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ORIGINAL RESEARCH

Unexpected median SEPs fluctuations during brain cavernous malformation resection with no post-operative deficit

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Abstract

Median nerve somatosensory evoked potentials (SEPs) may present changes during cavernous malformation (CM) resection unrelated to new post-operative sensory deficits. We performed intraoperative neurophysiological monitoring of median SEPs (m-SEPs) in three patients who underwent CM resection (surgery) near the sensory-motor cortex. The only preoperative clinical manifestations in all patients were seizures. All patients presented m-SEPs alterations on the side of the lesion during the procedure. Two patients presented permanent changes in the cortical potentials. In the third patient, the cortical and subcortical components suffered temporal fluctuations to return to baselines at the end of the surgery. None of these patients developed new post-operative clinical deficits. During brain cavernous malformation resection, significant fluctuations in the amplitude of different components of m-SEPs may occur. These changes may be due to excitability variations on m-SEP generators and do not translate into new post-operative neurological deficits.

Keywords Cavernous malformation · Hyperexcitability · Somatosensory evoked potentials · Giant SEP · Thalamocortical pathway · Intraoperative neuromonitoring

1 Introduction

Somatosensory evoked potentials (SEPs) are generated in afferent pathways, subcortical structures, and several areas of the cerebral cortex by stimulation of peripheral nerves. Short latency somatosensory evoked potentials within the first 20–40 ms consist of N20 and P25/P30, and originate in the Broadmann areas 3b and 1 of the somatosensory cortex after contralateral median nerve stimulation [1, 2].

A decreased amplitude or delayed latency of SEPs is frequently observed in patients with supratentorial lesions affecting the thalamocortical pathways [2, 3]. On the contrary, cortical SEPs have been enhanced in patients with tumors localized near the central sulcus, a phenomenon also observed in patients with myoclonic epilepsies [3–5].

Intracranial cavernous malformations (CMs) are characterized by abnormally dilated vascular cavities within the central nervous system surrounded by a single vessel wall [6]. The estimated prevalence varies between 0.4 and 0.9% [6]. Seizures are the most frequent clinical manifestation, caused by alterations in neuronal excitability [7].

Although the relationship between abnormalities of SEPs and lesions involving the primary sensorimotor area

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has been widely described and correlated with clinical sensory deficits [8–13], little is known about intraoperative alterations of median nerve SEPs (m-SEPs) related to CM resection.

2 Materials and methods

2.1 Subjects

All cases were patients with supratentorial CMs, with seizures as the only preoperative symptom.

Patient 1: a 60 years-old, right-handed female presented with two episodes of focal seizures consisting of headache, hemifacial numbness, weakness, and involuntary contractions on the right side of her face. She was diagnosed with a left frontal CM visible on magnetic resonance imaging (MRI) (Fig. 1a).

Patient 2: a 39 years-old, left-handed female with a previous medical history of three episodes of focal seizures secondary to a CM localized to the left central sulcus in the region of hand and arm primary sensory and motor cortex. Episodes consisted of numbness on the right side of her face, neck, and arm. She underwent resection of the lesion and remained seizure-free with a post-operative MRI that showed total removal of the CM. Two years later, she presented with focal seizures consisting of numbness along the right side of her face, arm, and leg. MRI showed a recurrence of CM (Fig. 1b).

Patient 3: a 39-year-old, right-handed male with a 12-year history of sporadic focal seizures, consisting of visual obfuscations and impaired awareness. MRI showed a right parietal CM (Fig. 1c).

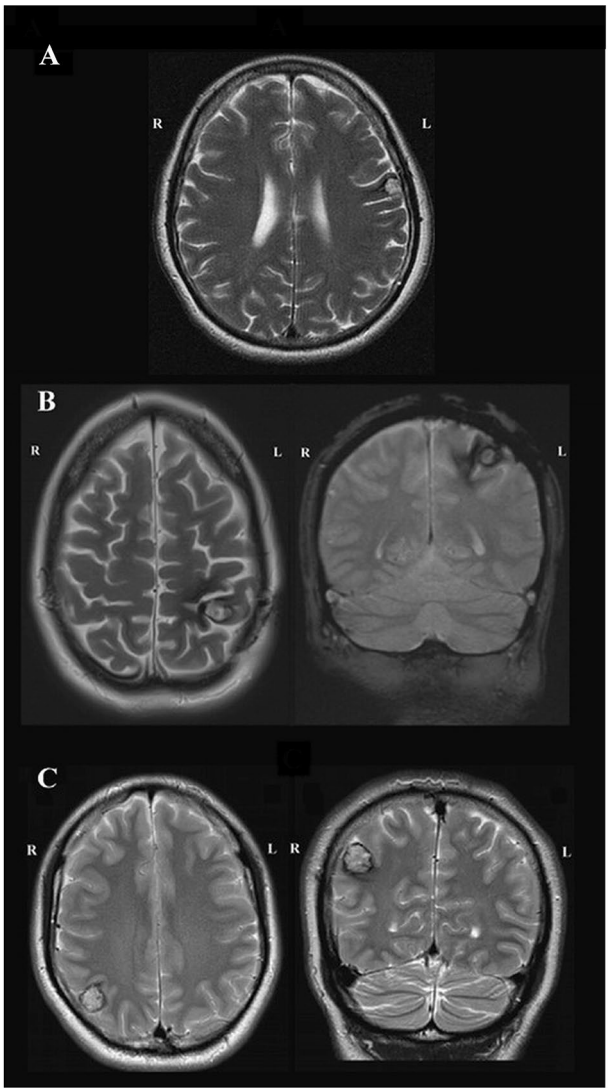

Fig. 1 Preoperative magnetic resonance image (MRI), T2 sequence **a** Patient 1, cavernous malformation observed on the left primary facial motor cortex, with no surrounding vasogenic edema or significant mass effect. **b** Patient 2, recurrent cavernous malformation on the left primary sensory cortex, with hemosiderin and vasogenic edema surrounding the lesion. **c** Patient 3, cavernous malformation on the right parietal sensory cortex with no evidence of surrounding vasogenic edema or significant mass effect

2.2 Methods

Neurophysiological data were recorded using a Modified Axon Sentinel 4 EP machine (Axon Inc., Hauppauge, NY, USA) (patient 1) and a Medtronic Eclipse 4 System (Medtronic Xomed, Inc., Jacksonville, FL) (patient 2 and 3). The low-pass filter of the machine amplifiers was set at 1 Hz and the high-pass filter at 3000 Hz, with a bandpass of 30–300 Hz.

Intraoperative neurophysiological monitoring (IONM) modalities included upper and lower extremities SEPs and motor evoked potentials (MEPs). When necessary, localization of sensorimotor cortex using phase reversal SEPs was recorded.

Median nerve SEPs (m-SEPs) were elicited with a repetitive single stimulus pulse (0.5 ms pulse duration) at 40 mA intensity and 0.7 Hz repetition rate. SEPs were recorded by corkscrew electrodes (Natus Neurology Inc., Gl. Landevej, Roskilde, Denmark) placed on the scalp following the 10–20 international EEG system. Derivations were C3′-Fz or C4′-Fz [8] and Fz-inion [9] for recording cortical and subcortical m-SEP components, respectively.

After informed consent was obtained, the patients underwent surgery. SEPs and MEPs baselines were taken after induction of anesthesia and before skin incision. Scalp corkscrew electrodes stayed in their initial position through the procedure and were not displaced after scalp incision or craniotomy.

Neurological outcome was evaluated immediately after surgery and at the post-operative follow-up (9 months). In

this study, the m-SEPs represents the evoked potential generated ipsilateral to the lesion side after stimulation of the contralateral median nerve.

2.3 Anesthesia

General anesthesia was induced in all patients, using short action muscle relaxant only for intubation purposes. Anesthesia was maintained with total intravenous anesthesia (TIVA) by using an infusion of propofol and Remifentanil. Blood pressure remained stable throughout the surgery, and no new agents were added that could alter the potentials during the surgery.

3 Results

Three different intraoperative m-SEPs patterns were observed among three patients during CM resection and subsequent hemostasis. In patient 1, the bilateral cortical and subcortical SEPs were symmetrical at the opening. During tumor resection, the amplitude of the N20/P25 components of the right m-SEPs progressively increased, from 1.5 µV at baselines to 3.3 µV at the end of the surgery (Fig. 2).

By contrast, patient 2 presented at opening baseline an enhanced N20 amplitude of the right m-SEPs compared to the left m-SEP. During CM resection, the amplitude decreased progressively, reaching its lowest value by the end of the surgery, half of the opening (from 7.1 to 3.1 µV) (Fig. 3).

In patient 3, median SEPs were symmetrical at the opening. During the procedure, left m-SEPs showed a decrease in the amplitude of the cortical potential, along with an increase in the amplitude of the subcortical thalamic component. Towards the end of the surgery, the cortical and subcortical components of the left m-SEPs progressively returned to their initial values (Fig. 4).

There were no changes in the MEPs or lower extremities SEPs. Bilateral cortical and subcortical m-SEPs latencies, as well as the amplitude of the m-SEPs contralateral to the side of the lesion, remained stable throughout the procedure, except for patient 1. This patient presented a shortening in the latencies of the bilateral median SEPs at closing compared to opening baselines, probably related to the increase in the patient's limbs temperature at the end of the surgery.

No new clinical sensory or motor deficits were identified after surgery and at nine months follow-up. All patients remained seizure-free while taking antiepileptic medication. Post-operative neurophysiological evaluation of m-SEPs was not performed in any of the patients.

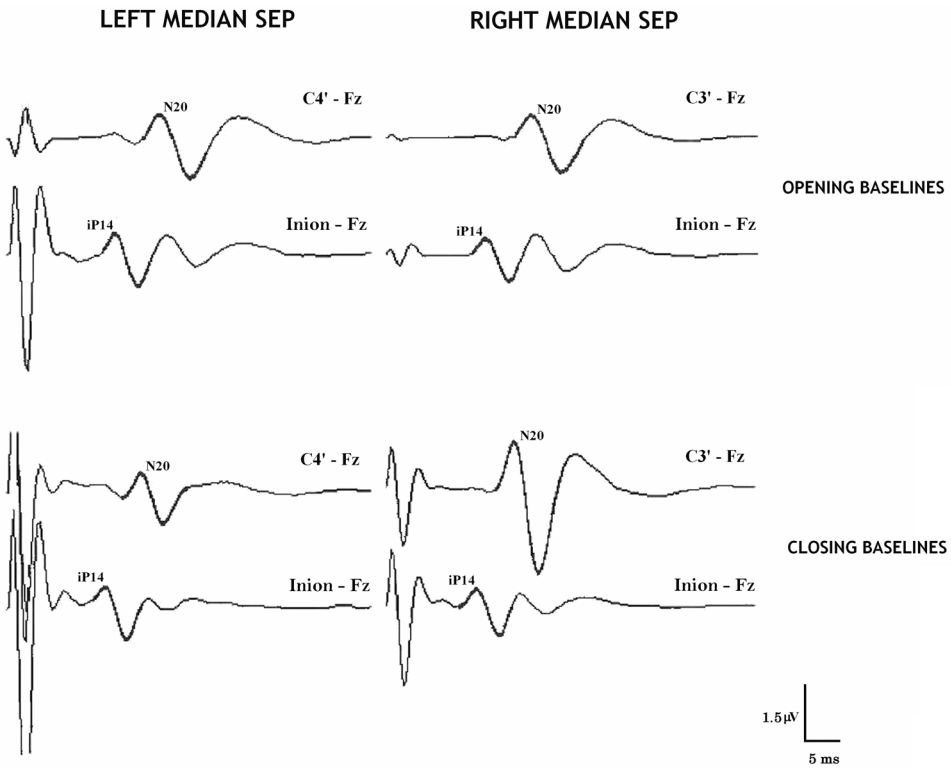

Fig. 2 Intraoperative median nerve SEPs of patient 1 Opening and closing baselines. Note the pronounced increase in the amplitude of the right cortical potential at closing after CM resection. Notice the shortening in the latency of the bilateral (cortical and subcortical) median SEPs at closing compared to opening baselines, related to the increase in the patient's limbs temperature at the end of the surgery. *iP14* inverted P14

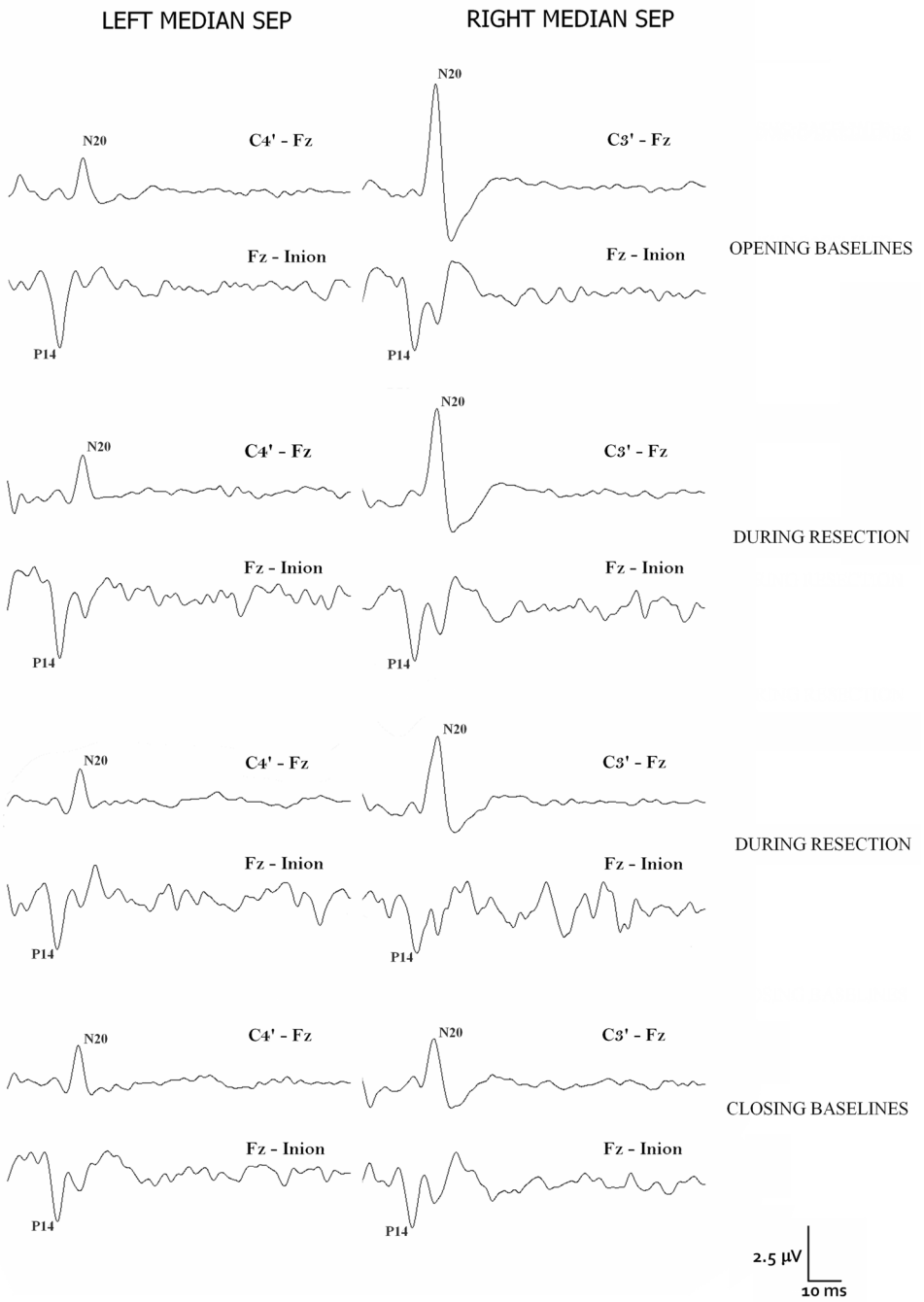

Fig. 3 Intraoperative median nerve SEPs of patient 2 Traces show bilateral cortical median SEP at the opening, during resection, and closing. Notice the progressive decrease in the amplitude of the cortical right median SEP during the CM resection. At closing, the right median SEP amplitude was halved compared to the opening baselines

4 Discussion

The present study details the dynamic progression of m-SEPs cortical and/or subcortical fluctuations during IONM of supratentorial CM resection in three patients and discusses the potential mechanisms involved. These m-SEPs changes are not associated with new clinical deficits.

Enlarged SEPs are a common finding in myoclonic epilepsies [5, 10–13] which are also described in vascular lesions [4, 14] and brain tumors [2–4, 15, 16]. However, only a few authors have reported alterations in the m-SEPs related to unilateral brain lesions without sensory disturbances [2, 3, 14, 15].

Enhanced P22-N30 SEPs components have been described in patients with space-occupying lesions [4, 15, 16]. Similarly, patient 1 showed an increment of the cortical N20-P25 potentials on the lesion side during CM resection, sustained until the end of the surgery. It has been proposed that the underlying mechanism of SEPs enhancement might be due to (i) insufficient neuronal inhibition of the

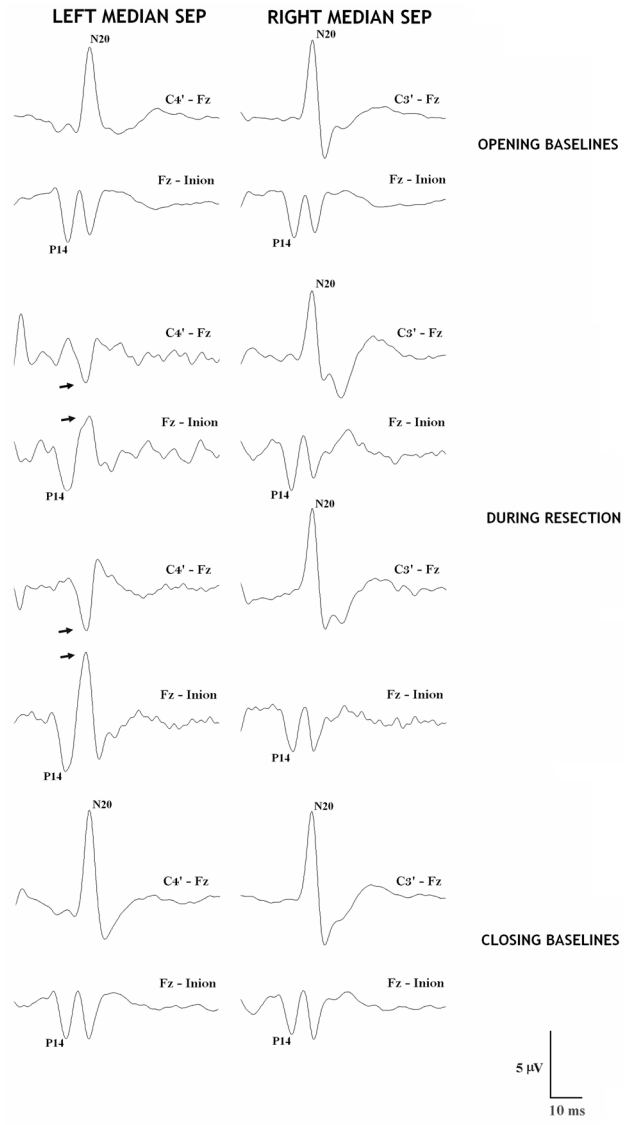

Fig. 4 Intraoperative median SEP of patient 3 Bilateral median SEP are symmetrical at the opening. Note that during CM resection, the left median SEP is altered, changing the morphology and amplitude of the cortical and subcortical components, returning to opening baselines at the end of the surgery. Arrows indicate a positive deflection with latency of 22.8 ms recorded from C4′-Fz that bears an exact temporal relationship to the negative N18 of 22.8 ms latency recorded from the Fz—Inion montage. The coincidence between these two positive and negative deflections leans toward the hypothesis that both responses are generated in the thalamic relay, with a polarity change. However, a cortical origin cannot be completely ruled out

somatosensory cortex via the pallidum and ventral group of the thalamic nuclei [14], (ii) sensitization of the motor cortex by degeneration of the cortico-cortical connections [4], or (iii) hyperexcitability of cortical or thalamocortical neurons [2, 3, 5, 10, 15].

Stetkarova [3] and Valeriani [15] proposed that lesions close to the central sulcus may trigger hyperexcitability of the sensorimotor cortex. Specifically, Stetkarova [3] reported increased N20-P22 potentials in three patients with a unilateral brain tumor, who presented an additional increment at 3 and 6 months after surgery. Also, Valeriani [15] described that two dipoles likely generate N20 potential: one tangentially oriented, in area 3b and another radially oriented, in area 3a, lesions close to these areas could provoke anatomical and functional modifications of these generators. We hypothesize that this mechanism could be involved in the SEPs enhancement observed in patient 1 during the lesion resection.

Patient 2 presented, before the incision, increased cortical N20 potential ipsilateral to the lesion, which progressively decreased during resection. No reports have described a decrement of thalamocortical excitability and consequently an m-SEPs amplitude decrement in patients with previously increased SEPs. Microhemorrhage is frequently associated with CM. The hemosiderin deposits contain iron that produces free radicals and lipid peroxidation reactions. This consecutively modifies cell membrane fluidity and causes functional changes of ionic channels receptors and transporters of excitatory neurotransmitters. Additionally, iron decreases glutamate reuptake in synaptosomes and inhibits glutamine synthetase, leading to hyperexcitability [7, 17, 18]. Excision of the lesion and the surrounding hemosiderin ring often results in subsequent control or even healing of hyperexcitability states [18]. We speculate that the lesion's excision and surrounding hemosiderin deposit could have provoked a progressive decrement of the excitability in the cortical or thalamocortical pathway, resulting in m-SEPs amplitude decrement observed at the end of the surgery.

Intracranial air acting as conduction attenuator between the signal generator and scalp recording electrodes should always be considered a possible technical mechanism of inexplicable changes on the scalp recordings SEP in any given craniotomy. This mechanism is critical for the resection of large space-occupying lesions. However, because the CMs in our series were all small lesions, the heterogeneous SEP changes presented here cannot be satisfactorily explained by the sole presence of intracranial air.

Anesthetic agents like ketamine or etomidate are known to enhance the amplitude of cortical SEP [19, 20], but neither of them was used in our patients during the surgery.

Perioperative hypothermia may occur accidentally. Lang [21] reported that median nerve SEP latencies are prolonged, and amplitude increases in patients with mild hypothermia during spontaneous circulation [21]. Moreover, as the temperature is reduced, pH increases. The pH is a potent modulator of NMDA receptor activity. A drop in the concentration of H+ could release the block on the NMDA channels and increase excitability [22]. Thus, the alkaline pH in the peritumoral area may enhance excitatory stimuli and diminish inhibitory ones [23].

The most striking event was observed in patient 3. During the last part of the CM resection, the cortical m-SEP (N20, 23.8 ms latency) progressively decreased in amplitude along with an increment of the subcortical cuneatus/thalamic P14/N18 amplitude (from 4.2 to 8.8 μV), recorded from the Fz-inion derivation [9]. This change temporarily altered the entire morphology of the potentials, returning to the initial amplitude and morphology at the end of the surgery. After N20 disappearance, an initial negative/positive complex followed by a more prominent positive/negative complex with 22.8/26.7 ms latency was recorded from the C4′-Fz derivation. This positive deflection with latency of 22.8 ms (indicated with an arrow in Fig. 4) bears an exact temporal relationship to the negative N18 of 22.8 ms latency recorded from the Fz-Inion montage. The coincidence between these two positive and negative deflections leans toward the hypothesis that both responses are generated in the thalamic relay, with a polarity change. Often unnoticed, subcortical components of SEP on scalp-to-cephalic montages can be recorded [9, 24–27]. Indeed, an m-SEP study in unilateral severe thalamic lesions by Mauguiere, Desmedt, and Courjon [24] described abolished N20/P22 cortical recordings with preserved P14 and N18 components, allowing for the widespread N18 features to be studied without interference from cortical components. Similarly, focal thalamic ischemia in baboons showed that the human N20-equivalent cortical potential was abolished due to loss of thalamocortical transmission [28]; however, there was a residual positive potential recorded on the cortical surface, corresponding in latency and morphology to the remaining positive wave recorded in the thalamus. Even more, scalp-to-cephalic montages, including cortical-to cortical derivations such as C3′-Fz and C4′-Fz, could yield subcortical components [29, 30]. However, because the subcortical components of SEP cannot be easily recorded in cortical-to-cortical derivations, a cortical origin of the positive deflection recorded in the C4′-Fz derivation cannot be completely ruled out.

Temporal changes observed in patient three possibly suggest variations in the volume conduction properties. The pressure from a tumor and peritumoral edema may disturb the corticothalamic feedback, indirectly changing the thalamic response [2]. Furthermore, ischemic lesions could distort the volume conduction properties of the tissue, either reducing local blood flow or generating intracellular or interstitial edema [3, 28]. Peritumoral edema is characterized by anaerobic metabolism and might cause energy failure with functional disruption of the white matter [3, 31]. In addition, a thalamic lesion might have a direct effect on the interactions between the relay neurons and the reticular neurons [2]. However, no ischemic lesions on the post-operative MRI or new clinical deficits were identified after the surgery.

Ooba et al. [2], studied the correlation between the amplitude of N20 and the intensity of the amplitude of high-frequency oscillations in patients with brain tumors. They suggest that an increasing amplitude of N20 is not necessarily accompanied by sensory alterations and might indicate the presence of subclinical changes, not only in patients with brain tumors but also in those with other brain diseases.

It is difficult to determine what mechanisms trigger an increase or decrease in the potential amplitude during the resection of CM. However, we hypothesize it might be related to the location of the lesion, the extent to which the thalamocortical loop and the connections are affected, and the magnitude of excitability changes established in the surrounding tissue. The potential underlying mechanism presented here for explaining these heterogeneous m-SEP changes during CMs resection remains hypothetical. Therefore, they should be addressed and further studied.

The most interesting finding of this report is the absence of new neurological deficits in any of our patients, despite significant alterations in m-SEPs during resection of CM. The effect of excitability variations dynamically observed during the surgery and the short- and long-term clinical outcomes of these patients should be thoroughly studied. The lack of m-SEP follow-up is a limitation of this study for understanding if the intraoperative changes observed were permanent and with clinical significance. From a practical IONM perspective, we suggest that these particular changes in m-SEPs amplitude during the surgery should be carefully interpreted.

5 Conclusion

During brain cavernous malformation resection, significant fluctuations in the amplitude of different components of m-SEPs may occur. These changes may be due to excitability variations on m-SEP generators and do not translate into new post-operative neurological deficits.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by RP-C, AD-B, MJT, JU, SG and SU. RP-C wrote the draft of the manuscript. All the authors made writing, review and editing. All authors read and approved the final manuscript.

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Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study. This study was approved by the IRB at Icahn school of Medicine at Mount Sinai (HS#: STUDY-21-01186).

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