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Neuropathic Pain in Leprosy Patients[1]

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ABSTRACT

The introduction of multidrug therapy by the World Health Organization has dramatically reduced the world prevalence of leprosy but the disease is still a public health problem in many countries, with a world prevalence of almost 600,000 cases in 2001. Damage to peripheral nerves is a key component of leprosy and the sensory and motor loss that follows is the basis for many of the classical features of this disease, such as skin wounds, cracks, plantar ulcers, clawed hands, drop foot, and incomplete closure of the eyelids. One of the most remarkable aspects of leprosy to lay persons and health care workers alike is that patients are reputed to feel no pain. However, neuropathic pain is arising as a major problem among leprosy patients. It can be nociceptive due to tissue inflammation, which mostly occurs during episodes of immune activation or neuropathic due to damage or dysfunction of the nervous system. This study, conducted among 358 leprosy patients, reveals a considerable prevalence of neuropathic pain and presents evidence that this common problem should be a high priority of those in charge of leprosy control programs.

RÉSUMÉ

L'introduction de la poly-chimiothérapie par l'Organisation Mondiale de la Santé a diminué de façon drastique la prévalence mondiale de la lèpre mais la maladie est encore un problème de santé publique dans plusieurs pays, avec une prévalence mondiale de presque 600 000 cas en 2001. L'atteinte des nerfs est une composante clef de la lèpre et les pertes sensorielles et motrices qui s'ensuivent forment la base des caractères classiques de cette maladie, comme les blessures cutanées, les fissures, les ulcères de la plante des pieds, les mains en crochets, les pieds tombants et la fermeture incomplète des paupières. Un des aspects les plus remarquables de la lèpre pour le grand public comme pour le prestataire de soins de santé est que les patients ont la réputation de ne pas ressentir de douleur. Cependant, les douleurs neurogènes sont en train d'émerger comme un problème majeur parmi les patients hanséniens. Elle peut être nociceptive, due à l'inflammation qui apparaît principalement durant les épisodes d'activation immunologique, ou bien neurogène, causée par une atteinte ou une dysfonction du système nerveux. Cette étude, menée chez 358 patients lépreux, révèle une prévalence considérable de douleurs neurogènes et présente des arguments afin que les responsables de santé publique et de contrôle de la lèpre considèrent ce problème comme une priorité.

RESUMEN

No obstante que la introducción de la poliquimioterapia por la Organización Mundial de la Salud ha reducido dramáticamente la prevalencia de la lepra a nivel mundial, la enfermedad es todavía un problema de salud pública en muchos países, con una prevalencia de casi 600,000 casos en 2001. El daño a los nervios periféricos es un componente crítico de la lepra y la pérdida sensorial y motora que le siguen es la base de muchas de las características clásicas de la enfermedad que incluyen heridas en la piel, cuarteaduras, úlceras plantares, manos en garra, pie caído y cierre incompleto de los párpados. Uno de los aspectos más remarcables de la lepra es la creencia general de que los pacientes no sienten dolor. Sin embargo, el dolor neuropático se está manifestando como un problema cada vez mayor entre los pacientes con lepra. El dolor puede ser enmascarado por la inflamación del tejido que ocurre principalmente durante los episodios de activación inmune o neuropática asoci-

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ada al daño o disfunción del sistema nervioso. El presente estudio, realizado en 358 pacientes, revela una considerable prevalencia de dolor neuropático, y presenta evidencias de que este es un fenómeno común que debe ser de alta prioridad para aquellos encargados de los programas de control de la lepra.

Since the introduction of an effective treatment based upon a multi-drug therapy (MDT) of dapsone, clofazimine, and rifampicin as recommended by the World Health Organization (WHO), the prevalence of leprosy has dramatically decreased ([13]). However, the disease is still a public health problem in many countries with an estimated global prevalence of near 600,000 cases as for the year 2003 ([14]).

Damage to peripheral nerves is a key component of leprosy and, together with typical skin lesions, accounts for the major traditional clinical features of the disease. Little is known about the mechanism by which the mycobacteria infect Schwann cells, but recently some evidence has emerged. A glycoprotein (α-dystroglican) that binds to the surface of *Mycobacterium leprae* also binds to a molecule on the surface of the Schwann cell surface and provides a potential mechanism for internalization of the bacilli by Schwann cells ([1, 9]).

The sensory and motor loss that follows nerve damage in leprosy is the basis for many of the classical features of the disease such as skin wounds, cracks, plantar ulcers, clawed hands, drop foot, and lagophtalmos. Sensory damage includes an early loss of pain and temperature perception followed by compromise of tactile and pressure senses. The distribution and onset of nerve damage can vary according to the type of leprosy, being more disseminated and gradual in the lepromatous cases, or localized and acute in tuberculoid and borderline cases. The indeterminate type is an initial presentation of the disease in which major nerve damage has not yet developed.

One of the most remarkable aspects of leprosy to lay persons and health care workers alike is that patients are reputed to feel no pain. This wide-spread impression is rapidly changing as many patients who have completed their WHO MDT are now reporting complaints of stimulus-independent ongoing pain, and seeking relief. Indeed, pain in leprosy can be nociceptive due to tissue inflammation, which mostly occurs during episodes of immune activation ["reversal reaction" (RR) and "erythema nodosum leprosum" (ENL)] or neuropathic due to damage or dysfunction of the nervous system. Nociceptive pain is due to activation of peripheral nociceptors on A-delta and C-fibers, secondary to nerve tissue injury during ENL or RR. There is a release of bradykinin, serotonin, substance P, histamine and prostaglandin, which facilitate the transmission of pain impulses from the periphery to the spinal cord.

The complex and stigmatizing burden of being diagnosed with leprosy may compel patients to focus solely upon curing the disease, which is actually accomplished with the WHO drug regimen, and to accept their symptoms as an inevitable concomitant or residual of the disease. However, the number of cases with pain problems seemed to us to be substantial ([4]). The aims of this study, conducted in a country where leprosy is endemic, were to estimate the prevalence of pain in patients with leprosy and to determine the main characteristics of their pain.

MATERIALS AND METHODS

The study was conducted at the Instituto Lauro de Souza Lima, Bauru, Brazil, a national referral center for leprosy patients. Brazil has a prevalence of 77.676 cases per 100,000, and an important detection rate of 24.1/100,000 (41.070 new cases in 2000), which makes it the second largest endemic country for leprosy in the world after India ([14]).

The study included 358 patients with leprosy who presented to the Dermatological clinic of Instituto Lauro de Souza Lima from October 1, 2001 to March 31, 2002. Among them, 215 were male (60.1%) and 143 were female (39.9%). The mean age was 54.8 yrs (S.D. = 16 yrs), with a range of 11 to 87 yrs.

The mean time from initial diagnosis was 18.3 yrs (range, 10 months to 68 yrs, S.D. = 18.5 yrs), and 178 (49.7%) patients were diagnosed over 10 years earlier. According to

the Madrid Classification ([8]), 207 patients (57.8%) were lepromatous, 92 (25.7%) borderline, 54 (15.1%) tuberculoid, and only 5 (1.4%) were indeterminate. All cases were receiving treatment except for 283 (79.1%) patients who had concluded their standard course by the time of the study. Treatment regimens included the WHO MDT, dapsone plus rifampicin, or dapsone as monotherapy in some previously treated cases.

Two hundred and one (56.1%) of the patients reported past or current moderate to severe chronic neuropathic pain that interfered with activities of daily living or disturbed sleep. None of these cases revealed signs or symptoms of RR or ENL as assessed by an experienced clinician. These cases underwent clinical neurological examination by trained health workers, including detailed anamnesis assessment focusing on the occurrence of pain, its localization, duration, pattern of symptoms onset, quality, and quantity. Localization of pain refers to the anatomical distribution and trunk of the most relevant affected peripheral nerve. Duration of pain was classified as less or greater than 6 months. The pattern of symptom onset was categorized as abrupt, insidious, or in repetitive bursts. Assessment of quality of pain was based upon the Brazilian Portuguese version of the McGill Pain Questionnaire ([12]). In addition, we inquired whether present pain was experienced as superficial, deep, or mixed. Pain intensity was verbally rated by patients as mild, moderate, or severe and was also rated on a graphic scale (empty to full water glass).

RESULTS

Using the day of interview and examination as the reference point, 148 (73.6%) patients reported episodes of pain only in the past and 53 (26.4%) had complaints at present. In the 148 patients with past pain only, leprosy had been diagnosed less than 10 years earlier in 59 cases (39.8%) and more than 10 years earlier in 89 cases (60.2%). In those with present pain, only 14 (26.4%) cases had been diagnosed over 10 years earlier. Pain had been present for 6 months or less in 55 cases (27.4%), whereas 141 (70.1%) reported pain for longer than 6 months. Only 5 patients (2.5%) could not estimate the duration of their pain. The nerve most often affected by pain was the ulnar (59.2%), followed by the tibial (30.3%), fibular (18.9%), median (4.5%), radial (2.0%), and trigeminal (1.5%). These percentages sum to greater than 100 because patients were free to indicate pain in the distribution of more than one nerve. Glove (22.4%) and stocking (24.9%) distribution of pain were also quite common (Fig. 1). The onset of episodes was reported as abrupt by 39 patients (19.4%), as insidious by 73 patients (36.3%), and as recurrent bursts by 89 (44.3%) patients. The assessment of quality of pain can be seen in Fig. 2.

In the 53 patients with pain present at the time of interview, the most affected anatomical layer was deep in 30 (56.6%) patients, superficial in 8 (15.1%) and mixed in 15 (28.3%). In these patients, pain was constant in 34 (64.2%) and episodic in 19 (35.8%). Verbal ratings of present pain were severe in 29 (54.7%), moderate in 17 (32.1%), and mild in only 7 patients (13.2%). On the graphic scale, 22 (41.5%) patients rated their pain as severe, 21 (39.6%) as moderate, and 10 (18.9%) as mild. These pain characteristics are summarized in The Table.

DISCUSSION

Lack of sensation is a paradigm of leprosy, and the diagnosis of this chronic infectious disease is assured by the presence of skin lesions (usually patchy) with marked sensory loss as assessed by Semmes-Weinstein monofilaments or a ballpoint pen tip. Abnormalities include loss of touch, temperature, and pressure sensation. Although clinical consensus regards leprosy as painless, in reality nerve pain in leprosy is often present during neuritis, a feature that accompanies acute leprosy reactions. These reactive episodes include entrapment of the nerve in selected sites (most often the ulnar canal at the elbow) due to edema from acute and severe inflammation of the nerve. In such a situation, activation of the nervi nervorum may be the main contributor to pain. Another possibility is that the acute neural inflammation can excite and sensitize nociceptors. In some cases, there is severe destruction of nerve fibers ([2]) and the partial regeneration that follows may produce discharges, diminution of stimulus thresholds, and exaggerated responses of nociceptors.

THE TABLE. *Some characteristics of neuropathic pain among 201 cases of leprosy with past (148) or present (53) pain.*

	Groups	Past pain*	%	Past pain*	%
Clinical form	Lepromatous	94	63	26	49
	Borderline	29	20	20	38
	Tuberculoid	24	16	7	13
	Indeterminate	1	0.6	0	0
Onset	Abrupt	30	20	9	17
	Insidious	47	32	26	49
	Bursts	71	48	18	34
Duration in months	<6 months	49	33	6	11
	>6 months	94	63	47	89
	Not known	5	3	0	0
Time of leprosy diagnosis	<10 years	59	40	39	74
	>10 years	89	60	14	26
Treatment completion	Yes	130	88	40	75
	No	18	12	13	25
Pain intensity	Mild	—	10	19	
	Moderate	—	21	40	
	Severe	—	22	41	
Verbal rating of pain intensity	Mild	—	7	13	
	Moderate	—	17	32	
	Severe	—	29	55	
Time of worst pain	Morning	—	7	13	
	Afternoon	—	9	17	
	Evening	—	15	28	
	Not specific	—	22	41	
Anatomical layer of involvement	Superficial	—	8	15	
	Deep	—	30	57	
	Mixed	—	15	28	
Evolution	Worsening	—	20	43	
	Stable	—	24	51	
	Remitting	—	9	19	
Character	Episodic	—	19	36	
	Constant	—	34	64	

*Number of patients

This study reveals that neuropathic pain not directly associated with an acute reactive episode may be present in a considerable proportion of patients with leprosy. In fact, out of 358 patients presenting to the outpatient dermatological clinic for other reasons, 56.1% reported prior or current episodes of neuropathic pain. Most of these patients reported that the intensity was severe and sufficient to interfere with activities of daily life or sleep.

According to the literature ([3, 5]), the most common nerve affected in leprosy is the ulnar nerve, and we confirmed the frequency of this as a painful site. However, a glove and stocking distribution of pain was also frequently reported by our patients. Although involvement of nerve trunks in leprosy is common, the superficial branches and their rami may be also compromised, particularly in lepromatous and borderline cases in which dissemination of the disease is a characteristic feature.

It is important to note that, among patients with present pain, 40 patients (75.4%) had completed antimicrobial treatment and, according to the present policy of leprosy control, are discharged from further follow-up. Such patients receive little further care. Therefore, a significant number of patients did not have ongoing access to care and could not seek assistance for relief of neuropathic pain and improvement of quality of life. In addition, 130 patients (87.8%) with past pain had already completed treatment by the time their pain occurred. Thus, successful completion of antimicrobial treatment does not appear to prevent occur-

rence of neuropathic pain. As a matter of fact, the teams caring for patients with leprosy are not generally aware of the problem of neuropathic pain. Furthermore, when considering the indication for classical drugs for both RR and ENL, there appears to be some misunderstanding as to what is responsible for the pain component. Sometimes, it appears that health personnel believe that thalidomide or steroids can act as analgesics, which is not true. Of course, their action on reducing edema and attenuating immunological aspects of reaction can lead to a reduction in pain. Conversely, in pure neurophatic pain there is no room for such drugs. Therefore, it is of utmost importance that control of neuropathic pain in leprosy be included as an issue to be dealt with by leprosy control program managers. Control and treatment of neuropathic pain in leprosy has not yet been well studied. However, the experience with the treatment of such pain in other conditions has stimulated the use of some standard drugs in cases of leprosy ([6, 7, 10, 11]). In this regard, some good results have been reported while using tryciclic antidepressant drugs such as aminotriptyline and imipramine. Anticonvulsant agents can also be used, such as carbamazepine and gabapentin. It is important to note that these drugs are analgesic with a central action and, therefore, do not interfere in the nerve damage process, either in its recovery or worsening.

CONCLUSION

This study reveals a considerable prevalence of neuropathic pain among patients with leprosy and presents evidence that this common problem should be a high priority among those in charge of leprosy control programs. In fact, given the present public health policy of shorter regimens and immediate discharge of patients after completion of treatment, this problem could worsen further. Thus, at present there is a strong need to review the concept of leprosy care to provide adequate attention to this disabling complication, and plenty of room for studies on new therapies to cope with this previously ignored clinical problem.

REFERENCES

1. Freedman, V. H., Weinstein, D. E., and Kaplan, G. How *Mycobacterium leprae* infects peripheral nerves. Lepr. Rev. **70** (1999) 136–139.
2. Garbino, J. A. Manejo clínico das diferentes formas de comprometimento da neuropatia hansênica. Hansen Int. **special** (1998) 93–99.
3. Hastings, R. C. *Leprosy,* 2nd ed. New York: Churchill Livingstone, 1993.
4. Hietaharju, A., Croft, R., Alam, R., Birch, P., Mong, A., and Haanpaa, M. Chronic neuropathic pain in treated leprosy. Lancet **356** (2000) 1080–1081.
5. Jopling, W. H., and McDougall, A. C. *Handbook of Leprosy,* 5th ed. New Delhi: CBS Publishers and Distributors, 1996.
6. Kloke, M., Hoffken, K., Olbrich, H., and Schmidt, C. G. Antidepressants and anticonvulsants for the treatment of neuropathic pain syndromes in cancer patients. Onkologie **14** (1991) 40–43.
7. Max, M. B., Culnane, M., Schafer, S. C., Gracely, R. H., Walther, D. J., Smoller, B., and Dubner, R. Amitriptyline relieves diabetic neuropathy pain with normal or depressed mood. Neurology **37** (1987) 589–596.
8. Opromolla, D. V. A. *Noções de Hansenologia*. Bauru: Centro de Estudos Reynaldo Quagliatto, 2000.
9. Rambukkana, A., Salzer, J. L., Yurchenco, P. D., and Tuomanen, E. I. Neural targeting of *Mycobacterium leprae* mediated by the G domain of the laminin-alpha 2 chain. Cell **88** (1997) 881–821.
10. Rockliff, B. W., and Davis, E. H. Controlled sequential trials of carbamazepine in trigeminal neuralgia. Arch. Neurol. **15** (1966) 129–136.
11. Rowbotham, M., Harden, N., Stacy, B., Bernstein, P., and Magnus-Miller, L. Gabapentin for the treatment of postherpetic neuralgia: a multicenter double-blind, placebo-controlled study. JAMA **280** (1998) 1837–1842.
12. Teixira, M. J., and Pimenta, C. A. M. Avaliação do doente com dor. In: *Dor: epidemiologia, fisiopatologia, avaliação, síndromes dolorosas e tratamento*. São Paulo: Moreira Jr., 2001. pp. 56–68.
13. World Health Organization. *Guide to Eliminate Leprosy as a Public Health Problem.* Geneva: World Health Organization, 2000.
14. World Health Organization. Weekly Epidemiol. Rec. 77 (2002).