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Reactivation of type 1 herpes simplex virus and varicella zoster virus in an immunosuppressed patient with acute peripheral facial weakness

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Abstract

We describe a 26-year-old man treated with azathioprine for myasthenia gravis who developed acute left-sided peripheral facial weakness. Brain magnetic resonance imaging (MRI) revealed enhancement in the left geniculate ganglion and in the intracanalicular and tympanic segments of the facial nerve. Analysis of cerebrospinal fluid (CSF) and serum revealed intrathecal synthesis of anti-varicella zoster virus (VZV) IgG antibody. Although previous analyses of saliva, blood mononuclear cells, serum antibodies, middle ear fluid, and auricular and geniculate zone skin scrapings have shown that a small but definite proportion of patients with idiopathic peripheral facial palsy (“Bell's palsy”) have the Ramsay Hunt syndrome zoster sine herpete (RHS ZSH), this is the first confirmation of RHS ZSH by intrathecal synthesis of anti-VZV IgG antibody. In addition, herpes simplex virus (HSV)-1 DNA was found in saliva of the patient on 3 consecutive days. Simultaneous reactivation of two alphaherpesviruses (HSV-1 and VZV) in our immunosuppressed patient underscores the need to consider opportunistic infection as a cause of facial weakness.

Keywords

VZV; HSV; peripheral facial weakness

1. Introduction

While no apparent cause is found in most cases of acute peripheral facial weakness (Bell's palsy), several infectious agents require consideration, particularly in immunocompromised patients. The infectious agents include herpes simplex virus (HSV), varicella zoster virus (VZV), HIV, *Borrelia burgdorferi* (the cause of Lyme disease) and inactivated influenza

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virus given intranasally [reviewed in ref. 1]. We describe a 26-year-old man treated with azathioprine for myasthenia gravis who developed acute left-sided peripheral facial weakness. Because Lyme disease is not endemic in Colorado and because our patient was neither at increased risk of HIV infection nor had received intranasal influenza vaccine, we focused on VZV and HSV as potential causal agents of the facial weakness. Immunological and virological analysis of serum, CSF and saliva revealed reactivation of two alphaherpesviruses (HSV-1 and VZV) in this immunosuppressed patient, emphasizing the importance of considering opportunistic infection as a cause of facial weakness.

2. Case report

On 3-12-11, a 26-year-old man with myasthenia gravis of 2 years' duration who had been taking azathioprine 100 mg daily for 9 months developed left-sided peripheral facial weakness associated with a "weird taste" of foods. Three days later, he was treated with prednisone 60 mg/day for 3 days, followed by 40 mg/day for 3 days, 20 mg/day for 3 days and 10 mg/day for 3 days. On 4-4-11, neurological exam revealed right-sided ptosis and minimal weakness of head flexion (longstanding features of myasthenia gravis) and severe left peripheral facial weakness. Brain MRI revealed enhancement of the left geniculate ganglion and the intracanalicular and tympanic portion of the left facial nerve (Fig. 1). On 4-12-11, cerebrospinal fluid (CSF) exam was acellular, and CSF protein was 52 mg%. Polymerase chain reaction (PCR) analysis of CSF revealed no amplifiable VZV or HSV-1 DNA. On 4-12-11, saliva was collected for 3 consecutive days, processed, and DNA was extracted and quantified for VZV and HSV-1 by real-time PCR as described [2], after which the patient was treated with valacyclovir, 1 g three times daily for 1 month. Although none of the 3 saliva samples contained VZV DNA, all three contained HSV-1 DNA (17,267, 97 and 4 copies per ml saliva, respectively). CSF analysis for antiviral antibody revealed anti-VZV IgG but not anti-HSV antibody. The serum-to-CSF ratio of anti-VZV IgG was markedly reduced (5.2) compared with ratios for total IgG (430) and albumin (211), indicative of intrathecal synthesis of anti-VZV IgG. Ten weeks after the onset of facial palsy, moderate facial weakness remained.

3. Discussion

Herein, we describe an immunosuppressed patient with myasthenia gravis who experienced acute peripheral facial weakness. Our search for the cause of the facial weakness provided evidence of active VZV and HSV-1 infection. Intrathecal synthesis of anti-VZV IgG antibody indicating active VZV infection confirmed the diagnosis of Ramsay Hunt syndrome zoster sine herpete (RHS ZSH). Amplifiable VZV DNA was not found in CSF, most likely because CSF was not examined until one month after the onset of facial palsy. Intrathecal synthesis of anti-VZV IgG, but not amplifiable VZV DNA, has also been detected in patients with chronic VZV vasculopathy [3], chronic VZV myelopathy [4], and chronic radiculopathy [5], all in the absence of zoster rash.

This is the first confirmation of RHS ZSH by intrathecal synthesis of anti-VZV IgG antibody. Other virological techniques have also shown that a small but definite proportion of "Bell's palsy" patients have RHS ZSH, verified by a 4-fold rise in serum antibody to VZV in 9.3% of patients with idiopathic peripheral facial palsy ("Bell's palsy") [6], or by the presence of VZV DNA in auricular skin, blood mononuclear cells (MNCs), middle ear fluid or saliva [7]. Furthermore, in 6 of 32 (19%) patients with isolated peripheral facial palsy who had a 4-fold rise in serum antibody to VZV, geniculate zone skin scrapings from 4 of those 6 patients were positive for VZV DNA [8]. Terada et al. [9] also found that blood MNCs from 4 of 17 "Bell's palsy" patients were positive for VZV DNA. Although VZV DNA was not found in our patient's saliva, again most likely because saliva was not sampled

until one month after the onset of facial palsy, early examination of saliva found VZV DNA in 20% of 10 [10] and 33% of 30 patients [11] with idiopathic peripheral facial palsy. VZV DNA was also detected in saliva of all of 54 patients with acute herpes zoster [12].

While neither HSV-1 DNA nor anti-HSV-1 IgG antibody was detected in CSF, HSV-1 DNA was found in saliva of our patient on 3 consecutive days. PCR analysis of saliva has previously revealed the presence of HSV-1 DNA in 29% of 38 [13], 30% of 10 [10] and 50% of 47 patients with idiopathic peripheral facial palsy [14]. HSV-1 DNA was also present in saliva in 6.3% of 1861 healthy individuals [15], a frequency that increased to 90% in 50 normal individuals whose saliva was analyzed twice daily for 30 days [16]. Nevertheless, it is not clear why HSV DNA was detected while VZV DNA was not found in saliva of our patient one month after the onset of peripheral facial weakness.

Furthermore, the issue of which virus was more important in the production of the facial palsy is not easily resolved. Certainly intrathecal anti-VZV IgG antibody production indicates active VZV infection and makes the diagnosis of RHS ZSH inescapable. The detection of HSV DNA on 3 consecutive days might be regarded as compelling evidence of the role of HSV in etiopathogenesis although HSV has been detected in normal adult saliva [16]. While the probability of detecting HSV-1 DNA in saliva sampled once daily for 3 consecutive days is not known, its potential value in diagnosis assumes even greater clinical significance in light of the successful amplification of HSV-1 DNA in endoneurial fluid of 11 of 14 (79%) patients with Bell's palsy [17].

Was the fact that our patient was immunosuppressed critical to detecting both viruses? We are unaware of data on the relative frequency of facial palsy in the immunocompetent compared to the immunocompromised patient. While the presence of both viruses might not have been coincidental, it is important to recognize that the patients with Bell's palsy in whose endoneurial fluid HSV-1 DNA was amplified [17] were immunocompetent. Furthermore, RHS, including RHS ZSH, occurs in otherwise immunocompetent individuals. Thus the exact role of immunosuppression in dual virus reactivation in our patient remains unknown.

After the detection of HSV-1 DNA in the endoneurial fluid of patients with Bell's palsy, antiviral agents along with corticosteroids became standard treatment, despite the unclear added benefit of antiviral therapy [18]. In fact, two large randomized double-blind control studies failed to show that antiviral treatment conferred additional benefit to corticosteroids [19,20], findings confirmed by a meta-analysis of treatments for Bell's palsy [21]. Nevertheless, de Ru et al. [22] noted that antiviral agents should be considered in patients with a severe or complete facial palsy, particularly in the context of high risk for zoster infection, even in the absence of zoster rash. In light of reactivation of two herpesviruses in our immunosuppressed patient, a short course of immediate antiviral treatment would have been warranted.

Finally, while it is unlikely that endoneurial fluid of patients with peripheral facial weakness will continue to be examined for HSV-1 DNA, the detection of HSV DNA in saliva has potential value and is rapid and noninvasive. Because HSV-1 DNA has been found in saliva in 6.3% of 1861 healthy individuals [15], a frequency that increased to 90% in 50 normal individuals whose saliva was analyzed twice daily for 30 days [16], clinical studies will require rigorous controls.

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References

1. Gilden DH. Bell's palsy. *N Engl J Med*. 2004; 351:1323–31. [PubMed: 15385659]
2. Mehta SK, Cohrs RJ, Forghani B, Zerbe G, Gilden DH, Pierson DL. Stress-induced subclinical reactivation of varicella zoster virus in astronauts. *J Med Virol*. 2004; 72:174–9. [PubMed: 14635028]
3. Nagel MA, Forghani B, Mahalingam R, Wellish MC, Cohrs RJ, Russman AN, et al. The value of detecting anti-VZV IgG antibody in CSF to diagnose VZV vasculopathy. *Neurology*. 2007; 68:1069–73. [PubMed: 17287447]
4. Haug A, Mahalingam R, Cohrs RJ, Schmid S, Corboy JR, Gilden D. Recurrent polymorphonuclear pleocytosis with increased red blood cells caused by varicella zoster virus infection of the central nervous system. Case report and review of the literature. *J Neurol Sci*. 2010; 292:85–8. [PubMed: 20170926]
5. Blumenthal DT, Shacham-Shmueli E, Bokstein F, Schmid DS, Cohrs RJ, Nagel MA, et al. Zoster sine herpette: virological verification by detection of anti-VZV IgG antibody in CSF. *Neurology*. 2011; 76:484–5. [PubMed: 21282595]
6. Morgan M, Nathwani D. Facial palsy and infection: the unfolding story. *Clin Infect Dis*. 1992; 14:263–71. [PubMed: 1315161]
7. Hato N, Kisaki H, Honda N, Gyo K, Murakami S, Yanagihara N. Ramsay Hunt syndrome in children. *Ann Neurol*. 2000; 48:254–6. [PubMed: 10939578]
8. Murakami S, Honda N, Mizobuchi M, Nikashiro Y, Hato N, Gyo K. Rapid diagnosis of varicella zoster virus infection in acute facial palsy. *Neurology*. 1998; 51:1202–5. [PubMed: 9781562]
9. Terada K, Niizuma T, Kawano S, Kataoka N, Akisada T, Orita Y. Detection of varicella-zoster virus DNA in peripheral mononuclear cells from patients with Ramsay Hunt syndrome or zoster sine herpette. *J Med Virol*. 1998; 56:359–63. [PubMed: 9829642]
10. Lackner A, Kessler HH, Walch C, Quasthoff S, Raggam RB. Early and reliable detection of herpes simplex virus type 1 and varicella zoster virus DNAs in oral fluid of patients with idiopathic peripheral facial nerve palsy: decision support regarding antiviral treatment? *J Med Virol*. 2010; 82:1582–5. [PubMed: 20648613]
11. Furuta Y, Ohtani F, Aizawa H, Fukuda S, Kawabata H, Bergstrom T. Varicella-zoster virus reactivation is an important cause of acute peripheral facial paralysis in children. *Pediatr Infect Dis J*. 2005; 24:97–101. [PubMed: 15702035]
12. Mehta SK, Tyring SK, Gilden DH, Cohrs RJ, Leal MJ, Castro VA, et al. Varicella zoster virus in saliva of patients with herpes zoster. *J Infect Dis*. 2008; 197:654–7. [PubMed: 18260763]
13. Lazarini PR, Vianna MF, Alcantara MP, Scalia RA, Caiaffa Filho HH. Herpes simplex virus in the saliva of peripheral Bell's palsy patients. *Braz J Otorhinolaryngol*. 2006; 72:7–11. [PubMed: 16917546]
14. Furuta Y, Fukuda S, Chida E, Takasu T, Ohtani F, Inuyama Y, et al. Reactivation of herpes simplex virus type 1 in patients with Bell's palsy. *J Med Virol*. 1988; 54:162–6. [PubMed: 9515763]
15. Miller CS, Danaher RJ. Asymptomatic shedding of herpes simplex virus (HSV) in the oral cavity. *Oral Surg. Oral Med. Oral Pathol Oral Radiol Endod*. 2008; 105:43–50.
16. Kaufman HE, Azcuy AM, Varnell ED, Sloop GD, Thompson HW, Hill JM. HSV-1 DNA in tears and saliva of normal adults. *Invest Ophthalmol Vis Sci*. 2005; 46:241–7. [PubMed: 15623779]
17. Murakami A, Mizobuchi M, Nakashiro Y, Doi T, Hato N, Yanagihara N. Bell palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. *Ann Intern Med*. 1996; 124:27–30. [PubMed: 7503474]

18. Gilden DH, Tyler KL. Bell's palsy – is glucocorticoid treatment enough? *N Engl J Med.* 357:1653–5. [PubMed: 17942879]
19. Sullivan FM, Swan IR, Donnan PT, Morrison JM, Smith BH, McKinstry B, et al. Early treatment with prednisolone or acyclovir in Bell's palsy. *N Engl J Med.* 2007; 357:1598–1607. [PubMed: 17942873]
20. Engström M, Berg T, Stjernquist-Desatnik A, Axelsson S, Pitkäranta A, Hultcrantz M, et al. Prednisolone and valacyclovir in Bell's palsy: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet Neurol.* 2008; 7:993–1000. [PubMed: 18849193]
21. Gilden D. Is antiviral medication for severe Bell's palsy still useful? *Lancet Neurol.* 2009; 8:510.
22. de Ru JA, van Benthem PP, Janssen LM. Is antiviral medication for severe Bell's palsy still useful? *Lancet Neurol.* 2009; 8:509–10. [PubMed: 19446267]

Fig. 1. T1-weighted gadolinium-enhanced axial image shows the temporal bones at the level of the facial nerve. Note enhancement in the left geniculate ganglion (long arrow) as well as in the intracanalicular segment (short arrow) and the tympanic segment (arrowhead). Curved arrow indicates the minimal physiologic enhancement of the right geniculate ganglion.