The Electrophysiological Study for Hemifacial Spasm

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Introduction

Hemifacial spasm (HFS) is an involuntary and irregular spasm of the facial muscles innervated by the facial nerve that typically progresses in severity an extent over time. The etiology of HFS has been attributed to vascular compression of the facial nerve at the root exit zone (REZ) [1]. This led to the development of surgical treatment called microvascular decompression (MVD) for HFS, and MVD has become established as the most effective treatment for HFS now [2]. Although much progress has been made on the cause and treatment for HFS, there has been a debate about the pathogenesis of HFS despite numerous electrophysiological studies on HFS until now. There are two hypotheses for the underlying mechanism (Fig. 1): (1) as the peripheral nerve mechanism, the compression of the facial nerve by a blood vessel causes an injury of the myelin sheath, facilitating ectopic excitation and ephaptic transmission between individual nerve fiber [3–7]; and (2) as the central mechanism, the hyperexcitability of the facial motor nucleus (FMN), triggered by antidromically propagated discharges, induces a spasm [8–14].

Many researchers have studied to elucidate the pathogenesis of HFS in clinical settings using electrophysiological studies involving the lateral spread response (LSR), blink reflex test, facial F-wave, and transcranial electrical stimulation (TES). Due to the efforts of many researchers, much progress has been made in elucidating the pathogenesis of HFS over the last 40 years. In this article, the previous main researches using each electrophysiological study for HFS will be discussed together.

Electrophysiological Study

Lateral Spread Response (LSR)

Lateral spread response (LSR) is an abnormal electromyographic findings in patients with HFS [3]. The LSR is the response of the muscles innervated by the other facial nerve branches by stimulating of one branch of the facial nerve. So, LSR is the most representative electrophysiological findings of HFS and thus has diagnostic value for HFS. Also, the disappearance of LSR usually occur immediately after identifying the offending vessels and performing sufficient decompression during MVD for HFS [15]. Therefore, LSR has been used not only as the diagnostic tool for HFS but also as an indicator of successful MVD. Until now, many electrophysiological studies using LSR have been conducted to elucidate the pathogenesis of HFS and to ensure sufficient MVD for HFS with the development of intraoperative monitoring. Surprisingly, however, there is still

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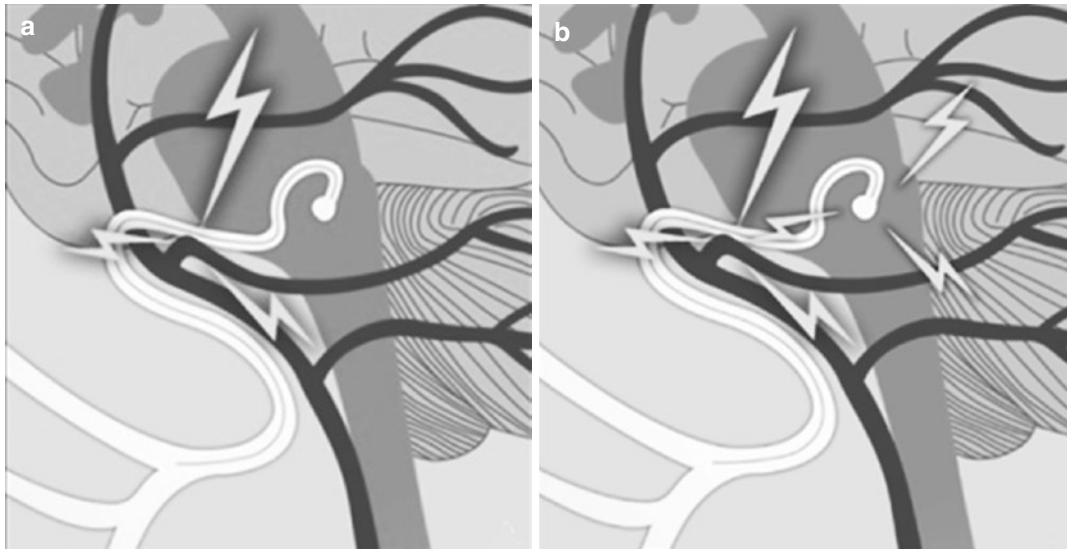

Fig. 1 The pathomegenesis for hemifacial spasm. (**a**) Peripheral ectopic excitation with ephaptic impulse transmission, (**b**) Hyperexcitability of the facial motor nucleus

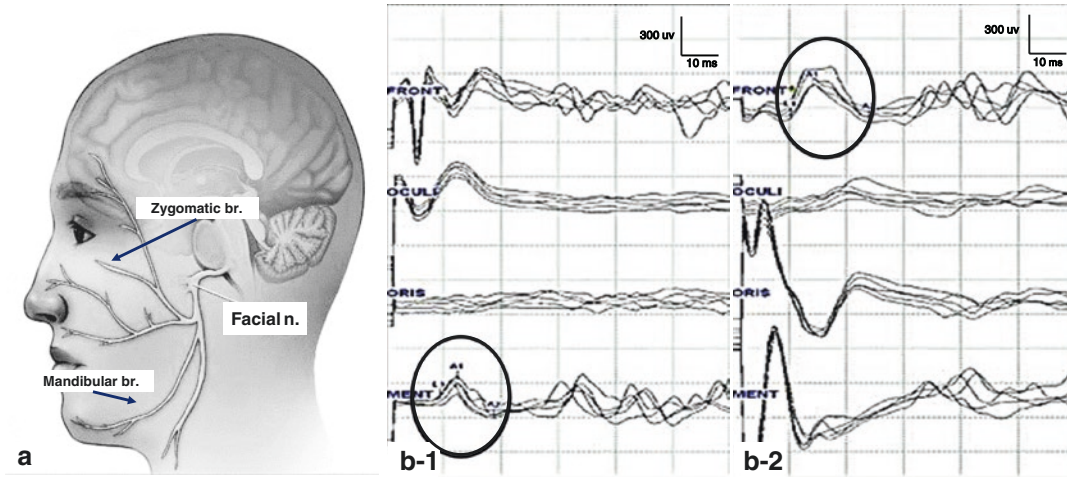

Fig. 2 The lateral spread response (LSR). (**a**) Facial nerve branch. (**b**). (1) LSR from mentalis muscle with stimulation of zygomatic branch of facial nerve. (2) LSR from frontalis muscle with stimulation of mandibular branch of facial nerve

much debate about the origin of the LSR with pathogenesis of HFS.

Methodology

Two types of LSR can be recorded by stimulating the upper and the lower branches of the facial nerve on the symptomatic side of HFS. By stimulating the zygomatic branches of the facial nerve on the symptomatic side, LSR can be recorded from the mentalis muscle. In addition, LSR can be also obtained from the orbicularis oculi muscle or the frontalis muscle by stimulating mandibular branch (Fig. 2). Constant current stimuli are applied for 0.1–0.2 ms with a bar electrode.

Resting motor threshold (rMT) is initially defined as the minimum intensity that could induce the amplitude of LSR of >10 μV in at least five successive trials. After defining the rMT, the LSR can be obtained by stimulating rectangular shock with a suprathreshold strength.

Results and Interpretation

Nielson reported that there was LSR on the symptomatic side of all 62 HFS patients, although there was no LSR on the asymptomatic side of those patients as in the healthy controls [3]. In this study, LSR on mentalis muscle was observed in all 62 patients, and that on the orbicularis oculi muscle in 60 of the 62 patients. The latency of LSR was an average of 9.3 ± 0.13 ms and 9.0 ± 0.13 ms for the orbicularis oculi and the mentalis muscle. Also, the amplitude of LSR was always much smaller about 20–30% than that of the maximal orthodromic response after stimulating the facial nerve. After the previous study, Nielson and Jannetta evaluated LSR for 59 patients with HFS before and after MVD [6]. LSR disappeared in 23% and changed from bidirectional to unidirectional in 45% patients within 1 week after MVD surgery. Within 2–8 months after MVD, LSR was observed in 27%, and unidirectional in 17%. Through these findings, Nielsen insisted that the peripheral mechanism including ephaptic transmission is the main pathogenesis for HFS though the delayed disappearance of LSR after MVD could not exclude the hyperexcitability of FMN as pathogenesis for HFS [4]. To define the origin of LSR in HFS, Møller and Jannetta analyzed the latency of LSR from orbicularis oculi muscle under anesthesia during MVD [10]. After obtaining the latency of the LSR (11.03 ± 0.66 ms) by stimulating the mandibular branch, they simultaneously measured the latency of the response from the facial nerve near the REZ (3.87 ± 0.36 ms). They also measured the latency of the response from the orbicularis oculi muscle by stimulation the facial nerve near the REZ (4.65 ± 0.25 ms). They showed that the latency of the LSR from the orbicularis oculi muscle by stimulating the mandibular branch was larger than the sum of the conduction time from the points of stimulation of the mandibular branch to the REZ of facial nerve and from REZ of the facial nerve to the orbicularis oculi muscle (8.52 ± 0.38 ms) (Fig. 3). Through this difference of the latency, they insisted that the LSR from orbicularis oculi muscle was not a direct result of ephaptic conduction at the site of the lesion, and hyperexcitability of FMN was involved in the synthesis of the LSR. To identify the origin of the LSR, there was the study using double stimulation instead of a

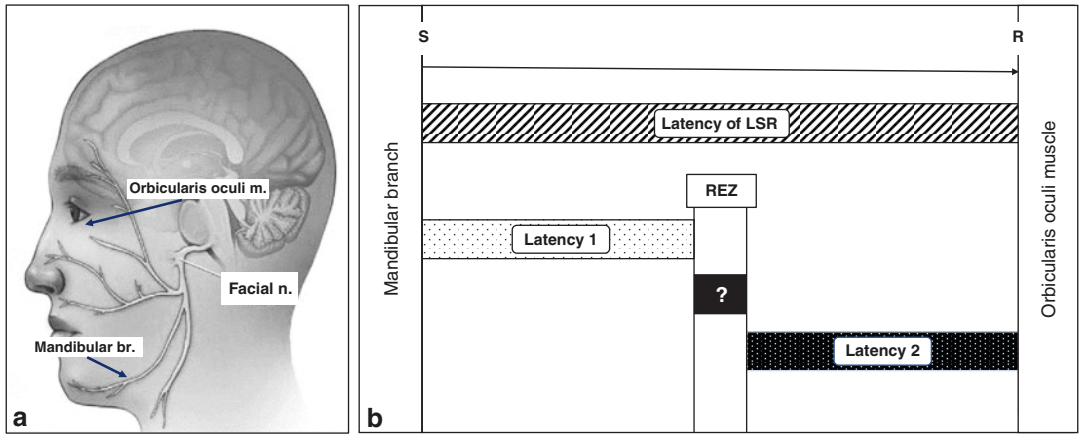

Fig. 3 The results of Møller and Jannetta's study about the origin of lateral spread response (LSR). (**a**) Schematic diagram of LSR method used in this study. The LSR was recorded from orbicularis oculi muscle by stimulating mandibular branch of facial nerve. (**b**) The difference between the actual measured value ant the calculated value of the latency of the LSR. The latency of the LSR from the orbicularis oculi muscle by stimulating the mandibular branch was larger than the sum of the conduction time from the points of stimulation of the mandibular branch to the root exit zone (REZ) of facial nerve and from REZ of the facial nerve to the orbicularis oculi muscle

single stimulus [16]. Yamashita et al. conducted double stimulation at interstimulus intervals (ISIs) ranging from 0.5 to 0.7 ms to evoke the LSR in patients with HFS. By this double stimulation, a total of 15 LSR consisting of two responses (R1 and R2) were obtained. R1 showed a constant latency and amplitude regardless of the ISIs, whereas R2 presented after a fixed refractory period without facilitation or depression in a recovery curve of latency and amplitude. As R2 showed no suppression, they suggested that LSR did not arise from FMN. To elucidate the origin of LSR, there were also studies using the central suppressive effect of anesthetics. Wilkinson et al. defined the changes in amplitude and latency of LSR according to the changes in the concentration of desflurane during MVD in 22 HFS patients [17]. According to their research, the LSR amplitude under 1 MAC desflurane with TIVA was significantly decreased than under TIVA. On the other hand, there was no change on the latency of LSR and on EEG according to the concentration of desflurane.

Blink Reflex Test

The blink reflex is the electrical correlate of the clinically evoked corneal reflex. The blink reflex is a true reflex with a sensory afferent limb, intervening synapses, and a motor efferent. The afferent limb of the blink reflex is mediated by sensory fibers of the supraorbital branch of the ophthalmic division of the trigeminal nerve (cranial nerve V1) and the efferent limb by motor fibers of the facial nerve (cranial nerve VII). Just as the corneal reflex, ipsilateral stimulation of the supraorbital branch of the trigeminal nerve elicits a facial nerve (eye blink) response bilaterally. Stimulation of the ipsilateral supraorbital nerve results in an afferent volley along the trigeminal nerve to both the main sensory nucleus of CN V (mid pons) and the nucleus of the spinal tract of CN V (lower pons and medulla) in the brainstem. Through a series of interneurons in the pons and lateral medulla, the nerve impulse next reaches the ipsilateral and contralateral facial nuclei, from which the efferent signal travels along the facial nerve bilaterally. The blink reflex has two components, an early R1 and late R2 response. The R1 response is only present on the side of stimulation, while the R2 response typically is present bilaterally. The R1 response is thought to represent the disynaptic reflex pathway between the main sensory nucleus of V in the mid pons and the ipsilateral facial nucleus in the lower pontine tegmentum. The R2 responses are mediated by a multisynaptic pathway between the nucleus of the spinal tract of V in the ipsilateral pons and medulla [18]. As mentioned above, because the blink reflex pathway is well known, and the pathway includes the entire facial nerve including FMN, many studies performed blink reflex study to clarify the pathogenesis of HFS.

Methodology

The blink reflex test is basically conducted in the method suggested by Kimura [19]. The cathode of the stimulating electrode is placed at the supraorbital foramen and the anode was placed immediately above (on the forehead), using a bar stimulator. The recording electrodes are placed over the orbicular muscle of both eyes (the mid-lower eyelid and the temple). To avoid stimulation of the nerve during spasm, stimulation was applied when the muscles were electrically at rest. Constant current stimuli of 0.1–0.2 ms in duration were delivered. After defining the threshold that could cause the minimal constant response, a suprathreshold stimulation is applied. To ensure the reproducibility and accurate response, at least five stimuli are applied to each side and then averaged. The latencies of the ipsilateral R1 and R2 responses were defined as the shortest time to the onset of the response. The maximum amplitude and duration of each of R1 and R2 responses were measured.

Results and Interpretation

Nielsen conducted the blink reflex study in 62 patients with HFS [5]. In this study, the latency and amplitude of the R1 response on the symptomatic side were increased as compared with the asymptomatic side and controls ($p < 0.001$). The latency of R1 response on the symptomatic side was increased by 2.1 ms than that of asymptom-

atic side, which was interpreted by focal demyelination over the lesion. Also, all patients showed a synkinetic response in the mental muscle on the symptomatic side, and after-activity and late-activity was observed after the reflex response. Based on these findings, ephaptic/ectopic excitation due to compression and demyelination of the facial nerve was proposed as the primary pathogenesis for HFS [4, 5]. However, Esteban et al. presented other results from the previous study using the blink reflex study. They also measured the values of the blink reflex study in the 53 patients with HFS, and then compared with healthy controls [8]. In this study, the latency of R1 response was not different between groups, and the latency of R2 response was shortened on symptomatic side in HFS patients unlike the results of Nielsen's study. Also, the duration of R2 response was greater on the HFS side when compared with those of asymptomatic side and healthy controls. So, they insisted that the hyperexcitability of FMN was the main pathogenesis for HFS. In performing the blink reflex study for HFS patients, Eekhof et al. showed findings different from the previous studies. In this study, the latency and amplitude of R1 and R2 responses from orbicularis oculi muscle present no significant difference between the HFS patients and healthy controls. However, both R1 and R2 response from the orbicularis oris muscle occurred significantly more often on the symptomatic side in HFS patients, and showed higher amplitude significantly compared to healthy controls [20]. Valls-Sole et al. studied blink reflex response in patients with HFS by applying double stimulation as well as single stimulation [21]. By applying single stimulation, the area of R1 and R2 responses was greater on the symptomatic side in patients with HFS as compared with the asymptomatic side and normal controls. Also, with double stimulation, the inhibitory effect of the conditioning stimuli upon the test stimuli R2 response, which was always observed in healthy controls, was significantly less pronounced at short ISIs in HFS. They reported that this enhanced recovery curve of R2 response was attributed to enhanced excitability of FMN in HFS. Møller and Jannetta conducted the blink reflex study under anesthesia using inhalational anesthetics (isoflurane and nitrous oxide) during MVD [22]. In this study, the R1 response on asymptomatic side was not evoked under anesthesia; however, the R1 response could be observed on the symptomatic side of HFS patients under anesthesia. Also, this R1 response of the symptomatic side was abolished after MVD. Through these findings under anesthesia, they insisted the hyperexcitability of FMN as the main mechanism for HFS.

F-Wave

F-wave is an antidromic pulse that propagates to an alpha motorneuron in the anterior horn cell of the spinal cord and then returns orthodromically down the same axon. So, the F-wave circuitry, both afferent and efferent, is pure motor. There is no synapse, so it is not a true reflex. In the extremities, F-waves have been considered as index of the excitability of anterior horn cell, and have been used as good reflection of lower motoneuron excitability. In the facial muscles, F-waves are also measurable, and those can be used for evaluation of the excitability of the facial motor nucleus. Therefore, there were many studies using facial F-waves to define the pathogenesis of HFS.

Methodology

Though facial F-waves could be obtained from orbicular oculi or the mentalis muscle by stimulating zygomatic branch or mandibular branch of the facial nerve, obtaining them from the mentalis muscle as long as possible by stimulating at the distal marginal mandibular branch is usually recommended to prevent an overlap between M-waves and F-waves. As the amplitude of facial F-wave is relatively small, it is necessary to perform the examination after the spasm has completely disappeared. After obtaining a flat baseline, stimulation was applied at the border or the mandible that was 10 cm from the stylomastoid foramen. Stimulation was performed with a bar electrode and was repeated 10–20 times using

a 0.2 ms square wave at the frequency of 1 Hz. The stimulation intensity was set to supramaximum. When a facial F-wave had a distinct peak and amplitude above 30 μV, it was regarded as F-wave. The parameters that can be analyzed using facial F-waves are as follows [9]: F/M amplitude ratio (the percentage of the peak to peak amplitude of the F-waves to the M-waves), total duration (from the initial deflection from the baseline to the final return of the F-wave), F-wave frequency (the percentage of 10–20 stimuli that produced F-waves with a distinct peak and amplitude above 30 μV), minimum latency (from the onset of the stimulus artifact to the first deflection of the F-wave from the baseline), and F chronodispersion (the difference between minimal and maximal latencies of the F-wave in a series of 10–20 waves).

Result and Interpretation

Ishikawa et al. obtained facial F-wave from the mentalis muscle by stimulating distal mandibular branch in 20 patients with HFS before MVD, and 10 HFS patients after MVD and 10 healthy controls [9]. In their study, F-wave duration F/M amplitude and frequency of F-wave on the symptomatic side of HFS patients were significantly increased when compared with asymptomatic side of HFS patients and health controls before MVD. On the other hand, there was no difference in minimum latency and chronodispersion between groups. They also showed that the enhancement of the facial F-wave eventually decreased at the same time as disappearance with LSR after MVD surgery. In another study, they compared facial F-waves from mentalis muscle and LSR from orbicularis oculi muscle by stimulating the marginal mandibular branch to investigate the origin of LSR in 10 HFS patients [23]. In this study, the LSR showed an afterdischarge after a constant response, and the afterdischarge of LSR with the facial F-wave duration tended to increase on symptomatic side of patients. Also, a lineal correlation between the facial F-wave duration and the afterdischarge duration was observed. (r^2 = 0.961, $p < 0.0001$). So, they insisted that facial F-waves and the LSR would have the same origin. Hai et al. measured LSR and facial F-waves like the previous study after creating an HFS animal model in 10 rabbits [24]. This study also presented that linear correlations between the amplitude ratio of LSR/M-waves and F-waves/M-waves and between the duration of LSR and F-waves. They reported that the peripheral mechanism including ephaptic transmission could not alone explain the increase of facial F-wave duration in HFS as the transmission time of the ephapses between nerve fiber is below 100–200 μs [25]. In another study, Ishikawa et al. conducted facial F-wave study with blink reflexes and LSR before and after MVD in 20 patients with HFS [26]. In this study, the facial F-wave and blink reflex on symptomatic side showed increased values than those of the asymptomatic side before MVD, and facial F-waves and LSR were still recorded in some patients within 1 month after the HFS had disappeared completely. Through these findings, they suggested that hyperexcitability of FMN would be the main cause of HFS.

Transcranial Facial Motor Evoked Potential (TcFMEP)

Transcranial facial motor evoked potentials (TcMEPs) are one of the most powerful tools in the intraoperative monitoring to monitor motor function, particularly for spine surgery. TcMEP are obtained by stimulating the motor pathways rostral to the site surgery. Activation of the motor pathways can be measured by recording waveforms as the impulse descends along the corticobulbar tract and corticospinal tract.

Like the blink reflex, the TcFMEP study can be a tool for examining the complete efferent pathway of the facial nerve.

Methodology

TcFMEPs from the facial muscles are elicited by using transcranial anodal electrical stimulation. Electrodes are placed on the scalp over C3 and C4 according to the international 10–20

system bilaterally. Stimulation electrodes are typically subdermal needle electrodes or corkscrew electrodes. Stimuli are applied as single shocks with a pulse width of 150–200 μs and a voltage range of 90–305 V. For the recording, subdermal needles are placed in pairs in orbicularis oculi, orbicularis oris, and mentalis muscles. Though most types of stimulation in clinical neurophysiology are cathodal, anodal stimulation in TcMEP is more effective, because the cell body and axon hillock, the sites of stimulation for TES, are more sensitive to anodal stimulation. In using TcFMEP, the TcFMEP must be excluded from analysis if the onset latency of TcFMEP is shorter than 10 ms, because they can be thought to be contaminated by direct current spread to the extracranial facial nerve [27]. By using the TcFMEP study, the threshold for FMEP as well as the latency and amplitude of FMEP is usually analyzed. The threshold of FMEP is defined as the minimum voltage required to elicit an FMEP of ≥30 μV in at least 50% of a minimum of several consecutive stimulation trials.

Result and Interpretation

Though not commonly performed, some have proposed that the myogenic facial motor evoked potentials elicited via transcranial electrical stimulation can be used to monitor the functional integrity of the corticobulbar tract, facial motor nucleus, and facial nerve during MVD surgery. Kaufmann et al. measured FMEP with LSR during MVD in 10 HFS patients and conducted FMEP study during MVD for 17 patients with trigeminal neuralgia (TN) [13]. They analyzed latency, amplitude, and duration of the FMEP before and after MVD. They suggested that the amplitude and durations of FMEP significantly decreased on the symptomatic side of HFS patients after MVD, whereas these changes were not observed from the asymptomatic side of HFS patients or TN patients. Also, they presented a dramatic reduction in amplitude and duration of FMEP with disappearance of LSR when decompression of the offending vessel. Otherwise the latency of FMEP revealed no significant change before and after MVD. In other study, they analyzed retrospectively the threshold of FMEP and the incidence of FMEP to the single pule TcMEP during surgery in 65 patients with HFS and 29 patients with skull base tumors [28]. In the study, the threshold of FMEP is significantly lower in HFS compared to skull base tumor patients. Also, FMEP to the single pulse stimulation were observed in 87% of HFS patients, whereas only 10% in patients with skull base tumor showed FMEP response to single pulse stimulation. Recently, Kaufmann et al. prospectively compared FMEP under total intravenous anesthesia (TIVA) with or without desflurane during MVD for HFS patients to define the hyperexcitability of FMN in HFS [14]. As inhalational anesthetics such as desflurane are well known for their suppressive effects on the level of the alpha motor neuron, they expected that there would be a difference in effect of desflurane on FMEP from symptomatic and asymptomatic side of HFS patients. By this study, they suggested that the suppressive effects of desflurane were less on the symptomatic side than on the asymptomatic side (59% vs. 79%, $p = 0.03$), although desflurane (1 minimum alveolar concentration) suppressed FMEPs on both sides. While showing that M-waves recorded from the mentalis muscle remained unchanged together, they also demonstrated that desflurane had no effect on the peripheral facial nerve or neuromuscular junction. Through such a series of research using TcFMEP, they suggested that the hyperexcitability of FMN might be the main pathogenesis for HFS.

Conclusion

There has been a long debate on the main pathogenesis of HFS: ephaptic transmission/ectopic excitation between individual nerve fiber vs. the Hyperexcitability of the FMN. To elucidate the pathogenesis of HFS, many electrophysiological studies have been conducted, including LSR, blink reflex test, facial F-wave, and TcMEP, so far (Table 1). Much progress about the pathogenesis for HFS has been made due to accumulation of knowledge and development of research meth-

Table 1 The summary of the main electrophysiological studies for hemifacial spasm

Researchers	Year	Subjects	The main findings	The pathogenesis[a]
Lateral spread response				
Nielson	1984	62 HFS, 14 TN	LSR was recorded on symptomatic side in all patients with HFS. Also, after-activity and late-activity were recorded on symptomatic side in HFS patients	Peripheral
Nielsen and Jannetta	1984	59 HFS	After MVD, LSR disappeared in 23% and changed from bidirectional to unidirectional in 45% patients in 1 week	Peripheral
Møller and Jannetta	1984	7 HFS	The latency of the LSR from the orbicularis oculi muscle by stimulating the mandibular branch was larger than the sum of the conduction time from the points of stimulation of the mandibular branch to the REZ of facial nerve and from REZ of the facial nerve to the orbicularis oculi muscle	Central
Yamashita et al.	2002	12 HFS	By using double stimulation, the second LSR presented after a fixed refractory period without facilitation or depression in a recovery curve of latency and amplitude regardless of the inter-stimulus intervals	Peripheral
Wilkinson et al.	2014	22 HFS	During MVD for HFS, desflurane with TIVA significantly decreased only LSR amplitude, not LSR latency than under TIVA	Central
Blink reflex test				
Nielson	1984	62 HFS	The latency and amplitude of the R1 response on symptomatic side were increased as compared with the asymptomatic side and controls	Peripheral
Esteban and Molina-Negro	1986	53 HFS, 20 HC	The latency of R2 response was shortened and the duration of R2 response was greater on symptomatic side in HFS	Central
Møller and Jannetta	1986	4 HFS	Under anesthesia using inhalational anesthetics, the R1 response was observed only on the symptomatic side of HFS patients	Central
Valls-Sole and Tolosa	1989	17 HFS	With double stimulation, the inhibitory effect of the conditioning stimuli upon the test stimuli R2 response was significantly less pronounced at short ISIs in HFS patients	Central
Eekhof et al.	2000	23 HFS, 10 PFPS, 22 HC	Both R1 and R2 response from the orbicularis oris muscle occurred significantly more often on the symptomatic side in HFS patients than HC	Central
Facial F-wave				
Ishikawa et al.	1996	20 HFS, 10 HC	On symptomatic side of HFS, F-wave duration, F/M amplitude ration, and frequency of F-wave significantly increased. However, minimum latency and chronodispersion had no difference between groups	Central
Ishikawa et al.	1996	10 HFS	On symptomatic side of HFS, the facial F-wave duration tended to increase, and a lineal correlation between the facial F-wave duration and the afterdischarge duration of LSR was observed	Central
Ishikawa et al.	1997	20 HFS	F-waves and LSR were still recorded in some patients after the HFS had disappeared completely, and then F-waves and LSR disappeared subsequently	Central
Hai and Pan	2007	10 HFS rabbits	There was a linear correlation between the amplitude ratio of LSR/M-waves and F-waves/M-waves and between the duration of LSR and F-waves	Central
Transcranial facial motor evoked potential				
Wilkinson and Kaufmann	2005	10 HFS, 17 TN	The amplitude and durations of Facial MEP significantly decreased on the symptomatic side of HFS patients after MVD. However, the latency of Facial MEP revealed no significant change before and after MVD	Central

Table 1 (continued)

Researchers	Year	Subjects	The main findings	The pathogenesis[a]
Wilkinson and Kaufmann	2014	65 HFS, 29 skull base tumors	The threshold of Facial MEP are significantly lower in HFS compared to skull base tumor patients. Also, FMEP to the single pulse stimulation were observed in 87% of HFS patients and only 10% in patients with skull base tumor	Central
Wilkinson et al.	2016	31 HFS	A significantly lower threshold of facial MEPs on the symptomatic side. Under desflurane during MVD, more less suppressive effects on facial MEPs of the symptomatic side	Central

HFS Hemifacial spasm, *TN* Trigeminal neuralgia, *PFPS* Post-facial palsy synkinesis, *HC* Healthy control, *MVD* Microvascular decompression, *LSR* Lateral spread response, *MEP* Motor-evoked potential
[a]Pathogenesis that the results of the studies favor more between the peripheral mechanism and the central mechanism

ods. Taken all the previous studies together, the hyperexcitability of the FMN is thought as the main pathogenesis of HFS.

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