutch Antilles, combined with the relatively high birth rates among the black population (3). As a result the incidence and prevalence of haemoglobinopathies in the Netherlands has increased as well. In 1984 the total number of children with SCD was reported to be 67 (4). This number increased to 128 children in 1992 and is estimated to be 350 in the last decade (5;6). These numbers may underestimate the true number of patients, as the surveys that reported those patients used data from a single source (doctors’ practices or laboratory data) and no verification for underreporting was performed.

Mortality

The World Health Organisation (WHO) estimates that haemoglobinopathies cause 3.4% percent of deaths worldwide in children younger than five years old (1). Several studies have been published on the survival of children with SCD. A study performed in the United States involving children diagnosed by neonatal screening showed an overall death rate among subjects with HbSS/HbS-β⁰-thalassaemia and HbSC/HbS-β⁺-thalassaemia of respectively 0.59/100 patient-years and 0.21/100 patient-years (7). A more recent English study, also including patients diagnosed by neonatal screening, published lower mortality rates in children with HbSS namely 0.13/100 patient-years (8). The estimated survival in this same study for HbSS patients at 10 and 20 years of age was 99% (95% CI 93.2-99.9). The differences in mortality rate can partly be explained by a free and easily accessible comprehensive SCD program in the United Kingdom. In The Netherlands, the health care system is comparable to the health care system in the United Kingdom. A neonatal screening program testing for SCD has been launched on January 1st 2007. Until this date only a few patients have been followed from birth. Therefore, no reliable death rates for the Dutch SCD population are known.
Chapter 1

**Genetics**

Haemoglobin is a protein consisting of two pairs of polypeptide chains, each folded around a haem molecule. Before birth two types of polypeptide chains are synthesized, i.e. \( \alpha \), and \( \gamma \) chains, resulting in foetal haemoglobin (HbF). After birth HbF is replaced by HbA1 (\( \alpha_2, \beta_2 \)) and HbA2 (\( \alpha_2, \delta_2 \)) and by the age of six months HbF will be fully replaced by HbA in healthy individuals. The gene for \( \alpha \) globin is located on the short arm of chromosome 16 and the \( \beta \), \( \gamma \), and \( \delta \) genes are positioned on the short arm of chromosome 11.

Due to defects in the haemoglobin gene two groups of diseases, called haemoglobinopathies are known. First, SCD is a qualitative disorder of haemoglobin. Second, thalassaemia is a quantitative disorder of haemoglobin. In SCD a single nucleotide mutation (GAG for GTG) in the sixth codon of the gene encoding \( \beta \)-globin results in a substitution of the amino acid glutamic acid for valine (9). This mutation in the haemoglobin molecule leads to the formation of haemoglobin S instead of the normal haemoglobin A. The inheritance of one sickle gene (\( \beta^s \)-globin) results in carriage for SCD (haemoglobin AS), whereas the inheritance of two abnormal \( \beta^s \)-globin genes leads to SCD (HbSS). In haemoglobin C the same codon is changed from GAG to AAG. In thalassaemia there is a decreased or absent production of \( \alpha \) or \( \beta \)-globin due to deletion in the gene encoding these proteins, leading to \( \alpha \) or \( \beta \)-thalassaemia respectively. As a result of a reduced or absent production of haemoglobin patients with thalassaemia will have mild or severe anaemia.

Sickle cell disease can be classified into four major genotypes of which homozygous SCD (HbSS) is the most common type. Other genotypes are compound heterozygous SCD (HbSC, HbS-\( \beta^0 \)-thalassaemia and HbS-\( \beta^+ \)-thalassaemia).

**Pathophysiology**

The main clinical features of SCD in all four genotypes are chronic haemolytic anaemia and microvascular obstruction resulting in acute and chronic ischemia, and subsequent organ damage due to infarction and fibrosis (10). As a result of lower haemoglobin HbSS and HbS-\( \beta^0 \)-thalassaemia disease usually have a (moderately) severe phenotype and are almost indistinguishable, whereas HbSC and HbS-\( \beta^+ \)-thalassaemia tend to have higher haemoglobin levels and a milder phenotype. Higher haemoglobin levels in the latter group are caused by less polymerisation of HbS as a result of HbC in HbSC disease and higher levels of HbA in HbS-\( \beta^+ \)-thalassaemia.

Polymerisation of HbS within the erythrocyte during deoxygenations is the core pathophysiological event in SCD. As a result of the altered gene for \( \beta \)-globin, HbS can polymerise within the erythrocyte during deoxygenation. Polymerisation depends on
intra-erythrocytic HbS concentration, pH and the intracellular concentration of HbF. Due to local microcirculatory conditions the transit time of the erythrocyte in the microvessels may be prolonged, causing lower oxygen tensions (11). As a result polymerisation and dehydration of the red blood cell the shape of the erythrocyte changes from biconcave into the shape of a sickle. This may occur within 2-4 minutes after deoxygenation. Repeated cycles of HbS polymerisation and thereby sickling and unsickling can cause severe erythrocyte membrane injury (12). This process may lead to abnormal cation haemostasis by opening the so-called Gardos channels inducing potassium and H₂O loss. This results in further dehydration and the development of dense cells and irreversibly sickled cells. Sickled cells supposedly exacerbate the haemolytic anaemia and vaso-occlusion by adhering to endothelium of postcapillary venules and leucocytes (11). In Figure 1 the pathophysiology of vaso-occlusion is shown.

**Figure 1** (A) Single nucleotide substitution (GAG for GTG). (B) HbS polymerisation. (C) Cell shape changes of HbS-polymer-containing erythrocyte. (D) Cross-section of microvascular bifurcation. EC=endothelium Cells. R=reticulocyte. ISC=irreversibly sickled cell. N=leucocyte. N=O*=NO bioavailability. RBC=red blood cell. Luminal obstruction has been initiated by attachment of proadhesive reticulocyte to endothelium with secondary trapping of irreversible sickled cells. Leucocytes participate in formation of heterocellular aggregates, and NO bioavailability crucial to vasodilation is impaired. Figure copied from reference 11 by permission of M. Stuart and the Lancet.

**Haemolysis and vaso-occlusion**

The morphological changes of the sickle cell result in haemolytic anaemia due to a more rapid breakdown of sickle cells compared to normal red blood cells. This breakdown mainly takes place in the spleen. The subsequent haemolysis contributes to complications
of SCD by releasing free haemoglobin in the blood plasma. As shown in Figure 2 this plasma haemoglobin consumes nitric oxide (NO) (13). Under normal circumstances NO causes relaxation of smooth muscle cells and vasodilation. When the freed haemoglobin consumes this NO, the normal balance between vasodilation and vasoconstriction is skewed towards vasoconstriction. Reduced endothelial NO availability also impairs downstream homeostatic functions of NO, where it inhibits platelet activation and aggregation of cell adhesion molecules. Low NO levels are thought to contribute especially to pulmonary hypertension, priapism, stroke and leg ulcers.

Figure 2 Intravascular haemolysis reduces nitric oxide bioactivity. Nitric oxide is produced by isoforms of nitric oxide (NO) synthase, using the substrate L-arginine. Intravascular haemolysis simultaneously releases haemoglobin, arginase, and lactate dehydrogenase (LDH) from red cells into blood plasma. Cell-free plasma haemoglobin stochiometrically inactivates NO, generating methaemoglobin and inert nitrate (A). Plasma arginase consumes plasma L-arginine to ornithine, depleting its availability for NO production (B). LDH also released from the red cell into blood serum serves as a surrogate marker for the magnitude of haemoglobin and arginase release. NO is also consumed by reactions with reactive oxygen species (O2-) produced by the high levels of xanthine oxidase activity and NADPH oxidase activity in vascular endothelium seen in SCD, producing oxygen radicals like peroxynitrite (ONOO-)(C). Figure copied from reference 13 by permission of G.J. Kato.

Besides haemolysis SCD is also characterized by vaso-occlusive complications such as acute painful episodes, splenic infarction, osteonecrosis and acute chest syndrome. Vaso-occlusion in SCD is a complex process not only caused by adhesion of sickle erythrocytes to the endothelium, but also by adhesion of leukocytes and platelets along with coagulative factors to the endothelial cells (14-17). The endothelium plays an important role in the regulation of the vascular tone, blood fluidity and coagulation (18). Besides occluding microvessels directly by adhesion to the endothelium, sickle cells may indirectly alter endothelial functions such as endothelium-dependent vasodilation. It has been suggested that sickle cell patients with higher haemoglobin levels have a
higher frequency of vaso-occlusive complications strongly related to polymerisation of sickle haemoglobin, resulting in erythrocyte sickling and adhesion. Most patients have a combination of vaso-occlusive complications and haemolysis-endothelial dysfunction. Patients with the co-presence of α-thalassaemia have a less severe phenotype as it reduces intracellular HbS concentration and thereby reduces haemolysis and the number of dense cells (10;13).

**Consequences of haemolysis and vaso-occlusion for organ function**

SCD affects all organs throughout the body. The most important pathological features, complications, and current knowledge gaps in sickle cell research will be described in the following organ descriptions.

**Spleen**

In some patients the spleen undergoes acute enlargement by trapping of red blood cells within the spleen, resulting in a rapid decrease of haemoglobin level. This so-called splenic sequestration is a life-threatening complication, occurs mainly in childhood, and is an important cause of death (10) due to anaemic shock.

Furthermore, as a result of ischemic infarcts due to vaso-occlusion, the spleen becomes progressively fibrotic and will eventually loose its function. Due to functional hyposplenia patients have an increased susceptibility for infections from the age of six months with encapsulated bacteria such as *Streptococcus pneumoniae*. Infections caused by hyposplenia can be prevented by penicillin prophylaxis in combination with immunisation (19;20).

Neonatal screening allows the installation of preventive measures before serious infections by *Streptococcus pneumoniae* have occurred. In January 2007, a neonatal screening program was launched in the Netherlands to detect SCD at an early age. Newborn screening leads to a decreased morbidity and mortality when coupled with prophylactic penicillin therapy, immunization to prevent pneumococcal infections, parental education and long term follow-up (20-26). However, not all children with SCD in The Netherlands are detected by newborn screening. Children born before January 1st 2007 and children who moved to The Netherlands at an older age and were born in countries without newborn screening will still be missed. It is presently unknown how many children do not benefit from neonatal screening for these reasons.
Chapter 1

**Brain**

Symptomatic (overt) and asymptomatic (silent) cerebral infarcts are common and debilitating complications of SCD.

Symptoms of overt infarcts consist of hemiparesis and focal seizures. In these patients blood flow to the brain may be reduced by stenosis of the large supplying arteries, ie the internal carotid arteries and the arteries in the circle of Willis, causing overt infarcts. The incidence of overt infarcts is the highest among children with HbSS disease, namely 0.61 per 100 patient-years, with a peak incidence between the ages of 2 and 9 years (27). The prevalence of overt infarcts with hemiparesis reaches up to 11% (28;29).

Children with silent infarcts have been recognized to have diminished neurocognitive functioning (30;31) and may have an increased risk of developing overt infarcts (32). Silent infarcts are thought to result from small vessel disease (microvasculopathy). Affected vessels may cause a lack of hemodynamic reserve capacity in the cerebral vasculature (33). 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. The percentage of the children who will suffer from silent infarcts is 11-35% (34-38), occurring already at young age (34;39).

Various diagnostic tests are available to detect parenchymal abnormalities of the brain and cerebral vasculopathy. Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA), visualise respectively the brain parenchym (overt and silent infarcts) and cerebral vasculopathy (stenosis, occlusion or formation of collateral vessels). Blood flow velocity in the anterior and middle cerebral artery and in the internal carotid artery, measured by Transcranial Duplex Ultrasound (TCD), can be used to detect children with SCD who are at risk for developing symptomatic cerebral infarcts (40). Patients with an increased flow (TCD > 200 cm/s) are at the highest risk (40%) of developing a cerebrovascular accident in the future (40). However, there are limitations to the current available diagnostic tests. TCD and MRA do not visualise microvasculopathy and do not contribute to the assessment of the risk of developing silent infarcts (35).

**Bones**

An acute painful episode, mostly referred to as bone crisis, is the most common symptom and cause of pain in patients with SCD. Vaso-occlusive events are caused by avascular necrosis of the bone marrow in the bones of the extremities, back, chest, hands and feet. These events may be elicited by cold, fever and dehydration. Adequate pain control and hyperhydration will reduce the pain. The femoral and humerus head are the most
common areas of bone destruction in patients who have SCD. Progressive occlusion of microcirculation within the femoral head may lead to increased intraosseous pressure and subsequent cell death (41), causing osteonecrosis. This complication is very painful and may lead to growth disturbances. Risk factors for osteonecrosis are frequent painful crises, a high haematocrit level and a low foetal haemoglobin level (42;43).

The incidence of bone crises is higher in patients with HbSS disease and HbS-β0-thalassaemia (0.8 and 1.0 episode per patient-year respectively) than in patients with HbSC or HbS-β+-thalassaemia (0.4 episodes per patient-year) and peaks at the end of the second decade of life (42). The overall prevalence of femoral head necrosis is 10% (43).

**Lungs**

The acute chest syndrome (ACS) in SCD is defined as a new infiltrate on chest radiograph associated with one or more symptoms, such as fever, cough, sputum production, tachypnea, dyspnoea or new-onset hypoxia (44). Causes of ACS are microbial infection (most common Chlamydia, Mycoplasma and viral infections), pulmonary vaso-occlusion, fat embolism from ischaemic/necrotic bone marrow or thromboembolism (44;45).

Clinically and radiographically ACS resembles bacterial pneumonia: patients may have fever, cough, tachypnea, dyspnoea, leucocytosis, pleural chest pain and chest radiographic findings may include segmental, lobar or multilobar consolidation. Is has been shown that chest radiograph can underestimate the degree of pulmonary involvement, for example perfusion lung scans have shown defects in areas which appeared normal on chest radiograph.

ACS is a frequent cause of hospitalisation in SCD and repeated ACS events may lead to chronic lung disease, abnormal pulmonary function tests, symptomatic hypoxia, pulmonary hypertension and death (46). Pulmonary hypertension, defined as a tricuspid regurgitation velocity of greater than 2.5 m/s, is a complication that is more common in adults (prevalence 32% at the mean age of 36 years) and is associated with an increased risk of death (47). As described previously, pulmonary hypertension is a complication that is particularly associated with higher rates of chronic haemolysis in SCD (48).

Incidence of ACS is highest in patients with HbSS and HbS-β0-thalassaemia and in 2-4 year old children (25.3/100 patient-years in HbSS). Incidence rates are lower in adults (8.8/100 patient-years) (49), which is believed to be related to excess mortality in the group that had ACS before and to fewer viral episodes in adults because of the adaptive immunity acquired at that age.
Liver and gallbladder

Hepatomegaly occurs in almost every patient with SCD as a result of congestion of red cells, prone to sickling, in the hepatic sinusoids. Hepatic sequestration ranges from modest to severe and can result in acute hepatic enlargement with a fall in haemoglobin level and well as in impaired hepatic function. High levels of bilirubin excretion due to haemolysis frequently result in the formation of gallstones (10). The risk of gallstone development increased with increasing mean cell volume (P < 0.002) and with decreasing foetal haemoglobin (P < 0.01) (50).

In a Jamaican cohort study from birth the prevalence of gall stones in 187 patients HbSS and 123 HbSC patients was respectively 52.7 events per 100 patient-years (95% CI 33.6 - 82.7) at age 25 years and 20.0 events per 100 patient-years (95% CI 9.0 - 44.5) by the age of 23 years (50). Nine percent of the HbSS patients with gallstones developed a cholecystitis in this study.

Kidney

Sickle cell nephropathy consists of a variety of renal abnormalities, i.e. tubular changes and glomerulopathy. Conditions in the renal medulla (low oxygen tension, acid pH and hypertonicity) are conducive of sickling, making the vasa recta system prone for vaso-occlusion, causing the vessels of the vasa rectae to become spiral, dilated and appearing to end blindly. This vascular disorganisation results in tubular changes (10;51). A frequent manifestation of glomerular injury is proteinuria. Other manifestations of nephropathy in SCD are hyposthenuria, haematuria and hypertension. Manifestations of hypertension, proteinuria, and increasingly severe anaemia predict end-stage renal failure in patients with sickle cell disease (52).

In a prospective study, the median age of disease onset for patients with HbSS or HbSC disease was respectively 23.1 and 49.9 years (52). Renal insufficiency is reported to occur in 4-18% of the SCD patients (51).

Penis

Priapism is a sustained, painful, and unwanted erection of the penis that is the result of either increased arterial inflow (ie, high flow) or, more commonly, the failure of venous outflow (i.e. low flow), resulting in blood trapping within the erectile bodies (53). Priapism has been associated with haemolysis. A relationship has been shown between pulmonary hypertension and priapism (OR 5.0 [95% CI 1.5-17.0]) (47).

The incidence of priapism in male patients is 35%; 21% of these patients reports erectile dysfunction (54).
Eyes
Proliferative sickle cell retinopathy (PSR) is the main contributor to visual loss in sickle cell anaemia. This complication is more common in patients with HbSC disease than in patients with HbSS disease. High haemoglobin levels and a low HbF are associated with PSR (10).

Incidence of proliferative PSR increases with age in both genotypes (55;56). The risk of developing PSR in patients with HbSC disease is highest in males between 15 and 24 years, in females the incidence is highest between 20 and 39 years. Patients with HbSS disease have the highest incidence between 25 and 39 years, both in males and females (55).

Heart
Cardiovascular changes are described in sickle cell disease. The cause of these changes has not yet been elucidated. Chronic anaemia leads to left ventricle dilation. Compared to healthy subjects, patients with SCD have left ventricle dilation in both systole and diastole, leading to an increased stroke volume but with a preserved left ventricle ejection fraction (57).

Most children with HbSS disease develop cardiomegaly in the first 5 years of life apparently without any major dysfunction. In adults left ventricular hypertrophy occurs in most patients and right ventricular hypertrophy is common. Myocardial infarction, coronary thrombosis and arteritis are rare in SCD (58).

Prevention of complications in sickle cell disease

Prevention of infections
Due to functional hyposplenia patients have an increased susceptibility for infections with encapsulated bacteria such as Streplococcus pneumoniae. Infections caused by hyposplenia can be prevented by penicillin prophylaxis in combination with immunisation (19;20).

Blood transfusions and iron chelation
Simple blood transfusions, reducing the HbS concentration by haemodilution, are used in acute situations (i.e. acute splenic and hepatic sequestration), prior to surgery or anaesthesia and as part of a chronic blood transfusion scheme. Chronic blood transfusions are mainly used in patients as primary (TCD > 200 cm/s) or secondary stroke prevention. Exchange transfusion reduces the concentration of HbS while limiting the volume
administered and is indicated in acute stroke and acute chest syndrome. Important medical complications are alloantibody formation, transfusion related infections and iron overload. Patients who receive regular blood transfusions are treated with iron chelation therapy. Two types of chelation therapy are often subscribed: Deferoxamine (Desferal®) and Deferasirox (Exjade®). Deferoxamine requires a continuous infusion, often by a subcutaneous pump, for at least 8 hours a day for 5 days a week. Deferasirox is a relatively new iron chelation therapy and is taken orally in the morning. Without therapy patients receiving regular blood transfusions will develop iron overload leading to heart and liver damage. Although complications by iron damage will be reduced by these therapies, compliance remains to be an issue.

**Hydroxyurea therapy**

Hydroxyurea (HU) induces foetal haemoglobin (HbF) synthesis, which cannot polymerise with HbS, and causes a reduction in neutrophil and reticulocyte counts (59). Adult patients taking hydroxyurea for frequent painful sickle cell episodes have a reduced mortality and a decreased frequency of vaso-occlusive events (60;61). In children hydroxyurea is not approved. A recent systematic review for efficacy and toxicity of hydroxyurea in children with SCD concluded that hydroxyurea reduces hospitalisation and the frequency of pain crises (62). A prospective study showed that hydroxyurea also lowers TCD velocities in children with SCD (63). A randomized, double-blind, placebo-controlled trial (BABY HUG study) is currently performed in the USA to determine if hydroxyurea can prevent the onset of chronic end organ damage in young children with SCD. Adverse events were reversible mild-to-moderate neutropenia, mild thrombocytopenia, severe anaemia, rash or nail changes and headache (62). Potential toxic effects include teratogenicity and carcinogenesis, although in several studies these side effects could not be confirmed (62;64).

**Transplantation**

Haematopoietic stem cell transplantation is the only curative therapy for SCD. In The Netherlands this therapy is rarely used currently, since there is no consensus on the indication for transplantation. In a French study the overall cumulative incidence of rejection after related myeloablative stem cell transplantation was 7.0% at 5 years and the estimated 5-year transplantation-related mortality rate was 6.9%, with all events occurring before the first 12 months after transplantation (65). The main complication of cord blood stem cell transplantation is graft rejection and graft versus host disease (66). In the French study no death was observed after the 40th transplantation or after cord blood transplantation (65). Unravelling predictors of a severe course in SCD might make it easier to make a decision which patients should undergo transplantation.
New therapies

Presently new off-label drugs in SCD are studied. Therapeutic interventions that might improve vasculopathy are, amongst others, agents that restore normal NO bioavailability or compensate for its deficiency and agents reducing haemolysis and oxidative stress. As NO is produced in the endothelium from its substrate L-arginine, increasing plasma arginine concentration is an important substrate of investigation. Oral L-arginine, direct administration of inhaled NO and Silfanedil (Viagra®) increase NO bioavailability. Hemolysis and oxidative stress are reduced by Arginine and Glutamine, which orally ingested is metabolised to citrulline and subsequently synthesised to arginine in the kidneys (source: ASH annual meeting, December 2008). Gardos-potassium channel inhibitors are being studied as anti-sickling agents. However, a recent definitive Phase III trial showed negative results (67).

Scope of the thesis

In the past decades the black population in the Netherlands has increased and consequently the population at risk of SCD has increased as well. At present the number of children with SCD in this country is based on a rough estimation. Applying a capture-recapture study design using both data acquired from paediatricians and laboratories, we obtained an accurate estimate of the prevalence of children with SCD in The Netherlands, as reported in Chapter 2.

In Chapter 3 we have documented the age of diagnosis and presenting symptoms in children with SCD in a population not subject to neonatal screening. From January 1st 2007 a neonatal screening program for SCD has been launched in The Netherlands. As children born before this date and children born outside The Netherlands are likely to be missed by this screening, it is important to identify presenting symptoms of these patients in a European country. We evaluated the presenting symptoms and age at diagnosis in a historical cohort of 88 unscreened children with SCD. The results of this study may aid in early recognition of symptoms by health care workers.

One of the challenges in SCD is the highly variable clinical picture. The determinants of a severe clinical course are largely unknown. It is important to increase our knowledge on determinants of a severe course, thereby unravelling the pathophysiological mechanisms underlying the disease process. This may provide targets for novel therapeutic interventions. Unfortunately, research aimed at finding determinants for a ‘severe sickle cell phenotype’ is hampered by the fact that there is no international consensus on the definition of a ‘severe phenotype’. Moreover, it is presently unclear which indices or instruments provide a valid measure of disease severity. A valid index should distinguish
patients according to their severity status, covering all items that are important. In Chapter 4 we systematically review all existing severity indices for SCD and we evaluate their content and methodological quality. Because this review reveals that there is no generally accepted severity index for SCD the aim of the study, as described in Chapter 5, was to develop and validate a severity assessment instrument for SCD. Item selection for this instrument was based on the systematic review. We investigated the construct validity of this instrument.

Silent infarcts are a devastating complication of SCD causing decreased neurocognitive functioning. Silent infarcts are thought to be the result of inadequate oxygen supply to the brain when metabolic demands increase or arterial pressure drops. The ensuing ischemia predisposes to cerebral infarctions. We need diagnostic methods to predict which children are at risk for silent infarcts. A new technique to measure Cerebral Blood Flow (CBF) is Continuous Arterial Spin Labeling MRI (CASL-MRI), which needs further evaluation. This non-invasive method quantifies CBF without the use of radiation or contrast. So far, data on CBF obtained by CASL-MRI in children with SCD are sparse. Chapter 6 describes CBF measurement by CASL-MRI in 24 children with SCD compared to 12 healthy control subjects matched for race, gender and age.

Taking care of a child with SCD places heavy strains on these caregivers. Previous studies have addressed the psychological effects of parenting children with SCD and reported symptoms of psychological distress (68-71). Effects of caregiving for a child with SCD may influence more aspects of life than mental health alone. Quality of life is a multidimensional concept that includes social, physical, psychological and emotional aspects. Studies in caregivers of children with various chronic illnesses have shown that these caregivers report an impaired quality of life compared to caregivers of healthy children (72-76). Chapter 7 is an assessment of the quality of life of caregivers of children with SCD. We hypothesised that caregivers of children with SCD have a lower quality of life compared to the healthy Dutch population and caregivers of healthy children with the same socio-economic status.


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Chapter 1


Introduction


Chapter 1


