The Face of Chronic Migraine Which Has Started to be Clarified
Kronik Migrenin Aydınlanmaya Başlayan Yüzü

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ABSTRACT
Recently, information about migraine which is generally characterized with attacks has gradually increased. In some patients with migraine, progression may be observed such that the frequency and time of the attacks are increased and an attack lasts for days. This condition is called chronic migraine (CM). According to the last classification, chronic migraine is defined as headache which occurs 15 days a month or more frequently at least 8 of which show the characteristic properties of migraine or response to migraine-specific treatment. The diagnostic criteria of chronic migraine, its differences from other chronic daily headaches and the question if it is a migraine form with a high frequency which transforms from episodic migraine or a completely different pathophysiological picture are still contradictory. Clarifying these issues is possible with clinical studies as well as increasing the studies directed to investigate the pathophysiological mechanisms. (Archives of Neuropsychiatry 2013; 50 Supplement 1: 21-25)

Key words: Chronic migraine, headache, chronic daily headache

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Definition
Migraine is usually characterized with attacks and we have been provided with increased information about migraine recently (1). The persistent tendency of the patients with migraine to attacks (2, 3), abnormalities in cortical function (4) and disrupted quality of life (5) even between attacks suggest that migraine is not only an episodic condition, but a chronic disease characterized with attacks (6).

In addition, progression such as increase in the frequency and in the time periods of attacks and lasting of attacks for days may be observed in some patients. This condition is named as chronic migraine (CM). This picture for which different views have been proposed on definition and criteria for a long time is one of the areas neglected in the first classifications of migraine and could not take the place it deserves in studies for long years. It differentiation from other chronic daily headache pictures including mainly chronic tension headache is important. Although changing and developing definitions have been proposed in years in the classifications of the International Headache Society-IHS, the definition of the last classification is as follows: chronic migraine occurs 15 days a month or more frequently and at least 8 of these attacks have
migrainous character or respond to migraine-specific treatment (Table 1) (7). It is important that drug overuse is questioned and excluded, if possible.

Triptans, serotonin 5-HT 1B/1D receptor agonists or ergotamine derivatives are accepted as migraine-specific treatment. A history of migraine without aura is present in 90% of the patients with CM. While headaches become frequent in months or years, the frequency and severity of related symptoms including photophobia, phonophobia and nausea decrease (8). Another important issue is the fact that CM was considered among migraine complications in the final classification (9). All etiologic causes should be excluded before a diagnosis of CM is made.

The issues about chronic migraine which are still being debated currently include the diagnostic criteria, if it is different from chronic daily headaches or it is a form of migraine with a high frequency transforming from episodic migraine or a completely independent pathophysiologic picture. Elucidation of these points is only possible with elucidation of the pathophysiologic mechanisms.

Epidemiology

Although the worldwide prevalence of chronic migraine changes according to different studies, it is approximately 1-3% (10,11,12). When chronic migraine is compared with episodic migraine (EM), it is generally considered a rare subtype of migraine, but it is observed more frequently compared to epilepsy and other neurological diseases (13).

According to a large population-based epidemiological study performed in our country, the prevalence of migraine is 16.4%. Approximately 10% of these patients with migraine have CM (Table 2). Chronic migraine occurs most frequently between 20 and 50 years of age (14).

The “American Migraine Prevalence and Prevention” study is a large study investigating the epidemiology of migraine and CM. According to this study CM was found approximately in 2% people (15). In addition, the mean age and body mass index of the patients with CM were found to be higher and the education level was found to be more frequently compared to epilepsy and other neurological diseases (13, 21).

The prevalence of chronic migraine in Turkey has started to be clarified. The prevalence of chronic migraine and probable chronic migraine in Turkey (14).

It has been shown that chronic migraine and EM are related with psychiatric and medical diseases. Especially, the relation of CM with comorbid diseases is stronger compared to episodic migraine. It has been observed that psychiatric and painful diseases are related with CM more frequently. In addition, the association of obesity and cardiovascular disease is more frequent in CM. The rates of other related diseases in CM and EM are given in Table 3 (16).

Chronic migraine affects social life and physical and occupational performance with a great extent (16, 17). The lives of patients with CM are affected with a higher rate compared to patients who have a lower frequency of migraine (18, 19). Because of a higher number of days with pain and higher disease load, the disability in CM is much higher compared to EM (18, 19).

When the patients were evaluated by MIDAS (Migraine Disability Assessment) questionnaire (20), it was observed that the mean score was higher in patients with CM compared to EM and the disability was observed to be 2-fold higher (CM: 20%, EM: 11.1%) (13, 21).

It has been observed that chronic migraine develops in approximately 2.5-3% of the patients with episodic migraine (22, 23). Risk factors for chronic migraine have been defined as low socioeconomical status, obesity, snoring, comorbid pain, neck and head trauma, stressful events, high caffeine intake, overusse of analgesics drugs, anxiety, depression and allodynia (22, 24).

Especially the relation between drug overuse headache and CM is similar to chicken-egg relation and it is not clear which one is the initiating factor in many cases. In cases of idiopathic intracranial hypertension without papilledema, intracranial hypotension and chronic meningitis should be considered in the differential diagnosis. Therefore, it is very important to perform

<table>
<thead>
<tr>
<th>Co-morbid disease</th>
<th>Chronic migraine (%)</th>
<th>Episodic migraine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>33.6</td>
<td>22.2</td>
</tr>
<tr>
<td>Non-migraine chronic pain</td>
<td>31.5</td>
<td>15.1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>30.2</td>
<td>18.8</td>
</tr>
<tr>
<td>Depression</td>
<td>42.2</td>
<td>25.6</td>
</tr>
<tr>
<td>Bipolar disease</td>
<td>4.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Obesity</td>
<td>25.5</td>
<td>21.0</td>
</tr>
<tr>
<td>Circulatory problems</td>
<td>17.3</td>
<td>11.4</td>
</tr>
<tr>
<td>Heart disease</td>
<td>9.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33.7</td>
<td>27.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Allergy</td>
<td>59.9</td>
<td>50.7</td>
</tr>
<tr>
<td>Asthma</td>
<td>24.4</td>
<td>17.2</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>19.2</td>
<td>12.9</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>9.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Emphysema or chronic obstructive lung disease</td>
<td>4.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>45.2</td>
<td>37.0</td>
</tr>
</tbody>
</table>
The relation between migraine (especially migraine with aura) and stroke has been known for a long time. Migraine with aura is a risk factor for subclinical ischemic lesions in the posterior system and brain stem. Supratentorial lesions have also been shown in individuals who have infratentorial lesion. It has been thought that this was caused by the hemodynamical changes during migraine attacks (31). No significant increase in possible ischemic risks for CM has been noted. In addition, migraine is also a risk factor for cardiovascular diseases. The risk of angina, myocardial ischemia and the mortality related with cardiovascular events is higher in patients with migraine with aura (32).

Conclusively, it is thought that migraine progression occurs by triggering of migraine attacks by the underlying mechanisms or some dysfunctions with an increase in the frequency of the attacks.

**Treatment**

Preventive treatment should be administered in all patients with chronic migraine, but it has been shown that only 3-13% of the patients used prophylactic drugs in population-based studies (22). Preventive treatment renders acute attack treatment more efficicent (33).

The drugs used in treatment of chronic migraine are the same drugs used in migraine prophylaxis. These include beta-blockers which are used in hypertension and cardiac rhythm disorders (propranolol, metoprolol, nebivolol), calcium channel blockers (verapamil, flunarizine), epilepsy drugs (valproic acid, topiramate, gabapentin, etc.), antidepressants (amitryptiline, venlafaxine, serotonin reuptake inhibitors), pizotifen ve memantine.

Currently, topiramate is one of the most commonly used drugs in treatment of CM. It has multiple mechanisms of action including GABA-A receptors, sodium channels, glutamate receptor antagonism, carbonic anhydrate, protein kinase inhibition, serotonin activity or possible neuroinflammatory factors. Topiramate was shown to have the same efficiency even without detoxification in patients with drug overuse who continued to receive acute attack treatment (34, 35).

Onabotulinumtoxin A (BTX) is a neurotoxin which blocks release of presynaptic acetylcholine irreversibly. It has been proposed that the mechanism of action includes inhibition of release of the neurotransmitters including P substance and calcitonin and impact on muscle spasm and nerve transduction (36, 37). BTX prevents progression of central sensitivity by inhibiting peripheral sensitivity (38, 39). In the PREEMPT study in which the efficiency of BTX in CM was shown, onabotulinumtoxin A or placebo was administered to 679 and 705 patients every 12 weeks for 32 weeks. The BTX groups was found to be moderately superior to the placebo group in terms of decrease in the number of days with headache, decrease in the severity of pain, disability and the number of days in which triptane was used (absolute benefit: 6.7% and 11% in PREEMPT 1 and 2, respectively) (40). The same efficiency was observed in CM both in the patients who used 100-200 mg/day topiramate and in the patients who used maximum 200 units BTX. In addition, fewer side effects were observed in the patients who received BTX (41).

Gabapentin and Pregabalin were shown to be partially effective in treatment of CM (42, 43).

Tizanidin is a muscle relaxants and alpha2-adrenergic agonist. It was shown to be effective in chronic headache compared to
placebo when administered at a dose of 24 mg/day. It is usually used as adjuvant treatment. Its side effects include somnolence, dry mouth, malaise and fainting (44).

Fluoxetine is a selective serotonin reuptake inhibitor. When is is administered as a dose of 40 mg/day, it was shown to be beneficial 3 months later in patients with chronic headache (45).

Zonisamide was also shown to be partially efficient a long time after administration of a mean dose of 337.9 mg in patients with resistant migraine (46).

Memantine (MEM) is a glutamergic N-methyl-D-aspartate (NMDA) receptor antagonist. When it is given at a dose of 10-20 mg/day to patients in whom at least one of the standard migraine prevention therapies was ineffective, a decrease of approximately 50% in the number of days with migraine and a decrease in disability was found after 3 months. The most common side effects include somnolence, asthenia and mood changes. It can be used in individuals who do not benefit from traditional treatment (47, 48).

A multiple approach is needed in treatment of chronic migraine. Education, social support, optimization of the level of expectation, close monitoring and lifestyle adjustments (sleep, diet, alcohol, coffee, etc.) are important. Behavioral strategies in addition to determining and preventing triggering factors are considered. Psychiatric evaluation is valuable in many cases.

References

47. Ramadan NM. The link between glutamate and migraine. CNS Spectr 2003; 8:446-449.