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SCIENTIFIC APPROACH TO MIGRAINE

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Summary

Migraine is a common episodic headache disorder; prevalence of migraine in most western countries is 10-12%. The mechanism of migraine pain development is not fully understood. The theory of neurogenic inflammation proposes that the main event is the inflammation in the vessel wall which leads to leakage of nociceptive substances, causing thickening of the vessel wall and dilatation of vascular smooth muscles. The release of vasoactive neuropeptides causes depolarization of trigeminal perivascular axons, thus causing pain. Triptans are recommended for acute migraine attacks; studies have shown that their use increases productivity at work and improves the quality of life. Preventive therapy is recommended in migraine patients with frequent, severe, long-lasting attacks, in cases where acute therapy is not efficient, if there is a contraindication to the drug, failure or unbearable side-effects from acute treatments, overuse of acute medications or in special cases such as hemiplegic migraine. Beta-blockers and tricyclic antidepressants were often used as first line therapy for migraine prevention. Other p reventive drugs include pizotifen, flunarizine, and anticonvulsives. Migraine is often associated with a number of commorbid diseases: allergies, hypotension, epilepsy, fatigue sy, gastritis, iritabile colon disease, vertigo; therefore, preventive and acute therapy should be tailored individually.

Key words: migraine; pathophysiology; diagnosis; therapy.

PREVALENCE OF MIGRAINE

Migraine is a common episodic headache disorder. Population-based epidemiological studies about headaches especially migraine, have been carried out

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in many countries. In western European countries and in the USA the prevalence of migraine is 10-12% (15-18% in women and 6% in men) [1,2]. The prevalence of migraine is higher in North America and Europe and lower in Africa and Asia [1]. Prevalence of migraine is consistently higher among women than men and varies from 1.5% to 33% in women and from 0.6% to 22% in men [1,2].

Studies show differences in prevalence of migraine between countries, even in the same country, which is most due to methodology of data collection. Majority of epidemiological studies were undertaken before the second edition of the International Classification of Headache Disorders (ICHD-2) [3] and assessed the prevalence of „strict migraine". Since clinical and epidemiological studies show that a proportion of the studied population does not fulfill all criteria for migraine but clinically most likely have migraine, a subgroup of „probable migraine" was introduced. Some studies published before the ICHD-2 criteria have classified migraine that does not fulfill all criteria for migraine as „border-line migraine" [4] and other as „probable migraine"[5,6].

We have also conducted an epidemiological survey in Croatia; the aims of this study were to assess the 1-year prevalence of migraine, probable migraine and tension-type headache in the Croatian population. The design of the study was a cross-sectional survey of an adult population sample using a self-completed questionnaire. The results of our study have shown that the 1-year prevalence of migraine in this study was 6.22% (women 8.3%, men 4.0%), probable migraine 8.78% (women 12.39%, men 5.0%) and tension-type headache 20.65% (women 23.8%, men 17.1%). The prevalence of combined migraine and probable migraine was 15.0% (women 20.6%, men 9.0%). Prevalence of migraine with aura was 2.5%. Total prevalence of headache (combined migraine, probable migraine and tension-type headache) was 35.65% (women 44.4%, men 26.1%). Prevalence of migraine was higher in continental than in Mediterranean areas of Croatia. We concluded that the prevalence of migraine and probable migraine is similar as in other Western countries. Certain demographic characteristics differ among patients with and without headache. Some studies have shown higher prevalence of migraine among people with high education level [7], while others have not [8,9]. Most studies have not shown a correlation between marital status and migraine, in one study more migraine patients were married, while other study showed greater prevalence of migraine in divorced and widowed [10,11]. One study showed no correlation of migraine and employment status, although retired had less migraine, the same study showed higher prevalence of migrai-

ne among employed. Higher migraine prevalence among urban areas has been shown in two studies [11,12].

PATHOPHYSIOLOGY OF MIGRAINE

The mechanism of migraine pain development is not fully understood. The theory of neurogenic inflammation proposes that the main event is the inflammation in the vessel wall which leads to leakage of nociceptive substances, causing thickening of the vessel wall and dilatation of vascular smooth muscles. The release of vasoactive neuropeptides causes depolarization of trigeminal perivascular axons, thus causing pain [13]. Epidemiological studies regarding the vessel lumen diameter and studies including changes of cerebral hemodynamics and vasoreactivity during migraine attack and in free periods contribute to the understanding of migraine pathomechanism [14-17].

There is a longstanding belief that hereditary factors are involved in migraine, this view is supported by the results of recent genetic mapping studies. Migraine is a polygenic multifactorial disorder; it seems likely that a combination of genetic factors interact with enviromental triggers to produce migraine in susceptible patients. Genetic factors likely account for 30% of the risk, with environmental factors contributing 70% of the risk). A gene for familial hemiplegic migraine has been mapped to chromosome 19 in most families. The genetics of the more frequent variants, migraine with and without aura, is more complex [17].

Evidence from other studies supports the view that PM is a form of migraine. A genetic study showed that PM and migraine without aura aggregate in some families [18]. If PM is a prevalent form of migraine, population studies focusing on strict migraine (ICHD-2 1.1 and 1.2) may underestimate the significance and impact of migraine. Therefore, diagnosis of PM in clinical practice is an important issue.

DIAGNOSIS OF MIGRAINE

There are, as yet, no tests that confirm the diagnosis of migraine [19-21]. The headache diary is the most important diagnostic tool and should be filled in for at least 3 months in which frequency, duration and intensity of migraine attacks are registered. The total number of hours with headache per month, presence of accompanying symptoms, the use of symptomatic therapy should be listed. Selective testing, including neuroimaging (computed tomography [CT] or

magnetic resonance imaging [MRI]), electroencephalogram, lumbar puncture, cerebrospinal fluid and blood studies, may be indicated to evaluate for secondary headache if causes of concern have been identified in the patient history or physical examination. Diagnosis may be complicated if several headache types coexist in the same patient. Neuroimaging is not usualy warranted for patients with migraine and normal neurological examination. For patients with atypical headache features or patients who do not fulfill the strict definition of migraine (or have some additional risk factors), a lower threshold for neuroimaging may be applied.

THERAPY OF MIGRAINE

Preventive therapy is recommended in migraine patients with frequent, severe, long-lasting attacks, in cases where acute therapy is not efficient, if there is a contraindication to the drug, failure or unbearable side-effects from acute treatments, overuse of acute medications or in special cases such as hemiplegic migraine. Treatment should be selected on individual basis taking into consideration co-morbidities, efficacy of the drug, adverse reactions, patient preference, availability and costs [20-25]. Prophylactic therapy for migraine should be based on guidelines from evidence-based medicine. Although double-blind placebo controlled studies provide un-biased results, they are sometimes difficult to carry out, therefore open-label studies offer additional data on the efficacy of pharmacological or non-pharmacological treatment. The chosen drug should be started in low dose and gradually increased, and should be given an adequate trial (at least three months).

Medications used in migraine prophylaxis come from different pharmacological classes and most have primary indications for other medical conditions [21,23,25]. Beta-blockers and tricyclic antidepressants were often used as first line therapy for migraine prevention. Other preventive drugs include pizotifen, flunarizine, and methysergid [26].

However, in some patients, in whom these medications are contraindicated, or who have comorbid diseases, antiepileptic drugs (AEDs) may be offered as an appropriate first-line prophylactic treatment. Trials with AEDs as prophylactic drugs in migraine have shown that certain AEDs can be offered in patients refractory to usual prophylactic treatment.

Valproate was the first AED recommended for migraine prevention. Divalproex sodium and sodium valproate (300-900 mg) in controlled studies have shown

consistent efficacy in reducing headache frequency compared with placebo [27,28]; compared with propranolol there was no significant difference in efficacy [29].

Several double blind placebo controlled studies have shown that topiramate is effective in migraine prophylaxis: one study showed a mean 28-day migraine frequency reduction by 36% in patients receiving topiramate vs 14% in placebo group; 26% achieved a 50% reduction in migraine frequency vs 9,5% in placebo group, 2 out of 19 topiramate treated patients discontinued treatment due to adverse events [30]. Topiramate was efficient in the prophylaxis of chronic migraines: reduction of headache frequency > 50% was 58,3% in episodic migraine and in 38.0% in chronic migraine patients on topiramate up to 100 mg twice daily; the mean headache severity was reduced from 6.2 to 4.8 on a 10-point scale, both results significant [31]. A double-blind, crossover clinical trial compared the efficacy of topiramate and sodium valproate in migraine prevention and the two drugs appear to be equivalent in efficacy and safety; a significant decrease in duration, monthly frequency and intensity of headache occurred in both groups: in valproate group the mean monthly frequency decreased from 5.4 to 4.0 and in topiramate group from 5.4 to 3.2 and headache intensity from 7.7 to 5.8 and from 6.9 to 3.7, respectively [32].

Gabapentin is among AEDs that has been evaluated for its effectiveness in migraine prevention [33-35]. In a 12-week open-label study gabapentin in dosage of 600-1800 mg was effective in episodic and chronic migraine, headache frequency decreased from 25.2 to 11.6 per month, side effects in this study were minimal [33]. A placebo controlled study with 98 patients receiving gabapentin and 45 placebo showed that gabapentin in dosage of 1800-2400 was effective in reducing the frequency of migraine attacks: the responder rate (50% decrease in attack frequency) was 46,4% in the gabapentin group and 16,1% in placebo; furthermore a 4-week migraine headache rate decreased from 4.2 to 2.7 in gabapentin group and from 4.1 to 3.5 in placebo group which was significant [34]. Lamotrigine has shown to be efficient in prophylaxis of migraine with aura. Three open label studies showed that lamotrigine reduces the number of migraine auras and the frequency of migraine attacks. In 13 out of 21 patients receiving lamotrigine 100 mg attacks were completely abolished and one patients was unresponsive to the treatment at the end of the third month [36]. In other two studies lamotrigine significantly reduced the number of migraine auras (from 4.2 to 0.7) [37], the duration of the migraine auras and the frequency of migraine attacks [38].

For acute attacks, triptans are widely recommended for migraine since studies have shown that their use increases productivity at work and improves the quality of life of migraine sufferers [39]. However, studies worldwide show

that the majority of migraine patients are using OTCs and the minority is using triptans [40-43]. Most studies worldwide show that in general population triptans are taking 3-19% of patients with migraine, while most patients are taking simple analgesics [40-43]. In some countries, higher percentages of triptan use have been observed, as 48.7% in Canada (44). Preventive treatment uses a low percentage of migraine patients, studies show a range from 6-12.4% [41,45].

Studies continuously show low rates of medical consultations in patients with headache, even in those patients who are aware of their condition [40,45]. A large number of migraine patients have no medical follow-up for their condition, and think that consultations are useless and that there is no cure for migraine [41]. Many migraine sufferers who do consult physicians for migraine do not receive a correct diagnosis. In a US study, 40% of migraine sufferers stated that they have not been told as having migraine even after consultation with a physician [46]. In another US study only 45 % of migraineurs who consulted for headaches were correctly diagnosed [47]. Many migraine patients who do consult their physicians find that their prescribed acute medications provide inadequate relief. In a population-based study in United States, only 29% of migraineurs reported that they were "very satisfied" with their usual acute treatment [48].

COMMORBID DISEASES

Migraine is often associated with a number of commorbid diseases: allergies, hypotension, epilepsy, fatigue sy, gastritis, iritabile colon disease, vertigo. Vertigo has been found to be three times more common in migraine patients than in the control group: vertigo occurred in 24-27% of migraine patients compared with controls (8-10%) [49,50]. Studies show that among patients with migrainous vertigo, vertigo was regularly associated with migrainous headache by 24% to 45%; [51,52]. Similar findings have been shown in other studies [49,53] as well as in a study performed at the Headache clinic at the Department of Neurology Sestre milosrdnice University Hospital: vertigo symptoms were associated with a migraine attack always in 38 (22.5%), sometimes in 38 (22.5%) and were not associated in 93 (55.0%). This means that the lifetime prevalence of migrainous vertigo is 23.2% in the population of our migraineurs according to the proposed criteria [54].

Migraine and probable migraine are associated with substantial disability measured by decrement in health related quality of life (HRQoL) and MIDAS score. Migraine causes significant burden for both the individual and society. Calculations of direct costs generally include physician visits, emergency department treatment, inpatient care and pharmacotherapy. Indirect costs include

lost work days and reduced performance at work; two-thirds of the financial burden is linked to indirect costs. Approximately ¾ of migraine sufferers have a reduced ability to function during attacks with more than half reporting severe disability or need for bed rest. Therefore, the diagnosis and treatment of migraine should be improved.

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Sažetak

Znanstveni pristup migreni

Migrena je česta glavobolja čija se prevalencija kreće u zapadnim zemljama između 10-12%. Mehanizam boli kod migrene nije sasvim razjašnjen. Po teoriji neurogene upale glavno zbivanje je upala stijenki krvnih žila koja dovodi do istjecanja nociceptivnih supstanci što uzrokuje zadebljanje zida arterija te dilataciju glatkih mišićnih stanica. Otpuštanje vazoaktivnih neuropeptida uzrokuje depolarizaciju trigeminalnih aksona što dovodi do pojave boli. Triptani se preporučaju u akutnim napadajima migrene; istraživanja su pokazala da se njihovom upotrebom u akutnom napadaju migrene povećava produktivnost na poslu i poboljšava kvaliteta života. Preventivna terapija se preporuča kod osoba s učestalim jakim i dugotrajnim napadajima, te u slučajevima kada akutna terapija nije učinkovita, ukoliko postoji kontraindikacija ili su izražene nuspojave za primjenu akutne terapije, te u slučajevima kada se radi o obiteljskoj hemiplegijskoj migreni. U preventivnoj terapiji preporučaju se beta blokatori i triciklički antidepresivi a od ostalih lijekova se preporučaju pizotifen, flunarizin te antiepileptici. Migrena je često udružena s komorbidnim bolestima poput alergija, hipotenzije, epilepsija, sindromom kroničnog umora, iritabilnim kolonom, gastritisom i vertigom; stoga se akutna i profilaktička terapija moraju individualno određivati.

Ključne riječi: migrena; patofiziologija; dijagnoza; terapija.