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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Chapter 1

General introduction
1. Introduction

In 1904, Dr. James Herrick, a cardiologist and professor of medicine, was the first to report “peculiar elongated and sickle shaped” red blood cells in a young African American patient. The patient was suffering from aches and pains in his muscles, abdominal pain, shortness of breath, and heart palpitations. He also frequently felt tired, suffered from headaches, experienced attacks of dizziness, and had ulcers on his legs. This first sickle cell patient came to Chicago in 1904 to study dentistry in one of the best schools of the United States of America, and was likely the only black student there. He was a wealthy, intelligent 20-year-old man from the West Indies; and, despite frequent hospitalizations for his illness, Walter Clement Noel completed his education, along with his classmates, three years later. He returned to Grenada and practiced dentistry until he died of pneumonia at the age of 32. He was buried in the Catholic cemetery at Sauteurs in the north of Grenada.

Nowadays, the bright, young and wealthy Walter Clement Noel would still make a rather exceptional case. The first reason for this is the increasing evidence that sickle cell disease (SCD), a hereditary anemia, may cause neurocognitive deficits, as (silent) cerebral infarctions frequently occur in this patient population. The second reason is that most patients with SCD in Western Europe come from families coping with social and financial problems, as the majority belongs to immigrant communities with a lower socio-economic status (SES). Consequences of the disease, such as neurocognitive deficits, in combination with consequences of low SES, may in turn cause behavioral and emotional problems and low health-related quality of life (HRQoL). As a result, the development and academic achievement of children with SCD may be hampered, and their full participation in society may be jeopardized.

2. Medical aspects of sickle cell disease

2.1 Prevalence and incidence

Sickle cell disease (SCD) is a hereditary red blood cell disorder that occurs predominantly in people of African ancestry (1). It results from an autosomal recessive genetic deficit and is classified by genotype. Persons affected with SCD demonstrate abnormal genes for hemoglobin (Hb) S, which produces a change in the shape of red blood cells from their normal disk shape to a sickle shape. These abnormally shaped cells obstruct normal blood flow and production of new blood cells, resulting in chronic anemia. The most common type of SCD is the homozygous condition, HbSS, which is caused by two abnormal genes for hemoglobin S. HbSS is associated with earlier, more frequent and more severe symptoms than other types. Other types include HbSC, HbSß0-thalassemia, and HbSß+-thalassemia.
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Worldwide, 275000 (0.2%) of the children born annually are affected by SCD, with the highest incidence (1.7%) in Western Africa. In Western Europe, SCD is increasingly common due to demographic changes. Nowadays, it is the most common genetic disorder in children in the United Kingdom, with an estimated number of approximately 12000 SCD patients. In the Netherlands, approximately 1000 children have SCD (2). In the past decades, the black population in the Netherlands has increased due to immigration from Western Africa, Surinam and the Dutch Antilles, in combination with the relatively high birth rates among the black population. In 2007, SCD was included in the national newborn screening program. As a result, the prevalence of SCD in the Netherlands has increased and is expected to increase further in the next few decades.

2.2 Medical consequences

The African medical literature already reported about SCD in the 1870s, when it was known locally as ogbanjes, meaning “children who come and go”, because of the very high infant mortality rate caused by the disease. Fortunately, the chance of survival has increased enormously since then, granting children with SCD to grow up into adulthood and to have a longer life expectancy. In the United Kingdom, the estimated survival for HbSS patients at 10 and 20 years of age was 99% (3). Results of a recent study in our hospital on the survival rate of children with SCD in The Netherlands have demonstrated an estimated survival of 98% at age 18 (4).

The decrease in childhood mortality has led to an increase in childhood morbidity. SCD is characterized by chronic hemolytic anemia and vascular occlusion, causing acute, extremely painful episodes and irreversible organ damage. SCD affects all organs throughout the body. Common complications of SCD include functional hyposplenia (impaired capacity of the spleen), causing increased susceptibility for infections, acute chest syndrome (vaso-occlusive crisis in the lungs), hepatomegaly (enlarged liver) and gallstone development, retinopathy (damage to the retina of the eye), and renal failure. However, the most devastating complication of SCD is cerebrovascular infarction.

One third of SCD patients show cerebral infarcts on MRI scans at the age of 18 years (5-9). Eleven percent of children experience an overt cerebral infarct, accompanied by neurological symptoms, and 11-35% of children suffer from silent infarcts (5-9). Overt infarcts are generally associated with stenoses of the large supplying arteries of the brain, i.e. the internal carotid arteries and the arteries in the circle of Willis. Silent infarcts may occur throughout the brain, but commonly occur in frontal lobe white matter, within the border zone between the middle and anterior cerebral artery distribution. Silent infarcts are the result of critical reductions in the delivery of oxygen to the brain through several interrelated mechanisms (10). Children with SCD have reduced oxygen carrying capacity due to their low hemoglobin levels. This may be further compromised in acute medical events such as acute chest syndrome or infection. Chronic lung disease may also reduce the oxygen content of the blood. Obstruction of small vessels is facilitated by sickled red blood cells, which are more adhesive than normal red cells. Furthermore, increased
blood viscosity, associated with HbS, may impair the flow of blood through narrowed vessels or in normal brain capillaries.

2.3 Treatment

Therapeutic options for SCD comprise preventive antibiotics, scheduled blood transfusions, administration of hydroxyurea, and hematopoietic stem-cell transplantation. Infections caused by hyposplenia can be prevented by penicillin prophylaxis in combination with immunisation. Scheduled blood transfusion is a therapeutic option used in acute situations, prior to surgery, or as part of a chronic blood transfusion schedule. Unfortunately, it is associated with iron accumulation, causing cardiac and endocrinological dysfunction when adequate chelation therapy to remove the iron is not installed. Another therapeutic option is hydroxyurea, which has proven to reduce the rate of painful vaso-occlusive crises. Finally, hematopoietic stem-cell transplantation is the only curative therapy for SCD, but may have severe side effects and therefore a careful balance between benefit and harm is necessary.

3. Psychological aspects of sickle cell disease: what is known

3.1 Neurocognitive sequelae

SCD has been associated with impairments in general cognitive functioning as measured by IQ. Children with SCD and overt stroke are most impaired, with a mean decrease of approximately 14 Full-scale IQ points (11), while children with silent infarcts have been described to score 4-7 Full-scale IQ points lower than children with normal MRI (12;13). However, it appears that there are cognitive effects of SCD for children with normal MRI as well (14-16).

Besides detrimental effects on IQ, SCD has been associated with deficits in specific areas of neurocognitive functioning including executive functioning (17-23) and visuo-motor functions (24;25). Deficits in these two areas are expected, given that silent infarcts commonly occur in frontal lobe white matter, within the border zone between the middle and anterior cerebral artery distribution (26;27). The frontal lobes play a major role in executive functions, which are higher order cognitive functions including abilities such as response inhibition, planning, working memory, and attention (28). These functions greatly affect other areas of neurocognitive functions and are generally strongly related to academic and behavioral problems. Sustained attention and working memory appear to be particularly vulnerable in children with SCD (17). Response inhibition and planning have been studied less extensively. White matter damage is thought to underlie deficits in visuo-motor functions. Although deficits on this neurocognitive domain have been recognized in children with SCD, findings remain inconsistent (17). Some researchers have reported average visuo-motor skills in children with SCD (19;29) while others found clear deficits compared to healthy siblings (24;25). Characteristics and main findings of
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previous studies on neurocognitive deficits in children with SCD compared to healthy siblings are summarized in Table 1.

3.2 Behavioral and emotional problems

Neurocognitive deficits may indirectly exert influence on the psychosocial well-being of children with SCD, but may also directly cause behavioral and emotional problems. As the frontal lobes seem to be especially vulnerable to infarctions (19;30), and children with SCD have repeatedly been found to experience deficits in attention and executive function (e.g. difficulties with impulse control) (17;19-23) they are particularly expected to have externalizing problems, such as hyperactive or aggressive behaviour. Although findings from previous studies have been inconclusive, they generally suggest a higher prevalence of internalizing problems, such as anxiety and depression (31-34). Surprisingly, no evident increased risk of externalizing problems has been revealed (31). Characteristics and main findings of previous studies on behavioral and emotional problems in children with SCD using the Child Behavior Checklist, Teacher Report Form or Youth Self Report are summarized in Table 2.

3.3 Health-related Quality of Life

Quality of Life (QoL) is defined as an individual’s perception of one’s position in life in the context of culture and value systems, as well as in relation to one’s goals, expectations, standards and concerns. Health-related QoL (HRQoL) is defined as QoL in which a dimension of personal judgement of one’s health and disease is added (35). The measurement of HRQoL, encompassing the physical, psychological, and social component of children’s well-being, is still in its infancy in children with SCD (36). For example, compared to over 400 studies on HRQoL in children with cancer, research on HRQoL of children with SCD is just scratching the surface (37). The relatively few studies that have been performed revealed that HRQoL of children with SCD is generally poor (38-43). Characteristics and main findings of these previous studies are summarized in Table 3.

4. The next step: what needs to be known

Since the life expectancy of children with SCD has drastically been improved, it is important to focus on influencing morbidity. The morbidity associated with cerebral infarcts is most relevant in children with SCD, as these occur so frequently and can have such devastating effects. Although previous psychological research in children with SCD has mainly focused on studying neurocognitive functioning, many studies used restricted assessment batteries or lacked adequate control groups to control for the low SES of most patients. Therefore, a comprehensive neurocognitive profile of children with SCD is currently unavailable and needs to be provided. It is also very
important to gain more knowledge about the etiology of neurocognitive deficits (i.e.,
the association between cerebral damage and neurocognitive functioning), as this issue
currently remains unresolved. If it would be evident which medical factors determine
neurocognitive functioning, it would become easier to detect children at risk at an early
stage, to prevent these children from developing academic and behavioral problems.

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 factors. The prevalence of behavioral and emotional problems
has mostly been investigated using parents as proxy-reporters, while the value of
multi-informant assessment of children’s behavior is clearly supported (44-46). In light of
the background of this patient population, it is important to determine the differential
effect of the disease and low SES on behavioral and emotional problems and HRQoL.
However, healthy siblings have scarcely been included as controls in studies on behavioral
and emotional problems, and not at all in studies on HRQoL. Finally, evidence of medical
and/or neurocognitive risk factors for behavioral and emotional problems could point
out which children are most at risk, and could lead to more targeted interventions.

5. AANPAK project

5.1 Purpose of the study
This thesis reports the results of the AANPAK project (AAndacht voor NeuroPsychologische
Aspecten bij Kinderen met sikkelcelziekte, attention for neurocognitive deficits in
children with SCD), which was initiated at the Comprehensive Sickle Cell Disease Care
Centre of the Emma Children’s Hospital, Academic Medical Centre, in Amsterdam, The
Netherlands. The study focused on three different aspects of psychological functioning
in children with SCD: neurocognitive deficits, behavioral and emotional problems, and
HRQoL. The AANPAK project was part of the research line of the pediatric psychology
program in the Emma Children’s Hospital, which focuses on studying psychosocial
consequences of growing up with a chronic disease and indicating specific risk factors
for the development of psychosocial problems. The AANPAK project aimed to (1) assess
neurocognitive functioning in children with SCD in comparison to healthy siblings (who
are comparable in age, gender, ethnicity and SES), (2) investigate the prevalence of
behavioral and emotional problems and evaluate HRQoL in children with SCD compared
to healthy siblings and a Dutch norm population, (3) identify medical determinants of
neurocognitive deficits in children with SCD, and (4) identify medical and neurocognitive
determinants of behavioral and emotional problems in children with SCD.

5.2 Theoretical background and research model
The theoretical model of the interrelatedness of all these aspects is depicted by the three
boxes in Figure 1. Within this model, behavioral and emotional problems and health-
related quality of life are regarded as outcomes of neurocognitive functioning, which in itself is regarded as an outcome of medical and socio-demographic determinants.

5.3 Research questions

This theoretical model forms the base for three research questions of the AANPAK project:
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?
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?

5.4 Study design

The AANPAK project is a cross-sectional case-control study. Behavioral and emotional problems were investigated in a large cohort of 106 children with SCD (HbSS, HbS-ß0-thalassemia, HbS-ß+ -thalassemia or HbSC) aged 6 to 18 years. Caregivers and teachers completed behavioral questionnaires and scores were compared to a control group of 37 healthy siblings and normative data, to gain more insight into the nature and prevalence of these problems.

Neurocognitive functioning and HRQoL were evaluated in a sub-cohort of 41 randomly selected children with SCD with a severe form of SCD (HbSS or HbS-ß0-thalassemia) aged 6 to 18 years. A large battery of neurocognitive tests as well as a self-report HRQoL questionnaire was administered in the outpatient clinic. Neurocognitive outcomes were compared to a control group of 38 healthy siblings, and HRQoL outcomes were compared to both controls and normative data. The factors and corresponding measures that were used in the AANPAK project are presented in Table 4.
5.5. Scope of the thesis

The first part of this thesis contains the results of our three case-control studies on neurocognitive functioning, behavioral and emotional problems, and HRQoL in children with SCD. In Chapter 2, we evaluated a broad range of neurocognitive functions in children with SCD compared to a control group of healthy siblings, in order to gain more insight into the specific deficits of these patients. Chapter 3 presents the results on the prevalence of behavioral and emotional problems in children with SCD compared to healthy siblings and a Dutch norm population. In Chapter 4 we investigated whether the HRQoL of children with SCD was associated with consequences of the disease, or with the low socio-economic status (SES) of this patient population, by comparing children with SCD to healthy siblings and a Dutch norm population.

In the second part of the thesis, we aimed to identify risk factors for neurocognitive deficits and behavioral and emotional problems. Therefore, we investigated the association of laboratory markers of disease severity and radiological parameters with neurocognitive functioning in children with SCD in Chapter 5. Finally, we explored the impact of medical factors and neurocognitive functioning on behavioral and emotional problems in Chapter 6. This thesis closes with a summary and discussion of the results of the preceding chapters (General discussion) Chapter 7.
Table 1. Neurocognitive functioning of children with SCD versus healthy siblings

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patients</th>
<th>Controls</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swift et al, 1989 (29)</td>
<td>N=21 children aged 7-16</td>
<td>N=21 healthy siblings</td>
<td>- Intelligence (WISC-R) - Verbal and visuo-spatial memory (Detroit Test of Learning Aptitude) - Visuo-motor functioning (Beery VMI)</td>
</tr>
<tr>
<td>Wasserman et al, 1991 (47)</td>
<td>N=43 children aged 7-16</td>
<td>N=30 healthy siblings</td>
<td>- Intelligence (WISC-R) - Verbal and non-verbal memory (Luria-Nebraska Neuropsychological Battery) - Motor functioning (Luria-Nebraska Neuropsychological Battery)</td>
</tr>
<tr>
<td>Brown et al, 1993 (48)</td>
<td>N=70 children aged 6-17</td>
<td>N=18 healthy siblings</td>
<td>- Intelligence (K-ABC) - Sustained attention (MFFT Continuous Performance Task) - Visual short term memory (Bead Memory subtest of the Stanford-Binet intelligence scale) - Visuo-motor functioning (Beery VMI)</td>
</tr>
<tr>
<td>Craft et al, 1999 (20)</td>
<td>N=29 children aged 6-17</td>
<td>N=20 healthy siblings</td>
<td>- Sustained attention (Test of auditory vigilance) - Verbal learning and memory (Children’s Auditory Verbal Learning Test) - Motor speed, Coordination (Finger tapping test) - Spatial organization (Object Assembly and Bock Design subtest of WISC-R, Benton Visual Retention Test, Spatial Relations subtest of Woodcock-Johnson Revised)</td>
</tr>
<tr>
<td>Steen et al, 1998 (49)</td>
<td>N=30 children aged mean 10.4</td>
<td>N=24 healthy siblings</td>
<td>- Intelligence (WISC-R or WISC-III)</td>
</tr>
<tr>
<td>Schatz et al, 1999 (23)</td>
<td>N=28 children aged 7-15</td>
<td>N=17 healthy siblings</td>
<td>- Sustained attention (TOVA) - Set shifting (WCST) - Planning (Tower of Hanoi) - Verbal learning and memory (CVLT) - Spatial organization (DAS)</td>
</tr>
<tr>
<td>Bernaudin et al, 2000 (13)</td>
<td>N=156 children aged 5-15</td>
<td>N=76 healthy siblings</td>
<td>- Intelligence (WISC-III) - Motor functioning (Purdue Pegboard)</td>
</tr>
</tbody>
</table>

Children with diffuse lesions performed less well on spatial organization than children with silent anterior lesions.

No significant differences between children with overt anterior strokes and children with overt diffuse lesions in attention/executive functions and spatial organization.

Correlation between SES and IQ.

Patients performed less well on sustained attention task, especially older children.

No significant differences in memory between patients and siblings younger than 12 years: patients performed better on all tasks except for visual short term memory.

No significant differences in memory between patients and siblings older than 12 years.

Children with diffuse lesions performed worse on all spatial measures than siblings.

Significant differences in Full-scale, Verbal and Performance IQ between patients and siblings.

No significant differences in visuo-motor functioning.

Significant differences in verbal and visuo-spatial memory between patients and siblings. Patients scored lower on visuo-spatial memory (> 1 SD).

Significant differences in Full-scale, Verbal and Performance IQ. Patients also had lower Verbal IQ, but this difference did not reach significance.

No medical determinants for neurocognitive functioning were found.
Main findings

- Significant differences in Full-scale, Verbal and Performance IQ between patients and siblings
- Significant differences in verbal and visuo-spatial memory between patients and siblings. Patients scored especially lower on visuo-spatial memory (>1 SD)
- No significant differences in visuo-motor functioning
- No medical determinants for neurocognitive functioning were found

- Significant differences in Full-scale and Performance IQ. Patients also had lower Verbal IQ, but this difference did not reach significance
- No significant differences in memory between patients and siblings older than 12 years
- Significant differences in memory between patients and siblings younger than 12 years: patients performed less well
- 29% of patients above cut-off (=critical level) versus 0% of siblings
- No significant differences in motor functioning

- No significant differences in IQ between patients and siblings
- Patients performed less well on sustained attention task, especially older children
- No significant difference in visual short term memory and visuo-motor functioning
- Hemoglobin level is significant predictor of IQ and visual memory
- Correlation between SES and IQ

- No significant differences between children with overt anterior strokes and children with overt diffuse strokes in sustained attention
- Children with silent anterior lesions performed less well on sustained attention than children with silent diffuse lesions and siblings
- No significant differences in memory
- No significant differences in motor speed
- Children with diffuse lesions performed less well on spatial organization than children with silent anterior lesions and siblings

- Significantly lower Full-scale IQ in patients with abnormal MRI than patients with normal MRI and healthy siblings
- FSIQ of total group of patients = 75
- FSIQ of healthy siblings = 88
- FSIQ of patients with normal MRI = 79
- FSIQ of patients with abnormal MRI = 71

- Significant differences between patients and siblings in attention/executive functions and spatial organization
- Patients with anterior lesions had selective deficits in attention/executive functions and spatial organization, but patients with diffuse lesions had general deficits on all tasks
- Both patients with anterior and diffuse lesions had lower score on planning task than siblings (only patients with anterior lesions also made more errors than siblings)
- Only patients with diffuse lesions performed worse on all spatial measures than siblings
- No differences in motor functioning and memory

Intelligence:
- Total group of patients had lower Full-scale, Verbal and Performance IQ than siblings:
  - FSIQ (83.9 vs 90.3)
  - VIQ (90.4 vs 96.7)
  - PIQ (80.6 vs 85.7)
- Higher proportion of FSIQ <75 in patients than siblings (30% vs 9%)
- Cognitive functioning was more impaired in patients with overt stroke, low hematocrit, high platelet count, or silent stroke + low hematocrit and/or high platelet count

Motor functioning:
- Patients with overt stroke scored lower on motor functioning compared to patients without stroke
- No significant differences between patients with silent stroke and patients without stroke
Table 1. Continued

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patients</th>
<th>Controls</th>
<th>Outcome measures</th>
</tr>
</thead>
</table>
| Schatz et al, 2001 (50) | N=19 children with SCD with silent infarcts, mean age 10.9 | N=18 healthy siblings | - Sustained attention (Cancellation A’s Task TOVA)  
- Speed for attention/ sequencing/ mental flexibility/visual search (Trail Making Test)  
- Set shifting (WCST)  
- Verbal learning and memory (CVLT / Wide Range Assessment of Memory and Learning (WRAML))  
- Motor functioning (Purdue Pegboard)  
- Spatial organization (DAS-Pattern Construction, Judgement of Line Orientation, Woodcock Johnson- Revised Visual Closure) |
| Hurtig & Park, 1989 (51) | N=33 children with SCD aged 12-17 | - | - CBCL (1983 version) |
- TRF (1986 version) |
| Kell et al, 1998 (52) | N=80 children with SCD aged 12-18 | - | - CBCL  
- YSR |

Table 2. Behavioral and emotional problems in children with sickle cell disease measured with the Child Behavior Checklist (CBCL), Teacher Report Form (TRF) and Youth Self Report (YSR)

<table>
<thead>
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</tbody>
</table>
- TRF (1986 version) |
| Kell et al, 1998 (52) | N=80 children with SCD aged 12-18 | - | - CBCL  
- YSR |
Table 1

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</tr>
</thead>
<tbody>
<tr>
<td>Schatz et al, 2001</td>
<td>N=19 children with SCD with silent infarcts, mean age 10.9</td>
<td>N=45 children without silent infarcts, mean age 10.7</td>
<td>Sustained attention (Cancellation A’s Task TOVA), Speed for attention/sequencing/mental flexibility/visual search (Trail Making Test), Set shifting (WCST), Verbal learning and memory (CVLT / Wide Range Assessment of Memory and Learning (WRAML)), Motor functioning (Purdue Pegboard), Spatial organization (DAS-Pattern Construction, Judgement of Line Orientation, Woodcock Johnson- Revised Visual Closure)</td>
</tr>
<tr>
<td></td>
<td>N=18 healthy siblings</td>
<td></td>
<td>Patients with silent infarcts showed significantly more neurocognitive deficits compared to patients without infarcts and siblings, mainly deficits in attention/executive functions. 53% of patients with silent infarcts had abnormal scores in attention/executive functions compared to 13% without silent infarcts and 0% siblings. 30% of patients with silent infarcts had abnormal scores in visual-spatial/motor functioning compared to 33% without silent infarcts and 0% siblings.</td>
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Table 2

<table>
<thead>
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<tbody>
<tr>
<td></td>
<td>Patients had more behavioral problems compared to low SES norm sample</td>
<td></td>
<td>Boys scored higher on all scales. Scores approached clinical range for Somatic Problems, Immaturity, and Hyperactivity scale</td>
</tr>
<tr>
<td></td>
<td>Girls scored higher on Somatic Problems, Schizoid, Depressed/Withdrawal, and Delinquent scale. Scores approached clinical range for Somatic Problems scale</td>
<td></td>
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</tr>
<tr>
<td>Brown et al, 1993</td>
<td>N=61 children with SCD aged 6-17</td>
<td>N=15 healthy siblings</td>
<td>CBCL:</td>
</tr>
<tr>
<td></td>
<td>Patients scored higher on Internalizing Problems than siblings</td>
<td></td>
<td>No significant differences on Somatic Problems scale</td>
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<td></td>
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<td></td>
<td>CBCL:</td>
<td></td>
<td>Family cohesion score and CBCL Externalizing Problems</td>
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<td></td>
<td>TRF:</td>
<td></td>
<td>Family adaptation score and CBCL Internalizing Problems</td>
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<td></td>
<td>Patients scored higher on Externalizing Problems, Inattention and Nervous/overactive</td>
<td></td>
<td>Self-reported depressive symptoms in children, CBCL Externalizing Problems, more social impairment according to teachers, less adaptive behaviour on Vineland, and less cohesion in family</td>
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<tr>
<td></td>
<td>Days absent from school was a significant predictor of Internalizing Problems</td>
<td></td>
<td>Associations were found between:</td>
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<tr>
<td></td>
<td>Diagnosis or gender did not appear as significant predictors</td>
<td></td>
<td>Familial stressors and CBCL Internalizing Problems</td>
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<td></td>
<td>CBCL:</td>
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<td>Associations were found between:</td>
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<td></td>
<td>YSR:</td>
<td></td>
<td>Familial stressors and CBCL Internalizing Problems</td>
</tr>
<tr>
<td></td>
<td>Patients scored higher on Internalizing Problems (without Somatic Problems scale) for boys with SCD on CBCL</td>
<td></td>
<td>No significant differences between parents and children in Internalizing or Externalizing Problems</td>
</tr>
<tr>
<td></td>
<td>Higher scores on Somatic Problems scale for boys and girls with SCD on CBCL and YSR</td>
<td></td>
<td>Adolescents rated their family as less competent than parents</td>
</tr>
<tr>
<td></td>
<td>Percentages with scores in clinical range:</td>
<td></td>
<td>Percentages with scores in clinical range for Somatic Problems</td>
</tr>
<tr>
<td></td>
<td>CBCL: 37% in clinical range for Somatic Problems</td>
<td></td>
<td>YSR: 43% in clinical range for Somatic Problems</td>
</tr>
<tr>
<td></td>
<td>YSR: 43% in clinical range for Somatic Problems</td>
<td></td>
<td>Percentages with scores in clinical range on other scales ranged between 1% and 14% (which is lower than in other studies)</td>
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<tr>
<td></td>
<td>Lower SES was not associated with behavioral problems</td>
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<td>Higher family competence was associated with fewer behavioral problems, especially in younger adolescents</td>
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<td>Higher family competence was associated with fewer behavioral problems, especially in younger adolescents</td>
</tr>
<tr>
<td></td>
<td>Girls seem to be more influenced by family competence than boys, reflected by more Internalizing Problems and Somatic Problems</td>
<td></td>
<td>Girls seem to be more influenced by family competence than boys, reflected by more Internalizing Problems and Somatic Problems</td>
</tr>
</tbody>
</table>

Main findings

- Patients with silent infarcts showed significantly more neurocognitive deficits compared to patients without infarcts and siblings, mainly deficits in attention/executive functions
- 53% of patients with silent infarcts had abnormal scores in attention/executive functions compared to 13% without silent infarcts and 0% siblings
- 30% of patients with silent infarcts had abnormal scores in visual-spatial/motor functioning compared to 33% without silent infarcts and 0% siblings

General introduction
### Table 2. continued

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patients</th>
<th>Controls</th>
<th>Outcome measures</th>
</tr>
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<tbody>
<tr>
<td>Thompson et al, 1999</td>
<td>N=289 children with SCD aged 6-15</td>
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<td>- CBCL</td>
</tr>
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<td>Trzepacz et al, 2004</td>
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<tr>
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<td>N=70 children with SCD aged 8-14</td>
<td>N=68 classroom controls</td>
<td>- CBCL (filled in by primary and secondary caregiver)</td>
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<td>Gold et al, 2008</td>
<td>N=41 children with SCD aged 7-17</td>
<td>N=97 healthy siblings</td>
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### Table 3. Health-related Quality of life in children with SCD

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patients</th>
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<th>HRQoL Measure</th>
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<tbody>
<tr>
<td>Kater et al, 1999</td>
<td>N=45 children with SCD aged 5-15 and their parents</td>
<td>-</td>
<td>- TACQOL Parent Form (5-11) - TACQOL Child Form (8-15)</td>
</tr>
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<td>Palermo et al, 2002</td>
<td>N=58 children with SCD aged 5-18</td>
<td>N=120 healthy African-American children</td>
<td>- CHQ Parent Form 50 - Other measures: demographics, disease complications</td>
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### Table 2. Mental health in children with SCD

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<tr>
<td>Thompson et al, 1999</td>
<td>N=289 children with SCD aged 6-15</td>
<td>- CBCL</td>
<td>Percentages with scores in clinical range: &lt;br&gt; - 25% on Total Problems &lt;br&gt; - 22% on Internalizing Problems &lt;br&gt; - 18% on Externalizing Problems</td>
<td>No changes over time in behavioral problems &lt;br&gt; Higher percentage in clinical range on Externalizing Problems for mothers who were never married than mothers who were married/divorced/widowed</td>
</tr>
<tr>
<td>Thompson et al, 2003</td>
<td>N=222 children with SCD aged 5-15</td>
<td>- CBCL</td>
<td>No changes over time in behavioral problems</td>
<td>9% with consistent behavioral problems over time</td>
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<td>Trzepacz et al, 2004</td>
<td>N=70 children with SCD aged 8-14</td>
<td>N=68 classroom controls</td>
<td>CBCL (filled in by primary and secondary caregiver)</td>
<td>Patients scored higher on Total and Internalizing Problems and lower on Total Competence &lt;br&gt; Percentages with scores in clinical range: &lt;br&gt; - More patients in clinical range on Total and Externalizing Problems &lt;br&gt; - Combination primary/secondary CBCL: 43% of patients in clinical range on at least 1 broadband scale versus 21% of controls &lt;br&gt; More patients in clinical range on Total and Externalizing Problems when compared to norm sample, prevalence is 2-3 times higher</td>
</tr>
<tr>
<td>Gold et al, 2008</td>
<td>N=41 children with SCD aged 7-17</td>
<td>N=97 healthy siblings</td>
<td>CBCL</td>
<td>Patients scored higher on Internalizing Problems and Somatic Problems &lt;br&gt; Percentages with scores in clinical range: &lt;br&gt; - More patients and siblings in clinical range on Total, Internalizing and Externalizing Problems when compared to norm sample, prevalence is 2-3 times higher</td>
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<td>N=45 children with SCD aged 5-15</td>
<td>and their parents</td>
<td>TACQOL Parent Form (5-11) TACQOL Child Form (8-15)</td>
<td>Compared to healthy non-White reference data: &lt;br&gt; Patients scored lower on physical functioning, motor functioning, autonomy, and negative mood according to both parents and children &lt;br&gt; No significant differences on cognitive, school, social, and positive mood &lt;br&gt; Parents scored lower on negative moods than children &lt;br&gt; No age differences were found</td>
</tr>
<tr>
<td>Palermo et al, 2002</td>
<td>N=58 children with SCD aged 5-18</td>
<td>N=120 healthy African-American children</td>
<td>CHQ Parent Form 50</td>
<td>Comparison between patients and healthy controls: &lt;br&gt; Lower summary scores for patients on Physical and Psychosocial domains &lt;br&gt; Significant differences on 13 of 14 subscales &lt;br&gt; Comparison between patients with SCD and patients with JIA: &lt;br&gt; Comparable scores on Physical domain &lt;br&gt; Lower scores on Psychosocial domain &lt;br&gt; Comparison between patients with SCD and patients with epilepsy: &lt;br&gt; Comparable scores on Psychosocial domain &lt;br&gt; Lower scores on Physical domain &lt;br&gt; Associations were found between lower Physical score and: &lt;br&gt; - increasing age &lt;br&gt; - female gender &lt;br&gt; - total number of disease-related complications &lt;br&gt; SES (measured as work status and educational level) was not predictive of Physical score &lt;br&gt; No predictors were found for Psychosocial score</td>
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<td>Author, year</td>
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<tr>
<td>Panepinto et al, 2005</td>
<td>N=53 children with SCD aged 5-18 N=95 parents N=49 child-parent pairs</td>
<td>-</td>
<td>- CHQ Parent Form 28 (5-18) - CHQ Child Form 87 (10-18) - Other measures: age, gender, education, race, medical and neurobehavioral comorbidities, SCD type, disease status</td>
<td></td>
</tr>
<tr>
<td>Palermo et al, 2008</td>
<td>N=56 children with SCD aged 8-17</td>
<td>-</td>
<td>- CHQ Parent Form 50 - Other measures: disease severity, pain intensity, depression, parent education, family income, distressed neighbourhood, Functional Disability Inventory</td>
<td></td>
</tr>
<tr>
<td>Barakat et al, 2008</td>
<td>N=42 children with SCD aged 12-18 and their parents</td>
<td>-</td>
<td>- CHQ 50 Parent Form - CHQ 50 Child Form - Other measures: Varni Pediatric Pain Questionnaire (PPQ), Behavioral Assessment System for Children (BASC), Pediatric Inventory for Parents (PIP), demographic form, disease severity as measured by pain and acute chest syndrome, Risk Index (to assess sociodemographic and psychological risk based on social and familial factors)</td>
<td></td>
</tr>
<tr>
<td>Panepinto et al, 2009</td>
<td>N=104 children with SCD (78% African American)</td>
<td>N=74 children without SCD</td>
<td>- PedsQL Parent Form (2-18) - PedsQL Child Form (5-18) - Other measures: family income, disease severity, age, presence of other chronic conditions (medical and neurobehavioral co-morbidities)</td>
<td></td>
</tr>
<tr>
<td>Panepinto et al, 2009</td>
<td>N=97 parents of children with SCD</td>
<td>N=73 parents of healthy children</td>
<td>- PedsQL Family Impact Module - PedsQL Parent Form</td>
<td></td>
</tr>
</tbody>
</table>
## Main findings

**Main findings**

### Panepinto et al, 2005

- **N=53 children with SCD aged 5-18**
- **N=95 parents**
- **N=49 child-parent pairs**

- **Measure:** CHQ Parent Form 28 (5-18)
- **Other measures:** age, gender, education, race, medical and neurobehavioral comorbidities, SCD type, disease status

**Main findings**

- No differences between older versus younger children
- No differences between stroke versus no stroke
- Lower physical HRQoL in children with acute chest syndrome/vaso-occlusive crises in past 3 years

**Association were found between:**

- Disease status – Physical score
- Neurobehavioral co-morbidities and parental education – Psychosocial score

**Child Form:**

- Lower scores on 3 subscales: physical functioning, general health perceptions, role/social physical
- In general, children did not perceive themselves as having worse psychosocial HRQoL, such as lower self-esteem
- Parents rate their children’s HRQoL lower than children do (except for bodily pain and other observable domains)

- **Mean Physical HRQoL T-score = 33.02 (compared to norms of healthy non-White children = 50.6)**
- **Mean Psychosocial HRQoL T-score = 45.40 (compared to norms of healthy non-White children = 49.9)**

**Within group comparisons:**

- No differences between older versus younger children
- No differences between stroke versus no stroke
- Lower physical HRQoL in children with acute chest syndrome/vaso-occlusive crises in past 3 years

**Association were found between:**

- Disease status – Physical score
- Neurobehavioral co-morbidities and parental education – Psychosocial score

**Main findings**

- Higher pain intensity – greater disability and lower physical score
- Higher family income – less disability and higher physical score, but lower psychosocial score
- Higher parental education - higher physical and psychosocial score
- Higher neighbourhood distress – lower physical score
- Greater depression – greater disability, lower psychosocial score
- Greater disease severity – lower psychosocial score

**Main findings**

- Parents of children with SCD were older, had higher income, and higher education
- Ceiling effects of the family impact module
- Lower score for parents of children with severe SCD on subscales worry and communication, compared to mild SCD and controls. No differences on other subscales.
- Lowest scores for severe SCD and medical + neurobehavioral comorbidities
- Correlations between family impact module and parent-proxy report
### Table 4. Factors and corresponding measures used in the AANPAK project

<table>
<thead>
<tr>
<th>Factors</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical parameters</td>
<td>- Cerebral MRI&lt;br&gt;- Right–left asymmetries in cerebral blood flow measured by continuous arterial spin labelling (CASL) MRI&lt;br&gt;- Transcranial Doppler ultrasonography (TCD) measured in the right and left middle cerebral artery, anterior cerebral artery and internal carotid artery&lt;br&gt;- Blood cell counts: lactate dehydrogenase, hemoglobin, reticulocytes, and leukocytes</td>
</tr>
<tr>
<td>Socio-demographic factors</td>
<td>- Age&lt;br&gt;- Gender&lt;br&gt;- Country of origin&lt;br&gt;- Parental marital status&lt;br&gt;- Maternal educational level&lt;br&gt;- Parental paid employment</td>
</tr>
<tr>
<td>Neurocognitive functioning</td>
<td>- Intelligence (WISC-III/WAIS-III)&lt;br&gt;- Executive functioning:&lt;br&gt;  - response inhibition and sustained attention (Stop task)&lt;br&gt;  - visuo-spatial working memory (N-back task)&lt;br&gt;  - verbal working memory (Digit span)&lt;br&gt;  - planning (Tower of London)&lt;br&gt;- Visuo-motor functioning (Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI))</td>
</tr>
<tr>
<td>Behavioral and emotional problems</td>
<td>- Child Behavior Checklist (CBCL)&lt;br&gt;- Teacher Report Form (TRF)&lt;br&gt;- Disruptive Behavior Disorder rating scale (DBD), caregiver and teacher version</td>
</tr>
<tr>
<td>Health-related Quality of Life</td>
<td>- KIDSCREEN-52 (child self-report)</td>
</tr>
</tbody>
</table>
References


Chapter 1


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