Clinical Neurophysiology 125 (2014) 1223–1230

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Lack of visual evoked potentials amplitude decrement during prolonged reversal and motion stimulation in migraineurs

Michal Bednář [a], Zuzana Kubová [b], Jan Kremláček [b,*]

[a] Department of Rehabilitation, Charles University in Prague, Faculty of Medicine in Hradec Králové and University Hospital, Hradec Králové, Czech Republic
[b] Department of Pathological Physiology, Charles University in Prague, Faculty of Medicine in Hradec Králové, Hradec Králové 500 38, Czech Republic

ARTICLE INFO

Article history:
Accepted 30 October 2013
Available online 19 November 2013

Keywords:
Migraine
Visual evoked potentials
Habituation
Visual processing
Visual motion

HIGHLIGHTS

- Blinded assessment of VEPs amplitude decay during 2.5 min examination supported the theory of repeated response decrement deficit in migraineurs.
- The repeated response decrement deficit was also observed during visual motion processing in the extrastriatal regions of the visual cortex.
- Pattern-reversal VEPs to low contrast stimuli did not show a significant repeated response decrement likely because of their high variability.

ABSTRACT

Objective: We evaluated response decrement during a short time repetitive low and high contrast reversal and low contrast motion stimulation in controls and migraineurs.
Methods: A total of 39 migraine patients (out of which 19 were in the interictal period and without prophylactic treatment) and 36 healthy volunteers were examined using pattern-reversal (PR-VEP) and motion-onset (M-VEP) visual evoked potentials. Binocular stimulation lasted 2.5 min and the decrement assessment was blinded.
Results: Evidence of significant decrement was observed in healthy volunteers for high contrast PR-VEP amplitude of P100-N75 ratios between the fifth and first blocks (0.9; $p = 0.001$) with a linear decline (−0.7 μV/min, $p = 0.001$) and in the P100-N145 amplitude with linear decline (−0.5 μV/min, $p = 0.004$). Significant decrement was also observed for the ratio between the fifth and first block P1-N2 amplitudes in M-VEP (0.9, $p = 0.006$). No significant decrement was noted in the low contrast PR-VEP or among migraineurs.
Conclusions: We confirm differences in decrease of VEPs amplitude during short term examination between controls and migraineurs. We showed the decrement deficit also in the extrastriatal regions of the migraineurs' visual cortex.
Significance: Low contrast and motion-onset stimuli in short time decrement assessment did not increase the test sensitivity.

1. Introduction

Migraine is currently understood as a paroxysmal neurological disease with no underlying structural correlation. In essence, it is the dysfunction of neural cortical excitability. Neurophysiological methods appear to allow at least partially an insight into the neural mechanisms at the level of the central nervous system in migraine. Based on results of various neurophysiological studies a deficit of reduction in response to any repeated sensory stimulus is presently considered to be the main biomarker specific to migraine during the interictal period and thus it is assumed to play an important role in the pathophysiology of migraines.

Schoenen et al. as the first in 1995, have described lack of decrement of pattern-reversal visual evoked potentials (PR-VEP) amplitude during repetitive stimulation compared with the expected decrement in healthy individuals (Schoenen et al., 1995). They equated the physiological decrement of PR-VEP amplitude with the term "habituation" and abnormal (insufficient) reactions in migraineurs with the term "habituation deficit". This terminology has been adopted by other authors who described "habituation deficit" in PR-VEP (e.g. Afra et al., 1998; Wang et al., 1999;

* Corresponding author. Tel.: +420 495 816 332.
E-mail address: jan.kremlacek@lfhk.cuni.cz (J. Kremláček).

1388-2457/$36.00
http://dx.doi.org/10.1016/j.clinph.2013.10.050

Bohotin et al., 2002; Ozkul and Bozlar, 2002; Di Clemente et al., 2005; Fumal et al., 2006).

From the physiological point of view the habituation covers various mechanisms on different levels of neural processing and it should be distinguished from a refractoriness, fatigue or manipulation of subject's attention, which can also lead to VEP amplitude decrement during prolonged stimulation. It is also uncertain whether the lack of VEP amplitude decrement usually observed in migraine patients involves just habituation deficit or if it includes some other processes as an increase of a sensitization (Groves and Thompson, 1970). For these reasons we will use the term *amplitude decrement* in following text. However, because most of former studies expressed their results in sense of habituation, even that they did not test the habituation utterly; we will discuss them as a *habituation/decrement* phenomenon in following.

Lack of habituation/decrement of visual evoked potentials amplitude in migraine during the interictal period has been reported in a number of research studies (see studies above and for review Coppola et al., 2009); the VEP habituation/decrement normalizes before and during an attack (Judit et al., 2000). Despite the overwhelming number of studies which reported habituation/decrement deficit, some other studies opposed these findings (Oelkers et al., 1999; Oelkers-Ax et al., 2005; Sand et al., 2008, 2009). A recent study on this topic (Omland et al., 2013) used blinded assessment of PR-VEPs and also failed to confirm amplitude decrement deficit in migraineurs during the interictal period.

An earlier article, published by the same authors (Omland et al., 2011), proposed the possibility of evaluating habituation using PR-VEP induced by reversal of a small square checkerboard over a short interval of 3 min. Such a short-time examination of the response decrement was affirmed by our pilot study on a group of healthy volunteers (Bednar et al., 2013). This pilot study also used motion-onset VEP (M-VEP) evoked by abrupt onset of visual motion. The amplitude of response to this stimulation, generated in extrastriatal structures of the visual cortex (Schellart et al., 2004; Pitzalis et al., 2012), habituated very rapidly, even in cases where direct adaptation, resulting in "motion after-effect", was avoided (Kremlacek et al., 2007). The main negative component of M-VEP proved to be a promising candidate for the measurement of habituation.

Beside the habituation/decrement dysfunction associated with migraine recent studies revealed also impairment of visual motion processing. The reports agree mainly on impaired detection of global motion (McKendrick and Badcock, 2004; McKendrick et al., 2006; Webster et al., 2011) on the level of V5, which corresponds to a lower phosphene threshold in this area (Battelli et al., 2002), higher BOLD response (Antal et al., 2011) or to anatomical findings of increased thickness in area V5 as well as in another motion processing area – the V3a (Granziera et al., 2006). These findings might also support the use of M-VEPs to evaluate repetition response suppression in migraine.

Another approach for the effective assessment of habituation may be reduction of the contrast of the checkerboard pattern, as has been previously postulated – the "weaker" the stimulus the more pronounced the habituation (Thompson, 2009).

When evaluating the sample population, on the basis of an inspiring article (Omland et al., 2013), we changed the strategy of evaluation to blind assessment. Great emphasis was placed on verifying the fulfillment of the diagnostic criteria for migraine, segregating migraine sufferers into three groups (no prophylactic treatment, in interictal and ictal phase of migraine and with prophylactic treatment) and defining the clinical phenotypes of migraineurs. Further attention was also given to information relating to hormonal changes in women within the group (menopause, menstruation cycle, etc.).

2. Study cohort

The study cohort was composed of two groups. The first (control) group included 36 healthy volunteers (doctors, nurses, porters, administrative staff and their relatives or friends) (27 women and 9 men, with a mean age of 37 ± 12.7 in the range 18–62 years), the other group comprised of 39 patients with the diagnosis of migraine (20 women and 9 men, with a mean age of 41 ± 11.3 in the range of 18–62 years) (treated at the University hospital in Hradec Kralove).

The group of migraine sufferers was further divided into three subgroups – 19 migraineurs in the interictal period (IntM) (13 women and 6 men, with a mean age of 37 ± 10.9 in the range 18–60 years), 10 migraineurs in the ictal period (IctM) (9 women and 1 man, with a mean age of 42 ± 11.6 in the range 19–62 years) and 10 migraineurs with chronic prophylactic treatment with anticonvulsant or anti depressive medication (MwT) (8 women and 2 men, with a mean age of 47 ± 8.4 years, range 25–57 years).

All the following clinical and demographic data were recorded by a questionnaire that each subject filled prior to his/her examination on the day of investigation. The healthy volunteers were included in the study under the condition that the questionnaire confirmed that, besides the absence of headaches in their history, they did not suffer from any disease of the central nervous system (neurological or psychiatric) and were not taking any medication that could influence brain function. In the group of migraineurs (patients with a clinical diagnosis of migraine), the questionnaire corresponded to the diagnostic criteria for migraine according to ICDH-II (The International Classification of Headache Disorders: 2nd edition, 2004). We excluded patients with chronic migraine. The distribution of migraine patients into their individual groups was based on the questionnaires and telephone contact 72 h after the examination. The migraineurs were included into the group of IntM when no headache was present 72 h before and 72 h after the examination. Patients who reported a headache during this period were included in the group of IctM. Furthermore, both groups also had to meet the condition of being on no chronic medication. Migraineurs whose questionnaires revealed that they were on chronic prophylactic anticonvulsant medication or antidepressant medication were included in the group of MwT. The group of MwT patients included 4× topiramate (three at a dose of 50 mg daily, one at 75 mg), 2× valproate (one at a dose of 500 mg daily and one at 800 mg daily) and 1 lamotrigine (100 mg daily), 3 SSRIs (Selective Serotonin Reuptake Inhibitors) respectively, 2× escitalopram (10 mg) and 1 citalopram (40 mg daily). The proportion of migraine patients receiving magnesium medication in any group was not high (three in IntM, one in IctM and three in MwT).

The group of 39 migraineurs consisted of 23 patients with the diagnosis of migraine without aura and 16 patients had migraines with aura (predominantly visual). The ratios of migraines without aura (MO) and with aura (MA) were 11:8, 7:3 and 5:5 in the IntM, IctM and the MwT groups respectively. The data from literature do not specifically differentiate MO and MA groups evaluation as no findings related to the general theme of the work showed any significant differences in the results (Omland et al., 2013).

In the group of migraine patients, the mean duration of migraines was 21 ± 12.7 in the range of 2–50 years (15 ± 9.8 in IntM, 24 ± 14.8 in IctM and 28 ± 10.4 in MwT). The average frequency of migraine attacks per month (over the last 6 months) in the group of migraineurs was 4 ± 2.7 in the range of 1–13 (4 ± 3.6 in IntM, 3 ± 2.3 in IctM and 3 ± 1.5 at MwT). Average duration of attacks in migraineurs was 24 ± 21.2 (26 ± 21.5 for IntM, 23 ± 21.2 for IctM and 21 ± 20.2 for MwT) in the range of 4–72 h in all groups. In women the questionnaire also collected data related to the menstrual cycle and hormonal contraceptive use, taking into consideration the presumption of hormonal influence on VEP