Kawasaki disease: Studies on etiology, treatment and long-term follow-up

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Chapter 10

QUALITY OF LIFE AND BEHAVIORAL FUNCTIONING IN DUTCH CHILDREN WITH A HISTORY OF KAWASAKI DISEASE

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ABSTRACT

Objective:
The authors evaluated health-related quality of life (HRQOL) and behavioral functioning in patients with a history of Kawasaki disease (KD).

Methods:
A cross-sectional study was conducted at a tertiary referral center for KD follow-up in 280 patients (mean age 8.6 years; 60.0% male). Patients were eligible when they were aged 0-18 years and had a history of KD. HRQOL was assessed using the TNO-AZL Preschool Children Quality of life (TAPQOL) for children 0-5 years old and the Pediatric Inventory of Quality of Life Core Scales 4.0 (PedsQL) for those 6-18 years old. Behavioral functioning was evaluated using the Strength and Difficulties Questionnaire (SDQ) (8-16 years proxy report and 11-16 years self-report). KD results were compared with Dutch norm data, and patients with and without coronary artery aneurysms were compared.

Results:
HRQOL was significantly worse for male patients aged 0-5 years on 4 of the 12 TAPQOL scales and for female patients on the motor functioning scale. At an older age, the HRQOL of patients was comparable with the norm population. Coronary artery status did not influence HRQOL. Parents reported more behavioral problems on the hyperactivity and emotional subscale in patients compared with the norm population.

Conclusions:
Although at older age the HRQOL of KD patients is comparable with the Dutch norm, HRQOL seems to be particularly impaired at younger age. Parents reported more hyperactivity and emotional problems in KD patients.
INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis of unknown etiology that predominantly affects children <5 years old. The most serious complication of the disease is the development of coronary artery aneurysms (CAA), occurring in <10% of the patients adequately treated with high-dose intravenous immunoglobulins. In developed countries, KD is the leading cause of acquired heart disease in childhood. The diagnosis of KD is made by the presence of several clinical criteria including persistent fever, bilateral non-exudative conjunctival injection, erythema of the lips and oral mucosa, swelling and redness of the extremities, polymorphous rash, and cervical lymphadenopathy. Extreme irritability is not one of the diagnostic criteria but is a common symptom during the acute KD phase. Other symptoms indicating central nerve system (CNS) involvement have also been reported and include severe lethargy, aseptic meningitis, semicoma, facial nerve palsy, sensorineural hearing loss, hemiplegia, and cerebral infarction. Studies in KD have mainly been focused on the etiology and the cardiac complications of the disease. Studies evaluating the long-term impact of the acute KD episode on health related quality of life (HRQOL) and psychosocial functioning in children are scarce and report contradictory results. Moreover, the few studies performed report on relatively small numbers of patients. The purposes of the present study were to evaluate HRQOL and psychosocial functioning in a large group of Dutch children and adolescents with a history of KD and to compare HRQOL of patients with and without coronary artery sequelae.

METHODS

Study population

This cross-sectional study was conducted between October 2010 and February 2011 at our multidisciplinary KD follow-up clinic. Patients were included if they were aged 0-18 years and had a history with KD according to the diagnostic criteria. Eligible patients and their parents received an invitational letter to participate in the study. When letters were undeliverable, attempts were made to verify the addresses and letters were sent again. If families consented with participation, they received a password for the study website (www.hetklikt.nu/twee/kawasaki). The computer system automatically selected the appropriate questionnaires (depending on the child’s age) and, subsequently, the patient (8–18 years) and/or parent (0–18 years) could start completing the questionnaires. In a second wave of recruitment, families were approached via telephone if they had not responded to the invitational letter. Patients were excluded if they had an insufficient knowledge of the Dutch language or if they had a history of a severe chronic illness or CNS dysfunction unrelated to KD. Eligible patients with KD who did not complete the questionnaires were defined as nonparticipants.
The study was performed according to the regulations of the medical ethical committee of our institute.

**Patient information**

Demographic and clinical characteristics of all eligible patients were collected retrospectively through a review of medical records. The presence of CNS symptoms during the acute KD phase was evaluated. A CAA was defined according to criteria established by the Japanese Ministry of Health in 1984 (i.e., luminal diameter >3 mm in children <5 years old, >4 mm in those >5 years old, or a diameter 1.5 times the size of an adjacent segment or an irregular lumen). Patients were divided into groups based on their coronary artery status (patients without CAA vs patients with a history of CAA) and based on the presence of CNS symptoms during the acute phase (patients presenting with CNS symptoms vs those presenting without CNS symptoms).

**Questionnaires**

**Socio-demographics**

Socio-demographic characteristics of participating children and parents were collected with the use of a general questionnaire completed by one of the parents. The following information was collected about the child: use of medication, educational level, and sports activities. From the parent, we obtained on age, sex, country of birth, parental education, and marital status. Parental educational was divided into 3 levels: primary school and primary vocational school (low), secondary school and secondary vocational school (middle), and higher vocational school and university (high).

**HRQOL**

Two questionnaires were used to evaluate HRQOL: the TNO-AZL Preschool Children Quality of Life questionnaire (TAPQOL) and the Pediatric Quality of Life inventory 4.0 (PedsQl 4.0).

**TAPQOL**

The TAPQOL is a generic, multidimensional HRQOL instrument for children aged 1 to 5 years. The 43-item questionnaire is based on proxy report. The TAPQOL assesses the child’s functioning on 12 multi-item scales: stomach (gastro-intestinal functioning), skin, lungs, sleeping, appetite, motor functioning, positive mood, anxiety, liveliness, problematic behavior, social functioning, and communication. The 12 scales cover the domains of physical, social, cognitive, and emotional functioning. Higher scores indicate a better HRQOL. Completion time is about 5–10 minutes and the psychometric properties are satisfactory. TAPQOL norm data from the Dutch general population are available.
**PedsQl 4.0**

The PedsQl 4.0 is a generic HRQOL questionnaire for children aged 6-18 years. The PedsQl has 2 versions: a child self-report and a parent proxy-report version. In this study both versions were used - the proxy-report for children aged 6-7 years and the self-report for the children aged 8-18 years. The 23 items of the PedsQl cover 4 subscales: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). Higher PedsQL scores indicate a better HRQOL. Completion time is about 5 to 10 minutes. The PedsQl 4.0 has a satisfactory internal consistency on all subscales, and representative norm data from the Dutch general population are available. The PedsQl has 2 different versions: the past-month or past-week version. The past-week version was used for this study.

**Behavioral functioning**

**SDQ**

Behavioral functioning was measured with the Dutch version of the Strengths and Difficulties Questionnaire (SDQ). The SDQ is a behavioral screening questionnaire. The SDQ provides balanced coverage of children’s and adolescent’s behavior, emotions, and relationships. The SDQ contains 25 items: 20 problem items across 4 subscales (emotional symptoms, conduct problems, hyperactivity, and peer relationship problems) and a 5-item prosocial behavior subscale. For each subscale, the score ranges from 0 to 10. Higher scores on the prosocial subscale indicate more strengths, whereas higher scores on the other 4 subscales indicate more difficulties. Summing the scores from all the subscales except the prosocial scale generates a total difficulties score ranging from 0 to 40. The psychometric properties of the SDQ have been examined in a sample of Dutch children and adolescents and have acceptable internal consistency and test-test stability. Dutch norm data are available for children aged 8-16 years. For the present study, the self-report (11-16 years) and the proxy report (4-16 years) versions were used.

**Statistical analysis**

The Statistical Package for Social Sciences (SPSS, Chicago, Illinois) version 16.0 was used for statistical analyses. First, differences between participants and nonparticipants were analyzed using independent t-tests and Chi² tests. Second, TAPQOL and PedsQL scores were analyzed. Before the final analyses were conducted, scales were constructed and missing data were imputed on the basis of the guidelines of the questionnaires used. TAPQOL and PedsQL scores of patients with KD and the norm population and of patients with KD with and without CAAs were compared using ANOVA by group, gender and age. Finally, one-way sample t tests were used to compare SDQ scores of patients with KD with mean Dutch norm data. Due to the multiple testing, we chose a 1% statistical significance level. To report the
strength of the differences, effect sizes were calculated by dividing the differences in mean 
scores between the patients with KD and the norm group by the SD of the norm group. 
Effect sizes up to 0.2 were considered to be small; between 0.2 and 0.8, moderate; and effect 
sizes >0.8, large.21

RESULTS

Socio-demographic and medical information

Of the 434 patients in our institutional database, 368 met the inclusion criteria for the study. Eight 
families were excluded because of an insufficient knowledge of the Dutch language 
(n=6) or other severe chronic illness of the child (n=2; 1 each with chronic granulomatous 
disease and West syndrome). Ten letters of invitation were undeliverable. In total, 280 of the 
350 approached families completed the study (response rate 80%). Clinical characteristics 
of participants and nonparticipants did not differ significantly, but in the participants there 
was a trend toward a younger age (mean age, 8.6±4.4 years vs 9.8±4.4 years, P=0.043) and 
shorter interval from disease onset to the study (mean interval in years 5.8±4.2 vs 7.1±4.3, 
P=0.017) (Table 1).

Table 1. Comparison of participants and non-participants for clinical KD characteristics

<table>
<thead>
<tr>
<th></th>
<th>Participants (n=280)</th>
<th>Non-participants (n=70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>168 (60.0%)</td>
<td>47 (67.1%)</td>
<td>0.272</td>
</tr>
<tr>
<td>Age (yrs), mean ± SD</td>
<td>8.6 ± 4.4</td>
<td>9.8 ± 4.4</td>
<td>0.043</td>
</tr>
<tr>
<td>Age at KD onset (yrs), median (range)</td>
<td>2.4 (0.1–14.0)</td>
<td>1.8 (0.2–12.1)</td>
<td>0.144</td>
</tr>
<tr>
<td>Interval from KD onset to the study (yrs), mean ± SD</td>
<td>5.8 ± 4.2</td>
<td>7.1 ± 4.3</td>
<td>0.017</td>
</tr>
<tr>
<td>Patients admitted to the PICU</td>
<td>8 (2.9%)</td>
<td>4 (5.7%)</td>
<td>0.230</td>
</tr>
<tr>
<td>Duration of hospital admission (days), median (range)</td>
<td>7 (1 – 57)</td>
<td>8 (2 – 106)</td>
<td>0.396</td>
</tr>
<tr>
<td>Patients with coronary artery aneurysms</td>
<td>47 (16.8%)</td>
<td>14 (20.0%)</td>
<td>0.526</td>
</tr>
</tbody>
</table>

Abbreviations: PICU=pediatric intensive care unit; SD=standard deviation; yrs=years.

Clinical and socio-demographic characteristics of the participating patients are shown in 
Table 2. The mean age was 8.6 ± 4.4 years, and the majority of patients were male (60%), 
reflecting the higher incidence of KD in male patients. Irritability (n=47), lethargy (n=8), and 
aseptic meningitis (n=9) were frequently reported during the acute KD phase, although a 
facial nerve palsy, hallucinations, and sensorineural hearing loss were only reported once in 
our cohort of patients.
HRQOL

Children aged 0-5 years (TAPQOL)

TAPQOL results are shown in table 3. Significantly lower scores were reported by parents in male patients compared with the Dutch norm group on 4 scales: skin, motor functioning, communication, and liveliness. In female patients, only the motor functioning scale was
significantly lower compared with the Dutch norm population. There was no difference in TAPQOL scores of patients with and without CAAs (data not shown).

### Children aged 6-18 years (PedsQl)

Table 4 shows PedsQl results of patients with KD compared with the Dutch norm population. In the groups aged 8-12 and 13-18 years old, no significant differences were found between patients and controls (self-report). HRQOL of patients with and without CAAs was comparable on all subscales, including physical health (data not shown).

### Behavioral functioning (SDQ)

Table 5 shows the SDQ results. Parents of male patients with KD (8-16 years old) reported significantly higher mean SDQ scores, indicating more difficulties, than the norm along the hyperactivity subscale. Parents reported more emotional problems for female patients. Higher mean scores along the subscale prosocial were found for male patients indicating more prosocial behavior.

Male patients with KD aged 11-16 years self-reported significantly less difficulties in terms of conduct problems and significant higher scores on the prosocial subscale than the Dutch norm. Female patients with KD reported significantly less peer problems.

SDQ results of patients presenting with and without CNS symptoms were compared within our KD cohort (aged 4–16 years). Mean SDQ scores did not differ significantly between pa-
tients with or without a neurological presentation (total difficulties score 8.7±5.5 vs 8.1±5.8; emotional symptoms: 2.4±2.0 vs 2.4±2.4; conduct problems: 1.5±1.4 vs 1.0±1.3; hyperactivity: 3.7±2.7 vs 3.7±2.8; peer relationship problems 1.3±1.6 vs 1.1±1.5; and prosocial behavior: 8.1±2.1 vs 8.6±1.5).

Table 4. Mean HRQOL scores (PedsQl) of male and female patients with Kawasaki disease compared with the Dutch norm population

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KD patients</td>
<td>Norm population</td>
</tr>
<tr>
<td></td>
<td>n  Mean(SD)</td>
<td>n  Mean(SD)</td>
</tr>
<tr>
<td>Group 6-7 (proxy report)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>34  81.2 (15.6)</td>
<td>28  87.2 (7.6)</td>
</tr>
<tr>
<td>Psychosocial health</td>
<td>34  78.2 (17.6)</td>
<td>28  84.7 (9.8)</td>
</tr>
<tr>
<td>Physical health</td>
<td>34  87.0 (15.2)</td>
<td>28  91.7 (5.9)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>34  74.6 (18.2)</td>
<td>28  79.5 (13.5)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>34  81.9 (19.2)</td>
<td>28  90.5 (11.0)</td>
</tr>
<tr>
<td>School functioning</td>
<td>34  78.1 (21.0)</td>
<td>28  84.1 (11.2)</td>
</tr>
<tr>
<td>Group 8-12 (self-report)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>56  81.9 (12.9)</td>
<td>92  83.3 (8.4)</td>
</tr>
<tr>
<td>Psychosocial health</td>
<td>56  79.2 (13.5)</td>
<td>92  82.2 (9.4)</td>
</tr>
<tr>
<td>Physical health</td>
<td>56  87.1 (13.7)</td>
<td>92  85.5 (9.3)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>56  76.2 (18.4)</td>
<td>92  79.5 (12.7)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>56  85.6 (14.1)</td>
<td>92  87.2 (10.6)</td>
</tr>
<tr>
<td>School functioning</td>
<td>56  75.7 (16.7)</td>
<td>92  79.8 (11.5)</td>
</tr>
<tr>
<td>Group 13-18 (self-report)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>29  86.2 (11.4)</td>
<td>62  83.1 (9.5)</td>
</tr>
<tr>
<td>Psychosocial health</td>
<td>29  83.5 (13.1)</td>
<td>62  80.7 (11.1)</td>
</tr>
<tr>
<td>Physical health</td>
<td>29  91.5 (13.8)</td>
<td>62  87.5 (9.3)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>29  86.6 (15.1)</td>
<td>62  79.5 (14.6)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>29  88.3 (13.5)</td>
<td>62  88.2 (13.0)</td>
</tr>
<tr>
<td>School functioning</td>
<td>29  78.5 (15.4)</td>
<td>62  74.4 (13.0)</td>
</tr>
</tbody>
</table>

PedsQL scores range from 0 to 100, higher scores represent a better HRQOL. d = effect size
* KD patients versus Dutch norm population
Our study demonstrates that young male patients with KD (aged 0-5 years) have a significantly impaired HRQOL compared with the norm on 4 of the 12 TAPQOL scales (skin, motor functioning, communication, and liveliness subscale). In female patients, a significant impairment of HRQOL was reported only on the motor functioning scale. Like in the male patients, lower scores were also reported on the skin and liveliness subscale in the female patients, but this was not a significant difference. The sex differences in this age group may be explained by the fact that a lower number of female patients participated in the study, which has limited the statistical power to identify significant differences.

In contrast to the impaired HRQOL in young patients, at older age (6-18 years) no differences were found between PedsQL scores of patients with KD and the norm population. Overall, HRQOL seems to be favorable and comparable with the healthy Dutch population in this age group. These findings are in line with previous studies evaluating HRQOL in patients admitted with an acute serious illness. One of these studies by Knoester et al evaluated HRQOL in a cohort of previously healthy children who were admitted unexpectedly to the pediatric intensive care unit. The authors found similar findings and also reported an

Table 5. Behavioral and emotional disorders assessed by the Strengths and Difficulties Questionnaire (SDQ) of male and female KD patients compared with Dutch norm data.

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KD patients</td>
<td>Dutch Norm</td>
</tr>
<tr>
<td></td>
<td>n, Mean (SD)</td>
<td>P 1, d</td>
</tr>
<tr>
<td>Parent SDQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-16 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>78, 2.2 (2.1)</td>
<td>0.081, 0.2</td>
</tr>
<tr>
<td>Conduct</td>
<td>78, 1.1 (1.3)</td>
<td>0.092, 0.1</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>78, 4.1 (2.5)</td>
<td>0.005*, 0.3</td>
</tr>
<tr>
<td>Peer problems</td>
<td>78, 1.2 (1.6)</td>
<td>0.204, 0.1</td>
</tr>
<tr>
<td>Prosocial</td>
<td>78, 8.7 (1.4)</td>
<td>0.002*, 0.3</td>
</tr>
<tr>
<td>Total difficulties</td>
<td>78, 8.6 (5.1)</td>
<td>0.192, 0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-report SDQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-16 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>39, 1.5 (1.5)</td>
<td>0.772, 0.1</td>
</tr>
<tr>
<td>Conduct</td>
<td>39, 1.1 (1.3)</td>
<td>0.000**, 0.4</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>39, 3.4 (2.0)</td>
<td>0.131, 0.8</td>
</tr>
<tr>
<td>Peer problems</td>
<td>39, 1.2 (1.8)</td>
<td>0.017, 0.4</td>
</tr>
<tr>
<td>Prosocial</td>
<td>39, 8.2 (2.0)</td>
<td>0.000**, 0.5</td>
</tr>
<tr>
<td>Total difficulties</td>
<td>39, 7.2 (5.1)</td>
<td>0.004*, 0.5</td>
</tr>
</tbody>
</table>

Higher scores on the SDQ subscales indicate more difficulties, except for the prosocial scale. $d$ = effect size

1 KD patients versus Dutch norm data

* Difference at p < 0.01 according to one-way sample t-test

** Difference at p < 0.001 according to one-way sample t-test
improvement of HRQOL over time. We therefore believe that our HRQOL findings reflect a rather general reaction to hospitalization because of an acute serious illness, especially in the patients without persisting coronary artery sequelae.

The difference in HRQOL between young and older patients may be explained by the different types of questionnaires used in this study (TAPQOL vs PedsQL), but there are 2 more likely explanations. First, because KD is a vasculitis that predominantly occurs in very young children, the mean time interval from disease onset to study participation increases with age. The younger patients have been diagnosed with KD more recently and may reasonably experience more problems. Second, the difference may be explained by the discrepancy between proxy and self-report. The imperfect agreement between self and proxy-report, termed cross-informant variance, has previously been described in HRQOL and psychosocial functioning measurements of sick and healthy children. A pediatric illness like KD not only affects the child but also the entire family, and especially the parents. Parents of KD patients undergo a great deal of stress and anxiety during the hospitalization period of their child associated with obtaining and dealing with the diagnosis of KD. Moreover, parents of children with coronary artery complications express persistent anxiety even years after the acute phase of the illness. Prior to KD, most children were perfectly healthy and it is an unexpected and probably traumatic event for parents to suddenly have a seriously ill child. Anxiety and concerns of the parents about the illness and the possible long-term complications may be reflected in their assessment of the HRQOL of their child. The experiences of the parents may be in contrast to the experiences of the patients themselves, who will in many cases not even remember the period of hospitalization at very young age. In combination with the increased interval from disease onset, the impact of KD on parents may thus explain the reported differences in HRQOL of young (proxy report) and older patients (self-report) with a history of KD.

**Psychosocial functioning**

The difference between self-report and proxy report was also demonstrated by the SDQ results. For children aged 11-16 years the SDQ was completed both by proxy and self-report. Parents reported more hyperactivity and emotional problems compared to the Dutch norm, whereas patients themselves reported no differences with the norm data on these 2 subscales. On all other problem subscales, parents reported no differences with the norm, whereas patients self-rated significantly less behavioral problems. To get more insight in behavioral problems in patients with KD, behavioral problems may be evaluated using the teacher-version of the SDQ or other neuropsychological assessments in future research. Hyperactivity problems were reported more frequently by parents of male patients with KD compared with the Dutch norm. Previously, King *et al* also reported more attention difficulties in patients with KD compared with their healthy siblings using the Achenbach Child Behavior Checklist. Hypothetically, the reported behavioral problems may be the result
from vasculitis of the cerebral arteries. In KD, the systemic vasculitis predominantly affects the coronary arteries but has also been shown to affect the cerebral arteries. Localized hypoperfusion has previously been observed in cerebral imaging studies in KD. In 1998, Ichiyama and co-authors reported transient cerebral hypoperfusion on single-photon emission computed tomography in 6 of 21 patients with KD without neurological symptoms. More recently, Hikita et al. also observed localized hypoperfusion in 13 of 18 patients with KD without a neurological presentation and in all 4 patients with neurological symptoms. The hypoperfusion was not restricted to the acute phase only but was also observed during follow-up single-photon emission computed tomography – both in patients with and without neurological symptoms. Localized hypoperfusion may reasonably result in (subtle) CNS damage. It is therefore possible that the reported behavioral problems have a pathologic substrate and are not only the result of the psychological consequences of having suffered from a serious disease of unknown etiology and future outcome. However, future studies are needed to investigate this.

Like Carlton et al., we have shown that parents rated more emotional behavioral problems in prior (female) patients with KD. We recommend pediatricians to keep this in mind and to be aware of the potential need for referral to a clinical psychologist in patients with a history of KD because of behavioral problems.

**Coronary artery status**

Although cardiovascular sequelae may have a negative influence on HRQOL in KD, it is reassuring that we found no difference in HRQOL of children with and without coronary artery aneurysms. Muta et al. previously investigated HRQOL in an adult Japanese population of patients with a history of KD in childhood. In agreement with the results of our study, no differences were found in HRQOL of patients with and without (giant) coronary artery aneurysms. The study of Muta et al. did not assess behavioral functioning and was performed in a different study population, consisting of patients aged >16 years.

**Limitations and future research**

Our study has some limitations. First, because of the cross-sectional design of this study, the course of HRQOL and psychosocial functioning over time cannot be assessed. Second, there was a difference in age and sex between the patients and the norm groups, but we have corrected for potential effects in the subsequent statistical analyses. Third, there was a trend toward differences in age and interval from disease onset between participants and nonparticipants. Participants were younger and, consequently, had a shorter interval from disease onset to the study. There is a potential for selection bias, in that the families who participated may have been more motivated or may have been more concerned because of shorter interval from the acute disease onset. However, the high response rate (80%) may have limited this potential bias. Fourth, patients were stratified for coronary artery
status based on the Japanese Ministry of Health criteria instead of z-scores because the dichotomous Japanese definition is still routinely used in our clinical practice. Patients can therefore be misclassified\textsuperscript{32,33}. Finally, 2 different HRQOL instruments were used (TAPQOL and PedsQL). The PedsQL questionnaire for children aged 2-4 years was not translated and validated in Dutch at the start of this study. We therefore choose to use the TAPQOL, which has previously been shown to be a reliable and valid instrument for HRQOL evaluation in preschool children\textsuperscript{15}.

Based on our findings, some suggestions for further research can be done. The behavioral problems reported in our cohort of patients with KD must be evaluated more extensively, preferably by neuropsychological assessments or semi-structured interviews by a child psychologist. The possible relation with a cerebral vasculopathy must also be delineated in future (imaging) studies. In addition, future research is needed to evaluate the impact on parents of having a child with KD. It is important to get insight in functioning of parents to provide comprehensive and high quality care for families with children with KD.

**CONCLUSIONS**

In conclusion, we found that HRQOL and psychosocial functioning of patients with a history of KD overall is favorable, regardless of the coronary artery status. However, especially in young patients HRQOL may be impaired and hyperactivity and emotional problems are more often being reported by parents in KD patients compared to Dutch norm data. We suppose that these findings reflect the psychosocial consequences of hospitalization because of an acute serious illness at young age, but a pathological substrate cannot completely be excluded. We recommend pediatricians to keep this in mind and to consider referral of KD families to a clinical psychologist where necessary.

**ACKNOWLEDGEMENTS**

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