Journal of NeuroVirology, 16: 1-5, 2010

ISSN 1355-0284 print / 1538-2443 online
DOI: 10.3109/13550280903552446

informa
healthcare

Mini review

Herpes simplex virus type 1 and Bell's palsy—a current assessment of the controversy

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Bell's palsy causes about two thirds of cases of acute peripheral facial weakness. Although the majority of cases completely recover spontaneously, about 30% of cases do not and are at risk from persisting severe facial paralysis and pain. It has been suggested that herpes simplex virus type 1 (HSV-1) may be the etiological agent that causes Bell's palsy. Although corticosteroid therapy is now universally recognized as improving the outcome of Bell's palsy, the question as to whether or not a combination of antiviral agents and corticosteroids result in a better rate of complete facial recovery compared with corticosteroids alone is now a highly contentious issue. The evidence obtained from laboratory studies of animals and humans that HSV-1 may be linked to facial nerve paralysis is first outlined. The discussion then focuses on the results of different clinical trials of the efficacy of antiviral agents combined with corticosteroids in increasing the rate of complete recovery in Bell's palsy. These have often given different results leading to opposite conclusions as to the efficacy of antivirals. Of three recent meta-analyses of previous trials, two concluded that antivirals produce no added benefit to corticosteroids alone in producing complete facial recovery, and one concluded that such combined therapy may be associated with additional benefit. Although it is probably not justified at the present time to treat patients with Bell's palsy with antiviral agents in addition to corticosteroids, it remains to be shown whether antivirals may be beneficial in treating patients who present with severe or complete facial paralysis. *Journal of NeuroVirology* (2010) 16, 1–5.

Keywords: aciclovir; antiviral agents; Bell's palsy; herpes simplex virus type 1

Introduction

Acute peripheral weakness of the facial nerve, which is the seventh cranial nerve, is a significant cause of patient suffering and morbidity. Although there are a number of specific medical conditions that are known to cause about a third of cases of acute facial weakness, including neuroborreliosis, amyloidosis, trauma, sarcoidosis, diabetes, parotid tumors, and Ramsay Hunt syndrome due to varicella-zoster virus (VZV) (Gilden and Tyler, 2007; Gilden, 2008), idiopathic Bell's palsy is the name given to the remainder (approximately two thirds) of acute facial palsy cases that occur in the absence of a definite cause. These latter patients are likely to represent a heterogeneous group, and the prognosis is generally very good, with about 70% completely recovering without treatment. However, the optimum therapy for Bell's palsy remains a crucially important issue, since the remaining 30% of patients risk major complications, including permanent paralysis, pain, and aberrant reinnervation of the facial nerve, that can be highly distressing (Gilden, 2008). The psychological sequelae of facial disfigurement should also be appreciated. Clearly, physicians must strive through drug or other therapy to minimize the development of such complications.

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The author thanks Drs. I. Steiner, R. Davenport, and I. Wirguin for helpful discussions.

Received 21 October 2009; revised 26 November 2009; accepted 2 December 2009.

For well over a decade, it has been thought by some that Bell's palsy is likely to be caused by an infectious agent, in particular herpes simplex virus type 1 (HSV-1); this view being based on several pieces of evidence (Hato *et al*, 2008). However, others do not find this view justified by the available evidence (Davenport *et al*, 2008). This issue is crucially important because if HSV-1 is indeed the cause of Bell's palsy, then an obvious consequence of this is that anti-HSV agents should be prescribed for such patients, and, indeed, there have now been several clinical trials of antiviral agents in Bell's palsy, and three recent meta-analyses of these trials. In this short review I shall outline critically the main pros and cons of the debate, one that is currently being pursued very vigorously on both sides, and then provide my personal conclusions on the basis of the available evidence on this highly controversial subject.

Summary and evaluation of the laboratory-based evidence for HSV-1 being the cause of Bell's palsy

HSV-1 is a pathogenic human herpes virus that is very familiar as causing recurrent episodes of 'cold sores,' blisters on the mouth or lip. Following a primary, usually asymptomatic, infection in children, the virus becomes latent in neurons in cranial ganglia, with the vast majority of adults becoming seropositive (Mitchell *et al*, 2003). It has been known for almost four decades that latent HSV is present in trigeminal ganglia (Bastion *et al*, 1972; Baringer and Swoveland, 1973), and, subsequently, latent HSV has been reported in other ganglia, including sacral, nodose, vagal, ciliary, geniculate, and vestibular ganglia (Baringer, 1974; Warren *et al*, 1978; Mitchell *et al*, 2003; Schultz *et al*, 1998). Attention has naturally focused on trigeminal ganglia in which HSV-1 may periodically reactivate from the latent state, either spontaneously or following a variety of triggering factors, to travel along the trigeminal nerve pathway to cause these characteristic oral and labial blisters. The fact that latent HSV-1 can also be detected in varying percentages of human geniculate ganglia (of the facial nerve) at autopsy (56% [Schulz *et al*, 1998], 71% [Furuta *et al*, 1992], 88% [Takasu *et al*, 1992] of ganglia) could be adduced as supporting the role of reactivated HSV-1 as causing facial palsy in an analogous way to latent HSV-1 in trigeminal ganglia and cold sores.

However, there are some problems with this notion. It is certainly the case that latent HSV-1 resides in geniculate ganglia, but, latent HSV-1, as has been seen, is also found in a variety of other cranial ganglia as well, including in the same studies, making it difficult to interpret the true significance of this finding. Although episodes of HSV-1 reactivation may be associated with mild sensory disturbances such as paraesthesia, it is important to note that HSV-1 reactivation in the form of cold sores is not associated with motor impairment. Further, HSV-1 reactivation does not occur in the absence of oral lesions, as opposed to VZV reactivation (herpes zoster, or 'shingles') in which the entity of 'zoster sine herpete' has been described whereby laboratory-proven VZV reactivation can cause the characteristic dermatomal pain in the absence of a zoster rash (Gilden *et al*, 1994). The significance of this contrast is that VZV, another human herpes virus, is definitely known to cause facial palsy, so direct extrapolations from VZV to HSV to in terms of motor weakness should not be assumed to be valid. Further, although it is not unusual for cold sore reactivations to recur multiple times, this is not the case for Bell's palsy, which is not as common as cold sore reactivations and seldom is recurrent.

There are reproducible, very useful, and extensively studied rodent, rabbit, and guinea pig models of HSV-1 latency (Kennedy *et al*, 1983; Steiner and Kennedy, 1995; Mitchell *et al*, 2003). For example, footpad or corneal inoculation of HSV-1 into experimental animals is followed by viral latency in neurons in trigeminal and dorsal root ganglia, and a great deal of information about the biology of HSV-1 latency has been gained from such models in laboratories all over the world. Although caution should always be maintained in extrapolating data from animals to the human situation, key insights such as the role of the latency-associated transcript (LAT) have been gained (e.g., Steiner *et al*, 1989; Thompson and Sawtell, 2001). In the current context, rodent models of HSV-1 and facial paralysis have been used. For example, Wakisaka *et al* (2002) induced facial paralysis by inoculating HSV-1 into the auricles of mice. Viral antigen was subsequently visualized along the entire course of the facial nerve; after 7 days, 60% of the mice showed facial paralysis with demyelination seen in the descending nerve roots. Although this was a certainly convincing demonstration of the motor effects of a direct HSV-1 infection of the ear leading to facial paralysis, in my view it is difficult to equate closely such models to possibly lower initial viral loads and different infection pathways that are likely to pertain during natural human infection.

In this latter context, it is very important to mention what some investigators consider to be the most compelling evidence for a direct role of HVS-1 in producing Bell's palsy. Murakami *et al* (1996) detected HSV-1 DNA in endoneurial fluid from the facial nerve and posterior auricular muscle from 11 of 14 patients with Bell's palsy during decompressive surgery, but not from patients with Ramsay Hunt syndrome or other controls. These findings can obviously be adduced as circumstantial evidence for HSV-1 being the etiological agent of Bell's palsy. However, there are a number of issues that need to be taken into consideration before making such an

assumption from this small study. The presence of a virus, or any infectious agent, in diseased tissues does not necessarily imply a cause and effect relationship between the virus and the disease. As the authors themselves pointed out, triggers that may have induced the Bell's palsy may also have nonspecifically reactivated HSV-1 from the geniculate ganglia. Further, any surgical or other traumatic procedure may reactivate HSV-1, although endoneurial fluid and muscle samples had been obtained within 2 h of beginning surgery, which makes this possibility less likely. Also, the 14 patients operated on had failed to respond to medical therapy and were selected from 170 patients with Bell's palsy so they were a very selected group. Despite these important caveats, this evidence must be taken into account in the debate. One other general point that should be made about patient samples in Bell's palsy relates to the potential significance of raised antibody titers to HSV-1. Increased antibody responses to a particular virus in a disease may not necessarily mean that the virus is playing a pathogenic role, since it may be a nonspecific response resulting from polyclonal activation of memory B cells from some other trigger.

Summary and evaluation of the clinical trial evidence that antiviral agents might improve the outcome of patients with Bell's palsy

The most clinically important and relevant test of whether herpes viruses cause idiopathic Bell's palsy is the response of patients to antiviral therapy. If HSV or VZV were playing some sort of role in the pathogenesis, this would be of little practical clinical importance unless aciclovir, or other oral agents such as valaciclovir, are effective treatments for the condition. Because Bell's palsy is known to be associated with edema and inflammation of the facial nerve, corticosteroid treatment in such patients, particularly in the early stages, was an obvious possibility. Although some earlier studies suggested that corticosteroid treatment probably improves outcome, two large recent studies have now established beyond doubt that treatment with prednisolone given within 72 h of the onset significantly improves the prognosis of Bell's palsy (Engstrom *et al*, 2008; Sullivan *et al*, 2007). Key studies of the use of antiviral agents in Bell's palsy have also included combinations of antivirals and corticosteroids, so it is important and useful to have this level of certainty about the effectiveness of corticosteroids. Aciclovir is generally a very safe drug, but it is not completely free of side effects, so, in addition to the financial implications of antiviral therapy, the question of giving aciclovir or valaciclovir to patients with Bell's palsy is a very important one to answer definitively.

The Scottish Bell's palsy study of 551 patients, which was double-blind, placebo-controlled, and randomized, showed that treating patients with Bell's palsy with aciclovir, either alone or in combination with prednisolone, produced no additional benefit when compared with patients who had received prednisolone alone (Sullivan *et al*, 2007). After 9 months, a complete recovery was seen in 94.4% of patients receiving prednisolone alone, 92.7% for aciclovir plus prednisolone, 85.2% for placebo alone, and 78% for acyclovir alone. Overall, 85.4% of those receiving aciclovir (with and without prednisolone) recovered fully versus 90.8% not receiving aciclovir (this difference was not significant but favored no aciclovir). This indicated that treatment with prednisolone was actually slightly better than prednisolone combined with aciclovir. A similar lack of efficacy of antiviral therapy was recently reported in a large Swedish study, which was also double-blind, placebo-controlled, and randomized in 16 centers over 6 years (Engstrom *et al*, 2008), that showed that there was no difference in time to recovery between the 413 patients treated with valaciclovir (3000 mg /day for 7 days, which should be effective against both HSV-1 and VZV), and the 416 patients who did not receive valaciclovir. At 12 months, recovery was seen in 71% of the patients receiving prednisolone plus placebo, 57% receiving placebo plus placebo, 58% of those receiving valaciclovir plus placebo, and 74% receiving prednisolone plus valaciclovir. Further, one smaller study from Japan showed that in 150 patients with Bell's palsy, there was no significant difference in the recovery rates between patients who had been treated with prednisolone alone or valaciclovir plus prednisolone (Kawaguchi *et al*, 2007). However, the findings of these three studies conflict with that of Hato and colleagues from Japan (Hato *et al*, 2007), which reported that a combination of valaciclovir (1000 mg/day for 5 days) and prednisolone was more effective than prednisolone alone, with the combined regime producing complete recovery in 96.5% of 114 patients compared with 89.7% of 107 patients receiving prednisolone and placebo. Further, 90.1% of cases with complete facial palsy receiving valaciclovir and prednisolone recovered fully, compared with only 75% of such severe cases receiving prednisolone and placebo. The reasons for this discrepancy are unexplained, but as has been pointed out by others, this latter study has some methodological flaws, including the fact that both treatment administration and Bell's palsy outcome assessment were carried out by investigators who were aware of the study-group assignments, only 75% of patients enrolled in the study underwent randomization, and patients comprising the 25% drop out rate were excluded from the analyses of results (Gilden and Tyler, 2007; Sullivan *et al*, 2007). Nevertheless, this study adds weight to the notion that valaciclovir may possibly have a role in treating severe cases of Bell's palsy. Interestingly, a further analysis of the data from the Scottish Bell's palsy

study did not show any benefit of aciclovir over corticosteroids in the more severe Bell's palsy cases (Sullivan *et al*, 2008). Moreover, a post hoc analysis of the data from the Swedish study (Engstrom *et al*, 2009) showed that there was no significant benefit obtained from valaciclovir therapy compared with prednisolone in improving the outcome of severe Bell's palsy.

To add further to the difficulty of the debate, two very recent meta-analyses of previous trials of antiviral agents in Bell's palsy have come to different conclusions. The meta-analysis by Quant *et al* (2009) included six trials and a total of 1145 patients and concluded that antivirals did not provide an added benefit in achieving at least partial facial muscle recovery compared with steroids alone in Bell's palsy. It was commented that the highest quality studies had the greatest effect towards showing no difference between the study arms. By contrast, the meta-analysis by de Almeida *et al* (2009) included 18 trials and 2786 patients and concluded that in Bell's palsy, antiviral agents, when administered with corticosteroids, may be associated with additional benefit in terms of facial recovery. Finally, the results of a Cochrane review on the use of antiviral treatment for Bell's palsy have just been published (Lockhart *et al*, 2009). The conclusions of this rigorous meta-analysis of 23 publications on the subject were that high-quality evidence showed no significant benefit from anti-HSV antivirals compared with placebo in producing complete recovery from Bell's palsy, and moderate-quality evidence showed that antivirals were significantly less likely than corticosteroids to produce complete recovery. One factor that should be borne in mind in evaluating clinical trials in Bell's palsy is that of possible bias in reporting positive more than negative results, and this could potentially bias the results of meta-analyses towards drug and treatment efficacy.

Conclusions

So how are we to reconcile the conflicting data about antiviral agents in Bell's palsy, a subject that has clearly generated such a striking polarization of opposite views in recent years? In my view, at the current time, the overall weight of evidence calls into question the efficacy of antiviral agents in aiding recovery from Bell's palsy and I doubt there is sufficient evidence at present to justify the routine use of antivirals in addition to corticosteroids in this condition. However, I do believe there remains the possibility that antiviral agents may have a role in treating severe cases of Bell's palsy and this is a question that will require a large prospective clinical trial to answer definitively. If Bell's palsy is a heterogeneous entity, then possibly there is a subset of cases caused by HSV-1 that are more severe and that might respond to antiviral therapy. In that case, the challenge would be to accurately identify such patients early enough to treat them successfully. Regarding the laboratory evidence from animal and human studies of HSV-1 and facial palsy, this seems to be somewhat tantalizing but at present mainly circumstantial and, as has been seen, is open to different interpretations, primarily relating to possible nonspecificity. Another intriguing question is whether failure of antiviral agents to improve the outcome of Bell's palsy necessarily excludes a possible role for HSV-1 in this condition. The rationale behind this question is that by the time antivirals are started in Bell's palsy, even when immediate, the bulk of the virally induced nerve damage may already have occurred so that blocking viral replication by the time of the facial palsy has very limited benefit. Although this cannot be entirely excluded, I think it very unlikely, especially since there is no logical reason why the facial nerve should be more susceptible to viral damage than the brain, which responds well to aciclovir in HSV-1 encephalitis. In the final analysis, what matters to the patient is that any therapy, antiviral or other, has a good chance of working.

Declaration of interest: The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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This paper was first published online on Early Online on 29 January 2010.