A Significant Correlation between Delayed Cure after Microvascular Decompression and Positive Response to Preoperative Anticonvulsant Therapy in Patients with Hemifacial Spasm

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ABSTRACT (150-250 words)

Objective

Although microvascular decompression (MVD) is a reliable treatment for hemifacial spasm (HFS), the postoperative course is varied. We retrospectively analyzed the resolution pattern of the spasm and specified predictors for delayed cure after MVD.

Methods

This study included 114 consecutive patients with typical HFS. All of them were followed-up for at least one year after operation. Patients were divided into three groups depending on the postoperative course: immediate cure, delayed cure, and failure. To identify the predictive factors for delayed cure after MVD, logistic regression analyses were applied using candidate clinical factors, such as duration of symptom, the tendency of the spasm, preoperative medical treatment and offending vessels.

Results

Among the 114 patients, 107 patients were cured. For those cured, 65 patients were classified as immediate cure and 42 patients were classified as delayed cure. Cumulative spasm free rate after one week, one month, and 3 months after MVD were 70%, 88%, and 97%, respectively. No predictive factors between the cured and failure groups were observed. According to multivariate analysis, preoperative anticonvulsant therapy was found to be the sole significant predictive factor for delayed cure after MVD ($p = 0.025$).

Conclusions

A significant correlation between delayed cure and preoperative anticonvulsant therapy was found in our study, which suggests that hyperexcitation of the facial nucleus plays an important role in pathogenesis of delayed cure. Therefore, if a patient demonstrating a positive response to preoperative anticonvulsant therapy showed a persistent spasm after MVD, reoperation should be delayed for at least 3 months after the initial operation.

Key Words: Anticonvulsant therapy, Clonazepam, Delayed cure, Hemifacial spasm, Microvascular decompression

INTRODUCTION

Hemifacial spasm (HFS) is unilateral twitching, tonic spasms, and synkinesis of the mimetic muscles innervated by the seventh cranial nerve. HFS is not life threatening, but it is an annoying disease for patients by limiting normal daily activities. Medical treatment (like anticonvulsants or GABAergic drugs) is generally ineffective and local botulinum neurotoxin A injections commonly wear off in 3-4 months. Microvascular decompression (MVD) of the facial nerve has been well-known as an effective and reliable treatment for HFS, which can achieve marked improvements in the majority of patients, with a cure rate of around 90%.[5, 7, 8, 12, 17] Interestingly, the postoperative course of MVD is variable even though the same surgical procedure is applied. Although the majority of patients become spasm-free immediately, others require a longer period of time after MVD surgery to become spasm-free. In rare instances, complete resolution of HFS takes over a year. Thus, the time when to conclude if the treatment has failed or not, remains unclear.

With regards to reoperation for HFS, Park *et al.* reported surgical outcome of second MVD was the comparable to those of primary MVD, with an acceptable rate of adverse effects, particularly for the patients who had no benefit with the first MVD.[16] In contrast, Barker *et al.* reported the second MVD brought higher risks, such as, failure to relieve spasm, facial palsy and loss of hearing.[1] Thus, how to identify the right candidates for reoperation remains controversial and physicians often have difficulty determining how long to wait before reoperation in patients with persistent spasm.

The aims of this study are to analyze the resolution pattern of the spasm and specify predictors in numerous clinical parameters for delayed cure after MVD. We also propose an appropriate timing of the second MVD for patients with persistent spasm.

METHODS

Patients

This retrospective study was conducted with institutional review board approval from Hokkaido University (015-0028). The study included consecutive 114 patients with typical HFS who were treated at the Hokkaido University Hospital and Teine Keijinkai Medical Center using the same treatment strategies. All of them have been followed up for at least one year after the initial MVD.

Patients are defined as “cured” if they had no spasm without any medication over one year follow-up period. According to the duration between MVD and resolution of spasm, resolution pattern was divided into two groups: “immediate cure” and “delayed cure”. The “immediate cure” is assigned to the group with the complete abolition of spasm on the next day of the operation. The remainder is defined as “delayed cure”. Patients are defined as “failure” if they had remaining spasm based on subjective patient assessments over the one year follow-up period.

We retrospectively analyzed patient’s clinical data and surgical findings. The following clinical data for the 114 patients were examined: age, gender, spasm side, duration of symptom, presence of synkinesis, the tendency of the spasm, associated symptoms, preoperative medical treatment, surgical outcome, offending vessels and any temporary and/or permanent postoperative complications. The tendency of the spasm was categorized into three groups: mild/occasional spasm; moderate/frequent spasm; and severe/continuous spasm. Preoperative medical treatment was divided into four groups: none, anticonvulsant, botulinum toxin injection and both. Patients took anti-epileptic drugs (AEDs) for longer than 3 months were classified into an anticonvulsant group. Regardless of symptom relief, patients ceased AEDs within 3 months because of side effect including drug eruption, fatigue and abnormal blood test were also classified into an anticonvulsant group. Surgical findings were obtained from operative records and videos. The Lateral spread response (LSR) was excluded from **logistic regression** analysis because of defective data. The degree of indentation of the root exit zone (REZ) was subjective and excluded for analysis.

Operative technique

The patient was placed in a lateral position, the head was fixed in a three-pin skull clamp with the neck flexed and the cranial vertex tilted slightly down toward the floor. Before draping, intraoperative neurophysiologic monitors including the auditory brainstem response (ABR) and the LSR were prepared. Paired surface electrodes were placed 5mm apart along the zygomatic branch of the facial nerve and the nerve was electrically stimulated. A normal muscle response was recorded with needle electrodes inserted into the orbicularis oculi muscle and LSRs were recorded by using needle electrodes inserted into the

mentalis muscle. The stimulating current was a 0.1 ms rectangular wave adjusted to supramaximal strength (5-20mA). The ABR was simultaneously monitored to minimize the risk of hearing loss.

A 6 cm-long curvilinear skin incision medial to the posterior margin of the mastoid body was made and the occipital bone opening laid one-third rostral and two-thirds caudal to the inferior nuchal line. Removal of the bone below the bottom turn of the sigmoid sinus facilitated caudal-to-rostral surgical trajectory that was the key element for adequate exposure of the root exit zone (REZ) of the facial nerve. The dura was incised in a C shape and reflected toward the sigmoid sinus. After identifying the spinal root of the accessory nerve in the cerebellomedullary cistern, arachnoid dissection was gradually advanced rostrally using microscissors to approach the cerebellopontine angle (CPA). We noted a triangular space bordered by the glossopharyngeal nerve, the cerebellar flocculus, and the choroid plexus. Dissecting between the flocculus and the glossopharyngeal nerve with lateral retraction of the choroid plexus allowed us to better access the REZ of the facial nerve. Since the hemifacial spasm is mostly caused by vascular compression at the REZ, we tried not to manipulate the vestibulocochlear complex and the distal part of the facial nerve. Only the possibility of distal compression was explored in the initial surgery if there were no apparent conflict vessels at the REZ.

Surgical technique of decompression depends on the size and anatomical configurations of the offending vessels. In order to achieve more secure decompression, we employed several strategies as described in the following paragraph, and often combined multiple techniques. We first attempted to translocate the vessel by wrapping a Teflon tape around it, pulling it up toward the petrosal bone, and fixing the both ends of the tape on the dural surface with fibrin glue. If the method was too difficult to perform, Teflon felt was then inserted as prosthesis between the vessel and the brainstem so as to keep the vessel away from the REZ. When sufficient decompression can be achieved, LSR usually disappears or markedly diminishes. To avoid postoperative hearing loss, ABR was sequentially monitored, and if the latency of the wave V was delayed for more than 1.0 ms, the intradural procedure was temporarily stopped to wait for the recovery.

Statistical analyses

All statistical analyses were carried out using R statistical software version 3.0.3. Continuously variable data, such as age and duration of symptom, were shown with mean values and standard deviations. The mean of continuous variables was compared by Welch t-test and the distribution of categorized data was compared by Pearson’s chi-squared test.

To identify the predictive factors for delayed cure after MVD, logistic regression analyses were applied using candidate clinical factors including patient’s age, gender, spasm side, duration of symptom,

presence of synkinesis, the tendency of the spasm, associated symptoms, preoperative medical treatment and offending vessels. Odds ratio, with confidence intervals (CIs), was calculated for each factor, and then multivariate analysis was performed using the factors for which the P-value was below 0.10. Statistical significance was defined as a p-value less than 0.05.

RESULTS

The demographic characteristics are summarized in Table 1. Among 114 patients, 70 were female and 44 were male, with the mean age of 55.3 years. The preoperative duration of symptoms was 51.1 months (range: 3 months to 30 years). Seventy-eight patients had moderate spasm tendency and high pitch tinnitus was the most frequent associated symptom (12.4%). Preoperative medication with AEDs was given to 47 patients (41.2%) and the mean duration of anticonvulsant medication was 23.4 months. AEDs include carbamazepine, diazepam, clonazepam, and phenytoin. Clonazepam, a benzodiazepine drug having anxiolytic, anticonvulsant, muscle relaxant, and sedative properties is the most common prescription drug. **Patients in the group of anticonvulsant therapy showed varied degrees of symptom improvement, but no patient was spasm free. Seven patients had continued medication for three years or more. Eight patients underwent surgery within one year. The other 30 patients have taken various doses of AEDs during one to three years. Two patients who showed marked symptom relief stopped medication within 3 months due to drug eruption and liver dysfunction**. Preoperative botulinum injection was performed in 18 patients (15.8%). Although the anterior inferior cerebellar artery was the most frequent offending vessel, 24 patients (20.5%) had multiple conflicting vessels.

In our cohort, 107 (93.9%) patients were cured. In the cured group, 65 (60.7%) patients were classified into the immediate cure group and those with delayed cure consisted of 42 patients (39.2%). **In the group of 42 patients with delayed cure, 26 patients were responsive to preoperative medication with AEDs (Table 2).** Cumulative spasm free rate at one week, one month, and 3 months after operation were 70%, 88%, and 97%, respectively. Seven patients with residual spasm over 1 year after operation were classified as failure. Patients in the failure group comprised 3 men and 4 women, with the mean age of 52.3 years and the mean preoperative duration of symptoms of 39 months.

The data analysis of LSR in 34 patients is shown in Table 3. After MVD procedure, the LSR disappeared in 29 patients and persisted in 5 patients. In the LSR-disappearance group, 8 patients showed residual spasm postoperatively. On the other hands, in the LSR-persistence group, three patients showed immediate cure. No statistical significance was found in categorized data by Pearson's chi-squared test (P=0.34).

There was no significant association between surgical outcome (cure or failure) and clinical factors (Table **4**). Two failed patients showing initial improvement and subsequent aggravation of HFS after MVD had excellent results after reoperation. The surgical finding showed a compressive vessel at the distal portion of the facial nerve in one patient and Teflon felt migration in another patient.

The major postoperative complications included permanent hearing loss in three patients (2.6%),

permanent facial palsy (H&B grade II) in one patient (0.9%) and CSF leakage in two patients (1.8%). There was neither death nor ischemic insults in our cohort.

Predictive factors for delayed cure

To identify which clinical factors influenced the delayed cure, we analyzed the cured group using the logistic regression model (Table **5**). According to multivariate analysis, preoperative anticonvulsant therapy was found to be the sole significant predictive factor for delayed cure ($p = 0.025$). There was no association between the duration of preoperative anticonvulsant therapy and pattern of symptom resolution. Although the factor of multiple offending vessels was one of the possible predictive factors based on univariate analysis ($p = 0.066$), no association was found between it and delayed cure in multivariate analysis ($p = 0.12$). The duration of symptom lasting longer than 3 years might be a negative predictor for delayed cure in univariate analysis ($p = 0.049$).

DISCUSSION

Assessment of persistent spasm after MVD

The exact reasons for surgical failure remain unclear. Therefore, the postoperative assessment of persistent HFS becomes a challenging decision regarding whether a repeat MVD should be performed. The percentage of delayed cure in this study (39%) was relatively high and similar to those reported by Shin *et al* (37.4%).[11, 15, 18] Zhong *et al.* stressed that a reoperation should be performed as soon as possible instead of expecting a delayed cure. They didn't observe any delayed cure during the 1 year follow-up period for those with persistent spasm patients.[24] On the other hand, Sindou *et al.* strongly advised to wait 1 year after the initial surgery before making a decision for reoperation, because 13% of their patients with excellent or good outcome had a delayed cure of 3 months to 1 year.[19] Kim *et al.* found the differences in clinical improvement between cured and unsatisfactory groups were not definite during the early follow-up period (post three days and post one month, $p = 0.826$ and $p = 1.00$) based on their statistically significant data.[8] Although some papers showed limited improvement with a high complication rate for preoperative MVD,[1, 10] recent surgical results of late reoperation didn't show significant differences from those undergoing their initial MVDs.[16, 21] Our results showed that cumulative spasm free rate at 3 months after operation was 97%. Taking the recent improvement of repeat MVD outcome into consideration, the surgical outcome should be assessed at least 3 months after the initial operation.

Preoperative anticonvulsant therapy as a predictive factor for delayed cure

In previous reports, factors, such as intraoperative LSR, the pattern of neurovascular compression, the good clinical outcome at 3 months after the operation, and severity of the REZ indentation, have been proposed as prognostic factors for better outcomes.[8, 9, 17] But none was previously found to be significantly different between immediate cure and delayed cure groups.[5, 6] In this extensive investigation, multivariate analysis revealed a significant correlation between preoperative anticonvulsant therapy and delayed cure after MVD. In Japan, prescription of anticonvulsants to HFS patients by neurologist has been very popular prior to botulinum neurotoxin injection or MVD. Almost all enrolled patients in this study have tried AEDs at least once before the study. Therefore, selection bias for the anticonvulsant group would be minimum regardless of a retrospective study.

Ephaptic transmission at the site of vascular compression and hyperexcitation of the facial nucleus might contribute in varying degrees to the HFS in each patient. Although medication for HFS is thought to be ineffective, some patients show obvious symptom improvement by taking AEDs. In these patients, hyperexcitation of the facial nucleus as a cause of HFS might be a larger contributor than those with no

response to AEDs. It would be physiologically logical that the effect of surgical decompression takes over several months to decrease and normalize the firing threshold of hyperexcited facial nucleus.

Pathogenesis of HFS

There has been much debate regarding the clinical usefulness and the cause of the lateral spread response (LSR) whether it is originated from ephaptic transmission or hyperexcitation of the facial nucleus.[13, 14, 22] Many papers have been published describing the prognostic value of the LSR resolution for predicting outcomes of MVD.[4, 6, 9, 17, 23] On the other hand, some papers have indicated that the persistence of intraoperative LSR doesn't necessarily predict a poor long-term outcome of MVD.[3, 20] Many authors have agreed that the pathogenesis of HFS might not have a single cause. If the LSR was caused by ephaptic transmission at the site of vascular compression, it is easily understood that HFS would persist despite complete intraoperative LSR resolution in patients of whom hyperexcitation of the facial nucleus is the main contributor to the genesis of HFS. In our cohort, these phenomena were observed in eight patients.

Recently Zhong *et al.* proposed a new pathogenesis of HFS based on their experimental studies using a HFS model in SD rats.[24] They concluded that the cause of HFS is an ectopic impulse emerging from the compressed facial nerve, which might be triggered by sympathetic endings in the offending arterial wall and delayed cure resulted from incomplete decompression.

A facial corticobulbar motor evoked potentials (FCoMEPs) reported by Fernando *et al.* showed a significant increment of the threshold for eliciting FCoMEP after MVD was completed. A simultaneous recording of LSR and FCoMEPs may add new insights for resolving the confusion surrounding the pathogenesis of HFS.[2]

CONCLUSIONS

In our cohort, 39% of patients were included in the delayed cure group and the cumulative spasm free rate at one week, one month, and 3 months after operation was 70%, 88%, and 97%, respectively. According to multivariate analysis, preoperative anticonvulsant therapy was found to be the sole significant predictive factor for delayed cure. This result strongly suggested that the phenomenon of delayed cure was caused by hyperexcitation of the facial nucleus. Our results showed that the time when to conclude if the treatment has failed or not should be delayed for at least 3 months after the initial surgery, especially in patients with positive response to preoperative anticonvulsant therapy.

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Table 1. Patient Characteristics

Age	(mean)	55.3 yrs. (± 12.7 yrs.)
Gender	Male	44
	Female	70
Side	Left	65
	Right	49
Duration of Symptom	(mean)	51.1 mos. (± 49.1 mos.)
Presence of synkinesis		91 (79.8%)
Tendency	Mild	14 (12.4%)
	Moderate	78 (69.0%)
	Severe	21 (18.6%)
Associated symptoms	Tinnitus	14 (12.4%)
	Hearing disturbance	7 (6.2%)
	Others (vertigo etc.)	8 (7.1 %)
Preoperative treatment	None	40 (35.1 %)
	Anticonvulsant only	47 (41.2%)
	Botox only	18 (15.8%)
	Anticonvulsant and Botox	9 (7.89 %)

Table 2. Preoperative medication and resolution pattern of the spasm

	Anticonvulsant only	None, other pre-op. medication
Immediate cure	19	46
Delayed cure	26	16
Failure	2	5

Table 3. The data analysis of lateral spread response

	Immediate cure	Delayed cure	Failure
Disappearance	20	8	1
Persistence	3	1	1

P=0.34 by qui-square test

Table 4. Association between surgical outcome and clinical factors

		Cure (n = 107)	Failure (n = 7)	P-values
Age		55.5 ±12.9	52.3 ±9.1	0.40*
Gender	Male	41	3	0.81
	Female	66	4	
Side	Left	60	5	0.43
	Right	47	2	
Duration of Symptom		52m ±50m	39m ±29m	0.33*
Presence of Synkinesis	Yes	84 (78.5%)	7 (100%)	0.17
Tendency	Mild	14	0	0.52
	Moderate	72	6	
	Severe	20	1	
Associated symptoms	Yes	28 (26%)	1 (14%)	0.48
Preoperative medication	None	37	3	0.62
	Anticonvulsant	45	2	
	Botulinum injection	16	2	
	Anticonvulsant & Botulinum injection	9	0	
Offending artery	single	85	5	0.61
	multiple	22	2	

*P-values were calculated by Welch's t-test

Table 5. Uni- and multi-variate analysis using logistic regression analysis on resolution pattern of the spasm after Microvascular decompression

		Univariate analysis			Multivariate analysis		
		Odds ratio	**95% CI**	**P value**	**Odds ratio**	**95% CI**	**P value**
Age*		0.99	0.96 – 1.02	0.67	-	-	-
Gender	Male	1.61	0.72 – 3.60	0.24	-	-	-
Side	Right	0.79	0.36 – 1.74	0.56	-	-	-
Duration of symptom	≧ 3 yrs.	0.45	0.20 – 0.99	**0.049**	0.46	0.20 – 1.04	0.065
Associated symptoms	Yes	0.98	0.40 – 2.36	0.97	-	-	-
Preoperative synkinesis	Yes	1.28	0.50 – 3.47	0.62	-	-	-
Tendency	Moderate	1.69	0.51 – 6.62	0.41	-	-	-
	Severe	2.05	0.49 – 9.55	0.34	-	-	-
Preoperative anticonvulsant	Yes	3.00	1.35 – 6.90	**0.008**	2.62	1.14 – 6.19	**0.025**
Preoperative Botox	Yes	1.29	0.51 – 3.20	0.58	-	-	-
Offending artery	Multiple and/or VBA	2.49	0.95 – 6.75	0.066	2.33	0.82 – 6.90	0.12

*Continuous variable

Bold means statistically significant. Multivariate analysis was performed using candidate factors which were P values less than 0.10 on univariate analysis.

Abbreviations: CI; confidence intervals, VBA: vertebro-basilar arteries