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Habituation of single CO₂ laser-evoked responses during interictal phase of migraine

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Abstract A reduced habituation of averaged laser-evoked potential (LEP) amplitudes was previously found in migraine patients. The aim of the present study was to assess the habituation of single LEP responses and pain sensation during the interictal phase in migraine patients. Fourteen migraine patients were compared with ten control subjects. The pain stimulus was laser pulses, generated by CO₂ laser, delivered to right supraorbital zone. Patients were evaluated during attack-free conditions. The LEP habituation was studied by measuring the changes of LEP amplitudes across and within three consecutive repetitions of 21 non-averaged tri-

als. In migraine patients the N2–P2 wave amplitudes did not show a tendency toward habituation across and, above all, within the three repetitions. Anomalous behaviour of nociceptive cortex during the interictal phase of migraine may predispose patients to headache occurrence and persistence.

Key words Migraine • Laser-evoked potentials • Habituation

Introduction

The majority of studies on evoked and event-related potentials in migraine have shown two abnormalities: increased amplitudes of averages of large numbers of trials and lack of habituation in successive trial blocks during the pain-free phase, which seems to reverse to normal pattern for a homeostatic mechanism [1]. This pattern has suggested an abnormal state of cortical excitability during the interictal phase of migraine, which is reversed during the attack for a homeostatic mechanism [1]. Clinical neurophysiological studies have shown that infrared laser CO₂, argon or thulium-YAG laser can be

used to generate an evoked potential that can be recorded from the vertex (late components) and temporal regions (early components) of the skull by selective activation of Adelta fibres (laser evoked potentials: LEPs) or C fibres (ultra-late LEPs) [2]. A reduced habituation pattern of the LEPs in response to repetitive noxious stimuli was found during the interictal phase of migraine, with respect to control subjects, according to the results obtained by the application of other event-related potentials [3]. The reduced habituation pattern seemed to involve mainly the vertex complex [3]. In a further study [4], we examined the behaviour of LEP amplitudes in three subsequent series of stimulation, which was correlated with the subjective pain sensation, during the non-symptomatic and

the acute phase of migraine. In controls, LEP amplitudes showed a progressive reduction in the three series, which corresponded to the decline of pain sensation. In migraine there was a clear reduction of habituation of both LEP amplitudes and pain sensation, during both the acute and the pain-free phase, with a loss of correlation between pain rating and LEP amplitudes, confirming abnormal behaviour of nociceptive cortex, which did not restore during migraine, differently from other modalities of sensory stimulation [1].

The averaging of the single responses within the single series may occult the development of habituation phenomena. It is known that a pattern of amplitude recovery after initial low-amplitude cortical responses during repetitive sensory stimulation causes reduced habituation, which may be a compensatory phenomenon of low pre-activation levels of sensory cortex [1, 5].

The aim of the present study was to perform further investigation of habituation phenomena to noxious stimuli in migraine, considering the single cortical responses within three consecutive series of CO₂ laser stimulation in a cohort of migraine patients during the pain-free phase compared with healthy controls.

Methods

Subjects

Fourteen migraine without aura patients, diagnosed on the basis of the IHS criteria (2004), were included in the study. They were 5 males and 9 females, aged 22–53. All patients were diagnosed after six months' follow-up. Patients with general medical, neurological or psychiatric diseases, and patients who were taking psychoactive drugs or prophylactic treatment for headache, or who were assessed as overusing analgesic drugs in the last two months were excluded from the study. All patients were evaluated at least 72 h after the end of the critical migraine phase and well before

the next attack, verified by the headache diary during a subsequent clinical examination. Ten healthy subjects, with no concomitant general, neurological or psychiatric disease, served as controls. They were 3 males and 7 females, aged 21–50.

CO₂ laser recording

The recording procedure has been detailed in a previous report [4].

Stimulation

The right supraorbital zone was stimulated, according to the procedure previously described [4]. Three consecutive repetitions of 21 single responses were performed.

LEP analysis

In the single repetitions, the single responses recorded to CZ derivation were detected and averaged off-line in groups of three consecutive responses. When the single response was not clear, a two-responses averaging was carried out. We obtained seven averaging for three repetitions in all cases. The N–P peak-to-peak amplitude was measured. The pain rating of the single stimuli (PR) was averaged across the repetitions.

Statistical analysis

A two-way ANOVA with LEP amplitudes or pain rating as variables, and repetitions and series as factors was carried out in each group. In order to compare the two groups, a three-way ANOVA with LEP amplitudes or pain rating as variables, and cases, repetitions and series as factors was computed. Post-hoc, the Bonferroni test was also performed.

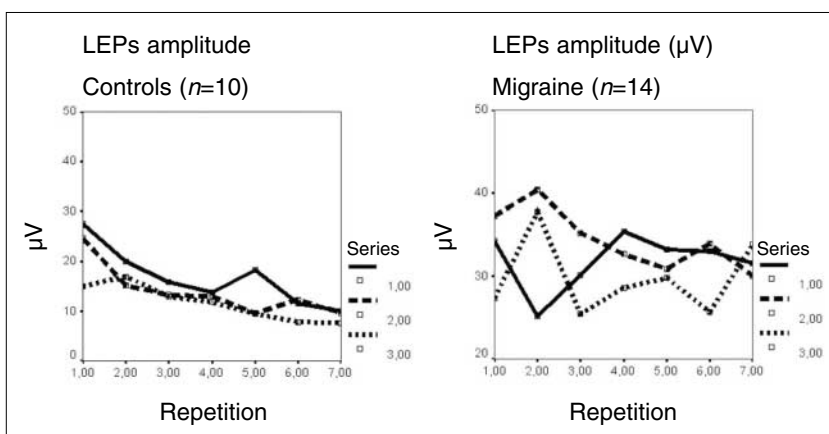


Fig. 1 Mean values of LEP amplitudes (μV) within the three series of stimulation and across the seven averaging of the 21 single responses in migraine patients and controls

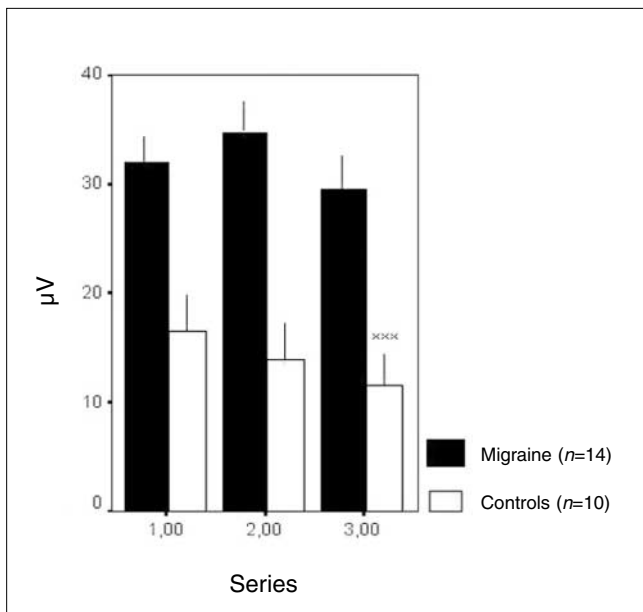


Fig. 2 Mean values and standard deviations of LEP amplitudes across the three series of stimulation. Results of Bonferroni test are shown: *** $p < 0.0001$ (first series vs. third series in control group)

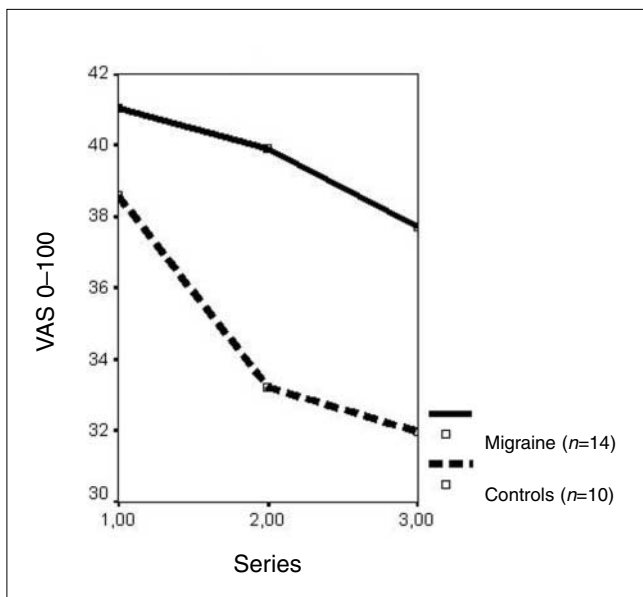


Fig. 3 Mean values and standard deviations of the pain rating of laser stimuli scored by a 0–100 VAS during the three series of stimulation in patients and controls

Results

An increased LEP amplitude was found across the seven consecutive repetitions in the three series in migraine patients with respect to controls (ANOVA with LEP

amplitudes as variable and cases as factor: $F=137.7$, $p < 0.0001$). In the control group, the LEP amplitude significantly decreased across the seven repetitions and the three series (ANOVA with repetition as factor: $F=11.77$, $p < 0.0001$; ANOVA with series as factor: $F=8.66$, $p < 0.0001$) (Figs. 1 and 2). The Bonferroni test revealed that there was a progressive decline of LEP amplitude in the three repetitions, which was significant between the first and third repetition ($p < 0.0001$) (Fig. 2). In the migraine group, no significant amplitude decline was observed across the seven repetitions ($F=0.140$, $p=0.991$) nor the three series of recordings ($F=0.84$; $p=0.43$) (Figs. 1 and 2). A slight and non-significant decline of pain rating was observed in migraine patients across the three repetitions ($F=0.23$, $p=0.79$). In the control group, the PR declined across the three repetitions ($F=5.17$, $p=0.049$). The Bonferroni test was not significant (Fig. 3).

Discussion

The present results confirmed a pattern of deficient habituation under repetitive painful stimulation in migraine patients during the attack-free phase [2, 4], which was linked with deficient habituation of subjective pain rating, according to a previous report [4]. The novelty of this study was the detection of a habituation pattern of LEPs within a single series of stimulation: migraine patients exhibited higher LEP amplitudes than controls at the starting phase of stimulation, with a reduced decline across the consecutive repetitions. While control subjects showed quite a regular pattern of progressive LEP amplitude reduction, in migraine patients the LEP amplitude development was irregular, shifting from decrease to increase, with a final maintenance of the original amplitude and a loss of habituation across the three series of stimulation. This phenomenon corresponded to a loss of the reducing pattern regarding the pain rating. The present results could confirm an abnormal elaboration of painful stimuli at cortical level in migraine. The nociceptive cortex which subtends the LEP vertex complex is consistent with the operculo-insular regions and, in a prevalent way, the anterior cingulate cortex [6]. These cortical areas seem basally overactive in migraine, with a reduced pattern of habituation. The pattern of initial reduced amplitude followed by a reduced habituation as a compensatory phenomenon was observed for repetitive sensory stimulation [1, 5] as a sign of lower pre-activation level of sensory cortex. In migraine the nociceptive cortex shows a peculiar behaviour under repetitive stimulation, with a continuous pattern of higher activation, probably facilitating the onset and the persistence of headache.

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