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 6

Medical and neurocognitive determinants of behavioral and emotional problems in children with sickle cell disease: exploratory results

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Chapter 6

Abstract

Aim: To explore the impact of medical factors and neurocognitive functioning on behavioral and emotional problems in children with sickle cell disease (SCD).

Methods: In 34 children with SCD aged 6–18 years, 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.

Results: 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.

Conclusion: These exploratory findings await replication, but imply that neurocognitive functioning is a stronger determinant of externalizing problems than medical factors.
Introduction

Sickle cell disease (SCD) is a hereditary red blood cell disorder which occurs predominantly in people of African ancestry and is characterized by chronic haemolytic anaemia and vascular occlusion, causing pain and irreversible organ damage. In Western Europe, most children with SCD belong to immigrant communities with a lower socio-economic status (SES) (1). There is increasing evidence that children with SCD are at risk of behavioral and emotional problems.

Studies on behavioral and emotional problems in children with SCD have demonstrated a higher prevalence of internalizing problems, such as anxiety and depression, than in healthy children (2-5). This was recently confirmed by a study in which caregivers and teachers perceived severe internalizing problems in almost one in four children with SCD (6). In contrast to previous studies (2), teachers in this study also reported externalizing problems, such as hyperactive or aggressive behavior, in a higher percentage of children with SCD compared to the norm population (11-18% versus 5%). Insight in determinants of both internalizing and externalizing problems in children with SCD will help us to understand the etiology of these problems, and may identify new targets for intervention.

Children with more severe disease seem to have a higher risk of behavioral and emotional problems, as we observed that children with more severe genotypes (HBSS or HbS-β0-thalassemia) had more behavioral and emotional problems compared to children with less severe genotypes of SCD (HbSC or HbS-β+-thalassemia) (6). On the other hand, previous studies measuring disease severity by variables such as pain frequency and number of days hospitalized demonstrated that these variables have a minimal effect on behavioral and emotional problems (3;7;8).

In order to further explore the association between disease severity and behavioral and emotional problems, we constructed a biopsychosocial model incorporating both medical and psychosocial factors, following Thompson and colleagues (9), and Wallander and colleagues (10-12). These previous models mainly focused on the influence of stress and coping to explain adaptation to SCD. In our model, we focused on medical factors that reflect cerebral damage, as these are considered to determine neurocognitive functioning, whereas neurocognitive functioning is subsequently regarded as a determinant of behavioral and emotional outcomes.

Cerebral damage is one of the most devastating complications of SCD. Cerebral oxygenation may be impaired by stenosis of the cerebral arteries, which can be detected by measuring increased cerebral blood flow velocity through the narrowed vessels with transcranial doppler ultrasonography (TCD). Adams et al (13) established reference values to identify children with stenosis of cerebral arteries. A TCD velocity <170 cm/s was classified as normal, 170–200 cm/s as conditional and >200 cm/s as abnormal). Cerebral damage may also ensue from small vessel disease or other pathological changes in the brain. The rate and extent of such pathological changes is supposed to be associated with the severity of the SCD phenotype, which in its turn is reflected by various markers,
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e.g. levels of hemoglobin, or lactate dehydrogenase. Previous studies documented the association between a reduction in hemoglobin and neurocognitive deficits (14-16).

The association between medical factors reflecting cerebral damage and behavioral and emotional problems has only scarcely been studied in children with SCD. Kral et al. (17,18) investigated the association between increased TCD velocities and behavioral and emotional problems. No differences were found between children with normal and increased TCD velocities on broad band measures of internalizing and externalizing behavior problems. However, children with abnormal TCD velocities did have more teacher-reported symptoms of inattention and executive dysfunction.

The association between neurocognitive deficits and behavioral problems has also received little attention in children with SCD. Previous descriptive studies on neurocognitive deficits in children with SCD have demonstrated SCD to be associated with impairments in general cognitive functioning as well as deficits in specific areas of neurocognitive functioning, mainly executive functioning deficits (such as sustained attention, response inhibition, working memory, and planning) (19-25) and visuo-motor deficits (26,27). As the relationship between executive functioning deficits and externalizing problems has been firmly established in children with psychiatric disorders such as Attention Deficit Hyperactivity Disorder (28), it is important to explore this association in children with SCD. Previous studies did not address this before, but focused on the effect of general cognitive functioning on behavioral and emotional problems in children with SCD.

Thompson and colleagues investigated the impact of both cognitive functioning (as measured by IQ) and family processes on behavioral and emotional problems in children with SCD (4,29). In their first study, family conflict, but not cognitive functioning, accounted for a significant proportion of the explained variance in mother-reported behavioral and emotional problems (29). In a longitudinal study, diminished cognitive functioning was associated with persistence of behavioral and emotional problems over time (4).

The studies by Kral et al. (17,18) and Thompson et al. (4,29) provide some support for the biopsychosocial model that we constructed to explain behavioral and emotional problems in children with SCD. In the present literature, there are no data available on the association between other medical factors, such as blood cell counts, or more specific outcome measures of neurocognitive functioning, such as executive and visuo-motor functioning, and behavioral and emotional problems in children with SCD.

The aim of the current study was to explore the association of both medical factors and neurocognitive functioning on behavioral and emotional problems in children with SCD. We included both TCD velocities and blood cell counts as medical factors that are representative of disease severity, and used a comprehensive set of well-defined and validated measures of key neurocognitive functions. These measures appeared to be sensitive for the effect of SCD in a former study (30). We hypothesized that children with SCD with more severe disease and worse neurocognitive functioning would have more behavioral and emotional problems, and would specifically display more externalizing problems.
Methods

Participants
From all children aged 6 to 18 years without prior overt stroke or cerebral bleeding receiving treatment for a severe form of SCD (HbSS or HbS-β⁰-thalassemia) at the Comprehensive Sickle Cell Care Center of the Academic Medical Center, Emma Children’s Hospital in Amsterdam, 42 children were randomly selected for participation. From these, 37 patients (88%) participated in the study (5 declined). All participants underwent neurocognitive assessment. Three participants (7%) were excluded from the analyses because they received scheduled blood transfusion for intracranial arterial stenoses, which changes TCD velocities and blood cell counts. Analyses included 34 participants. Most of these had an HbSS genotype (n = 30, 88%), the other four had an HbS-β⁰-genotype. The clinical condition of all children with SCD was stable at the time the neurocognitive assessment took place. Inclusion took place between October 2007 and October 2008.

Determinants

Medical factors
TCD studies of blood flow velocity in the basal arteries were performed by a radiologist as part of the standard medical care provided in our hospital. Velocities were recorded in 6 vascular anatomical areas: the anterior cerebral arteries (ACA), the proximal middle cerebral arteries (MCA) and the distal internal carotid arteries (ICA) in both hemispheres. All TCD measurements were performed within the year preceding neurocognitive testing, with a median length of 5 months between TCD and neurocognitive testing.

Mean plasma levels of lactate dehydrogenase (LDH), hemoglobin (Hb), reticulocyte, and leukocyte count were derived from assessments at 1-3 routine visits to the outpatient clinic within the year preceding neurocognitive testing, to increase reliability of the assessments. The average of these values was used in the statistical analyses.

Neurocognitive measures
Full-scale IQ was estimated by four subtests of the Wechsler Intelligence Scale for Children-III (31) or the Wechsler Adult Intelligence Scale-III (32) (depending on the child’s age): Vocabulary, Arithmetic, Block Design and Picture Arrangement. These subtests correlate in the low to mid .90’s with Full-scale IQ and therefore give a reliable estimate of Full-scale IQ. Verbal IQ was estimated by Vocabulary and Arithmetic, and Performance IQ was estimated by Block Design and Picture Arrangement.

Response inhibition and sustained attention were measured using the Stop task (33;34). This task requires the child to react as quickly and accurately to airplanes appearing on a computer screen and to occasionally inhibit a response upon presentation of a visual stop signal. Response inhibition was measured by stop signal reaction time (SSRT), an estimate of the speed of the inhibitory response. Sustained attention was measured by
the number of errors, and by mean reaction time (MRT) of correct responses, which was calculated for the first, second, third, and fourth part of the task. Sustained attention difficulties would become apparent in increased error rates and MRTs with progression of the task.

Planning ability was investigated using an adapted version of the Tower of London (ToL; (35)), with multiple difficulty levels. This task requires the child to rearrange three coloured balls on three vertical pegs of different lengths, to transform an initial configuration of the balls into a ‘tower’. The child has to plan the sequence of moves, as there are constraints on the number of moves allowed to solve the problem. The main outcome measure was the ToL score, which is based on the number of trials required to solve a problem, with higher scores indicating better performance. Additional outcome variables were Planning time (the time between presentation of an item and initiation of the first move) and Execution time (the time between initiation of the first move and completion of the final move). It was expected that Planning and Execution time would increase with increasing difficulty levels.

Visuo-spatial working memory was measured with a spatial variant of the computerized N-back task (36-38). Children were presented with a picture of an apple with four holes in it, from which a caterpillar appeared. Children were instructed to press one of four response buttons corresponding to the hole in which they had seen the caterpillar one move back (1-back condition) up to four moves back (4-back condition). For each difficulty level, 32 trials were administered. Total number of correct responses was used as measure of visuo-spatial working memory.

Verbal short term memory was measured with the maximum span on Digit Span forwards, and verbal working memory was measured with the maximum span on Digit Span backwards of the WISC-III (31) or WAIS-III (32) (depending on the child’s age). The forward part was administered first and consisted of repeating sequences of numbers increasing in length in the exact same order. For the backward part, children had to repeat sequences of numbers increasing in length in the reverse order.

Visuo-motor functioning was assessed using the Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI; (39)). In the Beery VMI, children had to reproduce 30 geometric shapes graded in difficulty level as accurately as possible. Total score was used as outcome measure.

Outcome measures

Behavioral questionnaires

The Child Behavior Checklist (CBCL) (40;41) is a 113-item caregiver-reported inventory, providing scores on eight syndrome scales and two broad-band scales: Internalizing Problems (which combines the syndrome scales Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints), and Externalizing Problems (which combines the syndrome scales Rule-Breaking and Aggressive Behavior).
Higher scores on the syndrome scales indicate greater severity of problems. Adequate psychometric properties for this rating scale have been established (40;41).

The Teacher Report Form (TRF) (40;42) is the teacher version of the CBCL. The TRF also consists of 113 items and yields scores on the same scales as obtained with the CBCL. Adequate psychometric properties have been established (40;41).

The Disruptive Behavior Disorder rating scale (DBD) (43;44) is a 42-item inventory that assesses all symptoms of externalizing behavior disorders as described in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The questionnaire can be completed by both caregivers and teachers and provides scores on 4 scales: Inattention, Hyperactivity/impulsivity, Oppositional Defiant Disorder and Conduct Disorder. Higher scores indicate greater severity of problems. Adequate psychometric properties have been established (44).

Procedure
The medical ethics committee of the Academic Medical Center in Amsterdam approved the study protocol. Written informed consent was obtained from parents and from children aged twelve years and older. Medical information (TCD velocities and blood cell counts) was obtained through review of computerized databases and medical charts. Neurocognitive tests were administered at our outpatient clinic in a fixed order by trained examiners, using standardized instructions. Administration of the entire test battery required a maximum of three and a half hours (including breaks). Caregivers were asked to fill out behavioral questionnaires (CBCL and DBD parent version) and to sign informed consent forms, by which they gave permission to send behavioral questionnaires (TRF and DBD teacher version) to the teachers. Teachers received both questionnaires, together with a copy of the informed consent form. Filling out the questionnaires required about 30 minutes.

Data Analysis
The Statistical Package for the Social Sciences (SPSS version 16.0) was used to manage and analyze the data. To reduce the number of determinants and outcome measures, exploratory principle-components analyses (PCA) were conducted. One PCA was performed on the correlation matrix of the neurocognitive measures with oblique rotation using the direct oblimin procedure. One factor was extracted, explaining 44% of the variance of the neurocognitive measures. All the neurocognitive measures loaded relatively high on the factor ($r$ between .51 – .84), the measures of visuo-spatial working memory and visuo-motor functioning had the highest loadings (> .80). Other PCA’s were performed on the correlation matrix of caregiver-reported externalizing problems (including the Externalizing Problems scale of the CBCL and the 4 DBD scales: Inattention, Hyperactivity/impulsivity, Oppositional Defiant Disorder and Conduct Disorder), and of teacher-reported externalizing problems (including the Externalizing Problems scale of the TRF and the 4 DBD teacher scales). In both PCA’s, one factor was extracted. For
caregiver-reported externalizing problems, this factor explained 56% of the variance (with all the scales loading between $r = 0.62 - 0.84$). For teacher-reported externalizing problems, this factor explained 58% of the variance (with all the scales loading between $r = 0.60 - 0.87$). The neurocognitive factor score and both the externalizing problems factor scores were used in subsequent regression analyses.

In line with our biopsychosocial model, in which medical factors are considered determinants of neurocognitive deficits, and neurocognitive deficits are regarded as determinants of behavioral and emotional problems, we conducted exploratory forced-entry hierarchical regression analyses. Medical factors were entered in the first step, followed by neurocognitive measures in the second step, to determine how much variance in behavioral and emotional problems was explained by neurocognitive functioning, above and beyond that of medical factors. For each regression model, the explained variance ($R^2$) was determined, as well as the change in explained variance ($R^2$ change). Variables predicting one of the outcome measures with $p < 0.05$ were considered significant determinants. As age was only associated with the determinants (medical factors and neurocognitive measures) but not with the outcome measures (CBCL, TRF and DBD), age was not included in the regression models. All participants were classified as children with a low socio-economic status (SES), based on the criterion of having a single parent, and/or lower education of mother and/or no parental paid employment (see Table 1). Therefore, SES was not included in the regression models either.

## Results

### Participants

Table 1 provides the demographic and medical characteristics of the participating children with SCD. All participants had TCD velocities less than 170 cm/s (considered normal), except for two children with TCD velocities of 170 to 199 cm/s, considered conditional. In previous work we provided detailed description of the mean scores of this patient group on the neurocognitive measures (30), and CBCL, TRF and DBD (6).

### Determinants of behavioral and emotional problems

Results from the exploratory forced-entry hierarchical regression analyses are summarized in Table 2. TCD velocities and blood cell counts were entered first as medical determinants in the regression analyses (step 1). Although the regression models did not reach significance, the explained variance of these medical determinants varied between 11-29%. No medical factors appeared as significant determinants of behavioral and emotional problems. Adding the neurocognitive factor score in step 2 did not result in significant regression models, but the neurocognitive factor score did appear as a significant determinant of teacher-reported Externalizing problems. On this outcome
measure, adding the neurocognitive factor score to the model resulted in a significant increase in the amount of variance explained, from 11% to 31%.

Table 1. Demographic and medical characteristics of children with SCD (n = 34)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in Years, M (SD)</td>
<td>11.8 (2.9)</td>
</tr>
<tr>
<td>Boys, n (%)</td>
<td>18 (53)</td>
</tr>
<tr>
<td>Country of origin</td>
<td></td>
</tr>
<tr>
<td>Surinam, n (%)</td>
<td>15 (44)</td>
</tr>
<tr>
<td>West/Central Africa, n (%)</td>
<td>17 (50)</td>
</tr>
<tr>
<td>Turkey, n (%)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Parental Marital Status</td>
<td></td>
</tr>
<tr>
<td>Married/Living Together, n (%)</td>
<td>14 (41)</td>
</tr>
<tr>
<td>Single, n (%)</td>
<td>20 (59)</td>
</tr>
<tr>
<td>Highest level of education of mother a</td>
<td></td>
</tr>
<tr>
<td>Lower, n (%)</td>
<td>17 (50)</td>
</tr>
<tr>
<td>Intermediate, n (%)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Higher, n (%)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Not Specified, n (%)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Parental paid employment</td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>21 (62)</td>
</tr>
<tr>
<td>No, n (%)</td>
<td>11 (32)</td>
</tr>
<tr>
<td>Not Specified, n (%)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Blood cell counts b</td>
<td></td>
</tr>
<tr>
<td>Lactate Dehydrogenase, U/L</td>
<td>504 (114)</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Reticulocytes, %</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Leukocytes, 10^9/L</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Transcranial Doppler ultrasonography c</td>
<td></td>
</tr>
<tr>
<td>MCA R, cm/s</td>
<td>120 (20)</td>
</tr>
<tr>
<td>ACA R, cm/s</td>
<td>99 (26)</td>
</tr>
<tr>
<td>ICA R, cm/s</td>
<td>112 (26)</td>
</tr>
<tr>
<td>MCA L, cm/s</td>
<td>112 (21)</td>
</tr>
<tr>
<td>ACA L, cm/s</td>
<td>98 (26)</td>
</tr>
<tr>
<td>ICA L, cm/s</td>
<td>101 (24)</td>
</tr>
</tbody>
</table>

a Levels of education: Lower = elementary education, general secondary education junior-level, lower vocational education; Intermediate = general secondary education-senior level, and vocational education-junior level; Higher = vocational education-senior level and university education. b Blood cell counts: Lactate dehydrogenase: reference value = 0-323; Hemoglobin: reference value = 6.5-10; Reticulocytes: reference value = 0.2-2; Leukocytes: reference value = 4-14. c Transcranial Doppler ultrasonography: MCA R = right middle cerebral artery; ACA R = right anterior cerebral artery; ICA R = right internal carotid artery; MCA L = left middle cerebral artery; ACA L = left anterior cerebral artery; ICA L = left internal carotid artery
**Discussion**

This study is the first to explore a biopsychosocial model of behavioral and emotional problems in children with SCD, by addressing the impact of both medical factors and subsequently neurocognitive functioning on behavioral and emotional problems in children with SCD. We were not able to confirm the hypothesis that children with SCD with more severe disease and worse neurocognitive functioning would have more behavioral and emotional problems, specifically externalizing problems, due to limited statistical power. The direction of the results and the amount of explained variance do imply that neurocognitive functioning is a stronger determinant than medical factors regarding teacher-reported externalizing problems in these children.

Previously, Thompson et al. concluded that IQ did not contribute to the development of behavioral and emotional problems, but that diminished cognitive functioning was associated with persistence of behavioral and emotional problems over time (4;29). Our results provide some new insight, by suggesting that a broader range of neurocognitive

**Table 2. Standardized Regression Coefficients β from the Hierarchical Regression Analysis predicting caregiver- and teacher-reported behavioral and emotional problems (n = 34)**

<table>
<thead>
<tr>
<th></th>
<th>Caregivers</th>
<th>Teachers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Internalizing</td>
<td>Externalizing</td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate Dehydrogenase</td>
<td>-0.136</td>
<td>0.002</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>-0.335</td>
<td>-0.036</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>-0.274</td>
<td>-0.531</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>0.121</td>
<td>0.138</td>
</tr>
<tr>
<td>MCA R</td>
<td>-0.191</td>
<td>-0.013</td>
</tr>
<tr>
<td>ACA R</td>
<td>0.019</td>
<td>0.446</td>
</tr>
<tr>
<td>ICA R</td>
<td>-0.110</td>
<td>-0.216</td>
</tr>
<tr>
<td>MCA L</td>
<td>0.127</td>
<td>0.259</td>
</tr>
<tr>
<td>ACA L</td>
<td>-0.361</td>
<td>-0.032</td>
</tr>
<tr>
<td>ICA L</td>
<td>0.318</td>
<td>-0.205</td>
</tr>
<tr>
<td>R²</td>
<td>0.29</td>
<td>0.25</td>
</tr>
<tr>
<td>F</td>
<td>0.90</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurocognitive factor score</td>
<td>-0.018</td>
<td>-0.280</td>
</tr>
<tr>
<td>Δ R²</td>
<td>0.00</td>
<td>0.05</td>
</tr>
<tr>
<td>R²</td>
<td>0.29</td>
<td>0.30</td>
</tr>
<tr>
<td>F</td>
<td>0.78</td>
<td>0.80</td>
</tr>
</tbody>
</table>

MCA R = right middle cerebral artery; ACA R = right anterior cerebral artery; ICA R = right internal carotid artery; MCA L = left middle cerebral artery; ACA L = left anterior cerebral artery; ICA L = left internal carotid artery. *p<0.05.
measures (combined in the neurocognitive factor score) could indeed be associated with externalizing problems in children with SCD, especially when measured with a sensitive instrument such as the DBD. However, these exploratory findings await replication.

Disease severity generally had a minimal effect on behavioral and emotional problems in previous studies (3;7;8). The present study adds to the literature on this subject, as the association between direct physiological measures, reflecting cerebral damage, and behavioral and emotional problems in children with SCD have scarcely been investigated. Findings of one previous study demonstrated an association between TCD velocities and behavioral and emotional problems. These findings should be interpreted with caution, as this study included children receiving scheduled blood transfusions, thereby altering the medical situation on which they were classified initially (18). In the present study, children receiving scheduled blood transfusions were not included in the analyses, which might explain the conflicting findings. On the other hand, we were not able to reveal any medical factors as significant determinants due to limited power. Nevertheless, the impact of disease severity on behavioral and emotional problems might indeed be minimal. Studies in pediatric oncology patients imply that perceived illness severity is associated with psychosocial functioning, and therefore may be more indicative of the intensity of the child’s disease than objective measures (45). This should be investigated further in children with SCD.

Some strengths of this study were that we assessed a broad range of neurocognitive functions, with well-defined and validated measures, and used multiple informants and multiple measures for the assessment of behavioral and emotional problems. By correlating medical and neurocognitive determinants to behavioral and emotional outcomes, we attempted to gain novel information on the complex process of these determinants. An evident limitation of this study was the small sample size, mitigating statistical power. Moreover, while the exclusion of patients on scheduled blood transfusions was necessary to prevent a confounding effect, this made our study sample less likely to reflect much variability in TCD velocities (i.e., all patients had TCD velocities <200 cm/s), which further reduces power. The sample size also precluded the use of a mediation model in the statistical analyses.

Only studies with more sufficient power can give more insight in the determinants of behavioral and emotional problems in children with SCD. These studies should have multicenter designs to broaden the sample size. We also recommend for these future studies to include more psychosocial factors as determinants in the biopsychosocial model, such as coping styles and family functioning, besides medical and neurocognitive parameters. This would provide more understanding of the independent and combined contributions of psychosocial and biomedical processes to child neurocognitive functioning and subsequent behavioral and emotional problems. Consequently, more factors that could serve as relevant intervention targets could be identified (46).
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References


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