Slow cortical potentials in migraine. Predictive value and possible novel therapeutic strategies to prevent an attack

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Summary

During the pain-free interval migraine patients display increased negative amplitudes in recordings of slow cortical potentials compared to healthy controls. This fact can be linked to diminished or absent habituation during the recording session. This difference in amplitude and habituation is at its maximum the day before the migraine attack. After the attack, amplitudes and habituation course are comparable with those of healthy controls. This observation enables the migraine patient to predict the next migraine attack and to become acquainted with other symptoms which indicate an imminent attack and which can be present one or two days before it. During this period, when the attack has begun but the pain has not yet developed, novel therapeutic strategies for preventing the full-blown attack can be introduced. These “pre-emptive” strategies – which may include intake of tranquillizers to reduce the high cortical arousal, but also non-medical relaxation methods – constitute neither acute treatment (because there is no acute pain) nor prophylaxis.

KEY WORDS: contingent negative variation, migraine prediction, pre-emptive strategy, relaxation.

Introduction

Migraine is characterized by intense, recurrent, unilateral pain attacks, with a frequency of one or more attacks per month, lasting 4-72 hours. The severity of the pulsating pain and accompanying symptoms, such as nausea, vomiting, photophobia and phonophobia, can cause a migraine patient to cease all work and social activities. The impact of the acute attack in migraine is severe. Current studies show that this disease is driven by enhanced neuronal activity in the brainstem (1). The relation between neuronal and vascular processes is emphasized by the theory of neurogenic inflammation (2). In current thinking, trigger factors seem to initiate a cascade of central processes which lead to a migraine attack. The trigeminal vascular system, in particular, plays an important role in the pathogenesis of migraine and in pain processing (3). It is a common observation that many migraine attacks may follow a physical or psychological stressor or internal biological event such as hormonal changes. There must be a diathesis, largely explained by inheritance, but, in addition, a stimulus to trigger the attack is needed (4). The migraine attack begins before the onset of the related pain. In the last few years, migraine research, especially migraine pathophysiology research, has focused on the days leading up to the attack. Often, migraine patients are able to predict their next attack by perceiving certain sensory and emotional states during the two days prior to it. They report feelings of tiredness and weariness, have difficulty concentrating, and they yawn more frequently (5). When recording visual evoked potentials (VEPs/P300) during the pain-free interval and in the acute attack, the most pronounced disturbances can be observed just before the migraine attack, whereas these functions normalize during the attack (6,7). On recordings of the contingent negative variation (CNV), migraine patients display a more pronounced negativity compared with healthy controls. The CNV is a slow event-related cortical potential that can be recorded on the brain cortical surface between two defined and contingent external stimuli (8): a warning stimulus (S1) that announces an imperative stimulus (S2) requiring a motor reaction. Between S1 and S2, the overall CNV (tCNV) occurs as a negative DC-potential shift. For statistical analysis, single-trial CNVs are grand-averaged. The CNV can be divided into three components: a) the overall CNV (oCNV), which is the mean amplitude between S1 and S2; b) the early component of the CNV (the amplitude between 550 and 750 ms after S1, known as the initial or iCNV), which indicates the level of expectancy mediated by the noradrenergic system; and c) the terminal component (last 200 ms before S2, tCNV), which reflects motor preparation and mobilization, and is related to the dopaminergic system (9). Higher noradrenergic activity induced by stimulation of the locus coeruleus leads to an improvement of signal detection and enhancement of attentional functions. These attentional functions correlate to a great extent with selective attentional features recorded in paper-pencil tests (10). During recording of CNV amplitudes in healthy adults over a period of minutes, habituation occurs. Therefore...
migraine attack may be interpreted as a neurohumoral reaction aimed at protecting the brain from noxious influences. The biobehaviour model by Welch (13) postulates that strong activators (e.g., stress, specific triggers, mood) may induce potential shifts in the frontal cortex leading to activation of the locus coeruleus by means of an orbitofrontal brainstem pathway. Welch emphasized that chronic stress may lead to a depletion of central noradrenergic (NA) "storages", whereas avoidable or weak stress and relaxation increases the excretion of NA catabolites. On the other hand, serotoninergic neurons in the raphe nuclei are minimally influenced by stress; moreover, during migraine attacks, increased levels of serotonin have been found in the blood (14). Thus, the normalized CNV during the migraine attack could be due to the depletion of noradrenergic activity in combination with increased serotoninergic transmission. We assume that normalization of the CNV during an attack reflects a protective cerebral mechanism and homeostasis secondary to cerebral exhaustion (11), triggered by stress or other individual factors.

**Periodicity**

In the few days immediately before the next attack, the CNV amplitude in migraine patients becomes more negative and habituation diminishes. These two quantifiable features correlate with the occurrence of the next attack: the more negative the amplitude and the more habituation is diminished the greater the likelihood of a new at-
Slow cortical potentials in migraine: predictive value

The differences in CNV amplitude between the period immediately before and the first day following a migraine attack are statistically significant, with a tendency for a more pronounced negativity in CNV amplitude before the migraine attack in relation to the mean CNV amplitude of all days. In the first day after an attack, CNV amplitude is significantly lower than the mean CNV amplitude. High CNV amplitudes in the days before an attack possibly indicate an effort to control hyperactive levels of intrinsic brain activity. There is evidence that these hyperactive levels refer to a paroxysmal brain dysfunction causing the migraine attack. The day after the attack, amplitudes are lower, indicating less hyperactive levels, possibly caused by a refractory period following the attack. The data from our first study (15) suggest that a migraine attack could occur every three days. However, because the average frequency of migraine attacks is about one to four per month, there must be other additional precipitating factors to pave the way for an attack. The aim of the present study was to evaluate high CNV amplitudes in migraine patients and their relation to an imminent migraine attack. On the basis of the findings reported earlier (15), data were evaluated in relation to their capacity to predict the next attack.

Materials and methods

Subjects

Twenty migraine patients were recruited. Headache was diagnosed according to the criteria of the International Headache Society (16). All patients fulfilled the criteria of migraine without aura. Table I shows the demographic data of the subjects.

Table I - Demographic data of the twenty migraine subjects.

<table>
<thead>
<tr>
<th>Age (median)</th>
<th>39 yrs (range: 28-56 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex : female/male</td>
<td>14/6</td>
</tr>
<tr>
<td>Years of migraine</td>
<td>24</td>
</tr>
<tr>
<td>Frequency of attacks/month</td>
<td>4</td>
</tr>
</tbody>
</table>

CNV recording

After obtaining the patients’ informed consent, the CNV amplitude was recorded daily (n=4) or every second day (n=16), in the morning, from Cz with linked mastoids. A CNV session consisted of 32 trials in which the subjects reacted to the target stimulus (GO response). Additionally, eight trials were randomly performed in which no reaction was required (NO-GO response). The warning stimulus, S1, for the GO response had a frequency of 1000 Hz and lasted 100 ms with an intensity of 75 dB. The S1 for the NO-GO response had a frequency of 200 Hz. The target stimulus S2 had a frequency of 2500 Hz, lasted a maximum of 1500 ms, and was interrupted by pressing a key. All the subjects were instructed to press the key as quickly as possible. Reaction time was defined as the period between the onset of S2 and the pressing of the key. The EEG was amplified with a bandpass of 0.03 to 35 Hz and digitized with a sampling rate of 100 Hz for each channel. The length of one recording was 6 s, with a randomized interval of 6 to 10 s between trials. Recording began 1 s before S1 and ended 2 s following the onset of S2. The interstimulus interval between S1 and S2 lasted 3 s. NO-GO trials were not analyzed. The vertical EOG was recorded too. CNV recordings containing eye blinks or artefacts were discarded. The period between recording onset and S1 was taken as the baseline for all measurements. The CNV session was terminated after 40 artefact-free trials (32 GO/8 NO-GO trials). The grand average of the 32 GO trials of each CNV session for all patients was calculated. Overall CNV amplitude (oCNV), initial component (iCNV), terminal component (tCNV), and reaction time were determined for each session. The oCNV was the mean amplitude between S1 and S2. The iCNV was calculated according to procedures developed by Böckler et al. (17). The maximum negative amplitude of all 32 GO trials between 550 ms and 740 ms after S1 was calculated and the latency of this maximum was used as a midpoint of a window of 200 ms duration. The mean amplitude of this individual window was defined iCNV. The tCNV amplitude was the mean amplitude during the 200 ms preceding S2. To determine the course of habituation, each individual session was divided into eight blocks of four consecutive trials. Habituation was calculated by a linear regression equation with the formula y=ax+b, with “a” as the habituation index and “b” as the y-intercept. Habituation is indicated by a negative, whereas dishabituation is marked by a positive slope.

Headache protocol

All the patients had to keep a diary (daily records of their attacks). This diary allowed us to correlate the day on which we recorded CNV abnormalities (high amplitudes, absent or reduced habituation) with the day on which the next migraine attack started.

Results

CNV amplitudes

The amplitudes of iCNV showed a rise in negativity during the two days immediately prior to the onset of the migraine pain. During the migraine attack, iCNV amplitude diminished significantly and remained low for the next few days (Table II).

Table II - Averaged iCNV-amplitudes for the migraine group based on 93 recordings at Cz.

<table>
<thead>
<tr>
<th>Day in relation to migraine attack (ma)</th>
<th>iCNV-amplitude</th>
<th>Habituation</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3</td>
<td>-4.9 (3.9)</td>
<td>–</td>
</tr>
<tr>
<td>-2</td>
<td>-6.9 (4.2)</td>
<td>–</td>
</tr>
<tr>
<td>-1</td>
<td>-9.0 (5.8)</td>
<td>–</td>
</tr>
<tr>
<td>ma</td>
<td>-2.1 (3.8)</td>
<td>+</td>
</tr>
<tr>
<td>+1</td>
<td>-4.8 (3.9)</td>
<td>+</td>
</tr>
<tr>
<td>+2</td>
<td>-5.2 (4.2)</td>
<td>+</td>
</tr>
<tr>
<td>+3</td>
<td>-7.9 (4.1)</td>
<td>–</td>
</tr>
<tr>
<td>mean:</td>
<td>-5.7 (3.8)</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Habituation

Whereas in the two days immediately before the attack no habituation occurred, during the attack and during the two days after it, iCNV showed habituation (Table II).

Comparison with the attack

A comparison based on high iCNV amplitudes alone led to 77% correct classification related to the attack [in other words, when iCNV amplitude became more negative (more than 20% above mean level), in 77% of cases the migraine attack started within the next two days]. On the other hand, a comparison based on habituation kinetics alone allowed 86% of migraine patients to be classified correctly (Table III).

Table III - Conditions observed in the two days prior to a migraine attack.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recordings</th>
</tr>
</thead>
<tbody>
<tr>
<td>a (iCNV &gt;20% of mean iCNV)</td>
<td>72 recordings (77%)</td>
</tr>
<tr>
<td>b (no habituation)</td>
<td>80 recordings (86%)</td>
</tr>
<tr>
<td>a+b</td>
<td>66 recordings (71%)</td>
</tr>
</tbody>
</table>

Discussion

Migraine is a serious disorder which affects 10-15% of the world’s population. The costs of effective prevention and acute therapy are very high, patients have to adapt and change their lifestyle to a large extent. The need for help is great and this has a major impact on the directions followed by scientific research. The iCNV amplitudes show great variability during the days around an attack. Amplitudes are higher (i.e., above mean level) just before an attack, and lower after one. The migraine attack occurs when iCNV amplitude is more negative compared with the overall mean CNV. During the attack, iCNV amplitude is significantly lower than the mean iCNV amplitude. Based on two criteria (significantly higher iCNV amplitude, missing habituation), about 70% of CNV recordings can be classified as “just before an attack”. Therefore, on the basis of daily recordings, it could be possible to predict migraine attacks.

What are the advantages of correct prediction of a migraine attack?

By paying attention to the days before an attack, patients can identify psychological, behavioural and neurological abnormalities which may indicate the start of a migraine attack. These abnormalities can be described in terms of an altered electrocortical preactivation level which may result from an impaired sensory and cognitive threshold and gain regulation in migraine patients (18). Were it possible to identify these abnormalities early enough, new therapeutic strategies could be employed to stop the attack before the migraine pain develops. This could be achieved through the administration of specific medication to normalize the altered cortical information processing level. This medication intake would constitute neither an acute treatment (since there is no acute pain) nor prophylaxis. Additionally, non-medical strategies could be applied. For example, relaxation training may slow down high iCNV amplitudes. There is also evidence that high CNV amplitudes can be reduced by neurofeedback, while the actual CNV amplitude is fed back by a visual or acoustic signal (19). These “pre-emptive” strategies could be applied selectively only during the “susceptible” days, on which there exist reliable methods for assessing the situation. Additionally, when patients become aware of the imminent next attack, they could respond, avoiding their individual migraine triggers (for example, reducing psychological stress). Possibly this avoidance strategy would be necessary only during the migraine-susceptible days. These strategies are summarized in Table IV.

Table IV - Possible novel therapeutic strategies to prevent the attack.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pre-phase</th>
<th>Prodrome phase</th>
<th>Migraine attack</th>
<th>Post-attack</th>
</tr>
</thead>
<tbody>
<tr>
<td>days</td>
<td>&gt;2</td>
<td>2-1</td>
<td>0</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Non-medical treatment</td>
<td>Relaxation (?)</td>
<td>Jogging</td>
<td>Pain coping</td>
<td>Jogging</td>
</tr>
<tr>
<td>Stress coping</td>
<td>Avoiding specific triggers: – visual stimulation (excessive TV/PC) – emotional stress – physical stress (sauna, red vine)</td>
<td>Jogging</td>
<td>Stress coping</td>
<td></td>
</tr>
</tbody>
</table>

Depending on the stage (pre-phase, prodrome, attack, post-attack) different strategies could be applied. During the prodrome stage, numerous medical and non-medical pre-emptive strategies could prevent the attack.
In summary, daily recordings of CNV in migraine patients may help to identify susceptible days before the next attack. When patients are aware of these days they can learn to “slow down” their cortical information processing by special medical treatment or by relaxation techniques. This would constitute a new kind of treatment.

References