ISSN 1220-8841 (Print)
ISSN 2344-4959 (Online)

ROMANIAN
NEUROSURGERY

Vol. XXXV | No. 1 March 2021

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DOI: 10.33962/roneuro-2021-005

Romanian Neurosurgery (2021) XXXV (1): pp. 29-35
DOI: 10.33962/roneuro-2021-005
www.journals.lapub.co.uk/index.php/roneurosurgery

The impact and causes of negative cortical mapping in primary motor area tumours

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ABSTRACT

Introduction: Intraoperative neurophysiological monitoring is the golden standard for lesions located in eloquent areas of the brain. On the one hand, positive mapping offers a view of the relationship between the anatomo-functional cortical organisation of the patient and the lesion, facilitating the choice of the cerebrotomy entry point and the resection until the functional borders are found. On the other hand, negative mapping does not offer certainty that the absence of the motor response, from the operative field, is the real feedback or is the result of the false-negative response. In such a situation, a differentiation between those two must be done.

Materials and methods: We evaluated the results of direct cortical stimulation of lesion located in or near the primary motor area, which were diagnosticated with contrast-enhancement head MRI and admitted to the Third Department of Neurosurgery, "Prof. Dr N. Oblu" Emergency Clinical Hospital, Iasi, Romania, between January 2014 and July 2018. Special attention was given especially to the negative mapping cases, regarding the histological type, imagistic localisation, symptoms and neurological outcome immediate postoperative, at 6 months and one-year follow-up.

Results: From all 66 patients meeting the inclusion and exclusion criteria in 9,09% (6 cases) we did not obtain any motor response after direct cortical stimulation. The imagistic localisations of those cases were: 3 – Rolandic, 2 – pre-Rolandic and one retro-Rolandic. Tumors histological types were: glioblastoma, anaplastic astrocytoma, oligoastrocytoma and oligodendroglioma each one case and two cases of fibrillary astrocytoma. The intensity range was between 6 – 18mA, the mode – 12mA and the median – 10mA. Postoperatively the neurological condition of 3 patients worsened (4,54% from all the cases), while 3 had a favourable evolution with symptom remission. At 6monts and one-year follow-up in one case (1,51%), we observed no improvement in contrast with the other two, where dysfunction remission was highlighted.

Conclusion: The possible technical, surgical and anesthesiologic causes of false-negative motor response must be eliminated to be able to differentiate from the real

Keywords
negative mapping,
positive mapping,
direct cortical stimulation,
primary motor area,
brain tumour

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ISSN online 2344-4959
© Romanian Society of Neurosurgery

First published
March 2021 by
London Academic Publishing
www.lapub.co.uk

absence of the functional area from the operative field. In the first scenario, the resection may be associated with permanent postoperative neurologic deficit and major life quality alteration while in the second one the patient presents no motor dysfunction after surgery and the resection may be extensive with multiple oncological benefits.

Introduction

Intraoperative neurophysiological monitoring (IOM) remains across time in the first line and have gotten the title of the golden standard procedure for lesion located in functional areas, even though we are witnessing a high development of functional imaging techniques especially 3D diffusion tractography and functional magnetic resonance imaging [1,9, 11].

A young age of presentation, paucisymptomatic cases, lesions with good survival rate make the life quality of the patients one of the main medical priorities and so an intraoperative real time feedback it is mandatory for a maximal surgical resection with a minimal neurological dysfunction. The presence of the tumour with its perilesional oedema modifies the normal functional cortical organisation and the topography of the eloquent areas is distorted. Brain mapping with direct cortical stimulation helps identify the functional tissue and differentiate the false-eloquent lesion from the real-eloquent ones, with a considerable impact over the degree of resection [4,5].

Positive mapping is recommended because reveals the anatomical-functional patients brain organisation, which has an interindividual degree of variability helping in choosing the best approach for the tumour resection considering the functional borders [31]. A negative mapping which means the absence of identification of the functional sites in the operative fields has the advantages of o smaller craniotomy, less time in performing the cortical stimulation and decrease the intervention time. A disadvantage of this technique is represented by the fact that negative is not equal with a shore absence of the functional tissue because of the possibility of occurrence of false negative response. The latter is associated with new, eventually permanent motor deficit. Hence the importance of clearing the false negative recordings and the real absence of functional cortex from the operative filed [27,33].

In the following article we present and discuss the poststimulation response after direct cortical stimulation performed on patients with tumors located in central area. The cases in which we did not obtain any response, even though radiologically the primary motor area was located in the operating field were study from clinical, histological and imagistic point of view.

Materials and methods

We present a study group which included patients with surgical lesions in primary motor area or in its vicinity, diagnosed using contrast-enhancement magnetic resonance imaging (MRI), who underwent surgery in the 3rd neurosurgery department of *Prof. Dr. N. Oblu* Clinical Emergency Hospital of Iasi, between 1 January 2015 and 1 July 2018. 76 patients were initially enrolled in the group, but 6 of them were excluded because they did not come to the 6-month and one-year follow-up examination after surgery, and 4 were excluded because they had a pacemaker. In the end, the group included 66 patients.

Inclusion criteria in the study group: tumor located in the primary motor area radiological diagnosed; age over 18 years; intraoperative use of IOM; presentation at the 6 months and one-year follow-up; consent to be included in the study.

Exclusion criteria in the study group: tumor located in the motor area, but inoperable; cases in which only stereotactic biopsy was performed; patients with pacemaker; incomplete patient data.

Intraoperative neurophysiological monitoring was performed using the Nim Eclipse device from Medtronic. Direct cortical stimulation was achieved by means of the short-train technique or train of five. The values of the parameters used in all patients were the following: frequency = 3 Hz, number of pulses = 5, duration = 500μsec, inter-stimuli interval = 4 msec, intensity interval: 6-18mA.The recording muscles were: abductor pollicis brevis, biceps brachii, deltoid, abductor hallucis and tibialis anterior muscle.

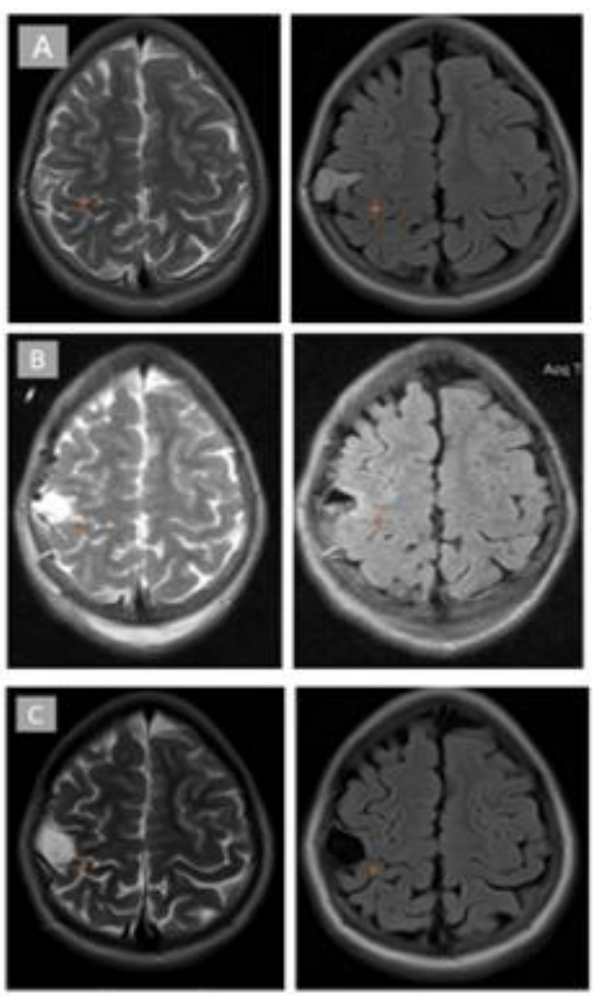
Results

76 patients were initially diagnosticated with a lesion in primary motor area, but after applying the inclusion and the exclusion criteria the study group included 66 patients. The age group distribution was 18 – 79 years and the male/female ratio: 32 (48.48%) / 34 (51.51%). As far as the clinical manifestation is concerned, Jacksonian seizures ranked first. The anatomopathological findings revealed a

glioblastoma (GB) predominance – 21 cases (31.81%), followed by meningioma (Mg) – 19 patients (28.78%), metastases (MTS) – 12 patients (18.18%), anaplastic astrocytoma (AA) – 4 cases (6.06%), fibrillary astrocytoma (AF) – 4 cases, oligoastrocytoma (OA) – 4 cases and oligodendroglioma (ODG) – 2 cases (3.03%).

The most frequent stimulation value that generated motor response was 12mA, then 8mA, followed by 10 mA and 9 mA; 13mA, 14mA, 15mA and 16mA, respectively, were necessary in a smaller number of cases. The peak value 18mA was used only when the stimulation produced no motor response at inferior values. The intensity range was between 6 – 18mA, the mode – 12mA and the median – 10mA.

No direct cortical stimulation response was received in 6 of all patients (9.09%). Preoperative lesions localization revealed by head MRI were: 3 – Rolandic, 2 – pre-Rolandic and one retro-Rolandic. From the anatomopathological point of view, there were 2 patients with AF and one case each following histological type: glioblastoma, anaplastic astrocytoma, oligoastrocytoma and oligodendroglioma. After surgery, the neurological condition of 3 patients worsened (4,54% from all the cases), while 3 had a favourable evolution with symptom remission. The functional status and extent of resection overlapped. Thus, 3 cases who underwent GTR showed motor deficit, while in the other 3 cases, where the resection was subtotal, the clinical manifestation improved. Overall, favourable outcome was achieved in 65,15% of the patients from the study group and new deficits or worsening of the pre-existent one was observed in 15,15% cases. At 6-months and one-year follow up, one case (1,51%) from those with no intraoperative motor response was stationary from the neurological point of view and the other two shown some functional improvement. An illustrative case is presented in **Figure 1**.



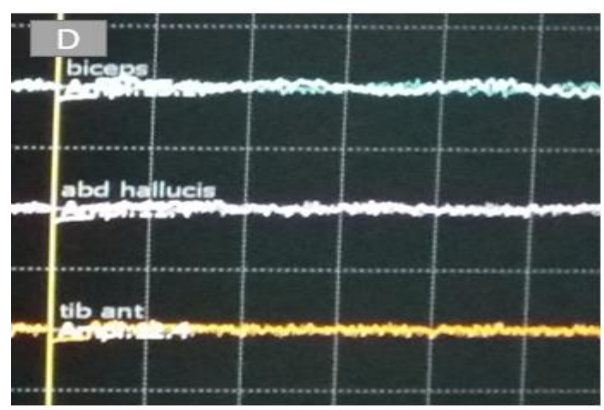


Figure 1. 28 years old female with right prerolandic oligodendroglioma (A-C) has presented with Jacksonian seizures which became drug resistant 2 years after the onset. She was operated using and IOM. Postoperatively she installed left brachial paresis even though intraoperative no cortical motor response was found at direct cortical stimulation (D). She slightly recovered the motor deficit at one year follow up. (A) preoperative head MRI: T2 and FLAIR weighted-images, the star – Rolandic area. (B) postoperative MRI hypersignal in hand area. (C) one year follow up images, oedema remission. (D) no motor response (intensity-18mA), standard baseline muscular recordings (biceps brachii, abductor hallucis, tibialis anterior muscle).

Discussion

For lesion with imagistic location in or near eloquent areas of the brain is extremely important to determine the precise relationship between the tumour and the functional cortex. In comparison with negative, positive cortical sites bring a higher confidence in choosing the cortectomy entry zone and in performing the maximal degree of resection with the aim of minimal postoperative neurological deficits. When in the operative field we do not have the presumed eloquent area is sometimes more stressful because we do not know its location and we are not sure of the postoperative neurologic status for cases with extensive resection [6, 36].

In our study group we had 6 cases in which we did not obtain the motor response. The percentage of 9,09% overlaps over the literature findings (Magill et al., reported 91% of positive mapping) [24].

The absence of the expected motor response or negative mapping creates uncertainty because we must differentiate form the false negative response over real absences of the functional cortex. The former is associated with new postoperative motor dysfunction and has technical, anaesthesiologic and surgical causes. The latter is often the result of neuroplasticity process and the patient remains neurological intact after tumour resection. Chang et al., revealed that 36% of his presumed eloquent cases, based on the radiological images, where in fact false-eloquent. This characterisation is associated with good outcome, because allows to perform an extended degree of resection. The impact of lesion location is considered especially in low grade glioma patients regarding the tumour ablation and progression free survival [5,8].

So et al., published an article in 2018 in which he showed that the motor response is not restricted only to the primary motor area, in 7% of the patient's motor response was observed and posterior to the central sulcus. In one-fourth of them positive sites were discovered anterior to the central sulcus. Tumours growth may be associated with displacement of the normal anatomy and of course of the functional areas, like in two-third of the tested patients [36]. Our results shown that only 3 lesions from those with negative mapping were situated strictly Rolandic and the other three were pre- and retro-Rolandic.

Regarding *technical causes*, those can be prevented by preoperative evaluation of the equipment quality, necessary for the procedure, e.g., the electrodes, the stimulation probe. Verification of the precise placement of the electrodes is particularly important for a correct recording with real assessment of the eloquent area, especially after the patient was positioned, looking for detachments. Another significative step is represented by performing the technique correctly intraoperatively, direct stimulating the cortex, avoiding other structures like blood vessels or through a high amount of cerebrospinal fluid [20, 21,25].

Other causes of negative mapping may be: stimulation with an intensity below the threshold value, shorter pulse duration, electric current transmission through the cerebrospinal fluid and stimulation during the refractory period (Pallud et al., 2017, Eseonu et al., 2018) [10, 27]. Therefor the parameters settings of the stimulation current are important and it's good to know de differences form the two methods of motor network assessment. The traditional technique – Penfield method uses a low frequency (LF) 50 – 60 Hz, a stimulus train of 1 – 4s of biphasic pulse, while short train technique or train of five (TOF, HF) uses a high frequency 250 – 500Hz, a stimulus train of 10 – 18milliseconds of monophasic pulse [3, 30, 32]. Those parameters are usually selected before the surgery and remain the same, the only variable being the value of the stimulus intensity. For our cases we chose the train of five technique and the intensity range was between 6 – 18mA, the mode – 12mA and the median – 10mA, for direct cortical stimulation.

In the speciality literature we usually find papers regarding one technique, but a comparison was made between the LF and HF used on the same patients, in an article from 2020 presented by Bander et al., and the results showed that bipolar HF technique allowed to identify the primary motor cortex in a proportion of 100% (13 cases) vs. 31% obtained using the bipolar LF stimulation [2].

Beside choosing from the two methods of performing IOM, we used, for brain mapping, the technique of stimulating the entire exposed cortex with a constant current value starting from an intensity of 6 mA, which was subsequently progressively increased with 1 mA until the motor response was generated or at a peak value of 18 mA. Another brain mapping technique consist in stimulating every single site with progressive higher current until the response is generated. This is based on the interindividual and intraindividual threshold variability [6, 22, 29].

Pourtain et all, in 2004 observed significative differences between frontal motor response, parietal/temporal language response and frontal language mapping, the mean stimulation threshold was: 8,4± 2,8mA, 12,3 ±2,9 mA, 9,3 ±3,6mA. This type of mapping has the disadvantage of an increased risk of producing the afterdischarge potentials which may induce intraoperative seizures. Maximizing the current intensity may be associated with less specific cortical eloquent sites identification due to adjacent and subcortical functional stimulation. Another drawback may be represented by the fact that is not time efficient. Both approaches are able to determine the functional sites and the absence of the response is not dependent of which method we use but on knowing the advantages and disadvantages of both of them. In general, if the current intensity is used in order to prevent the appearance of afterdischarge potentials and the threshold is less than the minimum necessary to identify the functional sites, then false negative response will be generated [12, 14].

The bias generated by false negative response may be due to the *learning curve* of the team including the surgeon, the anesthesiologist and the neurophysiologist. The knowledge and the ability of response interpretation has a great impact on the postoperative neurological status and on the degree of tumor resection. In a paper from 2020 Pan et al., reveal that the run-in period for his team was around two years and the unexpected postoperative new motor deficit happened in the first three year from the technique application [28]. In our study all the patients had been operated by the same members of the team and the technical aspects were under the responsibility of the same person.

Discussing the *surgical aspects* one cause for the absence of a response after stimulation may also be due to a smaller craniotomy with more limited cortex exposure. The literature study showed that intraoperative eloquent sites were identified in a proportion of 30% to 100% of the cases: e.g., positive mapping (PM) 58% (Eseonu et al., 2018), 65% (Kim et al., 2009), 91% (Magil et al., 2018) The new postoperative deficit was 51,5% in PM patients vs. 12,5% negative mapping (NM) patients (Eseonu et al., 2018), 12% PM vs. 9% NM (Kim et al., 2009), 60% - new / worsen deficit, not specified regarding the PM nor NM (Magil et al.,2018) [10, 19, 24]. In our study group positive mapping was achieved in 90,91% of the patients. The postoperative outcome was represented by new dysfunction in 15,15% of the cases, 4,54% being from those how did not respond after stimulation. At one-year follow-up in just one case, from the study group, the motor deficit persisted.

It is clear that small craniotomy may limit the identification of the eloquent sites but as showed before the new postoperative motor deficit was higher in positive mapping patients, this suggesting that is not mandatory to perform a large bone flap just for cortical stimulation. Tailored craniotomy which includes the tumor and the adjacent cortex may be enough [24, 33]. In literature it is mentioned that in some limited number of cases, not the dimension of the bone flap is the cause of the negative mapping or of the new installed motor deficit but rather omission or not including a group of muscle from recording setup. Most often it is citated transient orofacial paresis [25].

Other surgical manoeuvres like dissection in the proximity of the corticospinal tract, vascular occlusion of the Rolandic artery or vein may create inadvertence in recording motor evocated potentials. For centres where the subdural grid /stipe electrode is used more attention must be offered to the possible device displacement [37].

The third possible reason for negative mapping is represented by *anaesthesia*, which has an important role in obtaining the proper result after stimulation. Special protocols have been used in order to avoid the medication that causes muscle relaxation which is associated with false negative recordings [16, 18, 26]. Those agents (Lystenon®) were used by our anaesthesia team, in general, at the induction step of the orotracheal intubation, just to facilitate the procedure. The drug's effects are over until the beginning of the operation.

Because a large spectrum of drugs decreases the synaptic activity, the effect being dose dependent, other criteria for the anaesthetic agents to be included in the protocol are represented by the impact on the latency and the response amplitude. Currently there are two directions represented by total intravenous anaesthesia (TIVA) and the use of volatile agents [23, 38]. The latter determines an increase of response latency and a decrease of amplitude, inducing pyramidal inhibition, dose dependent. A concentration at the alveolar level of 0,5-1 have been found to be safe. The impact of TIVA is also dose dependent but in a smaller extent. Hence, due to their pharmacokinetic properties influence on motor response recordings, synthetic opioids such as Fentanyl and sedative-hypnotic agents represented by Propofol are preferred when IOM is used [13, 17]. These were included in the protocol used on the patients from our study.

From a histological point of view, even though our cases have a large category of tumor type, they have a common feature, namely slow development. This tumor characteristic allows for the neuroplasticity process to start. A consequence of this is function preservation, the main symptom of presentation of our patients being the Jacksonian seizures and not motor deficit.

Studying the neuroplasticity and searching for the reasons of paucisymptomatic cases it is important to understand the functional organisation of the primary motor area which depends on the strict equilibrium from inhibitory and excitatory intrinsic local mechanism. The main system involved in reorganization is represented by the horizontal connections. The redundant motor sites within this map may be reviled using GABAergic inhibition [34, 35]. Usually just this type of reshaping is not sufficient to maintain the function intact so other regions are recruited. First ipsilateral areas are involved e.g., premotor area, supplementary motor area and posterior parietal cortex. As a last resort contralateral "mirror" area participate to this process. In those situations, negative mapping may be found and the tumour resection is not associated with motor deficits [7, 15].

Conclusion

In cases where we do not have a motor response after direct cortical stimulation is applied, for lesion located in or near primary motor area is necessary to consider the step of the intervention to delineate the false negative recordings from real absence of the feedback. The three categories of causes must be eliminated starting with technical problems, anaesthesia and surgical issues. The differentiation from real absence of the motor response has an impact over the degree of resection and this in turn affects the survival rate and the progression free survival.

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