Original article

Reactivation of Human Herpesviruses 6 and 7 in Kawasaki Disease

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ABSTRACT

Objectives: Kawasaki disease (KD) is one of the most common childhood vasculitides. Some serological studies have suggested an etiological relationship between KD and human herpesvirus (HHV)-6 or HHV-7. However, primary or reactivated HHV-6 and -7 has not been fully investigated in patients with KD.

Methods: Twenty-three patients with KD were prospectively enrolled in this study. Peripheral blood was collected in the acute and convalescence phases, and HHV-6 and -7 viral loads were measured by real-time PCR.

Results: In the acute phase, HHV-6 and -7 DNA was detected in 7 (30%) patients each, compared to 13 (57%) and 9 (39%) patients in the convalescence phase, respectively. HHV-6 and -7 DNA loads were significantly higher in the convalescence phase than in the acute phase. Significant increases in HHV-6 and -7 DNA loads were not observed in disease control patients. Taking into account HHV-6 and -7 serostatus, reactivation of HHV-6 and -7 was observed in 7 and 9 patients, respectively. KD patients with HHV-6 reactivation showed higher C-reactive protein levels and more frequently required steroid therapies than patients without reactivation.

Conclusions: HHV-6 and -7 reactivation is frequent in KD patients. HHV-6 reactivation might exacerbate the severity of KD.

Introduction

Kawasaki disease (KD) is an acute, self-limited systemic vasculitis for which the etiology remains unknown. The clinical and epidemiological features of KD suggest that infectious agents might be triggers of the disease, but specific pathogens have not been identified (1). Human herpesvirus (HHV)-6 and HHV-7, causative pathogens of exanthema subitum, belong to the subfamily *betaherpesvirinae*. Both KD and exanthem subitum occur in young children, and some case reports and serological studies have suggested an etiological relationship between KD and HHV-6 or -7 (2-5). However, primary infection with or reactivation of HHV-6 and -7 has not been fully investigated in patients with KD. We encountered a case of severe KD with prolonged detection of HHV-7 DNA from the blood (6). Based on this case, we hypothesized that primary infection with or reactivation of HHV-6 or -7 might be associated with the pathophysiology and/or severity of KD. The present study prospectively enrolled KD patients and evaluated HHV-6 and -7 viral loads in blood by quantitative real-time PCR.

Patients and methods

Patients

Twenty-three consecutive patients (15 males, 8 females) with KD who were admitted to Okazaki City Hospital, ranging in age from 4 to 149 months (median age: 33 months), were prospectively enrolled in this study. KD was diagnosed based on the criteria in the fifth revision of the diagnostic guidelines for KD (7). We excluded patients diagnosed on or after day 10 of illness (day 1 of illness was defined as the day of fever onset) or those who were afebrile before enrolment. None of the enrolled patients had any underlying diseases. The Kobayashi score was determined as described previously, with a score ≥5 considered to indicate a high risk of no response to initial treatment with intravenous immunoglobulin (IVIG) (8). Among patients with a Kobayashi score ≥5 or showing resistance to initial treatment with IVIG, prednisolone (PSL)/cyclosporine A was given when informed consent was obtained from guardians. Dilation of the coronary artery lesion was defined as an internal diameter ≥3 mm in patients <5 years old or ≥4 mm in patients ≥5 years old. Peripheral blood was collected at the acute phase (at the time of diagnosis) and convalescence phase (>3 days after fever had subsided). The mean duration between sampling days of acute and convalescence was 18 days. Peripheral blood samples collected in the acute and convalescence phases from 9 age-matched patients with infectious diseases were used as controls. Among these controls, seropositivity for HHV-6 and -7 was seen in 7 and 5 patients, respectively. These patients included 4 patients with bronchitis/pneumonia, 2 with pharyngitis, 1 with peritonsillar abscess, 1 with gastroenteritis, and 1 with acute sinusitis. Furthermore, we retrospectively collected HHV-6 loads data of consecutive 12 pediatric living donor liver transplant patients between 2 and 19 years old as disease

controls with immunosuppression. These patients included 7 patients with biliary atresia, 3 patients with acute liver failure, 1 patient with Wilson disease, and 1 patient with congenital hepatic fibrosis. All study protocols were approved by the institutional review boards of Okazaki City Hospital and Nagoya University Hospital. Informed consent was obtained from all patients' guardians. The study was performed in accordance with the Declaration of Helsinki.

Measurement of DNA loads and HHV-6 and -7 antibodies

Viral DNA was extracted from whole blood using QIAamp DNA blood kits (Qiagen, Hilden, Germany). Real-time PCR assay was performed in a total reaction mixture containing 5 μl of DNA extract, 12.5 μl of QuantiTect multiplex PCR master mix (QIAGEN), forward and reverse primer, and probe as previously described (9). The number of HHV-6 and -7 DNA copies was calculated from standard curves and expressed as the number of copies per milliliter of whole blood. The detection limit of this real-time PCR assay is around 50 copies/mL. Anti-HHV-6 and -7 IgG antibody titers in sera collected before the administration of IVIG were measured using the fluorescent antibody (FA) method by a commercial laboratory (SRL, Tokyo, Japan). FA test values for HHV-6 and -7 were considered seropositive for titers ≥1:10.

Statistical analysis

Statistical analyses were performed using SPSS 23.0 software (IBM, Armonk, NY, USA). The Mann-Whitney *U* test and Fisher's exact test were used for comparisons of two groups of patients. The Wilcoxon signed-rank test was used to compare two sets of scores from the

same participants. Differences with $P < 0.05$ were deemed statistically significant.

Results

Characteristics of enrolled patients are shown in Table 1. At the initial treatment, 20 patients received IVIG and 3 patients with Kobayashi score ≥5 were treated with a combination of IVIG and PSL. Among them, 7 patients were resistant to initial treatment, and additional IVIG treatment with or without PSL/cyclosporine A was given. Kobayashi scores in patients treated with initial or additional PSL/cyclosporine A were significantly higher than in patients treated with IVIG alone (median: 8 vs. 3, $P = 0.008$). Transient dilation of coronary artery lesion was seen in 2 patients. HHV-6 and -7 antibodies were measured in 22 of 23 patients, and seropositivity was seen in 15 patients each.

In the acute phase, HHV-6 and -7 DNA was detected in 7 (30%) patients each, whereas they were detected in 13 (57%) and 9 (39%) patients at the convalescence phase, respectively. All 7 patients in whom HHV-6 DNA was detected in the acute phase were younger than 3 years old. Conversely, 6 of 7 patients with HHV-7 DNA detected in the acute phase were older than 3 years old.

HHV-6 and -7 DNA loads in patients with KD are shown in Fig. 1. In one HHV-6 seronegative patient, a high HHV-6 DNA concentration was detected in the acute phase (Fig. 1, dotted line), indicating that this patient had primary HHV-6 infection. The serostatus of HHV-6 and -7 was not determined in one patient in whom HHV-6 DNA was detected in the acute and convalescent phases. The other 11 patients with HHV-6 DNA detected in the convalescence phase and all 9 patients with HHV-7 DNA detected were HHV-6 or -7 seropositive, respectively. HHV-6 and -7 DNA loads were significantly higher in the convalescence phase than in the acute phase ($P = 0.039$ and $P = 0.008$, respectively). Among the 9 disease control patients with acute infection, HHV-6 DNA was detected in 3 (33%) patients each in the acute and convalescence phases. However,

no significant increases in HHV-6 DNA loads were observed (median: $10^{3.5}$ copies/mL vs. $10^{3.7}$ copies/mL, $P = 0.88$) in these patients. HHV-7 DNA was detected in 1 patient (11%) in each of the acute and convalescence phases ($10^{2.4}$ copies/mL and $10^{1.9}$ copies/mL, respectively). Among 12 pediatric liver transplant patients, HHV-6 DNA was detected in 3 (25%) patients, whereas significant increases in HHV-6 DNA loads were not observed when comparing two consecutive time points within 3 weeks post-transplant (median: $10^{3.4}$ copies/mL vs. $10^{3.5}$ copies/mL, $P = 0.83$).

We next compared the clinical features of KD patients with or without reactivation of HHV-6 and/or -7 (Table 2). Reactivation of HHV-6 and -7 was defined as the presence of IgG antibody with increased viral load in the convalescence phase (10). Increased HHV-6 DNA loads were observed in 8 patients, but serostatus was not determined in 1 patient. Based on the definition and results, reactivation of HHV-6 and -7 was observed in 7 and 9 patients, respectively. Furthermore, simultaneous reactivation of HHV-6 and -7 was observed in 5 patients. Patients with HHV-6 reactivation were older and had higher C-reactive protein (CRP) levels than patients without reactivation. Although the Kobayashi score to predict IVIG resistance did not differ between the two groups, PSL was more frequently administered to patients with HHV-6 reactivation. Conversely, patients with HHV-7 reactivation were older than patients without reactivation. However, no significant differences in other clinical or laboratory features were observed in patients with HHV-7 reactivation.

Patients with HHV-6 or -7 reactivation were older than those without reactivation, because some young infants were HHV-6 or -7 seronegative. We therefore compared clinical features among HHV-6- or -7-seropositive individuals, because differences in age distributions may have affected clinical features. Patients with HHV-6

reactivation showed higher CRP levels and more frequently required PSL than patients without reactivation, whereas there was no significant difference in age (Table 3). However, there were no significant differences in the clinical features of KD between patients with and without HHV-7 reactivation. Among HHV-6- or -7-seropositive individuals, KD patients without reactivation of these viruses did not require additional treatments with IVIG or PSL.

Discussion

This study utilized multiplex real-time PCR assays to investigate the association between HHV-6/-7 and KD. Generally, HHV-6 or -7 reactivation is defined as an increase in IgG antibody titer against the respective virus. However, this definition could not be used in the present study because all patients received IVIG for treatment of KD. We therefore defined HHV-6 and -7 reactivation as increased viral loads in seropositive patients. We found that increased HHV-6 and -7 DNA loads were observed in 47% and 60% of seropositive patients, respectively, suggesting that reactivation of HHV-6 and -7 frequently occurred in KD patients. Furthermore, one patient was considered to have primary HHV-6 infection. A few reports have shown KD patients in whom HHV-6 was isolated from peripheral blood or who had increased IgG antibody titers against HHV-6 (2) (11). Regarding HHV-7, only one study has demonstrated seroprevalence of HHV-7 in KD patients (3). Presently, HHV-6 and -7 are not considered to be the direct cause of KD. It is difficult to conclude that HHV-6 or -7 causes KD because these viruses are ubiquitous and the age distributions of exanthema subitum and KD overlap. Nevertheless, it might be possible that primary infection or reactivation of HHV-6 or -7 might affect the clinical features of KD.

Interestingly, we found that PSL was more frequently administered to KD patients with HHV-6 reactivation than to patients without reactivation. Reactivation rates of HHV-6 and -7 were significantly higher in patients treated with PSL than in patients treated without PSL (4/5 vs. 3/17, $P = 0.009$, and 4/5 vs. 5/17, $P = 0.04$, respectively). Immunosuppression with PSL therapy might potentially induce reactivation of HHV-6. However, no significant increases in HHV-6 DNA loads were observed in pediatric liver transplant patients > 2 years old within 3 weeks post-transplant. Primary HHV-6

infection accompanied by HHV-6 DNAemia has been shown to be common in seronegative pediatric patients shortly after liver transplantation (12, 13). Conversely, our observation may suggest that HHV-6 reactivation is not frequent among older children despite use of immunosuppressive agents. The HHV-6 reactivation shown in KD patients thus may not be solely explained by the use of PSL.

Furthermore, Walton et al. investigated the reactivation of multiple latent viruses in adult patients with sepsis, and found that DNA of herpesviridae such as Epstein-Barr virus and cytomegalovirus were frequently detected in blood samples from these patients (14). The primary hyperinflammatory phase of sepsis has been hypothesized to progress to a predominantly immunosuppressive state (15). This immunosuppressive state could potentially occur in the convalescent phase of KD and may induce reactivation of HHV-6 and -7. On the other hand, pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β have been considered to play important roles in the pathogenesis of KD, and HHV-6 reactivation might be triggered in response to pro-inflammatory cytokines (16, 17).

Conversely, HHV-6 reactivation might exacerbate the severity of KD, resulting in the use of PSL, because CRP levels were higher in patients with HHV-6 reactivation. HHV-6 has been demonstrated to upregulate the production of pro-inflammatory cytokines by peripheral mononuclear cells, and elevation of cytokine levels was shown in patients with drug-induced hypersensitivity syndrome associated with HHV-6 reactivation (18, 19). Therefore, it is possible that HHV-6 reactivation induces cytokine synthesis, thereby modulating the clinical features of KD.

In addition to HHV-6, reactivation of HHV-7 was also observed among relatively older children. However, there were no significant differences in the clinical

features of KD in patients with HHV-7 reactivation. The primary target cells of HHV-6 are considered to be $CD4^+$ T cells, whereas its cellular host range is wide and includes $CD8^+$ T cells, monocytes/macrophages and NK cells. In contrast, HHV-7 has narrow cell tropism, thus far being restricted to $CD4^+$ T cells (20). The difference in cell tropism of these viruses might explain the varied impact on the clinical features of KD.

To the best of our knowledge, this is the first study to investigate the association between KD and HHV-6/-7 by measuring viral loads. HHV-6 reactivation frequently occurs in KD patients may affect the clinical features of KD. However, we cannot yet definitively conclude that reactivation of HHV-6 was induced by an immunosuppressive state or that reactivation of HHV-6 exacerbated the severity of KD and required additional treatment with immunosuppressive agents.

Figure legend

Fig. 1. Comparison of HHV-6 and HHV-7 viral loads between acute and convalescence phases of patients with Kawasaki disease. The bold dotted line indicates a patient with primary HHV-6 infection. Differences between the two groups were evaluated using the Wilcoxon signed-rank test. The thin dotted line indicates the detection limit of real-time PCR.

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Conflict of interest

None

References

1. Kim KY, Kim DS. Recent Advances in Kawasaki Disease. Yonsei Med J. 2016;57(1):15-21.
2. Okano M, Luka J, Thiele GM, Sakiyama Y, Matsumoto S, Purtilo DT. Human herpesvirus 6 infection and Kawasaki disease. J Clin Microbiol. 1989;27(10):2379-80.
3. Burns JC, Newburger JW, Sundell R, Wyatt LS, Frenkel N. Seroprevalence of human herpesvirus 7 in patients with Kawasaki disease. Pediatr Infect Dis J. 1994;13(2):168-9.
4. Toyabe S, Harada W, Suzuki H, Hirokawa T, Uchiyama M. Large vessel arteritis associated with human herpesvirus 6 infections. Clin Rheumatol. 2002;21(6):528-32.
5. Kakisaka Y, Ohara T, Katayama S, Suzuki T, Sasai S, Hino-Fukuyo N, et al. Human herpes virus type 6 can cause skin lesions at the BCG inoculation site similar to Kawasaki Disease. Tohoku J Exp Med. 2012;228(4):351-3.
6. Hirayama Y, Kawano Y, Mamiya N, Tsuji T, Kawada J, Ito Y, et al. A case of severe Kawasaki disease with human herpesvirus 7detection by PCR. The Journal of the Japan Pediatric Society. 2015;119(2):239.
7. Ayusawa M, Sonobe T, Uemura S, Ogawa S, Nakamura Y, Kiyosawa N, et al. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). Pediatr Int. 2005;47(2):232-4.
8. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet. 2012;379(9826):1613-20.
9. Wada K, Kubota N, Ito Y, Yagasaki H, Kato K, Yoshikawa T, et al. Simultaneous quantification of Epstein-Barr virus, cytomegalovirus, and human herpesvirus 6 DNA in samples from transplant recipients by multiplex real-time PCR assay. J Clin Microbiol. 2007;45(5):1426-32.
10. Kamijima M, Wang H, Yamanoshita O, Ito Y, Xia L, Yanagiba Y, et al. Occupational trichloroethylene hypersensitivity syndrome: human herpesvirus 6 reactivation and rash phenotypes. J Dermatol Sci. 2013;72(3):218-24.
11. Hagiwara K, Yoshida T, Komura H, Kishi F, Kajii T. Isolation of human herpesvirus-6 from an infant with Kawasaki disease. Eur J Pediatr. 1993;152(2):176.

12. Yoshikawa T, Ihira M, Suzuki K, Suga S, Iida K, Saito Y, et al. Human herpesvirus 6 infection after living related liver transplantation. J Med Virol. 2000;62(1):52-9.
13. Ylinen E, Lehtinen S, Jahnukainen T, Karlsson T, Loginov R, Mannonen L, et al. Human herpes virus 6 infection in pediatric organ transplant patients. Pediatr Transplant. 2017;21(4).
14. Walton AH, Muenzer JT, Rasche D, Boomer JS, Sato B, Brownstein BH, et al. Reactivation of multiple viruses in patients with sepsis. PLoS One. 2014;9(2):e98819.
15. Munford RS, Pugin J. Normal responses to injury prevent systemic inflammation and can be immunosuppressive. Am J Respir Crit Care Med. 2001;163(2):316-21.
16. Mori M, Imagawa T, Hara R, Kikuchi M, Hara T, Nozawa T, et al. Efficacy and limitation of infliximab treatment for children with Kawasaki disease intractable to intravenous immunoglobulin therapy: report of an open-label case series. J Rheumatol. 2012;39(4):864-7.
17. Krug LT, Pellett PE. Roseolovirus molecular biology: recent advances. Curr Opin Virol. 2014;9:170-7.
18. Flamand L, Gosselin J, D'Addario M, Hiscott J, Ablashi DV, Gallo RC, et al. Human herpesvirus 6 induces interleukin-1 beta and tumor necrosis factor alpha, but not interleukin-6, in peripheral blood mononuclear cell cultures. J Virol. 1991;65(9):5105-10.
19. Yoshikawa T, Fujita A, Yagami A, Suzuki K, Matsunaga K, Ihira M, et al. Human herpesvirus 6 reactivation and inflammatory cytokine production in patients with drug-induced hypersensitivity syndrome. J Clin Virol. 2006;37 Suppl 1:S92-6.
20. Yamanishi K, Mori Y, Pellett PE. Human Herpesvirus 6 and 7. In: Knipe DM, Howley PM, editors. Fields Virology. 2. 6 ed: Lippincott Williams & Wilkins; 2013.

Table 1. Characteristics of enrolled patients

Characteristic		Subjects (*n*=23)
Sex (male/female)		15/8
Age, median months (range)	33 (4–149)	
WBC ($\times 10^3/mm^3$), median (range)	14.6 (4.8–27.3)	
% neutrophils, median (range)	78 (23–96)	
CRP (mg/dL), median (range)	8.3 (1.4–19.3)	
AST (IU/L), median (range)	32 (17–657)	
Albumin (g/dL), median (range)	4.0 (3.0–4.4)	
Positive for HHV-6 IgG		15* (68%)
Anti-HHV-6 IgG titer, GMT (range)	83.8 (10–640)	
Positive for HHV-7 IgG		15* (68%)
Anti-HHV-7 IgG titer, GMT (range)	26.4 (10–80)	
Initial treatment		
IVIG		20 (87%)
IVIG + PSL		3 (13%)
Resistant to initial treatment		7 (30%)
Additional treatment		
IVIG		4 (57%)
IVIG + PSL		1 (14%)
IVIG + IVMP + CsA		1 (14%)
IVMP + PSL		1 (14%)
Kobayashi score, median (range)	4 (0–10)	
Kobayashi score ≥5		11 (48%)
Coronary artery lesion		
Transient dilation		2 (9%)

WBC: white blood cells, CRP: C-reactive protein, AST: aspartate aminotransferase, HHV-6: human herpesvirus 6, HHV-7: human herpesvirus 7, GMT: geometric mean titer, IVIG: intravenous immunoglobulin, PSL: prednisolone, IVMP: intravenous methylprednisolone, CsA: cyclosporine A

*Antibodies were not measured in 1 patient.

Table 2. Comparison of KD patients with HHV-6, HHV-7, or HHV-6 + HHV-7 reactivation

	HHV-6			HHV-7			HHV-6 + HHV-7		
	Reactivation (n=7)	No reactivation (n=15)	*P*	Reactivation (n=9)	No reactivation (n=13)	*P*	Simultaneous reactivation (n=5)	No simultaneous reactivation (n=17)	*P*
Age, median months (range)	58 (22–149)	24 (4–135)	**.022**	56 (22–149)	17 (4–135)	**.035**	58 (22–149)	26 (4–135)	.066
WBC ($\times 10^3/mm^3$), median (range)	14.5 (8.7–27.3)	15.4 (4.8–19.2)	.944	14.5 (4.8–19.2)	15.9 (7.9–27.3)	.204	14.5 (8.7–16.9)	15.4 (4.8–27.3)	.531
CRP (mg/dL), median (range)	10.6 (4.8–19.3)	5.5 (1.4–15.3)	**.041**	10.6 (1.4–19.3)	8.2 (2.0–15.3)	.367	12.9 (4.8–19.3)	7.3 (1.4–15.3)	**.042**
AST (IU/L), median (range)	32 (21–459)	32 (17–107)	.698	30 (17–459)	32 (21–107)	.664	33 (28–459)	32 (17–107)	.256
Albumin (g/dL), median (range)	4.0 (3.7–4.2)	3.9 (3.0–4.4)	.094	3.8 (3.5–4.2)	4.0 (3.0–4.4)	.813	4.0 (3.7–4.2)	3.9 (3.0–4.4)	.341
Kobayashi score Patients with high risk (≥5)	5	5	.113	6	4	.110	4	6	.105
Resistant to initial treatment	2	4	.651	3	3	.477	2	4	.419
Total IVIG (g/kg), median (range)	2 (2–3)	2 (2–4)	.470	2 (2–3)	2 (2–4)	.820	2 (2–3)	2 (2–4)	.789
Use of PSL	4	1	**.021**	4	1	.067	3	2	.055
Fever duration after initial treatment (days), median (range)	0 (0–4)	0 (0–6)	.928	0 (0–4)	0 (0–6)	.798	0 (0–4)	0 (0–6)	.618
Total duration of fever (days), median (range)	5 (4–9)	5 (3–12)	.684	5 (3–12)	5 (5–12)	.399	6 (4–9)	5 (3–12)	.967
Coronary artery abnormalities	1	1	.545	1	1	.662	1	1	.411

KD: Kawasaki disease, HHV-6: human herpesvirus 6, HHV-7: human herpesvirus 7, WBC: white blood cells, CRP: C-reactive protein, AST: aspartate aminotransferase, IVIG: intravenous immunoglobulin, PSL: prednisolone. Laboratory findings of acute phase are shown.

Table 3. Comparison of KD patients with HHV-6 or HHV-7 among seropositive individuals

	HHV-6			HHV-7		
	Reactivation (n=7)	No reactivation (n=8)	*P*	Reactivation (n=9)	No reactivation (n=6)	*P*
Age, median months (range)	58 (22–149)	30 (5–135)	.083	56 (22–149)	40 (5–135)	.409
WBC ($\times 10^3/mm^3$), median (range)	14.5 (8.7–27.3)	16.8 (4.8–19.2)	.643	14.5 (4.8–19.2)	18.3 (10.6–27.3)	.059
CRP (mg/dL), median (range)	10.6 (4.8–19.3)	4.8 (2.0–15.3)	**.049**	10.6 (1.4–19.3)	6.9 (3.7–15.3)	.443
AST (IU/L), median (range)	32 (21–459)	27 (17–60)	.164	30 (17–459)	30 (21–32)	.679
Albumin (g/dL), median (range)	4.0 (3.7–4.2)	3.7 (3.3–4.4)	.090	3.8 (3.5–4.2)	4.0 (3.3–4.4)	.766
Kobayashi score						
Patients with high risk (≥5)	5	3	.214	6	2	.231
Resistant to initial treatment	2	0	.200	3	0	.185
Total IVIG (g/kg), median (range)	2 (2–3)	2 (2–2)	.285	2 (2–3)	2 (2–2)	.231
Use of PSL	4	0	**.026**	4	1	.294
Fever duration after initial treatment (days), median (range)	0 (0–4)	0 (0–0)	.118	0 (0–4)	0 (0–0)	.129
Total duration of fever (days), median (range)	5 (4–9)	5 (3–10)	.582	5 (3–12)	5 (5–10)	.626
Coronary artery abnormalities	1	1	.733	1	1	.657

KD: Kawasaki disease, HHV-6: human herpesvirus 6, HHV-7: human herpesvirus 7, WBC: white blood cells, CRP: C-reactive protein, AST: aspartate aminotransferase, IVIG: intravenous immunoglobulin, PSL: prednisolone

Laboratory findings of acute phase are shown.

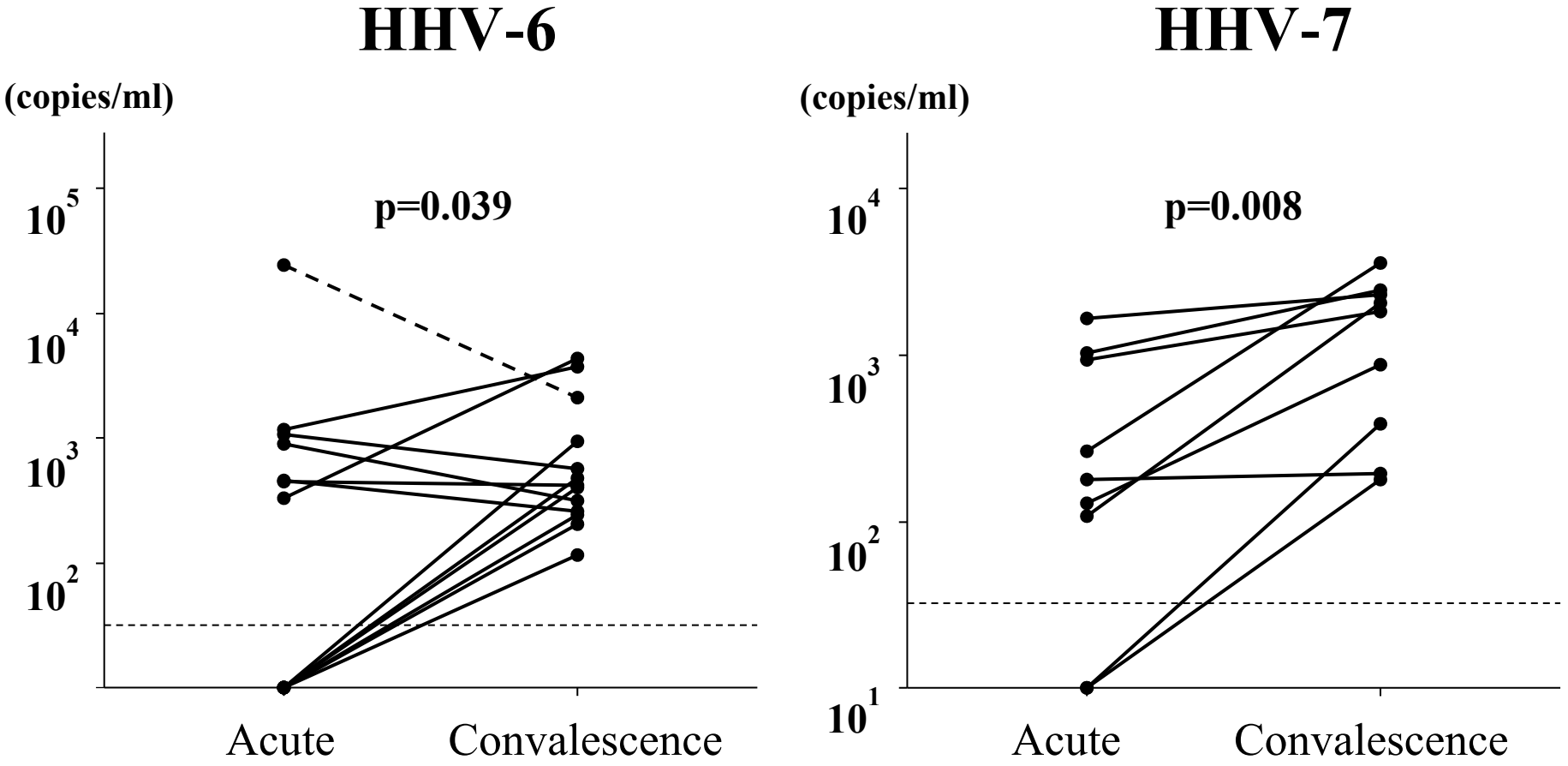
HHV-6
(copies/ml)
p=0.039
10^5
10^4
10^3
10^2
Acute
Convalescence
HHV-7
(copies/ml)
p=0.008
10^4
10^3
10^2
10^1
Acute
Convalescence

Fig. 1