Comorbidity of Migraine

Migren ve Hastalık Birlikteliği

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ABSTRACT

Migraine is a common neurological disorder and can be severely disabling during attacks. The highest prevalence occurs between the ages of 25 and 55 years. Prior studies have found that migraine occurs together with other illnesses at a greater coincidental rate than is seen in the general population. These occurrences are called "comorbidities". To delineate the comorbidities of migraine is important, because it can help improve treatment strategies and the understanding of the possible pathophysiology of migraine. (*Archives of Neuropsychiatry* 2013; 50 Supplement 1: S14-S20)

Key words: Migraine, comorbidity

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ÖZET

Migren yaygın görülen, ataklar sırasında ağır fonksiyonel kayba neden olan nörolojik bir hastalıktır. Özellikle 25-55 yaşları arasında yüksek prevalansta görülmektedir. Bugüne kadar yapılan çalışmalar raslantısal olmanın dışında migren baş ağrılarının bazı hastalıklarla sık birlikteliğini vurgulamaktadır. Bu birliktelik "komorbidite/hastalık birlikteliği" olarak adlandırılmaktadır. Bu durum tedavi stratejilerinin belirlenmesinde ve olası fizyopatolojik mekanizmaların anlaşılmasında önem taşımaktadır. (*Nöropsikiyatri Arşivi* 2013; 50 Özel Sayı 1: S14-S20)

Anahtar kelimeler: Migren, komorbidite

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Introduction

Migraine is one of the common neurological diseases affecting 16.4% of our population (24.6% in women, 8.5% in men) (1). It is a significant cause of disability. However, the disability caused by the disease is not generally considered much (2). Currently, sufficient efforts are not made in many countries in the diagnosis and treatment. At the present time, many patients do not have sufficient awareness about migraine and the outcomes of migraine.

Comorbidity/disease association was described by Feinstein for the first time (3). It is defined as one or more diseases accompanying the primary disease. Migraine is observed in association with psychiatric and somatic diseases in a wide spectrum. Scher classifies this association as psychiatric, neurological, vascular, cardiac diseases and other diseases (4). Intensive studies conducted on this issue have established subtitles in this association spectrum. In understanding the pathophysiology of migraine comorbidity, the clinical picture is significant in terms of diagnosis and treatment. Recognition of this association may provide understanding of overlapping and confusing clinical pictures (for example, migraine and stroke association) or controlling of both conditions with a single treatment in events

triggered by migraine (for example, migraine-depression or migraine-hypertension association). Migraine comorbidity is discussed on four basic mechanisms: presence of genetic and environmental factors, cause-effect relationship, mutual physiopathological background and completely accidental association. Absence of accidental associations is impossible in a chronic disease which is observed frequently like migraine. In this review, physiopathological conditions which are observed in association with migraine at the clinical base will be examined outside accidental association (4, 5).

Migraine and Cardiovascular Diseases

Many studies performed so far have shown the association of migraine and vascular problems. It is possible to evaluate this title as subtitles including migraine and stroke, subclinical brain matter lesions, coronary artery disease, hypertension and patent foramen ovale (PFO).

Stroke

The association of migraine and ischemic stroke (IS) has been known for long years based on case-control and cohort studies

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performed on this issue. In many case-control studies, migraine was considered a risk factor for stroke. The Collaborative Group for the Study of Stroke in Young Women compared patients with stroke who were hospitalized and population-based control groups. When compared with the population-based control group, the risk of stroke was found to be increased 2-fold in women with migraine, but the same result was not obtained in the hospital-based control group (6). Henrich and Horowitz showed a relation between migraine and stroke in hospital-based case-control studies, but similar results were not obtained, when stroke was adjusted for risk factors (7). Tzourio reported that the risk of stroke increased in women with migraine below the age of 45 years and this risk was increased with presence of smoking (8). In a longitudinal study, Henrich found the incidence of cerebral migraineous infarction to be 3,36/100000 and this ratio was found to be 1.44/100000 when individuals who carried other risk factors were eliminated (9).

In the study performed by Stang et al. in which the International Headache Society (IHS) diagnostic criteria were used, the odds ratio* (OR) of the participants for recording of headache for a life time was calculated. According to this assessment the OR of stroke and migraine with aura was reported to be 5.46, the OR of transient ischemic attack and migraine was reported to be 4.28 and the OR of IS (ischemic stroke) and migraine was reported to be 2.81 (10).

The "Women's Health Study" data of Kurth et al. in a large series stand out as a significant source for this association (11). According to this study, 40.000 healthy female subjects aged 45 years of age and above who had no history of stroke or TIA with normal neurological examination were followed up for a long period of 9 years. Presence of migraine and aura was accepted as the statements of the subjects as yes or no. The OR of IS was determined to be 2.25-fold in the subjects below the age of 55 years (11). According to subgroup analyses, it was found that the risk of IS increased in presence of active migraine with aura when cardiovascular risk factors including age, blood pressure, use of oral contraceptives (OC) and cholesterol level were added, but these factors were not related with migraine without aura (11). When cardiovascular risk factors including smoking, alcohol, menstrual status, hormone levels, use of oral contraceptives and cholesterol level were added and when active migraine with aura was present, the risk of IS was found to be increased, but they were not found to be related with migraine without aura.

According to the results of the study performed by the same investigators in which 20084 male physicians between the ages of 40 and 84 years who were known to be healthy were followed up for 15.7 years, an increased risk was found between migraine and IS below the age of 55 years (RR:1.84). At more advanced ages, it was not found to be significant (12).

In the population-based study of Bigal et al. (American Migraine Prevalence and Prevention (AMPP)), a significant relation was found between migraine with aura and migraine in adult women and men (13).

Migraine is an independent risk factor for stroke. Aura, age and presence of other risk factors for stroke (smoking, use of OC, presence of systemic diseases which increase the risk, female gender) increase the risk. In women below the age of 45, the risk increases 9.03-fold with smoking (8). Especially in women below the age of 45 years with migraine with aura, controlling of the present risk factors together with stroke, smoking and use of OC is important. When young women were excluded from the studies, migraine was not found to be a risk factor for ischemic stroke. At the age of 60 years, no difference was reported between the patients with migraine and the control group in terms of ischemic stroke. Patients with migraine do not carry a risk for hemorrhagic stroke.

Subclinical white Matter Lesions

In patients with migraine, white matter lesions were found with a rate of 6-46% on MR imagings. In patients with migraine with aura, subclinical infarction in the posterior circulation is observed with a 13.7-fold higher frequency (14). According to the case-control KAMERA study, lesions in the posterior circulation and subclinical white matter lesions were reported with a higher rate in patients with migraine and especially in patients with migraine with aura (15). No relation was found between white matter lesions and the clinical picture of migraine (16). Most infratentorial (88%) infarction-like lesions were shown in the localization of the cerebellar "borderzone" (17). The probable mechanism has been suggested to be hypoperfusion related with migraine attack and emboly (14). In the AGES-Reykjavik study conducted with middle-aged women who had long-term migraine with aura, cerebellar infarction-like lesions which are observed in advanced ages were found with a 2,1-fold higher frequency (17).

Hypertension

Although migraine and hypertension are two conditions which are mentioned together frequently, studies performed on this issue have given contradictory results. In studies performed in normotensive subjects, no significant change was shown in measurements performed during active migraine attacks and even a negative correlation was shown. In these subjects, presence of diastolic hypotension was reported during attacks (18, 19, 20, 21, 22). In the population-based study of Rasmussen and Olesen, no correlation was found (23). Subjects with migraine constitute a risk group in gestational hypertension (24). The GEM study and AMPP substudy showed a higher cardiovascular risk profile in patients with migraine with high cholesterol and blood pressure values (13, 25). These data do not support the data obtained in the "Women's Health Study" (26). Further studies are needed to evaluate the relation between blood pressure and other cardiovascular risk factors and migraine. Accidental associations and the fact that migraine is a long-term chronic disease should be considered. In presence of hypertension or newly-developed hypertension, treatment options should be determined according to this variable.

Gene Polymorphisms

In patients with migraine, 677C> metylenetetrahydrofolate reductase (MTHFR) gene and angiotensin converting enzyme (ACE) gene D/I polymorphisms were examined. According to the results of the "Women's Health Study", no relation with myocardial infarction (MI) was found (26). However, a major CV risk increase was observed with migraine with aura and gene polymorphism. No relation could be found between ACE D/I polymorphism and migraine of cardiovascular disease (27, 28).

Cardiac Diseases

Two controversial subtitles including coronary artery disease (CAD) and patent foramen ovale (PFO) will be evaluated under this title. Large-scale population-based studies on the relation between migraine and CAD have given controversial results. Rose et al. evaluated the risk of angina and coronary artery disease in patients with migraine with aura in 12409 participants in a follow-up period of 10 years. The prevalence risk for angina was found to be 3-fold higher, but no difference was found for a relation between CAD and migraine with aura (29, 30).

Kurth et al. (Women's Health Study) found a relation of migraine with aura not only with ischemic stroke but with all major cardiovascular diseases (MI; angina, coronary revascularization) (26). In subjects with a high Framingham risk score, an association of active migraine with aura and MI was shown in presence of high cholesterol (31). In another study (Physicians' Health Study), it was emphasized that the risk of MI increased by 42% in men with migraine and the risk of major cardiovascular disease increased by 24% when evaluated together with cardiovascular risk factors (12). In the AMPP substudy of Bigal et al., presence of an association with MI was reported in both migraine with aura and migraine without aura after cardiovascular risk factors were eliminated. (OR:2.86 1.85) (13). In patients with cardiac disease, migraine has a progressive or uncontrolled course. In fact, the point which should be considered during this natural course is treatment protocols. In patients with cardiovascular disease, no increase in the risk has been found with use of triptans which are the migraine-specific drug group used especially in attacks. However, physicians have a natural fear for these patients. These drugs should not be used in patients at advanced ages unless mandatory before necessary assessments are made (31).

In patients with migraine, PFO, atrial septal aneurism (ASA) and mitral valve prolapsus (MVP) are reported with a higher rate compared to the normal population. In presence of PFO, cryptogenic stroke, refractory hypoxemia, orthostatic oxygen desaturation, decompression sickness and migraine with aura are observed. In the normal population, the rate of PFO has been reported to be 27% in autopsy studies independent of race and gender. In patients with resistant migraine with aura, the rate of large PFO with right-left shunt was found to be 37.7% on transthoracic ECHO. ASA was found with a rate of 28.5% and MVP was found with a rate of 40% in patients with migraine with aura. It is assumed that the right-left shunt of this PFO can cause to paradoxal emboly and transition of vasoactive substances to the cerebral arterial system at high concentrations. In addition, possible mutual genetic background is considered (33). The results related with the effect of closure of PFO on attacks are controversial. According to the MIST (Migraine

Intervention with STARFlex Technology) study, no difference could be found in patients who underwent this procedure in the frequency of migraine attacks 6 months later compared to patients who did not underwent this procedure (34, 35).

Small Artery Disease

Migraine stands out as a significant part of the phenotype of many vasculopathies involving small arteries. These vasculopathies include CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts) and leukoencephalopathy, cerebral leukodystrophy and retinal vasculopathy, hereditary infantile hemiparesia, retinal vasculopathy, cerebral retinal arteriolar tortuosity and leukoencephalopathy. It is thought that small vessel diseases increase the risk of migraine by leading to direct vascular changes by way of endothelial dysfunction or via the neuronal pathway. This association is proposed because of mutual genetic factors on DNA gene (36, 37).

Psychiatric Diseases

Psychiatric diseases are observed commonly in association with migraine. This association is noted in depression, anxiety disorder, bipolar disorder, phobia and suicide ideation and attempt (Table 1) (37). This increases the progression and burden of the patient with migraine to a great extent. It has been thought that presence of serotonergic dysfunction, central sensitization and drug overuse might contribute to this association.

Depression

In the Zurich retrospective epidemiological cohort study, association of psychiatric disease was investigated in young

Table 1. Migraine and Psychiatric Diseases*.

Psychiatric Disease	Odds ratio**/ OR
Major depression (Merikangas et al., 1990; Breslau et al., 2003)	2.2-3.4
Bipolar spectrum (Merikangas et al., 1990; Breslau et al., 1991)	2.9-7.3
Anxiety (Merikangas et al., 1990)	2.7
Panic disorder (Merikangas et al., 1990; Breslau et al., 2001)	3.0-5.09
Diffuse anxiety disorder (Merikangas et al., 1990; McWilliams et al., 2004)	3.9-5.3
Agoraphobia (Merikangas et al., 1990)	2.4
Social phobia (Merikangas et al., 1990)	3.4
Suicide attempt ** (Breslau, 1992)	4.3
Suicide ideation ** (Breslau, 1992; Wang et al., 2009)	1.8-24

* Wang et al. Migraine comorbidity Frontiers in Neurology | Headache Medicine and Facial Pain 2010. (38,39,40,41,42)

** Examined only in migraine with aura

adults with migraine and a significant association was observed (OR:2.2) (39).

According to the results of the population-based studies in the perspective of bi-directional relation (migraine in depression and depression in migraine), the risk of new-onset migraine in patients with depression was found to be 2.8-3.5 and the risk of new-onset depression in patients with migraine was found to be 2.4-5.8 (39).

According to another population-based study performed using USA adult data, the rates of depression were assessed in presence of three painful conditions (migraine, arthritis and back pain); presence of clinical depression was confirmed in only 12.3% of the subjects who had no migraine and in 28.5% of the subjects with migraine (OR:2.8). In presence of psychological stress comorbidity, severe disruption in the quality of life was found in patients with migraine (42, 44). Tietzen found somatic complications (OR:8.6) and major depressive state (OR: 25.1) with considerable high rates in chronic headache leading to disability. It has been reported that especially exposure to chronic stress is important in association of migraine and major depression (45).

Diffuse Anxiety Disorder

The association of anxiety and migraine has been investigated in population-based and clinical studies. According to the results of these studies, diffuse anxiety disorder has been found with a high rate in migraine (OR:3.9-5.3). Presence of mutual environmental and genetic factors is emphasized (46, 47, 48).

Panic Disorder

Its incidence in patients with migraine is controversial (40). According to the study of Breslau, it was found to be high. In a population-based study, the temporal relation was evaluated and no significant difference was found in terms of lifelong prevalence of panic disorder and its prevalence in other headaches. Panic disorder is observed frequently in all severe headaches. It has not been found to be specific to migraine (49).

Suicide Ideation and Attempt

Suicide ideation and attempt in young adults with a history of migraine with aura was reported by Breslau et al. for the first time as two successive presentations (50,51). Wang et al. found a high rate of suicide ideation in adolescents with daily chronic headache (52). This association was not observed in patients with migraine without aura. Again, the same investigators found suicide ideation with a higher rate in adolescents aged 13-15 years with migraine with aura especially with a high frequency of headache (<7 days/month) compared to the normal population (OR:1.69) (43).

Bipolar Disorder

There are few studies evaluating bipolar disorder in migraine. In two population-based studies, a significant association was found between migraine and bipolar disorder in young adults (OR:2.9-7.3). As a result of a pharmacoepidemiological study in which Norwegian prescription database was used, the OR was found to be 3.16 in men and 2.21 in women (39, 53).

Epilepsy

Association of migraine and epilepsy is controversial. According to the data obtained from studies, migraine is found with a high prevalence in epilepsy patients (54, 55, 56, 57, 58, 59). Sometimes presence of a mutual history including trauma, chronic episodic course, gastrointestinal autonomic findings, mood, behavior and consciousness changes and focal motor and sensory symptoms is noted between epilepsy and migraine. Both conditions may trigger each other (epileptic seizures triggered by migraine or migraine attacks following epileptic seizures). The differential diagnosis is not very easy especially in the childhood. The prevalence of migraine was found to be 26-86% in patients with epilepsy (58). Especially migraine with aura is observed with a rate of 41.8% (25.8% in normal individuals). If the parents describe epilepsy, migraine is found with a rate of 24% in the child. Epilepsy was found with a rate of 5.9% in patients with migraine (0.5% in normal individuals) (55). Epileptic seizures during migraine aura were found with a rate of 11.3-16.5% and these seizures are called migralepsy (54). No relation was found between the risk of migraine and early-onset epilepsy (epilepsy period) (58).

It is thought that the common ground in these two periodical diseases is genetic background (60, 61, 62, 63). Definition of migraine in two families with adult-onset myoclonic epilepsy and autosomal recessive idiopathic epilepsy supports this common genetics (60,63). In a large Belgian family with association of occipital lobe epilepsy and migraine with visual aura, a connection locus was found on chromosome 9q21 and q22 involved in the association of migraine and epilepsy (61). Visual aura was defined in at least two members of 36 Finnish families and the same locus was found on genetic analysis (62).

Vertigo

Migraine and vertigo are two conditions which are observed frequently in the community. The lifelong prevalence is known to be 16% for migraine and 7% for vertigo. The rate of accidental association of these two conditions has been reported to be 1,1%. However, recent epidemiological studies have shown that the actual rate of association is higher. As a result of studies with large series, migraine was found to be the cause of recurrent vertigo with a rate of 35% in pediatric patients and with a rate of 5% in adults. In these patients, abnormal vestibular function was found with a rate of 34-80%, actual vertigo was found with a rate of 26%, movement disorder was found with a rate of 30-50% and idiopathic benign paroxysmal positional vertigo was found with a rate of 18,8%. As a result of clinical observations and epidemiological data, the concept of vertiginous migraine was presented. However, the diagnostic criteria of this title proposed by a group of investigators have not been included in the classification yet. They are planned to be included in the attachment in the third revised version of IHS. Debates are continuing on this issue (64, 65, 66).

Migraine and Movement Disorders

The lifelong prevalence of migraine in Parkinson's disease was found to be 9.3-27.8% in case-control studies. Remission was

observed in migraine attacks in 2/3 of the patients after disease symptoms started (67, 68).

Studies on Tourette syndrome are limited. Migraine attacks are observed with a 4-fold higher frequency compared to the normal population. Migraine attacks were reported with a rate of 39 in adults with Tourette syndrome and with a rate of 16% in children with Tourette syndrome. It is thought that obsessive compulsive disorder which is an element of the disease is not the underlying cause and it originates from different mechanisms (68, 69, 70). It is proposed that disruption in the thalamocortical pathway and aminergic, genetic and psychiatric mechanisms are involved (68, 69, 70).

In the beginning of the 1990s, uncontrolled studies showed that essential tremor (ET) which is the most common one among movement disorders was observed more frequently in patients with migraine compared to the normal population. Migraine was found with a rate of 36.5% in patients with essential tremor (18% in the normal population) and essential tremor was found with a rate of 17.2% in patients with migraine. In the bi-directional relation between ET and migraine, it is thought that these two conditions share some common pathophysiological mechanisms and they arise from progressive tremogenic mechanisms rather than a vascular pathology. However, it is possible that this association is accidental considering that the frequencies of migraine and ET are high (71, 72).

Sleep

Sleep disorders have been found widely in migraine. These are not always explained with presence of depression and anxiety. In one third of patients with migraine, difficulty in starting and continuing sleep was defined. More frequently defined sleep disorders in migraine include prolonged REM sleep latency, decrease in the REM time awakening index, somnambulism, narcolepsy and movement disorder in sleep. In a population-based study, all sleep symptoms examined were found with a significantly higher rate in children with migraine except for enuresis. Among parasomnias, only speaking during sleep, somnambulism and bruxism were reported (73, 74, 75). Migraine was found with a 2-4-fold higher rate in narcoleptic patients (74). Presence of sleep apnea and snoring were interpreted as poor prognostic markers in migraine. Increasing the quality of sleep has a positive effect on the prognosis (73).

Restless Leg Syndrome

Restless Leg Syndrome (RLS) is a common sensorimotor disease. The prevalence of RLS was found to be high in patients with migraine (11.4%) (76). This association is emphasized more frequently according to the results of recent studies and the possible mechanism is proposed to be disruption in dopaminergic system function and iron metabolism (77). In patients with migraine and RLS, accompanying symptoms were found to have a more severe course (tinnitus, vertigo, disruption of the quality of sleep). RLS affects daily life activities in patients with headache. No clear interpretation can be made on the effect of controlling RLS and increasing sleep quality on the frequency of migraine (76, 77, 78, 79).

Chronic Pain

According to the "The Nord-Trondelag Health Study" musculoskeletal pain was reported with a higher rate in patients with headache compared to patients without headache. Similar rates were found in migraine and non-migraine headaches. These ORs were found to be 1.9 for migraine headache and 1.8 for non-migraine headache (80). Von Korr defined headaches with the characteristics of migraine in patients with chronic spinal pain (OR:5.2). Similarly, the frequency of fibromyalgia was found to be 22-40% in patients with migraine (81, 82, 83). In these patients, high rates of insomnia, reduction in the quality of life, more intensive mental stress were noted (81). Fibromyalgia was found with a higher rate in female patients with migraine compared to male patients with migraine (84).

Cutaneous allodynia is a clinical manifestation of central sensitization. Cutaneous allodynia was found in approximately 60% of 1413 patients with migraine during migraine attack. Cutaneous allodynia was defined in at least one region in 23% of these patients and in four or more regions in 9%. In patients who described severe allodynia, the time of history of migraine was found to be longer compared to the other patients and anxiety and depression symptoms and smoking were reported in association (85).

Other Comorbid Conditions

According to the results of the "Head Hunt" study, it was proposed that asthma and chronic bronchitis were found with a 1.5-fold higher rate in migraine and non-migraine headaches and were related with the frequency of headache. In another study, it was found that diagnosis of new asthma was not different in patients with migraine compared to patients without migraine (OR:1.17). An independent relation is known to be present between allergic diseases and migraine (86, 87). The OR of migraine was found to be much higher (1,6) in patients with irritable bowel syndrome compared to patients without irritable bowel syndrome (83). Celiac disease was found more frequently in patients with migraine (88).

The prevalence of migraine was found to be high in patients with vasculitis. It was reported that it arises from vascular, neuronal and endothelial cell dysfunction and was closely related with disease exacerbations. In patients with Lupus, any headache was found with a rate of 32-78% and the prevalence of isolated migraine was found to be 25-66% (88, 89).

Conclusively, migraine is a complex chronic disease which may occasionally have a progressive course and which may be difficult to manage. Awareness of comorbidities is important and directive especially in terms of physiopathology and treatment. Comorbidities can be demonstrated with strong and well-structured epidemiological studies. New well-structured studies are needed in many titles which are still controversial.

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