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CLINICAL ASPECTS OF HEADACHES

Headache in multiple sclerosis and autoimmune disorders

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Abstract The headache may be considered among the neuropathic pain syndromes of multiple sclerosis (MS). Several studies have showed that it is more frequent in MS patients than in controls or general population. Headache may occur at the pre-symptomatic phase, at clinical onset and during the course of the disease. Tension-type headache and migraine without aura are the most common primary headaches reported in MS patients. The disease-modifying therapies, such as interferons, may cause or exacerbate headache, although the new available treatments do not seem to increase the risk of pain. Pharmacological and not pharmacological approach may be considered in selected patients to prevent the risk of headache, ameliorate quality of life and increase the adherence to treatment.

Keywords Multiple sclerosis · Vasculitis · Headache · Therapy

Introduction

Headache has been reported in patients with autoimmune disorders and in patients with multiple sclerosis (MS). In autoimmune disorders such as central vasculitis it has been mainly described at the onset of the disease. In MS patients, many studies have underlined that headache occurs more frequently than in general population, in any stages of the disease. It has been considered among the painful MS syndromes, such as trigeminal and occipital neuralgia and Lhermitte's sign [1]. A recent systematic review found that the overall pain prevalence in MS patients was 63 %, the most frequent painful syndrome being headache (43 %) [2].

However, conflicting results have been reported on the prevalence of headache in MS patients in general as well as during the course of the disease. Attention has been drawn to the occurrence of headache during immunomodulating therapies [3] and to the correlation with demyelinating lesions [4].

The aim of this study is to review the recent published data on headache in MS, to clarify the clinical aspects and the influence of MS therapies on headache incidence.

Headache in multiple sclerosis

Clinico-epidemiological aspects

Since 1950 [5] several studies have investigated the association between MS and headache. Variable frequencies have been reported, ranging from 4 to 69 % (Table 1), probably due to differences on study design and included population. In general, the results have showed that its prevalence is higher in MS patients (more than 50 %) than in controls [3]. Tension-type headache (TTH) and migraine without aura [6] are commonly reported. Ophthalmoplegic migraine-like [7], complicated migraine [8], cluster headache-like [9], may also occur in single cases.

The possibility of a link between migraine and MS was suggested over a half-century ago [10]. Both migraine and MS are relapsing disorders with occasional chronic evolution, are more frequent in women, may be due to a combination of environmental and genetic causes and are

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Table 1 Prevalence of headache in multiple sclerosis patients

References	Number of patients with headache (%)
Adams et al. [5]	389 (2.1)[a]
Compston and McAlpine [10]	250 (2.0)[a]
Abb and Schaltebrand [26]	1420 (37.5)
Bonduelle and Albaranes [27]	145 (5.5)
Poser et al. [28]	111 (8.0)
Kurtzke et al. [12]	234 (26.1)[a]
Watkins and Espir [29]	100 (27)
Clifford and Trotter [30]	317 (5.0)
Freedman and Gray [16]	1113 (4.0)
Rolak and Brown [31]	104 (52)
Pollmann et al. [32]	157 (40)
D'Amico et al. [24]	116 (57.7)
Gee et al. [17]	277 (56.6)
Vacca et al. [33]	238 (51.3)
Villani et al. [34]	102 (61.8)
Yetimalar [13]	21 (28.5)[a]
Martinelli Boneschi et al. [11]	428 (35.5)
Nicoletti et al. [6]	151 (57.4)
Putzki et al. [35]	491 (56.2)
Kister et al. [36]	204 (46)
Martínez Sobrepera et al. [37]	50 (69)
Kister et al. [38]	375 (28)
Kister et al. [1]	131 (69)

[a] At onset of the disease

influenced by hormonal factors. Furthermore, predisposing factors may be fatigue, insomnia, other neuropathic pain, depression and stress [1].

A correlation between type of MS and type of headache has been showed, migraine being more frequent in relapsing–remitting, while TTH in progressive MS. Females have a higher risk of migraine, while TTH seems to be associated with male sex and older age [11].

Headache at onset, already considered by Kurtzke [12] as a "minor" symptom, has been reported with variable frequencies, ranging from 1.6 to 28.5 % [3]. Headache has been also described in "asymptomatic MS" [13], but with radiological findings suggestive of the disease, before clinical conversion [14], currently called radiologically isolated syndrome [15].

Neuroradiological aspects

Freedman and Gray [16] found that half of the patients with headache during an attack of MS had clinical signs of brain stem involvement. MS patients with a plaque within the periaqueductal gray matter area have an increase in migraine-like headaches when compared to patients without this lesion [17, 18].

Severe headache associated with diplopia or trigeminal neuralgia, or cluster-like attacks have been reported in single patients with isolated brain stem demyelinating lesions, usually responsive to steroid treatment [19]. In one study, spinal cord lesions were more common in TTH patients [20]. Acute trigeminal autonomic cephalalgia, occipital neuralgiform pain may be symptomatic of demyelinating lesions of the brain stem or of the upper spinal cord (C1–C2) area [21].

Pharmacological aspects

Interferon-beta (IFN) is commonly used for long-term treatment of MS [22]. A systematic review showed that headache is significantly more frequent in MS patients treated with IFN as compared to placebo [23]. IFN may aggravate a pre-existing migraine or TTH and may precipitate their attacks [11]. In one study, about half of the patients with the novo headache after starting on IFN have developed migraine and the other half TTH [24]. Glatiramer acetate seems to have a minor headache-inducing potential [3].

It may be of interest that the new MS treatments do not seem to increase the risk of headache, considering the incidence of this adverse event, reported in the placebo-controlled clinical trials (Table 2).

Preventive therapies should be evaluated in selected patients to ameliorate adherence to treatment and quality of life. To the best of our knowledge, studies focused on the most effective preventive therapies are still not available.

Headache in autoimmune disorders

Autoimmune diseases are heterogeneous inflammatory disorders characterized by systemic or localized inflammation, leading to ischemia and tissue destruction. The headache is more commonly described in some diseases (e.g., giant cell arteritis and primary central nervous system vasculitis) and is mainly reported at the onset of the disease; the characteristic is often not specific, raising important diagnostic problems [25].

Conclusions

The main conclusion is that migraine is common in patients with MS, affecting more than 50 % of cases. Recent

Table 2 New drugs in MS: prevalence of headache in treated versus placebo groups

References	Therapy	Actively treated patients (%)	Placebo-treated patients (%)
Miller et al. [39]	Natalizumab	40	38
Kappos et al. [40]	Fingolimod	25.2	23
Gold et al. [41]	BG-12	<1	0
Miller et al. [42]	Teriflunomide	13	13

evidences confirm that it may occur at onset of the disease, similarly to what reported in other autoimmune disorders. In this case, a careful differential diagnosis is needed.

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

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