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Comorbidities of migraine: a user-friendly overview

Abstract Comorbidity of migraine is important from a number of different perspectives. Co-occurrence of different diseases may complicate diagnosis as a high degree of symptomatic overlap may occur among conditions associated with migraine. Furthermore, comorbidity has also important implications for treatment. The commonest comorbidities of migraine are represented by psychiatric disorders, epilepsy, tremor, stroke, and cardiovascular abnormalities.

Key words Migraine • Epilepsy • Tremor • Stroke

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Introduction

Comorbidity may be defined as the presence of any additional coexistent condition in a patient with a particular index disease as well as an association between two disorders that is more than coincidental [1]. The presence of a comorbidity may complicate any diagnosis because of the overlapping symptoms as in patients with both epilepsy and migraine in which an aura may originate from either epilepsy or migraine [1]. As stated by Lipton and Silberstein [2], comorbidity may arise by coincidence or selection bias, one condition may cause the other, both conditions may be related to shared environmental genetic risk factors, and the same environmental or genetic risk factors may determine a brain state that gives rise to both conditions. Comorbidities in migraine may involve mood disorders (e.g. depression, mania, anxiety, panic attack),

neurologic disorders (e.g. epilepsy, essential tremor, stroke) and other disorders such as allergy, asthma, ulcer, and irritable bowel disease, the latter not considered in this overview [1].

Migraine and psychiatric disorders

The prevalence of behavioral disorders such as major depression, mania, hypomania, generalized anxiety, and social phobia is higher in subjects with migraine than in those without migraine [3]. As reported by Breslau et al. [4], an association between migraine and affective disorders has been observed in many clinical and epidemiologic studies. Two alternative explanations may account for the association: migraine may cause major depression and, conversely, may be caused by it; again, migraine and major depression

can share either genetic or environmental etiologic factors. Besides, comorbidity of migraine with major depression is often characterized by coexisting anxiety disorders.

Migraine and epilepsy

Migraine and epilepsy are both chronic neurologic disorders with episodic attacks. Auras, hallucinations, changes in mood, behavior and consciousness, and focal sensory or motor symptoms may occur in both conditions. Many patients complain of headaches after seizures and in some cases the migraine aura can trigger seizures as anticipated by Andermann and Andermann [5], who coined the term *migraine epilepsy* specifically referring to such conditions. However, in many patients, migraine and epileptic attacks are not temporally related. According to Lipton et al. [6], the risk of migraine is more than twice as high in persons with epilepsy, whether probands or relatives, than in persons without epilepsy. Besides, the increased risk of migraine is greatest in persons with epilepsy caused by head trauma but occurs in every subgroup of epileptic patients, defined by seizure type, age at onset, etiology, or family history. The prevalence of epilepsy in patients with migraine ranges from 1% to 17%, with a median of 5.9%. This percentage greatly exceeds that found in the general population, which is approximately 0.5% [7]. On the contrary, the prevalence of migraine in patients with epilepsy ranges from 8% to 15% [8].

Migraine and tremor

As reported by Biary et al. [9] unexplainably, essential tremor and migraine occur together more frequently than just by chance alone. Accordingly, prevalence of migraine in patients with essential tremor is 36% compared with a prevalence of 18% in normal controls. Similarly, essential tremor occurs in about 17% of patients with migraine, compared with only 1% of controls.

Migraine and stroke

The relationship between migraine and stroke is more complex. As migraine-related strokes, Welch [10] considered: coexisting stroke and migraine; stroke with clinical features of migraine including symptomatic migraine and migraine mimic; migraine-induced stroke (with or without vascular risk factors); and uncertain conditions, when migraine and stroke appear related but a causal role is dif-

ficult to firmly establish, as may happen if vasoconstrictive medications are used or if the stroke follows cerebral angiography.

To speak of *coexisting stroke and migraine*, a clearly clinically defined stroke syndrome must occur remotely in time from a typical attack of migraine [10]. History of migraine may contribute to the risk of stroke through an unspecified mechanism. Several case-control studies investigated the relationship between migraine and stroke: the odds ratio was 4.3 (95% CI, 1.2–16.3) in women under 45 years of age according to Tzourio et al. [11] and 3.7 (95% CI, 1.5–9.0) according to Carolei et al. [12]. Besides, odds ratios were higher in patients with a history of migraine with aura than in patients with a history of migraine without aura. According to Carolei et al. [12], the rare association between migraine and cerebral ischemia is limited to women below the age of 35 years and suggests careful clinical evaluation of comorbidity in the presence of migraine with aura [13]. The added risk of stroke (odds ratios) to a female migraineur under the age of 45 doubles from 3 (in the presence of migraine without aura) to 6 (in the presence of migraine with aura), to 13.9 (in the presence of migraine and oral contraceptives use). A diagnosis of *stroke with clinical features of migraine* is possible when a structural lesion, unrelated to migraine pathogenesis, presents with the clinical features of a migraine attack. Under this heading two different subtypes are identified: symptomatic migraine and migraine mimic. *Symptomatic migraine* is diagnosed when an established structural central nervous system lesion, such as an arteriovenous malformation, produces typical episodes of migraine with neurologic aura.

Migraine mimic refers to cases of stroke caused by acute and progressive structural disease accompanied by headache and focal neurologic symptoms that are difficult to distinguish from migraine with aura. A differential diagnosis is particularly difficult in patients who continue to have migraine with aura late in life when the incidence of cerebrovascular diseases increases. As suggested by Welch [10], to diagnose *migraine-induced stroke* the neurologic deficit must exactly mimic the migrainous symptoms of previous attacks; the stroke must occur during the course of a typical migraine attack; all other causes of stroke must be excluded although stroke risk factors may be present. However, migraine-induced stroke, i.e. migraine as a cause of cerebral infarction, is extremely rare, is vastly overdiagnosed, and should be diagnosed only by exclusion. Migraine-induced stroke represents the same clinical entity considered in the International Headache Society's classification as *migrainous cerebral infarction* (IHS 1.6.2) [13] occurring when one or more symptoms and signs of migrainous aura are not fully reversible within 7 days and/or are associated with neuroimaging confirmation of ischemic infarction.

Migraine and cardiovascular diseases

Other migraine comorbidities are represented by mitral valve prolapse (MVP), platelet hyperaggregability, patent foramen ovale, and the antiphospholipid antibodies syndrome. A 20%–28% prevalence of MVP in migraine sufferers vs. 4%–6% prevalence in the general population has been reported [14, 15]. Intriguingly, both migraine and MVP sufferers may show platelet dysfunctions [16]. Platelet hyperaggregability predisposing to formation of intravascular platelet aggregates and mural thrombi [17]

has been documented during the migraine attack and during the aura [18]. Recently, a higher prevalence of migraine with aura has been found among subjects with patent foramen ovale than in subjects without the alteration (36% vs. 13%) [19]. Besides, a higher prevalence of serum antiphospholipid antibodies has been found in migraine sufferers than in controls (14% vs. 0%). No differences were found regarding age, attack frequency or duration, and presence of aura between migrainous patients with or without antiphospholipid antibodies [20].

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