Mind matters in pediatric sickle cell disease: evaluation of neurocognitive deficits, behavioral and emotional problems and health-related quality of life
Hijmans, C.T.

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Summary
Sickle cell disease (SCD) is a hereditary red blood cell disorder that occurs predominantly in the black population. In the Netherlands, an estimated number of 1000 children have SCD, with 40 newly diagnosed children each year. Most of these children come from families coping with social and financial problems, as the majority belongs to immigrant communities from Surinam and Central Africa, with a lower socio-economic status (SES). SCD is characterized by chronic hemolytic anemia and vascular occlusion, causing acute, extremely painful episodes and irreversible organ damage throughout the body. The most devastating complication of SCD is cerebral infarction: in one third of SCD patients, cerebral infarcts are detected on MRI scans at the age of 18 years. Although most infarcts are not accompanied by overt neurological symptoms – so-called silent infarcts – they can cause much harm. Consequences of the disease, in combination with consequences of the low SES, may result in diminished psychological functioning.

In this thesis, three different aspects of psychological functioning in children with SCD are described: neurocognitive deficits, behavioral and emotional problems, and health-related quality of life (HRQoL). The primary aim was to investigate whether potential problems on these three areas are the result of the disease or the low SES of the patient population. This resulted in the following 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?

A secondary aim was to determine risk factors for neurocognitive functioning and behavioral and emotional problems, leading to the following research questions:
2. Which are the medical determinants of neurocognitive functioning in children with SCD?
3. What is the effect of medical determinants and neurocognitive functioning on behavioral and emotional problems in children with SCD?

Chapter 1 is the general introduction to this thesis, describing medical and psychological aspects of SCD. Characteristics and main findings of previous studies on neurocognitive deficits, behavioral and emotional problems, and HRQoL in children with SCD are summarized. SCD is known to be associated with impairments in general cognitive functioning as well as with deficits in specific areas of neurocognitive functioning, but a comprehensive neurocognitive profile of children with SCD is currently unavailable. Medical determinants for neurocognitive functioning are also unknown. Behavioral and emotional problems and HRQoL have not been studied as much as neurocognitive functioning in children with SCD and have scarcely been correlated to medical or neurocognitive determinants. Therefore, the AANPAK project (AAndacht voor NeuroPsychologische Aspecten bij Kinderen met sikkelcelziekte, attention for neurocognitive deficits in children with SCD) was initiated at the Comprehensive Sickle Cell Disease Care Centre of the Emma Children’s Hospital, Academic Medical Centre, in Amsterdam, The Netherlands.

The first part of this thesis contains the results of three case-control studies on neurocognitive functioning, behavioral and emotional problems, and HRQoL in children.
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with SCD. In Chapter 2, neurocognitive functioning was extensively evaluated in 41 children with SCD and a control group of 38 healthy siblings. Results demonstrated that SCD was clearly associated with lower IQ scores. More than one in three children with SCD had a Full-scale IQ below 75, versus one in ten healthy siblings. Children with SCD also showed deficits in visuo-motor functioning. Some evidence was found for executive dysfunction. No significant differences were found between children with SCD and healthy siblings in terms of response inhibition and verbal working memory.

Chapter 3 describes behavioral and emotional problems in children with SCD, compared to healthy siblings and a Dutch norm population. The Child Behavior Checklist (CBCL), Teacher Report Form (TRF) and Disruptive Behavior Disorders rating scale (DBD) were filled out by caregivers and/or teachers of 106 children with SCD and 37 healthy siblings. Children with SCD had more severe internalizing problems than healthy siblings and the norm population. According to teachers, subgroups of both children with SCD and healthy siblings had more severe externalizing problems than the norm population. Children with SCD also functioned worse in school, showed less competent social behavior and tended to have more attention deficits than healthy siblings.

In Chapter 4, HRQoL of 40 children with SCD was evaluated using the KIDSCREEN-52, and compared to 36 healthy siblings and a Dutch norm population. In general, the HRQoL of children with SCD appeared comparable to the HRQoL of healthy siblings, while children with SCD had worse HRQoL than the Dutch norm population on five domains (Physical Well-being, Moods & Emotions, Autonomy, Parent Relation, and Financial Resources). Healthy siblings had worse HRQoL than the Dutch norm population on three domains (Moods & Emotions, Parent Relation, and Financial Resources). More than one in three children with SCD and healthy siblings had impaired HRQoL (≥1 SD) on several domains. These findings imply that reduced HRQoL in children with SCD is mainly related to the low SES of this patient population, with the exception of disease specific effects on the physical and autonomy domain.

In summary, findings of the case-control studies in the first part of this thesis indicate that children with SCD are at increased risk of neurocognitive deficits, behavioral and emotional problems, and low HRQoL. Although the majority of children with SCD are resilient, meaning they adjust rather well to the disease, it is relevant to search for risk factors for those children who do experience problems on these three psychological areas.

In the second part of the thesis, risk factors were investigated. In Chapter 5, we studied the association of laboratory markers of disease severity and radiological parameters with neurocognitive functioning in 37 children with SCD. All participants underwent extensive neurocognitive assessment. Further data (TCD values, laboratory test results and MRI data) was obtained from medical charts. Results demonstrated hemoglobin to be associated with a decrease in verbal short term memory. There was no association between TCD velocities and neurocognitive functioning, when controlled for age. Children with silent infarcts did not differ from children with normal MRI in
neurocognitive functioning. Children with right-left asymmetries in cerebral blood flow as measured by Continuous Arterial Spin Labelling (CASL) MRI had better sustained attention than children without asymmetries. We concluded that neurocognitive deficits are associated with the severity of anemia, indicating reduced oxygen delivery to the brain as an etiological mechanism. This implies that children with SCD and normal MRIs may still suffer from neurocognitive impairments, possibly affecting their academic development and full participation in society.

Finally, we explored the impact of medical factors and neurocognitive functioning on behavioral and emotional problems in Chapter 6. In 34 children with SCD, medical data (cerebral blood flow velocity, blood cell counts) were collected and neurocognitive functioning was assessed. Caregivers and teachers completed questionnaires on behavioral and emotional problems. Exploratory hierarchical regression analyses, including both medical factors and neurocognitive functioning as determinants of behavioral and emotional problems, did not result in significant regression models. Medical factors did explain 11-29% of variance in behavioral and emotional problems. Adding neurocognitive functioning resulted in a significant increase in the amount of explained variance in teacher-reported externalizing problems. These exploratory findings await replication, but imply that neurocognitive functioning is a stronger determinant of externalizing problems than medical factors.

In the final Chapter 7, a summary and discussion of the results of the preceding chapters is provided. Five key messages were formulated:

- 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

Next, limitations of the study are considered. 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. Based on these limitations, several recommendations for future research are suggested. Large, multicenter MRI studies should be performed to increase the participant pool and improve statistical power, and to find risk factors for neurological damage to increase understanding of the underlying pathophysiological mechanism of neurocognitive deficits. Longitudinal designs would allow evaluation of psychological functioning of SCD patients throughout the lifespan. Other recommendations for future research are to focus on protective mechanisms (both medical and psychosocial), to include pain and fatigue measures, and to set up and evaluate neurocognitive rehabilitation programs for children with SCD who suffer from severe cerebral damage. This thesis closes with implications of this study for clinical
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practice. Routine neurocognitive assessments, screening for behavioral and emotional problems, and monitoring of HRQoL should be implemented in daily clinical practice to detect those children in need of professional help, and to eventually improve the health care for these vulnerable children.

In closing, this thesis demonstrates that children with sickle cell disease do not only suffer from the physical consequences of their disease, but can experience various psychological consequences as well. Mind matters in pediatric sickle cell disease!