



# Incomplete Kawasaki Disease Associated With Human Herpes Virus-6 Variant B Infection and Aseptic Meningitis

Global Pediatric Health  
 Volume 7: 1–4  
 © The Author(s) 2020  
 Article reuse guidelines:  
[sagepub.com/journals-permissions](https://sagepub.com/journals-permissions)  
 DOI: 10.1177/2333794X20939759  
[journals.sagepub.com/home/gph](https://journals.sagepub.com/home/gph)  


Morouge M. Alramadhan, MD<sup>1</sup> , Ankur A. Kamdar, MD<sup>1</sup>,  
 Meaghan Lafferty-Prather, MD<sup>1</sup>, Elizabeth A. Aguilera, MD<sup>1</sup>,  
 and Susan H. Wootton, MD<sup>1</sup>

Received March 25, 2020. Received revised June 11, 2020. Accepted for publication June 15, 2020.

## Introduction

First described in 1967 by Tomisaku Kawasaki, Kawasaki disease (KD) is an acute febrile mucocutaneous lymph node syndrome of unknown etiology. KD mainly affects children aged <5 years and is a leading cause of heart disease in children. The diagnosis is primarily clinical.<sup>1</sup> Children who do not meet full clinical criteria may have incomplete KD (iKD) if they meet certain supplemental laboratory criteria.<sup>1</sup> Neurologic complications in KD are rare, occurring in 1.1% to 3.7% of children. Irritability, thought to be related to cerebrospinal fluid (CSF) pleocytosis, occurs in 40% of patients during the acute KD illness. There are many hypotheses regarding the etiology of KD including infection or an abnormal immune response to infection. To date, no specific pathogens have been identified.<sup>1</sup> In this article, we present the case of a child with iKD associated with human herpes virus-6 variant b (HHV-6b) who presented with aseptic meningitis. Initial treatment included intravenous immunoglobulin (IVIG) and steroids.

## Description

A healthy 12-month-old male presented with 5 days of fever (40 °C), increasing irritability, and draining pustules on his legs. On admission, his  $T_{max}$  was 40 °C, pulse 167 beats per minute, blood pressure 105/61 mm Hg, and respiratory rate 28 breaths per minute. He was fussy, had bilateral nonexudative conjunctivitis (perilimbal sparing was not noted) with mild periorbital edema, a few crusted lesions on both lower extremities distally, and some limitation of neck movement. His white blood cell (WBC) count was  $15.6 \times 10^3/\text{mm}^3$  with 77.8% segmented neutrophils, hemoglobin 9.4 g/dL, and platelets  $253 \times 10^3/\text{mm}^3$ . C-reactive protein was 46.5 mg/L and erythrocyte sedimentation rate 20 mm/h. Alanine aminotransferase was

47 U/L (normal = 0–65 U/L), aspartate aminotransferase 47 U/L (normal = 0–37 U/L), and albumin of 2 g/dL (normal = 3.8–5.4 g/dL).

A lumbar puncture showed elevated CSF WBC (593 cells/mm<sup>3</sup> with 81% segmented neutrophils) with normal red blood cells (RBCs; 4 cells/mm<sup>3</sup>) and protein >2500 mg/dL and glucose (43 mg/dL). CSF Gram stain had few WBCs but no organisms; CSF herpes simplex virus and enterovirus polymerase chain reaction (PCR) tests as well as CSF cultures were negative. Brain computed tomography scan was normal. Vancomycin and ceftriaxone were initiated; however, fever, lethargy, and irritability persisted. On hospital day 4, he had tremulous extremity shaking and intermittent staring spells. On examination, bilateral suboccipital lymphadenopathy and a transient erythematous maculopapular rash were noted (Figure 1). A repeat LP showed a decrease in CSF WBC (146 cells/mm<sup>3</sup> with 47% segmented neutrophils) and normal RBC (2 cells/mm<sup>3</sup>), protein (90 mg/dL), and glucose (54 mg/dL). Brain and spine magnetic resonance imaging with contrast as well as electroencephalography were normal. On hospital day 6, an echocardiogram showed diffuse dilatation of his coronary arteries (left main coronary artery 3.5 mm [Z score 3.65], left anterior descending 2.7 mm [Z score 4.25], and right coronary artery 2.8 mm [Z score 3.68]) consistent with iKD. Rheumatology was consulted as routinely done to coordinate KD care at our center (Figure 1).

<sup>1</sup>McGovern Medical School at The University of Texas Health Sciences Center at Houston, TX, USA

### Corresponding Author:

Susan H. Wootton, Division of Infectious Diseases, Department of Pediatrics, McGovern Medical School at The University of Texas Health Science Center Houston, 6431 Fannin Street, MSB 2.106, Houston, TX 77030, USA.  
 Email: [susan.h.wootton@uth.tmc.edu](mailto:susan.h.wootton@uth.tmc.edu)





**Figure 1.** Erythematous maculopapular rash over the whole body.

The patient was treated with IVIG 2 g/kg twice along with methylprednisolone 30 mg/kg daily for 2 days followed by prednisolone (1 mg/kg daily) taper over 3 weeks. Aspirin (30 mg/kg/day) was initiated and then decreased to low dose (3.75 mg/kg/dose) within 1 day of the second IVIG administration. He remained hospitalized for 14 days to complete empiric therapy for aseptic meningitis. Three weeks after collection, the human herpes virus CSF PCR was positive for HHV-6B (LabCorp). The patient was evaluated by cardiology as an outpatient. Follow-up echocardiograms showed improvement at 2 months (mild dilation of the left main coronary artery, normal Z scores for left anterior descending and right coronary artery) and resolution by 7 months. Low-dose aspirin was recommended for 1 year.

## Discussion

Our patient presented with iKD complicated by aseptic meningitis. Aseptic meningitis in KD is uncommon. In a series by Yu et al, only 2.73% of children with KD developed central nervous system (CNS) involvement in the form of aseptic meningoencephalitis.<sup>2</sup> Other CNS manifestations of KD include irritability, subdural effusion, ataxia, coma, facial palsy, sensorineural hearing loss, and seizures. Because LPs are rarely performed in children with KD, the prevalence of aseptic meningitis and specific CSF characteristics are unknown. A few case series have suggested that CSF results among KD patients are similar to patients with viral meningitis with CSF WBC medians 22.5 to 97/mm<sup>3</sup> (range = 7-580/mm<sup>3</sup>).<sup>3,4</sup> One case report<sup>5</sup> described a 3-year-old child who presented with fever, headache, and stiff neck followed by 4 additional criteria for KD. Our patient's CSF WBC (593/mm<sup>3</sup> with 81% neutrophil) was higher than

previous reports raising concerns, at least initially, of an infectious etiology.

Additionally, our patient's initial CSF had a markedly elevated protein (>2500 mg/dL). Such elevated CSF protein is unusual in the context of KD. In one retrospective study, CSF protein levels ranged from 9 to 474 mg/dL, with a median of 27 mg/dL among KD patients.<sup>4</sup> The differential for such elevated CSF protein is broad and includes both infectious and noninfectious etiologies.<sup>6</sup> Tuberculosis and hemorrhage were felt less likely as our patient's T-spot, chest X-ray, CSF RBC, and brain images were normal. We also considered Froin's syndrome. Characterized by xanthochromia, CSF protein levels up to 5 g/dL and marked CSF coagulation, Froin's syndrome is an alteration in CSF caused by inflammatory or neoplastic obstruction.<sup>7</sup> Our patient's CSF was colorless; repeat imaging and CSF protein were reassuring making Froin's syndrome unlikely. In hindsight, the initial CSF sample should have been retested as the protein result was not consistent with its appearance and diluted to determine the exact protein value. Such testing would have confirmed if a laboratory error had occurred. Such laboratory errors are uncommon; however, when they do occur contribute to delay in diagnoses, additional procedures, prolonged hospitalizations, and increase cost.<sup>8</sup>

Interestingly, our patient's CSF HHV-6b PCR was positive. HHV-6 has 2 variants: HHV-6A and HHV-6B. HHV-6A is described as more neurovirulent, whereas HHV-6B is more commonly associated with childhood infections such as exanthema subitum ("roseola infantum"), which is characterized by high fever (3-7 days) followed by a rash that appears once the fever has resolved. In our patient, the rash developed ~9 days into his fever, so his presentation was not typical for roseola infantum. CNS manifestations of HHV6B in children can also include bulging fontanelle, encephalopathy, or encephalitis. Although primary infection with HHV-6B was felt most likely based on our patient's age, chromosomal viral integration was also considered.<sup>9</sup> In approximately 1% to 2% of the US population, the HHV-6 genome is integrated (ciHHV-6) into the host germ line and vertically transmitted. Consequently, ciHHV-6 can complicate the interpretation of positive CSF HHV-6 PCR results.<sup>10</sup> Any positive CSF HHV-6 PCR should be followed by whole blood quantitative HHV-6 PCR testing to determine if the CSF result could be a false-positive. Our patient's HHV-6 viral load 1 month after presentation was negative, making ciHHV-6 less likely. Because the HHV-6 genome is covalently linked to human chromosomal DNA in patients with ciHHV-6, the clinical specimens (eg, whole blood, leukocytes, plasma, and tissue specimens) from such individuals will contain very high

levels of HHV-6 DNA when tested by PCR (>1 million copies per mL).<sup>11</sup> Ward et al reports the persistence of high HHV-6 DNA levels in some cases for several years.<sup>9,12</sup> The role of HHV-6 and KD is unknown. Several studies have evaluated the association of viral infections and KD including HHV-6, but links have not been firmly established.<sup>13</sup> In a small sample of patients, Kawano et al noted that HHV-6 reactivation frequently occurred in KD patients, which may affect the clinical features of KD through induction of cytokines synthesis exacerbating the severity of KD and resulting in the use of prednisolone.<sup>14</sup>

Finally, our patient was classified as high risk for coronary artery aneurysm (CAA) based on his Kobayashi score (3 variables out of 7, 4 points).<sup>15</sup> In a study by Sleeper et al,<sup>16</sup> the authors used 3 risk scores (Kobayashi, Egami, and Sano), which were developed in Japan, to predict resistance to IVIG treatment in children with KD. They found that these risk scores had good specificity but low sensitivity in the North American children (Kobayashi at a sensitivity of 33% and specificity of 87%) but found Kobayashi score was a significant predictor of CA Z scores for all segments. Our patient was also classified as high risk for CAA based on his echocardiogram results. Son et al<sup>17</sup> explored the relationship of CAA with baseline Z scores, risk scores, and a combination of baseline Z scores and risk scores. Among 261, CAA were strongly associated with baseline  $z_{\text{Max}} \geq 2$  versus  $< 2.0$  (12 [16%] vs 3 [2%], respectively,  $P < .001$ ). As per the American Heart Association guidelines,<sup>1</sup> which state longer courses of corticosteroids (eg, tapering over 2-3 weeks) together with IVIG and aspirin may be considered for treatment of high-risk KD patients, our patient received his second dose of IVIG with methylprednisolone followed by a 3-week oral prednisolone taper. Although debated, multiple clinical studies have shown use of steroid decrease the incidence rate of coronary artery abnormalities.<sup>18,19</sup>

In summary, our case represents a complex presentation of iKD associated with HHV-6B in a child with aseptic meningitis complicated by a delay in diagnosis. Such a case highlights several important points. First, children aged <2 years are more likely to have iKD and thus a high index of suspicion of KD is required.<sup>1</sup> Second, the differential of elevated CSF protein is broad including, although uncommon, laboratory error. Repeat sample testing is effective strategy for navigating such laboratory errors. Third, the role of HHV-6B infection and KD in our patient is unknown. We were able to exclude ciHHV-6 based on whole blood PCR testing. Finally, management of KD may include initial IVIG and steroids versus IVIG alone. For patients with high risk of

KD recurrence, the combination of IVIG and steroid may be effective.

### Acknowledgments

We thank the Clinical Microbiology Laboratory at Memorial Hermann Hospital and the Grant-A-Starr Foundation.

### Author Contributions

SHW, AAK and MMA made substantial contributions to the design, acquisition, analysis and interpretation of the work including drafting and revising it critically for important intellectual content. EAA and ML-P made substantial contributions to the acquisition, drafting and revisions of the work.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

### Ethical Approval

Ethics approval is not required, deemed not to constitute research.

### Patient Consent

Written informed consent was obtained from the patient's guardian for the publication of this case report. Patient's consent was not obtained as the patient was 12 months.

### ORCID iD

Morouge M. Alramadhan  <https://orcid.org/0000-0003-2502-3869>

### References

1. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135:e927-e999. doi:10.1161/CIR.0000000000000484
2. Yu JG, Wei Y, Zhao SY, Zou CC, Shu Q. Aseptic meningencephalitis in children with Kawasaki disease. *HK J Paediatr (New Series)*. 2010;15:270-275.
3. Dengler LD, Capparelli EV, Bastian JF, et al. Cerebrospinal fluid profile in patients with acute Kawasaki disease. *Pediatr Infect Dis J*. 1998;17:478-481. doi:10.1097/00006454-199806000-00008
4. Korematsu S, Uchiyama S, Miyahara H, et al. The characterization of cerebrospinal fluid and serum cytokines

- in patients with Kawasaki disease. *Pediatr Infect Dis J*. 2007;26:750-753. doi:10.1097/INF.0b013e3180f61708
5. Rossi M, Siani P, Grossi A, et al. Aseptic meningitis as onset of Kawasaki disease. *Minerva Pediatr*. 2020;72:135-137. doi:10.23736/S0026-4946.19.05384-2
  6. Deisenhammer F, Bartos A, Egg R, et al. Guidelines on routine cerebrospinal fluid analysis. Report from an EFNS task force. *Eur J Neurol*. 2006;13:913-922. doi:10.1111/j.1468-1331.2006.01493.x
  7. Garispe A, Naji H, Dong F, Arabian S, Neeki M. Froin's syndrome secondary to traumatic and infectious etiology. *Cureus*. 2019;11:e6313. doi:10.7759/cureus.6313
  8. Baker GR, Norton PG, Flintoft V, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *CMAJ*. 2004;170:1678-1686. doi:10.1503/cmaj.1040498
  9. Ward KN, Leong HN, Thiruchelvam AD, Atkinson CE, Clark DA. Human herpesvirus 6 DNA levels in cerebrospinal fluid due to primary infection differ from those due to chromosomal viral integration and have implications for diagnosis of encephalitis. *J Clin Microbiol*. 2007;45:1298-1304. doi:10.1128/JCM.02115-06
  10. Green DA, Pereira M, Miko B, Radmard S, Whittier S, Thakur K. Clinical significance of human herpesvirus 6 positivity on the FilmArray Meningitis/Encephalitis Panel. *Clin Infect Dis*. 2018;67:1125-1128. doi:10.1093/cid/ciy288
  11. Pellett PE, Ablashi DV, Ambros PF, et al. Chromosomally integrated human herpesvirus 6: questions and answers. *Rev Med Virol*. 2012;22:144-155. doi:10.1002/rmv.715
  12. Ward KN, Leong HN, Nacheva EP, et al. Human herpesvirus 6 chromosomal integration in immunocompetent patients results in high levels of viral DNA in blood, sera, and hair follicles. *J Clin Microbiol*. 2006;44:1571-1574. doi:10.1128/JCM.44.4.1571-1574.2006
  13. Okano M, Luka J, Thiele GM, Sakiyama Y, Matsumoto S, Purtilo DT. Human herpesvirus 6 infection and Kawasaki disease. *J Clin Microbiol*. 1989;27:2379-2380.
  14. Kawano Y, Kawada JI, Nagai N, Ito N. Reactivation of human herpesviruses 6 and 7 in Kawasaki disease. *Mod Rheumatol*. 2019;29:651-655. doi:10.1080/14397595.2018.1510758
  15. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation*. 2006;113:2606-2612. doi:10.1161/CIRCULATIONAHA.105.592865
  16. Sleeper LA, Minich LL, McCrindle BM, et al. Evaluation of Kawasaki disease risk-scoring systems for intravenous immunoglobulin resistance. *J Pediatr*. 2011;158:831-835. doi:10.1016/j.jpeds.2010.10.031
  17. Son MBF, Gauvreau K, Kim S, et al. Predicting coronary artery aneurysms in Kawasaki disease at a North American Center: an assessment of baseline z scores. *J Am Heart Assoc*. 2017;6:e005378. doi:10.1161/JAHA.116.005378
  18. Son MB, Newburger JW. Management of Kawasaki disease: corticosteroids revisited. *Lancet*. 2012;379:1571-1572. doi:10.1016/S0140-6736(12)60196-2
  19. Ogata S, Ogihara Y, Honda T, Kon S, Akiyama K, Ishii M. Corticosteroid pulse combination therapy for refractory Kawasaki disease: a randomized trial. *Pediatrics*. 2012;129:e17-e23. doi:10.1542/peds.2011-0148