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SECONDARY HEADACHES

Headache and multiple sclerosis: clinical and therapeutic correlations

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Abstract Headache is not generally considered as a symptom of multiple sclerosis (MS), but several studies have showed that it is more frequent (about 50%) in MS patients than in controls or general population. Headache may occur at onset and during the course of the disease. Tension-type headache and migraine without aura are the most commonly reported primary headaches; occipital neuralgia or cluster-like attacks have also been described, the location of demyelinating lesions (cervical or brain stem) could be strategic in these cases. Furthermore, disease-modifying therapies, such as interferons, may cause or exacerbate headache. These data suggest that MS patients have an increased risk of headache. Preventive therapies may be evaluated in selected patients during chronic treatments to ameliorate compliance.

Keywords Headache · Multiple sclerosis · Prevalence · Migraine · Tension-type headache · Cluster headache · Occipital neuralgia · Magnetic resonance imaging · Interferon

Introduction

Headache is not generally considered as a symptom of multiple sclerosis (MS), but several studies have investigated the association between these two conditions. Conflicting results have been reported on the lifetime prevalence of headache and frequency of headache as MS onset symptom [1–19]. Attention has been drawn to de novo headache and exacerbation of pre-existing headache in interferon-treated MS patients [20–22]. Furthermore, recent neuroimaging studies have suggested a correlation between the location of the demyelinating lesions and headache [13, 23].

The aim of this study is to review the published data on headache in MS patients, in order to clarify the clinical–radiological correlations and the influence of MS therapies on headache incidence.

Headache and multiple sclerosis: clinical aspects

Since 1950 [1] several studies have investigated the occurrence of headache in MS patients: variable frequencies ranging from 4 to 61.8% have been reported (Table 1) [1–19]. These discrepancies may be explained by differences on study design and patients' inclusion criteria. The results of the more recent studies, most of them prospective and/or case control survey, based on International Headache Society criteria for diagnosis and classification of headaches, have showed that the lifetime prevalence of headache is higher in MS patients (more than 50%) than in controls and general population, suggesting an increased risk of headache and a possible association between these two conditions [12, 14, 18].

Headache features seem to be non-specific for MS: migraine without aura and tension-type headache are the most commonly reported primary headaches [14, 18]. Ophthalmoplegic migraine-like [24], complicated migraine [25], cluster headache-like [26], have also been described in single cases.

The prevalence of headache in general was not related to MS form, illness duration or disability score [10, 19]. However, a correlation between type of MS and types of

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Table 1 Summary of results of studies on the prevalence of headache in MS patients

References	No. of patients/ controls	Percentage with headache	Percentage with headache as onset symptom
Adams et al. [1]	389	NR	2.1
McAlpine and Compston [2]	250	NR	2
Abb and Schaltenbrand [3]	1,420	37.5	8
Bonduelle and Albaranes [4]	145	5.5	2
Poser et al. [5]	111	8	NR
Kurtzke et al. [6]			
Retrospective	293	NR	9.9
Prospective	234	NR	26.1
Watkins and Espir [7]	100/100	27/12	NR
Clifford and Trotter [8]	317	5	NR
Freedman and Gray [9]	1113	4	1.6
Rolak and Brown [10]	104/100	52/18*	6.7
Pollmann [11]	157	40	NR
D′Amico [12]	116	57.7	1.7
Gee [13]	277	55.6	NR
Vacca [14]	238/238	51.3/23.9*	5.5
Villani [15]	102	61.8	NR
Yetimalar [16]	21	–	28.5
Martinelli Boneschi [17]	428	35.5	NR
Nicoletti [18]	151/101	57.4/37.2*	NR
Putzki [19]	491/447	56.2/72.7	NR

NR not reported

* Significant comparison

primary headaches has been showed, migraine being more frequent in relapsing–remitting and tension-type headache in progressive MS patients [12, 15, 17]. Female patients have a higher risk of tension-type headache and migraine [17].

Kurtzke [6] considered headache as a "minor" MS onset symptom and variable frequencies have been reported, ranging from 1.6 to 28.5% (Table 1). Headache has been also described as "unusual primary manifestation" in 6 out of 21 "asymptomatic MS patients" [16] and in 20 out of 30 "preclinical MS" patients, with MRI suggestive for MS, 11 of them had clinical conversion after a mean time of 2–3 years [27]. On the other hand, 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 [28–31].

Headache and location of demyelinating lesions

Kurtzke [6] already showed that headache was most common in MS patients with visual or brain stem symptoms. Freedman and Gray [9] found that half of patients with headache during an attack of MS had clinical signs of brain stem involvement. These clinical correlations have been clarified by the more recent imaging studies. Gee [13] has showed that MS patients with a plaque within the midbrain/periaqueductal gray matter area had a four-fold increase in migraine-like headaches when compared to MS patients without a lesion in the same region. Tortorella [23] has showed that migrainous MS patients have more significant involvement of the substantia nigra and periaqueductal gray matter compared with MS patients without migraine and migrainous patients.

On the other hand, the location of the demyelinating lesions could be strategic in some cases. 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 [32–34].

Headache in MS-treated patients

Interferon-β (IFN) is commonly used for long-term treatment of MS. Flu-like syndrome, dermal injection site reactions are the most common side effects [35]. A systematic review showed that headache is significantly more frequent in MS patients treated with IFN as compared to placebo [36]. Furthermore, several studies have evaluated the influence of chronic therapies on headache development or aggravation: variable frequencies, ranging respectively

Table 2 Summary of the results of studies on the incidence of headache in MS-treated patients

References	IMA, de novo headache Type of IMA, *N*/tot (%)	Worsening of pre-existing headache *N*/tot (%)
Brandles [20]	IFN 9/51 (17)	1/51 (2)
Pòllman [21]	IFN 9/53* (17)	IFN 18/53* (34)
	COP 1/49 (2)	COP 3/49 (6)
La Mantia [22]	IFN 38/79* (48)	IFN 17/41* (41)
	COP/aza 0/22	COP/aza 0/22
Vacca [14]	IFN 7/92 (8%)	IFN 13/92 (14)
	COP 0/14	COP 1/14 (7)
Martinelli Boneschi [17]	NR	IFN migraine 48.6, TTH 63.3
		COP migraine 0, TTH 25
Nicoletti [18]	IFN 7/49 (14.2)	IFN 4/49 (8)
Villani [15]	IFN 7/64 (11)	IFN 24/64 (37.5)
Putzki [19]	Not studied	NR
	Headache prevalence rates	
	IFN 28.3%, Cop 26.4%	

COP Glatiramer acetate, *aza* azathioprine, *IMA* immunomodulating agents, *NR* not reported

* Significant comparison

from 8 to 48% and from 2 to 41% have been reported in MS patients treated with IFN, while glatiramer acetate seems to have a minor headache-inducing potential (Table 2) [14, 15, 17–22].

Discussion

This review shows that the relationship between headache and MS is complex, since several aspects have been analyzed by the investigators: (1) the lifetime prevalence of primary headaches in MS patients; (2) the correlation between different types of headaches and the clinical features of MS; (3) the occurrence of headache at the onset of the disease; (4) the correlation between headache and central lesions; (5) the occurrence of headache during chronic MS treatments.

The main conclusion of this review is that primary headaches are common in MS patients, occurring in more than 50% of the cases, a higher proportion than reported in the matched controls or in the general population. The reasons for this significant association have not been clarified. Recent evidences suggest that demyelinating brain stem lesions might be among the factors responsible for the presence of migraine in MS patients [13, 23]. Familial susceptibility, young age, female gender may predispose to both conditions or may be considered as additional risk factors.

The possibility that headache may occur as MS onset symptom remains an open question. Headache is not generally considered as a symptom of MS, but, except for the types symptomatic of central lesions, the occurrence in patients without any other specific symptoms or signs of the disease, showed by some studies [16, 27], should be supported by a careful neuroradiological study and clinical monitoring.

Headache may be considered among the side effects of IFN, worsening of pre-existing headaches or development of de novo headaches have been reported in the IFN-treated patients, although with variable frequencies (Table 2). Different mechanisms have been suggested [22], including the presence of other comorbidities such as psychiatric disorders. Preventive therapies [20] should be evaluated in selected patients during chronic MS treatments to ameliorate compliance.

Overall, these data show that MS patients have an increased risk of headache and suggest that headache should be investigated in the clinical work-up of these patients, mainly considering the impact on quality of life.

Conflict of interest statement The author declares that there is no conflict of interest related to the publication of this manuscript.

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