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Dysimmune disorders and migraine: is there a possible common denominator?

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Abstract The association between headache, especially migraine, and some immunomediated diseases, in particular autoimmune diseases, is well known. The evidence in favor of this association comes prevailingly from epidemiological studies, as well as research aimed at assessing the onset and the course of migraine in relation with the onset and activity and the biological markers of autoimmune diseases. The most relevant findings in this regard concern celiac disease, systemic lupus erythematosus, and multiple sclerosis.

Key words Headache • Autoimmune diseases • Celiac disease • Systemic lupus erythematosus • Multiple sclerosis

Introduction

In some autoimmune disorders, headache, and in particular migraine, seems to occur with a higher prevalence than that in the general population. This occurrence has been described both for immunomediated diseases involving the central nervous system or other organ-specific dysimmune pathologies and for systemic dysimmune pathologies, although it has not always been confirmed. It is difficult to identify common pathogenetic mechanisms at the basis of the comorbidity of headache with dysimmune disorders, if any, when headache onset is recognized before the onset of dysimmune disorders. The involvement of common pathogenetic mechanisms seems to be more evident when headache, and in particular migraine, occurs at the beginning of the disease, or its onset or worsening occurs in conjunction with increased activity of the disease. For diseases which have brain structures as a target of immune-mediated events, the location of lesions could be in some cases strategic and involve brain areas devoted to the processing of head pain or initiating and maintaining attacks (putative migraine generators, supranuclear inhibitory pathways, trigeminal root or nucleus). The most relevant data concerning headache in an organ-specific dysimmune pathology (celiac disease), a systemic dysimmune disorder (systemic lupus erythematosus), and a brain-specific dysimmune disorder (multiple sclerosis) are reported.

Celiac disease

Studies carried out mainly on young and adult celiac patients demonstrated a prevalence of migraine of 18%–21%, without significant differences between sexes. Putative factors believed to be involved in the slightly greater prevalence of migraine in celiac patients are genetic factors, presumed but not yet investigated, and biochemical and neurotransmitter abnormalities such as reduced levels of serotonin which could predispose, at least in a subgroup of celiac patients, to migraine [1]. On

the other hand, a significant proportion of migraine patients have been suggested to have subclinical celiac disease (CD), as emerged from recent research carried out by Gabrielli et al. [2]. The authors determined serum anti-transglutaminase and antiendomysial immunoglobulin, IgG and IgA, respectively, in a total of 90 migraine patients and 236 blood donors. Four out of 90 migraine patients (4.4%; 95% CI, 1.2–11.00) were found to have CD as confirmed endoscopically compared with 0.4% (95% CI, 0.01–2.3) of the blood donors. During a 6-month gluten-free diet, one of the four patients had no migraine attacks, and the remaining three patients had an improvement in frequency, duration, and intensity of migraine. The four CD patients suffering from migraine also underwent a brain single photon emission computed tomography (SPECT) examination before and after the gluten-free diet. A reduction in brain tracer uptake emerged in all patients at baseline, which completely resolved at the 6-month follow-up. The suppression of some putative pathogenetic mechanisms related to CD immunological abnormalities has been advocated to explain the disappearance of severe migraine attacks after adequate treatment in celiac patients complaining of migraine at baseline [1].

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic, inflammatory, immune-mediated disease with several neurological and psychiatric manifestations, such as seizures, psychosis, cognitive dysfunction, and also headache. Headache is a common symptom in SLE and is a significant source of disability in these patients. Early studies attempted to establish the prevalence of migraine in SLE patients, but they were based on small numbers of patients and criteria used to define headache syndromes varied widely. Even the most recent studies failed to use criteria of the International Headache Society (IHS) to classify headache attacks in these patients. Vazquez-Cruz et al. [3] studied 76 SLE patients in whom migraine was diagnosed according to the 1962 criteria of the Ad Hoc Committee on Classification of Headache [4]. Migraine was diagnosed in 24 patients (common migraine in 15 and classic migraine in 9). Markus and Hopkinson [5] identified migraine in 31 (34%) of 90 SLE patients using diagnostic criteria proposed by Blau [6]. Montalban et al. [7] diagnosed migraine in 31% of 103 patients, tension-type headache in 20%, and cluster headache in less than 1% of the patients. A lower proportion of patients (8%) suffered from migraine in a study carried out by Sfikakis et al. [8], but in this study a diagnosis of migraine required at least one episode every 2 weeks,

whereas the 1988 IHS classification [9] requires five separate lifetime attacks and two lifetime attacks, respectively, for migraine without and with aura. In a more recent study carried out by Glanz et al. [10], 186 SLE patients completed the San Diego Migraine Questionnaire based on IHS criteria for migraine, which has been shown to accurately distinguish between migraine and nonmigraine headache syndromes. Of the patients, 115 (62%) reported headaches. Headache occurred in 63% of women and 43% of men. Seventy-two patients met diagnostic criteria for migraine (29% males and 39% females) and 43% described nonmigrainous headache. Of the patients with migraine, 40 (56%) met criteria for migraine without aura and 32 (44%) met criteria for migraine with aura. Statistical analysis did not show any significant association between headache type and age and duration of SLE, as well as the presence and levels of antinuclear, anti-DNA, anti-Sm, and antiphospholipid antibodies. The presence of migraine seemed also not to have been influenced by recent use of corticosteroids, nonsteroidal anti-inflammatory drugs, and antimalarial or immunosuppressive medication.

The failure to find an age-related decline in the prevalence of migraine in SLE patients included in the study of Glanz et al. suggests that migraine is an attribute of the underlying disease, with a higher prevalence than that in the general population. A similar picture emerged in a study carried out by Omdal et al., who found that 38% of 58 SLE patients suffered from migraine-type headache, and 36% from tension-type headache [11]. As in the study of Glanz et al., migraine occurrence appeared not to be related to the disease expression or severity, as measured by autoantibodies. Also, no relationship emerged, as in previous reports, with Raynaud's phenomenon and anticardiolipin antibodies. Moreover, the coexistence of anxiety and depression in the majority of patients with both migraine and tension-type headaches seemed to reflect problems of coping with the disease in these patients and underscores the already known relationship between these conditions and headache in general.

Both vascular and neuronal pathogenetic mechanisms have been advocated to explain the high prevalence of migraine in SLE, but their involvement remains hypothetical. Moreover, the appearance of headache, in particular migraine, does not necessarily indicate the presence of central nervous system (CNS) involvement. This finding emerged from a study carried out by Rozell et al. [12], in which there was no difference in the prevalence or severity of magnetic resonance imaging (MRI; cortical atrophy, ventricular dilatation, diffuse white matter changes, periventricular white matter changes, small focal lesions and gross infarct) or magnetic resonance spectroscopy (MRS) abnormalities (reduced levels of *n*-acetylaspartate/creatine ratio) in SLE patients with migraine, with nonmigraine headache, or without migraine.

Multiple sclerosis

The relationship between multiple sclerosis (MS) and headache has not been clearly established. In particular, whether MS can per se cause headaches is a matter of controversy. The classic study of clinical MS by Kurtzke et al. showed that 26% of patients had a headache with their first bouts of the disease [13]. With the aim of clarifying the association between MS and headaches, a prospective study was conducted by Rolak and Brown on 104 MS patients [14]. Fifty-four MS patients (52%) reported headaches, compared with 5 of 35 (14%) patients initially suspected to have MS but subsequently proven to have other disorders, and 18 of 100 (18%) matched patients with other neurological disorders. Headaches in MS patients were classified as either migraine or tension-type and there was no distinctive "MS headache." Seven of these patients had headaches at the onset of their first symptoms but in only one did headaches recur with future relapses.

Further retrospective studies and questionnaires have also found occasional patients with MS who recall significant headaches at the time of their first symptoms with percentages ranging from 2% to 8%. In particular, Freedman and Gray identified, from among the records of 1,113 patients with MS, 44 cases whose initial attack or subsequent exacerbations were heralded by a migraine-like headache [15]. Some of these patients were urgently referred to hospital with presumptive diagnoses of subarachnoid hemorrhage, complicated migraine, or other conditions associated with acute headache.

A potential association between the headaches and the affected regions of the brain in MS has been recorded. Freedman and Gray found that half of their patients with headache during an attack of MS presented with brain stem involvement. Galer et al. [16] reported a man who was awakened by the worst headache of his life 2 days before developing a left-sided third nerve palsy attributed to MS. MRI revealed at least 30 punctate hyperintense white matter lesions on T2-weighted images, but the sole brain stem lesion was in the left cerebellar peduncle. Evidence connecting acute headache and specific lesion location was offered by Nager et al. [17], who reported the case of an MS patient who was awakened from sleep by a severe non-throbbing left-sided migraine-type headache. Two hours later, facial numbness replaced acute head pain. MRI showed multiple areas of increased signal intensity on T2-weighted images, in particular lesions in the left lateral pons at the entry zone of the trigeminal nerve, and the authors attributed the headache to these lesions.

A further interesting report described a case of severe acute headache which occurred in conjunction with a solitary fresh lesion of MS in the periaqueductal gray matter. This particular event supports the recent evidence of a putative migraine generator in this area, which has been suggested to be responsible for the initiation and maintenance of migraine attack [18].

A case of a patient with simultaneous occurrence of cluster headache-like pain and MS should also be mentioned [19]. Both MRI and neurophysiological investigation by trigeminal-evoked potentials revealed a demyelinating plaque at the trigeminal root entry zone, on the side of the pain. Although this type of lesion is usually associated with trigeminal neuralgia pain, it can be hypothesized that in this particular case the described lesion, instead of just triggering sharp volleys of abnormal discharges and eliciting neuralgic pain, may have originated a more complex phenomenon influencing the trigeminovascular system and initiating a cascade of events which has been hypothesized as giving rise to a cluster headache-like attack.

Headache in MS, if present, can also be influenced by therapeutic strategies used in reducing the relapse rate and disease activity as measured by serial MRI scanning, and slowing the disease progression of MS. Therapy with interferon-beta may be associated with a number of adverse reactions. Relatively frequent side effects include flu-like symptoms and also headache. The type and frequency of headaches during immunomodulatory therapy in MS were determined in a recent study involving 167 consecutive patients [20]. In a prospective group of 65 patients beginning interferon-beta therapy, headache frequency and duration increased in 18% of all and in 35% of patients with preexisting headache by more than 50% during the first 6 months. In two retrospective groups, increased headache frequency was reported by 34% of 53 patients on interferon-beta, but by only 6% of 49 patients during at least 6 months of glatiramer acetate therapy.

Another interesting aspect of the complex relationship between MS and migraine in particular emerged from a recent case-control study assessing the risk of MS associated with a series of putative risk factors analyzed with multiple logistic regression analysis [21]. Migraine was found to be an independent risk factor for MS (OR=8.7; 95% CI, 1.0–75.4) together with familial susceptibility to MS (OR=12.1; 95% CI, 1.3–110.7), autoimmune diseases (OR=3.8; 95% CI, 2.0–7.1), and comorbidity with autoimmune disease (OR=6.8; 95% CI, 1.4–32.0) as well as vaccination against measles (OR=92.2; 95%, 12.1–700.2).

Conclusions

The occurrence of headache and in particular migraine in many autoimmune disorders has been recognized, but the mechanisms underlying this association remain to be established.

The relationship between migraine and CD is controversial. Even though migraine could be considered generally idiopathic in some CD patients, the possible effect of CD on the migraine course should be taken into account, since a gluten-free diet could be beneficial in these patients.

Headache incidence and frequency are markedly increased in SLE, but headache seems not to be associated with poorer outcome and is not a reliable surrogate marker of SLE activity, brain injury, disease severity, or serious organ involvement.

Patients with MS consistently report more headaches than matched controls or the general population at large. There does seem, therefore, to be a sort of association between headaches and MS, but the mechanism of headache production in MS is speculative.

It has been hypothesized that the cuffing of small blood vessels by inflammatory cells and also meningeal infiltrates can be responsible for activation of the trigeminovascular system and neurogenic inflammation, resulting in migraine attacks also in MS. Moreover, headache in MS might be due to the strategic location of the underlying lesions in the CNS. In this case migraine or cluster-like attacks can be due to lesions involving CNS areas such as the putative migraine centers or entry zone of the trigeminal root, respectively. Concomitant treatment can also exacerbate headache in MS patients, as demonstrated for interferon-beta. The relationship between migraine and MS seems to be much more complex. A migraine history has, in fact, been recognized to be associated with an increased risk of MS, together with other known risk factors such as familial susceptibility to MS, autoimmune diseases, and vaccination.

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