Interdisciplinary Neurosurgery: Advanced Techniques and Case Management 2 (2015) 16–20

Contents lists available at ScienceDirect

Interdisciplinary Neurosurgery: Advanced Techniques and Case Management

journal homepage: www.inat-journal.com

Case Reports & Case Series (CRP)

Alteration of the threshold stimulus for intraoperative brain mapping via use of antiepileptic medications

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ARTICLE INFO

Article history:
Received 2 October 2014
Revised 20 November 2014
Accepted 27 November 2014

Keywords:
Antiepileptic
Awake craniotomy
Anti-convulsant
Seizure
Mapping
Current

ABSTRACT

Intraoperative seizures during awake craniotomy with cortical and subcortical mapping are a common occurrence. Patients are routinely treated preoperatively with anti-convulsive medications to reduce seizure occurrence. Historically these drugs have not been believed to significantly affect awake craniotomy procedures. We report a patient undergoing intraoperative mapping with differential response and seizure occurrence based upon antiepileptic drug usage. A 43 year old female presented with history of seizures, right sided hemiparesis, electrical sensations, and difficulty with language function. She was determined to have a mass lesion involving the left frontal and temporal lobes and subsequently elected to undergo resection by awake craniotomy with intraoperative mapping. A first attempt at lesion resection was performed after a missed dose of anti-convulsant medication (levetiracetam) and was subsequently aborted because of repeated seizure activity. The threshold for seizure generation (1.75 mA) was observed to be significantly lower than expected. Therapy was begun with both levetiracetam and phenytoin prior to a second attempted resection one week later. Thresholds for cortical motor response in the second operation were significantly higher than expected (> 9.0 mA), and no intraoperative seizure activity was observed. To our knowledge this is the first quantitative example of antiepileptic drugs affecting the current required for intraoperative mapping. This case highlights the potential for higher current requirements in patients preoperatively treated with high doses of antiepileptic drugs, as well as the importance of confirming adequate dosage of antiepileptic drugs in patients at an increased risk of seizure generation.

Introduction

The increasing availability of functional magnetic resonance imaging, cortical magnetoencephelography, and Diffusion Tensor Imaging (DTI) has offered additional methods to pre-operatively map brain function and the associated functional white matter tracts. Despite these novel imaging techniques, awake craniotomy with direct cortical and subcortical stimulation remains the gold standard for brain mapping in order to identify which lesions or portions thereof may be removed with minimal clinical sequelae. However, unlike the aforementioned non-invasive imaging modalities, intraoperative seizures during an awake craniotomy with brain mapping are a relatively common complication of the procedure, with reported incidence as high as 32% [1,2]. From our experience seizures are more commonly observed with higher levels of stimulation, although there is no established threshold for seizure generation. Most seizures are sporadic and quickly aborted, and prior studies show that these intraoperative seizures rarely evolve into generalized seizures [1,3,4]. Research into this procedure has found the strongest correlation for intraoperative seizures in patients with a history of epilepsy, as well as patients taking multiple antiepileptic drugs [4,5].

In order to reduce the occurrence and severity of intraoperative seizures, antiepileptic drugs (AEDs) are routinely given preoperatively even to patients who have not had seizures. Historically these drugs have not been believed to have a significant negative effect on awake craniotomy procedures, although a recent review of 424 awake craniotomy procedures reported that phenytoin was significantly associated with communication failures during cortical mapping [6]. Although it is commonly understood that abrupt discontinuation of AEDs can lead to a transient period with a reduced seizure threshold, to our knowledge there have been no reports detailing the effects of antiepileptic drugs on the amount of current required to map eloquent cortex in awake craniotomies. We describe a case where antiepileptic use/disuse was thought to be directly related to both the amount of current required to elicit a motor response and the current needed to produce a seizure.

Case

We present the case of a 43 year old right-handed white female who presented to us with a 3 month history of electrical sensations in her right hand and right leg in addition to difficulty with word finding,

Abbreviations: DTI, diffusion tensor imaging; AED, antiepileptic drug; GBM, glioblastoma multiforme; mA, milliamperes.

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http://dx.doi.org/10.1016/j.inat.2014.11.004

comprehension, and memory. The patient had a right hemiparesis and was noted to have anxiety. The patient denied any history of seizure activity. MRI demonstrated a ring-enhancing mass lesion in the posterior aspect of the left frontal lobe with extension into the superior posterior left temporal lobe and insula with surrounding vasogenic edema. There was mass effect with mild effacement of the lateral ventricle. Pre-operative MRI images are shown in Fig. 1. This mass was biopsied stereotactically. The pathology specimen was determined to be a glioblastoma multiforme (GBM). DTI was performed and this demonstrated that the corticospinal tracts were likely to be anteromedial to the lesion. The arcuate fasciculus, however, appeared to be pushed superiorly via mass effect and was in much closer proximity to and possibly invaded by the lesion. Due to the proximity of eloquent cortex affecting language, motor, and sensory tracts, the patient was advised to undergo an awake craniotomy with intraoperative brain mapping and stealth guidance and this was arranged for the fifth day following her biopsy. She was discharged on lorazepam 1 mg TID PRN for anxiety, dexamethasone 4 mg QID, and levetiracetam 500 mg BID four days prior to her awake craniotomy. The levetiracetam was started on postoperative day 1 of the stereotactic biopsy, so this discharge regimen would allow the patient to take eight doses of levetiracetam before the surgery.

Surgical procedure and clinical course

An incision was fashioned based upon the location of the tumor. An adequate cortical surface was exposed to map the frontal cortex and associated language cortex. The location of the tumor was confirmed with the Stealth system and the proposed mapping sites were reconfirmed. Intraoperative mapping was undertaken using 4–5 s square wave pulses at a frequency of 60 Hz. The area of anticipated motor cortex was initially stimulated with 1 mA with no response. Two milliamperes then was used over the motor cortex and this produced tonic clonic movement that progressed to generalized seizure activity, requiring irrigation with iced lactated ringer's for resolution (see Fig. 2). The current was decreased and the motor cortex continued to show no response to stimulation with 1.5 mA, while repeated attempts using 1.75 mA reliably caused the patient to enter a generalized seizure, requiring iced lactated ringer's irrigation at each occurrence (see Figs. 2–4). Thus the decision was made to close the craniotomy and consult with the epilepsy neurology service to assist with institution of a superior preoperative AED regimen.

After the surgery, the patient's levetiracetam prescription was increased to 1000 mg BID, and the patient was started on phenytoin. The patient's dexamethasone was continued at 4 mg QID. Interestingly, after some questioning the patient admitted to being confused by her preoperative instructions. It was determined that the patient had taken her scheduled dose the evening prior to surgery, but had omitted her dose the morning of surgery. The patient remained neurologically stable, although she did experience some worsening of her expressive aphasia as a result of the seizure activity. The patient was transferred to the floor the next day, and discharged home on the 2nd postoperative day.

The patient returned to the hospital on the 7th postoperative day for another attempt at resection; however, this time she had a phenytoin level of 15.4 μg/ml and was taking an increased dosage of levetiracetam. This awake craniotomy proceeded as anticipated with a very different response to stimulation. As before, the motor cortex was stimulated with 1 mA and this elicited no response. The current was slowly increased and no motor response was seen until stimulation with 9.0 mA. This current was observed to be the threshold stimulation to elicit repetitive arm response. This same current was then used to complete speech and motor mapping. The procedure was successful in removing the vast majority of the tumor with only a small residual that was adherent to the middle cerebral artery. No intraoperative seizures were observed during this second craniotomy for resection.

Discussion

This case demonstrates the unique findings of a patient undergoing intraoperative cortical stimulation on two different AED regimens only one week apart. Although exact levetiracetam levels are not known, during the first surgery the patient's levels were likely lower after missing her dose the morning of the procedure, while the second surgery was performed with the patient on high dosage levetiracetam and a therapeutic phenytoin level. The threshold for motor stimulation was observed to increase from 1.75 mA during the first procedure to 9.0 mA in the second procedure. Additionally, seizure activity was initiated at 1.75 mA in the first procedure, while stimulation at levels up to 9.0 mA did not evoke seizure activity in the second procedure. Although this effect might be taken for granted by those who routinely pretreat their patients with AED's prior to intraoperative brain mapping, this is the first report of a quantitative increase in seizure and motor stimulation thresholds as a result of varying preoperative AED dosages in a single patient.

Phenytoin is a well-established anti-convulsant drug used to prevent repetitive firing of neurons and resulting generation and spread of seizure activity. Although phenytoin's mechanism of action is not completely understood, it is proposed to inhibit sodium flux through voltage dependent sodium channels on the neuronal membrane. This inhibition serves to stabilize membrane potential

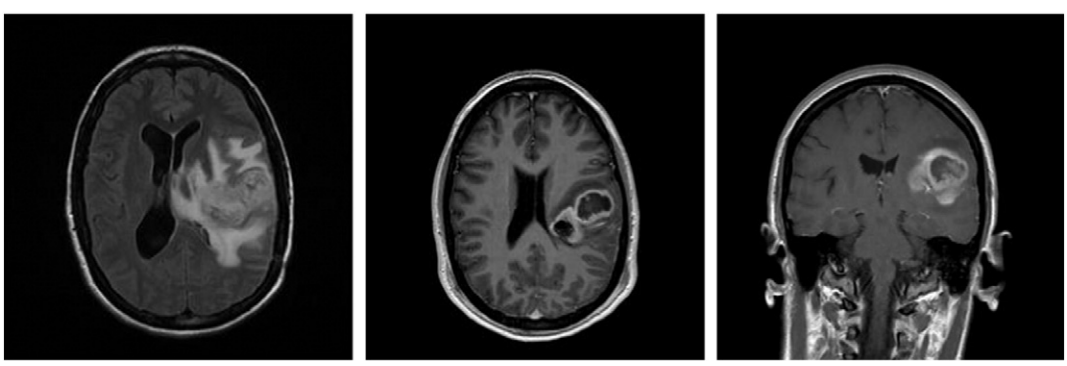

Fig. 1. Pre-operative MRI images: axial T2 flair (left), axial T1 post-contrast (center), and coronal T1 post-contrast (right). MRI illustrates edema, necrosis, and contrast enhancement characteristic of glioblastoma multiforme. Due to the proximity of the tumor to the temporal and insular lobes of the patient's dominant hemisphere, an awake craniotomy with intraoperative mapping was recommended for resection of the lesion.