Neurol Sci (2007) 28:133–135
DOI 10.1007/s10072-007-0805-1

ORIGINAL

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Multiple sclerosis and headache co-morbidity. A case-control study

Received: 16 December 2006 / Accepted in revised form: 9 April 2007

Abstract The prevalence of primary headache (PH) in a multiple sclerosis (MS) sample *vs*. control healthy subjects was investigated at a neurological clinic in 2004–2005: 122 of 238 (51%) MS patients and 57 of 238 (23%) controls proved to be affected by headache. The groups did not differ for the rates of PH types. Headache types of MS patients were comparable to those of PH patients that were observed at the same institute in a case-control comparison. First symptoms of headache preceded those of MS in two thirds of cases. Headache features did not significantly change after MS onset. Comorbidity of MS and PH could be explained by some common clinical and biological traits.

Key words Multiple sclerosis • Headache • Comorbidity

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Introduction

A high prevalence of headache in multiple sclerosis (MS) has been reported in the literature. Watkins and Espir diagnosed migraine in 27 of 100 MS patients *vs*. 12 of 100 hospital visitors [1], while Rolak and Brown found headache in 54 of 104 (52%) MS patients *vs*. 18 of 100 neurological patients [2]. D'Amico et al. reported a 57.7% lifetime prevalence of headache in 137 patients diagnosed with clinically definite MS [3]. Furthermore, migraine-like headaches were associated with the initial attack of MS or with subsequent exacerbations in about 4% of Freedman and Gray's survey [4]. The purposes of the study were to confirm the major prevalence of primary headaches (PH) in patients suffering from MS, to diagnose the headache types of these patients on the basis of the new international headache classification and to suggest possible mechanisms of association between PH and MS.

Patients and methods

Consecutive outpatients affected by MS, according to the criteria of the International Panel on the diagnosis of MS [5], who referred to our MS centre in 2004–2005, were considered eligible for the study. Control subjects were selected among their accompanying friends and matched for sex and age and comparable familial predisposition to headache, in accordance with the case-control study model. Patients' relatives were excluded, to prevent the bias of familial headache. All the subjects were requested to give their written informed consent to this observational non-profit study and received a semistructured interview dealing with the basic items for headache diagnosis by a medical doctor from the local headache centre. The interviewer asked the subjects to give information about pain frequency, intensity, duration and quality, and to describe the accompanying symptoms and the response of the headache to physical activities and to painkiller medications. MS patients were requested to recall the age at the onset of the headache with respect to that of the neurological symptoms and of the starting of immune treatments. Cases of headache due to other disorders were excluded. The types

of headache of the MS group were matched to those of a control group of PH patients that we observed in the same period at the local headache centre and diagnosed according to the International Classification of Headache Disorders (2nd edition) [6]. Selection of the control PH patients was performed by a medical doctor who was unaware of the headache diagnosis of the MS patients and who was requested to select the first control PH patient of the series matching the sex and age parameters of the corresponding MS case.

We calculated the relative risk and the confidence interval of the lifetime prevalence of headache and we compared the rates of the headache types between the groups by the Chi square test.

Results

We found 238 MS patients eligible for the study (F 156, M 82; median age 40 years, range 24–61). The median age at MS diagnosis was 26 years (range 14–52). The disease course was relapsing–remitting in 180 and secondary progressive in 58. The median EDSS score was 2.5 (range 1.5–6.5). None of them refused the informed consent. One hundred and seventy-two patients were on interferon beta (IFNβ) therapy and 22 on glatiramer acetate (Cop-1) therapy; the remaining 44 patients were receiving no immune treatment. The same number of control subjects were selected according to the methods described (F 156, M 82; median age 43 years, range 24–75). In the MS group 122 of 238 (51.26%) patients complained of headache (F 92, M 30) *vs*. 57 of 238 (23.94%) controls (F 35, M 22). Headache preceded MS onset in 85 of 122 MS patients (69.67%). The lifetime prevalence of headache in the MS group was more than double that of the control group (RR=2.14±0.173, 95% CI=1.97–2.31). The comparison was statistically significant only for women (Chi square test, $p<0.001$). The F/M ratio was higher in the MS group, but not significantly. The major headache prevalence in MS patients was also evident when the analysis was restricted to the portion of patients who presented PH before MS onset. The headache age of onset was similar in the two groups (respectively 18.35±8.44 and 22.13±11.84). The headache types were equally distributed between the groups (Table 1). One hundred and twenty-two PH patients were selected according to methods (F 156, M 82; median age 40 years, range 23–67). In the PH group the total number of diagnoses exceeded the number of patients because of cases who had a double diagnosis. We did not find any significant difference of the headache types between the MS and the PH groups (Table 2). In the MS group the illness onset did not generally modify the pre-existing headache. Only 13 (5.46%) MS patients reported suffering headache from the MS onset. Immune therapies for MS had variable effects on PH: amelioration, worsening and stabilisation of headache were observed. Of 92 patients on IFNβ therapy, headache *de novo* appeared in 7 (8%), worsened in 13 (14%), ameliorated in 22 (24%) and remained unchanged in 50 (54%), *vs*., respectively, none, 1 (7%), 2 (14%) and 11 (79%) of 14 patients on Cop-1 therapy. We were not able to perform a statistical comparison because of the small number of patients on Cop-1.

Discussion

Our data confirm a significant association between PH and MS. Headache features seem to be non-specific for MS, because there was no difference from controls in terms of onset, types and female prevalence and because they did not change after the illness onset. Moreover, headache types in the MS group did not differ from the PH group. We found no CH cases in the MS group (*vs*. 6 cases in PH group). Actually facial pain in MS, different from trigeminal neuralgia, has been described in the literature, as symptomatic migraine

Table 1 Rates (numbers) of headache types in MS and control groups

Groups	MO	MA	ETTH	CTTH	PMA
MS	63 (76)	7 (9)	12 (15)	2 (2)	12 (15)
C	53 (31)	10 (6)	24 (14)	0 (0)	12 (7)

C, controls; *MO*, migraine without aura; *MA*, migraine with aura; *ETTH*, episodic tension-type headache; *CTTH*, chronic tension-type headache; *PMA*, probable migraine without aura ($p>0.05$, Chi square test)

Table 2 Headache types in MS group vs. PH group

Groups	MO	MA	ETTH	CTTH	PMA	CH
MS	77	9	15	3	15	0
PH	74	20	9	27	12	6

MO, migraine without aura; *MA*, migraine with aura; *ETTH*, episodic tension-type headache; *CTTH*, chronic tension-type headache; *PMA*, probable migraine without aura; *CH*, cluster headache ($p>0.05$, Chi square test)

associated to plaques in brainstem areas, but in our cohort we did not observe any similar case [7, 8]. Our data concerning the influence of the immune therapies of MS on headache are limited, but they tend to support a minor headache-inducing potential of Cop-1 *vs*. IFNβ [9]. We think that MS patients do not develop headache as a reactive disorder to their illness, as headache frequently precedes MS onset and it is not substantially modified by the illness itself. We suggest that the explanations of the high PH prevalence in MS may be found in some biological features shared by these two disorders. According to an epidemiological study by Stewart et al. [10], with more than 12 000 US participants, the Caucasians had the highest prevalence of migraine, followed by the Africans and last the Asians. Rosati [11], reviewing epidemiological studies on MS, underlined the lower risk of illness among Asian and African peoples. The discovery of the CACNL1A4 gene and ATP1A2 gene mutations in some cases of familial hemiplegic migraine confirmed the genetic aetiology in selective headaches forms [12, 13], suggesting that a dysfunction of neuronal ion channels could also have a role in migraine with aura. In recent years new evidence has led to consideration of MS as an acquired channelopathy: the up-regulation of Kv1.3 channels in myelin-reactive T^{EM} lymphocytes, and the altered gene expression of sensory neuron-specific sodium channels in demyelinated Purkinje cells [14, 15]. Cytokine synthesis may be altered in both disorders, particularly IL-10, an anti-inflammatory cytokine, which is over-expressed both during MS relapses and during migraine attacks [16, 17]. Moreover, age at first symptoms, female prevalence (at least for migraine without aura), relapsing–remitting course, chronic evolution of some cases, relative remission during pregnancy and relapsing during puerperium, are all common features of both disorders.

In conclusion, a comorbidity of PH and MS occurs significantly and these disorders share some epidemiological, molecular and immune patterns.

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