Some aspects of the pathophysiology of migraine in children and adolescents

Wybrane aspekty patofizjologii migreny u dzieci i młodzieży

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ABSTRACT

Migraine is a common cause of severe headache in schoolchildren. Population-based studies estimate the prevalence rates of migraine in children and adolescents between 2.7% to 13.1% [1,2]. The prevalence of migraine increases with age, with male preponderance in children under 12, and female preponderance thereafter [1].

Although migraine is a long-known pathology accompanying mankind from the dawn of history, its pathogenesis remains unclear. Our understanding of migraine pathophysiology is a work in progress. As more is learned about migraine, it seems that the probability of identifying a single unifying explanation for this common disorder becomes less and less [3]. It is now believed that migraine is associated with an inborn predisposition to hypersensitive neurovascular reactions that may be induced by specific factors or may result from cyclic changes in the central nervous system [4,5]. The emerging complexity of migraine genetics suggests that an acute attack may be the final common expression of more than one type of initiating abnormality [3]. Every individual has an inborn migraine threshold with the degree of sensitivity depending on the balance between stimulation and inhibition at different levels of the nervous system. This balance may shift with age, with male preponderance in children under 12, and female preponderance thereafter [1].

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in common. The controversial role of oxidative stress in migraine, in particular during the pain-free period, is also discussed [6].

Based on clinical history, an allergic mechanism and the involvement of the immune system have also been hypothesized to be involved in migraine attack precipitation. [7]. The interaction between immune cells is finely regulated by several mechanisms and, among them, cytokines play a crucial role in modulating the quality and the intensity of immune responses. Studies on cytokines in patients with migraine have shown fluctuations of cytokine levels in adult migraineurs, but conflicting results have been reported on the mechanisms involved [7].

Although most neurophysiological tests have limited value for headache diagnoses, they have vast potential for exploring the pathophysiology and the effects of pharmacological treatment. The sequence of activation of the neuronal structures in migraine attack are still debated [3,5]. Electrophysiological techniques allow the study of some of the structures in vivo and enhance our knowledge of the controversial aspects of migraine pathophysiology, such as cortical excitability or central sensitization [8]. The advantage of evoked potential and EEG studies is that the method is non-invasive and can be repeated on the same individual at different time points. The interictal abnormalities of cerebral information processing in migraine were found by studying event-related potentials and different modality-specific evoked potentials: visual, auditory, and less frequently somatosensory. The results have been reviewed and summarized elsewhere [8,9]. Considering the great number and variety of neurophysiological tests, the lack of research protocol standardization, heterogeneous groups of patients, and central effects of certain pharmacological treatments, it is very difficult to interpret the conflicting results.

Moreover, most studies had been performed in adult migraineurs, some of whom had a long history of disease and medication. So, we focused on some aspects involved in migraine pathogenesis: oxidative stress, the role of cytokines and electrophysiological changes in children and adolescents with migraine. Elucidation of the mechanisms responsible for migraine attacks may create new possibilities for more effective treatment of this disease.

OXIDATIVE STRESS IN MIGRAINE

We found some disturbances of lipid peroxidation in children with migraine [10]. The study group consisted of 34 patients aged 10-18 years (mean ± standard deviation: 14.04 ± 2.29 years) suffering from migraine. The control group included 38 patients, aged 4-17 years (mean age 12.11 ± 3.46). The study objective was to assess the processes of lipid peroxidation with malondialdehyde (MDA) as its major indicator as well as the activities of antioxidative enzymes: superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and glutathione reductase (GSSG-R) in the serum and erythrocytes of adolescent patients with migraine with and without aura. MDA concentration and activities of SOD, GSH-Px and GSSG-R were determined in the serum and erythrocytes of all the patients. In the migraine group, the MDA levels in serum and erythrocytes were statistically significantly lower than in the control subjects (p<0.001). In the migraine group, serum GSH-Px activity was significantly higher (p<0.05). GSSG-R activity in the erythrocytes of migraine children was significantly higher compared with controls (p<0.001). SOD activity was decreased and GSH-Px was increased (not significantly) in erythrocytes of migraineurs. Our results confirmed the disturbances of lipid peroxidation processes in migraine and suggest the activation of antioxidative mechanisms [10]. Its important indicator seems to be the increase of GSSG-R activity in erythrocytes and GSH-Px activity in serum between migraine attacks. Because these results and other data from literature have been showed to impair oxygen metabolism and the possible role of oxidative stress, some researchers have suggested the involvement of some mineral, coenzyme, vitamin and other natural free radical scavengers defects in the pathogenesis of migraine [11]. In our next paper we focused on their potential therapeutic use in the preventive treatment for migraine [12]. Diet is commonly thought of as one of the many factors that can trigger migraine. However, conflicting reports have appeared in the literature confirming or denying the role of dietary precipitated migraine [12]. Furthermore, the drugs used in migraine have been postulated to be important factor affecting the oxidant-antioxidant balance. The major classes of medications for migraine prevention are beta blockers, calcium channel blockers, tricyclic antidepressants, anticonvulsants and non-steroidal anti-inflammatory drugs [13]. There are multiple mechanisms of action on which the preventive agents act. Free radicals scavengers, like fluunarizine, may provide a potential molecular basis for prophylactic antimigraine therapy by neutralizing nitric oxide overproduction and possibly preventing the formation of highly toxic peroxide [13,14].

CYTOKINE FLUCTUATIONS IN MIGRAINE

Cytokines are small proteins produced by most cells in the body; they possess multiple biologic activities that promote cell-cell interaction. In order to understand the role of cytokines in migraine, in our study we focused on selected pro-inflammatory cytokines [15]. The study group consisted of 21 children suffering from migraine with and without aura and also 24 subjects with episodic tension-type headache as controls. Plasma interleukin-1-alpha were undetectable in 19 controls with tension-type headache, but in 16 patients with migraine interleukin-1alpha was detectable. This could suggest that interleukin-1alpha levels could be higher than in the control group. Soluble receptor for tumor necrosis factor in the migraine group was significantly higher in comparison with the levels in the tension-type headache group (p<0.0005). Migraine patients tended to have increased tumor necrosis factor alpha level than controls. The interleukin-1alpha level was significantly higher in migraine with aura in comparison with migraine without aura (P<0.05). Tumor necrosis factor alpha and soluble receptor for tumor necrosis factor levels were also increased (non-significantly) in the migraine with aura subgroup. So, we have confirmed some fluctuations of proinflammatory cytokine levels in childhood migraine [15]. Moreover, our results suggest that pro-inflammatory cytokines may be involved in the pathogenesis of migraine.
attacks but cytokine level fluctuations in children could be different than in adults. A possible cause could be a long medical history of migraine in adult patients and frequent intake of analgesic drugs or prophylactic treatment.

In our next study, we focused on selected anti-inflammatory cytokines during the headache-free period in children with migraine [16]. We analyzed interleukin-4 (IL-4), interleukin-10 (IL-10) and interleukin-13 (IL-13) levels in plasma from children and adolescents with migraine and tension-type headaches during the interictal period. The study group consisted of 35 children and adolescents between 7 – 18 years old suffering from migraine headaches with or without aura. The control group consisted of 33 patients suffering from episodic tension-type headaches. IL-4 was detected in 17.1% of patients with migraine headaches and in 28.6% of patients with tension-type headaches. IL-13 was detected in 17.1% of patients with migraine headaches and in 15.2% of patients with tension-type headaches. IL-10 was only detected in 3 of 68 (4.4%) patients. Any significant correlations between measurable cytokine levels and age, gender, aura, duration of disease, frequency and severity of headaches were determined. No significant fluctuations of selected anti-inflammatory cytokines during the headache-free period in children with migraine and tension-type headaches have been found [16]. However, immune dysfunction in children with migraine could not be excluded.

THE ELECTROPHYSIOLOGY OF MIGRAINE

Electrophysiological techniques allow the study of some of the structures in vivo and enhance our knowledge on the controversial aspects of migraine pathophysiology, such as cortical excitability or central sensitization [8,9]. The advantage of evoked potential studies is that the method is non-invasive and can be repeated on the same individual at different time points. In our studies, we focused on non-invasive techniques that could be used as routine tests in children and that represented different modalities of activity in the cerebral cortex between attacks: 1) pattern-reversal-visual-evoked potentials (PR-VEP), 2) auditory-cognitive-event-related potentials (CERP), 3) short-latency somatosensory-evoked potentials (SEP) and 4) electroencephalography (EEG). The subjects were children and adolescents with newly diagnosed migraine, without previous prophylactic treatment.

The study of PR-VEP was carried out on 93 children and adolescents with recurrent headaches aged 7 – 18 years [17]. Fifty-one children had been diagnosed with migraine. In this group, 30 children had migraine without aura, and 12 children had migraine with aura. Nine patients had complicated migraine syndromes, including cases of hemiplegic, ophthalmoplegic and basilar migraine. Forty-two children were classified as episodic tension-type headaches. The P100 mean latency was significantly longer and amplitudes N1-P100 and P100-N2 were higher in migraineurs compared to patients with tension-type headache. The mean amplitudes of N1-P100 and P100-N2 were significantly lower in migraine with aura compared to subjects without aura. There were no statistically significant differences of other PR-VEP parameters between groups.

Only 25% of the migraineurs had PR-VEP abnormalities of latency or amplitude above mean value ± 2 standard deviations value in the tension-type headache group.

The clinical observations, neuropsychological evaluations, and neurophysiological tests of cognitive abilities in adult and adolescent migraineurs indicated an association between migraine (especially those with aura) and short- and long-term impairment of cognitive abilities, such as memory, attention, visuomotor processing and reasoning [8]. So, in our next studies we focused on Cognitive Event Related Potentials [18,19]. The study sample included 111 children and adolescents aged 7 to 18 years: 27 suffered from migraines with aura (MA), 36 suffered from migraine without aura (MO), and 48 had episodic-tension-type headaches (TTH). CERP was performed interictally at least two days after the last headache attack. The latencies N2 and P3 of CERP were significantly longer in the group of all migraineurs in comparison with the TTH group. In the MO group, not only were N2 and P3 latencies longer, but also P2 latency and the N1/P2 amplitude were significantly higher than in the TTH group [19]. We found a correlation between P3 latency and the age of patients with migraine. There were no statistically significant correlations for either headache type between CERP parameters and illness duration, gender, and unilateral localization of pain [18].

We also analyzed the median SEPs in children between headache attacks [19]. Statistical analyses revealed no significant asymmetry between the left and right median nerve SEPs recorded at the right and left scalp location in the MO, MA, and TTH groups. There were no significant differences in the SEP latency averages between all migraineurs (MO and MA subgroups) and TTH subjects. However, the N9 and N13 latency averages were significantly lower (P<0.05) in the MO group compared with the MA and TTH groups. In the migraine subgroups (MA and MO), the mean values of N20, P25 component latencies, and the peripheral and central conduction times were not significantly different from those of the TTH group. We found positive correlations between the age of the patient and N9, N13 and N20 latency. We found no significant correlations between the SEP parameters and disease duration, family history of migraine, and unilateral localization of pain.

Although EEG is not recommended for the clinical diagnosis of recurrent headaches in children, EEG has vast potential to help explore the pathophysiology of migraine [8]. Qualitative and quantitative EEG analysis in children and adolescents with migraine was performed [20,21]. Patients with epilepsy or a history of seizures were excluded. EEGs were performed interictally at least 24 hours after the last headache attack. Interictal EEGs of 116 patients aged 7-18 years with recurrent headaches were studied [20]. Twenty artifact-free 2 sec.-epochs of EEG from F3-Pz and O1 leads were selected and analyzed for alpha, theta, beta, and delta bands. Abnormal EEGs were found for 69 (59.5%) children with all types of headache [20]. Quantitative analysis of the EEGs did not show significant differences between groups MA, MO and TTH. In our next study, we studied 128 children and adolescents
ranging in age from 7 to 18 years: 35 had migraine with aura, 45 had migraine without aura, and 48 had episodic tension-type headaches [21]. The EEGs were interpreted as abnormal for 62.9% of the children with migraine with aura, 45 had migraine without aura, and 48 had episodic tension-type headaches. Epileptiform discharges were detected in about 50% in each group with recurrent headaches. The migraine without aura group showed a higher incidence of attenuation of EEG activity and focal slow activity, as well as a lower incidence of generalized epileptic activity and generalized slow activity. There was an obvious trend towards a higher incidence of epileptic activity in response to photic stimulation in migraine vs. tension-type headaches, particularly in migraine without aura. There were no significant differences in the distribution of the alpha, beta, theta and delta rhythms in the background EEG activity in patients with recurrent headaches. The results of these studies, based on children without a history of seizures suggested that the increased incidence of EEG abnormalities in childhood migraine do not necessarily point to an epileptic origin. Some differences between the interictal EEG patterns could confirm a central neuronal hyperexcitability in migraine. EEG evaluation could also be useful for exploring the effects of pharmacological treatment. We studied the effects of piracetam and flunarizine in migraine prophylaxis [22]. In quantitative EEG analysis, the percentage of frequency bands before and after 3 months of therapy was compared. We found a significant increase in the alpha band and a decrease in the theta and delta bands in the piracetam group [22].

CONCLUSIONS
1. Our results confirmed the disturbances of the lipid peroxidation processes in migraine. They suggest the activation of antioxidative mechanisms. Its important indicator seems to be the increase of GSSG-R activity in erythrocytes and GSH-Px activity in serum between migraine attacks. We suppose that it could be an antioxidant defense reaction to the oxidant stress in a migraine attack.
2. Our results suggest that cytokines TNF-α, sTNF-RI and interleukin-1 alpha may be involved in the pathogenesis of migraine attacks. The pro-inflammatory cytokine level fluctuations in children could be different than in adults.
3. No significant fluctuations of selected anti-inflammatory cytokines during the headache-free period in children with migraine have been found, but immune dysfunction in migraineurs during migraine attack could not be excluded.
4. In accordance with similar studies in adult migraineurs, our results of cortical evoked potentials and event-related potentials confirmed a dysfunction in cortical information processing in children with migraine with and without aura between headache attacks.
5. The results of EEGs based on children without a history of seizures suggested that the increased incidence of EEG abnormalities in childhood migraine do not necessarily point to an epileptic origin. Some differences between the interictal EEG patterns could confirm a central neuronal hyperexcitability in migraine.
6. The diagnosis of migraine in children currently remains predominantly based on medical history. However, laboratory and neurophysiological tests could be helpful methods in studying the pathogenesis of different forms of migraine.

REFERENCES
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