Ictal and interictal hypoactivation of the occipital cortex in migraine with aura. A neuroimaging and electrophysiological study

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Summary

In recent studies, several authors have highlighted and studied an altered blood oxygenation level dependent (BOLD) signal in subjects affected by migraine with aura, using functional magnetic resonance imaging (fMRI) during the migraine attack or during the period between two attacks.

Using fMRI, we assessed a 27-year-old man affected by migraine with aura at two different times: during the migraine attack, and a fortnight later, in order to look for differences in regional cerebral blood flow after visual stimulation. In addition, during the attack-free period we carried out a series of electrophysiological examinations.

Our results demonstrate different activation patterns of the occipital cortex during the asymptomatic period and during the migraine attack. Furthermore, the electrophysiological data obtained demonstrated altered activity due to the patient’s disease.

KEY WORDS: BOLD signal, CSD, fMRI, migraine with aura.

Introduction

Recent functional magnetic resonance imaging (fMRI) studies have highlighted an altered blood oxygenation level dependent (BOLD) signal in subjects affected by migraine with aura (1,2). Several authors have studied migraine patients using fMRI in the interictal period and during attacks induced by visual stimulation (3,4).

Various electrophysiological, metabolic and vascular phenomena are widely known to be involved in triggering migraine attacks and some “changes” even persist into the interictal phase.

In this study we report the data obtained in a subject affected by migraine with aura who was evaluated using a combined neuroimaging and electrophysiological protocol both during the attack and in the asymptomatic phase, in order to obtain detailed information about the changes occurring within the central nervous system (CNS) during this type of primary headache (5-7).

Materials and methods

We assessed a 27-year-old man affected by migraine with aura (with unilateral right-sided pain), who experienced approximately twice-monthly attacks lasting 48 hours. His headache was diagnosed according to the ICHD-II criteria (8), and his most recent attack had occurred 20 days earlier. The subject, who was under no prophylactic or CNS depressant therapy, underwent fMRI during the painful phase of the migraine attack and again a fortnight later, during the asymptomatic phase; he was also submitted to a series of electrophysiological examinations. For comparison, a control group of 10 healthy volunteers (6 females and 4 males, average age 34.7 years) was recruited from among the staff and students at our centre. All gave their written informed consent before entering the study, which had received local ethics committee approval.

Our patient underwent fMRI examination on a Siemens Magnetom Vision system operating at 1.5 T. BOLD contrast echo planar imaging scans were performed. A localizer pulse sequence was carried out for correct positioning of 16 slices along the AC-PC axis, as well as a detailed anatomical T1-weighted sequence of these.

The selected images extended from the rostral part of the external cortex to the culmen of the cerebellum caudally. We used an MRI-compatible monitor for visual stimulation and a personal computer to generate a chessboard made up of 3x3 cm red and green squares that flashed at a frequency of 2.5 Hz/sec. We performed visual stimulation, in accordance with a typical block design fMRI protocol. Stimulation was alternated with a rest period, during which the monitor was darkened. During the acquisition of the functional epi-BOLD sequence, we performed eight rest/stimulus cycles each lasting 32 seconds (16 seconds rest/16 seconds stimulus). After motion correction, activation maps were generated using dedicated statistical software. Values were considered significant at p<0.05.

The electrophysiological protocol consisted of: EEG recording, recording of motor potentials evoked by tran-
scranial magnetic stimulation (TMS) with resting motor threshold (after identification of the hot spot), recording of motor evoked potentials (MEPs) from the adductor brevis pollicis of the dominant limb, assessment of silent period duration, and assessment of the intracortical excitability using paired TMS (pTMS) with interstimulus intervals (ISIs) of 3, 5, and 15 ms. Data were collected for statistical analysis.

Results

The migraine patient's EEG was altered, showing polyspiked trains mixed with spike-wave complexes of about 2 seconds' duration in both hemispheres. The silent period duration in the patient was significantly reduced with respect to the values observed in the control group (Fig. 1). The degree of intracortical inhibition assessed by pTMS was significantly lower in the migraine patient with respect to the control group. In fact, at ISIs of 3 ms, the MEP amplitude in the migraine patient was 57.2% with respect to unconditioned MEP amplitude, as opposed to 16±3% in the control group. Moreover, at ISIs of 15 ms, MEP amplitude was increased by 214% with respect to single shot MEPs, whereas the increase in the control group was 122%.

The fMRI activation map obtained during the painful period showed that activation of the calcarine area was greatly reduced with respect to the control group. Furthermore, the larger cluster is located in the left hemisphere, while only a small cluster is visible in the right hemisphere (Fig.s 2, 3). During the interictal phase, the fMRI activation map showed a more extensive and bilateral activation than in the painful state, without however reaching the activated area recorded in the control group (3775 activated voxels in the interictal phase, 206 during the attack) (Fig. 4).

Discussion

In this migraine patient, we observed reduced occipital activation and high basal cortical excitability. Other fMRI studies show a progressive decrease in rCBF in subjects affected by migraine with aura during the onset of the visual aura and the subsequent painful state (1,4), thus showing a correlation between worsening migraine

Figure 1 - Silent period duration in patient and control group.

Figure 2 - fMRI: activation during migraine attack.

Figure 3 - fMRI: average activation in the control group.

Figure 4 - fMRI: activation in migraine patient during the interictal period.
fMRI in migraine with aura

symptoms and rCBF. While the use of a block design fMRI protocol prevented us from showing a detailed temporal correlation of the rCBF, on the other hand, the data obtained has greater statistical power (9) and allows efficient comparisons of the overall BOLD signal during the ictal and interictal period of migraine with aura.

In our opinion, the elevated cortical excitability observed in the electrophysiological examinations could be responsible for the reduced activation seen in the fMRI maps, thus we believe that elevated basal cortical excitability at rest is responsible for a less intense BOLD signal during the visual stimulation phase. This would explain why our results show less intense activation in the occipital area with respect to healthy subjects and why there is a reduced signal in the right occipital area during the painful phase (given that our subject suffers visual aura and migraine attack on the right side) (1). Moreover, several studies, using event-related fMRI protocols, showed that prolonged visual stimulation (> 40 minutes) triggers cortical spreading depression (CSD) in man (1,4,10). Until now, this mechanism has been associated with migraine aura. However, recent reviews on CSD have shown that this phenomenon has still not been fully clarified. The triggering might be due to a neuronal and vascular phenomenon arising from different cerebral sites such as the red nucleus, the brainstem, and the periaqueductal grey (10,11).

Cortical spreading depression has been studied through event-related fMRI in order to compare data from animal and from experiments on the human brain in vivo (e.g., the speed of electric wave spreading), but it has not yet been established whether CSD is due to the presence of aura or to a subclinical phenomenon. Our results demonstrate different activation patterns of the occipital cortex during the asymptomatic period and during the migraine attack. The electrophysiological data we recorded are in agreement with findings reported in the literature (12-14). The increased cortical excitability observed in migraine probably determines the duration of the asymptomatic period and therefore frequency of attacks (15,16). In this case report, we describe a patient with elevated cortical excitability during the interictal phase compared to the control group, and an extra elevated excitability during the ictal phase. These findings seem to suggest that altered expressions of cortical excitability play an important role in triggering migraine attacks.

Electrophysiological and neuroimaging studies have helped us to understand the cerebral changes occurring during the migraine attack, modifying the concept of vascular or vasomotor migraines into one of neurovascular migraines. However, further studies are necessary, in subjects affected by migraine with aura, during the attack and in the interictal phase, in order to obtain more accurate data regarding the mechanisms, and role of facilitation and/or inhibition, of the different cerebral areas that control pain.

References

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