

The presence of Uhthoff's phenomenon and fatigue in the spinal optical form of multiple sclerosis

A presença do fenômeno de Uhthoff e a fadiga na forma óptica espinhal da esclerose múltipla

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ABSTRACT

Objective: To describe the frequency and characteristics of Uhthoff's phenomenon and its association to fatigue in spinal optical MS patients, and to evaluate quality of life and depression. **Methods:** MFIS-BR scale, Beck's depression inventory, quality of life SF-36 scale and a questionnaire based of FDS elaborated by the authors on the influence of heat on fatigue, visual dysfunction and other neurological manifestations were applied. **Results:** The final sample consisted of 32 patients and 29 healthy individuals. Uhthoff's phenomenon was found in 31.25% and fatigue on 30% of patients, with significant difference between the groups (6.9%; $p=0.018$). Strong positive correlation was found between fatigue and depression, and vitality of quality of life domain obtained a higher negative correlation to fatigue. There was no association between fatigue and Uhthoff's phenomenon. **Conclusion:** Uhthoff's phenomenon is present in 1/3 of spinal optical MS patients and is associated to the number of visual events (optical neuritis). Heat mainly worsens fatigue and induces temporary visual dysfunctions in MS. Fatigue is associated to depression and negative impact in quality of life.

Keywords: Uhthoff's Phenomenon, Fatigue, Multiple Sclerosis.

RESUMO

Objetivo: Descrever a frequência e as características do fenômeno de Uhthoff e a sua associação à fadiga em doentes com EM espinal óptica, e avaliar a qualidade de vida e a depressão. **Métodos:** Foram aplicadas a escala MFIS-BR, o inventário da depressão de Beck, a escala SF-36 da qualidade de vida e um questionário baseado no FDS elaborado pelos autores sobre a influência do calor na fadiga, disfunção visual e outras manifestações neurológicas. **Resultados:** A amostra final consistiu em 32 pacientes e 29 indivíduos saudáveis. O fenômeno de Uhthoff foi encontrado em 31,25% e a fadiga em 30% dos pacientes, com diferença significativa entre os grupos (6,9%; $p=0,018$). Foi encontrada uma forte correlação positiva entre a fadiga e a depressão, e a vitalidade do domínio da qualidade de vida obteve uma correlação negativa mais elevada com a fadiga. Não houve associação entre a fadiga e o fenômeno de Uhthoff. **Conclusão:** O fenômeno de Uhthoff está presente em 1/3 dos doentes com EM espinal óptica e está associado ao número de eventos visuais (neurite óptica). O calor agrava principalmente a fadiga e induz disfunções visuais temporárias na EM. A fadiga está associada à depressão e ao impacto negativo na qualidade de vida.

Palavras-Chave: Fenômeno de Uhthoff, Fadiga, Esclerose Múltipla.

1 INTRODUCTION

Multiple sclerosis is an inflammatory chronic disease that affects the central nervous system myelin sheath, characterized by the spread in time and space. Young adults, especially women are more commonly affected by this disease, and the most frequent clinical course is outbreak and remission¹. Four clinical forms of disease are accredited: relapsing-remittent, with partial or complete symptom remission after exacerbations; secondary progressive, when at a given moment in the course, symptoms no longer remit and disabilities settle in and slowly evolve; primary progressive, of insidious onset with progression of symptoms without remission; and progression with outbreaks, when residual deficits are accumulated causing significant disabilities and restrictions of daily life activities².

The benign clinical form has been attributed to individuals with more than 10 years of disease with a disability index (EDSS) lower or equal to 3 (walking without assistance). The most common symptoms of the benign form are sensitive or episodes of optic neuritis, individuals do not present restrictions of daily activities and tend to live satisfactorily³. Multiple sclerosis may present a great variety of signals and symptoms, corresponding to the place of injury such as paresis, plegia, ataxia, paresthesia, decreased sensitivity, urinary and / or fecal incontinence, decreased visual acuity, visual cloudiness,

mood swings, among others. The functional systems affected are: pyramidal, cerebellar, brainstem and sensory, vesical, intestinal, visual and mental functions. The functional system most commonly affected is the pyramidal, and the initial signs are generally sensitive, optical, and medullary⁴.

Fatigue is one of the more prevalent and incapacitating symptoms in Multiple Sclerosis patients and interferes in the quality of life. The main factor that leads to the onset and worsening of fatigue in MS is heat. Sensibility to heat was described as the main difference of fatigue in MS when compared to other conditions which also lead to the onset of symptoms⁵.

The optic neuritis (ON), characterized by acute visual disability due to inflammatory lesion of the optic nerve, is another frequent symptom of MS. The ON may be the initial manifestation of the disease in the form of isolated clinical syndrome or occur in a recurrent form along the course of MS. A sub group of patients with RRMS present medullar optic phenotype, characterized by recurrent outbreaks of optic neuritis and transverse myelitis, exclusively. This clinical aspect is frequent among Asiatic and African, and very rare in caucasian⁶.

In 1890, Wilhelm Uhthoff, a German ophthalmologist, described the worsening visual transient due to the exercise associated to optic neuritis⁷, in four of 100 MS patients.

Later new triggering factors were described besides exercise, such as the exposure to high temperatures, fever, hot baths, and smoking⁸. In addition, it was identified that not only the visual system was affected by these factors⁹.

The frequency of Uhthoff's phenomenon post optic neuritis was estimated in 30% of patients with the conventional MS form^{9,10}. There is no data in the literature on this frequency in patients with the medullar optic form, where all patients present at least one event of optic neuritis during the disease.

In order to elucidate this issue, we describe the frequency and characteristics of Uhthoff's phenomenon and its association to fatigue and depression in a series of patients with the medullar optic MS form in Rio de Janeiro, where the majority of population is afro descendant. We also analyze the quality of life of these patients.

2 MATERIAL AND METHODS

The study design was cross-sectional analytical. The study was approved by the ethical and research committee of the Gafreè and Guinle University Hospital on May 24th, 2015.

Participants

Patients diagnosed with relapsing-remitting Multiple Sclerosis (RRMS) with optical medullary phenotype, treated at the neurology service of the Lagoa Federal Hospital (Rio de Janeiro, Brazil), were invited to participate in the study. Healthy individuals selected among relatives, patient caretakers and staff belonging to the health team composed the control group. The study was approved by the ethical and research committee of the Gafreè and Guinle University Hospital on May 24th, 2015 – CAAE 43503915.2.0000.5258.

3 METHODS

The research was carried out in a single visit between June 2015 and February 2016. Participants were evaluated and submitted in person to the following scales: EDSS, MFIS-BR, Beck depression inventory, SF-36 and a questionnaire on the Uthoff phenomenon based on the Fatigue Descriptive Scale (FDS). All participants signed a free and informed consent term.

Instruments

The clinical history of each MS patient and all demographic data were collected from medical records.

The following inclusion criteria were applied: age between 18 and 60, with no outbreak for at least one month. And exclusion criteria: patients with neuromyelitis optica according to the 2006 criteria, less than 1 year of disease duration, and other presentations of MS. Those with cardiorespiratory diseases, smokers, acute infection, active cancer and hyperthyroidism, which are secondary fatigue causes, were excluded from both groups.

EDSS (Expanded Disability Status Scale)

Originally developed by John Kutzke in 1983, EDSS consists of 8 independent functional systems (pyramidal, cerebellar, brain stem, visual, vesical, intestinal, sensitive and mental) which together reflect all incapacities and disabilities of multiple sclerosis. Each functional system has a punctuation that varies between 0 to 6, zero corresponding

to a normal neurological exam and 6, the highest level of disability¹¹. The final score varies from 0 to 10 with intervals of 0.5 points, and depends of the attributed punctuation to each functional system evaluated. Degrees of disability up to 4.0 indicate there is no walking impairment.

Questionnaire on the Uhthoff phenomenon

Based on the Fatigue Descriptive Scale¹², a questionnaire was set up and applied to patients to investigate the influence of heat in MS symptoms, triggering factors and the frequency of Uhthoff's phenomenon (figure 1).

Figure 1. Questionnaire set up by the author, based on FDS

<p>III- Influence of heat</p> <p>Does the hot temperature produce impairment in your symptoms? In wich symptoms? Is there a visual impairment with the heat? If the answer is positive, for how long does this worsening last? Are you more tired if it is hot or not? At what situations? () after exercising () fever () steam room () hot locals () sun exposure () others Is there a total recovery of this symptoms? In wich part of the day do you feel worse? () early morning () afternoon () night If you have optic neuritis, is there a relation between the ON onset and the worsening of the symptoms by heat?</p>

MFIS-BR

The MFIS-BR scale consists of 21 items that address fatigue in three domains: physical (9 items), cognitive (10 items) and social (2 items). The physical domain with scores ≥ 16 indicates physical fatigue, ≥ 18 indicates fatigue in the cognitive domain, and ≥ 8 fatigue in the social domain. The result is given by the addition of the three domains, values higher than 38 indicate fatigue impact in the individual's life.

Beck

Beck's depression inventory is a self-applicable questionnaire consisting of 21 items. The cutoff points are: 0-9 no depression, 10-17 suggest dysphoria, and values above 17 detect depression. 20-30 being moderate depression and above 30, severe.

SF-36

The quality of life questionnaire consists of 36 items comprehended in 8 dimensions (functional capacity, physical aspects, pain, general health state, vitality, social aspects, emotional aspects and mental health). Each item has a punctuation that varies from 0 (worse general health) to 100 (best general health).

Statistical analysis

Data collected were analyzed by the SPSS program for Windows 14.0. Differences between patients and control were analyzed by the Mann Whitney test, for non-normal numerical variables, considering the statistically significant p value <0.05 . The association between categorical variables was made by Chi-square test with Fisher correction. The correlation between scales was made by Spearman test. Results were classified by the variation of “rho” (between 0 to 1) in the following categories: poor correlation (0.0 to 0.19), weak (0.20 to 0.39), reasonable (0.40 to 0.59), strong (0.60 to 0.70) and very strong (above 0.80 to 1.00). For association calculation, demographic and clinical variables were dichotomized by median values.

4 RESULTS

At whole, 32 patients and 29 healthy individuals participated in the study. He majority was of white women with mean age of 33.86 ± 12.04 (among patients), and 44.72 ± 11.59 (in the control group).

The patient clinical profile pointed to an average age of disease onset of 30.8 ± 10 years, and an disease time that varied from 1 to 32 years (mean 13.63 ± 7.80); disease was onset in 21 patients by unilateral ON and in 11 by partial transverse myelitis (Table 2). A mean of 6.69 ± 3.83 (2 – 17) outbreaks per patient, affecting exclusively the optic nerve of the spinal medulla. EDSS evaluated was < 3 in 84%, and only one patient presented EDSS 6.5 (graphic 3). The benign form of MS (EDSS < 3 in more than 10 years of disease) was identified on 50% of the sample. The majority was using immunomodulators and immuno-suppressants for treating MS including beta interferon (31.25%), fingolimode (12.5%) and glatiramer acetate (9.38%); 34.38% did use preventive drugs for the disease.

ON Description

The number of optic neuritis episodes varied from 1 to 5 (mean 1.88 ± 1.26). Regarding the severity of the initial optic neuritis, 23 (72%) patients were classified as

severe in the first event, and 9 as not severe (28%). Recovery from the first optic neuritis was complete in 26 patients (81%), and partial in 6 patients (19%). Time interval from the latest optic neuritis until the latest evaluation (latest follow up) varied from 6 months to 27 years (mean 9.3 ± 6.1 years). 81% of patients had optic neuritis for over a year since the date of evaluation for this study, 19% had a time interval less than or equal to 1 year. Evaluation of this visual function in the latest follow up showed that 72% of patients did not have visual sequel (FSV 0), 15% minimal sequel (FSV 1), 9% moderate sequel (FSV 3), and 3% light sequel (FSV 2).

Uhthoff's phenomenon

The research for the presence of Uhthoff's phenomenon showed that 1/3 the sample (10 patients) referred a visual worseness due to heat. In this group of patients with Uhthoff's phenomenon, the average age was slightly higher than of the group without this phenomenon, as well as the total time of disease and the total number of outbreaks, although with no significant statistical value. The number of visual events and the number of patients who had more than one optic neuritis episode was higher in the Uhthoff group (8/10 versus 6/22 patients), with a significant difference ($p < 0.005$).

Fatigue

According to the total score of the MFIS scale 31.3% of patients and 6.9% of the control group presented fatigue ($p = 0.018$). In patients the most affected domain was the physical (43.8%), followed by cognitive (31.3%) and social domains (6.3%). Table 1 describes the difference between groups.

Table 1. Fatigue by MFIS-BR

	PATIENTS FREQUENCY	%	CONTROLS FREQUENCY	%	P VALUE
MFIS COG	10/32	31,3%	1/29	3,4%	0.005
MFIS FÍS	14/32	43,8%	4/29	13,8%	0.011
MFIS SOC	2/32	6,3%	0/29	0%	0.175
MFIS TOTAL	10/32	31,3%	2/29	6,9%	0.018

Sensitivity to heat

The worsening of symptoms with the increased intra or extracorporeal temperature was identified in 84.4% of patients (Graphic 8). The main outbreak factors were: exercise (43.8%), sun expose (53.1%), and hot places (56.3%). Besides these, using stoves (n=3), hot baths (n=3), saunas (n=4), fever (n=4), stress (n=1) and much lighting (n=1), were also referred.

The increase of temperature also influenced the aggravation of the fatigue symptom in 84% of patients (graphic 10). There was no statistical difference in the perception of fatigue with heat when compared to the groups with or without Uhthoff's phenomenon ($p=0.637$). Besides fatigue, symptoms such as muscular weakness and paresthesia in the extremities were referred in 25% of the sample.

Among patients with sensitivity to heat, 100% referred that worsening of symptoms was transitory, achieving full recovery after heat ceased. When asked about the duration of the worsening of symptoms and the worse moment of the day, 68% answered as few minutes, and 50% referred that the afternoon was the worst moment.

Beck

Beck's inventory was applied to the sample and as result: 23 patients did not show depression, five, only dysphoria, and four, moderate depression. In the control group, four presented dysphoria and the other 23 did not show depression. There was no significant difference between groups ($p=0.067$).

The correlation between depression researched by Beck scale and fatigue by the MFIS-BR was calculated and as result there was a strong positive correlation ($\rho=0.707$ for physical fatigue sub-item; $\rho=0.714$ for cognitive fatigue sub-item; $\rho=0.618$ for social fatigue sub-item; $\rho=0.733$ for the total MFIS-BR score).

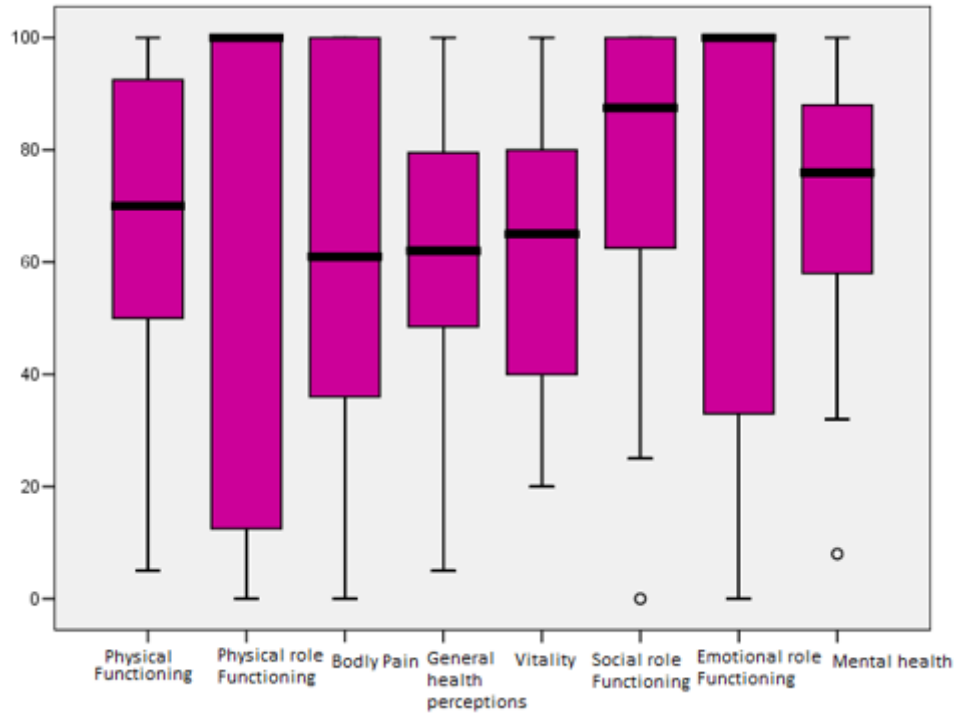
SF36

In patients with OSMS compared to the control group there was a reduction of quality of life only in the general health and vitality domains ($p=0.001$ and $p=0.040$). Graphic 1 describes score values of SF-36 in both groups.

There were no differences found for quality of life domains among the MS groups with and without presence of Uhthoff's phenomenon ($p=0.819$).

A strong negative correlation was demonstrated between fatigue and quality of life, especially in vitality ($\rho= -0.838$; $p=0.000$).

Graphic 1. Results of the SF-36 quality of life scale



Factors associated to fatigue

The potential association between fatigue and demographic and clinical variables was evaluated. Patients were divided in subgroups according to the presence or not of fatigue. An association of depression with two quality of life sub-items was identified (table 2). However, in the bivariate analysis only depression remained associated ($p=0.02$). General health state and vitality lost significance ($p=0.734$ and $p=0.998$, respectively).

Table 2 . Variables associated to fatigue

Variables	Subgroups	Without fatigue	With fatigue	p
Sex	Female	20	7	0.293
	Male	2	3	
Present age	Equal or >44 years	12	5	1.000
	<44 years).	10	5	
Colour	White	15	4	0.244
	Afrodecendant	7	6	
Age at beginning of disease	Equal or >30 years	13	4	0.450
	<30 years).	9	6	
Number of optic neuritis	Higher than 1	11	3	0.446
	Equal to 1	11	7	
Time of disease	Equal or >13 years	10	5	

	<13 years).	12	5	1.000
EDSS	Equal or >3.0 years	2	3	0.293
	<3.0	20	7	
Treatment	Yes	14	7	1.000
	No	8	3	
Depression	Yes	2	7	0.001
	No	20	3	
Vitality	Equal or >65 years	14	1	0.001
	<65	8	9	
General health state	Equal or >62 years	15	3	0.044
	<62	7	7	

Factors associated to Uhthoff's phenomenon

The result of the association of Uhthoff's phenomenon and the demographic and clinical variables is described in table 3. Among all variables analyzed, only the number of optic neuritis was associated to Uhthoff's phenomenon (p=0.008).

Table 3. Factors associated to Uhthoff's phenomenon

Variables	Subgroups	Without phenomenon N=22	Uhthoff's With phenomenon N=10	Uhthoff's p
Sex	Female Male	18 4	9 1	1.000
Present age	Equal or >44 years <44 years).	10 12	7 3	0.265
Colour	White Afrodecendant	13 9	6 4	1.000
Age of beginning of disease	Equal or >30 years <30 years).	12 10	5 5	1.000
Number of optic neuritis	Higher than 1 Equal to 1	6 16	8 2	0.008
Time of disease	Equal or >13 years < 13 years).	10 12	7 3	0.265
EDSS	Equal or >3.0 years <3.0	2 20	3 7	0.293
Treatment	Yes No	14 8	7 3	1.000
Depression	Yes No	6 16	3 7	1.000
Vitality	Equal or >65 years <65	11 11	4 6	1.000
General health state	Equal or >62 years <62	12 9	5 5	1.000

5 DISCUSSION

In this study we analyzed Uhthoff's phenomenon in a group of patients with the medullary optic form of MS. This phenotype is characterized by recurrent myelitis and ON events, exclusively. In the present study, the number of visual events varied from 1 to 5, and the majority had ON as an initial symptom.

Among all variables analyzed, only the number of visual events was associated to the presence of Uhthoff's phenomenon, which occurred in 1/3 of the sample. The hypothesis that the greater the lesion of the optic nerve and the higher the number of demyelinated fibers, higher are the chances of these patients develop deterioration of the symptom with a little increase in body temperature, was then represented. This hypothesis was also suggested in the 1970's, in which more demyelinated fibers presented reversible blockage in nerve conduction, and those less affected, only a reduction in the speed of conduction¹³.

The reverse nature of the phenomenon is described since its first evidence in literature and the hypothesis is that it is associated to the degree of demyelination of fibers and consequent slowness of nervous conduction, and to the reorganization of sodium channels along the axon. In all patients in the sample the worsening of symptoms was transitory, confirming results of other studies in literature, in which symptoms disappear after eliminating the heat triggering factor¹⁴⁻¹⁷.

Uhthoff's phenomenon was researched by a self-applicable questionnaire similar to a British study with 48 individuals that indicated similar results⁹. The result of 1/3 of patients having referred visual cloudiness due to high temperatures intra and extracorporeal has also been reported previously¹⁰. The usage of easy questionnaires for the research of the phenomenon may then be widely spread.

Despite the original description of Uhthoff's phenomenon be attributed to the deterioration of vision after exercising, further studies demonstrated other triggering factors such as hot baths, emotional disorders, psychological stress, fever, menstruation, increase of lighting, exposure to the sun, use of hair blower, and even smoking^{8,14,15}. In the present study, hot places was the factor described most frequently, which can be explained by Rio de Janeiro's climate. Exercising obtained the third highest frequency, confirming data discovered by Wilhelm Uhthoff in his first description⁷. In addition, hot baths, psychological stress and increase in lighting were also referred corroborating with previously mentioned studies.

Sensitivity to heat in MS patients, also analyzed in this study, was recognized from initial descriptions of the disease. In this study, besides the vision worsening, other symptoms were referred in response to heat, especially fatigue. A recent North American study demonstrated that physical fatigue was associated to high body temperatures in RRMS patients at rest, even without expose to heat. It was suggested that an endogenous factor of body temperature rise may influence negatively in the physical fatigue of these patients¹⁹.

The high prevalence of sensitivity to heat and the strong influence of the same MS symptomatology, mainly to fatigue, were reported previously²⁰. Thus, to include information of the interference of external factors, such as heat, especially in fatigue, has become important for the description of this MS symptom.

Fatigue scales do not encompass the evaluation of heat and how much changes in temperature may influence disease symptoms, and consequently, in the quality of life of individuals. Only the Fatigue Descriptive Scale (FDS) proposed by Iriarte¹², includes among its five items, two questions on the influence of heat in the MS symptoms:” Is there worsening of symptoms with high temperatures?” and “Do you feel more tired if you are or not feeling hot?” For not being as yet validated in the Portuguese language, we used our own questionnaire based on FDS to investigate the presence of Uhthoff’s phenomenon in the sample.

Previous studies concluded that patients with a recent history of clinical exacerbation demonstrated greater deterioration, being more sensitive to heat^{17,21}. In this study, non-association of the time interval of the most recent optic neuritis at the date of the latest evaluation may be attributed by the limitation we found, having in view that only six patients had had a visual outbreak one year ago or less.

Uhthoff’s phenomenon did not present association with any demographic or clinical variable, or with fatigue. In addition, fatigue presented high frequency when questioned related to heat, and was present in 1/3 of the sample by applying MFIS-BR. The presence of fatigue even in patients without disability was demonstrated in in approximately 1/3 of patients in another study carried out in Rio de Janeiro²².

In relation to the control group, all domains of MFIS-BR obtained significantly higher scores in the group of patients, the physical domain being the most affected (43.8%). Strong positive correlations were found between fatigue by MFIS and Beck’s depression inventory, as among MFIS and the dimension Vitality of the SF-36 quality of life scale.

Positive correlations between depression and fatigue were widely studied and verified in previous Brazilian and international studies. In a recent study it was proven that fatigue has a positive correlation to depression and disability, and a negative correlation to quality of life in MS patients²³.

In a cohort of 281 MS patients in Iran, the same scales used in our study to analyze fatigue (MFIS) and depression (Beck) were applied to correlate them to quality of life, finding a significant association between variables, which was confirmed in the present study. In addition, scores obtained in Beck's inventory associated negatively to the physical and mental domains of quality of life ²⁴. In the present study, depression correlated strongly to cognitive fatigue.

Fatigue, depression and reduction in quality of life are variables intimately related, having in view that the lack of energy induces lack of motivation which influences negatively in quality of life. A previous study correlated the three factors and found that severity of fatigue and depression had a significant impact in quality of life, especially in mental health of MS patients with different evolutionary forms²⁵. In this study, fatigue showed a negative impact in quality of life of patients, especially in vitality. This domain evaluates the quality of energy, sensation of exhaustion and enthusiasm in four questions in the SF-36 scale.

In the present study there was reduction in all quality of life dimensions in the SF-36 in relation to the control group, especially in the general health state ($p=0.001$) and vitality ($p=0.040$). A study carried out in Rio de Janeiro also described reduction of all domains of SF-36 in a group of 61 patients with RRMS with $EDSS \leq 3.5$ (70%), being the main domain affected related to the physical function and associated to fatigue and to EDSS²⁶.

6 CONCLUSION

Uhthoff's phenomenon occurs not only due to exercise, but also due to intra or extracorporeal heat, and is associated to the number of ON occurred throughout the disease. Besides the visual symptom, other symptoms are also influenced by heat, such as muscular weakness, paresthesia of extremities and especially fatigue. Fatigue occurs even in patients with the benign form, and is associated to depression and related to low quality of life.

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