Cortical Hyperexcitability in a Migraine patient before and after Sodium Valproate Treatment

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ABSTRACT

DC-MEG waveforms arising during migraine aura were utilized to determine effectiveness of prophylactic medication therapy on neuronal hyperexcitability. Seven patients were prescribed valproate (Depakote) for migraine prophylaxis. MEG scans were recorded during visual stimulation before commencing medication and again after 30 days of daily use of Depakote. Cortical brain activity was recorded during stimulation with a black and white circular checkerboard pattern alternating at 8 Hz and analyzed with MR-FOCUSS. Large amplitude DC-MEG signals, imaged to extended areas of occipital cortex, were seen prior to therapy. After 30 days of prophylactic treatment, reduced DC-MEG shifts in the occipital cortex and reduced incidence of migraine attacks were observed. Using visual stimulation, we have confirmed the hyperexcitability of widespread regions throughout occipital cortex in migraine patients, explaining the susceptibility for triggering SCD and migraine aura. This study confirmed that MEG can non-invasively determine the status of neuronal excitability pre and post therapy. This may be helpful in determining which prophylactic medications will be most effective in reducing hyperexcitability in particular patients.

KEYWORDS: DC-MEG, Migraine, valproate, MR-FOCUSS

INTRODUCTION

Excitability of cell membranes appears to be a fundamental factor in the brain’s susceptibility to migraine attack [Welch, 2003]. We have previously used MEG to study the DC-MEG shifts that arise in visually stimulated Migraine patients [Bowyer, 2001]. DC-MEG shifts provide direct measurement of neuronal excitation and suppression. We demonstrated DC-MEG field shifts arising during spontaneous and visually induced migraine aura, resembling those previously reported from spreading cortical depression (SCD) crossing a sulcus in animal models, in which electrocorticography (ECoG) was used to confirm SCD depolarization [Bowyer, 1999, 1999].

We present a preliminary study of patients with migraine who received prophylactic treatment with sodium valproate and underwent MEG studies prior to start of treatment and at follow up, in an attempt to define MEG waveform characteristics that are associated with good response to treatment.

METHODS

Seven patients with migraine (3 with aura and 4 without aura) as diagnosed based on the International Headache Society [IHS, 2004], were recruited from the outpatient headache clinic at Henry Ford Hospital. Mean age was 37±13 years old, 5 women and 2 men. The treating physician had prescribed sodium valproate (Depakote® 125 mg twice daily, for migraine prophylaxis, as part of their routine clinical care. Each patient gave written informed consent to participate in this study, which was approved by the Institutional Review Board of Henry Ford Hospital.

The MEG studies were performed using a 148-channel Neuromagnetometer (4D Neuroimaging WH2500). Patients were prepared for studies in our customary way [Bowyer, 2001]. The visual stimulus pattern, a circular checkerboard, was previously described in Bowyer [2001]. The stimulus pattern alternated black and white at 8 Hz. DC MEG fields were recorded during visual stimulation by the checkerboard pattern, prior to commencement of medication. Patients returned to the MEG laboratory 30 days later after continuous daily use of the prescribed dose of sodium valproate and the same visual stimulations and MEG recordings were performed.

All data were digitized at 254 samples per second, band passed at 0–100 Hz. Data were filtered at 0.001–100 Hz to remove equipment drift, which was coherent in all 148 channels. The data were then decimated from 254 to 11 samples per second to simplify computer analysis. These two steps eliminated most of the high frequency signals and artifacts without significantly affecting the slowly varying DC shifts, which occurred over minutes. The data were analyzed for DC-MEG shifts. To correlate MEG areas of cortical activity with specific anatomical structures, a standard volumetric MRI scan was manually rescaled to the patient’s digitized head shape [Moore, 2000]. The magnetic resonance imaging (MRI) scan was a sagittal T1 image, 124 slices, and 256x256 matrix that included the entire skin surface of the head. The MRI was used to constrain cortical images obtained by MR-FOCUSS [Moran, 2001] to lie within the cortical gray matter. The results were then displayed on the volumetric MRI scan which was co-registered to the subject’s MEG x, y, z coordinate system. These coordinates were established during data acquisition.

MR-FOCUSS provides whole brain images of both focal and extended sources, which may be simultaneously active. The MR-FOCUSS results were displayed on the subject’s MEG x, y, z coordinate system. Selection of significant activation is determined by setting the display threshold to 25 % (color coded white, see figure 1) of the maximum cortical source amplitude and for significant locations 80–100% (color coded black). For the MR-FOCUSS solution in this study, approximately 60 percent of all source locations have amplitudes less than 0.5% of the maximum amplitude. For the 25 % display threshold, the most active 5 to 10 percent of the cortex is depicted in each gray scale color-coded functional image of figure 1, with black representing approximately the top 0.3 percent most active sites (9 out of 2900 sites).

RESULTS

Prior to initiation of treatment with sodium valproate, DC-MEG shifts were seen in the extended occipital and parietal cortex, as well as frontal cortical regions in all seven patients, confirming the hyper-excitability of the occipital cortex to visual stimulation. Figure 1A shows the DC-MEG results prior to medication in one patient. Note the extended cortical areas of activation in the occipital, parietal, and frontal cortex. Average MR-FOCUSS analysis of the imaged MEG activation data are displayed on a standard anatomical MRI scan. The average is over the initial first 400 seconds.

Thirty days after initiation of sodium valproate treatment, migraine attacks in three out of four patients were much less frequent. The other three of the initial seven subjects did not return for the follow up study. Following 30 days of continuous treatment, MEG recordings revealed a reduction of DC shifts in three patients, an indication that the medication inhibited the cortical hyper-excitability or changed the threshold for induction of SCD or an SCD like event. In these three patients there were corresponding reductions of migraine occurrence over the month. The one subject who did not have a reduction in DC shifts also did not have a reduction in migraine occurrence. Figure 1B displays the DMEG results seen after 30 days of prophylactic migraine treatment in the same patient displayed in figure 1A. Reduced cortical activity in the occipital cortex is seen in the averaged MR-FOCUSS analysis of the imaged activation results on the coronal MRI scans. The average is again over the initial first 400
seconds. Frontal cortical activation was noted, likely from temporal muscle clenching during the visual stimulation. This appears on both pre and post medication MEG studies.

We compared the finding from this patient to those of normal controls. Control subjects displayed no DC-MEG shifts as previously reported in [Bowyer, 2001].

**DISCUSSION**

This study confirmed the hyperexcitability of the occipital cortex in patient’s with migraine. It also supported the hypothesis that cortical excitability was reduced after 30 days of prophylactic drug treatment, which could correlate with the patient’s clinical response to prophylactic therapy.

Using visual stimulation techniques, we have confirmed the hyperexcitability of widespread regions throughout occipital cortex, similar to our previous report [Bowyer, 2001]. This helps explain the susceptibility for triggering SCD or SCD-like events in migraine sufferers, and suggests that such neuroimaging studies pre and post migraine drug therapy may increase understanding of how sodium valproate, and perhaps other anti-migraine drugs, exert their antimigrainous action. We have shown that the use of MEG can determine the status of neuronal excitability pre- and post- prophylactic medication therapy non-invasively. If further studies reveal a reduction in DC shifts or normalization of the VECMF after other prophylactic drug therapy has been initiated, then the relationship between the drug used and the underlying hyper-excitability will be established.

The MEG DC shift changes observed from the baseline to the post-treatment study are likely linked to the use of sodium valproate as migraine prophylaxis, and correlate well with the patient’s clinical response to the treatment. A concern here could be that the observed change after sodium valproate is a reflection of normal fluctuations in brain excitability and not a response to the drug. However, in previous studies of migraine patients and controls [Bowyer, 2001] we have not observed any significant fluctuations, therefore ruling out this possibility and confirming that the change is indeed linked to the sodium valproate use. This is an important finding because MEG may offer information about response to prophylactic therapy early in the course of treatment, and thus could be used as a tool for selecting the appropriate prophylactic medication for each patient. MEG could be used through out the treatment process to adjust medication therapy accordingly for the benefit of the patient. Since patients may indicate a reduction in headache occurrences, which may or may not be the result of the prophylactic medication therapy they are usually kept on the same medication for several months before a change in medication is implemented. MEG can be used to guide therapy after the initial 30-day drug intervention by indicating the actual impact of the drug on cortical excitability. This should be demonstrated in the context of a larger study, in which patients are subjected to a variety of prophylactic agents.

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**REFERENCES**


