Neurol Sci (2008) 29:S146–S148
DOI 10.1007/s10072-008-0908-3

ORAL COMMUNICATION

Primary headache and multiple sclerosis: preliminary results of a prospective study

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Abstract The aim of this study was to explore the association between different types of headache (HA) and the clinical features of multiple sclerosis (MS). The relationship between HA and MS-specific therapies was also analysed. A total of 102 MS patients were recruited at the MS Centre of S. Andrea Hospital in Rome. According to International Headache Society criteria, the lifetime prevalence of primary HA was 61.8%. Migraine was observed more often in young relapsing–remitting MS patients, whilst tension-type HA was associated with older age, male gender and a secondary progressive course. Sixty-four patients had a history of ongoing or past interferon beta (IFNb) exposure. Of these, 17 subjects did not have a history of HA, while 24 complained of an increase in frequency of migraine attacks and 7 reported an IFNb-induced HA. Investigating and treating HA in MS patients starting IFNb therapy may improve MS-specific medication compliance.

Keywords Migraine · Headache · Multiple sclerosis · Interferon beta

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Background

The link between multiple sclerosis (MS) and primary headache (HA) is poorly understood and studies investigating their relationship have produced conflicting results. The prevalence of HA in MS patients has been reported to be between 4% and 58% and the frequency of HA as an onset symptom of MS between 1.6% and 26% [1–4]. Several studies suggested that Interferon beta (IFNb) treatment may induce *de novo* HA and exacerbation of pre-existing HA [3, 5, 6].

The primary goal of this study was to investigate the association between MS and HA. The secondary aim of the study was to evaluate the correlation between different types of primary HA and the clinical features of MS. The relationship between HA and MS-specific medication for MS was also evaluated.

Methods

Between October 2006 and January 2007 we prospectively recruited consecutive MS patients, according to the McDonald criteria [7], regularly attending at the MS Centre of S. Andrea Hospital in Rome. We collected demographic and clinical variables for each patients: gender, age at MS onset, previous and ongoing therapy for MS, duration of MS-specific treatment and level of disability assessed by the Expanded Disability Status Scale (EDSS) [8].

All patients underwent: the ID migraine, a semistructured interview guided by a questionnaire based on International Headache Society (IHS) criteria [9] to evaluate and classify HA, the Beck Depression Inventory (BDI) and the Toronto Alexithymia Scale (TAS-20). Patients diagnosed as affected by HA also underwent the Migraine

DIsability Assessment Scale (MIDAS) and the Headache Impact Test-6 (HIT-6) for the assessment of migraine disability.

Data have been analysed using SPSS software. Statistical significance was calculated by the Pearson's Chi-squared test or the Student's independent-samples *t*-test, when appropriate. *p*-values less than 0.05 were considered significant.

Results

A total of 102 MS patients (71 females, 31 males) were recruited. Mean age was 38.7±9.5 years (median 38, range 15–68); mean MS duration was 8.8±7.6 years (median 6, range 1–41). Eighty-three patients had a relapsing–remitting form, while 19 had a secondary progressive (SP) course. Mean EDSS score of whole study population was 2.4±1.6 (median 2.0, range 0–7.0). Twenty patients did not receive any specific MS treatment, while 82 subjects were on therapy with MS-specific drugs: 37 with an IFNβ formulation, 22 with immunosuppressant agents, 18 with natalizumab and 5 with glatiramer acetate.

According to IHS criteria, 63 patients suffered from a primary HA, while 11 patients had a secondary form (7 reported an IFNβ-induced HA as a part of flu-like symptoms, 4 had an atypical neuralgia).

The lifetime prevalence of primary HA in the whole population was 61.8%. HA started at younger age compared with MS onset (21.7±11.9 vs. 29.7±8.8 years; p=0.002). Migraine was observed more often in RR than SP MS patients. Conversely, tension-type HA (TTH) was associated with older age, male gender and progressive course of MS. No relationship between MS duration, age at MS onset, EDSS score and HA was detected (see Table 1).

Sixty-four patients had a history of ongoing or past IFNβ exposure. Among these, 17 (26.5%) did not have a history of HA, 7 (11%) reported an IFNβ-induced HA, 16 (25%) migraineurs reported no changes in frequency of migraine attacks, 24 (37.5%) complained of an increase in frequency (10.5±9.5 vs. 6.5±6.5 days/month; p=0.05) and a slightly higher HIT-6 score (53.6±13.6 vs. 44.0±19.6; p=0.08). We also observed that frequency and intensity of HA was not significantly related with IFNβ dosage, type of molecule (i.e., IFNβ-1a or -1b) and frequency of administration. However, the migrainous subjects taking IFNβ thrice per week or every other day had a higher median number of attacks (2/month vs. 6/month, p=0.05) and higher BDI score (9.6±6.0 vs. 5.3±4.6, p=0.05) than patients treated once weekly.

Table 1 Demographic and clinical characteristics of study population according to subtypes of HA

	Migraine (n=46)	Chronic HA (n=8)	TTH (n=9)	Secondary HA (n=11)	No HA (n=28)	Pooled (n=102)
Gender*						
Female	38	8	3	8	14	71
Male	8	0	6	3	14	31
Current age**						
<30 years	13	0	1	2	4	20
30–40 years	17	5	0	3	13	38
>40 years	16	3	8	6	11	44
Education						
≤8 years	6	0	2	2	3	13
9–13 years	29	6	5	6	19	65
>13 years	11	2	2	3	6	24
MS course**						
RR	40	8	5	9	21	83
SP	6	0	4	2	7	19
MS onset						
<20 years	7	0	0	0	3	10
20–30 years	23	3	3	5	11	45
>30 years	16	5	6	6	14	47
MS duration						
<2 years	6	2	1	3	5	17
2–10 years	23	6	4	5	14	52
>10 years	17	0	4	3	9	33
EDSS score						
≤1.5	21	3	3	3	12	42
2.0–3.5	16	4	2	7	9	38
≥4.0	9	1	4	1	7	22

No HA, patients without headache; *RR*, relapsing–remitting MS; *SP*, secondary progressive MS
*p<0.01 and **p=0.05

Conclusions

Our study shows that HA is common in people with MS: the lifetime prevalence (61.8%) of HA was the highest reported in the literature. We confirmed high prevalence of pre-existing migraine and low prevalence of TTH, which represented the most common type of HA in older males affected by a SP course of MS. Although migraine preceded MS onset by about 8 years, this study cannot rule out the hypothesis that migraine might represent a first symptom of the disease. Further efforts are required to clarify the real link between migraine and MS.

In patients treated with IFNβ we performed an accurate classification of HA aimed to differentiate HA due to flu-like syndrome from primary HA. Treatment with IFNβ triggered *de novo* HA in few subjects, while the majority of patients showed an increased frequency of pre-existing HA. In particular, subjects receiving high-frequency IFNβ treatment had a greater number of migraine attacks and higher BDI score than those on therapy with once weekly administration.

Because of the small number of subjects considered, these finding should be taken with caution, although the head-to-head study comparing every-other-day IFNβ-1b vs. once-weekly IFNβ-1a demonstrated a minor occurrence of HA among patients treated by low-frequency formulation [10].

On the contrary, the association between increased level of depression and high-frequency IFNβ dose recorded in our work conflicts with the results of both the dose-comparison studies showing no differences in prevalence of depression during a follow-up period ranging from 12 to 24 months [11]. However, it has been observed that frequency and duration of migraine attacks is associated with depression or anxiety [12].

We suggest that investigating and treating HA in MS patients starting IFNβ therapy may improve MS-specific medication compliance.

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