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ORIGINAL ARTICLE

Risk factors of facial herpes simplex after percutaneous microballoon compression for trigeminal neuralgia: A retrospective case-cohort study.

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Abstract

BACKGROUND: Percutaneous microballoon compression (PMC) is an important clinical technique for the treatment of trigeminal neuralgia (TN). Some studies have shown that patients may be infected with herpes simplex virus type 1 (HSV-1) after surgery. However, the prevalence and associated risk factors are unclear yet. This study aimed to explore the potential risk factors of facial herpes simplex (FHS) in patients with TN treated by PMC retrospectively.

METHODS: A retrospective study included 181 patients with TN undergoing PMC treatment between September 2019 and August 2020 in Sichuan Cancer Hospital and Institute. Depending on whether the patient was infected with HSV-1 after PMC operation or not, the patients were divided into two groups, FHS group and non-FHS group, respectively. Demographic, clinical, laboratory, and surgical data of the patients were collected. Univariable and multivariable logistic regression analysis were used to explore the risk factors of infecting with HSV-1 in patients with TN after PMC.

RESULTS: Among 181 patients with TN treated by PMC surgery without FHS. 49 patients were diagnosed with FHS after operation, and the diagnosis was confirmed by PCR detection of HSV-1. All patients had no FHS before operation, the occurrence of FHS was 27.07% (49/181) in patients underwent PMC. Variables with $p<0.05$ in univariable analysis included gender (male/female), age, duration of disease and CD8+ T cells count. The results of multivariable logistic regression analysis showed the independent risk factors of FHS after PMC were gender (male/female) ($p<0.01$, OR 0.061, 95% CI 0.009~0.428), age ($p<0.001$,

OR 1.169, 95% CI 1.065~1.283), duration of disease (p<0.001, OR 1.361, 95% CI 1.206~1.535) and CD8+T cells count (p<0.01, OR 0.993, 95% CI 0.989~0.998).

CONCLUSIONS: In our study, we found that elderly patients and duration of disease were the risk factors of occurring FHS in TN patients after PMC surgery. CD8+T cells count and male gender were the protective factors for not developing FHS.

Abbreviations:

PMC	- Percutaneous Microballoon Compression
TN	- Trigeminal Neuralgia
FHS	- Facial Herpes Simplex
HSV-1	- Herpes Simplex Virus Type 1
MVD	- Microvascular Decompression
BMI	-Body Mass Index
ASA	- American Society of Anesthesiologists
NRS	- Numeric Rating Scale
SD	- Standard Deviation
DSA	- Digital Subtraction Angiography
IQR	- Interquartile Range
CI	- Confidence Interval
OR	- Odds Ratio

INTRODUCTION

The annual incidence of trigeminal neuralgia (TN) was estimated at 3–5 per 100,000 people, whereas the prevalence of TN more than 150 per 100,000 people. TN may develop at any age, and the incidence reached a peak after 50 years or older. The incidence of female is higher than male, with an average gender ratio of 1 males to 1.7 female (Zakrzewska & Linskey, 2016).

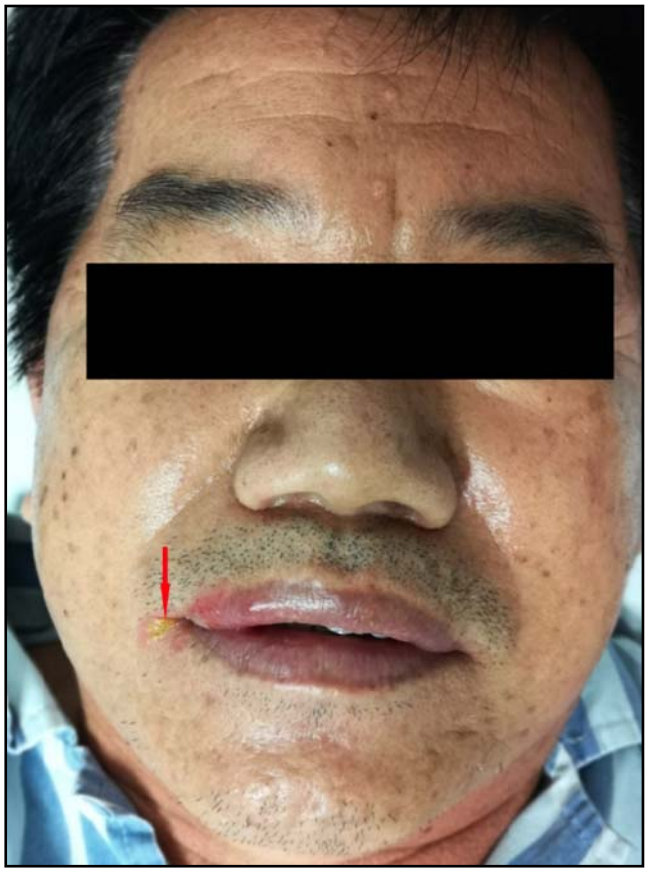

Fig. 1. Area where herpes appeared on the patient's head and face

The main current therapies include drug therapy, microvascular decompression (MVD), percutaneous microballoon compression (PMC), surgical radiofrequency rhizotomy and glycerol neurolysis (Maarbjerg *et al.* 2017). PMC was first reported by Mullan in 1983 for the treatment of trigeminal neuralgia (Mullan & Lichtor, 1983). In terms of patient comfort, doctors' convenience and medical economic burden, PMC is more recommended than MVD, radiofrequency and gamma knife. (Fransen, 2012). It has been observed previously that patients who cannot tolerate oral medications or relapse after other interventional procedures should choose PMC treatment (Liu *et al.* 2007). All surgical procedures may come with complications. The procedure-related complications after PMC including facial numbness, masseter weakness and facial herpes simplex (FHS) (de Siqueira *et al.* 2006). Lots of studies have shown that TN patients undergoing PMC surgery have an increased risk of developing specific postoperative complications. Approximately 30% patients complain the occurrence of facial herpes simplex after surgery, and typical symptoms usually last around 10 days (Berra *et al.* 2019; Pazin *et al.* 1978). The use of antivirals can decrease the incidence of herpes simplex viral reactivation, the healing time, and the extent of herpetic skin lesions after surgery (Chen *et al.* 2017). Despite this measure, TN patients are still suffered from substantial medical and economic burdens. So far, the prevalence and associated risk factors of PMC infected with herpes simplex virus type 1 (HSV-1) have not been reported. Therefore, this retrospective case-cohort study was aimed to investigate prevalence and associated risk factors of facial herpes simplex after PMC in TN patients.

PATIENTS AND METHODS

Ethics statement

This study was approved by the Ethics Committee of Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China. In consideration of the retrospective nature of the study, there was no need to obtain informed consent from patients.

Patients

Between 1 April 2019 and 31 August 2020, a single-center case cohort of 195 TN patients undergoing PMC was collected. The following inclusion criteria were applied: (1) All patients included in this study met the diagnostic criteria of primary trigeminal neuralgia as described in the International Classification of Headache Disorders (3rd edition). (2) The patients received PMC surgery with endotracheal tube insertion and general anesthesia. (3) The patients didn't

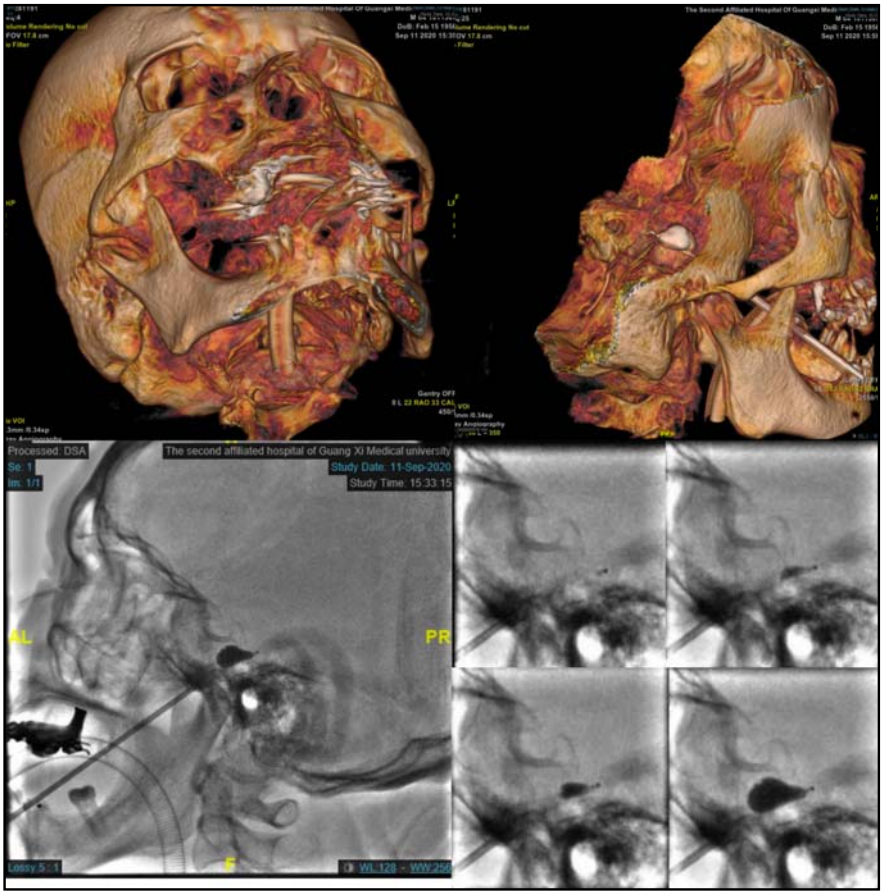

Fig. 2. Operation process of percutaneous microballoon compression for trigeminal neuralgia patients

have any adhesion of trigeminal ganglion tissue caused by PMC surgery or other minimally invasive interventional therapy. The exclusion criteria included: (1) The patients with Secondary trigeminal neuralgia. (2) The patients received re-operation due to the unsatisfactory analgesic effect. (3) The patients with incomplete medical records. (4) The patients with history of herpes zoster virus infection in head and face. Diagnostic criteria of facial herpes simplex after PMC: (1) Careful historical analysis and physical examination were performed for all patients, none of the patients had HSV-1 infection in their medical history. (2) Cluster herpes occurred at the mucosal junction near the inner oral angle, nostril, and eyelid on the affected side within 7 days postoperative (Fig.1). (3) HSV-1 was isolated from oropharyngeal swab samples of the patients who developed facial herpes simplex after PMC, then we sent the sample to test for polymerase chain reaction (PCR).

Surgical procedures

The details procedure was as follows (Fig.2) (Huo *et al.* 2014):(1) Dyna-CT scan assisted positioning was performed to determine the anterior puncture path. (2) Under general anesthesia, the end of the trocar was sent to the foramen ovale under the guidance of Digital subtraction angiography (DSA) image. The catheter was inserted through intrathecal needle to the upper part of the trigeminal nerve semilunar ganglion, and the location of the catheter was confirmed by fluoroscopy. (3) Then, the iodic contrast medium was injected slowly, and the lateral radiograph showed that the balloon at the end of the catheter was like the shape of a pear. We used 0.52±0.15 ml contrast agent totally, kept the pressure of microballon for 1.5–2 min. (4) Finally, the miroballoon was deflated, and the catheter was removed.

Data collection and analysis

Data were collected by two researchers independently. We collected four kinds of data totally: (1) The general demographics of the patients, including sex, age, and body mass index (BMI), American Society of Anesthesiologists (ASA) grade, duration of disease, nerve distribution of FHS, preoperative and postoperative Numeric Rating Scale NRS (NRS). (2) Surgical-related data, including surgical duration, the time of balloon dilation during the treatment, contrast agent's dose and the time of mechanical ventilation. (3) Results of a variety of laboratory tests, including white blood cell count, neutrophils count, lymphocyte count, $CD4^+$T cells count, $CD8^+$T cells count, concentration of TNF-α and IL-6. (4) Hospital stays and hospitalization expenses. All measurement data were presented as mean ± standard deviation (SD) when the p value of normality test >0.1, we considered the data to be normally distributed. Otherwise, it should be presented

as median with interquartile range (IQR). When data satisfied criteria for normality and homogeneity of variance, statistical analysis was performed through independent samples t-test. Otherwise, statistical analysis was performed through Mann-Whitney U test. For count data, risk factors of facial herpes simplex after percutaneous microballoon compression for trigeminal neuralgia. All analyses were performed with SPSS version 23.0 (IBM, Armonk, NY, USA) statistical software.

RESULTS

General data of patients

One hundred ninety five cases met the criteria, all the patients completed the PMC successfully. Fourteen patients received secondary surgical treatment due to pain recurrences. The pharyngeal swabs of 181 patients were collected to detect HSV-1 by PCR postoperatively. The 181 patients included 94 males and 87 females, aged from 45 to 78 years old (median 61, IQR 11), body mass index 18–25 (median 23, IQR 6.9), average hospital stays were 9.6±0.8 days, the average hospitalization expenses were 29754.68 ± 826.95 yuan. Meanwhile, 49 cases (27.07%) occurred FHS after PMC. There was no significant difference in the general clinical characteristics between the excluded patients and the included patients.

Comparison of general characteristics of clinical data

The data included age, gender, ASA grade, body mass index, duration of disease, nerve distribution of FHS, preoperative and postoperative NRS. As shown in Table 1, age in FHS group was significantly older than that in non-FHS group (t=6.725, p<0.001). The proportion of female in FHS group was significantly higher than that in non-FHS group (χ^2=8.845, p<0.05), but the female subject's categorization (premenopausal/peri and postmenopausal) was no statistical significantly between the two groups (χ^2=0.607, p>0.05). Duration of disease in FHS group was significantly longer than that in non-FHS group (t=14.518, p<0.001). However, there was no statistical difference in ASA grade, body mass index, nerve distribution of FHS, preoperative and postoperative NRS between the two groups (p>0.05).

Tab. 1. Comparison of general characteristics of patients

	FHS group (n=49)	Non-FHS group (n=132)	*p*-value
Age(years)	61.49±9.53	51.99±8.01	< 0.001
Gender			<0.01
Male	21	73	
Female	28	59	0.607
Premenopausal period	4	10	
perimenopause period	8	22	
Postmenopausal period	16	27	
Body mass index (kg/m^2)	24.3±4.5	23.1±5.5	0.174
ASA			0.139
I	28	79	
II	12	42	
III	9	11	
Duration of disease	35.51±9.51	15.05±7.99	<0.001
right	26	69	0.549
left	23	62	
V1	0	1	0.426
V2	11	35	0.577
V3	12	37	0.634
V1-V2	5	9	0.449
V2-V3	16	39	0.686
V1-V2-V3	4	12	0.921
preoperative-NRS (months)	6.08±0.89	5.86±1.12	0.221
postoperative-NRS (months)	1.15±0.25	1.27±0.47	0.091

FHS, facial herpes simplex; ASA, American Society of Anesthesiologists; NRS, Numeric Rating Scale

Tab. 2. Comparison of surgical data

	FHS group (n=49)	Non-FHS group (n=132)	*p*-value
surgical duration (minutes)	31.72±5.88	30.55±6.35	0.263
The time of balloon dilation for the treatment (seconds)	152.35±32.84	156.10±33.48	0.502
contrast agent's dose (ml)	0.58±0.16	0.62±0.15	0.119
the time of mechanical ventilation (minutes)	49.99±5.02	48.86±4.78	0.165

FHS, facial herpes simplex

Tab. 3. Comparison of Laboratory tests

	FHS group (n=49)	Non-FHS group (n=132)	*p*-value
White blood cell count, $\times10^9$/L	5.48(3.43-8.50)	5.35(3.21-9.45)	0.202
Neutrophils count, $\times10^9$/L	4.13(3.13-5.70)	3.91(2.33-5.66)	0.858
Lymphocyte count, $\times10^9$/L	2.01(1.1-3.2)	2.44(1.16-2.75)	0.921
$CD8^+$T cells count, $\times10^6$/L	184(106-879)	667(320-1250)	<0.001
$CD4^+$T cells count, $\times10^6$/L	778(550-1440)	832(458-1559)	0.332
TNF-α(pg/ml)	40.32±8.28	38.08±8.45	0.114
IL-6(pg/ml)	27.36±4.93	26.65±5.25	0.416

FHS, facial herpes simplex

Comparison of surgical data

As shown in Table 2, surgical data were compared between FHS group and non-FHS group, including surgical duration, the time of balloon dilation during the treatment, contrast agent's dose, and the time of mechanical ventilation. There was no statistical difference in all surgical data between the two groups ($p>0.05$).

Comparison of Laboratory findings

As shown in Table 3, laboratory tests postoperative were compared between FHS group and non-FHS group, $CD8^+$T cells count in FHS group was significantly more than that in non-FHS group (Mann-Whitney U test, $Z=-5.172$, $p<0.001$). Nevertheless, there was no statistical difference in white blood cell count, neutrophils count, lymphocyte count, $CD4^+$T cells count, and TNF-α and IL-6 levels between the two groups ($p>0.05$).

Hospital stays and Hospitalization expenses

As shown in Table 4, hospital stays in FHS group were 10 (5-13) days, and in non-FHS group were 6 (4–12) days. There was significant statistical difference between the two groups (Mann-Whitney U test, $Z=10.26$, $p<0.001$). In addition, hospitalization expenses in FHS group were significantly more expensive than that in non-FHS group ($p<0.001$).

Logistic regression analysis

As shown in Table 5, 181 patients were included in the retrospective analysis. Overall, 19 variables with a P value less than 0.05 in univariable analysis were included in the multivariable model to identify risk factors associated with facial herpes simplex. The results indicated that gender (male/female) ($p<0.01$, OR 0.061, 95% CI 0.009~0.428), age ($p<0.001$, OR 1.196, 95% CI 1.065~1.283), duration of disease ($p<0.001$, OR 1.361, 95% CI 1.206~1.535) and CD8+T cells count ($p<0.01$, OR 0.993, 95% CI 0.989~0.998) were independent risk factors associated with the occurrence of FHS in patients with TN after PMC.

DISCUSSION

This study shows that FHS development rate is 27.07% in TN patients after PMC, the incidence of facial numbness and masseter weakness were higher than that in non-FHS group. Our study has demonstrated that possible risk factors of the development of FHS in TN patients after PMC including female, age, long disease duration and decline of $CD8^+$T cells count lymphocytes. Meanwhile, this complication may lead to a measurable increase in hospitalization costs and average hospital stays.

HSV-1 has infected up to 80% of people worldwide (Sisignano *et al.* 2019; Srivastava *et al.* 2017), which establishes a lifelong latent infection in host cells, including sensory neurons of the human (Thompson *et al.* 2009). It's reported that HSV-1 may reactivate in nearly 12% infected people, which more than twice a year (Forbes *et al.* 2019). A previous study has demonstrated that HSV-1 may hide in the trigeminal ganglion after the initial infection (Cohen *et al.* 2018). Direct mechanical injury, insignificant and short-lasting

Tab. 4. Hospital stays and Hospitalization expenses

	FHS group (n=49)	Non-FHS group (n=132)	*p*-value
Hospital stays (days)	11 (9-13)	7 (4-9)	<0.001
Hospitalization expenses (yuan)	31134 (29473-32680)	28056 (26874-29246)	<0.001

FHS, facial herpes simplex

Tab. 5. Logistic regression analysis

	B	S.E	Wald	*p*-value	OR	95%CI
Gender (male/female)	-2.806	0.998	7.899	<0.01	0.061	0.009~0.428
Age	0.156	0.048	10.760	<0.01	1.169	1.065~1.283
Duration of disease	0.308	0.061	25.103	<0.001	1.361	1.206~1.535
$CD8^+$T cells count, $\times 10^6$/L	-0.007	0.002	9.197	<0.01	0.993	0.989~0.998

B, regression coefficient; S.E, standard error; OR, odds ratio; CI, confidence interval

noxious stimuli could be an inducting factor for the reactivation of herpes simplex virus in trigeminal ganglia (Lu *et al.* 2019). PMC and MVD are performed as the main treatment of TN, PMC may lead a direct mechanical injury which could increase rates of postoperative HSV-1 reactivation on trigeminal ganglion neurons (Shi *et al.* 2020). Tenser suggested that HSV reactivation is a surrogate marker of ganglion neuron injury and is not important for surgical treatment efficacy (Tenser, 2015).

Most patients presented with clustered vesicles appearing at the mucosal junction of the mouth, nostril, and eyelid, however, the pathophysiological mechanism is not clear and completely understood eventuality. Advanced age is known to be an important factor in postoperative infection and reactivation of latent virus. Cell mediated immunity plays an important role in antiviral defense, generally, elderly patients have low immune function, which leads to the low levels of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$T cells (Bektas *et al.* 2019). In our study we found that TN patients with decreased of $CD8^+$T cells count lymphocytes was an independent risk factor of reactivation of latent HSV-1 after PMC. $CD8^+$T cells have been reported to prevent virus reactivation from latently infected trigeminal ganglion and to be responsible for inhibition and clearance of HSV-1 infection (Roy *et al.* 2019). Based on the statistics, the incidence of TN in females is approximately 2 times than males (Katusic *et al.* 1990). Moreover, several studies revealed more sensitivity at serologic testing in HSV-1 among females than males, this may be a reason to explain the higher incidence in women with FHS after PMC (Fatahzadeh & Schwartz, 2007; McIver *et al.* 2009). Although the hormone changes of premenopausal and perimenopausal women may affect the immune response (Fatahzadeh & Schwartz, 2007; McIver *et al.* 2009), our female subject's categorization that developed FHS was no different between premenopausal and postmenopausal.

In our study, duration of disease in the FHS group were significantly longer than that in the non-FHS group. TN patients with long disease duration may have some underlying psychological distress, particularly anxiety and depression, which may lead to the decline of the body's immunity (Chojnacka-Szawłowska *et al.* 2019; Ray *et al.* 2017). Depression and anxiety are frequently observed in patients with other chronic pain, which may lead to endocrine and immune system disorders (Lopez *et al.* 2018). Thus, we speculate that the main reason for HSV-1 reactivation after PMC is emotional disorder. However, this study lacked the psychological state assessment data complete data in some TN patients. Thus, we cannot directly get the conclusion that the long course of disease accompanied by emotional disorder leads to the reactivation of HSV-1.

Our study analyzed risk factors for HSV-1 reactivation after PMC in TN patients. However, this study was a retrospective cohort study, which relied on the accurate medical records, some potential important laboratory and clinical data were missing. Additionally, we have not conducted a case-control study on patients with microvascular decompression, radiofrequency, and other surgical methods. Besides, our current study had certain limitations. We only included Chinese adults living in Sichuan Province, these cases may be not consistent with other populations. At present, we lack of diagnostic definition of secondary facial herpes simplex after PMC, and the accuracy of inclusion criteria and exclusion criteria is still uncertain. At the same time, we need more clinical evidence to verify the contribution of emotional disorders and $CD8^+$T cells count in the occurrence of the disease.

CONCLUSION

The risk factors of the development of facial herpes simplex after PMC operation include age, female, long course of disease and decreased of $CD8^+$T cells count.

Thus, we anticipate some effective methods to prevent and reduce the occurrence of facial herpes simplex such as improving the patient's immunity or prophylactic use of antiviral therapy after operation, which could shorten the hospitalization time of patients, and reduce the medical burden of patients.

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AUTHORS' CONTRIBUTIONS

Aimin Zhang and Hongwei Zhang conceived the ideas. Aimin Zhang and Qin Li designed the research. Aimin Zhang, Qin Li, Hengyi Huang and Huaiming Wang collected data. Aimin Zhang analyzed the data and wrote the manuscript. Hongwei Zhang supervised the study. All authors read and approved the final version of the manuscript.

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