LETTERS TO THE EDITOR

FOCAL CONDUCTION BLOCK IN n-HEXANE POLYNEUROPATHY

We read with great interest the case report of focal conduction block in n-hexane polyneuropathy by Chang et al.[1] They expressed the opinion that in n-hexane polyneuropathy focal conduction block is rare.[2–4]

We evaluated the frequency of such block in our material of 35 patients (24 men and 11 women; age 18–49, mean 29.7 years) with subacute n-hexane polyneuropathy. In all cases the disease was a result of occupational exposure to n-hexane in small purse-makers' factories. Toxicological investigation revealed markedly increased concentration of n-hexane in the glue used in these factories at the time. Clinical and laboratory evaluation excluded other causes of polyneuropathy.

The clinical course was typical, with numbness and burning paresthesias, more pronounced in the feet than hands, as the first symptoms. Sensory symptoms were followed by weakness, sometimes severe, of the lower extremities. Worsening of symptoms after termination of the exposure was common.

The initial neurophysiological examination was done 4–6 weeks after onset of clinical symptoms. Motor nerve conduction studies of 127 nerves (70 peroneal, 36 median, 17 ulnar, and 4 tibial) were performed. Focal conduction block [defined as more than 50% reduction in both the compound muscle action potential (CMAP) amplitude and the negative-peak area] was found in 8 (22.9%) patients; in 5 (14.3%) cases it was present in more than one nerve. It was more frequent in the peroneal (8 persons) and tibial (4 persons) nerves than in nerves of the upper extremities (1 median and 1 ulnar nerve). Amplitudes of CMAPs were normal or only moderately reduced after distal stimulation of these nerves. The presence of block was associated with rather moderate slowing of the conduction velocity (usually to not less than 30 m/s in lower extremities) and prolonged distal latencies. The second examination revealed dramatically diminished CMAPs and focal conduction block was no longer observed. The worsening of neurophysiological parameters paralleled the progression of clinical impairment.

In our opinion, focal conduction block is a relatively frequent finding in early stage of n-hexane polyneuropathy and can be the main cause of the initial clinical symptoms, as suggested by Kuwabara et al.[2] However, it is rarely seen in more than one nerve, in contrast to inflammatory demyelinating polyneuropathy.

Andrzej Bogucki, MD, PhD

Department of Neurology, Dr K. Jonscher Hospital, Milionowa 14, 93-113 Łódź, Poland

Anna Głuszcz-Zielińska, MD, PhD

The Nofer Institute of Occupational Medicine, Św. Teresy 8, Łódź, Poland

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Reply

We appreciate receiving the comments of Dr. Bogucki et al., and are intrigued by their findings. While reduced amplitude and slowed conduction velocities are typical hallmarks of n-hexane polyneuropathy, their findings of focal conduction block as seen in 8 of 35 patients would certainly support this as a unique characteristic not commonly recognized. Previous series have focused on the conduction velocity and amplitude as diagnostic criteria.[1,2] Our suspicion is that with further refinement in electrodiagnostic technology, focal conduction block has become more readily apparent, and adds a unique electrophysiological quality to this unusual toxic neuropathy.

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Andrew P. Chang, MD

Department of Neurology, Henry Ford Hospital and Health Sciences Center, Detroit, Michigan 48202, USA

John D. England, MD
Austin J. Sumner, MD

Department of Neurology, Louisiana State University Medical Center, New Orleans, Louisiana, USA

Carlos A. Garcia, MD

Departments of Neurology and Pathology, Tulane University Medical Center, New Orleans, Louisiana, USA

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F WAVES

We commend Drs. Fisher and Rivner for their erudite F-wave discussion. Their conclusion that F waves have some utility is fundamentally sound. However, we submit that they are more useful than generally appreciated for assessing compression neuropathies and less useful than generally appreciated in the assessment of proximal demyelination.

F waves represent the subpopulation of largest, fastest, most myelinated motor fibers. F-wave abnormalities identify large motor fiber pathology but specify neither the site nor the etiology. Thorough F-wave analysis should include side-to-side F-wave minimum latency (FWML) comparisons of the same nerve as well as intralimb comparisons of adjacent nerves. If such abnormalities are identified, then additional testing should identify the site and clarify the underlying pathophysiological process. Two main pathophysiological processes cause FWML abnormalities, primary myelinopathies and primary axonopathies. Myelinopathies may be further classified into dysmyelinating (inherited) and acquired (compression or acquired demyelinating).

F-wave analysis may help affirm or disprove a compression neuropathy. Many electrodiagnostic evaluations for carpal tunnel syndrome (CTS) compare analogous ipsilateral median and ulnar nerve conduction studies. Due to length differences, the ulnar FWML is usually longer than that of its ipsilateral median counterpart. CTS and median nerve compression will cause focal demyelination resulting in FWML prolongation. This is statistically significant when the FWML from 10 consecutive stimuli in the median exceeds that of the ulnar by 1 ms or more.[1] Not only is this the most sensitive test of motor fiber involvement, but its sensitivity meets or exceeds that of digital sensory studies. F waves may also provide evidence against a compression neuropathy. Many ulnar neuropathies are inappropriately diagnosed solely on the basis of a ''slowing across the elbow.'' If a sufficient number of large motor fibers are demyelinated to cause motor nerve conduction velocity (NCV) slowing, then this should be reflected in the FWML. If this is not the case, then a measurement error is probably the cause. Similar reasoning can be used for a diagnosis of peroneal nerve compression.

F waves are useful for diagnosing dysmyelinating neuropathies in that concordant or symmetric F-wave prolongation based on side-to-side or intralimb comparisons is often noted. However, an absent or prolonged F wave with normal distal motor nerve conduction studies (NCS) is not diagnostic of proximal demyelinating pathology. Any pathological process, demyelinating or axonal, that affects proximal motor fibers may be reflected in the F wave. Our laboratory has noted these findings in patients with spinal cord trauma, nerve root avulsion, and neurofibromatosis. Moreover, sparing of a few largest motor fibers may yield a normal FWML as noted by Dr. Rivner's radiculopathy data. Early stages of demyelinating neuropathies may present with normal F wave and motor NCV data even in a patient with profound weakness. In such instances, root simulation should be employed, as it is more likely to detect proximal conduction block.[2]

In summary, F waves are underutilized in compression neuropathy analysis and often misused in the diagnosis of proximal motor nerve pathology.

Daniel L. Menkes, MD
Michael R. Swenson, MD, MSc

Department of Neurology, University of Louisville, Louisville, Kentucky, USA

1. Menkes DL, Hood DC, Bush AC. Inversion of the F-waves in median neuropathy at the wrist (carpal tunnel syndrome): an adjunctive electrodiagnosic method. J Contemp Neurol 1997;1:1–10.
2. Menkes DL, Hood DC, Ballesteros RA, Williams DA. Root stimulation improves the detection of acquired demyelinating polyneuropathies. Muscle Nerve 1998;21:298–308.

Reply

The comments by Drs. Menkes and Swenson are consistent with my own thoughts that the clinical utility of F waves is an area for continued discussion and evaluation. I also agree that F waves will be affected by pathology of any type. At the same time, prominent slowing of F waves argues for demyelination; and F-wave abnormalities can be the only definable electrophysiological abnormality in patients with proximal demyelination, especially if the process is acute.

The authors may be correct that relative prolongation of median in comparison to ulnar F waves may be the most sensitive test of motor involvement in carpal tunnel syndrome (CTS). There are, however, issues not addressed in the letter supporting this position as well as the statement that median and ulnar F waves should be ''employed in all electrodiagnostic evaluations for CTS''.[2] The authors base their criteria on 1-ms differences in minimal F-wave latencies in series of 10 F waves. Even if the data were reviewed ''blinded,'' it is often difficult to be certain of individual F-wave latencies to within 1 ms because of the nature of F

waves themselves. This is particularly true in hands where F waves arise from an unstable baseline. It is for this reason as well as others that the use of mean F-wave latency measurements has been advocated,[1] especially when analyses are dependent on small latency differences in F waves. Even if one wishes to use minimal F-wave latencies, simultaneous reporting of mean values would strengthen the force of the argument. One should also provide the range of latency abnormalities. The force of the argument would again be strengthened if abnormalities were in general based on differences larger than the minimally abnormal value of 1 ms. Avoiding false positives is more important than avoiding false negatives. Finally, the argument that the median and ulnar F waves should be performed in all patients with CTS is questionable unless such information can be shown to change the diagnosis or management.

The above points are made to encourage a dialogue about the information needed when reporting F-wave studies as well as about the clinical utility of F waves in order to enhance the acceptance of F-wave studies wherever the level of injury. Drs. Menkes and Swenson are to be commended for emphasizing the potential usefulness of F waves for peripheral compression neuropathies.

Morris A. Fisher, MD

Department of Neurology, Loyola University Medical Center and the Hines VAH, Hines, Illinois, USA

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Reply

Drs. Menkes and Swenson argue that F waves are useful for the diagnosis of carpal tunnel syndrome and cite the article by Menkes et al.[1] as evidence. After reviewing this article, I am still unconvinced about their usefulness in the diagnosis of this condition. These authors found a greater than 1 ms difference between the median and ulnar F-wave latencies in 75% of 57 patients diagnosed with carpal tunnel syndrome. It is of note that all patients in this study were selected because they had prolonged median palmar distal latencies. The median-to-ulnar palmar latency difference has been shown to be an even more sensitive test for carpal tunnel syndrome.[3] I am unsure why one would want to employ F waves in this situation when directly measuring the conduction across the lesion in question is a more sensitive and specific test. Measuring the latency of the F wave, which involves the entire length of the nerve, is prone to error. Proximal lesions may also prolong the F wave, so this finding is not specific for carpal tunnel syndrome.

While we are often frustrated by the fact that patients who have classic symptoms for carpal tunnel syndrome have normal electrodiagnostic studies, adding a less specific and sensitive test is not sensible. As I have discussed in a previous article,[4] adding additional testing will only increase the likelihood of an abnormality occurring in a normal person. Under these circumstances, I cannot support F-wave testing for carpal tunnel syndrome.

Using F waves to exclude an abnormality in an asymptomatic patient as suggested by these authors makes more sense. In asymptomatic patients, ulnar slowing across the elbow must be interpreted cautiously. Requiring an abnormality in a second test, such as the ulnar F wave, makes sense. Testing the sensory conduction across the elbow or repeating the ulnar motor studies in this setting makes more sense. In the final analysis, electrophysiological abnormalities must be interpreted in conjunction with clinical findings.

Finally, F-wave testing is useful in patients with suspected proximal nerve lesions because proximal nerve conduction studies are difficult to perform. I agree that proximal nerve root stimulation is a useful test in this setting. Menkes et al.,[2] cited in the letter by Menkes and Swenson, showed that F waves were abnormal in 45% of nerves in patients with proximal neuropathies. Nerve root stimulation demonstrated a block in 65% of nerves, indicating that this is a better test. However, it is of note that in 31% of nerves only F waves were abnormal and not proximal nerve root stimulation. Based on the arguments made above, a single abnormal finding when multiple tests are done may not be enough to make a diagnosis. On the other hand, this finding, when coupled with other nonelectrophysiological abnormalities and the proper clinical picture, is important.

Michael H. Rivner, MD

Department of Neurology, Medical College of Georgia, Augusta, Georgia, USA

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THE ELECTROMYOGRAM IN OBSTETRIC BRACHIAL PALSY IS TOO OPTIMISTIC: FIBER SIZE OR ANOTHER EXPLANATION?

We agree with Van Dijk et al.[4] that the needle electromyogram (EMG) in obstetric brachial plexus lesions (OBPL) is mostly too optimistic. Their explanation is that the smaller fiber size allows the EMG needle to ''see'' more muscle fibers than in adult patients. However, in 1983 Nandedkar and Stålberg[3] found in their model that smaller muscle

fibers have smaller potential fields, compensating for the fiber size. We could find in the literature only one experiment, dating back to 1957,[1] in which the electric field potential from muscle fibers was measured and correlated with fiber size. In this article, Håkansson found that the extracellular potential field increased in proportion to the square of the fiber circumference and that the muscle fiber amplitude decreased linearly with the logarithm of the distance from the axis of the fiber. These findings conflict with the concept presented by Van Dijk and coworkers.

In our patient group of several hundred patients with OBPL and a group of the same size with traumatic adult brachial plexus lesions, all analyzed using a fixed EMG and nerve conduction study protocol and in whom the findings were correlated with the findings from computed tomography myelography and during operation, we found evidence for extra innervation from the other roots (luxury innervation) in the neonate, which is lost during normal later life except when the dominant innervation is lost. We also measured a fiber density[5] of 1.5 in the biceps brachii of an infant with only a partial root lesion of C6, which is the same as in adults, indicating that smaller muscle fibers have smaller potential fields. We agree with McComas[2] and Van Dijk et al. that central mechanisms are probably responsible for the clinical paresis that is found in these infants.

J.W. Vredeveld, MD, PhD
R. Richards
C.A.M. Rozeman, MD, PhD

Department of Clinical Neurophysiology, Atrium Medisch Centrum, Heerlen, The Netherlands

G. Blaauw, MD, PhD
A.C.J. Slooff, MD, PhD

Academic Neurosurgical Centre Limburg, Atrium Medisch Centrum, Heerlen, The Netherlands University Hospital, Maastricht, The Netherlands

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Reply

Our hypothesis was that the smaller diameter of infants' muscle fibers causes more fibers to be ''seen'' by the needle.[4] We had taken into consideration that muscle fiber action potential (MFAP) amplitude, related to diameter, would be smaller, and hypothesized that the increase in apparent fiber number would outweigh the decrease in MFAP amplitude. Vredeveld et al. question this hypothesis on theoretical grounds. An essential notion here is that the EMG is judged in terms of the recruitment and firing behavior of motor units, and not in terms of the activity of single muscle fibers. If the EMG pattern was simply the product of *x* MFAPs with *y* amplitude, then indeed decreasing fiber diameter would have no effect, as the increase in *x* would compensate for the decrease in *y*. Since the EMG is not a simple voltage product, but is organized in motor units, more motor units are present within the needle uptake area, simply because the fibers are smaller. In other words, a larger fraction of the whole muscle is in the field of view, compared to the adult situation. No additional assumptions on differences in volume conductor characteristics are needed. We felt and feel that the above simple reasoning provided a sufficient basis on which to base our hypothesis. Its validity will have to be settled through experiment, rather than through further theory. It has the advantage of explaining the discrepancy between the apparent number of motor units and the degree of weakness.

We look forward to publication of the evidence that muscles in OBPL are innervated through roots other than the normal ones, and to proof that this fetal innervation pattern remains present as a result of injury. We had rejected this explanation because available evidence showed that polyneural innervation in man was replaced by mononeural innervation well before birth.[1] Based on recent findings,[2] polyneural innervation in infants may however be considered possible. Still, there was no evidence that the multiple nerve endings on one muscle cell in fact derived from multiple neurons.[2]

Finally, our hypothesis was not meant to be exclusive; other oddities of the EMG in OBPL need explaining as well, such as the finding that fibrillation potentials disappear remarkably frequently and quickly.[3] Vredeveld et al. will probably agree with us that denervation in neonates differs enough from that in adults to warrant a fresh look at the EMG, unburdened by ideas that may apply in adults only.

J. Gert van Dijk, MD, PhD

Department of Neurology and Clinical Neurophysiology, Leiden University Medical Centre, Leiden, The Netherlands

Martijn J.A. Malessy, MD

Department of Neurosurgery, Leiden University Medical Centre, Leiden, The Netherlands

Dick F. Stegeman, PhD

Department of Clinical Neurophysiology, Nijmegen University Hospital, Nijmegen, The Netherlands

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EFFECTS OF A LOW-DOSE L-CARNITINE SUPPLEMENT ON AN ADULT PATIENT WITH MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFICIENCY

Mitochondrial trifunctional protein (TP) is a multienzymatic complex occurring in long-chain fatty acid β-oxidation. Mild to severe lactic acidemia is characteristic in patients with a TP deficiency because the β-oxidation intermediates of long-chain fatty acid inhibit mitochondrial oxidative phosphorylation.[4] Carnitine removes these toxic fatty acid intermediates by the formation and urinary excretion of long-chain acyl carnitine,[1] and secondary carnitine deficiency is therefore a feature of TP deficiency. We evaluated chronic L-carnitine treatment for an adult patient with TP deficiency who had recurrent exertional myoglobinuria associated with lactic acidemia and severe carnitine deficiency based on results of the ergometer exercise loading test.

The patient, now 26 years old, has been described elsewhere.[2] From age 15, he experienced recurrent myoglobinuria after prolonged exercise during fasting. Hypoglycemia and liver dysfunction were not found. Blood lactate and the plasma acyl/free carnitine (A/F) ratio at rest were markedly increased. The A/F ratio reflects the ratio of mitochondrial esterified/free coenzyme A (CoA).[3] The respective free and acyl carnitine levels in the muscle were 4.7 and 15.8 nmol/mg non-collagen protein (normal mean and SD, 23.2 ± 3.7 and 5.0 ± 1.7 nmol/mg noncollagen protein). Urinary acyl carnitine analyses showed large amounts of the long-chain acyl carnitine esters C_{10} sebacyl-, C_{12} dodecanedioyl-, $C_{12:1}$ dodecenedioyl-, and $C_{14:1}$ tetradecenedioyl-carnitine. Cycle ergometry exercise for 15 min at 15 W produced nausea and muscle pain in the lower extremities, associated with markedly increased blood lactate concentrations in the pretreatment condition (Table 1). A diet rich in carbohydrates (about 70% of the calories) and poor in fat (about 10% of the calories) that included carnitine 30–40 mg/day was maintained during L-carnitine treatment. One month after starting high-dose L-carnitine treatment (1500 mg/day), blood lactate after exercise and the A/F ratio had decreased with no negative symptoms. But 3 months later he sometimes complained of muscle pain accompanied by increases in blood lactate and the A/F ratio. His symptoms persisted until L-carnitine supplementation was stopped. Six months without oral L-carnitine intake produced severe muscle pain with low plasma free carnitine. Serum creatine kinase was elevated to 18,700 U/L (normal, <180 U/L) after exercise loading. We therefore started a low-dose oral L-carnitine supplement (300 mg/day). The patient has been asymptomatic, and marked elevation of blood lactate after exercise test prior to treatment has decreased to less than 1.5-fold the control value. The plasma-free carnitine concentration has remained at subnormal levels and the A/F ratio in the steady state for 2 years (Table 1). Urinary acyl carnitine levels have reflected the dose of oral L-carnitine.

Potentially toxic metabolites in our patient recurrently accumulate and form acyl carnitine esters that are excreted at an excessive rate in the urine for long periods, leading to chronic and severe depletion of the muscle store of carnitine. The initial symptom-free period in our patient after starting L-carnitine supplementation may reflect the time needed to fully recover the muscle stores. A 3-year follow-up study showed that a high-dose supplement of L-carnitine failed to prevent rhabdomyolysis with lactic

Table 1. Laboratory findings before and during oral L-carnitine treatment.

	Months									
	0	1	3	6	12	18	24	30	36	
	Dosage (mg/day)									
	←——— 1500 ———→		←— 900 —→		←— 0 —→	←——— 300 ———→				Normal (n = 6)
Blood lactate										
Before exercise (mmol/L)	2.5	1.3	1.9	2.0	2.3	1.5	1.4	1.5	1.4	<1.5
After exercise (mmol/L)	12.8	2.7	5.8	7.0	8.2	3.7	3.1	2.8	2.4	0.6–2.0
Plasma carnitine										
Free (nmol/mL)	16.5	96.5	62.4	40.0	20.2	31.0	31.2	31.5	32.0	39.5 ± 8.3
Acyl (nmol/mL)	12.6	22.3	21.8	18.5	11.9	9.8	9.5	9.1	9.0	7.2 ± 1.8
Acyl/free ratio	0.76	0.23	0.35	0.46	0.59	0.31	0.30	0.29	0.28	0.18 ± 0.04
Urinary acyl carnitine*										
Sebaryl	0.17	0.40	0.31	0.27	0.30	0.20	0.18	0.15	0.12	0.07–0.19
Dodecanedioyl	0.19	0.50	0.42	0.36	0.32	0.18	0.15	0.12	0.10	0
Dodecenedioyl	0.25	0.62	0.42	0.33	0.40	0.23	0.20	0.20	0.15	0
Tetradecenedioyl	0.19	0.66	0.40	0.32	0.48	0.28	0.21	0.16	0.12	0

**Relative ion intensity/mg creatinine.*

acidosis during exercise, whereas a low dose that maintained a subnormal concentration of plasma-free carnitine improved his exercise tolerance. Excessive loading of L-carnitine may lead to elevation above the maximal rate of supply of long-chain fatty acids to the mitochondrial matrix, thereby producing the toxic accumulation of β-oxidation intermediates. The low-dose L-carnitine may balance two opposing effects: (1) a positive effect of shifting the high ratio of esterified/free CoA back to normal; and (2) a negative effect of increasing the importation of long-chain fatty acids into the mitochondria.[1,3] The long-term treatment with low-dose L-carnitine may be beneficial to our patient, as there is less tendency for the toxic accumulation of long-chain intermediates during catabolic states.

Hiroaki Miyajima, MD
Satoshi Kohno, MD
Hiroyuki Tomiyama, MD
Eizo Kaneko, MD

First Department of Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan

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MUSCULAR NECROTIZING VASCULITIS AS THE INITIAL MANIFESTATION OF BEHÇET'S DISEASE

Behçet's disease is a heterogeneous syndrome with variable involvement of many different organ systems including the central or peripheral nervous system.[6,11] Vasculitis is a key feature of Behçet's disease, but its cause is still unclear.[3,10] A commonly agreed set of diagnostic criteria is established and consists of recurrent oral ulcerations in addition to at least two minor symptoms such as eye or skin lesions, recurrent genital ulcerations, or a positive pathergy test.[7] In contrast to these well-known clinical symptoms, localized muscle pain is an unusual feature of Behçet's disease and has not previously been recognized as its primary manifestation.

A 22-year-old Turkish man developed muscle pain of gradual onset in the right calf. Whereas serum levels of muscle enzymes were not elevated and electromyographic findings were normal, magnetic resonance imaging and ultrasonography of the calf showed edema of the gastrocnemius muscle. Biopsy of the right gastrocnemius muscle demonstrated a segmental necrotizing vasculitis, predominantly affecting small perimysial arteries (Fig. 1). Arterial walls and perivascular areas were infiltrated by lymphocytes and macrophages. The macrophages showed a positive acid phosphatase and an anti-CD68 reaction. The lymphocytic infiltrate consisted predominantly (80%) of CD3-positive T cells, which were made up of CD4-positive (80 %) and CD8-positive (20 %) cells. CD79a-positive B cells were intermingled to a minor degree. The inflammatory infiltrates encroached on the adjacent endomysium, but did not invade muscle cells.

Six weeks later the patient developed oral and genital ulcerations and the pathergy test was positive, therefore fulfilling diagnostic criteria for Behçet's disease. Despite extensive diagnostic efforts, there was no evidence of systemic vasculitis, involvement of the central or peripheral nervous system, or involvement of any other organs. Except for elevated circulating immune-complexes, no further indication of collagen vascular disease was found. There was no association with HLA type B5 or B51. Immunosuppressive therapy with prednisolone and azathioprine was effective and the clinical complaints diminished. Eight weeks later, clinical evaluation showed no tenderness, weakness, or atrophy of the right gastrocnemius muscle, and the magnetic resonance imaging of the involved calf was normal.

To our knowledge, localized muscle pain as the initial symptom of Behçet's disease has not been described previously. One case of Behçet's disease which manifested as generalized myalgia has been documented.[9] Nevertheless subclinical muscle involvement in Behçet's disease may occur.[5] Among cases verified by histology, muscle pain in Behçet's disease has usually been attributed to generalized[1,9] or localized myositis.[4,12] Reference is sometimes made to an additional diffuse perivascular infiltration[2] or accompanying vasculitis.[8] An isolated, segmental necrotizing vasculitis, clinically manifested solely in skeletal muscle without any evidence of an additional myositis, must be a very rare feature of the disease. Our case underlines the

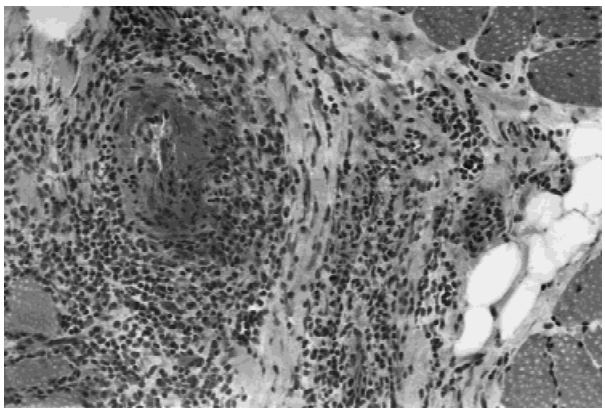

FIGURE 1. Muscle biopsy specimen (right gastrocnemius muscle, hematoxylin and eosin, original magnification ×80): segmental necrotizing vasculitis predominantly affecting small, perimysial arteries and, to a lesser degree, small veins. No necrosis of muscle cells was detected.

role of vascular inflammation in Behçet's disease and exemplifies an initial clinical manifestation that differs from the more common clinical presentations of the disease.

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Haiko Kazarians, MD
Hans-Ulrich Voelter, MD
Guenther Schwendemann, MD

Department of Neurology, Zentralkrankenhaus Bremen Ost, Bremen, Germany

Markus Bergmann, MD

Institute of Clinical Neuropathology, Zentralkrankenhaus Bremen Ost, Bremen, Germany

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Erratum

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Due to a printer's error, the Erratum that appeared in December 1998 should have indicated that in the short report published in the May issue (*Muscle Nerve* 21:640–642) entitled ''Cervical Paraspinal Muscle Abnormalities and Symptom Duration: A Multivariate Analysis,'' Table 1 on page 641 contained typographical errors. The numbers 3.85* and 2. should not have been placed in the table next to C5–C6 and C6 innervation levels under the paraspinal column. We regret this error.