Original Article

Implications of hepatic dysfunction in Kawasaki disease: Time-related changes in aspartate aminotransferase, alanine aminotransferase, total bilirubin, and C-reactive protein levels

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ABSTRACT
Importance: The cause of the hepatic dysfunction that commonly accompanies Kawasaki disease (KD) remains unclear.
Objective: We tried to clarify the cause of the hepatic dysfunction.
Methods: A total of 381 consecutive patients with acute KD, who had undergone inpatient treatment with intravenous immunoglobulin until the 7th day of illness, were divided into a group of 199 patients with an alanine aminotransferase (ALT) level ≥ 40 IU/L on admission (group I), a group of 52 patients with an ALT level ≥ 40 IU/L at some point after admission (group II), and a group of 130 patients with ALT levels consistently < 40 IU/L throughout hospitalization (group III). Aspartate aminotransferase (AST), ALT, total bilirubin (T-Bil), and C-reactive protein (CRP) levels were analyzed over time, and time-courses were compared.
Results: In the initial stage of illness, in group I, AST, ALT, T-Bil peaked on days 1–3, and AST tended to improve significantly on the 4th day (P < 0.001). T-Bil improved on day 5 (P < 0.01), and ALT improved significantly on day 6 (P < 0.001). CRP increased every day up to day 6 (P < 0.001). In group II, AST and ALT increased after admission, and thereafter CRP increased, then decreased. The frequency of use of aspirin and aspirin doses did not differ significantly in the three groups.
Interpretation: Recovery from liver dysfunction occurred in the initial stage of illness in group I—within the period of CRP exacerbation, which is an indicator of systemic inflammation.

KEYWORDS
Kawasaki disease, Dysbiosis, Fecal calprotectin, Gut inflammation, Pathogenesis, Portal vein

INTRODUCTION
In the 56-year period from January 1961 to December 2016, there were 362,710 cases of Kawasaki disease (KD) recorded in Japan.\textsuperscript{1,2} Despite numerous studies reported to date, the etiology and mechanism of KD onset remain unknown, the number of patients increases yearly, and there are no effective measures to stop it.

It has been suggested that hepatic dysfunction in KD is...
a complication resulting from systemic inflammation or systemic vasculitis, and that some cases are the result of adverse reactions to aspirin, intravenous immunoglobulin (IVIG), or other drugs.\textsuperscript{3,6} However, as well as C-reactive protein (CRP), leukocytes, platelets, and age, other risk factors for IVIG refractoriness and coronary aneurysm have been identified including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin (T-Bil).\textsuperscript{3,6} Therefore, relationships between hepatic dysfunction and KD severity have been suggested.

The nature of the hepatic dysfunction that commonly accompanies KD is not fully understood, and the etiology and mechanism of onset of KD remain unknown. In the present study, we investigated hepatic dysfunction over a time-course, in an attempt to determine its cause, the therapeutic mechanism of IVIG, and its relationship with the pathogenesis of KD. We also investigated measures required to achieve further developments in KD research.

**METHODS**

The study population comprised a total of 381 consecutive non-selected patients with acute KD who received inpatient treatment with IVIG by the 7th day of illness, at the Department of Pediatrics in Kobe City Medical Center General Hospital in Japan between 1983 and 2001. The study population is identical to that of a study previously reported in 2013.\textsuperscript{7} This study was conducted after the approval of our institutional ethical committee.

Out of a total of 381 patients, 176 received 200–400 mg/kg IVIG daily for 5 days (1983–1992), and 205 received 1–2 g/kg IVIG once or twice (1992–2001). The mean age of the 381 patients was 25.3 months, and 159 were female and 222 were male. The mean number of days of illness at admission was 4.3. The mean number of preceding days of illness at the start of IVIG administration was 5.1. Of the 381 patients, 75 received aspirin at doses of 10–30 mg/kg. The mean number of blood tests per patient was 4.7. Patients with coronary artery aneurysm were handled accordingly, if their aneurysm persisted for 1 month after (Table 1).

The patients were divided into three groups based on ALT status, 199 with an ALT ≥ 40 IU/L on admission (group I), 52 with ALT ≥ 40 IU/L at some point after admission (group II), and 130 with a ALT levels that were constantly < 40 IU/L throughout hospitalization (group III). Group I was subdivided into two subgroups, 110 patients who received collective doses of IVIG (group Ia), and 89 patients who received divided doses of IVIG (group Ib) (Table 1).

AST (IU/L), ALT (IU/L), T-Bil (mg/dL), and CRP (mg/dL) levels in groups I, Ia, Ib, II, and III were evaluated by day of illness from the onset of pyrexia. To minimize bias pertaining to the number of examinations and the days of illness, the days of illness were divided into 12 time-points; days 1–3, day 4, day 5, day 6, day 7, day 8, day 9, day 10, day 11, day 12, days 13 and 14, and days 15–17 of illness. Median AST, ALT, T-Bil, and CRP values were calculated for each of the 12 time-points, and the results from groups I, Ia, Ib, II, and

| Group | Characteristics of subjects among different groups |
|-------|---------------------------------------------------|

| Overall |                | Number of cases | Onset age (months) | F/M | Day of illness on admission | Start day of IVIG | Cases with aspirin therapy | Number of blood examinations | Coronary aneurysm |
|---------|----------------|-----------------|--------------------|-----|---------------------------|------------------|---------------------------|--------------------------|-------------------|
| ALT ≥ 40 IU/L on admission (Group I) |                | 199 (52.2)      | 27.2 ± 22.5        | 97/102 | 4.3 ± 1.3                | 5.0 ± 1.1        | 37 (18.6) | 5.0 ± 1.5    | 17 (8.5)        |
| ALT ≥ 40 IU/L after admission (Group II) |                | 52 (13.6)       | 20.9 ± 25.6        | 16/36 | 3.8 ± 1.6               | 5.2 ± 1.5        | 10 (19.2) | 5.0 ± 1.5 | 2 (3.8)         |
| ALT < 40 IU/L consistently (Group III) |                | 130 (34.1)      | 24.1 ± 20.7        | 46/84 | 4.5 ± 1.4               | 5.3 ± 1.4        | 28 (21.5) | 4.2 ± 1.3    | 1 (0.8)          |
| Total |                | 381 (100)       | 25.3 ± 22.4        | 159/222 | 4.3 ± 1.4            | 5.1 ± 1.3        | 75 (19.7) | 4.7 ± 1.5 | 20 (5.2)        |

| Collective dose of IVIG |                | Number of cases | Onset age (months) | F/M | Day of illness on admission | Start day of IVIG | Cases with aspirin therapy | Number of blood examinations | Coronary aneurysm |
|-------------------------|----------------|-----------------|--------------------|-----|---------------------------|------------------|---------------------------|--------------------------|-------------------|
| ALT ≥ 40 IU/L on admission (Group Ia) |                | 110 (53.7)      | 26.6 ± 22.9        | 54/56 | 4.1 ± 1.4               | 5.0 ± 1.1        | 28 (25.5) | 5.3 ± 1.7 | 8 (7.3)         |
| ALT ≥ 40 IU/L after admission |                | 25 (12.2)       | 24.4 ± 26.2        | 7/18 | 3.5 ± 1.5               | 5.2 ± 1.5        | 6 (24.0) | 5.8 ± 1.6 | 0 (0.0)         |
| ALT < 40 IU/L consistently |                | 70 (34.1)       | 24.8 ± 23.0        | 22/48 | 4.4 ± 1.4               | 5.5 ± 1.5        | 19 (27.1) | 4.4 ± 1.4 | 1 (1.4)         |
| Total |                | 205 (100)       | 25.7 ± 23.2        | 83/122 | 4.1 ± 1.5               | 5.2 ± 1.3        | 53 (25.9) | 5.1 ± 1.5 | 9 (4.4)         |

| Divided doses of IVIG |                | Number of cases | Onset age (months) | F/M | Day of illness on admission | Start day of IVIG | Cases with aspirin therapy | Number of blood examinations | Coronary aneurysm |
|----------------------|----------------|-----------------|--------------------|-----|---------------------------|------------------|---------------------------|--------------------------|-------------------|
| ALT ≥ 40 IU/L on admission (Group Ib) |                | 89 (50.6)       | 28.1 ± 22.0        | 43/46 | 4.5 ± 1.1               | 5.0 ± 1.1        | 9 (10.1) | 4.4 ± 1.1    | 9 (10.1)        |
| ALT ≥ 40 IU/L after admission |                | 27 (15.3)       | 17.7 ± 25.1        | 9/18 | 4.2 ± 1.7               | 5.2 ± 1.5        | 4 (14.8) | 4.3 ± 1.0 | 2 (7.4)         |
| ALT < 40 IU/L consistently |                | 60 (34.1)       | 23.2 ± 17.8        | 24/36 | 4.8 ± 1.3               | 5.1 ± 1.1        | 9 (15.0) | 3.9 ± 1.0 | 0 (0.0)         |
| Total |                | 176 (100)       | 24.8 ± 21.4        | 76/100 | 4.6 ± 1.3               | 5.0 ± 1.2        | 22 (12.5) | 4.3 ± 1.1 | 11 (6.3)        |

Data are presented as n (%) or mean ± SD. ALT, alanine aminotransferase; F/M, female/male; IVIG, intravenous immunoglobulin.
III were compared. Specifically, data derived from all time-points after the days 1–3 time-point were compared with data from that initial time-point, to ascertain whether there were any significant differences (Table 2). All data presented in Table 2 and in the figures are expressed as medians. In group I, the AST/ALT ratio was also analyzed by day of illness. To determine data reproducibility, as well as dividing the subjects based on ALT threshold of ≥ 40 IU/L and < 40 IU/L as described above, they were also divided into group with ALT levels ≥ 50 IU/L and < 50 UL/L, and the same analyses were performed.

The significance of differences between data derived from the various time-points was assessed using the non-parametric Mann-Whitney U test. Differences pertaining to gender, aspirin treatment, and the frequency and proportion of coronary artery lesions were assessed using the Pearson’s chi-square test via an add-in statistical analysis software program for Microsoft Excel, “Excel statistics 2010” (SSRI, Tokyo, Japan).

RESULTS

There were no significant differences in age at onset, days of illness at admission, days of illness at the start of IVIG, or aspirin administration ratio between groups I, Ia, Ib, II, and III. However, groups II and III had significantly fewer female patients (P < 0.01) and significantly lower incidences of coronary artery aneurysm than group I (P < 0.01). The frequency of blood testing tended to be lower in group III (P < 0.05) (Table 1).

In group I, AST, ALT, and T-Bil peaked on days 1–3 of illness, AST improved rapidly on day 4 (P < 0.001). T-Bil improved on day 5 (P < 0.01), and ALT improved significantly on day 6 (P < 0.001). The difference between AST and ALT was attributable to their different half-lives. The half-life of AST is 11–15 h, while that of ALT is approximately 3 times greater, 40–50 h. Interestingly, CRP has a half-life of approximately 20 h, CRP concentration tended to increase up to day 6. Hence, although hepatic dysfunction tended to be improved by day 4, CRP—an index of systemic inflammation—tended to worsen up to day 6 (Figure 1). In addition, on day 4 the AST/ALT ratio fell below 0.87, the recovery period for acute hepatitis (Figure 2, Table 2).

### TABLE 2 Median values of each element in each period and significant difference test for each element

| Days of illness | 1–3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13–14 | 15–17 |
|-----------------|-----|---|---|---|---|---|---|----|----|----|-------|-------|
| Group I AST (IU/L) | 140.0 | 82.0 | 51.0 | 34.5 | 29.0 | 34.0 | 34.0 | 38.0 | 35.0 | 40.0 | 35.0 | 34.5 |
| ALT (IU/L) | 129.0 | 117.5 | 102.0 | 75.0 | 57.0 | 44.0 | 36.0 | 35.0 | 32.0 | 32.5 | 24.0 | 20.0 |
| T-Bil (mg/dL) | 1.00 | 0.95 | 0.60 | 0.40 | 0.30 | 0.30 | 0.30 | 0.30 | 0.30 | 0.30 | 0.30 | 0.30 |
| CRP (mg/dL) | 7.20 | 8.70 | 9.70 | 10.80 | 8.45 | 6.60 | 3.90 | 3.10 | 2.50 | 1.50 | 1.00 | 0.50 |
| Group Ib AST (IU/L) | 144.0 | 71.0 | 48.0 | 34.5 | 29.0 | 34.0 | 34.0 | 35.0 | 40.5 | 37.0 | 42.0 | 37.0 | 42.5 |
| ALT (IU/L) | 139.0 | 108.0 | 94.0 | 75.0 | 57.0 | 44.0 | 41.0 | 35.0 | 34.0 | 34.0 | 29.0 | 25.0 |
| T-Bil (mg/dL) | 1.10 | 1.05 | 0.60 | 0.50 | 0.35 | 0.20 | 0.20 | 0.30 | 0.30 | 0.30 | 0.30 | 0.30 |
| CRP (mg/dL) | 6.95 | 7.60 | 8.85 | 9.60 | 7.30 | 6.10 | 3.50 | 1.70 | 1.70 | 1.00 | 1.05 | 0.45 |
| Group Ia AST (IU/L) | 119.0 | 93.0 | 57.0 | 35.0 | 28.0 | 33.5 | 32.0 | 35.0 | 33.0 | 34.0 | 33.0 |
| ALT (IU/L) | 84.0 | 154.0 | 155.0 | 78.5 | 61.5 | 43.0 | 34.0 | 38.5 | 30.0 | 31.0 | 21.0 | 17.0 |
| T-Bil (mg/dL) | 0.80 | 0.85 | 0.50 | 0.40 | 0.30 | 0.30 | 0.40 | 0.30 | 0.40 | 0.30 | 0.40 | 0.30 |
| CRP (mg/dL) | 7.40 | 9.30 | 10.6 | 11.10 | 11.90 | 8.90 | 6.40 | 5.05 | 3.60 | 2.80 | 1.60 | 0.50 |
| Group II AST (IU/L) | 29.2 | 28.0 | 30.0 | 27.8 | 29.5 | 48.0 | 62.0 | 54.0 | 70.5 | 45.0 | 58.0 | 47.0 |
| ALT (IU/L) | 17.5 | 17.0 | 21.0 | 33.0 | 21.5 | 49.5 | 54.5 | 35.0 | 55.0 | 34.0 | 58.0 | 44.5 |
| T-Bil (mg/dL) | 0.80 | 0.40 | 0.35 | 0.40 | 0.30 | 0.30 | 0.25 | 0.20 | 0.30 | 0.30 | 0.30 | 0.30 |
| CRP (mg/dL) | 7.65 | 8.80 | 9.00 | 11.20 | 9.80 | 7.75 | 2.55 | 1.60 | 1.30 | 4.10 | 0.50 | 0.25 |
| Group III AST (IU/L) | 27.0 | 28.0 | 25.0 | 26.0 | 26.0 | 29.0 | 32.0 | 35.0 | 34.5 | 35.0 | 32.0 | 32.0 |
| ALT (IU/L) | 15.5 | 13.0 | 14.0 | 15.0 | 13.0 | 14.5 | 14.0 | 14.0 | 14.0 | 18.5 | 13.0 | 15.0 |
| T-Bil (mg/dL) | 0.50 | 0.50 | 0.30 | 0.30 | 0.20 | 0.20 | 0.20 | 0.20 | 0.20 | 0.20 | 0.20 | 0.30 |
| CRP (mg/dL) | 7.50 | 8.30 | 7.55 | 6.90 | 6.30 | 4.70 | 2.90 | 2.00 | 1.10 | 0.75 | 0.50 | 0.15 |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-Bil, total bilirubin; CRP, C-reactive protein.

* P < 0.05; ** P < 0.01; *** P < 0.001 (Mann-Whitney U test between days 1–3 and each day of illness).
FIGURE 1 Relationships between AST, ALT, T-Bil and CRP levels in group I (ALT ≥ 40 IU/L on admission; 199/381 cases, 52.2%). Brown, green, purple, and blue dots and lines respectively indicate AST (IU/L), ALT (IU/L), T-Bil (mg/dL), and CRP (mg/dL). AST, ALT, and T-Bil peaked on days 1–3 of illness. AST tended to exhibit recovery on the 4th day of illness (P < 0.001), T-Bil began to normalize on the 5th day of illness, and ALT began to normalize on the 6th day of illness. CRP gradually increased until the 6th day of illness (P < 0.01). AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-Bil, total bilirubin; CRP, C-reactive protein.

FIGURE 2 The AST/ALT ratio in group I. The AST/ALT ratio was < 0.87 from the 4th day of illness, which is regarded as the beginning of the recovery period of acute hepatitis. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Analysis of the mode of IVIG administration showed that ALT amelioration occurred on day 6 in group Ib (treated with divided doses of IVIG), which was later than in group Ia (treated with collective doses of IVIG), and CRP also worsened and reached high levels up to day 7 (Figures 3 and 4, Table 2).

FIGURE 3 Relationships between AST, ALT, T-Bil, and CRP in group Ia (collective doses of IVIG; 110/199 cases, 1983–1992). AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-Bil, total bilirubin; CRP, C-reactive protein.

FIGURE 4 Relationships between AST, ALT, T-Bil, and CRP in group Ib (divided doses of IVIG; 89/199 cases, 1992–2001). Brown, green, purple, and blue dots and lines respectively indicate AST (IU/L), ALT (IU/L), T-Bil (mg/dL), and CRP (mg/dL). ALT amelioration occurred on the 6th day of illness in group Ib, which was later than in group Ia, and CRP also worsened and reached high levels up to the 7th day of illness. AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-Bil, total bilirubin; CRP, C-reactive protein.

AST and ALT increased after admission in group II, and thereafter CRP increased slightly again, and then decreased (Figure 5). In group III, AST, ALT, and T-Bil were already significantly lower in the initial stage of illness (P < 0.01), and the CRP increased and peak levels tended to be lower than they were in in groups I and II (P < 0.05) (Figures 1, 5 and 6, Table 2).

The frequency of administration of aspirin and the amount of aspirin administered did not differ significantly in groups I, II, and III, nor was there a significant difference in the frequency of hepatic dysfunction between the IVIG collective-dose group and the IVIG divided-dose group (Table 1).

With regard to classification based on ALT values of ≥ 50 IU/L and < 50 IU/L, the study population of 381 patients consisted of 182 in group I (47.7%), 50 in group II (13.0%), and 149 in group III (39.3%), with subgrouping of 99 patients in group Ia and 83 in group Ib. All these groups underwent the same comparative analyses. The results obtained were similar to those of the analyses with the patients grouped based on ALT values of ≥ 40 IU/L and < 40 IU/L, suggesting that the results obtained in the present study are likely reliable.

DISCUSSION

Hepatic dysfunction in KD

The results of the current study suggest that hepatic dysfunction did not occur as a secondary complication of systemic inflammatory disease. Hepatic dysfunction was not attributable to any adverse reactions to aspirin or other drugs. In the group with existing hepatic dysfunction at the time of admission (group I), recovery from the disorder occurred in the initial stage of illness, within the period of exacerbation of CRP, which is an indicator of systemic inflammation. Thus, the hepatic dysfunction observed in KD is unlikely to be a secondary complication of systemic...
inflammation. In addition, there was no significant difference in the frequency of aspirin treatment between patients with and without hepatic dysfunction, nor were there any significant differences between the various IVIG therapies; suggesting that these therapies were unlikely to be involved. Aspirin recipients accounted for slightly less than 20% of the entire study population, a lower percentage than that has been reported in other hospitals. This is because aspirin was administered mainly as an antiplatelet drug in patients with suspected coronary artery aneurysms, and there is no clear evidence of therapeutic effects of low-dose aspirin in the initial treatment of KD.\textsuperscript{3,6} The significantly higher incidence of coronary artery aneurysm in group I suggests a close relationship between hepatic dysfunction and the severity and prognosis of KD. Hence, hepatic dysfunction is not a simple complication of KD, rather it is likely closely related to the etiology and mechanism of KD onset.

**Suggested mechanism of action of IVIG**

AST, ALT, and T-Bil have been suggested as risk factors for IVIG refractoriness.\textsuperscript{3-6} It has been suggested that these factors may be associated with the severity and mechanism of onset of KD. In the present study, the collective-dose IVIG treatment is considered to have been more effective than the divided-dose treatment. Evaluation of this difference will likely facilitate elucidation of the therapeutic effects of IVIG. Although more definitive conclusions may be reached by comparing patients who received IVIG treatment with those who did not, at our hospital patients who did not receive IVIG were all treated prior to 1982, and thus sufficient data were difficult to compile. Therefore, such a comparison was not performed in the present study.

Collective-dose IVIG treatment significantly ameliorated hepatic dysfunction and improved ALT. Specifically, these things occurred earlier. It also suppressed subsequent CRP elevation earlier and to a greater extent than divided-dose IVIG treatment. Hence, IVIG may have suppressed the systemic inflammatory exacerbation of KD by treating the cause of hepatic dysfunction (Figures 3, 4).

**Present status of KD etiology**

Candida\textsuperscript{10,11} and Lactobacillus extracts\textsuperscript{12,13} have been reportedly induce vasculitis resembling that seen in patients with KD. Some patients with Yersinia infections experience symptoms that are indistinguishable from KD\textsuperscript{14,17} and reddening at the sites of bacillus Calmette-Guérin scars is evidently induced by heat shock protein.\textsuperscript{18,19} Other KD studies suggest that super-antigens may be related to its mechanism of onset,\textsuperscript{20-22} that it may be caused by an unidentified pathogen from the airway,\textsuperscript{26-28} that dysbiosis may be a causal factor,\textsuperscript{6,29,30} and that circumpolar westerly winds, aerosols, and Candida may be causal factors.\textsuperscript{31} Despite numerous reports and etiology hypotheses, the etiology and mechanism of onset of KD remain unknown, the number of patients increases yearly, and there are no effective measures to stop it. With regard to our dysbiosis with translocation of gut microbiota theory, intestinal mucosal inflammation preceding the onset of KD has not yet been demonstrated.

**Liver histopathology in KD**

Autopsied liver histopathologic examinations and liver biopsies derived from patients with KD have been reported to reveal inflammatory cell infiltration, edema, and dilation in the portal vein region.\textsuperscript{32-35} Such findings suggest that some or all of the associated pathogens may have entered the body via the portal vein. Pathogen entry into the body via the portal vein is a distinct theoretical possibility with regards to causation and the onset of hepatic dysfunction in the initial stage of illness in KD. It is difficult to demonstrate however, and further advances will be necessary.

Orally ingested nutrients are transferred to the liver
by transporters in the small intestine via absorption by epithelial cells in processes involving the mechanisms of passive diffusion, active transportation, and then diffusion mainly via the portal vein system. Pathogen entry may be enabled by a disorder of any of these mechanisms in epithelial cells. This cannot be possible, however, in the absence of inflammation of the small intestine; thus it is necessary to demonstrate the existence of inflammation.

**Interpretation of the group with no hepatic dysfunction**

Group III consistently lacked hepatic dysfunction, and exhibited the smallest increase in CRP among groups I, II, and III \(P < 0.01\). It is well known that albumin and immunoglobulins in the blood are reduced by secretion and leakage of plasma proteins in strong and wide disorders of the skin and mucous membranes \(P < 0.01\). Notably, in previously reported study a group of subjects with hepatic dysfunction tended to have significantly less elevated serum IgA and IgM than a group with no hepatic dysfunction in the initial stage of illness.\(^7\) The most likely cause is that the severity of local mucosal disorder at the site of pathogen entry into the host was mild in the group with no hepatic dysfunction. However, possible differences in the sites of inflammation cannot be ruled out. While the sites of pathogen entry into the host may include the portal vein, it is reasonable to consider that lymph ducts, veins, and other routes are also possible sites of entry. The amounts and routes of pathogen entry and the proportions of the amounts of pathogen entry via the portal vein, lymph ducts, and veins may differ depending on the intensity of inflammation.

**Is intestinal mucosal inflammation present in KD?**

From its first edition to the most recent fifth edition, the Diagnostic Guide to Kawasaki Disease includes gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain for reference purposes.\(^3^8\) Amano et al\(^3^9\) noted catarrhal enteritis of the small intestine in their histopathological autopsy-based study. Intestinal mucosal inflammation was observed by Nagata et al\(^4^0\) and Yamashiro et al\(^4^1\) in duodenal biopsy investigations, and by Miura et al\(^4^2\) in gut immunohistological investigations in autopsied cases. Other reported findings suggestive of intestinal mucosal inflammation include suspected entry of an endotoxin \(P < 0.01\) and Bifidobacterium tended to decrease, and that this finding was consistent with the contention that KD patients are in a state of dysbiosis.

It currently remains unknown whether intestinal mucosal inflammation is present in all KD patients, and the details of onset time, mechanism, site, frequency, and severity are also unknown. Gut inflammation is inherently complex, and many aspects of it are not yet understood. While further metagenomics analysis of the intestinal bacterial flora and various cytokines \(P < 0.01\), it is necessary to concurrently utilize more direct approaches to the investigation of gut inflammation. Although abdominal echography may be able to available to detect gastrointestinal inflammation in some cases, it is unreliable in this respect. Unfortunately, methods of diagnostic imaging such as abdominal computed tomography, magnetic resonance imaging, and positron emission tomography, and invasive examinations such as endoscopy and biopsy cannot be performed in some patients. Moreover, it is unlikely that such procedures could be utilized repeatedly.

The most convenient currently available test that is relatively noninvasive and can be used repeatedly is fecal examination to detect inflammatory substances such as calprotectin and lactoferrin.\(^4^5\)-\(^4^7\)

**Future prospects for fecal calprotectin analysis**

Fecal calprotectin (FC) analysis over a time-course is expected to yield the following information:

1) FC peak time-point;
2) Changes in FC values before and after IVIG treatment;
3) Various factors for associated with increased FC.

If these things are clarified, the understanding of the etiology and mechanism of onset of KD, and determination of the effects of therapy, risk factors, and other aspects of the disease will be enhanced, which in turn may facilitate abatement of the recent trend of an annual increase in the number of patients diagnosed with KD.

**Study limitations**

The present study was not a planned randomized controlled study, it was a retrospective statistical analysis of test results. In addition, the patients in the treatment period differed in that some received divided-dose IVIG \(1983–1992\) and some received collective-dose IVIG \(1992–2001\) (Figure 2). Notably however, the study yielded reproducible results that exhibited the same trend regardless of whether patients were classified based on ALT thresholds of \(\geq 40\) IU/L and \(< 40\) IU/L, of \(\geq 50\) IU/L and \(< 50\) IU/L. It is necessary to confirm the reproducibility of the results of the current study in similar studies in patients at other hospitals. We suggested that logistic analysis of liver dysfunction using various
examination values and clinical symptoms is warranted, henceforth.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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