PAIN IN TROPICAL SPASTIC PARAPARESIS/ HTLV-I ASSOCIATED MYELOPATHY PATIENTS

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Abstract – **Objective:** Tropical Spastic Paraparesis/HTLV-I Associated Myelopathy (TSP/HAM) is a chronic myelopathy, and pain has been mentioned as a frequent sensory symptom in this condition. The authors aimed at analyzing this symptom in a TSP/HAM patients series. **Method:** For this, 46 patients were analyzed considering demographic and clinical characteristics and complaint of pain as to verbal description, time of onset and classification, correlated with the degree of motor disability and type of pain. **Results:** Among the 46 TSP/HAM patients, 28 (60.8%) complained of pain, predominant in the early phase of the disease. Most of the patients exhibited neuropathic characteristics of pain, correlated with increased motor disability. **Conclusion:** Pain in TSP/HAM patients is a frequent and early symptom, and the neuropathic type is predominant (57.1%) and paralleled with increased incapacitation. The pathogenic involvement of cytokines may possibly be involved in the meaning of this symptom in this condition.

KEY WORDS: TSP/HAM, HTLV-I, pain, inflammatory nociceptive and neuropathic, cytokines.

Dor em pacientes com paraparesia espástica tropical/mielopatia associada ao HTLV-I

Resumo – **Objetivo:** A Paraparesia Espástica Tropical/Mielopatia Associada ao HTLV-I (PET/MAH) é uma mielopatia crônica, e a dor tem sido mencionada como um sintoma sensitivo freqüente nessa condição. Os autores objetivam analisar esse sintoma numa série de pacientes com PET/MAH. **Método:** Para isso, 46 pacientes foram analisados considerando características demográficas e clínicas, e queixa de dor do ponto de vista da descrição verbal, tempo de início e classificação, correlacionados com o grau de incapacitação motora e o tipo de dor. **Resultados:** Dentre os 46 pacientes com PET/MAH, 28 (60,8%) se queixavam de dor, predominando na fase inicial da doença. A maioria dos pacientes evidenciou características de dor neuropática, correlacionada com aumento da incapacitação motora. **Conclusão:** A dor em pacientes com PET/MAH é um sintoma freqüente e inicial, sendo o tipo neuropático predominante (57,1%) e em paralelo com maior incapacitação. O envolvimento patogênico das citocinas poderá possivelmente estar relacionado com o significado desse sintoma nessa condição clínica.

PALAVRAS-CHAVE: PET/MAH, HTLV-I, dor, nociceptiva inflamatória e neuropática, citocinas.

Tropical spastic paraparesis/HTLV-I associated myelopathy (TSP/HAM) is a chronic myelopathy associated to HTLV-I[1,2] clinically expressed by spastic paraparesis, bladder and bowel dysfunction and variable sensory symptoms. The criteria used to diagnose this condition are primarily clinical with limited investigation of blood and CSF[3] or incorporate more extensive investigation as the degree of exclusion of other disease as well as the nature of the presentation determine whether a definite, probable or possible diagnosis is made[4]. Both sets of criteria seem to be comprehensive and to concur[5]. Among the sensory symptoms, pain has been mentioned as frequent[1,6-12], with no emphasis, however, on its pathogenic origin or its meaning. Its presence in most pa-

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Received 20 January 2009, received in final form 30 June 2009. Accepted 4 July 2009.

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tients represents an incapacitating symptom, compromising the patient's quality of life.

Pain may be classified into inflammatory nociceptive and neuropathic pain. Inflammatory mediators are concerned with the nociceptive peripheral type[13], whereas lesion or dysfunction of the peripheral and central nervous system[14] or, according to the new classification, lesion or disease affecting the somatosensory system[15] is related to the neuropathic category. In both types, cytokines such as TNF-α, IL-1, IL-6 and IL-8 are involved[16-19] at least in the initial or late stages of the conditions. Patients with TSP/HAM seem to present both types of pain, although this distinction has not been accurately made by the authors.

This paper aims to outline the frequency of pain in our series of TSP/HAM patients and in previous reports of the literature and to comment on the possible meaning of pain in those patients.

METHOD

For this analysis, 46 patients from a cohort with TSP/HAM were reviewed. These patients had been diagnosed with TSP/HAM according to the WHO criteria[3] and as definite, probable or possible TSP/HAM according to the new staging criteria[4]. For pain analysis in the patients, only definite TSP/HAM was considered.

To define the category of pain, symptoms were matched with verbal descriptors for neuropathic and nociceptive pain, as reported by Boureau et al.[20] and Bouhassira et al.[21], which showed that verbal descriptors such as burning, cold, stabbing, shooting, paresthetic, dysesthetic, pruriginous and numb pain were significantly suggestive of neuropathic pain, being other expressions suggestive of non-neuropathic or nociceptive pain.

Motor disability, according to Kurtzke's Disability Status Scale (DSS)[22], was also correlated with the category of pain (neuropathic, nociceptive or mixed). Need of support (6 in the scale) was the parameter used for evaluating the patients. The degree of spasticity could not be measured and so pain was not correlated with it in these patients.

For time definition of early or late pain onset matched with neurological symptom, the limit of 3 years evolution was considered, according to the evolutive neuropathological classification shown by Iwasaki [23].

The patients signed a written informed consent and the study was approved by the Research Ethics Committee of the Department of Physiology and Pharmacology of the Federal University of Ceará.

RESULTS

Among the 46 TSP/HAM patients, 28 (60.8%) complained of pain. Twenty-one of them were women and 7 were men, and they had a mean duration of disease of 10.42 years.

All 28 patients were diagnosed as definite TSP/HAM, i.e. they had a non-remitting progressive spastic paraparesis, sensory symptoms and urinary and anal sphincter signs, and they had also anti-HTLV-I antibodies in serum and CSF; other disorders that may resemble TSP/HAM were excluded[4]. All patients exhibited then spasticity and paraparesis in a limited extend but not so severe as to become bedridden.

Among the 28 patients, 23 reported pain in an early stage of the disease, whereas in 5 of them pain was only reported in the late phase (>3 years) (Table 1).

As to pain complaints, arthralgia, knee, leg and back/lumbar pain were reported by 7 (25.9%) patients as examples of nociceptive pain. Three of them reported in the early phase of the disease and 4 in the late stage. Burning pain in feet and legs, paresthesias in the legs, shooting, dysaesthesic and leg pain were seen in 16 (57.1%) patients, suggesting neuropathic pain, according to Boureau[20] and Bouhassira et al.[21] verbal descriptors. Most of them (14 patients) presented it in the early phase of the condition. Mixed nociceptive/neuropathic pain was seen in 5 (17.8%) patients. Three of them had it in the initial phase and 2 of them in the late phase. In short, 7 had nociceptive pain, 16 had neuropathic pain and 5 had mixed nociceptive/neuropathic pain, evidencing, this way, neuropathic components in 21 patients (Tables 1 and 2).

Considering the correlation between motor disability according to Kurtzke's Disability Status Scale[22] and type of pain, there was a correlation between increased disability and neuropathic pain (Table 3), suggesting increasing involvement of the central nervous system, as also evidenced by the prominent pyramidal signs present in all patients.

DISCUSSION

Pain is a frequent symptom, as seen in our and others' series, in patients with TSP/HAM[6-12]. However, the meaning of this symptom was overlooked in all these reports. Moreover in our series, most of the patients complained of pain in the early phase of TSP/HAM, as also shown in other series[6,26-28] and this may correlate with predominant inflammatory activity in this phase[23,29].

According to Boureau[20] and Bouhassira et al.[21] verbal descriptors, nociceptive and neuropathic pain symptoms have been identified in the description of TSP/HAM patients, by previous authors, as shown below.

Possible examples of inflammatory nociceptive pain have been shown by Morgan[12], who evidenced lumbar pain in 70% of TSP patients, Castañeda and Deza[30], which described a patient who began her symptoms with knee pain, and by Zunt et al.[9] who showed that among 34 TSP/HAM patients, 21 (61.8%) had pain in the joints and 9 (26.5%) in the arms. Back pain is mostly considered as inflammatory nociceptive type; however, roots compression is frequent-

Table 1. TSP/HAM patients and pain time of onset, description and type.

Patients	Diagnostic level of ascertainment	Time of onset		Pain description	Pain type		
		< 3 years	>3 years		Nocic	Neurop	Mixed
1	Definite	–	4 years	Knee pain	+	–	–
2	Definite	–	4 years	Burning feet + Arthralgia	–	–	+
3	Definite	1 year	–	Paresthesiae	–	+	–
4	Definite	>1 year	–	Burning feet	–	+	–
5	Definite	< 1 year	–	Burning legs	–	+	–
6	Definite	–	>3 years	Leg pain	+	–	+
7	Definite	< 1 year	–	Leg pain / Numbness	–	–	–
8	Definite	< 1 year	–	Knee pain + Leg numbness	–	–	–
9	Definite	< 1 year	–	Feet burning / Shooting pain	–	+	–
10	Definite	–	>3 years	Arthralgia	+	–	–
11	Definite	< 1 year	–	Right leg paresthesiae	–	+	–
12	Definite	< 1 year	–	Legs paresthesiae	–	+	–
13	Definite	< 1 year	–	Knee pain	+	–	–
14	Definite	< 1 year	–	Burning feet	–	+	–
15	Definite	–	>3 years	Knee pain	+	–	–
16	Definite	>1 year	–	Shooting pain	–	+	–
17	Definite	< 1 year	–	Lumbar pain + Feet paresthesiae	–	–	+
18	Definite	< 1 year	–	Burning pain / Lumbar	–	–	+
19	Definite	< 1 year	–	Burning feet	–	+	–
20	Definite	–	>3 years	Burning feet	–	+	–
21	Definite	< 1 year	–	Feet paresthesiae / Leg pain	–	–	+
22	Definite	< 1 year	–	Lumbar pain	+	–	–
23	Definite	< 1 year	–	Lumbar pain	+	–	–
24	Definite	>1 year	–	Burning and shooting pain in feet	–	+	–
25	Definite	>1 year	–	Legs paresthesiae	–	+	–
26	Definite	< 1 year	–	Legs allodynia and numbness	–	+	–
27	Definite	< 1 year	–	Feet burning pain	–	+	–
28	Definite	< 1 year	–	Legs dysesthesiae	–	+	–

Nocic: nociceptive; Neurop: neuropathic.

ly associated, what may give it, in some cases, a neuropathic/nociceptive mixed nature[31] as also shown in Morgan's[12] cases. Back pain has also been described by Gessain and Gout[24] in 49% of 380 TSP/HAM patients, by Zunt et al.[9] in 24 out of 34 patients (70.6%), as well as in other series[10,25], and even in juvenile cases[32].

Neuropathic pain is mainly expressed in the form of paresthesias, leg pain, burning and shooting pain. Complaints of burning pain, pin-and-needles, cramps, numbness or tingling occurred in around 40% of TSP patients, persisting for long time[11,24,25,33]. Leg pain and paresthesias have also been described by De Castro-Costa et al.[6], Gessain and Gout[24], Sheremata et al.[34], Haussen and De Vecchino[35], Cartier et al.[33], Biglione et al.[36] and Zunt et al.[9].

Mixed nociceptive and neuropathic pain may also be present in TSP/HAM patients. Possibly they may occur simultaneously or in different phases of the disease. Smadja et al.[25] reported varied pain in 60% of 271 TSP/HAM patients, including lumbar and thigh pain, sensation of electric discharges in the lower limbs. Similar mixed pain conditions have also been reported by others[7-9,36].

As all patients had spasticity, could this be the pain origin, in a form of muscle spasm? Most of the patients reported symptoms of inflammatory nociceptive pain (joint and back pain) or neuropathic dysesthetic pain. The localization of the pain condition (joint and back pain) does not relate with spasticity as a possible source of pain. As shown above, neuropathic pain is consequent to lesion

Table 2. Type of pain and time of onset in TSP/HAM patients.

Type of pain	Number of patients and time of onset respective to disease		Total
Nociceptive	< 3 years	>3 years	
Arthralgia		1	
Leg pain	1		
Knee pain	1	2	
Back/Lumbar pain	2		
Neuropathic	4	3	7 (23.3%)
Paresthesiae (pricking, itching)	4		
Burning feet	7	1	
Burning legs	1		
Shooting (shock)	1		
Alodynia/Numbness	1		
Leg pain and numbness	1		
Leg dysesthesia	1		
Neuropathic/non-Neuropathic (Mixed)	15	1	16 (57.1%)
Burning feet and arthralgia		1	
Knee pain + Legs numbness	1		
Lumbar pain + Feet paresthesia	1		
Burning and lumbar pain	1		
Feet paresthesia / Leg pain	1		
	4	1	5 (17.8%)

Table 3. TSP/HAM patients motor disability according to Kurtzke's, Disability Status Scale (DSS) and pain type.

Kurtzke's DSS	Number of patients	Pain type		
		Nociceptive	Neuropathic	Mixed
< 6	10	4	4	2
≥6	20	3	13	4
Total	30	7	17	6

or disease affecting the somatosensory system of the peripheral or central nervous system[14], what could not be the case affecting the corticospinal tract compromised in the spasticity. Moreover, not all patients with pain took baclofen as an anti-spastic treatment. However, even in those patients who used it, this drug has also analgesic action, such as in spinal cord injury[37], as well as in neuropathic experimental pain[38].

This high prevalence of pain in TSP/HAM patients stimulates a search for its meaning in this condition. Could this symptom be predictive of another pathological event?

It is known that in TSP/HAM the key pathological event is an inflammatory demyelinating lesion in the spinal cord consequent upon immune mechanisms involving cytokines, such as IFN-γ and TNF-α[39,40], and this may be expressed mainly in the beginning of the neurological symptoms, but also along the disease, declining, however, with the disease duration[41]. It is also clear that in inflammatory nociceptive and neuropathic pain, cytokines such as TNF-α, IL-1, IL-6 and IL-8[16-19] are mainly implicated. It is reasonable therefore to propose that pain may be a clinical marker of impending or continuing lesion. Accurate clinical and laboratory follow-up of the patients for evidence of increased cytokines in the spinal fluid and blood serum, perhaps correlated with increased proviral load or viral expression and occurrence of pain, would help clarify such a hypothesis. In addition it is worth noting that in some patients a clinical response to pulsed high-dose corticosteroids is associated with dramatic, albeit temporary

alleviation of pain[39]. Again, correlation of cytokine production before and after therapy with quantitative pain scores will contribute to our understanding. Finally, specifically targeting cytokines in the treatment of TSP/HAM may complete the picture.

ACKNOWLEDGMENT – The authors thank Mr. Sílvio A. Costa for his technical assistance.

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