

The Effect of Kawasaki Disease on Cognition and Behavior

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Objective: To determine whether there are associated long-term deficits in the cognitive, academic, or behavioral outcomes of children with a previous episode of Kawasaki disease.

Design: Cohort analytic study.

Setting: A tertiary care pediatric hospital in Ottawa, Ontario.

Participants: Thirty-two patients with a past diagnosis of Kawasaki disease. Siblings of the patients with Kawasaki disease were eligible to be controls.

Measures: A blinded psychometrist (Y.K.) assessed cognition by the appropriate Wechsler Intelligence scale, academic achievement by the Wechsler Individual Achievement Test, and behavior by the Achenbach Child Behavior Checklist.

Results: No differences were found in cognitive or academic measures and the mean scores corresponded closely to national norms. Parents rated their children who had Kawasaki disease as having significantly more internalizing ($P < .03$) and attentional ($P < .02$) behavior problems than controls; the risk of a clinically significant behavioral score was 3.3 times greater ($P < .03$; 95% confidence interval, 1.1-9.9) than for sibling controls.

Conclusions: While no effect on cognitive development or academic performance was demonstrated, these results provide preliminary indication of a post-Kawasaki disease deficit in internalizing and attentional behavior.

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KAWASAKI DISEASE, a multi-system vasculitis of unknown cause, is an acute illness of early childhood with an estimated annual incidence of 6.2 children per 100 000.^{1,2} Cardiac involvement is the most serious complication, but treatment with intravenous γ -globulin (IVGG) can reduce the incidence of coronary artery abnormalities from 20% to less than 5%.^{1,3,4} Extreme irritability is also a common feature during the acute illness.⁵ Direct evidence of central nervous system (CNS) involvement, such as aseptic meningitis, has been found in at least 25% of patients who have undergone lumbar puncture,⁶ and case studies have reported severe lethargy, semi-coma, facial nerve palsy,⁷⁻¹⁰ sensorineural hearing loss,¹¹ hemiplegia,¹² and cerebral infarction.¹³⁻¹⁵ Concern regarding CNS involvement has led some investigators to recommend long-term monitoring for neurologic problems.¹⁶

While major neurologic sequelae can occur in a small number of those affected, most escape clinically apparent CNS injury. No studies have examined whether the

acute symptoms are followed by subtle but clinically important changes in CNS function, or whether IVGG treatment can modify these effects. We therefore designed this retrospective cohort study, with siblings used as controls, to examine the effect of an acute episode of Kawasaki disease on cognitive ability, school achievement, and behavioral function. Recognition of subtle neurocognitive involvement is important, as current research supports the beneficial effects of early identification and appropriate treatment.^{17,18} Conversely, if cognitive or behavioral sequelae are not found, parents can be reassured that the effects of acute Kawasaki disease on the CNS are transient and unlikely to have an effect on future development.

RESULTS

SUBJECT CHARACTERISTICS

We reviewed 97 medical records, of which 75 met eligibility criteria; 29 potential subjects could not be located from the last known address, telephone number, or family physician listed on the medical record.

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SUBJECTS AND METHODS

STUDY DESIGN

A cohort analytic study was selected as the most feasible method to explore our question, as Kawasaki disease is a relatively uncommon disorder. Siblings of the patients with Kawasaki disease were selected as controls in an attempt to minimize the influence of genetics and environment on development. The study was approved by the research ethics committee at the Children's Hospital of Eastern Ontario, Ottawa, and informed, written consent was obtained from all participants and/or parents.

SUBJECTS

Patients with Kawasaki disease (defined by diagnostic code 446.1 of the *International Classification of Diseases, Ninth Revision, Clinical Modification*¹⁹) seen at our institution between January 1, 1975, and December 31, 1994, were eligible if they (1) satisfied the Centers for Disease Control and Prevention diagnostic criteria for Kawasaki disease,²⁰ (2) were between the ages of 4 to 18 years at the time of psychometric testing, (3) had been diagnosed as having the disease at least 1 year previously, (4) spoke English as their first language, (5) had a biological sibling, and (6) had no history of CNS dysfunction or acute illness unrelated to the Kawasaki disease but known to involve risk of CNS damage. Controls were selected from among the biological siblings of patients with Kawasaki disease and were matched by age (± 2 years). Siblings were excluded if they had a history of CNS dysfunction or an acute illness known to involve risk of CNS damage. Whenever possible, a sibling of the patient with Kawasaki disease was enrolled as his or her control, resulting in 25 subject-sibling matches. When a within-family match could not be made, the subject was matched with another child within the sibling pool, yielding another 7 matches. Six patients could not be matched either from their own families or from the sibling pool.

ASSESSMENT MEASURES

The assessment measures were completed in a single visit by a psychometrist (Y.K.) blinded to the Kawasaki disease subject or control status. Cognitive ability at all age levels was assessed by the appropriate Wechsler scale: the Wechsler Preschool and Primary Scale of Intelligence—Revised,²¹ the Wechsler Intelligence Scale for Children,²² or the Wechsler Adult Intelligence Scale—Revised.²³ Academic achievement was assessed by the Wechsler

Individual Achievement Test²⁴; all children were administered the screening subtests and the word identification subtest of the Wechsler Individual Achievement Test, while the written expression subtest was included for children 7½ years and older. Behavior rating scales were chosen to provide summaries of behavior problems, externalizing and internalizing features, and ratings of specific problem areas. Parents completed the Achenbach Child Behavior Checklist (CBCL)²⁵ for all patients and controls. Teachers of children aged 5 to 12 years were asked to complete the Teacher's Report Form,²⁶ while adolescents aged 13 to 18 years completed a self-rating questionnaire, the Youth Self-Report.²⁷ A telephone questionnaire was completed by a research assistant to obtain information on demographics, socioeconomic status, development, school, and health.

CLINICAL MANIFESTATIONS

Prior to the start of the study, 2 of the investigators (W.J.K. and N.B.) reviewed the medical records of the patients with Kawasaki disease and classified the cardiac and CNS findings as normal or abnormal. Abnormal findings were subclassified according to type: cardiac findings as myocarditis/pericarditis and coronary artery abnormalities (dilatation, ectasia, or aneurysm); and CNS findings as irritability and/or lethargy, aseptic meningitis, or focal neurologic defect. Inflammatory markers, including fever, white blood cell count, erythrocyte sedimentation rate, and platelet count, were also recorded.

DATA ANALYSIS

Statistical Product and Service Solutions statistical software, version 3.0 (SPSS Inc, Chicago, Ill), was used to carry out the data analyses. Outcome measures were analyzed using the matched group of 32 subject-sibling pairs, while the clinical manifestations and the effect of treatment with IVGG were analyzed using the entire group of 38 patients with Kawasaki disease. To avoid multiple comparisons, only the Wechsler IQ scores and the summary scores of the Wechsler Individual Achievement Test and the CBCL were used to test the study hypotheses; subtest score analysis was carried out only if summary scores were significant. Paired *t* test comparisons were used for all continuous outcome measures. Logistic regression (risk analysis) was performed on the parents' behavior ratings using the CBCL to assess their clinical significance, and χ^2 comparisons and Pearson correlations were used to analyze the relationships between Kawasaki disease clinical manifestations and test scores. Dichotomous variables yielded by the parent interviews were analyzed by means of the χ^2 statistic.

Therefore, 46 families were contacted, 5 of which did not wish to participate and 3 of which were unable to schedule appointments, resulting in a total of 38 enrolled families. There were an equal number of patients with Kawasaki disease who had and had not received IVGG treatment (19 each). From the 38 enrolled families, we were able to match 32 sibling controls with similar demographic profiles and socioeconomic status as detected by the Green score²⁸ (predominantly middle-range). Complete sex matching was not possible within the con-

straints of the sibling pool, but the sex ratios of the group with Kawasaki disease (22 boys and 10 girls) and the control group (18 boys and 14 girls) did not show a significant difference ($\chi^2 = 1.07, P = .30$).

CLINICAL MANIFESTATIONS AND TREATMENT OUTCOMES

The untreated patients with Kawasaki disease were older than those treated with IVGG, although the median ages

Table 1. Characteristics and Outcome Measures for Treated (Intravenous γ -Globulin) and Untreated Patients With Kawasaki Disease*

| Characteristics | Treated (n = 19) | Untreated (n = 19) | P† |
|-----------------------------------|------------------|--------------------|-----|
| Male-female | 1.1:1 | 5.3:1 | .08 |
| Age at testing, median (range), y | 9.0 (5.0-14.4) | 14.3 (10.2-18.1) | .36 |
| Mean (SE) SES score | 56.6 (6.3) | 56.8 (5.9) | .94 |
| Cardiac involvement, No. (%) | | | |
| Myocarditis/pericarditis | 3 (16.8) | 5 (26.3) | .69 |
| CAA | 2 (10.5) | 5 (26.3) | .60 |
| Duration of fever, d | 8.9 (4.3) | 10.6 (4.5) | .25 |
| Wechsler IQ,‡ mean (SD) | | | |
| Verbal | 99.5 (13.3) | 99.7 (13.9) | .96 |
| Performance | 110.4 (14.3) | 108.9 (14.6) | .76 |
| Full-scale | 105.1 (13.2) | 104.4 (14.4) | .88 |
| WIAT score, mean (SD) | | | |
| Internal | 55.2 (10.2) | 57.6 (12.2) | .57 |
| External | 52.3 (10.2) | 51.3 (10.2) | .76 |
| Total | 54.5 (12.6) | 54.7 (12.0) | .96 |

*All dichotomous variables: χ^2 with correction for continuity. SES indicates socioeconomic status; CAA, coronary artery abnormality; and WIAT, Wechsler Individual Achievement Test.
 †Paired t test.
 ‡The Wechsler Preschool and Primary Scale of Intelligence-Revised, Wechsler Intelligence Scale for Children, and Wechsler Adult Intelligence Scale-Revised scores were combined for analysis.

of the groups were not significantly different, and no differences were noted in cardiac involvement, neurologic symptoms, or days of fever (**Table 1**). These groups were therefore combined for further analysis. Cardiac involvement and neurologic symptoms were not significantly correlated with any of the cognitive or behavioral outcome measures (Wechsler, Wechsler Individual Achievement Test, or CBCL). Thirty-four percent of the families reported thinking that the episode of Kawasaki disease had had a lasting effect on their child. While 2 parents noted emotional effects (fear of physicians and night terrors) and another 2 were concerned about a learning disability, most concerns were general and related to a perception that their child was "sickly" or more susceptible to illness than their other children. The parental perception that the Kawasaki disease had a lasting effect on their child was not significantly related to the parental behavior ratings ($P = .27$; Fisher exact test).

COGNITIVE, ACADEMIC, AND BEHAVIORAL OUTCOMES

As shown in **Figure 1** and **Table 2**, there were no differences found in the cognitive or academic measures for patients with Kawasaki disease and sibling controls; group mean test scores were comparable and corresponded closely to national norms. Parent ratings identified patients with Kawasaki disease as having significantly more behavior problems than their healthy siblings ($P < .02$). These problems were predominantly internalizing ($P < .02$) and reflected a cluster of specific difficulties, including somatic complaints ($P < .01$), anxious-depressed behavior ($P < .01$), and social problems ($P < .01$). These children were also rated as having

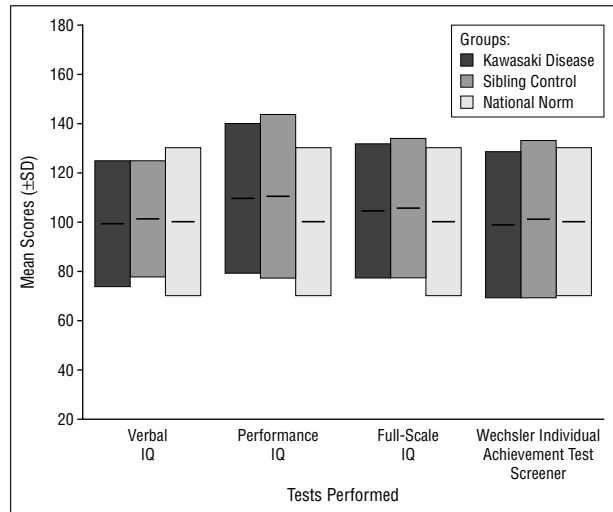


Figure 1. Cognitive and academic achievement testing.

Table 2. Cognitive, Academic, and Behavioral Outcome Measures for Matched Pairs: Patients With Kawasaki Disease and Controls*

| | Patients With Kawasaki Disease | Controls | Mean Difference (SE) | P |
|----------------------------|--------------------------------|--------------|----------------------|-----|
| Wechsler IQ scores† | | | | |
| Verbal | 99.4 (12.7) | 101.4 (11.7) | 1.9 (2.1) | .36 |
| Performance | 109.6 (15.2) | 110.2 (16.6) | 0.5 (2.7) | .84 |
| Full-scale | 104.5 (13.6) | 105.6 (14.1) | 1.1 (2.2) | .61 |
| WIAT score‡ | 101.4 (16.1) | 101.1 (15.9) | 0.2 (2.6) | .92 |
| Internal | 56.3 (13.7) | 51.6 (11.0) | 5.2 (2.2) | .02 |
| Somatic complaints | 57.5 (8.0) | 53.7 (5.6) | 3.8 (1.1) | .01 |
| Anxious-depressed behavior | 59.0 (10.7) | 54.9 (7.1) | 4.1 (1.5) | .01 |
| Social problems | 57.7 (10.8) | 52.9 (5.7) | 4.8 (1.7) | .01 |
| External | 51.1 (10.8) | 50.9 (10.6) | 0.9 (2.1) | .68 |
| Attention difficulties | 58.5 (11.9) | 54.1 (6.4) | 4.3 (1.8) | .02 |
| Total | 54.4 (13.0) | 48.8 (10.4) | 5.5 (2.3) | .02 |

*Paired t test. All data are given as mean (SD) unless otherwise indicated. WIAT indicates Wechsler Individual Achievement Test.
 †The Wechsler Preschool and Primary Scale of Intelligence-Revised, Wechsler Intelligence Scale for Children, and Wechsler Adult Intelligence Scale-Revised scores were combined for analysis.
 ‡Subscores are indented and included only if $P < .05$.

significantly more attention difficulties than their healthy siblings ($P < .02$). A separate measure of behavior, using either the Teacher's Report Form²⁶ or the Youth Self-Report,²⁷ was completed for 92% ($N = 59$) of the participants with no difference in ratings detected between the Kawasaki disease group and the control group ($P = .57$; Mantel-Haenszel χ^2).

Stepwise logistic regression was performed to determine the differential risk of obtaining a CBCL summary and specific subscale scores in the clinical range (defined as CBCL score ≥ 60 [**Figure 2**]). When compared with their matched controls, the patients with Kawasaki disease had a 3.3 times greater risk ($P < .03$; 95% confidence interval, 1.1-9.9) of scoring within the clinical range for the internalizing scale; the somatic complaints subscale showed a 4.3 times greater risk ($P < .02$; 95% con-

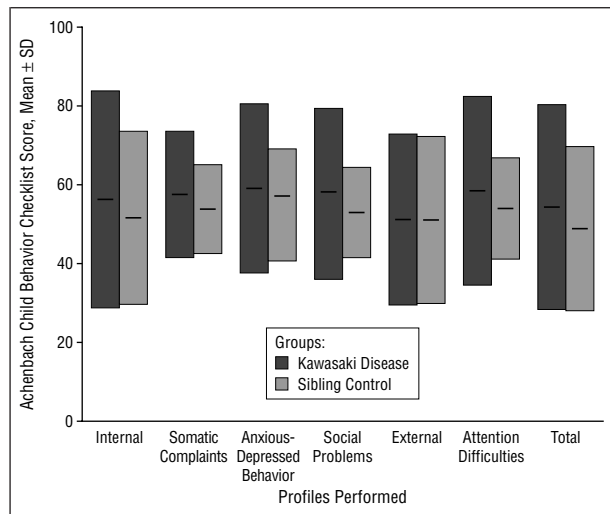


Figure 2. Parent rating of behavior with Achenbach Child Behavior Checklist. Scores of 60 or more represent clinically significant behavior problems.

fidence interval, 1.2-14.7); and the social problems subscale had a trend toward significance with a 3.4 times greater risk ($P < .06$; 95% confidence interval, 0.96-10.83). Odds ratios for the remaining scales did not reach significance. **Table 3** gives the characteristics of all patients with Kawasaki disease with CBCL internalizing scores in the clinical range. Patients with Kawasaki disease with coronary artery abnormalities were not significantly different from their sibling controls for CBCL behavioral scores in the clinical range ($P = .68$; Fisher exact test).

This study did not demonstrate differences in cognitive or academic function in patients after an acute episode of Kawasaki disease when compared with sibling controls or standardized norms. We did, however, identify a preliminary indication of behavioral difficulties (somatic complaints, problems with socialization, anxious-depressed feelings, and attentional problems) in children with previous Kawasaki disease. The risk for internalizing behavior difficulties was 3.3 times greater in our patients with Kawasaki disease and was independent of cardiac involvement or receiving IVGG treatment. Moreover, a large proportion of the parents in our study perceived that the episode of Kawasaki disease had a long-lasting effect on their child, although this perception was often vague and was not related to the increased risk of behavior problems.

Both generalized^{3,7} and localized⁷⁻¹⁵ CNS symptoms have been reported in Kawasaki disease. Autopsy findings have shown varying degrees of inflammatory changes in brain vasculature, which are usually less extensive than coronary artery involvement. Aseptic meningitis is also seen in patients with Kawasaki disease,⁷ although it is not thought to cause any long-term sequelae.²⁹ This is consistent with evidence that children with aseptic meningitis secondary to viral CNS infections before 1 year of age had no impairments in intelligence, academic achievement, and/or behavior.^{30,31} While neurologic sequelae may occur in a small number of patients with Kawasaki disease, the vast majority escape serious

CNS damage and our data suggest that milder CNS effects, in the form of cognitive and academic difficulties, are rare.

The behavioral difficulties may be due to residual CNS effects of the disease process, the experience of an acute illness and hospitalization, and/or continued family anxiety after the illness. Heightened parental anxieties about children who have completely recovered from an illness can lead to overprotective relationships that may contribute to difficulties in the psychological development of their children.³² While the lack of behavior problems identified on both the Teacher's Report Form and the Youth Self-Report Form supports a problem with parental perception, it should be noted that the problem behavior reported was internalizing and therefore less likely to be noted by the teachers. The behavioral rating scales were chosen to give a broad base of possible behavioral sequelae. While the CBCL contains a subjective element to the assessment, it is a commonly used test that has been validated to provide maximum differentiation between clinical (children referred with behavior problems) and normal subjects.²⁵ Now that a difference has been demonstrated within families, it would be important to repeat this study with a hospitalized control group and to include a more detailed measure of parental anxiety.

Is increased parental worry after Kawasaki disease appropriate? While most children in our study with clinically significant behavior problems did not have echocardiographic evidence of a coronary artery abnormality, the long-term risk for residual cardiac disease is uncertain. Reports suggest that there may be decreased coronary artery elasticity, even in the absence of residual coronary artery dilatation.^{33,34} In light of this uncertainty, recommendations for clinical follow-up need to be carefully considered and have the potential either to alleviate or to amplify parental worry. The American Heart Association (Dallas, Tex) has recommended that pediatric cardiology follow-up and diagnostic testing is not indicated beyond the first year for children with risk level I criteria (no echocardiographic evidence of coronary artery abnormality at any time during the illness).³⁵ Results of cohort studies, in which patients are followed up with serial echocardiograms, should help to determine whether such investigations are identifying residual abnormalities with sufficient frequency to warrant any mixed messages that may be sent to parents (eg, "Your child's coronary arteries look fine. We'd like to see you again in. . ."). Certainly, the medical information given to these parents at the time of the original illness and subsequently may have a significant effect on their perception of their child's well-being. The importance of clarifying the extent of parental concerns regarding the illness and identifying and minimizing parental anxiety cannot be overstated.

There were several strengths and limitations of our study. The retrospective cohort design is well suited to relatively uncommon diseases where the cost of performing a prospective trial would be high and the outcomes of interest may not be evident until several years after the diagnosis. Sibling controls, with close similarity of genetic background, socioeconomic status, and child-

Table 3. Characteristics of Patients With Kawasaki Disease With Internalizing Behavior Scores in the Clinical Range*

| Patient | Age, y | | IVGG | CAA | Achenbach Child Behavior Checklist Scores* | | TRF/YSR Scores† |
|---------|-----------|------|------|-----------------|--|---------------|-----------------|
| | Diagnosis | Test | | | Internalizing | Externalizing | |
| 1 | 0.5 | 18 | No | Multiple | 65 | 60 | Normal |
| 10 | 1.5 | 17 | No | No | 61 | 73 | Normal |
| 13 | 1.0 | 13 | No | No; infarction? | 61 | 47 | Normal |
| 16 | 1.5 | 12 | No | No | 85 | 59 | Clinical |
| 20 | 2.5 | 13 | No | No | 75 | 55 | Normal |
| 21 | 5.0 | 16 | No | No | 60 | 47 | Normal |
| 24 | 4.5 | 19 | No | Yes; resolved | 60 | 45 | Normal |
| 25 | 3.0 | 12 | No | No | 77 | 69 | Clinical |
| 32 | 5.0 | 13 | Yes | No | 77 | 69 | Clinical |
| 33 | 7.5 | 16 | Yes | No | 67 | 65 | Normal |
| 35 | 3.0 | 10 | Yes | No | 65 | 57 | Normal |
| 49 | 7.5 | 11 | Yes | No | 61 | 54 | Normal |
| 60 | 3.5 | 6 | Yes | No | 63 | 60 | Normal |
| 61 | 5.0 | 8 | Yes | No | 71 | 64 | Normal |
| 63 | 3.0 | 6 | Yes | No | 60 | 53 | NR |
| 67 | 2.5 | 6 | Yes | No | 77 | 68 | NR |

*Clinical range, Achenbach Child Behavior Checklist score of 60 or above. IVGG indicates intravenous γ -globulin; CAA, coronary artery abnormality; TRF, Teacher's Report Form; YSR, Youth Self-Report; and NR, no response.
 †Clinical refers to a score on either the TRF or the YSR in the clinical range.

rearing practices, were used in to minimize potential bias. In spite of these clear advantages, we did encounter difficulty in matching age and sex as closely as we would have liked. Our initial sample size was to be 38 matched pairs, which would have yielded a power of 0.80 to detect a medium effect in matched-sample analyses.³⁶ The 32 matched pairs that we were able to recruit, determined by sibling availability, had a power of approximately 0.70. Though we did not achieve our target sample size and slightly increased the possibility of a type II error, the difference in cognitive and academic outcomes between the groups was so close that if a true difference did exist, it was small and likely clinically insignificant. The small sample size, in particular the small number of children with cardiac involvement, did not allow us to fully explore the effect of cardiac involvement on the parental perception of child health. Finally, there is a potential for selection bias, in that the families we tested may have been more motivated or may have had a higher level of underlying anxiety, and as we were unable to contact 29 of the eligible families and a further 5 families declined testing.

We conclude that after a child has an acute episode of Kawasaki disease, parents may be reassured that there appears to be no effect on cognitive development or academic performance. While our study identifies a potential for the development of mild behavioral difficulties in affected children, further research is needed to confirm our findings, to better define the source(s) of the behavioral difficulties, and to identify ways to reduce the effect of these concerns on the child.

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