LETTERS TO THE EDITOR

DISTRIBUTION OF FIBRILLATION POTENTIALS IN RADICULOPATHIES

The report by Dillingham et al.[1] questions the general electromyographic (EMG) wisdom that fibrillation potentials develop and resolve earliest in proximal muscles in a damaged root distribution. The data presented do not allow the authors to make such a judgment. Apparently, patients were selected for entry into the study based on EMG features of cervical radiculopathy requiring denervation in at least two muscles in the diagnosed root distribution, but we are not informed of the criteria by which specific root level diagnoses were made.[2] A number of patients were entered into the study based on the presence of paraspinal fibrillation only (''indeterminate levels''). Some patients demonstrated multilevel paraspinal fibrillation potentials and evidence of bilateral cervical radiculopathies (''multiple radiculopathies''), further confusing the issue of the timing of the onset of the radiculopathy, and the segmental source of the fibrillation potentials. Five of the patients included in the analysis were said to have fibrillation potentials in a cervical root distribution 5 years after onset of the symptoms, adding doubt to the cause of the paraspinal fibrillation and the timing of onset. Clinical criteria used for the inclusion of patients with cervical radiculopathy were not reviewed in the methods section and there was no information about the underlying structural causes of the radiculopathies or their anatomic correlation with the root levels diagnosed by EMG.[2] Regardless of the quality of the statistical analysis, the lack of precision in the data on which the statistics were based prevents any conclusions from being drawn.

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Muscle Nerve **22:** 287–292

CCC 0148-639X/99/020287-06

Reply

We appreciate the comments by Dr. Levin on our study examining the relationship between symptom duration and the probability of finding denervation potentials in upper limb muscles among patients with cervical radiculopathy.[1] Dr. Levin raises questions about our ability to reach conclusions based on our sample selection criteria and the lack of information about the underlying cause of the radiculopathy. Although these are important issues for other investigations, we believe that Dr. Levin's concerns are not relevant given the focus of our study.

The proposition that paraspinal and other limb muscles demonstrate a defined time course of denervation and reinnervation presupposes that the radiculopathy can be electrodiagnostically confirmed. There are cases in which a radiculopathy is suggested either clinically or by imaging studies, yet electromyographic (EMG) muscle assessment produces normal results. Conversely, an EMG study may be suggestive of a radiculopathy even in the absence of structural findings. Because our purpose was not to evaluate structural causes of radiculopathy but rather to examine the relationship between denervation and symptom duration, the inclusion criteria of electrodiagnostically confirmed cervical radiculopathies was most appropriate. As stated in our article, root level classification was based upon the minimum number of root levels necessary to account for all abnormal muscles.

Dr. Levin's contention that a lack of precision in the data prevents any conclusions from being drawn is incorrect. The large number of cases studied, capturing a broad time spectrum, ensured adequate power to detect statistically significant relationships. As Dr. Levin pointed out, 5 patients reported symptom durations of many years. Simply discarding these patients from the analyses would misrepresent the sample. The absence of a significant association between symptom duration and the probability of denervation potentials for any muscle examined suggests that this relationship does not exist.

Of note, similar nonsignificant findings were found in our analyses of lumbosacral radiculopathies.[2] As discussed

in our article, however, our results are based on a retrospective study using data from a single institution. These findings should be verified in a prospective multicenter trial.

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HYPOGLOSSAL VERTEBRAL ENTRAPMENT SYNDROME

The intracranial vertebral artery can compress the extramedullary portion of the hypoglossal nerve, a condition termed hypoglossal vertebral entrapment syndrome (HVES).[5,9] We performed a neurophysiological study in a patient with this syndrome.

In 1990 a 61-year-old woman noted loss of bulk of the left side of her tongue. Neurological examination revealed an isolated palsy of the left hypoglossal nerve. Cranial and skull base computed tomography and magnetic resonance (MR) imaging and hematological and biochemical screening tests were normal. Three years later, neurological examination confirmed isolated palsy of the left hypoglossal nerve, with marked atrophy and abundant fasciculations of the tongue. MR imaging was again normal, except that the intracranial left vertebral artery was lodged between the medulla and the proximal portion of the left hypoglossal nerve, with mild impingement on the latter and torsion of the medulla toward the left side. MR angiography showed an elongated and tortuous left intracranial vertebral artery. Motor and somatosensory evoked potentials and brain stem auditory evoked potentials were normal. Concentric needle electromyography showed fibrillation in the left side of the tongue at rest. The tracing showed a discrete motor unit firing pattern when the patient protruded her tongue (Fig. 1C). Conduction of the hypoglossal nerves was evaluated with surface electrode recording and electric stimulation in the submandibular region and

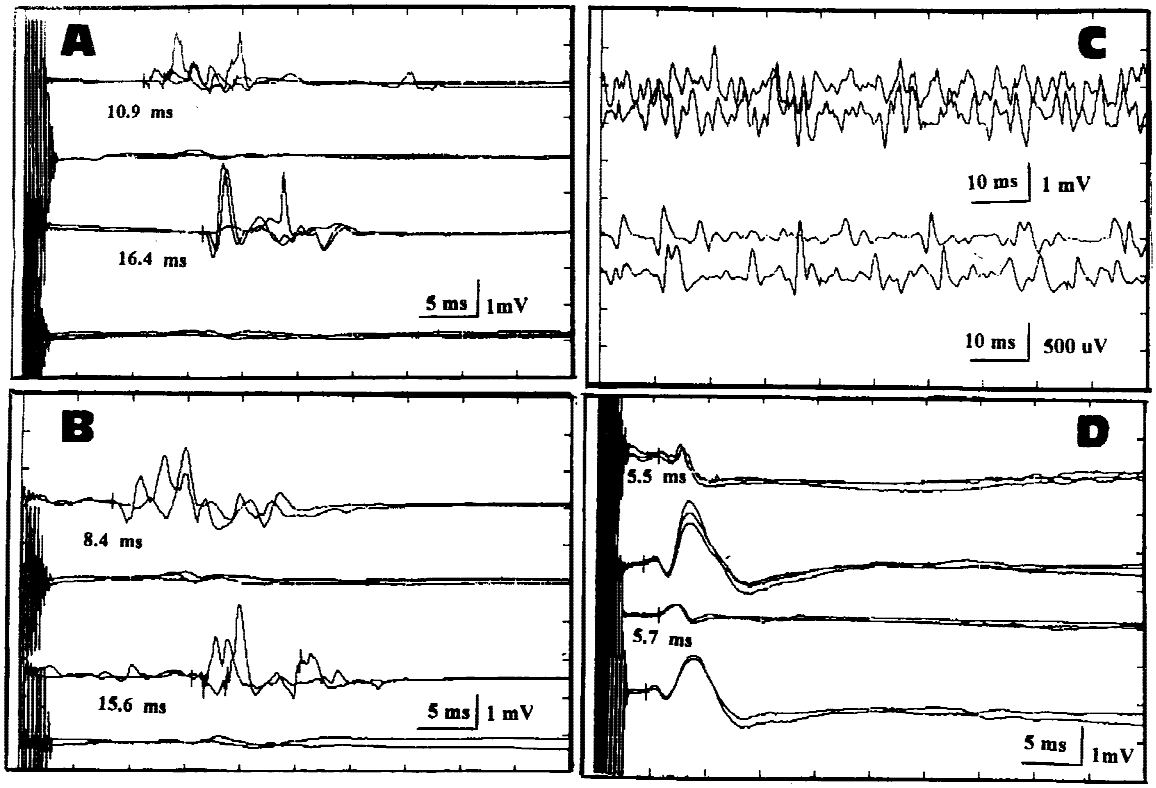

FIGURE 1. Transcranial magnetic stimulations at vertex at rest **(A)** and with activation **(B)** show increased latency in left (third line from the top) as compared to right (first line) hypoglossal nerve. The other lines refer to recordings of right (second line) and left (fourth line) facial muscles. EMG of right (top) and left (bottom) side of the tongue during voluntary activity **(C)** shows a discrete motor unit firing pattern in the left half of the tongue. Magnetic stimulation at inion **(D)** shows minimal differences of latency of the evoked potential in right (top line) and left (third line from the top) side of the tongue. The second and fourth lines refer to recordings from right (second line) and left (bottom line) nasal muscles.

magnetic transcranial stimulation at the vertex and inion.[1,7] Recordings of facial muscles during magnetic stimulation were also taken for comparison.[4]

With stimulation at the vertex, response latency was increased on the affected side (Fig. 1A,B). The latency difference between affected and unaffected sides was considerably reduced when stimuli were delivered at the inion (Fig. 1D), consistent with axonal damage or conduction delay after emergence of the hypoglossal nerve. Response latencies were symmetric with submandibular stimulation. Four years later the neurological examination and neuroimaging findings were unchanged.

Isolated unilateral hypoglossal palsy is rare and can be caused by skull base and neck tumors, trauma, surgery, infectious mononucleosis, schwannoma, and percutaneous procedures. It is less widely known that it can also be caused by neurovascular pathology involving the extracranial internal carotid artery[3,6,8,10] or the intracranial vertebral artery.[5,9] MR imaging in our patient showed contact of an elongated and tortuous intracranial vertebral artery with the clinically affected hypoglossal nerve, and impingement and dislocation of the nerve itself and adjacent brain stem. The study of hypoglossal nerve conduction supported the MR imaging findings by pointing to a lesion in the cisternal portion of the hypoglossal nerve. In fact, since vertebrobasilar dolichoectasia is a frequent finding in asymptomatic patients, transcranial magnetic stimulation may help to establish a causal relationship among cranial neuropathies and abnormalities of the vessels course in the posterior cranial fossa.

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MITOCHONDRIAL MYOPATHY MIMICKING FIBROMYALGIA SYNDROME

Fibromyalgia syndrome (FS) is a common, painful clinical disorder, the diagnostic criteria for which include widespread muscle pain and the presence of tender points at specific anatomical sites.[1] The etiology of this condition is still unclear.

We here report on a 45-year-old woman whose past medical history was uneventful until age 40, when she first complained of diffuse muscle pain. Treatment with either nonsteroidal anti-inflammatory drugs or tranquilizers did not relieve her symptoms. Family history was unremarkable. When examined by us, the patient complained of widespread muscle pain, which worsened upon compression of several muscles, including trapezius, vastus lateralis, and deltoid muscles. Also, there was mild proximal muscle weakness. No clinical signs or symptoms commonly associated with mitochondrial myopathies were found. In particular, neither ptosis nor external ophthalmoparesis was clinically observed.

Routine laboratory tests performed included erythrocyte sedimentation rate, blood count, electrolytes, creatinine, alanine-aminotransferase, creatine kinase, thyroid function, rheumatoid factor, and tests for antinuclear antibodies. The results of all these tests were normal. A blood test for lactate and pyruvate, performed before and after exercise, yielded the highest value within our group of normal controls. Electromyography (EMG) did not show spontaneous activity at rest in any examined muscles, but motor unit potentials of small amplitude and reduced duration were recorded in proximal muscles.

To further investigate the patient's clinical profile, a skeletal muscle biopsy was obtained from the right trapezius muscle. It was snap frozen in liquid nitrogen-cooled isopentane. Transverse cryostat sections were stained with routine histochemical methods.[4] Light microscopy showed some variability in fiber size with occasional internal nuclei. With the hematoxylin-eosin and modified Gomori-trichrome stainings, characteristic ''ragged red fibers'' (RRF) were observed (Fig. 1A). Furthermore, an increase in red staining material in the subsarcolemmal region of many fibers was also observed. The oxidative

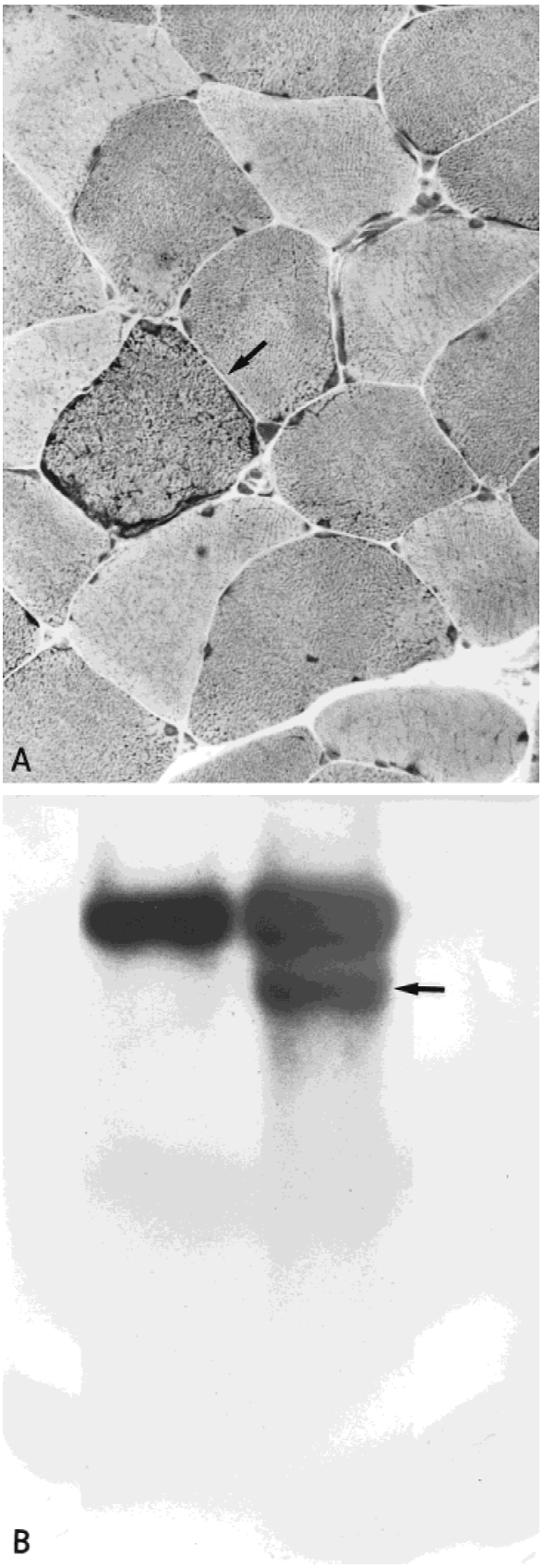

FIGURE 1. (A) Cryostat section stained with hematoxylin and eosin showing a characteristic "ragged red fiber." **(B)** Southern blot hybridization analysis of DNA from a healthy control (left) and our patient (right). Note the presence of another mtDNA species of smaller size (arrow), which represents a deletion in the muscle of our patient.

enzyme reactions showed increased staining for succinate dehydrogenase (SDH) in RRF, while the same muscle fibers resulted negative for cytochrome *c* oxidase (COX) staining. Electron microscopy revealed the aggregation of abnormal mitochondria in most of the muscle fibers.

The above-listed features are characteristically observed in patients with mitochondrial encephalomyopathies. On the basis of the results of histological studies, Southern blot analysis was performed on our patient's muscle DNA using whole mitochondrial DNA (mtDNA) as a probe. Quantitation of deleted species was performed by densitometry. In combination with wild-type molecules, we observed another mtDNA species of about 12.5 kb (Fig. 1B). The latter corresponds to a single, large-scale mtDNA deletion of about 4 kb, which accounted for 45% of total mitochondrial genomes. No other rearrangements were detected by our analyses.

The presence of RRF in muscle biopsies of patients with FS has been previously described.[2,3,5] However, these pathological findings have been considered nonspecific. In our study, we show that RRF in the muscle biopsy of our patient were associated with a single mtDNA deletion. This led us to conclude with certainty that our patient was suffering from a mitochondrial disorder. We believe that a muscle biopsy in patients with FS could be useful in ruling out other disorders in which muscle pain is present, such as a mitochondrial myopathy. If RRF are found, mtDNA analyses should be considered, as a mitochondrial disorder could surface, along with new pathogenetic or therapeutical implications.

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BIFOCALS AND CERVICAL RADICULOPATHY: A CLINICAL REMINDER

In 1972, Johnson and Wolfe described the relationship of cervical radiculopathy, spondylosis, and bifocals.[1] They reported 25 patients in whom radicular symptoms coincided with the onset of bifocal use or the change from bifocals to trifocals. Since that publication, no specific report has dealt with the role of eyewear in the occurrence of cervical radiculopathy. We have seen 2 patients in the last month with radicular symptoms following the onset of bifocal use. Our experience may serve as a useful clinical reminder to readers of the journal.

The first patient, a 45-year-old computer programmer, began wearing bifocals and within 1 month noted neck pain and accompanying referred paresthesias to the third digit in the left upper limb. He had no history of trauma. Physical examination revealed weakness in the C7 myotome. The triceps muscle stretch reflex was slightly decreased. Cervical spine plain films revealed mild degenerative changes at C6–7. Magnetic resonance imaging (MRI) of the cervical spine demonstrated degenerative changes with foraminal encroachment on the C7 nerve root. Electromyography (EMG) revealed membrane instability in the C7 myotome.

The second patient, a 46-year-old woman, reported 4 weeks of cervical discomfort and pain in a left C6 dermatomal distribution. She gave no history of injury, but reported periods of cervical extension while cross-stitching. Bifocal use had started 6 weeks prior to presentation. Physical examination revealed slight weakness in the C6 myotome. Cervical spine plain films and MRI revealed degenerative changes at C5–6. EMG demonstrated mild membrane instability in a C6 myotomal distribution.

Both patients were placed in formal physical therapy consisting of heavy intermittent cervical traction and cervicothoracic stabilization exercises. A tapering course of oral prednisone was also used. The reading segment of the patients' bifocals was placed at the top. Within 4 weeks, both individuals had significantly reduced symptomatology and markedly improved physical examinations.

Age-related changes in the cervical spine have been well reported in the medical literature, with 50% of patients in the fifth decade and 90% of those in the seventh decade having such changes.[2] Most people with these findings are asymptomatic. However, the biomechanics of the cervical spine can cause an individual who may be predisposed to nerve root compromise due to spondylitic changes to manifest clinical signs and symptoms of nerve root irritation. Johnson and Wolfe described at length the effect that bifocals can have on the position of the cervical spine, which can in turn affect the cervical nerve root. Careful history and physical examination in a patient who presents without an obvious inciting event for a cervical radiculopathy/radiculitis can reveal findings similar to those discussed above. Treatment as outlined for our 2 patients should be beneficial. Paramount to this treatment program may be placement of the reading segment at the top of the lens of the bifocals.

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SINGLE MOTOR UNIT H REFLEXES RECORDED IN THENAR MUSCLES AT REST

While estimating the thenar motor unit number by the adapted multiple point stimulation method (AMPS)[8] in 36 amyotrophic lateral sclerosis (ALS) patients, surface-recorded single motor unit H reflexes (MUP_H) were evoked in 3 patients. We have taken the opportunity to evoke in the same motor unit a direct motor response (M) and a single MUP_H to test the hypothesis that, with increasing stimulation intensity, the reflex responses are suppressed due to a collision between ascending and descending impulses in the motor fibers. The surface recording and stimulating electrode placements have been described previously.[8]

Each thenar single MUP_H was evoked by subthreshold stimulation for motor axon (Fig. 1A). When the stimulus intensity was slightly increased, either a direct motor unit potential (MUP) or a single MUP_H was recorded. In the case illustrated by Figure 1B, a direct MUP was recorded in 157/200 stimuli and a single MUP_H was observed in 43/200 stimuli; but direct and reflex responses were never observed together after one stimulus. When the stimulus intensity was further increased, other direct MUPs were evoked; the H reflex, however, continued to be inhibited despite the fact that a greater number of sensory afferent fibers was recruited by peripheral stimulation.

The physiological explanation of the disappearance of the H reflex when stimulus intensity is raised remains debated. Several hypotheses are currently proposed. (a) There may be a collision, just distal to the alpha motoneurons, between the centrifugal H-reflex impulses and action potentials propagating antidromically in the motor nerves.[5] (b) Anterior horn cells may be incapable of generating an H reflex from monosynaptic Ia inputs because they are in a refractory state after F-wave generation.[3] (c) Motoneurons are submitted to Renshaw or Ib inhibition.[2,6,7]

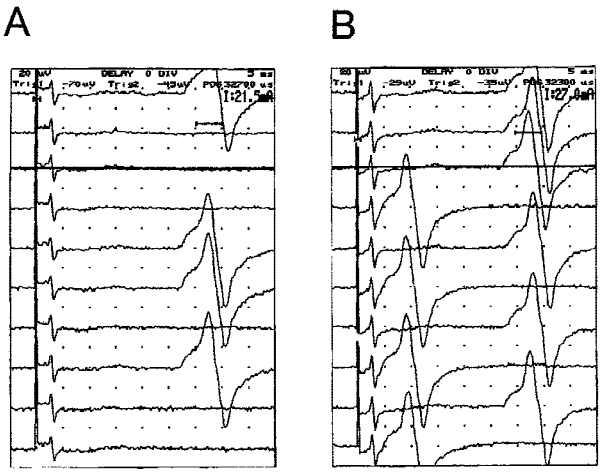

FIGURE 1. Surface-recorded single thenar motor unit H reflex (MUP_H) in a amyotrophic lateral sclerosis patient. Identical shape and size of early and late motor responses were observed on several occasions with an all-or-nothing relationship, which indicated that only one motor unit was involved in these responses. **(A)** At 21.5 mA, a response was evoked in some trials with a 27-ms latency without a direct motor response. An early sensory potential was systematically recorded indicating afferent sensory fiber activation. Thus, this late motor response presented characteristics of an H reflex and clearly differed from an F wave, which is seen only if the motor unit involved in the late response is previously directly recruited by peripheral stimulation. **(B)** At 27 mA, the single MUP_H was systematically suppressed as early as the motor unit involved in the reflex was directly recruited.

For discussion, two situations have to be distinguished: MUP_H evoked by subthreshold (Fig. 1A) and near-threshold (Fig. 1B) stimulation of motor axons. When evoked by subthreshold stimulation (Fig. 1A), the pattern might suggest active inhibition, since the same stimulus evoked H reflexes in only some trials. As no direct motor response was evoked, Renshaw inhibition and antidromic refractoriness of motoneurons can be excluded. Thus, only transient reduction in Ib inhibition might explain the intermittent evocation of MUP_H. However, Ib inhibition is rarely proposed to explain the relationship between stimulus intensity and disappearance of H reflexes. In fact, Ib fiber conduction velocity is usually lower than that of Ia fibers; moreover, the Ib inhibitory pathway involves an interneuron that would introduce an additional delay. Finally, Ib inhibition has been proposed to induce disappearance of H reflexes solely after stimuli of maximum strength.[7] Thus, the absence of a motor response in Figure 1A does not reflect Ib inhibition, but depends on an Ia input that is not strong enough to bring motoneurons to discharge.

With near-threshold stimulation, either a direct MUP or a MUP_H with an identical shape may be evoked (Fig. 1B). MUP_H was suppressed as soon as the motor unit was directly recruited by peripheral stimulation; with increase of the stimulus intensity, it was neither recruited again nor replaced by an F wave. These results are not in favor of active inhibition. In fact, Renshaw cell inhibition requires discharge of 20–40% of motoneurons.[1] Thus, Renshaw inhibition should not in principle be activated by the discharge of a single motor unit. Moreover, the motoneurons supplying the small muscles of the digits, at least in the cat, have no Renshaw cells.[4] Ib inhibition is ruled out on the basis of the arguments discussed above. Finally, if active inhibition or antidromic refractoriness of motoneurons was responsible, either a direct MUP and a single MUP_H or a direct MUP and a single MUP_F should sometimes be evoked together after one stimulus. After several hundred trials, we have never recorded this combination of early and late responses. We therefore believe that a collision mechanism explains the H-reflex suppression that occurs with elevation of stimulus intensity.

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