Occurrence of Herpes Simplex Virus Reactivation Suggests a Mechanism of Trigeminal Neuralgia Surgical Efficacy

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Common to the types of surgery that are effective for the treatment of trigeminal neuralgia (TN) is reactivation of herpes simplex virus (HSV). It is likely that such HSV reactivation following surgery indicates altered trigeminal ganglion neuron function, which was caused by the surgery. It is not thought that HSV infection is related to the cause of TN or that HSV reactivation is important for surgical treatment efficacy. Rather, it is thought that HSV reactivation is a marker of altered trigeminal ganglion neuron function resulting from the TN surgery. It is suggested that HSV reactivation is a surrogate marker of ganglion neuron injury. The correlation between effective types of surgery and evidence that they alter ganglion neuron function suggests that altered trigeminal ganglion neuron function may be the basis of the surgical efficacy.

The etiology of trigeminal neuralgia (TN) has in part been argued from the efficacy of treatment. Specifically, vascular decompression of the trigeminal root has been successful in alleviating the pain of TN, suggesting that vascular compression may be the cause of TN. However, although arteries and veins have been visualized adjacent to the trigeminal root, possibly compressing it, in some instances such vessels have not been so visualized (5, 26, 28, 30, 32, 35, 43). In these instances, because nerves typically have vessels running with them, one could speculate that neurovascular contact is of pathogenic importance. Alternatively, it could be argued that vessel effects are not the etiologic cause of TN. This was discussed at length by Adams (1). That vessel effects on the trigeminal root may not be the etiological cause of TN is suggested from three lines of evidence.

TN IN MULTIPLE SCLEROSIS IS NOT DISTINGUISHABLE FROM SPORADIC/IDIOPATHIC TN

First, TN occurs with increased frequency in patients with multiple sclerosis (MS), an illness of the central nervous system (CNS). In considering TN in MS, it is important to emphasize that the pain syndrome is essentially the same as sporadic/idiopathic TN type 1 of Burchiel (32). The neurological examination in idiopathic TN and in TN in MS patients is benign, while in patients with secondary TN due to compression from skull base mass lesions, neurological abnormalities are common (44). Secondary TN is not further discussed in this review. The clinical description of the pain and the lack of apparent deficit on neurological examination in idiopathic and MS-related TN are similar, as is the response to medical therapy. These observations support a common pathophysiological etiology. A common cause is also supported by the efficacy of the same surgical treatments for MS-related TN and for sporadic/idiopathic TN. Although microvascular decompression surgery is thought by some to not be first-line therapy for TN in MS patients (2, 10, 12, 36, 38, 56), decompression surgery has been reported to be effective in treating MS-related TN (4, 13, 14, 22). Compression (36, 38), glycerol (10, 12, 33, 36), radiofrequency (10, 12, 18), and stereotactic radiosurgery (6, 18) of MS-related TN have been more frequently used. Although possibly not as long-lasting as after the surgical treatment of idiopathic TN, the efficacy of the same surgical treatments for MS-related TN and for idiopathic TN supports the conclusion that both have a similar pathophysiology.

DECOMPRESSION AND COMPRESSION SURGERY ARE BOTH EFFECTIVE IN TREATING TN

Second, several surgical treatments other than decompression are effective for TN, including seemingly disparate procedures such as compression, glycerol neurolysis, and rhizotomy. The efficacy of all of these treatments would seem to argue against the vascular compression hypothesis of TN. If decompression efficacy is taken

Key words
- Herpes simplex virus reactivation
- Trigeminal neuralgia surgery

Abbreviations and Acronyms
CNS: Central nervous system
HSV: Herpes simplex virus
MS: Multiple sclerosis
PCR: Polymerase chain reaction
TN: Trigeminal neuralgia

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to support a vascular compression hypothesis, it would seem that the efficacy of compression surgery supports an alternative hypothesis. The apparent paradox of decompression and compression surgery were both effective for TN, and the present incomplete understanding of TN pathophysiology was noted by others (45). One could speculate that the varied surgical procedures are effective, for example, via alteration of ephaptic conduction, but the effectiveness of all of the procedures would seem to argue against the vascular compression hypothesis.

REACTIVATION OF HERPES SIMPLEX VIRUS (HSV) OCCURS AFTER SURGICAL TREATMENT OF TN

The third line of evidence to argue against concluding that vascular compression/decompression are the etiology/treatment of TN is to note an effect, other than improvement of TN, of both decompression surgery and compression/neurolysis/rhizotomy surgery. Emphasized are the reports of HSV reactivation following the various types of effective surgery. Reactivation of HSV after surgical rhizotomy for TN has been known for many years (16, 17, 20, 30). More recent are reports of HSV reactivation after decompression surgery (27, 30, 39, 40, 52), balloon compression surgery (11, 31), glycerol neurolysis (3, 9, 10, 15, 33, 41, 55), and radiofrequency rhizotomy (10). The older literature also noted HSV reactivation after trigeminal ganglion alcohol treatment for TN (25).

It is not suggested that HSV causes TN or that surgical effectiveness is dependent on HSV reactivation. Rather, it is suggested that HSV reactivation after surgery is a marker of an effect these multiple types of effective surgery have on trigeminal ganglion neurons. It is suggested that TN surgery alters neuron function (indicated to have occurred by HSV reactivation) and that this results in the alleviation of pain.

HSV reactivation, which occurs after decompression and the other types of TN surgery, indicates the occurrence of altered trigeminal ganglion neuron function. Therefore common to the various types of effective TN surgery is that they alter trigeminal ganglion neuron function, and it is suggested that this neuronal effect may be the basis of the TN surgical efficacy.

HSV reactivation occurs after decompression, balloon compression, glycerol neurolysis, surgical rhizotomy, and radiofrequency rhizotomy, although the true frequency after each is not known. Estimates of HSV reactivation frequency depend on the type of reactivation measurement used: 1) the occurrence of clinically symptomatic HSV lesions (e.g., herpes labialis), 2) shedding of infectious HSV in oral secretions, 3) shedding of HSV DNA in oral secretions. Reports of HSV reactivation after neurosurgical procedures to treat TN have primarily noted the occurrence of clinically apparent herpes lesions (3, 9, 10, 15-17, 20, 30, 33, 39-41, 52, 55). Investigators have also noted that the true incidence of HSV reactivation after TN surgery is not known (11, 30, 34). Jannetta and colleagues investigated HSV reactivation after TN surgery by determining HSV shedding in oral secretions and by determining HSV lesions (herpes labialis). They noted a higher frequency of HSV shedding than of clinical HSV lesions (27, 39, 40).

FREQUENCY OF HSV LATENCY AND HSV REACTIVATION

HSV establishes a latent infection in most people, including those without a history of oral-facial herpes infections. In a routine autopsy study, latent HSV infection was detected in the trigeminal ganglia of 67% of individuals (19). During HSV latency, viral DNA is present in ganglion neuronal nuclei in episomal form (37). A single HSV-encoded RNA termed the latency associated transcript is expressed in latently infected neuronal nuclei (24), and other viral RNAs are minimally if at all expressed (23). When HSV reactivation occurs in latently infected neurons, HSV is transported by axoplasmic flow to oral-nasal-ocular-mucosal surfaces, and asymptomatic shedding of virus or clinically apparent infection results. Although causes of reactivation are incompletely known, removal or manipulation of human or experimentally infected animal ganglia results in reactivation of virus (23, 24). In experimentally infected mice, we showed that sciatic neurectomy led to in vivo HSV reactivation in latently infected dorsal root ganglion neurons (51).

Frequency of HSV reactivation can be measured in several ways. Studies of human HSV reactivation unrelated to TN have reported that the frequency of shedding of HSV DNA, determined by polymerase chain reaction (PCR) technology, is higher than shedding of infectious HSV (44). As noted earlier, the frequency of shedding infectious HSV after TN surgery was greater than the frequency of clinically apparent HSV lesions (27, 39, 49). It is likely that frequencies of HSV reactivation after TN surgery would be shedding of HSV DNA> shedding of infectious HSV> clinically apparent HSV lesions. Some individuals do not have latent HSV infection of their trigeminal ganglia (19), and HSV reactivation in them would not be expected to occur after TN surgery. However, surgery is likely to be as effective for them as for those who reactivate HSV. Reactivation of HSV is thought to be a marker of neuronal injury due to TN surgery and is not thought to be important per se for the efficacy of surgery.

DISCUSSION

Common to the multiple types of surgery that are effective for the treatment of TN is that they result in HSV reactivation, and the occurrence of reactivation provides evidence of altered trigeminal ganglion neuron function. The correlation between altered trigeminal ganglion neuron function and effective surgical methods suggests that altered ganglion neuron function may explain the surgical efficacy. This hypothesis would be consistent with a trigeminal ganglion basis of TN as suggested by Devor et al. (21). However, TN in MS would seem to require a CNS cause, and this suggests a possible CNS etiology of idiopathic TN as well. It is hypothesized that altered ganglion neuron function resulting from TN surgery alters CNS pain transmission, possibly by altering ganglion neuropeptide transport to the CNS.

It is suggested that surgically induced alterations in trigeminal ganglion neuron function, evidenced to have occurred by HSV reactivation, result in modified CNS function. Altered or damaged sensory ganglion neuron function affects ganglion neuron neuropeptide expression (53) and neuropeptide transport to the spinal cord substantia gelatinosa (50).

Adams discussed operative manipulation and nerve/ganglion injury as the basis of the effectiveness of TN surgery (1). Others have also suggested the possible importance of mechanical injury for the effectiveness of TN surgery (5, 11, 15, 35, 41, 43, 46). The correlation between surgery that is effective in