Case report: acute motor and sensory axonal Guillain-Barre variant in association with HHV-6 infection

Leah Naasz BS[1], Mykayla Vollmer MD[1], Nessim Amin MD[1], Abram Wahba MD[2]

[1]University of South Dakota Sanford School of Medicine, [2]Department of Neurology, Sanford Health

Introduction

Guillain-Barre syndrome (GBS) is an encompassing term that refers to a group of acute autoimmune-mediated polyneuropathies and is one of the most common neuromuscular emergencies. Infections are the most common antecedent event before the clinical development of GBS, yet several noninfectious factors have also been reported as preceding the condition, such as trauma, surgery, or medications.[1] Human herpesvirus 6 (HHV-6) is an etiological cause of roseola infection—a common childhood infection that manifests as exanthem subitum or benign febrile disease and has been observed as a concomitant infection in GBS but the association has been rarely reported. [2] While rare, HHV-6 has been observed as an infectious agent responsible for the development of GBS, and possibly a concomitant infection.[2] According to an article published by the Journal of Clinical Virology, patients observed to have GBS in the setting of HHV-6 infections often have HHV-6 specific antibodies in their CSF and is a strong indication of active virus replication within the central nervous system.[2] However, while HHV-6 has been linked to classic GBS, there has yet to be an identified association between HHV-6 and development of GBS variant disease. The variants of GBS include axonal variants, localized variants, and Miller Fischer Syndrome. Classification of these variants is based on clinical, pathophysiological, and pathologic features. The focus of this case report will be on axonal variants, which can be further divided into acute motor axonal neuropathy (AMAN) and acute motor-sensory axonal neuropathy (AMSAN). While these two axonal variants can be distinguished based on sensory involvement, they also have differing clinical courses. AMAN is more common in Asia, is preceded by diarrheal illness, and usually affects children. AMSAN, however, is less associated with geographical location, is preceded by respiratory illness, and is more prevalent in adults.[1] This case study aims to outline the presence of GBS variant disease, specifically AMSAN, in the setting of HHV-6 infection.

Case Presentation

The patient was a 44-year-old male with a past medical history significant for seropositive rheumatoid arthritis, recently started on adalimumab, who was initially hospitalized for acute necrotizing pancreatitis thought to be secondary to alcohol use disorder. The patient was treated with fluid resuscitation and had clinically improved. Upon preparation for discharge, physical therapy assessed the patient and noted profound weakness in the distal lower extremities, which the patient reported had been progressing over the last several days.

When neurology saw him, he had intact mental status, intact speech, and intact cranial nerve examination. However, motor examination was as follows in Table 1.

Table 1. Motor examination at time of consultation.

Motor movement	Right side	Left side
Ankle dorsiflexion	2/5	4/5
Ankle plantar flexion	2/5	4/5
Knee extension	5/5	5/5
Knee flexion	5/5	5/5
Hip Flexion	4/5	4/5
Digital interossei	3/5	3/5
Wrist extension	3/5	4/5
Wrist flexion	3/5	4/5
Upper arm flexion	5/5	5/5
Upper arm extension	5/5	5/5

Muscle bulk and tone were normal, and no pronator drift was noted. All reflexes were 2/2 and Babinski was down going bilaterally. Repeat exam after one week showed diminished and symmetric patellar and Achilles reflex. Sensory exam showed intact sensation to light touch and pinprick in the bilateral upper extremities, with notable diminished sensation to light touch and pinprick to ankle in the right lower extremity and to mid-shin in left lower extremity. Temperature sense was intact in bilateral upper and lower extremities. Vibration sense was 50% diminished in bilateral upper extremities, 50% diminished left lower extremities over the big toe and ankle, and 75% diminished over big toe and ankle in right lower extremity. Proprioception was impaired bilaterally over big toes and wrists. Gait was not assessed due to profound weakness.

Over the course of several days, both his weakness and sensory loss gradually progressed to involve the proximal upper and lower extremities, with the distal extremities being more profoundly affected. The patient had complete loss of grip strength bilaterally as well as progressive weakness of his lower extremities. In addition to sensory and motor changes, there was prominent pitting edema of bilateral lower extremities. There were also noted skin changes with necrosis over the right metacarpophalangeal (MCP) joint, the distal end of his digits bilaterally, and the distal end of his first hallux bilaterally.

The physical exam findings were localized to an ascending asymmetric sensorimotor neuropathy. Given

Table 2: Sensory nerve conduction study results.

Sensory Nerve	Side	Parameter	Patient Value	Normal Range
Median (2nd digit)	Right	Amplitude (microVolts)	NR	>10.0
		Velocity (m/s)	NR	>36.0
		Distal latency (ms)	NR	<4.0
Median (2nd digit)	Left	Amplitude (microVolts)	NR	>10.0
		Velocity (m/s)	NR	>36.0
		Distal latency (ms)	NR	<4.0
Radial	Left	Amplitude (microVolts)	4.9	>7.0
		Velocity (m/s)	43	
		Distal latency (ms)	2.3	<2.8
Superficial Fibular	Right	Amplitude (microVolts)	NR	>3.9
		Velocity (m/s)	NR	>30.0
		Distal latency (ms)	NR	<4.2
Superficial Fibular	Left	Amplitude (microVolts)	NR	>3.9
		Velocity (m/s)	NR	>30.0
		Distal latency (ms)	NR	<4.2
Sural	Right	Amplitude (microVolts)	NR	>4.0
		Velocity (m/s)	NR	>30.0
		Distal latency (ms)	NR	<4.5
Sural	Left	Amplitude (microVolts)	NR	>4.0
		Velocity (m/s)	NR	>30.0
		Distal latency (ms)	NR	<4.5
Ulnar	Right	Amplitude (microVolts)	3.8	>6.0
		Velocity (m/s)	45	>36.0
		Distal latency (ms)	3.1	<4.0
Ulnar	Left	Amplitude (microVolts)	3.8	>6.0
		Velocity (m/s)	47	>36.0
		Distal latency (ms)	3	<4.0

the acute course and asymmetric pattern, an inflammatory process was suspected. Laboratory workup was notable for an elevated CRP and ESR, 141.9 and 101, respectively. ANCA, serum autoimmune, acute hepatitis panel, HIV, and Lyme panel came back normal. MRI with and without contrast showed no cord abnormality or severe stenosis.

Cerebrospinal fluid (CSF) studies from lumba r puncture performed within the first 5 days of presentation demonstrated mild elevation of white blood cells with a cell count of 6 cells/uL, protein of 27.6, and red blood cell count of 3 cells/uL. Viral meningitis and encephalitis panel returned positive for HHV-6 on PCR and negative for HSV, CMV, and West Nile.

Nerve conduction studies were performed on day 5 of symptom onset and was notable for absent CMAP and SNAP responses in multiple nerves and reduced amplitude with preserved velocity in other nerves (see table 2 and 3). This is consistent with severe axonal sensorimotor neuropathy affecting the upper and lower extremities. Needle EMG could not be performed at bedside due to lack of availability.

Table 3: Muscle nerve conduction study results.

Motor Nerve	Side	Parameter	Patient Value	Normal Range
Common Peroneal (Tibial)	Left	Amplitude (microVolts)	0.5 fib, 0.4 pop	NA
		Velocity (m/s)	62	NA
		Distal latency (ms)	3.8 fib, 5.4 pop	<4.9
		F-wave	NA	NA
Common Peroneal (Tibial)	Right	Amplitude (microVolts)	NR	NA
		Velocity (m/s)	NR	NA
		Distal latency (ms)	NR	<4.9
		F-wave	NA	NA
Common Peroneal (Extensor Digitorum Brevis)	Left	Amplitude (microVolts)	NR	>1.3
		Velocity (m/s)	NR	>36
		Distal latency (ms)	NR	<6.5
		F-wave	NA	NA
Common Peroneal (Extensor Digitorum Brevis)	Right	Amplitude (microVolts)	NR	>1.3
		Velocity (m/s)	NR	>36
		Distal latency (ms)	NR	<6.5
		F-wave	NA	NA
Median	Left	Amplitude (microVolts)	0.4 wrist, 0.4 elbow	>4
		Velocity (m/s)	39	>48
		Distal latency (ms)	3.3 wrist, 9.4 elbow	<4.5
		F-wave	34.06	<33
Median	Right	Amplitude (microVolts)	NR	>4
		Velocity (m/s)	NR	>48
		Distal latency (ms)	NR	<4.5
		F-wave	NR	<33
Tibial	Left	Amplitude (microVolts)	NR	>4.4
		Velocity (m/s)	NR	>34
		Distal latency (ms)	NR	<6.1
		F-wave	NR	<61
Tibial	Right	Amplitude (microVolts)	NR	>4.4
		Velocity (m/s)	NR	>34
		Distal latency (ms)	NR	<6.1
		F-wave	NR	<61
Ulnar	Left	Amplitude (microVolts)	3.6 wrist, 3.4 B elbow, 3.5 A elbow	>6
		Velocity (m/s)	60 B/A elbow, 67 wrist/B elbow	>51
		Distal latency (ms)	3.2 wrist, 6.7 B elbow, 8.2 A elbow	<3.7
		F-wave	29.33	<36
Ulnar	Right	Amplitude (microVolts)	3.0 wrist, 2.8 B elbow, 2.8 A elbow	>6
		Velocity (m/s)	68 B elbow/A elbow, 71 wrist/B elbow	>51
		Distal latency (ms)	3.2 wrist, 6.3 B elbow, 7.7 A elbow	<3.7
		F-wave	26.86	<36

With positive HHV-6 in CSF in the setting of an axonal peripheral neuropathy, there was a high concern for reactivation of HHV-6 infection leading to a variant form of GBS. Rheumatology and infectious disease consulted due to immunocompromised status in the setting of HHV-6 infection and determined to hold the patient's upcoming dose of adalimumab. The patient was started on a treatment course of valganciclovir 900 mg twice daily for 3 days as well as intravenous (IV) solumedrol 1000 mg daily for 3 days for a presumed autoimmune process. After initiation of treatment, patient was responsive and had mild, gradual improvement in both sensory and motor symptoms bilaterally. He was deemed steroid-responsive and the duration of IV solumedrol was extended to five days. In addition, the patient underwent five days total of plasma exchange therapy. There continued to be mild improvement through hospital course. The patient worked aggressively with physical therapy and after several days desired to return home with therapy. Following discharge, results from ganglioside antibody panel returned positive for IgM Disialo, GD1b. Given this finding and the nerve conduction studies showing axonal involvement, as well as the clinical findings of loss of motor and sensory capabilities, this patient was found to have an acute motor and sensory axonal neuropathy in the setting of HHV-6 infection.

Discussion

Human herpesvirus 6 (HHV-6) is a double-stranded deoxyribonucleic acid (DNA) virus that further targets CD4+ T lymphocyte cells. It can be further categorized into HHV-6A and HHV-6B within the herpesvirus family.[3] HHV-6B is most known for infecting infants and children and often presents as an undifferentiated febrile illness, though a small subset of patients will develop the classic roseola infantum (also known as exanthem subitum).[3] The primary infection is generally self-limiting and requires no treatment other than supportive measures such as antipyretics. Alternatively, HHV-6A is more commonly associated with immunocompromised hosts, and less is known about this variant, which is thought to be acquired in adulthood and primarily presents as asymptomatic infections.[3] Currently, there is no serologic testing available to differentiate between HHV-6A and HHV-6B.[4] Incidence of HHV-6 is ubiquitous, with an estimated 95% of individuals over the age of two suspected to test seropositive for either HHV-6A or HHV-6B variant.[4] The detection method for HHV-6 is polymerase chain reaction (PCR).[5]

Following the primary infection, the virus tends to remain latent with the viral DNA residing in peripheral mononuclear blood cells, and those carrying it will generally remain asymptomatic.[6] However, HHV-6 has now been recognized as an opportunistic infection in immunocompromised patients, leading to reactivation of the virus.[3] Both HHV-6A and 6B are thought to play a role in development of opportunistic infections in immunocompromised patients.[5] In the setting of immunosuppression, HHV-6 has been recognized to enter reactivation phase and is associated with a wide variety of disease processes, including but not limited to diseases affecting the central nervous system (CNS).[7-9]

Additionally, this patient's CSF contained anti-GD1b antibodies, and in the clinical context, was pointing towards immune-mediated axonal neuropathy. Although anti-GD1b antibodies are most commonly associated with motor-predominant axonal neuropathies such as AMAN, emerging evidence supports their relevance to AMSAN. AMAN and AMSAN are increasingly understood as part of a pathophysiologic continuum, sharing overlapping immunologic profiles and nodal pathology rather than representing distinct entities.[11] Mechanistic studies demonstrate that anti-GD1b antibodies can disrupt nodal function in both motor and sensory fibers, providing a biologic basis for the combined axonal involvement seen in AMSAN.[12] Thus, the presence of anti-GD1b antibodies in this case supports the diagnosis of an axonal Guillain-Barré spectrum disorder involving both motor and sensory fibers.

In two-thirds of cases, GBS is preceded by a prodromal illness, most commonly gastrointestinal or respiratory symptoms.[10] Although noninfectious antecedents such as trauma, surgery, medications (including immune checkpoint inhibitors), and systemic disorders have been reported, infections remain the most common trigger preceding the clinical onset of GBS.[11] GBS can be further categorized into two subtypes: demyelinating, which is by far the most common and represents 85-90% of cases, and axonal forms.[13] Typically, GBS is associated with more motor neuropathy as opposed to sensory and presents with ascending weakness, which is often accompanied by hyporeflexia or areflexia. The presented case had findings consistent with an ascending sensorimotor neuropathy and findings as discussed above, which is most consistent with an acute motor and sensory axonal neuropathy. It is presumed in this case that the GBS was potentially triggered by reactivation of HHV-6 infection. Patients observed to have GBS in the setting of HHV-6 infections often have HHV-6-specific antibodies in their CSF, which is a strong indication of active virus replication within the central nervous system.[2] As mentioned, the patient described was immunocompromised from treatment with TNF-alpha inhibitors, making him more susceptible to reactivation of HHV-6 infection. Of note, there have been prior case reports which described GBS associated with HHV-6 reactivation in immunocompromised hosts, specifically after hematopoietic stem cell transplants.[7,8] GBS in the setting of HHV-6 reactivation is uncommon, and this is the first report of the AMSAN variant of GBS in this setting.

The association between HHV-6 and GBS has not been well studied, and therefore, treatment options are also not well understood.[14] HHV-6 virus has been shown to be effectively treated with ganciclovir, foscarnet, and cidofovir.[15] The patient in this case was started on valganciclovir as opposed to ganciclovir due to concern for toxicity. While IVIG and plasma exchange are typically used in GBS, we did not do so in this case because of the evidence of the HHV6

infection and we elected to treat with antivirals and high dose solumedrol. Steroids have been reported to provide benefit in some cases of inflammatory neuropathies, although their use in GBS remains controversial.[16,17]

Conclusion

While rare, HHV-6 has been observed as a concomitant infection in some GBS cases.[2] However, while HHV-6 has been linked to classic GBS, there has yet to be an identified association between HHV-6 and development of GBS variant disease. We report a case of AMSAN-variant GBS in association with HHV-6 in an immunocompromised patient. The patient received antiviral treatment and high dose steroids with improvement of symptoms.

Citations

1. Continuum (Minneap Minn). Peripheral nerve and motor neuron disorders. *Continuum (Minneap Minn).* 2023;29(5):1327–56. *(PMID not found in PubMed.)*
2. Galvan M, Rotola A, Govoni V, et al. Simultaneous Guillain-Barré syndrome and active human herpesvirus 6 infection in the central nervous system. *J Clin Virol.* 2007;38(3):271–2. doi:10.1016/j.jcv.2006.12.003. PMID: 17222581 dokumen.pub+6pubmed.ncbi.nlm.nih.gov+6scribd.com+6
3. King O, Syed HA, Al Khalili Y. Human herpesvirus 6 [Updated 2025 May 5]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. Available from: https://www.ncbi.nlm.nih.gov/books/NBK540998/ *(No PMID assigned, as this is an online book chapter.)*
4. Braun DK, Dominguez G, Pellett PE. Human herpesvirus 6. *Clin Microbiol Rev.* 1997;10(3):521–67. *(PMID not retrieved.)*
5. Agut H, Bonnafous P, Gautheret-Dejean A. Update on infections with human herpesviruses 6A, 6B, and 7. *Med Mal Infect.* 2017;47(2):83–91. doi:10.1016/j.medmal.2016.09.004. *(PMID not retrieved.)*
6. Caserta MT, Mock DJ, Dewhurst S. Human herpesvirus 6. *Clin Infect Dis.* 2001;33(6):829–33. doi:10.1086/322691. *(PMID not retrieved.)*
7. Rodriguez V, Kuehnle I, Heslop HE, et al. Guillain-Barré syndrome after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transpl.* 2002;29:515–7. *(PMID not retrieved.)*
8. Tomaszewska A, Nasilowska-Adamska B, Dzieciatkowski T, et al. Simultaneous human herpesvirus 6-associated encephalitis and Guillain-Barré syndrome in a patient after matched unrelated donor haematopoietic stem cell transplantation. *Arch Med Sci.* 2010;6(2):288–90. doi:10.5114/aoms.2010.13912. *(PMID not retrieved.)*
9. Zerr DM, Corey L, Kim HW, et al. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. *Clin Infect Dis.* 2005;40:932–40. *(PMID not retrieved.)*
10. Doets AY, Verboon C, van den Berg B, et al. Regional variation of Guillain-Barré syndrome. Brain J Neurol 2018;141(10):2866-2877. doi:10.1093/ brain/awy232
11. Kuwabara S, Yuki N. Axonal Guillain-Barré syndrome: concepts and controversies. Lancet Neurol. 2013 Dec;12(12):1180-1188. PMID: 24229616. doi:10.1016/S1474-4422(13)70215-1.
12. Susuki K, Yuki N, Schafer DP, Hirata K, Zhang G, Funakoshi K, Rasband MN. Dysfunction of nodes of Ranvier: a mechanism for anti-ganglioside antibody-mediated neuropathies. Exp Neurol. 2011 Dec 8;233(1):534-542. PMID: 22178332. doi:10.1016/j.expneurol.2011.11.039.
13. Habib AA, Waheed W. Guillain-Barré syndrome. *Continuum (Minneap Minn).* 2023;29(5):1327–56. doi:10.1212/CON.0000000000001289. *(PMID not found.)*
14. Sokolovska L, Cistjakovs M, Matroze A, et al. From viral infection to autoimmune reaction: Exploring the link between human herpesvirus 6 and autoimmune diseases. *Microorganisms.* 2024;12(2):362. doi:10.3390/microorganisms12020362. PMID: 38399766 continuum.aan.com+1pubmed.ncbi.nlm.nih.gov+1
15. Prichard MN, Whitley RJ. The development of new therapies for human herpesvirus 6. *Curr Opin Virol.* 2014;9:148–53. doi:10.1016/j.coviro.2014.09.019. *(PMID not retrieved.)*
16. Hughes, R. A., Brassington, R., Gunn, A. A., & van Doorn, P. A. (2016). Corticosteroids for Guillain-Barré syndrome. *The Cochrane database of systematic reviews*, *10*(10), CD001446. https://doi.org/10.1002/14651858.CD001446.pub5
17. van Lieverloo, G. G. A., Peric, S., Doneddu, P. E., Gallia, F., Nikolic, A., Wieske, L., Verhamme, C., van Schaik, I. N., Nobile-Orazio, E., Basta, I., & Eftimov, F. (2018). Corticosteroids in chronic inflammatory demyelinating polyneuropathy : A retrospective, multicentre study, comparing efficacy and safety of daily prednisolone, pulsed dexamethasone, and pulsed intravenous methylprednisolone. *Journal of neurology*, *265*(9), 2052–2059. https://doi.org/10.1007/s00415-018-8948-y