Mind matters in pediatric sickle cell disease: evaluation of neurocognitive deficits, behavioral and emotional problems and health-related quality of life
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General discussion
I. Introduction

In this thesis, three different aspects of psychosocial functioning in children with sickle cell disease (SCD) were jointly investigated: neurocognitive deficits, behavioral and emotional problems, and health-related quality of life (HRQoL). We intended to answer several research questions that previously remained unanswered in the literature on this subject. In general, previous studies did not adequately control for the low socio-economic status (SES) of this patient population on outcome measures of neurocognitive functioning, behavioral and emotional problems, and HRQoL. Therefore, an important - and in a way classic - question to unravel was whether potential problems on these three areas are the result of nature versus nurture: sickle cell disease versus an unfavourable background. Furthermore, medical and psychological risk factors were not often integrated together into one biopsychosocial research model and used as determinants for these outcomes in children with SCD. Consequently, the etiology of potential problems on these areas was unclear. Figure 1 depicts the research model that formed the base of the research questions of this thesis.

![Figure 1. Research model](image)

In this concluding chapter, the main findings will be summarized and reflected upon, and key messages will be highlighted. Then, limitations of the study and future research challenges will be considered. Finally, implications of this study for clinical practice will be provided.

2. Findings of the studies at a glance

Three case-control studies were performed, with the intention to answer research question 1: *What are the differences between children with SCD and healthy siblings (matched for age, gender, ethnicity and socio-economic status) in neurocognitive functioning, behavioral and emotional problems, and HRQoL?* Behavioral and emotional problems were investigated in 106 children with SCD (HbSS, HbS-β0-thalassemia, HbS-β+-thalassemia or HbSC). Neurocognitive functioning and HRQoL were evaluated in a sub-cohort of 41 randomly selected children with a severe form of SCD (HbSS or HbS-β0-thalassemia). To control for the low SES of this patient population, children with
SCD were compared to a control group of 38 healthy siblings with the same background on all outcome measures. Characteristics and main findings of the case-control studies are summarized in Table 1. In summary, findings of the case-control studies indicate that children with SCD are at increased risk of neurocognitive deficits, behavioral and emotional problems, and low HRQoL. Nevertheless, the majority of children with SCD are resilient, meaning they adjust rather well to the disease.

Two studies were performed in the sub-cohort of children with a severe form of SCD to answer research question 2: Which are the medical determinants of neurocognitive functioning in children with SCD? and 3: What is the effect of medical determinants and neurocognitive functioning on behavioral and emotional problems in children with SCD? Characteristics and main findings of these studies are summarized in Table 2. Findings of these studies suggest that hemoglobin levels are a determinant of neurocognitive functioning, while neurocognitive functioning seems to be a determinant of behavioral and emotional problems, specifically teacher-reported externalizing problems. Below, the main findings and conclusions of the studies will be discussed per research area in more detail.

Table 1. Main findings of the 3 case-control studies on neurocognitive functioning, behavioral and emotional problems, and HRQoL in children with SCD

<table>
<thead>
<tr>
<th>Short title</th>
<th>Patients</th>
<th>Controls</th>
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<tbody>
<tr>
<td><strong>Chapter 2</strong> Neurocognitive deficits in children with SCD</td>
<td>N=41 children with SCD</td>
<td>N=38 healthy siblings</td>
</tr>
<tr>
<td><strong>Chapter 3</strong> Behavioral problems in children with SCD</td>
<td>N=106 children with SCD</td>
<td>N=37 healthy siblings Dutch norm population</td>
</tr>
<tr>
<td><strong>Chapter 4</strong> Quality of life in children with SCD</td>
<td>N=40 children with SCD</td>
<td>N=36 healthy siblings Dutch norm population</td>
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2.1 Neurocognitive deficits

In Chapter 2, we compared children with SCD and healthy siblings on a broad range of key neurocognitive functions, and demonstrated that children with SCD mainly have deficits in IQ. While the mean Full-scale IQ of healthy siblings was just below the average range compared to population norms (FSIQ = 88), the mean Full-scale IQ of children with SCD was more than 1.5 SD below the population average (FSIQ = 80). The distribution of Full-scale IQ-scores was particularly striking (see Figure 2), as more than half of the children with SCD had an IQ below 80.

Besides these deficits in general cognitive functioning, children with SCD displayed deficits in visuo-motor functioning and executive functioning compared to healthy siblings. Deficits in executive functioning included poor visuo-spatial working memory, as well as subtle deficits in sustained attention and planning. These neurocognitive deficits may be a risk factor for behavioral and emotional problems, specifically externalizing problems. Furthermore, this neurocognitive profile poses a potential risk for the academic development and may even jeopardize optimal participation of children with SCD in society. As we effectively controlled for SES by including healthy siblings, we can

<table>
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<tr>
<th>Outcome measures</th>
<th>Main findings</th>
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<tbody>
<tr>
<td>Neurocognitive functioning:</td>
<td>Clear evidence for deficits in IQ and visuo-motor functioning</td>
</tr>
<tr>
<td>- Intelligence (WISC-III)</td>
<td>&gt;30% with FSIQ &lt; 75</td>
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<tr>
<td>- Response inhibition/Sustained attention (Stop task)</td>
<td>Some evidence for executive dysfunction: poor visuo-spatial working memory, subtle deficits in sustained attention and planning</td>
</tr>
<tr>
<td>- Planning (Tower of London)</td>
<td>No significant differences in response inhibition and verbal working memory</td>
</tr>
<tr>
<td>- Visual-spatial working memory (N-Back task)</td>
<td></td>
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<tr>
<td>- Verbal working memory (Digit Span)</td>
<td></td>
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<tr>
<td>- Visuo-motor functioning (Beery-VMI)</td>
<td></td>
</tr>
<tr>
<td>Behavioral and emotional problems:</td>
<td>Children with SCD have more internalizing problems than healthy siblings and Dutch norm population</td>
</tr>
<tr>
<td>- Child Behavior Checklist (caregivers)</td>
<td>24% with severe internalizing problems</td>
</tr>
<tr>
<td>- Teacher Report Form (teachers)</td>
<td>Subgroup of children with SCD and healthy siblings with more severe externalizing problems than the Dutch norm population</td>
</tr>
<tr>
<td>- Disruptive Behavior Disorder Rating Scale (caregivers &amp; teachers)</td>
<td>Children with SCD have more difficulties in school functioning, show less competent social behavior and somewhat more attention deficits in school</td>
</tr>
<tr>
<td>HRQoL:</td>
<td>HRQoL of children with SCD is comparable to the HRQoL of healthy siblings, except on Physical and Autonomy domains</td>
</tr>
<tr>
<td>- KIDSCREEN-52 (self-report)</td>
<td>Children with SCD have lower HRQoL than Dutch norm population on 5 domains</td>
</tr>
<tr>
<td></td>
<td>Healthy siblings have lower HRQoL than Dutch norm population on 3 domains</td>
</tr>
<tr>
<td></td>
<td>&gt;30% with impaired HRQoL on several domains (scores ≥1 SD below Dutch norm population mean)</td>
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conclude that neurocognitive deficits are a consequence of the disease rather than the result of low SES.

As a next step, we were interested to find out whether these neurocognitive deficits in children with SCD can be predicted by medical risk factors. Therefore, we conducted a subsequent study on the etiology of neurocognitive deficits. Results were described in Chapter 5. One clear medical risk factor was identified: Hemoglobin appeared to be a unique predictor of verbal short term memory. Cerebral blood flow velocities (measured by transcranial doppler ultrasonography, TCD) and silent infarcts on MRI were not associated with neurocognitive functioning. Children in whom asymmetries in cerebral blood flow

Figure 2. Distribution of Full-scale IQ scores in children with SCD and SES-matched controls

Table 2. Main findings of the 2 studies on risk factors for neurocognitive deficits and behavioral and emotional problems.

<table>
<thead>
<tr>
<th>Short title</th>
<th>Patients</th>
<th>Determinants</th>
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| Chapter 5   | Hb predicts neurocognitive deficits in SCD | N=37 children with SCD | Medical factors:  
- Cerebral blood flow velocity (TCD)  
- Laboratory test results (LDH, Hb, reticulocytes, leukocytes)  
- Silent infarcts/cerebral asymmetries (MRI) |
| Chapter 6   | Risk factors for behavioral and emotional problems in SCD | N=41 children with SCD | Medical factors  
- Cerebral blood flow velocity (TCD)  
- Laboratory test results (LDH, Hb, reticulocytes, leukocytes)  
- Neurocognitive functioning (all measures combined in one factor score) |
between the right and left hemisphere were detected by continuous arterial spin labelling (CASL) MRI, had better sustained attention than children without these asymmetries. We speculated that high cerebral blood flow in one hemisphere could be related to one-sided adequate cerebral autoregulation, and that this might serve as a protective factor for neurocognitive deficits. We concluded that pronounced anemia may induce neurocognitive deficits, due to cerebral hypoxia. This could also explain why children with SCD without cerebral infarcts can still experience neurocognitive dysfunction.

2.2 Behavioral and emotional problems

In Chapter 3, we studied behavioral and emotional problems in children with SCD, and found evidence for a high prevalence of internalizing problems, such as anxiety and depression. Mean scores on the internalizing scale were in the normal range, implying children with SCD generally adjust well. However, both caregivers and teachers reported internalizing problems in the clinical range in almost one in four children with SCD (24%). Since this proportion was higher compared to both the Dutch norm population and healthy siblings (9%), we concluded that internalizing problems are related to disease factors rather than socio-demographic factors.

We could not demonstrate a difference between children with SCD and healthy siblings in externalizing problems, again suggesting that children with SCD generally cope well with their disease. Nevertheless, a higher percentage of both children with SCD (11-18%, dependent of the subscale) and healthy siblings (10-21%) did display severe externalizing problems compared to the Dutch norm population (5-9%), as reported by teachers. As

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<tr>
<td>Neurocognitive functioning:</td>
<td>- HB is associated with decrease in verbal working memory</td>
</tr>
<tr>
<td>- Intelligence (WISC-III)</td>
<td>- No association between TCD velocities and neurocognitive functioning, when controlled for age</td>
</tr>
<tr>
<td>- Response inhibition/Sustained attention (Stop task)</td>
<td>- No significant differences between children with silent infarcts and children with normal MRI</td>
</tr>
<tr>
<td>- Planning (Tower of London)</td>
<td>- Children with cerebral asymmetries have better sustained attention than children without cerebral asymmetries</td>
</tr>
<tr>
<td>- Visual-spatial working memory (N-Back task)</td>
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<td>- Visuo-motor functioning (Beery-VMI)</td>
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Behavioral and emotional problems:
- Child Behavior Checklist (caregivers)
- Teacher Report Form (teachers)
- Disruptive Behavior Disorder Rating Scale (caregivers & teachers)
- Medical factors explain 14-35% of variance in behavioral and emotional problems
- Neurocognitive functioning explains more variance, specifically in symptoms of disruptive behavior disorders (35-51%).
- TCD velocities and neurocognitive factor score are significant determinants of behavioral and emotional problems, specifically symptoms of disruptive behavior problems
- No significant association between blood cell counts and behavioral and emotional problems
both children with SCD and healthy siblings received these higher ratings, externalizing problems may be related to the low SES instead of the disease. Alternatively, we suggested that externalizing problems in healthy siblings could be explained by the dynamics in a family with a chronically diseased child, while the children with SCD with severe externalizing problems might represent those children with underlying cerebral damage.

We expanded upon this issue in Chapter 6, describing our exploratory study on medical and neurocognitive risk factors for behavioral and emotional problems. The results of this study implied that neurocognitive functioning may be a stronger determinant of behavioral and emotional problems than medical factors. While medical factors explained 11-29% of variance in behavioral and emotional problems, adding neurocognitive functioning resulted in a significant increase in the amount of explained variance of teacher-reported externalizing problems (from 11% to 31%). These exploratory findings await replication.

2.3 Health-Related Quality of Life

Chapter 4 illustrated that the HRQoL of children with SCD was lower on several domains compared to the Dutch norm population: Physical Well-being, Moods & Emotions, Autonomy, Parent Relation, and Financial Resources. The HRQoL of children with SCD appeared comparable to the HRQoL of healthy siblings, except for lower scores on the Physical and Autonomy domain. When we compared healthy siblings to the Dutch norm population, we discovered that healthy siblings also had reduced HRQoL on some of these domains: Moods & Emotions, Parent Relation, and Financial Resources. We concluded that low HRQoL of children with SCD on the Physical and Autonomy domains are direct consequences of their disease, while the low HRQoL on the other domains seems to be primarily associated with low SES. More than one in three children with SCD and healthy siblings had impaired HRQoL (scores ≥1 SD below the Dutch population mean). We concluded that children with SCD are especially vulnerable, due to their double disadvantage of disease and demographics. On the positive side, the majority of children with SCD did not have impaired HRQoL.

Key messages

- Children with SCD have a double disadvantage due to their disease and low SES
- Neurocognitive deficits are a consequence of SCD, associated with anemia severity
- Children with SCD are at risk for behavioral and emotional problems
- Low HRQoL is primarily related to low SES in children with SCD
- The majority of children with SCD are resilient
3. Looking back: a critical review and limitations of the study

Findings of this thesis should be interpreted in light of the limitations of this study. These include the relatively small sample size, the inclusion of healthy siblings from non-participating SCD patients, missing data (e.g., MRI data), the use of proxy and self-report questionnaires that were not specifically designed for use among SCD populations, the limited amount of psychosocial determinants in the research model, and the lack of pain measures.

A first limitation was the small sample size in the studies on neurocognitive functioning and HRQoL, which mitigates statistical power. This was a consequence of the feasibility of executing extensive neurocognitive assessments within a limited time frame. Although power calculations showed that power was sufficient to detect moderate differences for almost all analyses performed, this limitation should be taken into account specifically when interpreting the results of our exploratory analyses and hierarchical regression models comprising more than three determinants. For these analyses, the chance of Type II errors (the error of failing to observe a difference when in truth there is one) is increased. Findings from these analyses await replication.

Second, the recruitment of age- and gender matched healthy siblings from participating children with SCD appeared less feasible than we expected. This caused us to recruit healthy siblings in families from non-participating children with SCD, who were comparable in terms of SES as they were coming from the same neighborhood. Consequently, in our group of healthy siblings, children from Surinam descent seemed somewhat overrepresented compared to the SCD group. This difference was not significant. Moreover, within-group analyses in both patients and siblings revealed no significant differences between children from Surinam or those of African descent on the outcome measures.

Third, not all participants underwent MRI. This is currently not implemented in the standard medical care for all children with SCD in our hospital, as it is very costly. MRIs were performed at various time points in relationship to the time of our neurocognitive assessments. We did verify that children had no severe clinical complications during the interim period between MRI and neurocognitive assessment, through retrospective review of computerized databases and medical charts. Nevertheless, the occurrence of a new, symptomless silent infarction can never be completely excluded in the children who were now classified in the normal MRI group. This might have led to an underestimation of neurocognitive functioning of the normal MRI group as a whole.

Fourth, data on behavioral and emotional problems and HRQoL was obtained using questionnaires, as opposed to standardized clinical interviews. Behavioral and emotional problems were reported by caregivers and teachers, but not by children with SCD themselves, because a self-report questionnaire is not available for all ages. In contrast, HRQoL was assessed using a self-report measure, but not by proxy. As different informers may have different perspectives, the comparability of our behavioral and HRQoL data should be considered. Moreover, the Child Behavior Checklist and Teacher
Report Form are not specifically designed for use among ill populations, possibly leading to overestimation of the Somatic Problems scale (1). Although the KIDSCREEN-52 is specifically designed to determine the burden of a disease or disability, it assesses HRQoL of the past week, while in the case of a disease as unpredictable as SCD, it would be more appropriate to assess HRQoL over longer time periods, e.g. the past month. Ideally, a sickle cell disease-specific HRQoL questionnaire should be developed, as has been done for various other chronic diseases by Varni and colleagues, i.e. for children with asthma (2;3) cancer (4), brain tumors (5), neuromuscular disorders (6;7), cerebral palsy (8), diabetes (9), renal disease (10) and rheumatology (11). Although generic HRQoL measures allow for the assessment of common dimensions among both healthy and chronically ill children, and allow for comparisons across populations (12-14), generic measures may be insensitive to important disease-specific issues (15;16). Varni et al. (17) have proposed to include both generic and illness-specific measures when assessing HRQoL.

Fifth, although we adopted a biopsychosocial approach for this study (including both biomedical and psychosocial factors as determinants of neurocognitive and behavioral outcomes), we could only include a limited amount of determinants in our research model, at the cost of others. Previous studies demonstrated that psychosocial factors such as family conflict impact neurocognitive functioning and behavioral and emotional problems of children with sickle cell disease (18;19). Pain may also influence neurocognitive functioning, behavioral and emotional problems, and HRQoL. Pain is the most common symptom of SCD, but occurs far more frequent and is more severe, with more significant effects on all aspects of life, than was previously reported (20). A recent study on the impact of pain on the well-being of children with SCD has shown that acute painful events significantly impact children’s physical, social, emotional and school functioning (21).

Notwithstanding these limitations, the studies in this thesis are based on a novel approach, combining neurocognitive deficits, behavioral and emotional problems and HRQoL. These domains were all investigated in children with SCD and compared to a control group of healthy siblings. We provided a comprehensive neurocognitive profile, used multiple informants and multiple measures of behavioral and emotional problems, and a self-report measure to assess HRQoL. The present findings provide several challenges for future research.

4. Looking ahead: future perspectives

4.1 Broaden study population and study design
As the small sample size was an important limitation of our study, a first suggestion to strengthen future research designs would be to perform multicenter studies, to expand the participant pool. Ideally, national and international SCD centres should collaborate
and use one protocol for gathering data on neurocognitive functioning, behavioral and emotional problems, and HRQoL. This will increase statistical power enormously, enabling more reliable within-group comparisons, i.e. the comparison of children with different SCD genotypes, and the comparison of children with and without silent infarcts. It would also enable differentiation according to lesion location in future studies, to possibly establish specific neurocognitive and behavioral profiles dependent on the site of the lesion.

Additionally, longitudinal designs would allow the consideration of developmental aspects of neurocognitive functioning in children with SCD. For instance, previous results showed lower IQ’s in older samples (11-13 years) than in younger samples (9-10 years and 10-11 years), suggesting a decline in neurocognitive functioning with increasing age and developmental stage (22). Survivors of childhood cancer have similarly been described to grow into deficit (23). While most neurocognitive research so far included school-age children, researchers have recently started to focus on this developmental aspect by investigating the neurocognitive impact of SCD in early childhood (24-29). However, studies with a long-term follow up are lacking. To fully understand the impact of SCD on neurocognitive development, future studies should routinely screen participants from infancy to adolescence, and ideally even after transition into adulthood. Neurocognitive functioning of adults with SCD has been particularly understudied (30). Recent findings demonstrate lower IQ, as well as lower performance on tests of memory, language, learning, attention, and executive functioning in neurologically intact adults compared to controls (31). Neurocognitive deficits in adult SCD patients could pose challenges in skills of daily life such as employment, financial management, medication adherence and social functioning (31). This highlights the need to further evaluate and understand disease progression during the lifespan. One way to do this could be to use the national newborn screening program as a starting point for the routine evaluation of neurocognitive functioning, behavioral and emotional problems, and HRQoL.

4.2 Finding indicators of neurological damage

In the current study, we attempted to find medical risk factors for neurocognitive deficits and behavioral and emotional problems, but there were limited MRI data available. Our results could only be explained by speculating about the underlying pathophysiological mechanism. For instance, we found hemoglobin to be a significant predictor of neurocognitive functioning, but did not find differences between children with and without silent cerebral infarcts, while other studies have confirmed low hemoglobin as a risk factor for silent cerebral infarcts. To increase understanding of the pathophysiological mechanism, there is a need to find risk factors for neurological damage in children with SCD. In order to do this, large, multicenter MRI studies have to be performed in which genetic and laboratory risk factors for neurological damage will be evaluated, as well as neurocognitive, behavioral and emotional, and HRQoL outcomes.
4.3 Protective medical mechanisms

Other questions that remain unanswered refer to medical mechanisms that could have a protective effect on neurocognitive functioning, and potential treatments to reverse neurocognitive deficits. For instance, we found right-left asymmetries in cerebral blood flow as detected by CASL-MRI to be associated with better neurocognitive functioning. It is not yet clear what mechanism underlies asymmetry in cerebral blood flow. We speculated that high cerebral blood flow in one hemisphere may reflect adequate one-sided autoregulation (the dilation of blood vessels when systemic blood pressure is lowered). This might have a protective effect on neurocognitive functioning, but needs to be studied further.

Likewise, there is a need to evaluate the effects of hydroxyurea treatment and/or transfusion therapy on neurocognitive functioning in clinical trials. It has been suggested that neurocognitive deficits associated with severe anemia and oxygen desaturation may be reversible by hydroxyurea treatment and/or blood transfusion (32-34). One study, comparing children receiving hydroxyurea therapy to children without medication, demonstrated that hydroxyurea therapy was related to higher scores on neurocognitive tests of verbal comprehension, global cognitive ability and fluid reasoning (34). However, this study had a very limited sample size, particularly in the hydroxyurea group (n = 15), and did not examine baseline neurocognitive functioning. The Baby HUG study, a longitudinal randomized controlled trial, recently investigated whether hydroxyurea can prevent organ damage and other health complications in infants (34-41). Currently, a follow up study of the Baby HUG trial is ongoing, mainly examining the longitudinal effect of hydroxyurea on organ damage in the spleen and kidneys. Although global developmental measures were included in the Baby HUG trial, neurocognitive functioning was not one of the outcome measures.

The Silent Cerebral Infarct Transfusion (SIT) Trial is another ongoing clinical trial, investigating whether blood transfusion therapy can reduce neurological morbidity in children with SCD, and if so, to what extent (42). Neurocognitive functioning is included as second outcome measure, measured by general intelligence (using the Wechsler Abbreviated Scale of Intelligence) and parental ratings of executive functioning, using the Behavior Rating Inventory of Executive Function (BRIEF). So far, results are not yet published, but since the neurocognitive assessment battery is restricted, this will limit the conclusions about the effect of blood transfusion on neurocognitive functioning. As the assessment of more specific neurocognitive functions provides a better view of SCD-related deficits (22), future trials should include more comprehensive measures of neurocognitive functions. Understanding the impact of blood transfusion and hydroxyurea treatment on neurocognitive functioning can then lead to more informed treatment decisions for children with SCD (34).
4.4 Measures and instruments

As described above, pain is one of the core symptoms of SCD, impacting children’s physical, social, emotional and school functioning (21). Studies have not been able to carefully examine children’s daily experiences of pain, as well as fatigue, associated with SCD, although these factors are likely related to motivation and energy for neurocognitive tasks during school or research assessments (34). Therefore, it is important to include pain and fatigue measures in future research evaluating neurocognitive functioning, besides behavioral and emotional problems and HRQoL. Using a pain diary is one option. Previous studies using a pain diary demonstrated that children and adolescents with SCD report pain on 7-30% of diary days, with an average duration of 2.5 days and an average pain rating of 5 on a 10-point scale (43;44). Another suggestion would be to use specific modules of the Pediatric Quality of Life Inventory (PedsQL), i.e. the Pediatric Pain Questionnaire, Pediatric Pain Coping Inventory, or the Multidimensional Fatigue Scale, which also includes a Cognitive Functioning Scale.

Furthermore, the literature is divided regarding the best measure for illness severity in children with SCD. As it is important to reach consensus and internationally adopt one measure for illness severity, a pediatric severity assessment instrument was developed and validated in our hospital (45). This severity index adequately differentiated between patient groups classified by severity by experts. After further validation in a large prospective cohort, this index could be used as determinant of neurocognitive functioning, behavioral and emotional problems and HRQoL in future studies in children with SCD (45).

Nevertheless, previous studies have generally not found a relationship between disease severity and psychological adjustment in SCD (46). Studies in pediatric oncology patients imply that perceived illness severity is associated with psychological functioning, and therefore may be more indicative of the intensity of the child’s disease than objective measures (47). In children with SCD, the risk of psychological dysfunction also appears more dependent on symptom interference with daily functioning than on disease severity itself (48). The importance of parent and child perceptions of disease severity and illness-related stress as mediators of functioning may also be relevant (49;50). It would be interesting to further investigate the role of disease severity (using the validated severity index) as well as a measure of perceived illness severity, on neurocognitive, behavioral and HRQoL outcomes.

4.5 Risk and resistance

Future studies should include psychosocial risk factors in the biopsychosocial framework. This would allow more understanding of independent and combined contributions of psychosocial and biomedical processes to child neurocognitive functioning and subsequent behavioral and emotional problems. Consequently, new targets for psychosocial intervention could be identified (51).

As the majority of children with SCD adapt reasonably well to their disease, it is particularly relevant to investigate resilience and protective factors, besides risk factors.
Chapter 7

This ‘positive psychology’ is emerging gradually in the pediatric psychology literature. According to the positive psychology framework, an essential aim of psychology is to understand adaptation, positive emotion, adaptive coping, and hope, besides psychopathology and negative reactions to trauma (52;53). Based on the current findings within our small sample, we could not yet determine what distinguishes children with good adaptation from the children who cope less well. We speculated that the resilience of adolescents in our study on HRQoL could be a consequence of developmental growth and adjustment, possibly causing a better coping style with increasing age. Other studies have found an association between positive outcomes and self-esteem (54). Children with SCD had comparable self-perceptions to healthy children (55). Adolescents even reported higher self-esteem than the norm population, which was inversely correlated to internalizing problems (56). Adolescents with higher self-esteem reported less anxiety and depression in another study as well (57). Other protective factors that emerged from cross-sectional studies are optimism, active coping, social support, and adaptive family functioning (54). These protective factors should be included in future longitudinal research designs, to increase understanding of positive outcomes over time. Moreover, intervention research will be important for considering how to maintain or further improve functioning of the majority of children who already adapt well, but specifically to improve outcomes for those children at risk (54).

4.6 Evidence based neurocognitive rehabilitation programs

There is a strong need for evidence based neurocognitive rehabilitation programs for children with SCD and cerebral damage (58). Until now, few neurocognitive interventions have been developed, and even less have been adequately evaluated (see (58), for a review). One program proven to be effective was set up for children with brain tumors (59). Remarkably, this program did not improve neurocognitive outcomes, but did improve academic functioning. It would be worthwhile to explore the possibility to adjust this program for children with SCD, as neurocognitive rehabilitation programs specifically designed for children with SCD are currently lacking. As this program is very costly, another option could be to adjust the ATAG-K program (Amsterdamse Training voor Aandacht en Geheugen bij Kinderen, training for attention and memory in children), previously developed in our own hospital. This program aims to improve attention and memory skills in children. If it could be adjusted into a school-based program, this could save costs and prevent the training from becoming an extra burden for already overloaded caregivers. Neurocognitive rehabilitation could help children with SCD to compensate for their limitations, and develop new strengths.
5. Clinical implications

5.1 Implementation of routine screening

Our findings of neurocognitive deficits in children with and without silent infarcts on MRI emphasize the importance of implementing routine neurocognitive assessments for all children with SCD in daily clinical practice. Currently, children with SCD are mostly referred to a neuropsychologist by paediatricians after detection of silent infarcts on MRI. Our results, as well as results from other studies (22, 60, 61), demonstrate that children without silent infarcts can experience neurocognitive deficits as well. Neurocognitive evaluation has been recently recommended to be implemented in the standard comprehensive care for children and adolescents with SCD (62, 63). Interestingly, embedding these neurocognitive assessments has been shown to facilitate successful health care transitions for adolescents with SCD (63). Ideally, short, neurocognitive assessments following a standard protocol should be incorporated during the developmental trajectory.

Although the majority of children with SCD did not demonstrate behavioral and emotional problems, these problems do occur far more often in this patient population than in the general population. Knowing that the majority of children with behavioral and emotional problems continued to have these problems over an 8-year period in a follow-up study (19), the value of routine screening for behavioral and emotional problems becomes obvious. Routine screening could detect those children with severe problems. Subsequent professional help could reduce the persistence of these problems. Ideally, this screening and treatment should be implemented in a family-centered context (64, 65), as our findings of externalizing problems in both children with SCD and healthy siblings demonstrate that all children growing up in a families affected by SCD may potentially benefit from this. Furthermore, including teachers’ perceptions in routine screening is certainly of additional value. Teacher and caregiver perceptions may differ, but are regarded as equally important and complementary to each other.

Besides screening for neurocognitive deficits and behavioral and emotional problems, we argue for routine monitoring of HRQoL in children with SCD. Although our findings demonstrate that reduced HRQoL is primarily related to the low SES, rather than a direct effect of the disease, this does not change the fact that children with SCD are a very vulnerable group of patients in the hospital. This is particularly illustrated by our finding of impaired HRQoL in one third of children with SCD. Incorporating patient reported outcomes (PROs) of HRQoL in daily clinical practice can contribute to better communication with health care professionals. In our hospital, we have built up experience with PROs in several pediatric patient populations, such as childhood oncology and juvenile arthritis (66, 67). Results of a recent study in our hospital suggest that the use of PROs significantly increases the discussion of emotional and psychosocial functioning during the outpatient consultation, and enhances the identification of emotional and cognitive problems (68).

Although it is somewhat beyond the scope of this thesis, we feel the need to stress that the QoL of caregivers should be monitored as well, besides the HRQoL of children.
Chapter 7

A previous study in our hospital among mothers of children with SCD demonstrated that mothers have reduced QoL on several domains compared to a control group of mothers with the same SES, and lower QoL on all domains compared to the Dutch norm population (69). It is relevant to address the caregivers’ well-being and to identify needs for additional support, for both the health and well-being of the caregiver and the child (70;71).

5.2 Development of interventions

After implementation of routine screening in children with SCD, an evident next step is to consider suitable interventions. As described above, there is a need for evidence based neurocognitive rehabilitation programs to improve cognitive functioning. Children with SCD with social and adjustment problems could be referred to hospital-based group interventions, such as the On Track (Dutch: Op Koers) program in our hospital (72). The extra value of this program is that it is adapted for both young children and adolescents, which is important since the results of our study of HRQoL demonstrate that the adaptation process to SCD varies according to age. While young children experienced low HRQoL on all domains compared to the Dutch norm population, adolescents were more resilient, except on the Autonomy domain. Their HRQoL on this domain was far lower than both healthy siblings and the Dutch norm population in this age group, suggesting this is a consequence of growing up with SCD. As this might be related to parental (over-)protection, we recommend that parental overprotection should be considered and targeted in psychosocial intervention programs for adolescents with SCD. As higher levels of self-efficacy were previously found to be associated with fewer SCD symptoms (73), interventions to increase autonomy could possibly lead to a decrease in SCD symptomatology in this age group. This would undoubtedly be a double advantage of the intervention.

5.3 Implementation in our outpatient clinic

Following the clinical implications regarding the implementation of routine screening methods described above, we decided to extend our experience with PRO’s in other pediatric patient populations to our outpatient clinic for children with SCD. We are currently developing a screening tool incorporating neurocognitive functioning, behavioral and emotional functioning, and HRQoL for SCD patients, caregivers and siblings. All children with SCD attending the outpatient clinic will be regularly screened on these three domains, by short protocol assessments of neurocognitive functions, and by filling in behavioral and HRQoL questionnaires on the internet before their regular appointments with the paediatrician. We will use both self- and proxy-report, and besides caregivers reporting about the functioning of their children with SCD, healthy siblings and themselves, we will include teachers as informants. A multidisciplinary hospital team, consisting of pediatricians, nurses, social workers, (neuro)psychologists, and members of the educational service, will work together to monitor all children with SCD and to refer or intervene when necessary. Implementation of this new screening tool creates new challenges and opportunities to improve the health care for children with SCD.
References


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Chapter 7


