Prognostic Significance of QT Interval Dispersion in the Response to Intravenous Immunoglobulin Therapy in Kawasaki Disease

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Background: Kawasaki disease (KD) is classified as a systemic vasculitis syndrome and QT interval dispersion (QTD) has been associated with cardiac involvement and disease activity in patients with cardiovasculitis. We examined whether baseline QTD could predict a response to intravenous immunoglobulin (IVIG) in KD.

Methods and Results: QTD was recorded in 86 patients with KD before IVIG, who were separated into IVIG responders (R group; n=62) and nonresponders (N group; n=24). The association between baseline QTD and response to IVIG was investigated, and the predictive response value was compared with conventional risk scores from Gunma and Kurume universities. Baseline-corrected QTDs with Bazett’s (QTbcD) and Fridericia’s (QTfcD) formulae were significantly increased in the N group (R group vs. N group: 31.6 [28.3, 44.0] ms vs. 66.6 [50.5, 76.3] ms and 27.4 [25.2, 39.1] ms vs. 55.2 [42.4, 66.3] ms, respectively, both P<0.001). Multiple logistic regression analysis revealed QTfcD as an independent predictor of a response to IVIG after adjustment for conventional scores (odds ratio: 1.133, 95% confidence interval: 1.061–1.210, P<0.001). Moreover, QTfcD provided incremental predictive value for IVIG nonresponders over Gunma score (increment in global $\chi^2=25.46$, P<0.001).

Conclusions: QTD was significantly associated with a response to IVIG in KD patients and may represent a useful identifier of IVIG nonresponders with high risk of coronary aneurysm.

Key Words: Intravenous immunoglobulin therapy; Kawasaki disease; QT interval dispersion; Risk factors
required additional therapy. refractory to the first and second IVIG treatments and comprised patients who were responders to the first or second IVIG therapy, and N group patients who were non-responders to IVIG.

Study Population and Design

We retrospectively reviewed the clinical records of 86 patients who were diagnosed as having KD between 2010 and 2015 at 13 medical institutions in Nagano Prefecture in Japan (55 boys; median age, 2.2 years, range, 0.3–10.1 years). Criteria for KD included fever >38°C accompanied by at least 4 of the following 5 findings: bilateral conjunctival injection, changes in the lips and oral cavity, non-purulent cervical lymphadenopathy, polymorphous exanthema, and changes in the extremities. These diagnostic criteria were compliant with the Diagnostic Guidelines for Kawasaki Disease.

The patients were divided into 2 study groups: R group comprised patients who were responders to the first or second IVIG therapy, and N group patients who were refractory to the first and second IVIG treatments and required additional therapy.

Methods

Statistical Analysis

Statistical analyses were carried out using SPSS statistical software, version 18.0J. Normality of distribution was assessed through the use of the Shapiro-Wilk test. Data are expressed as the mean±SD or the median (interquartile range). To determine the significance of differences between 2 independent groups, the unpaired t-test was used when appropriate. If the unpaired t-test showed a high degree of significance, the Mann-Whitney test was used instead.
The incidence of CAA during and after therapy was higher in the IVIG nonresponders, although there was no significant statistical difference (R group vs. N group: 6 [9.7%] vs. 5 [20.8%], P=0.17 by Chi-square test).

Prediction of IVIG Nonresponders
According to receiver-operating characteristic (ROC) curve analysis, the area under the curve (AUC) of QTfcD (0.89) was similar to those of the conventional risk scores (Gunma: 0.88, Kurume: 0.76). According to a cutoff value of 42.6 ms, the sensitivity and specificity of QTfcD were 75.0% and 88.7%, respectively (Figure 2).

In the univariate logistic regression analysis, QTD,
QTbcD, QTfcD, Gunma score, and Kurume score significantly correlated with an increased incidence of IVIG non-response. There were no significant differences in AST or platelet count values between responders and nonresponders to IVIG therapy (Table 3).

In the multivariate logistic analysis after adjustment for Gunma score, QTfcD was found to be a significant and independent predictive factor of a response to IVIG (odds ratio (OR): 1.174, 95% confidence interval (CI): 1.095–1.258, P<0.001) (multiple-adjusted model 1, Table 4). Similar findings were seen after adjustment for Kurume score (OR: 1.129, 95% CI: 1.073–1.187, P<0.001) (multiple-adjusted model 2, Table 4). The incremental value of QTfcD to predict the response to IVIG is shown in Figure 3. The QTfcD provided an additional benefit over conventional risk score (Gunma score).

**Discussion**

QTD is an indicator of the degree of myocardial repolarization inhomogeneity that can prognosticate heart failure and fatal arrhythmia in adults and ventricular arrhythmia, cardiomyopathy, and cardiac sudden death in both children and adults. In the present study, QTD and QTfcD at baseline were significantly associated with a response to IVIG therapy in KD patients.

Higham et al reported that a prolonged QTD was caused by regional changes in action potential duration and conduction, local populations of cells with afterdepolarizations, and neurohormonal factors, all of which are affected by myocardial ischemia. Osada et al described increased QTD as correlated with the severity of coronary lesions in KD, and that >60 ms dispersion had a higher sensitivity in detecting severe coronary aneurysms. One possible mechanism of the increased QTD in KD is myocardial ischemia caused by coronary involvement. Thus, QTD may have been influenced by the extent of ischemic myocardial damage. In the present study, although nonresponders had more than double the incidence of abnormal coronary lesions, there was not a significant difference, because of the small number of patients. The patients with coronary dilatations, which all transiently regressed, did not have ischemic sign such as chest pain, or abnormal ECG findings.

Meanwhile, others have found no correlation between QT interval and coronary involvement. Moreover, QTD was higher in acute-phase KD patients without overt CAA as compared with a healthy control group. Amoozgar et al noted that increased QTD in KD patients might also be caused by cardiovascular inflammation, such as carditis. The observed cardiac pathologies in acute-stage KD include early vasculitis with coronary artery involvement, pericarditis, myocarditis, endocarditis, valvulitis, and conduction system inflammation. These changes are followed

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>0.455 (0.309–0.668)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>1.002 (1.000–1.004)</td>
<td>0.079</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>1.003 (1.000–1.005)</td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td>PIt</td>
<td>0.964 (0.919–1.010)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>1.131 (1.066–1.199)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>1.247 (1.089–1.429)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Gunma score</td>
<td>2.136 (1.547–2.950)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Kurume score</td>
<td>2.228 (1.453–3.415)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>QTD</td>
<td>1.174 (1.095–1.258)</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>QTbcD</td>
<td>1.108 (1.062–1.156)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>QTfcD</td>
<td>1.129 (1.073–1.187)</td>
<td>&lt;0.001</td>
<td></td>
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CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

**Table 3. Univariate Logistic Regression Analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTbcD</td>
<td>1.133 (1.061–1.210)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Gunma score</td>
<td>2.235 (1.405–3.564)</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Kurume score</td>
<td>1.344 (1.344–4.930)</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1,3.

**Figure 2.** Receiver-operating characteristic (ROC) curve. The area under the curve (AUC) for corrected QT dispersion (0.89) was similar to that for the conventional risk scores (Gunma=0.88, Kurume=0.76).

**Figure 4A.** Results of univariate logistic regression analysis. OR, odds ratio; CI, confidence interval; AUC, area under the curve; Spearman’s rank correlation coefficient.

**Figure 4B.** Results of multiple adjusted logistic regression analysis. OR, odds ratio; CI, confidence interval; AUC, area under the curve; Spearman’s rank correlation coefficient.

**Figure 4C.** Results of multiple adjusted logistic regression analysis. OR, odds ratio; CI, confidence interval; AUC, area under the curve; Spearman’s rank correlation coefficient.
QT Interval Dispersion in KD

Figure 3. Incremental value of QT dispersion over conventional risk score. Addition of corrected QT dispersion (QTcD) to a Cox model of the Gunma score resulted in a significant improvement in the predictive value for unresponsiveness to immunoglobulin therapy in a patient with Kawasaki disease.

Figure 4. Changes of QT interval dispersion (QTD) and corrected QT interval dispersion (QTcD) during the clinical course of nonresponders to intravenous immunoglobulin (IVIG) therapy. QTD (A) and QTcD (B, C) improved significantly at 2 weeks and 4 weeks after the onset of Kawasaki disease following commencement of additional treatment. *P<0.01 vs. value at baseline; †P<0.01 vs. value after 2nd IVIG therapy; ‡P<0.05 vs. value after 2nd IVIG therapy.

Conclusion

QTD and QTcD were significantly associated with a response to IVIG in KD patients. Subclinical myocardial involvement by coronary artery panvasculitis and aneurysm formation, and in rare cases progress to chronic myocarditis or cardiomyopathy caused by myocarditis. A significant increase in cardiac troponin I level has been documented before IVIG therapy in acute-stage KD, suggesting that acute myocarditis or myocardial cell injury begins in the early phase of the disease and that myocyte injury or inflammation is likely to occur before the onset of definitive clinical symptoms and signs of myocarditis.

QTD has been associated with cardiovascular involvement and disease activity in systemic cardiovasculitides such as SLE and Behçet’s disease. Hence, prolonged QTD is a potentially useful method of early detection of subclinical cardiac involvement, such as pericarditis, myocarditis, and coronary arteritis, similar to that in KD. As KD has been classified as a systemic vasculitis syndrome, we hypothesized that QTD could enable assessment of disease severity. In our study, QTD and QTcD were presumed to be associated with the grade of inflammation during the clinical course because they both decreased after additional therapy (e.g., infliximab, plasma exchange) in nonresponders who might have had severe cardiovasculitis. This finding indicated the possibility that QTD at baseline reflected the severity of myocardial inflammation at the onset of KD. Accordingly, QTD may be predictive of a response to IVIG therapy, in addition to conventional risk scores. QTD could be helpful for making decisions about alternative initial therapy or additional therapy following IVIG (e.g., IVIG plus steroid and additional infliximab, steroid following initial IVIG) because there are IVIG nonresponders who are not identified even by the conventional risk scores.

Measurement of QTD and QTcD is easy, safe, and non-invasive for evaluation of the risk of resistance to IVIG therapy. However, the relatively small number of subjects in this study reflects the difficulty in precisely evaluating the effect of QTD and QTcD values on the response to IVIG in KD. A large, prospective, multicenter study may resolve this limitation and determine the cutoff value of QTD as a predictor of KD prognosis. Further investigations are warranted to clarify the mechanisms underlying QTD and to fine-tune the use of this parameter in routine clinical practice.
may be indicated by repolarization abnormalities. In patients with KD, this parameter might represent a useful and noninvasive marker for the identification of IVIG nonresponders with severe vasculitis and a high risk of coronary aneurysm.

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Conflict of Interests

All authors have no conflicts of interest to disclose.

References