

# Migraine in 746 patients with multiple sclerosis

## Enxaqueca em 746 pacientes com esclerose múltipla

Yara Dadalti FRAGOSO<sup>1</sup>, Tarso ADONI<sup>2</sup>, Soniza V. ALVES-LEON<sup>3</sup>, Samira L. APOSTOLOS-PEREIRA<sup>4</sup>, Marcos A. Diniz CARNEIRO<sup>5</sup>, Edila M. CHIKOTA<sup>6</sup>, Denise Sisterolli DINIZ<sup>5</sup>, Audred C. B. EBONI<sup>7</sup>, Sidney GOMES<sup>8</sup>, Marcus Vinicius M. GONÇALVES<sup>9</sup>, Ricardo Pereira GONCALVES<sup>10</sup>, José Luiz INOJOSA<sup>11</sup>, Thiago F. JUNQUEIRA<sup>12</sup>, Suzana Costa MACHADO<sup>13</sup>, Fabiola Rachid MALFETANO<sup>14</sup>, Letícia Fezer MANSUR<sup>15</sup>, Maria Fernanda MENDES<sup>4</sup>, Andre MUNIZ<sup>16</sup>, Adauto W. NOBREGA JUNIOR<sup>17</sup>, Guilherme Sciascia do OLIVAL<sup>18</sup>, Monica Fiuza PAROLIN<sup>19</sup>, Maria Lucia V. PIMENTEL<sup>15</sup>, Cristiane Franklin ROCHA<sup>20</sup>, Heloisa Helena RUOCCO<sup>21</sup>, Gutemberg C. SANTOS<sup>22</sup>, Fabio SIQUINELI<sup>23</sup>, José Otavio D. SOARES<sup>24</sup>, Nise Alessandra C. SOUSA<sup>25</sup>, Carlos Bernardo TAUIL<sup>26</sup>, Thereza Cristina A. WINCKLER<sup>27</sup>

### ABSTRACT

Migraine adds to the burden of patients suffering from multiple sclerosis (MS). The ID-migraine is a useful tool for screening migraine, and the Migraine Disability Assessment questionnaire can evaluate disease burden. The aim of the present study was to assess the presence and burden of migraine in patients with MS. **Methods:** Patients diagnosed with MS attending specialized MS units were invited to answer an online survey if they also experienced headache. **Results:** The study included 746 complete responses from patients with MS and headache. There were 625 women and 121 men, and 69% of all the patients were aged between 20 and 40 years. Migraine was identified in 404 patients (54.1%) and a moderate-to-high burden of disease was observed in 68.3% of the patients. **Conclusion:** Migraine is a frequent and disabling type of primary headache reported by patients with MS.

**Keywords:** Migraine; headache; multiple sclerosis.

### RESUMO

Enxaqueca piora o sofrimento do paciente que tem esclerose múltipla (EM). ID-migraine é uma ferramenta útil para seleção de pacientes com enxaqueca e *Migraine Disability Assessment* (MIDAS) é um questionário que avalia o impacto da doença. O objetivo do presente estudo foi avaliar a presença e impacto de enxaqueca em pacientes com EM. **Métodos:** Pacientes diagnosticados com EM e tratados em clínicas especializadas foram convidados a responder um questionário online se também apresentassem cefaleia. **Resultados:** O estudo incluiu 746 participantes com cefaleia e EM que preencheram completamente as respostas. Foram 625 mulheres e 121 homens, sendo 69% dos pacientes com idade entre 20 e 40 anos. Enxaqueca foi identificada em 404 pacientes (54,1%) e moderado a grave impacto da doença foi observado em 68,3% dos casos. **Conclusão:** Enxaqueca é uma cefaleia primária frequente e incapacitante relatada por pacientes com EM.

**Palavras-chave:** Transtornos da enxaqueca; cefaleia; esclerose múltipla.

<sup>1</sup>Universidade Metropolitana de Santos, MS & Headache Research, Santos SP, Brazil;

<sup>2</sup>Hospital Sírio-Libanês, São Paulo SP, Brazil;

<sup>3</sup>Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro RJ, Brazil;

<sup>4</sup>Hospital das Clínicas, Universidade de São Paulo, São Paulo, SP, Brazil;

<sup>5</sup>Universidade Federal de Goiás, Goiânia GO, Brazil;

<sup>6</sup>Saúde Global, Joinville SC, Brazil;

<sup>7</sup>Neurovie, Joinville SC, Brazil;

<sup>8</sup>Hospital Beneficência Portuguesa, São Paulo SP, Brazil;

<sup>9</sup>Universidade da Região de Joinville, Joinville SC, Brazil;

<sup>10</sup>Hospital Pompeia, Caxias do Sul RS, Brazil;

<sup>11</sup>Universidade Federal de Pernambuco, Recife PE, Brazil;

<sup>12</sup>Escola Bahiana de Medicina e Saúde Pública, Salvador BA, Brazil;

<sup>13</sup>Neuroclínica, Florianópolis SC, Brazil;

<sup>14</sup>Universidade Federal do Rio de Janeiro, Rio de Janeiro RJ, Brazil;

<sup>15</sup>Santa Casa da Misericórdia do Rio de Janeiro, Rio de Janeiro RJ, Brazil;

<sup>16</sup>Clínica AMO, Salvador BA, Brazil;

<sup>17</sup>Universidade Federal de Santa Catarina, Florianópolis SC, Brazil;

<sup>18</sup>Santa Casa da Misericórdia de São Paulo, São Paulo SP, Brazil;

Patients with multiple sclerosis (MS) are consistently reported as having a higher prevalence of headaches, particularly migraine<sup>1</sup>. The reason for this finding is yet to be clarified, but the predominance of inflammatory cytokines and adverse events from medications rate high among the potential causes of increased prevalence of headache among MS patients<sup>2</sup>. In addition, demyelinating lesions in and around the periaqueductal grey area may be associated to (often intractable) headaches in patients with MS<sup>3,4</sup>. Adverse events relating to MS therapy may also account for the onset or worsening of migraine<sup>5,6</sup>.

The ID-Migraine is a simple three-item questionnaire that is used for screening migraine patients in primary care. However, it has only rarely been used in MS clinics<sup>7</sup>. It has been validated in several languages, including Brazilian Portuguese<sup>8</sup>. Only one previous study has investigated the potential use of ID-Migraine among patients with MS<sup>9</sup>. In this previous Italian study, ID-Migraine showed high sensitivity (91%) and specificity (94%) for identifying migraine in 144 patients with MS. The burden of migraine was assessed using the Migraine Disability Assessment (MIDAS)<sup>10</sup>, in the Brazilian validated version<sup>11</sup>. The MIDAS has already been used in a few studies on migraine in MS identifying a moderate-to-high burden of disease<sup>12</sup>. Using these validated tools, the present study assessed headache in a population of Brazilian patients with MS.

## METHODS

This was a cross-sectional study carried out in specialized MS units. Ethics Committee approvals were obtained in accordance with the rules and regulations of each participating MS center. Patients with MS attending regular consultations at these centers were invited to reply to an online questionnaire that sought clinical and demographic data, headache characterization, ID-Migraine data and MIDAS responses. The neurologists in charge of the patients told them about the study and its characteristics, and patients'

associations in each region were informed of the national survey. The survey was set up in such a way that only the responses of patients who answered every question would be accepted for inclusion in the study. Nonetheless, these potential study participants were completely free to abandon the survey at all times. All information was obtained online without personal identification of patients: they were only asked to state their age, sex and number of years of formal schooling.

Patients with episodic and chronic migraine and tension-type headache were diagnosed in accordance with the criteria of the International Headache Society (ICDH-3 beta version)<sup>13</sup>. Details of these patients' MS therapy were recorded. No healthcare professional had any influence on the responses that patients gave. Only patients with at least one year of confirmed diagnoses of MS were included in the study. The results are presented mainly in a descriptive manner.

## RESULTS

Seven hundred and forty-six patients entered this study. The Table shows a summary of the results. There were 625 women and 121 men, and 69% of all the patients were aged between 20 and 40 years. The majority of the patients (97.6%) had had 12 or more years of schooling and 70.9% of the sample were at university at the time or had already obtained a university degree. The duration of their MS was less than 10 years for 72.7% of all the patients. Migraine was identified in 404 patients with MS (54.1%), and tension-type headache affected 320 patients with MS (42.9%). Primary headache lasting longer than 15 days per month for more than three months was reported by 158 (21.1%) patients. Moderate or severe pain during the headache attacks were reported by 499 patients (69.9%). Headache identification was not possible in 22 patients and it was decided not to register "possible" or "probable" cases of a certain headache.

<sup>19</sup>Neurology Clinic, Curitiba PR, Brazil;

<sup>20</sup>Neurology Clinic, Belo Horizonte MG, Brazil;

<sup>21</sup>Universidade Federal Fluminense, Niterói RJ, Brazil;

<sup>22</sup>Universidade Estácio de Sá, Rio de Janeiro RJ, Brazil;

<sup>23</sup>Hospital Santa Isabel, Blumenau SC, Brazil;

<sup>24</sup>Hospital Santo Ângelo, Santo Ângelo RS, Brazil;

<sup>25</sup>Hospital Universitário Getúlio Vargas, Manaus AM, Brazil;

<sup>26</sup>Universidade de Brasília, Brasília DF, Brazil;

<sup>27</sup>Universidade Positivo, Curitiba PR, Brazil

Yara Dadalti Fragoso  <https://orcid.org/0000-0001-8726-089X>

**Correspondence:** Yara Dadalti Fragoso; Departamento de Neurologia da Faculdade de Medicina/UNIMES; Avenida Conselheiro Nébias, 536; 11045-002 Santos SP, Brazil; E-mail: yara@bsnet.com.br

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**Table.** Summarized data on patients with multiple sclerosis (MS) and headache. Results are presented as percentage, and absolute values are found in the text.

Variables	Parameters (n = 746)
Sex	
Female	83.8%
Male	16.2%
Age group (years)	
≤ 45	78.6%
> 45	21.4%
Years of schooling	
≤ 12	29.1%
> 12	70.9%
MS disease duration (years)	
≤ 3	63.9%
> 3	36.1%
Had headache before MS?	
No	22.4%
Yes	77.6%
Headache onset or worsening after MS diagnosis?	
No	52.5%
Yes	47.5%
Headache onset or worsening due to MS treatment?	
No	44.6%
Yes	55.4%
Diagnosis of migraine by ID-Migraine and IHS criteria	54.1%
Diagnosis of tension type headache by IHS criteria	42.9%
Unclassifiable headache	3.0%
Moderate or high disability by migraine (MIDAS)	68.3%
≥ 15 days per month of headache	22.0%

F: female; M: male; IHS: International Headache Society; MIDAS: migraine disability assessment.

The ID-Migraine identified 409 individuals as migraineurs in this study. Using the ICDH-3 criteria, 404 patients with MS had all the necessary symptoms for diagnosing migraine. Thus, ID-Migraine presented 98.2% specificity, since five patients could be classified as having tension-type headache according to the IHS criteria but were identified as having migraine using this tool. The questionnaire showed 100% sensitivity, since no patients with migraine were identified using the ICDH-3 criteria that were not already identified through ID-Migraine.

The MIDAS identified 276 cases of moderate or high disability among the 404 patients with migraine (68.3%). Migraine attacks were described as occurring on 7-15 days per month in 102 patients (25.2% of the migraineurs) and on more than 15 days per month in another 49 patients (12% of the migraineurs), and the presence of continuous

headache was reported by a further 40 patients with MS (10% of the migraineurs). In summary, 47.2% of the patients with migraine and MS had at least seven days of pain per month.

Acetaminophen was the medication of choice for treating headache attacks for 36.1% of the patients, while 43.8% made use of metamizole sodium. Non-steroidal anti-inflammatory drugs were used by 34.3% of the patients. Oral tablets with ergot and caffeine were used by 30.6% of the patients who did not respond to the above-mentioned analgesics or anti-inflammatory drugs. For refractory pain, triptans were used by 8.6% of the patients, while tramadol was used by 11.3%. All of these medications were often used in association with or in sequence for the same attack.

Prophylactic treatment with beta-blockers, topiramate, valproate or tricyclic drugs had been prescribed for 32.6% of the patients. Antidepressants, anti-anxiety drugs and other unspecific drugs had been used as preventive treatment for 21.1% of the patients. However, this study was not designed to evaluate the effect of therapy among patients with MS.

Onset or worsening of headache episodes at or soon after receiving the diagnosis of MS was reported by 354 patients (47.5%). Interferon beta was prescribed at some point during the therapy for 457 patients with MS in these units. Irrespective of the mode of administration of this drug (subcutaneously or intramuscularly), the use of interferon beta led to the onset or worsening of headache in 266 patients (58.7% of those who used interferon beta at any point). On the other hand, glatiramer acetate was prescribed for 344 patients with MS at some point in their treatment and led to headache as an adverse event in 14.4% of these individuals. Fingolimod led to the onset or worsening of previous headaches in 73.1% of 208 patients who received this treatment at any time, while natalizumab was reported to worsen headache in 58% of 190 patients who were treated with this monoclonal antibody. Glatiramer acetate was the drug least related to headache as an adverse event ( $p < 0.001$  in comparisons with interferon beta, fingolimod and natalizumab). Other drugs had not been used in large enough numbers of patients to allow conclusions regarding headache triggering. There were only a few cases of patients using (or having used) teriflunomide, dimethyl fumarate, alemtuzumab or ocrelizumab, because of the reimbursement system within the Brazilian Ministry of Health protocol for treating MS. This study was not designed to identify which type of headache was associated with each of the treatments.

## DISCUSSION

This large population study brought detailed information on headache affecting 746 patients with MS. The five-times higher prevalence of headache in women may be

due to the higher prevalence of both MS and headaches in women. Only for a small number of patients (< 3%) was it not possible to classify their headache through the online questionnaire. A similarly low number of unclassified headache cases (2%) was observed in a recent large Turkish study<sup>14</sup>. The other patients in our study had either migraine or tension-type headache.

The ID-Migraine was a sensitive and specific tool for screening migraine in patients with MS. Only one study had previously used ID-Migraine among patients with MS, and that study showed that the prevalence of migraine was 53.5%<sup>9</sup>. In the present study, a similar prevalence of migraine was identified among patients with MS.

The ID-migraine is an easy-to-use self-applicable test that can be routinely used in specialized MS centers. With this simple tool, patients in need of special attention for their headache can be identified and treated. Multiple sclerosis clinics tend to concentrate efforts on maintaining good neurological function, through assessing mobility, coordination, visual function, cognition, control of neuropathic pain (such as trigeminal neuralgia) and sphincter ability, but may not have any specific programs for attending to primary headaches. Both MS and migraine can negatively influence patients' quality of life, mood, sleep and cognition.

The burden of migraine in patients with MS was shown to be moderate or high in nearly 70% of these migraineurs. About a quarter of the migraineurs with MS suffered from headache attacks on 7-14 days every month. Over 21% of the migraineurs with MS had between 15 and 30 days of pain per month. The pain intensity was described as moderate or high in over 68% of the patients enrolled in this study.

Most of the patients used analgesic and anti-inflammatory drugs to treat their attacks and less than one third of them had received prophylactic treatment for migraine. The dosage, duration and adherence to these prophylactic drugs was not established through the present study. Almost all the patients with MS participating in the present study treated their headache attacks mainly with painkillers and anti-inflammatory drugs. This finding is in agreement with that reported by Villani et al.<sup>12</sup>, who also reported that the use of triptans by these patients was remarkably rare. These authors showed that less than 10% of the patients had received prophylactic treatment for their migraine. In the present report, a larger number (nearly one third of all migraineurs) had received prophylaxis. However, the dose, duration and efficacy of these preventive therapies cannot be assessed through the methodology used here.

Interferon beta, fingolimod and natalizumab seemed to increase the frequency and severity of headaches in patients with MS. Interferon beta has systematically been reported to be a triggering or worsening factor for migraine in patients with MS<sup>5,6,15</sup>. The present study identified headache as a frequent adverse event of both fingolimod and natalizumab. In making therapeutic choices, these findings need to be considered, as some adverse events may deter the patients' adherence to MS therapy. It is important to address migraine in patients with MS when aiming for a holistic approach to the well-being of people under neurologists' care<sup>16,17</sup>.

In conclusion, migraine is a frequent and disabling condition in patients with MS. An adequate approach towards controlling both diseases is paramount if quality of life and adherence to treatment are sought.

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