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Clinical Correlates of Herpes Simplex Virus Viremia Among Hospitalized Adults

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Abstract

Background—The quantification of herpes simplex virus (HSV) DNA from the peripheral blood is often used to evaluate patients suspected of having disseminated HSV infection. Few studies have examined the clinical correlates of HSV viremia among adults.

Methods—We conducted a retrospective analysis of blood samples sent to a reference molecular virology diagnostic facility at a university hospital for quantification of HSV DNA between October 2001 and June 2006. Medical records of patients with detectable HSV DNA were reviewed to abstract relevant clinical characteristics.

Results—HSV DNA was detected in 37 (4.0%) of 951 samples from 29 individual patients. 19 (65.5%) were >16 years of age, and detailed medical records were available for review from 13 (68.4%) of 19 adults patients. Of the 10 patients whose HSV infection was typed, 6 (60%) had HSV-2, 3 (30%) had HSV-1, and one had evidence of both HSV-1 and HSV-2 infection. All viremic patients were treated with antiviral medications. The most common clinical findings were hepatitis (62%), fever (54%), CNS alterations (46%), skin lesions (38%), abdominal pain (31%), and sepsis (31%). Respiratory failure (23%) was uncommon. Patients with HSV viremia were observed to have a high mortality rate (6 of 10 immunocompromised and 1 of 3 immunocompetent individuals).

Conclusions—HSV viremia may be associated with a variety of morbid signs and symptoms in hospitalized immunocompetent and immunocompromised adults, and is associated with high rates of mortality, though causality can only be determined by additional studies.

INTRODUCTION

Herpes Simplex Virus (HSV) is a double-stranded DNA virus which exists in either a lytic or latent phase of infection [1]. Newly acquired or reactivated infections cause either ulcerative gingivostomatitis (typically with HSV-1) or genital ulceration (typically with HSV-2) in children and adults. Other less common manifestations include meningitis, encephalitis [2,3], pneumonitis [4] and hepatitis [5–7]. Polymerase chain reaction (PCR) has been pioneered as a technology to rapidly and accurately detect and quantify HSV DNA from clinical specimens [8–10]. Despite over a decade of experience with PCR, little is known about the frequency and clinical correlates of HSV viremia.

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Viral dissemination to bloodstream and viscera can be seen in neonates [11] and immunocompromised patients, including those with hematologic malignancies [12,13], transplant recipients [14,15], or persons immunosuppressed with medications [16]. Immunocompetent individuals, including pregnant patients [17] and those with no other identified immunosuppressive condition [5,18–20], may also present with disseminated disease. In addition, up to 25% of patients with primary genital HSV have PCR-detectable virus in their peripheral blood [21]. We undertook a retrospective chart review of patients identified with HSV viremia at a molecular virology reference laboratory to analyze the clinical correlates and response to treatment of patients with HSV viremia.

METHODS

Identification of Patient Population

The University of Washington (UW) Molecular Virology Laboratory has offered quantitative HSV PCR for the detection of HSV from clinical samples since 2000. Samples from the UW Molecular Virology Laboratory are received mainly from regional hospitals in the Northwest including Seattle Children's Hospital, Harborview Medical Center, University of Washington, and the Fred Hutchison Cancer Research Center. A computer-based search was used to identify all patients with peripheral blood samples sent to the virology lab for detection and quantification of HSV DNA by PCR over a 56 month period of time (between October 2001 and June 2006). Patients were included in the study if they were at least 16 years old, had detectable HSV DNA by PCR from the peripheral blood, and were from one of the three institutions from which approval to review medical records was obtained (University Medical Center at the University of Washington, Harborview Medical Center, and Fred Hutchinson Cancer Research Center). These institutions all share a common electronic medical information system.

Herpes Simplex Virus quantitative PCR

Viral DNA was extracted from the serum and plasma samples with a Qiagen Biorobot 2000 and the PCR reaction was performed as previously described [8–10,22]. Added to the HSV PCR reaction was an internal control consisting of a 126 bp fragment of jellyfish sequence which was co-amplified in the same mix with primers GCCTGGTGCAAAAATTGCTT and TCGTTCATTTGTTCTTTTGTGGAA and a VIC labeled probe CAGCTATTGCAAACGCCATCGCAC. Quantitation of viral DNA was performed by real-time PCR with the Taqman system using the optimized forward primer CCG TCA GCA CCT TCA TCG A, and reverse primer CGC TGG ACC TCC GTG TAG TC, and probe CCA CGA GAT CAA GGA CAG CGG CC to detect DNA from conserved regions of herpes viral glycoprotein B [23]. Quantification was performed using a standard from known amounts of DNA with a reproducible lower limit of detection of 250 copies/ml. A PCR-based HSV-typing assay was also used in some cases as previously described [24].

Data collection

Patient charts meeting the above inclusion criteria were reviewed for presenting symptoms, physical exam, underlying illnesses, pertinent laboratory values, previous HSV serologic tests, peripheral blood HSV viral load, HSV type, treatment and outcome.

Role of the Funding Source

Neither the NIH nor the Doris Duke Foundation played a role in the present study design.

RESULTS

DESCRIPTION OF PATIENT POPULATION

Between October 2001 and June 2006, we identified 951 serum or plasma samples sent to the lab for HSV PCR analysis. Thirty eight (4.0%) samples from 29 patients had detectable peripheral blood levels of HSV (Figure 1). Ten (34%) of these 29 patients were <6 years of age (9 were less than 1 year old), and 18 (62%) were female. Of the 19 identified adult patients (≥16 years old), 13 were at the hospitals where permission was obtained to view medical records. A total of 17 peripheral blood samples had HSV DNA detected, including 15 (88%) serum samples and 2 (12%) plasma specimens. Our group and others have found these two types of specimens to be comparable for the detection of HSV DNA (data not shown), and therefore all 17 samples are reported together. A summary of the patients is shown in Table 1. The median age of those represented was 49 years (range 25–66 years). Four (31%) men and 9 (69%) women had HSV detectable in the peripheral blood.

CLINICAL PRESENTATION

Three (23%) of 13 patients were immunocompetent with no previous medical history or medications to explain predisposition to disseminated HSV. Of the 10 immunosuppressed patients, 5 (50%) had an underlying illness (HIV, immunodeficiency, or hematologic malignancies), and 4 (40%) underwent solid organ (2 liver, 1 kidney) or bone marrow transplantation. Eight of the 10 immunosuppressed patients (80%) were also receiving immunosuppressants such as steroids or cyclosporine. The remaining immunocompetent patients (patients 6, 9, and 13), had not been given immunosuppressant medications within the last two years.

Disease presentation and clinical course was highly variable amongst those with HSV viremia. Patients typically had multiple presenting complaints. Seven (54%) of the 13 patients presented with fever within 72 hours of detection of HSV in peripheral blood, 6 (46%) had CNS symptoms (altered mental status, obtundation), 5 (38%) had herpetic-like skin lesions, 5 (38%) presented with or developed sepsis syndrome (defined as hypotension requiring pressors and tachycardia), 4 (31%) had abdominal complaints, and 3 (23%) had respiratory failure (requiring mechanical ventilation). Five (38%) of the patients had concurrent illnesses or pathogens that could explain their presenting symptoms and clinical course other than HSV (see Table 1). The remaining 8 had either fevers, sepsis, liver failure, or ARDS in the absence of cultures positive for bacterial organisms (patients 2, 3, 5, 6, 8, 9) or encephalitis thought to be due primarily to HSV (Patients 11 and 13). Patients with no alternative diagnosis to explain their acute illness tended to have increased frequency of hepatitis, fever and abdominal pain, and decreased frequency of skin lesion Table 2. Ten (77%) had another body fluid with HSV detected by PCR or culture (CSF, bronchoalveolar lavage, peritoneal fluid, skin (mouth or labia)).

LABORATORY ABNORMALITIES

The most common laboratory abnormality identified was hepatitis (62%), defined as an alanine aminotransferase (ALT) level of >120 units per liter (3 times upper limit of normal). Leukopenia, a white blood cell count (WBC) of < 4.0 thousand per microliter, was seen in 6 (54%) patients concurrent with detectable HSV, and leukocytosis, a WBC of > 10 thousand per microliter, was seen in 2 (15%).

HSV TYPING

HSV type was obtained by direct genotyping or confirmatory cultures in 10 (77%) of patients; 6 had HSV-2 (60%), 3 (30%) had HSV-1 and 1 (10%) had evidence of both HSV-1 and HSV-2. Seven (54%) of 13 patients had HSV serologies sent concurrently with PCR-detectable HSV.

Two of 7 patients had no detectable HSV antibody consistent with primary infection (both were identified as HSV-2). Of the remaining 5 patients, 3 had positive serologies drawn within 2 weeks of symptom onset, suggesting reactivation disease (2 with HSV-2 and 1 with HSV-1); 2 of 5 patients had positive IgG antibody results but they were drawn 4 weeks or greater after the onset of symptoms (both HSV-1) and therefore reactivation could not be distinguished from primary infection following seroconversion.

QUANTITY OF HSV DETECTED

The quantity of HSV DNA per milliliter of serum or plasma varied widely between individuals (Median = 2.79 $\log_{10}$ copies per milliliter, Interquartile Range = 2.43–6.18 $\log_{10}$ copies/mL). By Wilcoxon rank-sign test, no significant differences in peripheral blood HSV copy number were seen in immunocompetent versus immunocompromised individuals (Median HSV DNA quantity 6.34 $\log_{10}$ copies/ml in immunocompetent vs 2.55 $\log_{10}$ copies/ml in immunocompromised, p=0.06), or patients who did and did not survive (Median HSV DNA 2.90 $\log_{10}$ copies/ml in survivors vs 2.79 $\log_{10}$ copies/ml in those who died, p=0.39).

OTHER ANATOMIC SITES OF HSV INVOLVEMENT

Of the 8 patients with no explanation for presenting illness apart from the detection of HSV, 5 also had HSV detected from visceral organs or body cavities (Lung, alveolar lavage, liver, CSF or ascitic fluid) confirming dissemination of the virus to either the CNS (patients 11 and 13) or other organs (Patients 2, 6, and 8). The remaining three patients either had no samples sent (patient 3 and 5), or had only vaginal mucosal samples that were positive (patient 9). Interestingly both patients 6 and 12 were thought to have recurrences of aggressive HSV disease. Acyclovir-resistant HSV developed in Patient 6 (7) and was cultured from lung at autopsy. Patient 12 had acyclovir-resistant HSV cultured from the rectum, duodenum, and BAL. Despite altered mental status occurring in 6 (46%) of our patients, only 3 (23%) of the patients had CSF examined for HSV, and only 2 (15%) of these patients had detectable HSV by PCR. In all three cases, CSF samples were collected after peripheral blood collection.

THERAPY AND OUTCOME

All 13 adult patients with HSV detected in their peripheral blood were treated with antiherpetic antivirals; 10 with acyclovir (all but one intravenously), 2 with ganciclovir, and 1 with foscarnet. Ganciclovir was chosen by clinicians in Patients 1 and 4 due to the concurrent detection of both HSV and CMV. Patient 12 was placed on foscarnet due to worsening HSV skin lesions on acyclovir. Two of 13 patients had serial measurements of peripheral blood HSV DNA quantity while receiving acyclovir. These documented symptomatic improvement concomitant with virologic suppression. However, Patient 6 had increases in peripheral blood HSV quantity and hepatic injury (documented by increased AST levels) after transition to oral medications (Figure 2).

Six (46%) of the 13 patients responded to antiviral therapy and were discharged from the hospital. Two of the six patients discharged from the hospital died months later; one from unknown causes, the other from respiratory failure from a viral pneumonia (HSV was confirmed on bronchoscopic alveolar lavage specimens, but HSV pneumonitis was not confirmed on autopsy). Only 4 of the remaining patients discharged from the hospital have survived years later. One of the 4 patients remains on prophylactic valacyclovir up to 2 years afterwards, while the remaining three were treated with defined anti-viral regimens varying between 21 days and 6 months.

Six (60%) of 10 immunosuppressed and 1 (33%) of 3 immunocompetent individuals died during their initial hospitalization (combined mortality rate of 54%). The cause of death for 3 of the 7 patients was sepsis, ARDS, and multisystem organ failure (including liver failure)

presumably secondary to HSV infection. Three patient deaths were attributed to factors apart from HSV infection, including Pneumocystis pneumonia leading to ARDS (patient #4), Pneumococcal meningitis (patient #7), and relapsed CNS lymphoma (patient #7). Patient #8 was diagnosed with sepsis in the absence of positive bacterial cultures, developed thrombocytopenia and myelosuppression, and eventually succumbed to bilateral intracranial hemorrhages.

DISCUSSION

Our study details the clinical characteristics of hospitalized adults with HSV DNA detected in the peripheral blood by PCR. Our series, derived from nearly 1000 clinical tests performed over 5 years, was notable for several features. First, the identification of 13 adult patients with HSV DNA in the peripheral blood over the span of 4 years within one group of hospitals in Seattle suggests that hospitalized patients with HSV viremia may be encountered by many practicing health care providers. Second, detection of HSV by PCR in the peripheral blood is associated with both primary HSV infection and reactivation disease. Third, approximately 1/4 of patients with HSV detected in the peripheral blood were immunocompetent. Fourth, we found detection of HSV in the peripheral blood to be accompanied by a myriad of clinical signs and symptoms, but the minority of patients had mucocutaneous lesions identified.

Our series relied on the detection of HSV DNA in the peripheral blood by PCR. None of the study patients had viral cultures of the peripheral blood performed to verify that the detection of HSV DNA represented the presence of HSV virions in the peripheral blood. However, members of our research group have recently shown that 60% of persons with high quantities of HSV DNA by PCR in peripheral blood in the setting of primary genital herpes likely had DNA contained within virions, as the samples were resistant to DNAase digestion [21].

The presence of HSV in the bloodstream of individuals with no previously identified immunodeficiency suggests that there may be unidentified genetic predispositions to more severe HSV disease. Previous studies of neonates with disseminated HSV have hypothesized that variation in Toll-like receptor 2 and human leukocyte antigens may influence severity and frequency of HSV infections [25,26], and recent work on HSV-2 in adults supports the role of TLR-1 polymorphisms in determining the virologic severity of disease [27]. There is evidence that other immunodeficiencies with Mendelian inheritance (STAT-1, NEMO, UNC-93b, CD40L and CD16a) in the adult can also predispose to severe and recurrent HSV infection [28–32]. Genetic factors related to the innate immune system play a critical role in the protection from HSV-1 infection and may be important in preventing dissemination of the disease beyond initial sites on infection.

The most frequent clinical signs and symptoms were fever and CNS symptoms, and the most frequent laboratory abnormality was hepatitis. Sepsis syndrome was seen in 4 patients. Aseptic meningitis is a common clinical manifestation of primary genital herpes and occurs more frequently in women than men [33]. In our study, only 2 (15%) of these patients had detectable HSV by PCR in spinal fluid after peripheral blood detection, but 6 (46%) presented with altered mental status; the true incidence of detectable HSV in the CSF remains uncertain as only three out of six patients with altered mental status had CSF sent for PCR.

Approximately 60% of immunosuppressed and 33% of immunocompetent individuals died after HSV was detected in the peripheral blood. The most common cause of death was sepsis followed by multi-organ failure. The high mortality seen in this study raises a number of questions. Is HSV the primary cause of sepsis and multi-organ failure, or does detectable HSV in the blood stream represent viral reactivation in an individual whose immune system is impaired by ongoing sepsis syndrome by another causative organism or other underlying

disease? Others have shown that another herpes virus, CMV, can be detected in critically ill immunocompetent patients and is associated with prolonged hospital stay and death [34]. In our series, the high mortality rate despite treatment could be due to multiple causes. First, study patients may have been diagnosed too late in the course of illness to have clinical improvement with aggressive therapy. Second, another organism (such as *S. pneumonia* in Patient #7) may have caused the patients' sepsis. Third, the patient may have suffered from a significant and terminal co-morbid illness (such as large B cell lymphoma in patient #10). Ultimately, however, our study design precluded making definite conclusions as to whether there was a causal association between HSV viremia and mortality.

While we found the detection of HSV by PCR in the peripheral blood to be present in patients with high mortality, treatment was at least partially effective. The reasons for treatment failure despite administration of an effective antiviral should be investigated further but may include delay in diagnosis, inability to halt a "cytokine storm" or "sepsis syndrome," or emergence of acyclovir-resistant virus (as was discovered in post-mortem viral cultures in Patient #6) [5]. The length of treatment varied and some responded well to relatively short courses of therapy (as little as 3 weeks), while others were treated with longer courses (from 6 months to life-long suppression). Recurrence of HSV was not uncommon, occurring in 2 of the 13 patients (patients 6 and 12).

Our study was limited by its observational and retrospective design. We are clearly not able to describe the true prevalence of HSV viremia, as only patients in whom the diagnosis was entertained had samples sent to the laboratory for analysis. Accurate estimation of the frequency and clinical consequence of HSV viremia in hospitalized patients would require a larger prospective study. PCR is an extraordinarily sensitive tool for the detection of viral DNA, and observations based on PCR must be careful to avoid laboratory contamination. In our study, we feel this is extremely unlikely given our stringent negative controls and quality assurance. A recent analysis of the performance of our PCR assay for detecting genital HSV shedding found that misclassification (false positive and negative test results) occurred less than 1% of the time when a cutoff for positive test results was set at > 50 copies per mL[9].

In summary, HSV DNA may be detected by PCR in the peripheral blood of some hospitalized inpatients with unexplained sepsis syndrome, evidence of hepatitis, and/or CNS infection with fever. Prospective studies are needed to determine the true prevalence, and clinical significance of HSV DNA detection in the peripheral blood, and to establish whether the HSV viremia is causality related to the concurrent acute illness.

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Lawrence Corey, MD directs the University of Washington Virology Laboratory which has acted as a reference laboratory for the diagnosis of HSV infections. The laboratory has received grant support from GSK, a pharmaceutical company that makes antivirals for HSV. Dr Corey is a consultant to Immune Design Corporation and Antigenics regarding HSV candidate vaccines.

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REFERENCES

1. Whitley, RJ. Herpes Simplex Virus. In: Knipe, DM.; Hensley, PM., editors. Fields Virology. Vol. 4th ed. Vol. Vol. 2. Philadelphia: Lippinscott, Williams, and Wilkins; 2001. p. 2461-2506.

2. Olson LC, Buescher EL, Artenstein MS, Parkman PD. Herpesvirus infections of the human central nervous system. N Engl J Med 1967 Dec 14;277(24):1271–1277. [PubMed: 4294512]

3. Whitley RJ. Herpes simplex virus infections of the central nervous system. A review. Am J Med 1988 Aug 29;85(2A):61–67.

4. Feldman S, Stokes DC. Varicella zoster and herpes simplex virus pneumonias. Semin Respir Infect 1987 Jun;2(2):84–94. [PubMed: 3321272]

5. Czartoski T, Liu C, Koelle DM, Schmechel S, Kalus A, Wald A. Fulminant, acyclovir-resistant, herpes simplex virus type 2 hepatitis in an immunocompetent woman. J Clin Microbiol 2006 Apr;44(4):1584–1586. [PubMed: 16597901]

6. Flewett TH, Parker RG, Philip WM. Acute hepatitis due to Herpes simplex virus in an adult. J Clin Pathol 1969 Jan;22(1):60–66. [PubMed: 4306578]

7. Joseph TJ, Vogt PJ. Disseminated herpes with hepatoadrenal necrosis in an adult. Am J Med 1974 May;56(5):735–739. [PubMed: 4363476]

8. Harel L, Smetana Z, Prais D, et al. Presence of viremia in patients with primary herpetic gingivostomatitis. Clin Infect Dis 2004 Sep 1;39(5):636–640. [PubMed: 15356775]

9. Magaret AS, Wald A, Huang ML, Selke S, Corey L. Optimizing PCR positivity criterion for detection of herpes simplex virus DNA on skin and mucosa. J Clin Microbiol 2007 May 1;45(5):1618–1620. [PubMed: 17329447]

10. Wald A, Huang ML, Carrell D, Selke S, Corey L. Polymerase chain reaction for detection of herpes simplex virus (HSV) DNA on mucosal surfaces: comparison with HSV isolation in cell culture. J Infect Dis 2003 Nov 1;188(9):1345–1351. [PubMed: 14593592]

11. Stanberry LR, Floyd-Reising SA, Connelly BL, et al. Herpes simplex viremia: report of eight pediatric cases and review of the literature. Clin Infect Dis 1994 Mar;18(3):401–407. [PubMed: 8011823]

12. Muller SA, Herrmann EC Jr, Winkelmann RK. Herpes simplex infections in hematologic malignancies. Am J Med 1972 Jan;52(1):102–114. [PubMed: 4550795]

13. Ramsey PG, Fife KH, Hackman RC, Meyers JD, Corey L. Herpes simplex virus pneumonia: clinical, virologic, and pathologic features in 20 patients. Annals of internal medicine 1982 Dec;97(6):813–820. [PubMed: 6293356]

14. Johnson JR, Egaas S, Gleaves CA, Hackman R, Bowden RA. Hepatitis due to herpes simplex virus in marrow-transplant recipients. Clin Infect Dis 1992 Jan;14(1):38–45. [PubMed: 1571460]

15. Kusne S, Schwartz M, Breinig MK, et al. Herpes simplex virus hepatitis after solid organ transplantation in adults. The Journal of infectious diseases 1991 May;163(5):1001–1007. [PubMed: 1850439]

16. Kaufman B, Gandhi SA, Louie E, Rizzi R, Illei P. Herpes simplex virus hepatitis: case report and review. Clin Infect Dis 1997 Mar;24(3):334–338. [PubMed: 9114181]

17. Frederick DM, Bland D, Gollin Y. Fatal disseminated herpes simplex virus infection in a previously healthy pregnant woman. A case report. The Journal of reproductive medicine 2002 Jul;47(7):591–596. [PubMed: 12170540]

18. Fahy RJ, Crouser E, Pacht ER. Herpes simplex type 2 causing fulminant hepatic failure. Southern medical journal 2000 Dec;93(12):1212–1216. [PubMed: 11142460]

19. Farr RW, Short S, Weissman D. Fulminant hepatitis during herpes simplex virus infection in apparently immunocompetent adults: report of two cases and review of the literature. Clin Infect Dis 1997 Jun;24(6):1191–1194. [PubMed: 9195081]

20. Zahariadis G, Jerome K, Corey L. Herpes simplex virus-associated sepsis in a previously infected immunocompetent adult. Annals of internal medicine 2003 Jul 15;139(2):153–154. [PubMed: 12859170]

21. Johnston C, Magaret A, Selke S, Remington M, Corey L, Wald A. Herpes Simplex Virus Viremia during Primary Genital Infection. The Journal of infectious diseases 2008 May;9

22. Ryncarz AJ, Goddard J, Wald A, Huang ML, Roizman B, Corey L. Development of a high-throughput quantitative assay for detecting herpes simplex virus DNA in clinical samples. J Clin Microbiol 1999 Jun;37(6):1941–1947. [PubMed: 10325351]

23. Jerome KR, Huang ML, Wald A, Selke S, Corey L. Quantitative stability of DNA after extended storage of clinical specimens as determined by real-time PCR. J Clin Microbiol 2002 Jul;40(7):2609–2611. [PubMed: 12089286]

24. Corey L, Huang ML, Selke S, Wald A. Differentiation of herpes simplex virus types 1 and 2 in clinical samples by a real-time taqman PCR assay. J Med Virol 2005 Jul 1;76(3):350–355. [PubMed: 15902702]
25. Kurt-Jones EA, Belko J, Yu C, et al. The role of toll-like receptors in herpes simplex infection in neonates. The Journal of infectious diseases 2005 Mar 1;191(5):746–748. [PubMed: 15688290]
26. Kurt-Jones EA, Chan M, Zhou S, et al. Herpes simplex virus 1 interaction with Toll-like receptor 2 contributes to lethal encephalitis. Proceedings of the National Academy of Sciences of the United States of America 2004 Feb 3;101(5):1315–1320. [PubMed: 14739339]
27. Bochud PY, Magaret AS, Koelle DM, Aderem A, Wald A. Polymorphisms in TLR2 are associated with increased viral shedding and lesional rate in patients with genital herpes simplex virus Type 2 infection. The Journal of infectious diseases 2007 Aug 15;196(4):505–509. [PubMed: 17624834]
28. Casrouge A, Zhang SY, Eidenschenk C, et al. Herpes simplex virus encephalitis in human UNC-93B deficiency. Science (New York, NY 2006 Oct 13;314(5797):308–312.
29. Dupuis S, Jouanguy E, Al-Hajjar S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. Nature genetics 2003 Mar;33(3):388–391. [PubMed: 12590259]
30. Garcia-Perez MA, Paz-Artal E, Corell A, et al. Mutations of CD40 ligand in two patients with hyper-IgM syndrome. Immunobiology 2003;207(4):285–294. [PubMed: 12952351]
31. Jawahar S, Moody C, Chan M, Finberg R, Geha R, Chatila T. Natural Killer (NK) cell deficiency associated with an epitope-deficient Fc receptor type IIIA (CD16-II). Clinical and experimental immunology 1996 Mar;103(3):408–413. [PubMed: 8608639]
32. Puel A, Reichenbach J, Bustamante J, et al. The NEMO mutation creating the most-upstream premature stop codon is hypomorphic because of a reinitiation of translation. American journal of human genetics 2006 Apr;78(4):691–701. [PubMed: 16532398]
33. Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. Annals of internal medicine 1983 Jun;98(6):958–972. [PubMed: 6344712]
34. Limaye AP, Kirby KA, Rubenfeld GD, et al. Cytomegalovirus reactivation in critically ill immunocompetent patients. JAMA 2008 Jul 23;300(4):413–422. [PubMed: 18647984]

Table 1

Demographic and Clinical Characteristics of Hospitalized Adults with Disseminated HSV Infection

This table summarizes epidemiologic, demographic and clinical characteristics obtained by medical chart review from 13 individuals with HSV DNA detected in peripheral blood over the span of 4 years and 8 months at three medical institutions in Seattle. Summary of the virologic diagnostic data including quantification of polymerase chain reaction (PCR) copies per milliliter in peripheral blood. HSV type was determined either by type specific PCR assay or by serologic analysis. Alanine aminotransferase (ALT) levels are expressed in units per liter (U/L); blood urea nitrogen (BUN) and creatinine (Cr) are expressed in milligrams per deciliter (mg/dL).

Pt	Age	Gender	Underlying Condition	Immuno-suppresive medications	Presenting signs and symptoms	HSV type	Copies per ml of peripheral blood	Abnormal Labs	Concurrent illnesses explaining symptoms	Treatment	O
1	59	F	Liver Transplant. Autoimmune hepatitis	FK506 Immuran Prednisone	Anorexia, diarrhea	Unk	81	BUN 50 ALT 106 WBC <4	Yes, (CMV viremia)	IV GCV	S
2	42	M	Liver Transplant HCV cirrhosis	FK506 Immuran Prednisone	Generalized fatigue, Abdominal Pain	HSV-2	1.5×10^6	ALT 298 WBC <4 HSV by culture and PCR in ascitic fluid	No	IV ACV	S
3	44	M	CVID Agranulocytosis Sarcoidosis	None	Neutropenic fever, sepsis	Unk	300	BUN 107 WBC <4	No	IV ACV	D
4	37	F	HIV (CD4 count 14)	None	Pneumonia, sepsis	HSV-1 and HSV-2	4000	ALT 143 Alk P 780 HSV by culture from mouth and anus	Yes (PCP pneumonia)	IV GCV	D
5	54	F	Perinuclear anti-neutrophil cytoplasmic antibody (+)	Prednisone	SOB, syncope, weakness, abdominal pain, AMS	Unk	2.6×10^9	ALT 7848 Cr 5.5 WBC <4	No	IV ACV	D
6	25	F	Ideopathic thrombocytopenic purpura	None within 2 years, previously Prednisone	Fever, Chills, myalgias, Abdominal pain, Skin lesion	HSV-2	3.5×10^6	ALT 1910 Cr 3.3 HSV Cultured from Post mortem lung tissue	No	IV ACV, oral vACV, then IV ACV	D
7	58	F	None	Dexamethasone	Fever, AMS, Pneumococcal meningitis, Skin lesion (Labial)	HSV-2	420	CSF 1290 Nucleated cells 89% PMNs HSV Cultured from Labia	Yes (*S. Pneumo* meningitis, bacteremia)	IV ACV × 1d then oral vACV	D

Pt	Age	Gender	Underlying Condition	Immuno-suppresive medications	Presenting signs and symptoms	HSV type	Copies per ml of peripheral blood	Abnormal Labs	Concurrent illnesses explaining symptoms	Treatment	C
8	66	F	Breast cancer, Hodgkins Lymphoma	Prednisone	Dyspnea, Fever, hypoxia fatigue, Sepsis, ARDS, AMS	HSV-1	270	ALT 149 WBC <4 HSV Cultured from BAL	No	IV ACV	I
9	61	F	None	None	Abdominal Pain, Skin (labial) Lesions	HSV-2	2.2×10^6	ALT 600 Cr 3.8 WBC <4 HSV Cultured from labia	No	IV ACV then oral vACV	S
10	57	M	Renal Transplant Large B cell Lymphoma	Prograf, Cellcept, Prednisone	Memory problems, AMS, Headache, L hemiparesis, Skin Lesions Gait abnorm-alities	HSV-2	610	WBC<4 HSV Cultured from skin on back	Yes (PTLD, S. Aureus bacteremia)	vACV PFA	I
11	37	F	Cranio-pharyngioma HSV encephalitis DM	Dexamethasone	HSV encephalitis s/p Tumor resection, AMS	HSV-2	110	ALT 200 Alkph 929 HSV by PCR from the CNS	No	IV ACV	S c a
12	40	F	CML Bone marrow Transplant	FK506 MMF Prednisone	Worsening HSV skin lesions on acyclovir	HSV-1	110	ALT 164 HSV initially Cultured from mouth, in 2nd admission from duodenum, rectum and BAL	Yes (GVHD)	PFA	S c a
13	49	M	Intrathecal Fentanyl pump for pain	None	Headaches Seizures AMS	HSV-1	5800	CSF 520 cells (90% lymphs) HSV by PCR from CNS	No	IV ACV	S

Abbreviations. ARDS- Acute respiratory distress syndrome, ACV- acyclovir, ALT- Alanine aminotransferase, ALKPH – Alkaline phosphatase, AMS- Altered Mental Status, BUN- Blood urea nitrogen, CSF- Cerebral Spinal Fluid, CML- Chronic myelogenous leukemia, CVID- Chronic variable immunodifficiency, Cr- Creatinine, CVA- Cerebral vascular accident, F – female, PFA- Foscarnet, GCV- gancyclovir, GVHD- Graft versus host disease, HCV- Hepatitis C Virus, HIV- Human immunodeficiency virus, IVIntravenous, lymphs- Lymphocytes, M- Male, MSOF- Multiple system organ failure, pANCA- Perinuclear anti-neutrophil cytoplasmic antibody, PCR- Polymerase Chain Reaction, PMN- Polymorphonuclear leucocyte, PTLD- Post-transplant lymphoproliferative disorder, vACV- Valacyclovir, UNK- Unknown.

Table 2

Presenting Clinical Characteristics Based on Whether Patient had Alternative Diagnosis to Explain Symptoms

Charts were reviewed and patients were determined to have abnormal laboratory values (hepatitis (ALT > 3× upper limit of noraml) or leukopenia (WBC < 4.0 thousand per microliter)). Documentation of initial history and physical was reviewed to determine clinical signs of fever (Tm < 100.5), CNS symptoms (AMS or obtundation), skin lesions, sepsis (hypotension requiring pressors and tachycardia), abdominal complaints, or respiratory failure (mechanical ventilation). Patient who had no alternative diagnosis to explain symptoms had negative bacterial cultures or PCR-confirmed HSV meningitis.

Condition	HSV Viremia *without* Alternative Explanation for Acute Illness (n=8)	HSV Viremia *with* Other Potential Diagnoses to Explain Acute Illness (n=5)	Total (n=13)
Hepatitis	75	40	62
Fever (72h)	75	20	54
Mortality	50	60	54
Leukopenia	50	40	46
CNS	50	40	
symptoms			46
Sepsis	50	20	38
Skin lesions	25	60	38
Abd Pain	50	0	31
Respiratory	25	20	
Failure			23