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Behavioral and Emotional Problems in Children With Sickle Cell Disease and Healthy Siblings: Multiple Informants, Multiple Measures

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Background. Behavioral and emotional problems in children with sickle cell disease (SCD) may be related to disease factors, or to socio-demographic factors. The aim of this study was to investigate the prevalence of behavioral and emotional problems in children with SCD living in a Western European country, compared to healthy siblings (who were comparable in age, gender, ethnicity, and socio-economic status—SES), and to a Dutch norm population. **Methods.** The Child Behavior Checklist (CBCL), Teacher Report Form (TRF) and Disruptive Behavior Disorders rating scale (DBD) were distributed among caregivers and teachers of 119 children with SCD aged 6–18 years and among caregivers and teachers of 38 healthy siblings. **Results.** Questionnaires were returned by caregivers and/or teachers of 106 children with SCD and 37 healthy siblings. According to caregivers and teachers, 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 had more difficulties than healthy siblings in terms of school functioning, showed less competent social behavior and tended to have more attention deficits. **Conclusions.** Children with SCD are at increased risk of developing internalizing problems as a result of their disease. Subgroups of children with SCD are at increased risk of developing severe externalizing problems, which may either be related to socio-demographic factors, or to disease factors, such as neurocognitive deficits associated with cerebral infarction. Pediatr Blood Cancer 2009;53:1277–1283. © 2009 Wiley-Liss, Inc.

Key words: behavioral and emotional problems; children; sickle cell disease

INTRODUCTION

Sickle cell disease (SCD) is a hereditary red blood cell disorder that occurs predominantly in people of African ancestry [1]. SCD is increasingly common in Europe due to demographic changes. Nowadays, it is the most common genetic disorder in children in the United Kingdom. In the Netherlands, an estimated number of 1,000 children, originating from Surinam and Central Africa, have SCD. The unpredictable course of SCD places a heavy strain on affected children and their families. Besides the medical problems, most families with a child with SCD have to cope with social and financial problems, as the majority belongs to immigrant communities with a lower SES and is single parented [2]. The combined effects of the disease and socio-demographic factors may lead to behavioral and emotional problems in children with SCD. To establish whether these problems are mainly related to disease factors or to socio-demographic factors, research on the prevalence of these problems needs to take socio-demographic factors into account. Subsequently, adequate health care can be provided.

The clinical picture of SCD is characterized by chronic hemolytic anemia and vascular occlusion, causing recurrent painful episodes (vaso-occlusive crises) and irreversible organ damage. The most devastating complication of SCD is cerebral infarction. At the age of 18 years cerebral infarcts are present on MRI scans in one-third of SCD patients [3–7]. Although most of these infarcts are not accompanied by focal neurological deficits, they appear to be associated with diminished neurocognitive functioning [8,9]. This may hamper the development and academic achievement of children with SCD, jeopardizing full participation in society. As a result, neurocognitive deficits may indirectly exert influence on the psychosocial well-being of these children. Neurocognitive deficits may also directly cause behavioral and emotional problems. As the frontal lobes seem to be especially vulnerable to infarctions [10,11], children with SCD have repeatedly been found to experience deficits in attention and executive function (e.g., difficulties with impulse control) [8,10,12–15]. These neurocognitive deficits are particularly associated with externalizing problems, such as hyperactive or aggressive behavior.

Although findings from previous studies have been inconclusive, they generally suggest a higher prevalence of internalizing problems, such as anxiety and depression, but no increased risk of externalizing problems [16]. This might be due to several methodological issues. Most researchers used the Child Behavior Checklist (CBCL) [17] as the only measure for the assessment of behavioral and emotional problems [18–24]. Although this is a well-validated, empirically based instrument, it neither encompasses all symptoms of externalizing behavior disorders nor correspond well to the terminology of the DSM-IV [25]. Furthermore, in light of the background of children with SCD, the frequent use of children from the general population as the only comparison is questionable [16]. Yet, only a limited number of investigators included a healthy comparison group matched for age, gender, ethnicity, and SES [18,19,24]. In addition, most researchers solely relied on parental ratings of behavioral and emotional problems, while the value of multi-informant assessment of children's behavior is clearly supported [26–28]. Besides these

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methodological issues, a more general limitation is that most studies have been performed in the United States of America, where the healthcare system and the patient population are different from Europe.

The aim of the current study was to investigate the prevalence of behavioral and emotional problems in children with SCD living in a Western European country compared to (1) healthy siblings (who are comparable in age, gender, ethnicity, and SES) and (2) a Dutch norm population, using multiple informants and multiple measures. We hypothesized that children with SCD would receive higher scores on questionnaires assessing behavioral and emotional problems than healthy siblings and the Dutch norm population. Specifically, we expected caregivers and teachers to report more externalizing problems in children with SCD.

METHODS

Participants

All 119 children aged 6–18 years with SCD (HbSS, HbSβ0-thalassemia, HbSβ+-thalassemia or HbSC) receiving treatment at the Comprehensive Sickle Cell Care Center of the Emma Children's Hospital, Academic Medical Center in Amsterdam, were eligible for inclusion. For the control group, 38 healthy (full or half) siblings of these SCD patients, matched for age and gender, were selected. Inclusion took place between August 2007 and October 2008.

Measures

The *Child Behaviour Checklist* (CBCL) [17,29] is a 118-item caregiver-reported inventory, providing scores on eight syndrome scales: Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior. In addition, it provides scores on the broad-band scales Internalizing Problems (which combines Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints), Externalizing Problems (which combines Rule-Breaking and Aggressive Behavior), and Total Problems (which combines all syndrome scales). The CBCL also contains three competence scales (Activities, Social Competence, and School Performance), which together form another broad-band scale: Total Competence.

T scores are computed from raw scores; higher scores on the syndrome scales indicate greater severity of problems. A T score of 63 (90th percentile) demarcates the clinical range, which is an indication that a child needs professional help. For the competence scales, lower scores indicate greater severity. A T score <37 indicates the clinical range. Adequate psychometric properties for this rating scale have been established [17,29].

The *Teacher Report Form* (TRF) [17,30] is the teacher version of the CBCL. Scores result in the same scales as described above, with the exception of Total Competence and its subscales. In the TRF the fourth broad-band scale is Adaptive Functioning, encompassing the scales Academic Performance, Working Hard, Behaving Appropriately, Learning and Happy.

The *Disruptive Behavior Disorder rating scale* (DBD) [25,31] is a 42-item inventory that assesses all symptoms of externalizing behavior disorders as described in the DSM-IV. The questionnaire can be completed by both caregivers and teachers and provides scores on four scales: Inattention, Hyperactivity/impulsivity, Oppositional Defiant Disorder, and Conduct Disorder. Higher

scores indicate greater severity of problems. Scores above the 95th percentile represent the clinical range. Adequate psychometric properties have been established [25].

Procedure

The medical ethics committee of the Academic Medical Center of Amsterdam approved the study protocol. The CBCL and DBD were sent to the caregivers' home address. Caregivers signed informed consent forms, by which they gave permission to send the TRF and the DBD to the teachers. Teachers received both questionnaires, together with a copy of the informed consent form. Filling out both questionnaires required about 30 min. Initial non-responders were contacted and motivated to return the questionnaires.

Data Analysis

SPSS version 15.0 was used to analyze data. Before conducting the final analyses several preparation analyses were conducted. First, missing data were imputed using the Estimation Maximization procedure [32]. The percentage of missing data was <10%. Next, raw scores were normalized by applying a Van der Waerden transformation [33]. Thirdly, independent *t*-tests and Chi square tests were used to compare respondents to non-respondents regarding demographic and medical characteristics.

Linear mixed models were used to compare normalized raw scores of children with SCD and healthy siblings on the caregiver forms. The linear mixed model allows for the investigation of group differences while controlling for the non-independency of data (i.e., caregivers completed questionnaires for more than one child per family, which resulted in related measurements within groups and between groups). Therefore, group was used as factor, and family as random effect to account for within family correlation. As teacher forms were independent measurements, normalized raw scores of children with SCD and healthy siblings on these forms were compared using independent sample *t*-tests.

To protect for Type 1 errors, results from the broad-band scales were examined first. If significant results were found, subscales were analyzed. A significance level of $P < 0.05$ was used; levels of $P < 0.10$ were reported as trends. Effect sizes (d) were calculated by dividing the difference in mean score between children with SCD and healthy siblings by the standard deviation of the scores of healthy siblings. According to Cohen [34], effect sizes of up to 0.2 were considered to be small, effect sizes of about 0.5 to be moderate and effect sizes of about 0.8 to be large.

In addition to comparing mean scores, the proportion of children with SCD with scores in the clinical range on the CBCL, TRF, and DBD was compared to the proportion of healthy siblings using Chi square test. Confidence intervals were calculated [35] for comparison to the proportion of children in the Dutch norm population. Furthermore, caregiver and teacher forms were combined, to compare proportions of children with scores in the clinical range reported by at least one informant on at least one of the scales.

Within-group analyses were performed to compare children with more severe genotypes of SCD (HbSS or HbSβ0-thalassemia) to children with less severe genotypes of SCD (HbSC or HbSβ+-thalassemia). All CBCL and TRF analyses were performed using normalized raw scores, although T scores are reported in the tables to facilitate comparisons with previous studies. Normalized raw

scores were used for DBD analyses as well; raw scores are depicted in the tables, because standard scores were only available for Dutch children aged 6–12 years, and this study population exceeded that age range.

RESULTS

Respondents

The CBCL and DBD were returned by caregivers of 95 children with SCD (response rate 80%). Most forms were completed by mothers (71%), followed by fathers (19%), and others (10%; e.g., stepparents, grandparents). Caregivers of 35 healthy siblings returned the questionnaires (92%). In this group, most forms were completed by mothers as well (80%), followed by fathers (14%), and others (6%). Teachers of 101 children with SCD (85%) and of 29 healthy siblings (76%) returned the TRF and DBD.

Regarding differences between children of participating caregivers and children of non-participating caregivers, the age and gender distribution did not differ, but disease severity did: 78% of participating caregivers had a child with a more severe genotype (HbSS, HbSβ0), as opposed to 31% of non-participating caregivers.

Participant characteristics are depicted in Table I. No significant differences between the age and gender distribution of both groups were found. Of the children with SCD that were included, four (4%) had previously experienced a symptomatic stroke. Nine children (9%) received scheduled blood transfusion, either for stroke (4%), intracranial stenoses of arteries as detected on MRI (3%), cerebral bleeding (1%), or an extremely high frequency of vaso-occlusive crises (1%). One child (1%) had previously undergone an unsuccessful bone marrow transplantation.

Caregiver Report: CBCL and DBD

Results from the CBCL showed that children with SCD differed significantly from healthy siblings on two broad-band scales (Table II). Children with SCD had higher mean scores on Total Problems and Internalizing Problems. There was a trend for lower scores of children with SCD on Total Competence.

Further analysis of the syndrome scales demonstrated that children with SCD scored significantly higher than healthy siblings on Somatic Complaints and Social Problems, and lower on Social Competence. There was a trend for a higher mean score on Anxious/ Depressed.

Results from the DBD revealed no significant differences between mean scores of children with SCD and healthy siblings.

TABLE I. Characteristics of Children With SCD and Healthy Siblings for Whom Completed Questionnaires Were Returned by Either Their Caregiver, or Their Teacher, or Both

	Children with SCD (n = 106)	Healthy siblings (n = 37)
Age, M (SD)	12.3 (3.6)	11.6 (3.2)
Boys, n (%)	65 (61)	19 (51)
Disease severity		
HbSS, n (%)	77 (73)	
HbSC, n (%)	21 (20)	
HbSβ0, n (%)	6 (6)	
HbSβ+, n (%)	2 (2)	

One in four children with SCD (24%) scored in the clinical range on Internalizing Problems (Table III). This proportion was significantly larger than both the proportion of healthy siblings and the norm sample. Total Competence scores were in the clinical range in 40% of both children with SCD and healthy siblings. This is a fourfold increase in comparison to the norm sample. For Externalizing Problems and Total Problems, the proportion of children with SCD with clinical scores was comparable to both healthy siblings and the norm sample. Similarly, for the DBD no differences were found in the proportion of children with SCD with clinical scores, compared to the proportion of both healthy siblings and the norm sample.

Teacher Report: TRF and DBD

Results of the TRF showed that children with SCD differed significantly from healthy siblings on one broad-band scale: children with SCD received lower scores on Total Adaptive Functioning, and its subscales Academic Performance and Behaving Appropriately (Table IV). Results from the DBD revealed no significant differences in mean scores, but there was a trend for higher scores of children with SCD on Inattention.

Nineteen percent of children with SCD had scores in the clinical range on Internalizing Problems, which was significantly larger than the proportion of healthy siblings and the norm sample (Table V). Both among children with SCD and healthy siblings, a high proportion of children obtained scores in the clinical range on Externalizing Problems. Similarly, a high proportion of both children with SCD and healthy siblings had scores in the clinical range on all DBD scales.

Caregiver and Teacher Report Combined

When the CBCL and the TRF were combined, 51% of children with SCD had problems in the clinical range reported by at least one informant on at least one of the broad-band scales, as opposed to 33% of healthy siblings ($\chi^2 (1) = 2.635$, $P = 0.105$). Combining the caregiver and teacher DBD, proportions with clinical scores reported by at least one informant on at least one of the scales were large in both children with SCD (48%) and healthy siblings (41%) ($\chi^2 (1) = 0.439$, $P = 0.508$).

Genotype

Within-group analyses revealed that caregivers of children with more severe genotypes of SCD reported higher mean scores on Total Problems and Internalizing Problems compared to caregivers of children with less severe genotypes. Children with more severe genotypes also had higher scores on Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, and Rulebreaking Behavior (all t's > −4.56; $P < 0.05$). There was a trend for higher scores of children with more severe genotypes on Social and Thought Problems. Moreover, 17% of the children with more severe genotypes received scores in the clinical range on Total Problems, ($\chi^2 (1) = 3.822$, $P = 0.051$) and 31% had scores in the clinical range on Internalizing Problems ($\chi^2 (1) = 7.714$, $P = 0.005$), as opposed to 0% of the children with less severe genotypes. Teachers of children with more severe genotypes reported behavioral and emotional problems at levels similar to teachers of children with less severe genotypes of SCD.

TABLE II. Caregiver Report: Child Behavior Checklist and Disruptive Behavior Disorder Rating Scale Scores for Children With SCD and Healthy Siblings

Questionnaire	Children with SCD (n = 95)		Healthy siblings (n = 35)		Effect size	
	Mean	SD	Mean	SD	d	F
Child Behavior Checklist						
Total Problems	52.6	9.5	48.0	10.2	0.5	5.9**
Internalizing Problems	56.0	9.7	50.7	9.5	0.6	7.2***
Anxious/Depressed	54.5	5.7	52.6	4.6	0.4	3.1*
Withdrawn/Depressed	56.6	6.9	55.0	4.8	1.2	1.8
Somatic Complaints	61.1	9.2	56.2	6.8	0.6	7.0***
Externalizing Problems	48.5	9.5	47.2	9.8	0.2	0.49
Rule-breaking Behavior	53.0	4.4	52.8	4.1	0.2	0.83
Aggressive Behavior	53.4	5.0	53.2	4.4	0.1	0.30
Other syndrome scales						
Social Problems	55.6	5.6	52.8	4.3	0.6	8.4**
Thought Problems	54.7	5.5	53.8	6.9	0.3	1.2
Attention Problems	54.9	5.0	53.5	4.4	0.4	2.4
Total Competence	37.3	7.4	39.0	7.5	0.3	3.8*
Activities	36.5	9.2	34.9	11.1	0.0	0.12
Social Competence	43.4	8.1	47.0	6.6	0.5	4.8**
School Performance	44.8	7.2	46.0	6.4	0.3	2.4
Disruptive Behavior Disorders						
Inattention	3.9	4.1	3.2	3.1	0.1	0.46
Hyperactivity/impulsivity	3.2	3.6	3.2	3.7	0.0	0.01
Oppositional Defiant Disorder	2.3	2.7	1.8	2.3	0.2	1.1
Conduct Disorder	0.7	1.5	0.5	0.8	0.1	0.01

Range CBCL (0–100), mean = 50, ranges DBD: Inattention and Hyperactivity/impulsivity (0–27), ODD (0–24), CD (0–48). The four broad-band scales of the CBCL are underlined. Syndrome scales of the CBCL are in italics. *$P < 0.10$; **$P < 0.05$; ***$P < 0.01$.

DISCUSSION

This study investigated the prevalence of behavioral and emotional problems in children with SCD living in a Western European country, compared to healthy siblings (comparable in ethnicity and SES) and a Dutch norm population, using multiple informants and multiple measures. Both caregivers and teachers perceived more internalizing problems in children with SCD in comparison to both healthy siblings and the norm population. Teachers identified more externalizing problems in subgroups of both children with SCD and healthy siblings in comparison to the norm population. Children with SCD were also perceived to have more difficulties than healthy siblings in school functioning, to demonstrate less competent social behavior and to tend to have more

TABLE III. Caregiver Report: Proportions of Children With SCD and Healthy Siblings With Behavioral Problem Scores in the Clinical Range Compared to the Dutch Norm Population

Questionnaire	Children with SCD (n = 95)			Healthy siblings (n = 35)		
	n	%	95% CI	n	%	95% CI
Child Behavior Checklist						
Total Problems	13	14	8–22	3	9	2–23
Internalizing Problems	23	24**	16–34[a]	3	9	2–23
Externalizing Problems	5	5	2–12	0	0	—
Total Competence	39	41	31–52[a]	14	40	24–58[a]
Disruptive Behavior Disorder						
Inattention	3	3	1–9	0	0	—
Hyperactivity/impulsivity	2	2	0–7	1	3	0–15
Oppositional Defiant Disorder	3	3	1–9	0	0	—
Conduct Disorder	5	5	2–12	1	3	0–15

CI, confidence interval. [a]95% Confidence interval exceeds proportion in the Dutch norm population. In the Dutch norm population 9% of children have scores in the clinical range on CBCL broad-band scales; 5% of children have scores in the clinical range on DBD scales; **Significant difference at $P < 0.05$ between children with SCD and healthy siblings.

TABLE IV. Teacher Report: Teacher Report Form and Disruptive Behavior Disorder Rating Scale Scores for Children With SCD and Healthy Siblings

Questionnaire	Children with SCD (n = 101)		Healthy siblings (n = 29)		Effect size	
	Mean	SD	Mean	SD	d	t
Teacher Report Form						
Total Problems	54.2	8.6	52.4	8.6	0.2	1.1
Internalizing Problems	54.5	9.6	51.6	8.3	0.4	1.5
Externalizing Problems	54.7	9.1	53.2	10.3	0.2	0.79
Total Adaptive Functioning	45.2	7.6	48.0	7.3	0.5	−2.2**
Academic Performance	47.2	7.4	50.3	8.2	0.5	−2.4**
Working Hard	47.1	7.8	49.2	7.9	0.4	−1.6
Behaving Appropriately	45.4	7.0	47.8	7.4	0.4	−2.1**
Learning	45.8	7.4	47.7	7.8	0.3	−1.5
Happy	46.2	7.9	48.7	8.2	0.3	−1.6
Disruptive Behavior Disorder						
Inattention	5.6	5.6	4.0	5.3	0.4	1.7*
Hyperactivity/impulsivity	4.0	5.8	3.1	5.3	0.2	0.85
Oppositional Defiant Disorder	3.2	4.3	2.5	3.5	0.2	0.96
Conduct Disorder	0.7	1.4	0.7	1.5	0.2	0.88

Range CBCL (0–100), mean = 50, ranges DBD: Inattention and Hyperactivity/impulsivity (0–27), ODD (0–24), CD (0–48). *$P < 0.10$; **$P < 0.05$.

attention deficits. Caregivers reported more behavioral and emotional problems in children with more severe genotypes of SCD than in children with less severe genotypes.

Internalizing problems in children with SCD were not exclusively attributable to higher ratings of somatic problems, in contrast to recent findings [19]. In the present study, caregivers reported slightly more problems related to anxiety and depression as well, which is in concordance with other previous studies [18,24]. Although mean scores on the internalizing scale were in the normal range, the high prevalence of severe internalizing problems in children with SCD, as reported by both informants and compared to both healthy siblings and the norm sample, is of clinical relevance. Chronically diseased children are generally found to be at increased risk of developing internalizing problems [36]. The present findings suggest that, in children with SCD, internalizing problems are also mainly related to disease factors, as opposed to socio-demographic factors.

The fact that caregivers rated children with SCD to be significantly impaired in their social functioning, is congruent with results of other studies [24,37–39]. These problems could be related to disease factors like severe fatigue and pain, which possibly constrain children with SCD to form close friendships with their peers. Another explanation can be found in previous research on social information processing, in which children with SCD displayed neurocognitive impairment on tasks of facial and vocal emotional decoding, leading to difficulties comprehending subtle social situations [40].

TABLE V. Teacher Report: Proportions of Children With SCD and Healthy Siblings With Behavioral Problem Scores in the Clinical Range Compared to the Dutch Norm Population

Questionnaire	Children with SCD (n = 101)			Healthy siblings (n = 29)		
	n	%	95% CI	n	%	95% CI
Teacher Report Form						
Total Problems	14	14	7–21	4	14	4–32
Internalizing Problems	19	19**	11–26[a]	1	3	0–18
Externalizing Problems	18	18	10–25[a]	6	21	8–40
Total Adaptive Functioning	17	17	10–24[a]	3	10	2–27
Disruptive Behavior Disorder						
Inattention	11	11	5–17	5	17	6–36[a]
Hyperactivity/impulsivity	14	14	7–21[a]	3	10	2–27
Oppositional Defiant Disorder	15	15	8–22[a]	4	14	4–32
Conduct Disorder	11	11	5–17	4	14	4–32

CI, confidence interval. [a]95% Confidence interval exceeds proportion in the Dutch norm population. In the Dutch norm population 9% of children have scores in the clinical range on TRF broad-band scales; 5% of children have scores in the clinical range on DBD scales; **Significant difference at $P < 0.05$ between children with SCD and healthy siblings.

In contrast to our expectations, both caregivers and teachers did not report significant differences between children with SCD and healthy siblings on the externalizing problems scales of the CBCL and TRF. However, on the more detailed scales of the DBD, teachers did report slightly more attention deficits. Strikingly, in comparison to the norm population, teachers reported high rates of externalizing problems in the clinical range for both children with SCD and healthy siblings. This finding replicates recent findings in caregivers [19]. However, in a previous study, teachers reported more externalizing problems in children with SCD than in healthy siblings [18], which may reside in the relatively high mean score that was found in children with SCD (T = 66), possibly indicating a selection bias.

Our finding of a similar extent of severe externalizing problems in children with SCD and healthy siblings can be interpreted in several ways. The most evident interpretation would be that severe externalizing problems in children with SCD are not disease specific, but mainly related to socio-demographic factors, influencing both patients and siblings. Alternatively, externalizing problems in children with SCD could indeed be disease related, whereas the externalizing problems in siblings would have a different cause. Disease-related externalizing problems might only occur in the most severely affected subgroup of patients, with neurocognitive deficits associated with cerebral infarction. This effect may be diluted in the current study, which included a rather heterogeneous sample with respect to severity. However, the results of our explorative within-group analyses do show that caregivers rate children with more severe genotypes to be more impaired, which could be interpreted as first evidence for a severity hypothesis. Correlating biological and neuropsychological parameters to behavioral data will therefore be a future direction of our work.

Externalizing problems of healthy siblings could alternatively be caused by family dynamics; healthy siblings may experience feelings of frustration growing up in a family with a chronically diseased child [19]. In a previous study, caregivers did rate children with SCD to have more externalizing problems compared to a SES-matched control group of children derived from the same classroom [24]. This lends support to the idea that externalizing problems of healthy siblings are rather related to family dynamics than to socio-demographic factors. Healthy siblings may specifically act out in school, as opposed to at home (where most of the attention and energy of the caregivers necessarily goes to the ill child), which would explain the different views of caregivers and teachers. Yet, these differences may also be related to different perspectives of the informants; the classroom setting generally is much more structured than the home environment, possibly allowing for better observation of externalizing behavior [11]. Another explanation for these differences could be that caregivers and teachers might be from culturally different backgrounds, leading to different views and interpretations of behavior.

Since caregivers and teachers are equally important in the assessment of behavioral and emotional problems, it is particularly relevant to note that half of all children with SCD received a clinical score on at least one problem scale, when caregiver and teacher forms were combined. According to previous results of a longitudinal study, the majority of children with SCD who initially had behavioral and emotional problems in the clinical range, continued to have these problems over an 8-year period [23]. Following this, we can conclude that children with SCD are especially vulnerable and need specific care. The value of routine

screening for behavioral and emotional problems has been pointed out before, as has the implementation of interventions in a family centered context [19,24]. We strongly support this, as our results demonstrate that not only children with SCD but also their healthy siblings may potentially benefit from this. Additionally, we suggest that screening and interventions should also incorporate the academic and social development of children with SCD, which could be translated into school-based interventions, including social skills' training.

While interpreting the results of this study, strengths and limitations should be taken into account. This is the first study that used multiple informants and multiple measures for the assessment of behavioral and emotional problems in a population of children with SCD living in a Western European country. A sensitive instrument for the evaluation of externalizing problems was included in the design. Moreover, we included a control group of healthy siblings with the same ethnicity and SES, using robust statistical methods to take within family correlations into account. Furthermore, we achieved high response rates in a patient population that is generally difficult to obtain for socio-demographic reasons. However, despite the relatively large sample size of children with SCD, the control group was quite small, limiting the power of the study. A second limitation is that participating caregivers had children with a more severe genotype of SCD than non-participating caregivers. Although the ratio of severe versus milder genotypes in our study sample is similar to the ratio in our total patient population, this may have influenced the results. Third, data were obtained by proxy and not from children with SCD themselves, because a self-report questionnaire (like the Youth Self-Report, the child version of the CBCL and TRF) is not available for all ages. Finally, the CBCL and TRF are not specifically designed for use among ill populations, possibly leading to overestimation of the Somatic Problems scale [16].

Notwithstanding these limitations, the results of this study suggest that children with SCD are at increased risk of developing severe internalizing problems, as a result of their disease. Subgroups of children with SCD also appear to be at increased risk of developing severe externalizing problems, which may either be related to socio-demographic factors, or to disease factors, such as neurocognitive deficits associated with cerebral infarction. Future investigations will have to provide more insight into the causes of the behavioral and emotional problems observed.

ACKNOWLEDGMENT

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