C-reactive protein and N-terminal pro-brain natriuretic peptide discrepancy: a differentiation of adenoviral pharyngoconjunctival fever from Kawasaki disease

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Purpose: To differentiate adenoviral pharyngoconjunctival fever (PCF) from acute Kawasaki disease (KD) using laboratory tests before results of virus-real time polymerase chain reaction and ophthalmologic examination are obtained.

Methods: Baseline patient characteristics and laboratory measurements were compared between 40 patients with adenovirus infection and 123 patients with KD.

Results: The patients with adenovirus infection were generally older than those with KD (median: 3.9 years vs. 2 years, P=0.000). White blood cell and, platelet count, and aspartate aminotransferase, alanine aminotransferase, and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels showed significant differences between the 2 groups, but the C-reactive protein (CRP) levels did not (6.8±3.0 mg/dL vs. 8.3±5.8 mg/dL, P=0.126). In the adenovirus infection group, the CRP levels were <1, <3, <10, and ≥10 mg/dL in 2 (5%), 3 (7.5%), 30 (75%), and 5 patients (12.5%), respectively. The cutoff NT-proBNP level was 265 pg/mL. Discrepancy was defined as CRP and NT-proBNP levels of ≥3 or <3 mg/dL, and <265 or ≥265 pg/mL, respectively. Among the 35 patients with adenovirus infection whose CRP levels were ≥3 mg/dL, 29 (82.9%) showed a discrepancy. Conversely, of the 103 patients with KD whose CRP levels were ≥3 mg/dL, 83 (80.6%) showed no discrepancy. Between the groups, a significant difference in discrepancy rate was observed (P=0.000). None of the patients with adenovirus infection had CRP and NT-proBNP levels of <3 mg/dL and ≥265 pg/mL, respectively.

Conclusion: With a sensitivity of 82.9% and a specificity of 80.6%, CRP and NT-proBNP levels may differentiate between adenoviral PCF and acute KD.

Key words: Adenovirus, Kawasaki disease, C-reactive protein, NT-proBNP, Discrepancy

Introduction

Among the protean manifestations of adenovirus infection, pharyngoconjunctival fever (PCF) is likely to be misdiagnosed as Kawasaki disease (KD) due to many similar clinical presentation, including fever, conjunctival injection, pharyngitis, or skin rashes. PCF, however, has some distinct symptoms: the occurrence of conjunctivitis with or without pharyngitis or respiratory symptoms. It usually begins in one eye and spreads contralaterally, despite the possibility of simultaneous infection. Mild pain or discomfort, pruritus, and morning crusting may also be common. Uveitis is not present, and tonsillar exudate may be associated. Nonetheless, we often experience difficulty in differentiating between KD and PCF at the early phase of the disease. Therefore, we sought to determine which laboratory tests may be best suited for
differentiating adenoviral PCF from acute KD, before needing to obtain the results of virus-real time polymerase chain reaction (PCR) and ophthalmologic examination.

Materials and methods

During the period between May 2016 and July 2016, a total of 135 children were clinically diagnosed with adenovirus infection. Patients were excluded when (1) adenovirus was not identified by real-time PCR in nasopharyngeal secretions, (2) coinfection was present with other respiratory viruses, (3) antmycoplasma antibody IgM was positive in the serum, (4) uveitis was detected by a slit-lamp examination, and (5) laboratory tests were omitted. Finally, a total of 40 patients were retrospectively enrolled in the adenovirus infection group.

During the 23-month period (November 2008–September 2010), a total of 123 children who met the diagnostic criteria for KD were enrolled in the KD group. This group of patients was reported as subjects in a previous study. We measured the white blood cell (WBC) count, percentage of neutrophils in WBCs (% neutrophils), hemoglobin, hematocrit, platelet counts, serum sodium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), protein, albumin, C-reactive protein (CRP), and N-terminal pro-brain natriuretic peptide (NT-proBNP) at presentation.

We compared the basic patient characteristics and laboratory values between KD and adenovirus patients.

1. Definition
The duration of fever was defined as the number of days (24-hour period) elapsed from the onset of disease to presentation. Fever was defined as a temperature≥38°C. The definition of discrepancy was described in the results section.

2. Statistical analysis
The IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA) was used to compared the 2 groups. Data are presented as the median, as well as the mean±standard deviation, or as numbers and percentages of patients. Continuous variables between the groups were compared using Student t test. When the variables in either group are not normally distributed, Mann-Whitney test was used. Categorical variables were compared using the chi-square test. To determine the cutoff values of parameters, a receiver operating characteristic (ROC) curve was used. Multivariate logistic regression analysis was performed using age plus laboratory variables that had been selected by univariate analysis to determine the independent parameters in differentiating the groups, and the results were expressed as an odds ratio with a 95% confidence interval (CI). A 95% CI that did not include 1.0 was interpreted to indicate statistical significance. A 2-tailed P<0.05 was considered to have statistical significance.

The study was approved by the Institutional Review Board of Ewha Womans University (#2017-09-033-001). Written informed consent by the patients was waived due to a retrospective nature of our study.

Results

1. Adenovirus patients
The median age of adenovirus patients at presentation was 3.9 years (interquartile range, 3.2–5.0). They were older than KD patients (P=0.000). They had a fever for a median duration of 4 days. There was no difference in the fever duration between the 2 groups (P=0.514). Conjunctival injection was present in 23 patients, tonsillar exudate in 7, skin rashes in 8, and cervical lymphadenopathy in 2. All adenovirus patients were proved by a positive real-time PCR result in nasopharyngeal secretions, without any evidence of uveitis. A comparison of basic patient characteristics between KD and adenovirus patients is shown in Table 1.

2. Comparison in laboratory values between KD and adenovirus patients
KD and adenovirus patients did not differ in the percentage of neutrophils, hemoglobin, hematocrit, serum sodium, protein, and albumin. No difference in CRP was found (P=0.126), although the mean values of CRP were elevated in both groups. However, there were significant differences between the 2 groups with respect to WBC (v=0.000), platelet (v=0.000), AST (v=0.001), ALT (P=0.000), and NT-proBNP (P=0.000). The mean values of these 5 parameters in adenovirus patients were lower than those in KD patients (Table 2).

3. Independent parameters for differentiation of adenovirus PCF from KD
A multivariate logistic regression analysis included age, WBC, platelet, AST, ALT, and NT-proBNP. Among them, WBC, platelet, and NT-proBNP proved to be the independent parameters for differ-

Table 1. Comparison of the basic characteristics of the patients with KD and adenovirus infection
| Variable                        | KD (n=123) | Adeno (n=40) | P value |
|---------------------------------|------------|--------------|---------|
| Age (yr)                        | 2.5±1.7    | 4.1±1.8      | 0.000   |
| Mean±SD                         |            |              |         |
| Median (range)                  | 2 (0.2–8.9) | 3.9 (0.8–11.3) |         |
| Sex, male:female                | 66:57      | 20:20        | 0.715   |
| Duration of fever (day)         | 4          | 4            | 0.514   |
| Mean±SD                         | 4.4±1.7    | 4.2±1.3      |         |
| Median (range)                  | 4 (1–9)    | 4 (1–7)      |         |

KD, Kawasaki disease; Adeno, adenovirus infection; SD, standard deviation.
The cutoff value for these parameters was determined by the ROC curve: the WBC cutoff value of 10,820/mm$^3$ provided a sensitivity of 72.5% and a specificity of 75.6%, with an area under the curve (AUC) of 0.77 (95% CI, 0.68–0.87; $P=0.000$); the platelet cutoff value of 300,500/mm$^3$ provided a sensitivity of 80% and a specificity of 58.5% (AUC=0.74; 95% CI, 0.66–0.83; $P=0.000$); and the NT-proBNP cutoff value of 265 pg/mL yielded a sensitivity of 85% and a specificity of 75.6% (AUC=0.89; 95% CI, 0.83–0.94; $P=0.000$).

### 4. CRP and NT-proBNP in KD and adenovirus patients

The values of CRP and NT-proBNP in both groups of patients are shown in Table 4 and plotted in Fig. 1. In 40 adenovirus patients, the CRP levels of $<$1 mg/dL, $<$3 mg/dL, $<$10 mg/dL, and $\geq$10 mg/dL were found in 2 (5%), 3 (7.5%), 30 (75%), and 5 (12.5%), respectively. Almost 90% of adenovirus patients had a CRP level of $\geq$3 mg/dL. Therefore, we arbitrarily defined the diagnostic value for adenoviral PCF as a CRP level of 3 mg/dL, and this value matched the criterion of the American Heart Association for the evaluation of suspected incomplete KD.

Using a CRP level of 3 mg/dL and a NT-proBNP cutoff value of 265 pg/mL, the discrepancy was defined as CRP$\geq$3 mg/dL and NT-proBNP$<$265 pg/mL, or as CRP$<$3 mg/dL and NT-proBNP$\geq$265 pg/mL. The discrepancy rate was 72.5% (29 of 40) and 24.4% (30 of 123) in adenovirus patients and KD patients, respectively ($P=0.000$). Among the 35 adenovirus patients with CRP$\geq$3 mg/dL, 29 patients (82.9%) showed a discrepancy and 6 showed no discrepancy. Conversely, out of the 103 KD patients with CRP$\geq$3 mg/dL, 83 (80.6%) showed no discrepancy and only 20 showed discrepancy.

### Table 2. Comparison of laboratory values between the patients with KD and adenovirus infection

| Variable       | KD (n=123) | Adeno (n=40) | $P$ value |
|----------------|------------|--------------|-----------|
| WBC ($/mm^3$)  | 13,769±4,269 | 9,921±3,962 | 0.000     |
| % Neutrophils  | 62.9±15.4   | 57.3±15.8    | 0.052     |
| Hemoglobin (g/dL) | 11.3±1.0   | 11.5±0.9     | 0.377     |
| Hematocrit (%) | 33.2±2.7    | 34.0±2.3     | 0.076     |
| Platelet ($\times10^3/mm^3$) | 336±92    | 265±59       | 0.000     |
| Sodium (mEq/L) | 137±3      | 138±2        | 0.112     |
| AST (IU/L)     | 114±252    | 33±9         | 0.001*    |
| ALT (IU/L)     | 104±185    | 15±7         | 0.000*    |
| Protein (g/dL) | 6.6±0.5    | 6.5±0.4      | 0.513     |
| Albumin (g/dL) | 3.8±0.4    | 3.7±0.3      | 0.077     |
| CRP (mg/dL)    | 8.3±5.8    | 6.8±3.0      | 0.126     |
| NT-proBNP (pg/mL) | 1,211±2,398 | 160±120     | 0.000*    |

Values are presented as mean±standard deviation. KD, Kawasaki disease; Adeno, adenovirus infection; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

* $P$ value by Mann-Whitney test.

### Table 3. Multivariate logistic analysis for the differentiation of adenovirus infection from KD

| Variable       | $P$ value | Odds ratio | 95% CI         |
|----------------|-----------|------------|----------------|
| WBC ($/mm^3$)  | 0.014     | 0.819      | 0.698–0.961    |
| Platelet ($\times10^3/mm^3$) | 0.014 | 0.987      | 0.974–0.997    |
| NT-proBNP (pg/mL) | 0.000  | 0.992      | 0.988–0.996    |

KD, Kawasaki disease; CI, confidence interval; WBC, white blood cell; NT-proBNP, N-terminal pro-brain natriuretic peptide. Age, aspartate aminotransferase, and alanine aminotransferase in addition to 3 variables in this table (WBC, platelet, and NT-proBNP) were included in the multivariate logistic analysis.
null
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