



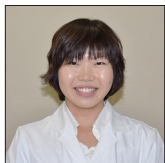
Original Article

Clinical features of herpes simplex virus reactivation after microvascular decompression for trigeminal neuralgia: Experience of 200 patients and a literature review

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ABSTRACT

Background: Herpes simplex virus (HSV) reactivation occasionally develops in the early postoperative period after microvascular decompression (MVD) for trigeminal neuralgia (TN). Therefore, the present study investigated the clinical features of this phenomenon.

Methods: The study cohort comprised 200 patients with 125 women aged between 17 and 90 years (median age, 66 years) who underwent MVD for TN between January 2010 and December 2020. Characteristics were compared between patients with and without HSV reactivation and clinical features were analyzed.

Results: Twenty patients had HSV reactivation: herpes labialis in 18 and herpes zoster (final diagnosis) in 2. A multivariate analysis revealed independent correlations between postoperative HV reactivation and a previous history of herpes labialis (odds ratios [OR]: 6.32, $P = 0.0003$) and reoperation for recurrent or persistent pain (OR: 5.06, $P = 0.0211$). No significant differences were observed in pain relief, postoperative facial numbness, or Barrow Neurological Institute Pain Intensity/Facial Numbness Scores in the past follow-up between patients with and without HSV reactivation. HSV reactivation manifested at a median of the 4th postoperative day (1–10 days) and its location was not related to the preoperative distribution of facial pain. All patients were treated with local acyclovir and were completely cured within 1–2 weeks.

Conclusion: HSV reactivation occurred in 10% of patients after MVD including 1% of herpes zoster. A previous history of herpes labialis and reoperation was identified as risk factors for reactivation. Symptoms were completely cured by antiviral drugs within 1–2 weeks. It is important to note that cases of herpes zoster may be confused with cases of HSV after MVD.

Keywords: Herpes simplex, Herpes zoster, Microvascular decompression, Reactivation, Trigeminal neuralgia

INTRODUCTION

Burdick *et al.*^[7] initially reported herpes simplex following decompression surgery for trigeminal neuralgia (TN), with approximately one-third of patients developing herpes simplex on skin supplied by the manipulated nerve. Pazin and Ho^[11,19,20], who developed and established the microvascular decompression (MVD) procedure, investigated herpes simplex virus (HSV) reactivation after MVD of the trigeminal nerve in 1978. Reactivation was detected in 28 out

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of 56 patients, and a history of recurrent herpes labialis was associated with an increased risk of reactivation after surgery. These findings indicated that a minimal stimulation or inapparent trauma to the trigeminal sensory root was sufficient to activate latent HSV. HSV reactivation has since been identified as one of the postoperative complications that develop after various lesioning procedures, including glycerol injection,^[2,3,4,6,16,25] percutaneous balloon compression,^[5,9] surgical and radiofrequency rhizotomy,^[4,8,15] and MVD.^[5,9,15,18] Although only HSV reactivation has been detected, the symptoms of herpes zoster may be included in the literature. These clinical features have not yet been clarified in sufficient detail. We, herein, report our experience of 200 consecutive patients who underwent MVD for TN derived from prospectively collected data and outcome measures based on follow-up notes and responses to a mailed questionnaire. The incidence and features of HSV reactivation in the literature are also reviewed.

MATERIALS AND METHODS

Between January 2010 and December 2020, 293 consecutive patients with TN underwent MVD in the Tokyo Women's

Medical University Medical Center East (currently Adachi Medical Center). Figure 1 shows a flowchart of case selection for the retrospective analysis. The study cohort included 200 patients. All clinical and surgical data were extracted from a prospectively maintained computer database, while the assessment of outcome measures was based on follow-up notes and responses to a mailed questionnaire. The research protocol was approved by the Institutional Review Board of Tokyo Women's Medical University (No. 2741).

All surgeries were performed by the senior author (H.K.) after patients had provided their informed consent, as previously reported.^[13] After surgery, patients were generally observed overnight in Neuro-ICU. An initial assessment of pain relief was conducted and head CT was routinely performed the day after the intervention. Since we detected herpes labialis in patients after MVD for TN in 2009, we, carefully, examined patients for any signs or symptoms of herpes labialis and facial/oral vesicles. Since patients were not always aware of these symptoms by themselves, they were carefully monitored and we have been making a prospectively collected database. Patients were discharged approximately 1 week after surgery and the first follow-up was conducted within 1–2 weeks at an outpatient clinic.

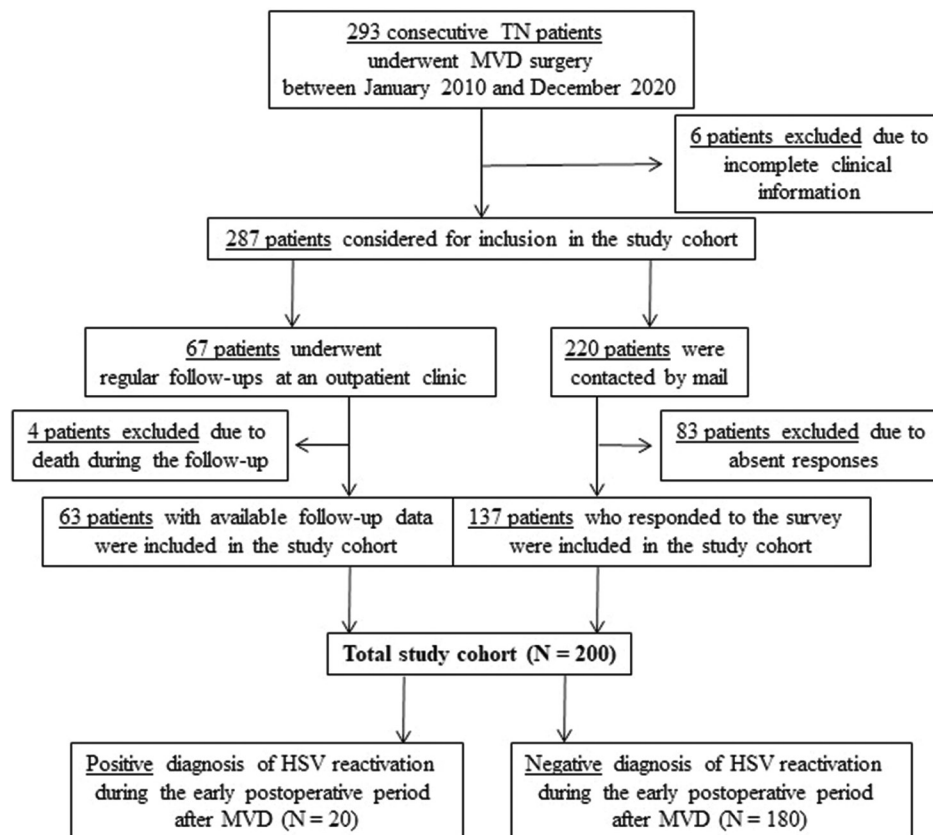


Figure 1: A flowchart of case selection for this retrospective analysis. HV: herpes virus, MVD: microvascular decompression, TN: trigeminal neuralgia.

Pain relief and facial numbness were assessed according to the Barrow Neurological Institute (BNI) Pain Intensity and Facial Numbness Score.^[21]

Statistical analysis

Subgroup comparisons were performed using Fisher's exact test and the Wilcoxon signed-rank sum test for categorical and continuous variables, respectively. The level of significance was defined as $P < 0.05$. Factors demonstrating significant or borderline ($P < 0.1$) relationships with the variable of interest ("postoperative HSV reactivation") in the univariate analysis were included in multivariate modeling using logistic regression and odds ratios (OR) and their 95% confidence intervals (CI). All calculations were performed using the free software R: a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The characteristics of patients in the study cohort are shown in Table 1. Briefly, 186 (93%) patients underwent primary MVD for TN, and 14 (7%) were reoperated for recurrent or persistent pain after the initial intervention either in our center or elsewhere. There were 125 (63%) women and 75 (38%) men aged between 17 and 90 years (median age, 66 years). Pain was localized solely within the areas of the ophthalmic (V1), maxillary (V2), and mandibular (V3) divisions of the trigeminal nerve in 6 (3%), 52 (26%), and 48 patients (24%), respectively. The remaining patients developed pain in more than two divisions. Forty-two (21%) patients had a previous history of herpes labialis. The superior cerebellar artery was the most commonly affected vessel (in 106 patients [53%]) and facial numbness was the most common complication (in 31 patients [16%]). Immediate complete pain relief was achieved in 181 patients (91%). Symptoms recurred in 30 (15%) patients at a median follow-up of 58 months. BNI pain intensity and facial numbness scores^[20] in the last follow-up were I/II in 168 (84%) and 192 patients (95%), respectively.

Among 200 patients with TN after MVD, the reactivation of HSV was detected in 20 patients: 18 with herpes labialis, one with face, oral, and tongue vesicles, and one with face vesicles. Dermatologists finally diagnosed the latter two as herpes zoster [Table 2], one of which was confirmed serologically. Immunoserological testing showed a positive result for varicella-zoster virus (CF: Complement fixation) 8× (normal: 0–3×).

Comparisons of patients with and without a positive diagnosis of HV reactivation during the early postoperative period after MVD revealed significantly higher rates of reoperation (20% vs. 6%, $P = 0.0380$) and a previous history of herpes labialis (55% vs. 17%, $P = 0.0004$). In addition, the absence

of the intraoperatively identified offending vessel was more frequently noted ($P = 0.0653$) in patients with postoperative HSV reactivation. An analysis of these three predictive factors in the multivariate model revealed independent correlations between HSV reactivation and a previous history of herpes labialis (OR: 6.32, 95% CI: 2.34–17.08, $P = 0.0003$) and reoperation (OR: 5.06, 95% CI: 1.28–20.06, $P = 0.0211$). None of the other factors evaluated significantly differed between the subgroups. Furthermore, no significant differences were observed in pain relief, postoperative facial numbness, or BNI Pain Intensity/Facial Numbness Scores at the last follow-up between patients with and without HSV reactivation [Table 1].

Symptoms appeared at a median of the 4th postoperative day (1–10 days). One patient exhibited symptoms on the opposite site, whereas ten patients developed herpes labialis elsewhere to the division of neuralgia [Table 2]. Encephalitis was not detected in any patients. All patients were treated by the oral administration or local application of acyclovir and were completely cured within 1–2 weeks. In two cases of herpes zoster, neither subsequently developed post zoster neuralgia.

DISCUSSION

HSV reactivation occurred in 10% of patients after MVD for TN, including 1% with herpes zoster, and a herpes history of herpes labialis and reoperation was identified as risk factors for reactivation. The most common symptoms are herpes labialis, with 3–5 vesicles on the vermillion border of the lip preceded by pain, while the incidence of herpes simplex encephalitis following neurosurgery due to virus reactivation is very low.^[17] Most patients may simply be monitored, particularly if they are not immunocompromised, and the risk of developing severe disease or complications is low.^[23]

When HV reactivation occurs in patients with atopic dermatitis or those in an immunocompromised state, it may have a severe clinical presentation called Kaposi's varicelliform eruption, for which the head, neck, and trunk are the predominant sites. Complications include keratoconjunctivitis, meningitis, and encephalitis.^[1]

Patients in the present study were treated with systemic and local antiviral drugs and herpes labialis was completely cured within 1–2 weeks without deterioration. Oral acyclovir reduces the time to the loss of crusts from approximately 7 to 8 days, but does not alter the time required for complete healing.^[23]

Herpes zoster is included in HSV reactivation after MVD. Cushing,^[10] initially, reported herpes zoster on the face at the area of anesthesia in 1905 and it was accompanied by a concomitant lesion on the lower sacral posterior root ganglia in two out of 20 patients following the removal of the Gasserian ganglion for TN. Carton and Kilbourne^[8] detected herpes simplex in 16 out of 17 patients after trigeminal sensory root section for TN. Based on the location of lesions, two cases were

Table 1: Characteristics of 200 TN patients who underwent MVD.

Evaluated characteristics	Total	HSV reactivation during the early postoperative period after MVD for TN		
		Positive*	Negative	P-value
Number of patients	200	20	180	NA
Type of surgery				0.0380
Primary	186	16	170	
Reoperation for recurrent or persistent pain	14	4	10	
Median age in years (range)	66 (17–90)	64 (47–84)	65 (17–90)	0.6912
Sex				0.3303
Women	125	15	110	
Men	75	5	70	
Facial pain side				0.3376
Right	129	15	114	
Left	71	5	66	
Facial pain distribution				
V1	6	0	6	1.0000
V2	52	6	46	0.7883
V3	48	5	43	1.0000
V1/V2	32	3	29	1.0000
V2/V3	46	5	41	0.7841
V1/V2/V3	16	1	15	1.0000
Previous history of herpes labialis	42	11	31	0.0004
Intraoperative findings of offending vessels				
SCA	106	9	97	0.4864
AICA	23	3	20	0.7089
VA	9	0	9	0.6028
Vein	52	5	47	1.0000
No offending vessel	10	3	7	0.0653
Postoperative complications				
Facial numbness	31	5	26	0.2060
CSF leakage	2	0	2	1.0000
Infection	3	0	3	1.0000
Hearing disturbance	2	0	2	1.0000
Pain outcome after surgery				
Immediate complete pain relief	181	18	163	1.0000
Delayed complete pain relief	10	0	10	0.6026
Decreased pain intensity without complete relief	9	2	7	0.2233
Median length of the follow-up in months (range)	58 (4–133)	59 (6–131)	58 (4–133)	0.7991
Pain recurrence during the follow-up	30	3	27	1.0000
BNI Pain Intensity Score in the past follow-up				0.5347
I/II	168	16	152	
III/IV/V	32	4	28	
BNI Facial Numbness Score in the past follow-up				0.5764
I/II	192	19	173	
III/IV	8	1	7	

HSV: Herpes simplex virus, MVD: microvascular decompression, TN: trigeminal neuralgia, SCA: superior cerebellar artery, AICA: anterior inferior cerebellar artery, VA: vertebral artery, BNI: Barrow Neurological Institute, NA: not applicable. Bold: Statistically significant values. *Including two cases of herpes zoster

suspected to be herpes zoster. Since Cushing reported herpes zoster reactivation after trigeminal nerve surgery, difficulties are associated with differentiating between herpes simplex and zoster.^[5] Herpes zoster has not been reported in many studies, even those with a large number of patients [Table 3]. Any facial and oral vesicles other than on the vermillion

border suggest herpes zoster, the characteristics and clinical course of which differ from those of herpes simplex. Simms and Dunn^[22] reported that a patient developed herpes zoster of the maxillary division of the trigeminal nerve after MVD. This may result in severe ocular complications, including blindness. In cases, in which an unusual type of herpes labialis was

Table 2: Characteristics of 20 patients with postoperative herpes simplex virus reactivation after microvascular decompression surgery for trigeminal neuralgia.

Case number	Age (years)	Sex	Affected side	Affected area	Previous history of herpes labialis	Recurrent surgery	Cause of trigeminal neuralgia	Pain relief	Postoperative facial numbness	Characteristics of postoperative HSV reactivation				
										Day of clinical manifestation	Affected side	Herpes labialis	Other symptoms possibly caused by herpes zoster	Treatment
1	70	F	Right	V2	No	SCA	SCA	Immediate		2	Right	Upper/Lower		Systemic
2	49	F	Right	V3	No	SCA	SCA	Immediate	Yes	3	Right		V2 face oral vesicle V3 tongue vesicle	Systemic
3	51	F	Right	V2	Yes	Yes	Teflon granuloma Vein	Immediate		2	Left	Lower		Systemic
4	47	F	Right	V3	Yes		SCA	Immediate		6	Right	Upper		Systemic
5	54	M	Left	V2V3	No		SCA	Incomplete		5	Left	Lower		Local
6	72	M	Left	V2	No		SCA	Immediate	Yes	1	Left	Lower		Systemic
7	54	F	Right	V2	Yes	Yes	SCA	Immediate		2	Right	Upper		Systemic
8	49	M	Right	V2V3	Yes		Vein	Immediate	Yes	5	Right	Upper/Lower		Local
9	84	F	Left	V1V2	No		SCA	Immediate		10	Left	Upper/Lower		Local
10	64	F	Right	V3	Yes		SCA	Immediate		3	Right	Lower		Local
11	76	F	Right	V1V2V3	Yes	Yes	Teflon granuloma	Immediate		6	Right	Upper/Lower		Local
12	71	F	Left	V3	No		AICA	Immediate	Yes	7	Left	Upper		Local
13	59	F	Right	V2V3	Yes		Vein	Immediate		3	Right	Lower		Systemic
14	73	F	Right	V2V3	Yes		Vein	Incomplete		6	Right	Upper/Lower		Systemic
15	62	F	Right	V2V3	Yes		AICA	Immediate		4	Right	Lower		Local
16	67	M	Right	V1V2	No		Vein	Immediate	Yes	4	Right		V1V2 face vesicle	Systemic
17	63	F	Right	V1V2	No		SCA	Immediate		2	Right	Upper/Lower		Systemic
18	83	M	Left	V3	Yes		AICA	Immediate		4	Left	Upper/Lower		Systemic
19	57	F	Right	V2	Yes		SCA	Immediate		3	Right	Upper/Lower		Systemic
20	69	F	Right	V2	No	Yes	Teflon granuloma	Immediate		7	Right	Upper/Lower		Systemic

F: Female, M: Male; V1, V2, and V3: ophthalmic, maxillary, and mandibular divisions of the trigeminal nerve, respectively; SCA: superior cerebellar artery; AICA: anterior inferior cerebellar artery; HSV: herpes simplex virus

Table 3: Incidence of herpes simplex virus reactivation after various procedures on the trigeminal nerve in patients with trigeminal neuralgia.

Year	Author	Procedure	N	Herpes labialis (n)	Other symptoms possibly caused by herpes zoster (n)	Reactivation (%)
1905	Cushing ^[10]	Removal of the Gasserian ganglion	20	0	2	10
1952	Carton and Kilbourne ^[8]	Sensory root section	17	11	5	94
1960	Burdick <i>et al.</i> ^[7]	MVD	148	49	0	33
1978	Pazin <i>et al.</i> ^[19]	MVD	56	28	0	50
1979	Pazin <i>et al.</i> ^[20]	MVD	37	24	0	65
1984	Ho and Pazin ^[11]	MVD	55	22	5	40
1982	Lunsford ^[16]	Glycerol injection	27	8	0	27
1986	Beck <i>et al.</i> ^[3]	Glycerol injection	58	5	0	9
1986	Arias ^[2]	Glycerol injection	100	10	0	10
1988	Young ^[25]	Glycerol injection	162	61	0	38
1988	Burchiel ^[6]	Glycerol injection	60			5
1992	Klun ^[15]	MVD	178			≈50
		Partial sensory rhizotomy	42			≈100
2008	Oh <i>et al.</i> ^[18]	MVD	27	0	1	4
		Gamma knife	18	0	1	6
2013	Bender <i>et al.</i> ^[4]	Glycerol injection	470	37	0	8
		Radiofrequency thermocoagulation	287	10	0	3
2018	Chen <i>et al.</i> ^[9]	MVD	68	10	0	15
		PBC	42	15	0	36
2019	Berra <i>et al.</i> ^[5]	MVD	58	18	0	31
		PBC	34	12	0	35
2022	Kikuchi	MVD	200	18	2	10

MVD: Microvascular decompression, PBC: Percutaneous balloon compression

detected, herpes zoster was diagnosed based on the clinical course and subsequent immunological tests.

Varicella-zoster virus is a pathogenic human herpes virus that causes varicella (chickenpox) as a primary infection, following which it becomes latent in peripheral ganglia. Decades later, the virus may reactivate spontaneously or after a number of triggering factors to cause herpes zoster (shingles).^[14] Herpes zoster presents as a unilateral, self-limited dermatomal rash. Antiviral therapy for acute herpes zoster is indicated for patients with nontruncal involvement.^[12] Antiviral agents are effective if promptly commenced. We administered antiviral drugs to patients with herpes simplex and zoster. The careful diagnosis of herpes zoster and administration of antiviral drugs to patients is strongly recommended.

HSV reactivation did not always occur at the area of facial pain or on the side of the manipulation. Since the whole trigeminal root is manipulated in MVD, the area of HSV reactivation is not always the same division of the trigeminal nerve. We, previously, encountered one patient who developed symptoms on the other side of surgery.^[7]

HSV reactivation occurred in 10% of patients after MVD for TN, including 1% of herpes zoster, and a herpes history

of herpes labialis and reoperation was identified as risk factors for reactivation. HSV reactivation occurs in infected HSV patients with a history of herpes labialis, although primary infections are commonly asymptomatic.^[24] Most patients may simply be monitored, particularly if they are not immunocompromised, and the risk of developing severe disease or complications is low.^[23] Not only direct trauma to the nerve but also systemic surgical stress may activate the other side of the infected ganglion.

The incidence of HSV reactivation after various procedures on the trigeminal nerve in patients with TN is shown in Table 3. We hypothesize that the degree of procedural trauma to the trigeminal nerve plays an integral role in the development of HSV. This may be true due to the higher rate of reactivation after sectioning of the trigeminal nerve than with other procedures. However, MVD also stimulated HSV reactivation and no significant differences were observed between patients with and without postoperative facial numbness in the last follow-up, which confirmed the observation that a minimal stimulation or inapparent trauma to the trigeminal sensory root was sufficient to activate latent HSV.^[19,20]

CONCLUSION

HSV reactivation occurred in 10% of patients after MVD including 1% of herpes zoster. A previous history of herpes labialis and reoperation was identified as risk factors for reactivation. A minimal stimulation or inapparent trauma to the trigeminal sensory root is sufficient to activate latent herpes virus. Symptoms were mild and cured by normal treatment without severe complications. It is important to note that cases of herpes zoster may be confused with those of HSV.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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