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Multiple Sclerosis and HTLV-I associated myelopathy/tropical spastic paraparesis are two distinct clinical entities

Fidias E Leon-S[1,2], Kimiyoshi Arimura[1], Mitsuhiro Osame[1]
[1]Third Department of Internal Medicine, Kagoshima University School of Medicine, Kagoshima, Japan; [2]UIS-Santander University School of Medicine, Bucaramanga, Colombia

Multiple sclerosis (MS) and HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP) can overlap in their clinical features and thereby cause difficulties for clinicians in relation to diagnosis and therapy. However, epidemiological biochemical, immunological, virological and radiological studies point to a number of significant differences. Recent comparative neurophysiological data, including blink reflex studies, obtained in these disorders, is briefly reviewed here and provides additional evidence of difference. The abnormal blink reflex in patients with MS consist of prolonged latencies and absences of R1 and R2 responses and are mainly due to demyelinating lesions around the pons. In contrast, in HAM/TSP the blink reflex abnormalities frequently include an unusual early response, R1k, which is probably a consequence of interneuronal hyperexcitability around the brainstem. Thus these findings provide further support for our contention that HAM/TSP and multiple sclerosis are distinctly different both as clinical entities and in their underlying pathomechanisms.

Keywords: *Multiple sclerosis; HAM/TSP; neuroepidemiology; blink reflex; neurophysiology*

Introduction and background

MS and HAM/TSP are two neurological entities, each with its own defined criteria for recognition,[1,2] though some, mostly clinical similarities have also been reported.[3,4] These similarities pose a challenge to clinicians dealing with these disorders, and have implications for therapy. It is relevant therefore that the studies described below, including our own, seem to be helpful in distinguishing these diseases.

In Japan, where MS distribution conforms to the pattern found elsewhere in the world, we have previously shown that geographical distribution of HAM/TSP is significantly different.[5] Data derived from studies of cerebrospinal fluid (CSF) may also be helpful in distinguishing the two dieseases. For example, Neopterin concentration in CSF has been found to be higher in HAM/TSP than in MS and may be a useful diagnostic marker for the former.[6] In another study, in an Iranian population, intrathecal antibody production against HTLV-I was described in patients with HAM/TSP but not in those with MS.[7] There is also clear evidence that the radiological and pathological picture in the MS is different than that reported in HAM/TSP.[3,4,8,9] Electromyographic studies too, performed at paraspinal muscles can be helpful in distinguishing HAM/TSP from other myelopathic processes.[10] Furthermore we have recently noted, on clinical neurophysiological ground, that the mainly supraspinal distribution of central nervous systems lesions in patients with HAM/TSP is different from that observed in patients with MS.[11,12] (Figure 1).

Correspondence: FE Leon-S
**Present address: Department of Neurology, The University of Alabama at Birmingham, UAB Station, Birmingham, Alabama 35294, United States of America*
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The blink response in MS and HAM/TSP

It was also noteworthy for us that the BR in HAM/TSP behaved in a different manner than that described in MS.[12,13] In this context it is widely known that the BR in humans, obtained after electrical stimulation of the supraorbital nerve displays three responses called R1, R2, and R3 which are usually recorded at the orbicularis oculi muscles.[14] The afferent limb of the BR is the trigeminal nerve and the efferent one is the facial nerve. **R1** is the earliest response, carried out by A beta fibers, and is not clinically visible. It appears between 8 and 15 milliseconds, ipsilateral to the site of stimulation.[15,16]

R2 is a middle response which occurs, grossly, simultaneously with the visible eye closure, and is also carried out by A beta fibers. It is recorded at between 25 and 50 milliseconds, bilaterally, regardless of the site of stimulation.[15,16] **R3** is a late response, which has been linked to the strongest and maintained eye closure produced by painful stimulations and is carried out by the high threshold unmyelinated C fibers located at the supraorbital nerve.[17,18] R3 is recorded, at between 60 and 100 milliseconds, and as in the case of R2, bilaterally and regardless of the site of stimulation.[18] Thus, BR is considered a very sensitive indicator of the trigemino-facial muscle reaction in both central and peripheral nervous systems in humans.[19]

In patients with MS, R1 usually has prolonged latencies or is absent either uni- or bilaterally,[19] and such abnormalities can be present in up to 80% of patients depending on the clinical state and case selection.[19,20] R2 is also prolonged or absent in some patients with MS but in a smaller proportion, than R1.[19,20] R3 has not, to our knowledge, been investigated in MS. The features of BR in MS are related to demyelinating lesions, located mostly around the pons, and these electrophysiological findings are different from those observed in patients with HAM/

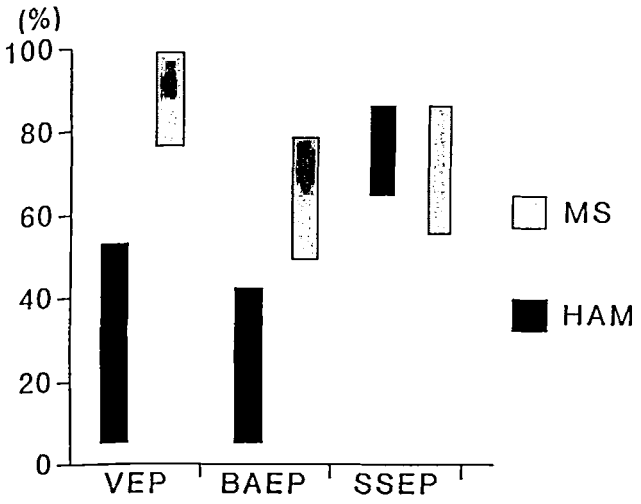

Figure 1 Percentage of abnormalities (%) in visual evoked potentials (VEP), brainstem auditory evoked potentials (BAEP), and somatosensory evoked potentials (SSEP) in patients with HAM/TSP and MS. Note that the main neurophysiological difference is at the supraspinal level of the central nervous system (Modified from Leon-S et al*[11,12] and Halliday[13])*

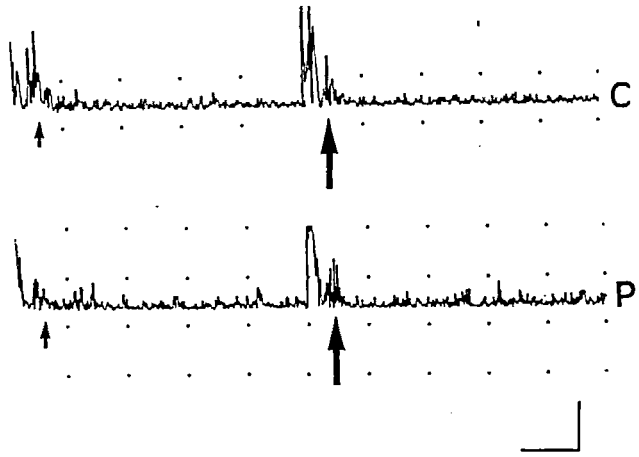

Figure 2 Blink Reflex (BR) obtained from a 52-year-old female patient with HAM/TSP (P). Note the enhanced recovery of R2 (large arrow) displayed 500 milliseconds after a conditioning test (small arrow), compared with that obtained from a control subject (C). Calibration: horizontal=100 milliseconds; vertical=200 microvolts

TSP. In a test of 50 randomly selected patients with HAM/TSP aged from 34 to 76 years who had no clinical evidence of facial nerve involvement, we found that only 1 patient had a unilateral absence of R1. This is in marked contrast to the type and frequency of BR abnormalities found in MS and discussed above.[17] Moreover, an unusual early BR, called R1k, was found in 69% of the patients with HAM/TSP[16,17] Those displaying the R1k response were more likely than others to also show an exaggerated jaw jerk reflex. Also, the higher the disability score, the stronger the possibility of displaying R1k. Furthermore, we noted that 50% of those patients displaying R1k had a shorter duration of illness than those who did not.[18] Likewise, those patients presenting R1k had a statistically significant shortened latency of R2 and an enhanced recovery after giving a paired electrical stimulus at the supraorbital nerve as shown in Figure 2. Instability of R3 was also observed in those patients with HAM/TSP who showed R1k.[14] A wider discussion of these clinical and neurophysiological findings has been published elsewhere.[14,16,17]

Some of these findings on the BR observed in patients with HAM/TSP and R1k mostly have been described in people with either peripheral disorders/pathologies such as facial nerve palsy, contacture post-facial, facial hemispasm, or central ones such as Parkinson disease, blepharospasm and oromandibular dystonia.[16] In these latter cases R1k is considered to be due to a lack of presynaptic inhibition on the facial nuclei at the supraspinal levels,[16,17] and all of these facts support our suggestion that an interneuronal hyperexcitability is present around the brainstem of patients with HAM/TSP.[14,16,17]

In conclusion, the differences found between MS and HAM/TSP on epidemiological, biochemical, immunological, radiological, neurophysiological, virological and pathological grounds seem to be more than coincidental and allow us to state that these diseases are two distinct clinical entities. Accordingly, their pathomechanisms must also be different.

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References

1 Schumacher GA, *et al.* (1965) Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Ann NY Acad Sci* **122**: 552–568.
2 Osame M, *et al.* (1990) Nationwide survey of HTLV-I-associated myelopathy in Japan: association with blood transfusion. *Ann Neurol* **28**: 50–56.
3 Kuroda Y, *et al.* (1995) Assessment of MRI criteria for MS in Japanese MS and HAM/TSP. *Neurology* **45**: 30–33.
4 Godoy AJ, *et al.* (1995) Characterization of cerebral white matter lesions of HTLV-I-associated myelopathy/tropical spastic paraparesis in comparison with multiple sclerosis and collagen vasculitis: a semiquantitative MRI study. *J Neurol Sci* **133**: 102–111.
5 Kubota H, *et al.* (1992) Comparative study of clinical features of HTLV-I associated myelopathy and multiple sclerosis. *J Trop Geog Neurol* **2**: 38–40.

6 Nomoto M, Utatsu Y, Soejima Y, Osame M. (1991) Neopterin in cerobrospinal fluid: a useful marker for diagnosis of HTLV-I associated myelopathy/tropical spastic paraparesis. *Neurology* **41:** 457.
7 Kitze B, *et al.* (1992) Differential diagnosis of HTLV-I associated myelopathy and multiple sclerosis in Iranian patients. *Clin Inv* **70:** 1013–1018.
8 Osame, McArthur JC. (1992) Neurological manifestations of infection with human T cell lymphotropic virus type 1. In: Asbury AK, McKhan GM, McDonald WI (eds). *Diseases of the Nervous System, Clinical Neurobiology,* Vol.2 WB Saunders: Philadelphia: pp. 1331–1339.
9 Katz D, *et al.* (1993) Correlation between magnetic resonance imaging and lesion development in chronic, active multiple sclerosis. *Ann Neurol* **34:** 661–669.
10 Arimura K, *et al.* (1995) How useful is the paraspinal EMG performed in patients with HAM/TSP? *Muscle and Nerve* **18:** 248–250.
11 Leon-S FE, *et al.* (1994) Tropical spastic paraparesis: subclinical and neurophysiological differences in different parts of the world. *Rev Med Chile* **122:** 265–273.
12 Leon-S FE, *et al.* (1995) Clinical neurophysiological comparative study in patients with HTLV I associated myelopathy/tropical spastic paraparesis. *Arch Med Res* **26:** 397–403.
13 Halliday AM. (1993) The comparative value of the different evoked potentials and other paraclinical tests in the diagnosis and prognosis of demyelinating disease. In: Halliday AM (ed). *Evoked potentials in Clinical Practice.* Churchill Livingstone: Singapore pp. 467–475.
14 Leon-S FE, *et al.* (1994) Instability of R3 response of the blink reflex in patients with HAM/TSP. *Funct Neurol* **8:** 199–202.
15 Levin KH. (1994) Special nerve conduction studies: Clinical Neurophysiology Review Course, Cleveland.
16 Leon-S FE, *et al.* (1995) El reflejo orbicular de los ojos en pacientes con HAM/TSP y otras enfermedades neurologicas. *Acta Med Col* **20:** 22–29.
17 Leon-S FE, *et al.* (1995) Contralateral early blink reflex in patients with HTLV-I associated myelopathy/tropical spastic paraparesis. *J Neurol Sci* **128:** 51–57.
18 Leon-S FE, Arimura K, Suwazono S, Arimura Y, Osame M. (1996) The effects of Shonosui the three responses of the blink reflex in man. *Muscle and Nerve:* (in press).
19 Kimura J. (1989) Electrodiagnosis in diseases of nerve and muscle: principles and practice, 2nd edn. F.A. Davis: Philadelphia.
20 Alonso F, *et al.* (1992) Brainstem lesion in multiple sclerosis: blink reflex and brainstem evoked potentials. *Arch Neurobiol* **55:** 89–98.