"BIOLOGICAL MARKERS" FOR MIGRAINE ?

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Objective

Migraine prevalence in childhood increases while the age of onset decreases. Diagnosis is difficult because of high psychiatric comorbidity and subjectivity of diagnostic criteria. This study was to investigate if visual evoked potential (VEP) parameters could be useful as additional objective criteria, and to further elucidate involvement of two parallel visual pathways in migraine pathophysiology.

Migraine is regarded as a cerebral information-processing disorder associated with central hypersensitivity, which might be at least partly inherited (Gerber and Schoenen, 1998). Visual symptoms and photophobia are common features of migraine, but are not exclusively confined to attacks. Hypersensitivity to light and specific gratings and altered visual processing (Coleston et al,. 1994) were found even in the migraine-free interval. This might be due to affection of two visual pathways in migraine, which has been proposed previously (Diener et al., 1989). The Y system receives input mainly from the retinal periphery via the magnocellular pathway (dorsal layers of lateral geniculate nucleus) and is very sensitive to contrast (Kubová et al., 1995). It processes movement and luminance. The X system receives input mainly from foveal and perifoveal areas via the parvocellular pathway (ventral layers of the lateral geniculate nucleus) and requires higher luminous intensities. It processes contrast and contour. Luminance- and contour processing pathways can be investigated by means of pattern-reversal visual evoked potentials (VEPs). Large patterns (i.e. low spatial frequency, 0.5 and 1 cpd) are mainly conducted by the Y system, whereas for small patterns (2 and 4 cpd) both the X system and the Y system are involved (Kulikowski, 1978). Thus, VEP parameters (latencies and amplitudes) vary as a function of check size. But pathway affection in migraine has yet not been investigated using electrophysiological methods, since all prior VEP studies were performed using only one single check size for stimulation. The aim of the present study was to clarify the affection and interaction of these two visual pathways in migraine by means of pattern reversal VEP. For that VEP components at four different spatial frequencies were compared to healthy controls.

Methods

Components of pattern-reversal VEPs were compared between young adult migraineurs (n=26) and healthy volunteers (n=28) in the headache-free interval (> 72 h before/after an attack). 13 had migraine without aura (MO, code 1.1) and 13 had migraine with aura (MA, code 1.2, Headache Classification Committee, 1988). Patients were included who reported having episodes of migraine headaches for at least two years (mean±SD 17.1±6.9 years) and had suffered at least 2 attacks per month in the last quarter year. Only subjects reporting no recurrent migraine-like headaches or ongoing medication were included into the control group.

Black-and-white checkerboard patterns (contrast >99%, reversal frequency 1 Hz) were binocularly presented, spatial frequencies (0.5, 1, 2, and 4 cpd) were applied in increasing order, i.e. proceeding from large to small checks. In addition, subjects had to rate (visual analogue scale): i) the visual discomfort provoked by each pattern, ii) the acoustic discomfort provoked by the white noise used for acoustic shielding, iii) aversive effects (eyeache, queasy feeling, headache, nausea, dizziness) and iv) the number of illusions (colors, shadows, grids etc.) after each block.

Statistical analysis was carried out with SPSS for windows, version 7.4. Results were compared by analysis of variance (MANOVA) for repeated measures. Subjective ratings were compared using non-parametric tests (Kruskal-Wallis test, Mann-Whitney U test). The a-level was set to 0.05.

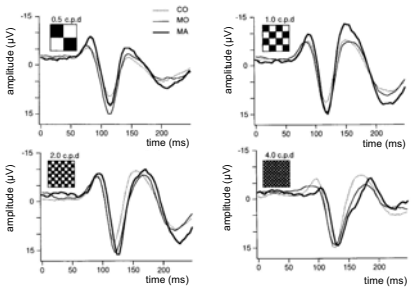

Fig. 1: Grand means of VEP at 0.5 cpd, 1 cpd, 2 cpd and 4 cpd in migraine with aura (MA), migraine without aura (MO) and controls (CO).

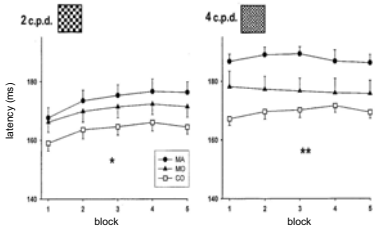

Fig. 2: Latencies of the N2 component (mean +/- SEM) at 2 and 4 cpd each with five consecutive blocks à 50 responses in migraine with aura (MA), without aura (MO) and controls (CO): Asterisks indicate significant differences between groups:

** 4 cpd: between-subjekt factor "aura":(MA vs. MO vs. CO): p=0.000; between-suvjekt factor "migraine": (MA + MO vs. CO): p=0.001.

* 2 cpd: between-subjekt factor "aura": (MA vs. MO vs CO): p=0.046; between-subjekt factor "migraine": (MA + MO vs. CO): p=0.017.

Results

Observed differences were dependent on VEP spatial frequency. Grand means of the VEP recordings are presented in Figure 1. Only at high spatial frequency N2 latency was significantly prolonged in migraineurs. At 4 cpd, latency prolongation was most pronounced in MA patients (first block 186.8±2.5 ms) but also found in MO patients (first block 178.2±5.3 ms) when compared with controls (first block 167.1±2.2 ms). Differences were significant between the three groups at 2 (p<0.05) and 4 cpd (p<0.001, Figure 2). N2 latency at the smallest check-size was longer than 172 ms in 80.7% of migraineurs but only in 21.5% of controls (chi-square test: p<0.001). N2 latencies at low spatial frequency (0.5 and 1 cpd) were not significantly different between groups.

Migraineurs reported significantly more color and figure illusions at all spatial frequencies (Figure 4). The number of illusions increased in both groups when small checks were presented, i.e. at high spatial frequency. The percentage of subjects reporting one to three aversive effects was augmented at high spatial frequencies in migraineurs but not in control subjects. Differences were statistically significant at 2 and 4 cpd (p<0.01). Rating of the white noise used for acoustic shielding revealed significantly higher discomfort in migraineurs at high spatial frequencies (p<0.05). Rating of visual discomfort was not significantly different between groups, but MA patients tended to experience more visual discomfort at 2 and 4 cpd (data not shown).

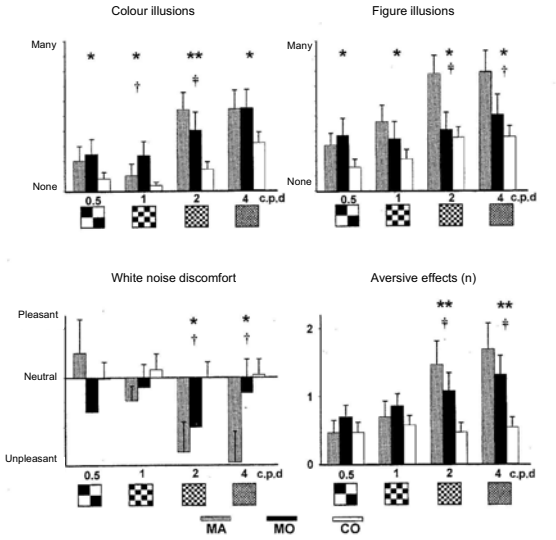

Fig. 3: Subjective ratings (visual analogue scales, mean) of VEP recordings at 0.5 cpd, 1 cpd, 2 cpd and 4 cpd in migraine with aura (MA), migraine without aura (MO) and controls (CO).

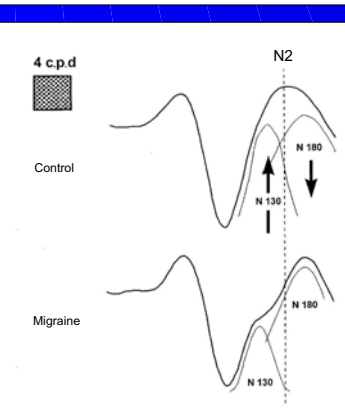

Fig 4:
Model of VEPs at high spatial frequency (4cpd). N2 can be regarded as a superposition of N130 and N180 with strong predominance of N130 in normal subjekts. In megraineurs, attenuation or lacking of a contour-specific N130 may cause a delayed N2 consisting mainly of the lumianance-dependent N180.

Conclusions

Migraineurs have prolonged N2 latencies when small checks are applied, no differences were found at low spatial frequencies, i.e. when large check sizes were used. VEP parameters vary as a function of check size. The N2 component at low spatial frequencies (N180) is ascribed mainly to the Y system. At high spatial frequencies, the N2 component is a superposition of an earlier contour specific component (called N130) and N180. In migraineurs, delayed N2 latency at high spatial frequencies may be due to an attenuated or absent N130 and/ or a relatively predominant N180 (Figure 5). This might reflect an imbalance of the two visual pathways with relative predominance of the luminance-dependent Y system.

Spatial frequency also influenced the psychophysical ratings. Subjective discomfort and aversive effects similar to symptoms of migraine attacks (eye-ache, queasy feeling, headache, nausea, dizziness) are particularly reported at high spatial frequencies in the migraineur group. The parallelism of objective and subjective findings might indicate that X-Y imbalance as a dysfunction of precortical visual processing might be relevant in migraine pathophysiology and is probably involved in triggering attacks.

Prolonged N2 latency at high spatial frequency may be useful as an additional objective criterion in migraine. It is currently investigated whether differences i) are specific for migraine, ii) are present in childhood migraine and iii) can be influenced by a psychotherapeutic pain group programme. For that VEPs of children and adolescents aged 6-18 yrs. with migraine (n=60), tension headache (n=60) or without headaches (n=60) are investigated. All headache patients are asked to take part in a psychotherapeutic pain group programm (Seemann et al, Medical Psychology of Heidelberg University). Participants will be reinvestigated 0 and 6 months after termination of the psychotherapeutic group programm to clarify whether or not clinical improvement has influence on VEP parameters.

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References

Coleston DM, Chronicle E, Ruddock KH, Kennard C. *Precortical dysfunction of spatial and temporal visual processing in migraine.* J. Neurol Neurosurg Psychiatry 1994;57:1208-11.

Diener HC, Scholz E, Dichgans J, Gerber WD, Jäck A, Bille, A, Niederberger U. *Central effects of drugs used in migraine prophylaxis evaluated by visual evoked potentials.* Ann Neurol 1989;25:125-30.

Gerber WD, Schoenen J. *Biobehavioral correlates in migraine: the role of hypersensitivity and information-processing dysfunction.* Cephalalgia 1998;18 Suppl 21:5-11.

Kubová Z, Kuba M, Spekreijse H, Blakemore C. *Contrast dependence of motion-onset and pattern-reversal evoked potentials.* Vision Res 1995;35:197-205.

Kulikowski JJ. *Pattern and movement detection in man and rabbit: Separation and comparison of occipital potentials.* Vision Res1978;18:183-9.

Oelkers R, Grosser K, Lang E, Geisslinger G, Kobal G, Brune K, Lötsch J: *Visual evoked potentials in migraine patients - alterations depend on pattern spatial frequency.* Brain 122:1147-55, 1999.