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Asymmetric gelastic seizure as a lateralizing sign in patients with hypothalamic hamartoma☆

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ABSTRACT

Gelastic seizure (GS) is a cardinal symptom of hypothalamic hamartoma (HH), which is intractable but surgically remediable. Although facial asymmetry with GS has not been extensively discussed, asymmetric GS has been frequently recognized in our large series. We hypothesized that asymmetric GS represents a lateralizing sign caused by the epileptic propagation from the attachment of the HH. To examine this hypothesis, the positive predictive value (PPV) and diagnostic odds ratio (DOR) of asymmetric GS were validated to predict the side of HH attachment. In 103 cases registered to the present analysis, asymmetric GS was recognized in 71 patients and symmetric GS in 32. Asymmetric GS with a lopsided grimace was exclusively observed on the side contralateral to unilateral HH in 39 patients and to the dominant attachment of 23 HHs with bilateral attachment (true positive, n = 62). In contrast, asymmetric GS was exhibited independently on both sides in 4 patients with bilaterally attached HH and on the side ipsilateral to the dominant attachment in the other 4. Symmetric HH attachments were identified in 1 patient (false negative, n = 9). Asymmetric GS was a reliable lateralizing sign with high DOR (6.08) and PPV (78%) to predict the side of epileptic propagation. Furthermore, the present study demonstrated the probability of seizure propagation from bilateral attachment, and this evidence provides a new rationale to the surgical strategy of bilateral disconnection for HH with bilateral attachment.

1. Introduction

Gelastic seizure (GS) is a rare epileptic seizure and a cardinal symptom in patients with hypothalamic hamartoma (HH), which is intractable but surgically remediable [1–3]. The excellent surgical strategy of stereotactic radiofrequency thermocoagulation (SRT) was developed as a feasible procedure with minimal invasiveness and high effectiveness against all forms of HH [1–3]. Hypothalamic hamartoma shows intrinsic ictogenesis [1–7]. Neural networks involving the hypothalamus and mediodorsal nucleus of the thalamus (MD) are suggested to be partly responsible for the clinical symptoms of GS [7]. This is the rationale behind the concept of disconnection surgeries such as SRT for HH to achieve seizure control [1–3,7].

Gelastic seizure usually presents with a symmetric facial expression of a smile or laughter. Facial asymmetry in GS has not been discussed extensively for HH cases. However, the asymmetric facial expression of GS has been reported as a part of the semiology in a large series of patients with HH [2]. Because asymmetric GS was exclusively exhibited on the side contralateral to the attachment in cases of unilateral HH, unilateral hemispheric propagation from HH attachment seems plausible. We hypothesized that asymmetric GS represented a new lateralizing sign, caused by epileptic propagation. The approach side for SRT is usually determined based on the side of unilateral HH or of the dominant attachment in those cases of HH showing bilateral attachment [1–3] to avoid simultaneous involvement of bilateral hypothalamus. In cases of HH with bilateral attachment, additional information comprising lateralizing findings of semiology, electroencephalogram (EEG), or single-photon emission computed tomography (SPECT) is necessary [1–3]. However, hemispheric information from EEG and SPECT is limited in HH patients because HH shows a subcortical epileptogenesis [1,7–9].

To examine this hypothesis, the present study sought to validate the positive predictive value (PPV) and diagnostic odds ratio (DOR) of asymmetric GS as a new lateralizing sign of seizure propagation to the

Abbreviations: ACC, anterior cingulate cortex; DOR, diagnostic odds ratio; EEG, electroencephalogram; FLAIR, fluid-attenuated inversion recovery; GS, gelastic seizure; HH, hypothalamic hamartoma; MD, mediodorsal nucleus of the thalamus; MRI, magnetic resonance imaging; PPV, positive predictive value; SISCOM, subtraction ictal SPECT coregistered to MRI; SMA, supplementary motor area; SPECT, single-photon emission computed tomography; SRT, stereotactic radiofrequency thermocoagulation; STIR, short-T1 inversion recovery.

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unilateral hemisphere and to discuss the pathophysiological mechanisms contributing to this semiology.

2. Patients and methods

2.1. Patient profiles

A total of 121 consecutive patients (71 males, 50 females) who underwent SRT for HH between March 2011 and August 2015 were retrospectively reviewed. Age at surgery ranged from 1.7 to 50 years (median, 7 years). Two patients without GS were excluded, including one patient who had only dacrystic seizures and another with only other types of seizure. Written informed consent was provided before conducting preoperative evaluations and undertaking surgery.

2.2. Seizure semiology

To confirm seizure semiology, two coauthors independently evaluated the data from video-EEG monitoring. The laterality of facial expression during GS was carefully analyzed to confirm asymmetric GS. The duration of asymmetric GS was not measured. Hemifacial smiling or laughing with a lopsided grimace was defined as asymmetric GS, with all other cases defined as symmetric GS.

2.3. Magnetic resonance imaging

Axial, coronal, and sagittal images were routinely examined using a 1.5-T MRI system (Signa HDx; GE Healthcare, Boston, CT). T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and short-T1 inversion recovery (STIR) sequences were used. Three-dimensional (3D) MRI was used to analyze the laterality of the attachment. Hypothalamic hamartoma findings on coronal MRI were simply classified into 3 subtypes using previously reported criteria [1,2]: intrahypothalamic type, parahypothalamic type, and mixed hypothalamic type with uni- or bilateral attachment. Maximum diameter of the HH in any dimension was measured. To determine the laterality of HH attachment as a predicted condition, dominance in bilateral attachments, vertical length, highest position, or anteroposterior length of the attachment in the third ventricle were evaluated on each MRI section.

2.4. Ictal EEG and SPECT studies

Ictal EEG was evaluated by reviewing the long-term video-EEG monitoring by two coauthors independently. The sides of focal or lateralized epileptiform discharges were identified to compare with the side of asymmetric GS. Lateralized findings of ictal EEG were judged as a predicted condition.

To evaluate intrinsic hyperperfusion in the HH attachment and focal hyperperfusion related with hemispheric propagation, subtraction ictal SPECT coregistered to MRI (SISCOM) was analyzed according to previously reported methods [1,7] after ictal and interictal SPECT studies using ^{99m}Tc-ethylcysteinate dimer. Lateralized findings from SISCOM were defined as a predicted condition.

2.5. Interictal EEG

Findings of focal, hemispheric, or generalized epileptiform discharges in interictal EEGs were analyzed by two coauthors to evaluate hemispheric irritability. Lateralized findings of interictal EEG were judged as a predicted condition.

2.6. SRT

Our surgical strategies for SRT have been reported previously [1–3]. The approach side for SRT was usually determined based on the laterality of HH attachment. If bilateral attachment of HH was almost symmetric, then asymmetric GS and the lateralized findings of SISCOM were also considered to decide the approach side.

2.7. Predictive values

According to our hypothesis, asymmetric GS was defined as a positive condition and symmetric GS as a negative condition. In terms of the correlation between GS and HH attachment, cases of asymmetric GS on the side contralateral to unilateral HH and to the dominant HH attachment on MRI were defined as a positive predicted condition (true positive). Otherwise, cases of asymmetric GS on both sides and on the side ipsilateral to the dominant attachment, or having symmetric HH attachments were defined as a negative predicted condition (false negative). In cases of symmetric GS, unilateral HH was defined as a negative predicted condition (true negative) whereas HH with bilateral attachment was defined as a positive predicted condition (false positive). The PPV and DOR of asymmetric GS were calculated by a two-by-two contingency table.

In addition, the lateralized findings of EEG and SISCOM were defined as a predicted condition between the two groups of asymmetric and symmetric GS under the premise that asymmetric GS was a lateralizing sign. The PPV and DOR of asymmetric GS in comparison with respective lateralized findings were calculated by the respective two-by-two contingency tables.

3. Results

3.1. Seizure semiology and asymmetric GS

In 119 patients (70 males, 49 females) with GS, ictal facial expression was not confirmed in video files of 16 patients, who were not registered for the present analysis. Asymmetric GS was confirmed in 71 patients, with 31 exhibiting GS on the left side, 36 on the right side, and the other 4 independently on both sides. In contrast, symmetric GS was identified in 32 patients.

3.2. Classification of HH

Unilateral attachment was seen for 53 HHs (left-sided, $n = 26$; right-sided, $n = 27$) and bilateral attachment for 50 HHs. Hypothalamic hamartoma had a median maximum diameter of 15 mm (range, 5–80 mm). Subtypes of HH included intrahypothalamic type ($n = 27$), parahypothalamic type ($n = 3$), and mixed hypothalamic type with unilateral attachment ($n = 23$) and bilateral attachment ($n = 50$). Dominance in bilateral attachment was judged as the left side in 24 HHs and the right side in 24 HHs. Symmetric attachments were identified in 2 HHs. Maximum diameters and subtypes of HHs did not differ significantly between groups of asymmetric and symmetric GS.

3.3. Correlation between asymmetric GS and HH attachment

Asymmetric GS was exclusively exhibited on the side contralateral to the unilateral attachment in 38 HHs and to the side of dominant attachment in 24 HHs with bilateral attachment (true positive, $n = 62$). Asymmetric GS is illustrated in three representative cases (Fig. 1). On the other hand, asymmetric GS was exhibited independently on both sides of bilateral attachment in 4 patients and on the side ipsilateral to the dominant attachment in 4 patients. These lines of evidence demonstrated a probability of bilateral seizure propagation through bilateral attachments. The remaining 1 patient had symmetric HH attachments (false negative, $n = 9$). In 32 patients with symmetric GS, there were 15 patients with unilateral HH (true negative) and 17 with bilateral attachment of HH (false positive). The PPV and DOR of asymmetric GS for the side of HH attachment were calculated as 78% and 6.08 (95% confidence interval: 2.27 to 16.28; significance level: $p = 0.0003$), respectively.

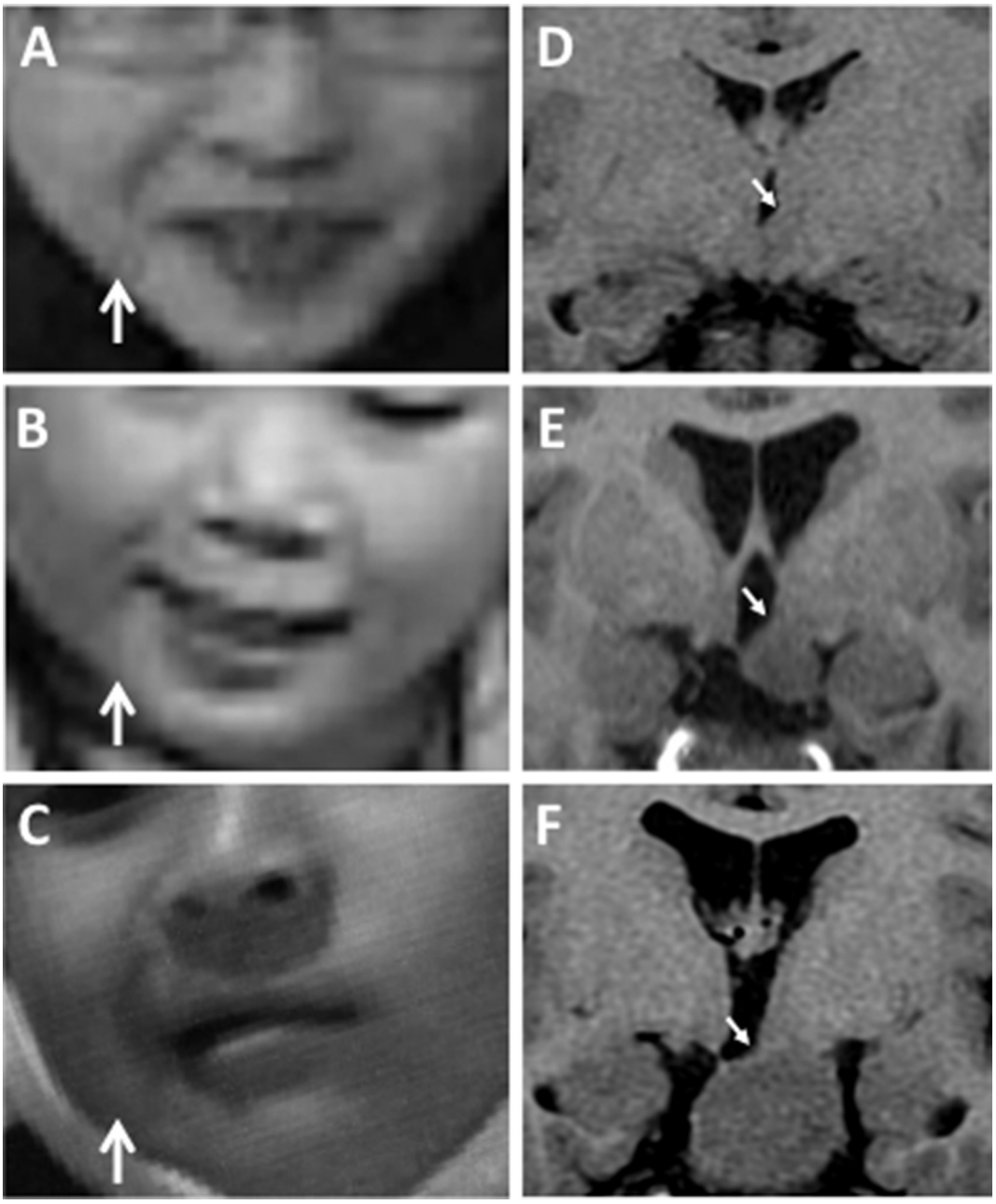

Fig. 1. Asymmetric GS and HH attachment shown in three representative cases. A–C) Magnified pictures of lower-half faces exhibiting asymmetric GS (arrows) on the right side, recorded by respective long-term video-EEG monitoring in three representative cases. D–F) The attachment of HH (arrows) on coronal MRI was recognized on the side contralateral to asymmetric GS in each case.

3.4. Correlation between asymmetric GS and ictal EEG

Lateralized epileptiform discharges on the side contralateral to asymmetric GS were identified in 5 patients (true positive). Generalized epileptiform discharges or diffuse electrodecremental patterns were recognized in 34 patients, and no ictal discharges were confirmed in 32 (false negative, n = 66). In patients with symmetric GS, unilateral EEG findings were identified in 2 (true negative) and no ictal epileptiform discharges in 30 (false positive). The PPV and DOR were calculated as 14% and 0.005, respectively.

3.5. Correlation between asymmetric GS and SISCOM

Ictal SPECT study failed in 19 patients, who were then excluded from analysis. In patients with asymmetric GS (n = 57), hyperperfusion of HH attachment on the side contralateral to asymmetric GS was identified in 16 patients (true positive) whereas hyperperfusion on the side ipsilateral to asymmetric GS was recognized in 6 and no hyperperfusion of HH attachment in 35 (false negative, n = 41). In patients with symmetric GS (n = 27), hyperperfusion of HH attachment was unilateral in 10 (true negative) whereas no hyperperfusion (n = 16) or bilateral hyperperfusion of HH attachments (n = 1) was judged in the remaining cases (false positive, n = 17). The PPV and DOR for asymmetric GS were calculated as 48% and 0.23, respectively.

In relation to epileptic propagation, hemispheric hyperperfusion was seen on the side contralateral to asymmetric GS in 25 patients (true positive) whereas hyperperfusion on the side ipsilateral to asymmetric GS was seen in 11 and no hyperperfusion was apparent in 21 (false negative, n = 32). In patients with symmetric GS, unilateral hemispheric hyperperfusion was identified in 19 (true negative)

whereas bilateral hyperperfusion and no hyperperfusion were recognized in 8 (false positive). The PPV and DOR for asymmetric GS were calculated as 75% and 1.86, respectively.

3.6. Correlation between asymmetric GS and interictal EEG

Lateralized epileptiform discharges on the side contralateral to asymmetric GS were identified in 23 patients (true positive) and on the side ipsilateral to asymmetric GS in 48 (false negative). In patients with symmetric GS, unilateral EEG findings were evaluated in 18 (true negative) whereas generalized findings or no epileptiform discharges were disclosed in 14 (false positive). The PPV and DOR for asymmetric GS were calculated as 62% and 0.62, respectively.

3.7. SRT

At the first SRT, the side of surgical approach was determined because of the side of unilateral HH (n = 53) or of the dominant HH attachment (n = 47). In two patients with symmetric HH attachments, the approach side was determined according to SISCOM findings. In the other patient who exhibited asymmetric GS independently on both sides (Fig. 2, A, B), SRT was performed on the nondominant side of bilateral attachments (Fig. 2, C) by reference to the lateralized findings of SISCOM, and a second SRT was performed to complete bilateral disconnection (Fig. 2, D) to achieve seizure freedom.

4. Discussion

4.1. Asymmetric GS

The present study confirmed asymmetric GS as a new lateralizing sign in patients with HH. Asymmetric GS has a highly PPV for the side of seizure propagation. Gelastic seizure is a rare seizure type, and the prevalence of patients with epilepsy with HH is quite low [10]. Investigators, therefore, pay little attention to asymmetric facial expression during GS. In our early series of patients with HH, we could not recognize ictal facial asymmetry [1]. Facial asymmetry of GS has not been discussed in great detail. However, asymmetric GS has been reported as one of the semiologies in patients with HH [2]. The utility of various lateralizing signs has been studied to detect epileptogenic zone in partial epilepsy. Loddenkemper and Kotagal [11] reviewed facial asymmetry in patients with temporal lobe epilepsy. They mentioned facial asymmetry as emotional facial paresis contralateral to the temporal focus. Oehl et al. [12] did not report facial asymmetry of GS in the analysis of the seizure semiology in patients with HH. Harvey and Freeman [8] reported that lateralized tonic facial contraction of GS was concordant with the side of attachment of unilateral HH or the dominant attachment in asymmetric HH. Tonic facial contraction might have differed from asymmetric GS in the present study.

4.2. Seizure propagation of GS

Gelastic seizure is a cardinal seizure type associated with HH. Hypothalamic hamartoma is well known for the intrinsic epileptogenesis of GS [1–7]. In terms of the propagation network for GS, Kahane et al. [6] proposed the mammillothalamic pathway of the medial limbic circuit for seizure propagation of GS. Our previous study of ictal SPECT disclosed that ictal hyperperfusion resided in the pontine tegmentum bilaterally and in the contralateral cerebellar hemisphere in addition to ipsilateral hyperperfusion in the hypothalamus and MD [7]. Although the pathway between the MD and facial nucleus is anatomically obscure, our SPECT study provided evidence of a functional correlation between them [7]. Following unilateral seizure propagation from HH, bilateral facial expression of GS may be created within brainstem polysynaptic reticular formations, like a late bilateral response (R2) in the blink reflex [13]. The basolateral limbic circuit is crucial to causing symptomatogenesis of GS [7], and MD is a major component of this circuit [14,15]. The epileptogenesis propagated to ipsilateral MD had

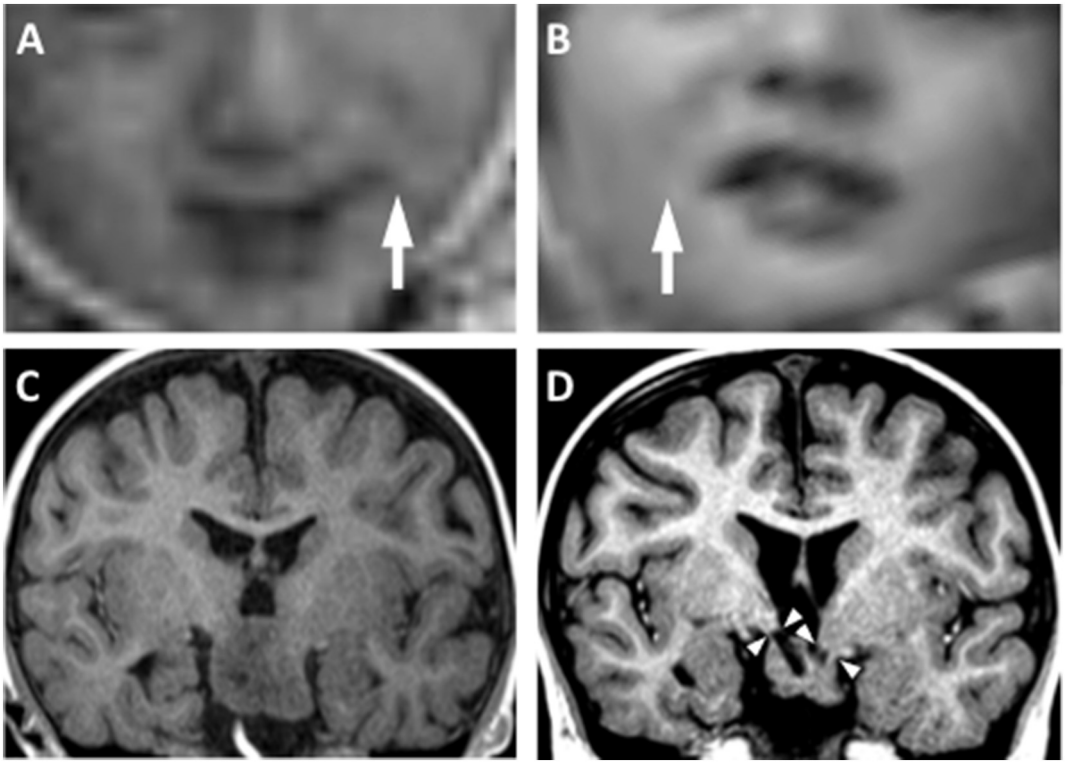

Fig. 2. A case of asymmetric GS exhibited independently on both sides. A, B) Magnified pictures of lower-half faces exhibiting asymmetric GS (arrows), recorded independently on both sides. C) Preoperative MRI shows a giant HH with bilateral attachment. D) Complete disconnection (arrowheads) of bilateral attachments of HH is confirmed on postoperative MRI.

been indicated to generate laughing automatism as symptomatogenesis [7]. Epileptic symptoms directly involving the facial nucleus involve hemifacial spasm and eye blinking rather than GS in patients with extremely rare hamartoma of the floor of the fourth ventricle [16–18]. Such evidence suggests that the facial nucleus is not a generator, but MD may be a central pattern generator of laughing motion. Central pattern generators are neural networks that can produce rhythmic patterned outputs without sensory feedback [19]. This nucleus might play a role as a network pacemaker for laughing rhythmic movement in the basolateral limbic circuit. In addition, MD shows many reciprocal connections with the anterior cingulate cortex (ACC), medial and dorsolateral prefrontal cortices, supplementary motor area (SMA), and parietal cortex [15]. Kahane et al. [6] identified ictal involvement of the ACC by stereotactically implanted intracranial EEG recording in patients with HH. Morecraft et al. [20] emphasized that facial expression involved roles for the primary motor cortex, premotor cortex, SMA, and ACC. These cortical facial areas give rise to corticobulbar projections that end in the facial nucleus. However, the anatomy of the corticobulbar tract for volitional or emotional facial movements has not been completely elucidated. Moreover, the SMA projects to many subcortical targets such as the basal ganglia and cerebellum through the pontine nucleus for motor initiation and sustained spontaneous and automatic motor activity [21].

4.3. Symptomatogenesis of asymmetric GS

Why does asymmetric GS represent hemispheric propagation? The lateralization of neural networks for asymmetric facial expression is elucidated by clinical studies and electrical stimulation. Electrical stimulation of the amygdala induced ipsilateral facial movements in monkeys [22]. Patients with mesial temporal lobe epilepsy exhibited hemifacial movement ipsilateral to the focus [22]. Our previous report using ictal SPECT demonstrated that the epileptic network passed the ipsilateral pathway from the HH to MD and the facial nucleus [7].

From another perspective, direct stimulation of the rostral SMA elicited contralateral facial movements [20]. Morecraft et al. [20] also mentioned that the facial region of the SMA included functions for the control of eye movements, speech, and laughter and played a role in the preparatory or planning phases of facial movement. Low-current electrical stimulation of the rostral SMA elicited smiling, predominantly on the contralateral side of the face [23]. Laplane et al. [21] emphasized that the function of the SMA is to initiate motor activity and sustain spontaneous and automatic motor activity. Moreover, Sperli et al. [24] reported that electrical stimulation of the ACC induced either laughter or smile according to the level of intensity. Experimental lesioning of the ACC bilaterally caused reduced facial expression and vocalization in primates [25]. These results suggest that the ACC plays a role in the facilitatory modulation of facial expression. Kim et al. [26] reported that both the SMA and ACC showed close functional correlates based on the results of surgical resection. In addition, emotional facial paresis was caused by postoperative disorders of the SMA [20,21], in which activation of the contralateral facial muscles was impaired with emotion but showed normal voluntary activation. Emotional facial movement is known to be preserved despite transient volitional hemifacial paresis after resection of the primary face motor cortex because of the epileptic focus [27]. Different pathways for emotional and volitional facial movements may exist. In our cases of HH, therefore, seizure propagation to ipsilateral ACC and/or SMA secondarily emphasizes contralateral facial expression as asymmetric GS.

4.4. SRT for HH

Direct propagation from HH to the hypothalamus had been implicated in the symptomatogenesis of GS [7]. This was the rationale behind the concept of disconnection in SRT [1–3,7] or endoscopic surgery [28]. In deciding the approach side for SRT, asymmetric GS and laterality of the HH attachment offer reliable predictors on the side of seizure propagation. Asymmetric GS and hemispheric hyperperfusion in SISCOM are more reliable than EEG findings to determine the approach side for the HH with bilateral attachment. Furthermore, the present study demonstrated the probability of bilateral seizure propagation in HH with bilateral attachment. This evidence provides a new rationale for the surgical strategy underlying bilateral disconnection for HH with bilateral attachment to achieve relief from GS.

5. Conclusions

The present study confirmed our hypothesis that asymmetric GS represents a new lateralizing sign on the side contralateral to seizure propagation from HH. Asymmetric GS is helpful for deciding the side of SRT approach for HH with bilateral attachment. We speculate that the symptomatogenesis of asymmetric GS is implicated in SMA and/or ACC as a facilitatory modulator for the contralateral facial expression. This lateralizing sign and the speculative neural mechanisms generating asymmetric GS should be supported by accumulating evidence from further studies. Moreover, the probability of bilateral seizure propagation from a bilateral attachment offers a new rationale for bilateral disconnection surgery for both attachments of HH.

Disclosure

The authors report no conflicts of interest concerning this study or the findings specified in this paper. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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