

NEUROLOGY

Safety, tolerability, and efficacy of orally administered cannabinoids in MS
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Neurology 2003;60;729-730

This information is current as of October 23, 2006

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.neurology.org/cgi/content/full/60/4/729-a>

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Ptosis in patients with hemispheric strokes

To the Editor: The article by Averbuch-Heller et al.¹ reports ptosis in about one-third of 64 prospectively studied patients with acute hemispheric stroke. They identified bilateral ptosis as an important poor prognostic sign of imminent herniation in a few with acute large infarction. They found that patients were more likely to have hemiparesis, rightward gaze deviation, upgaze paresis, and right-sided cortical infarction on imaging studies.

Although we agree with the authors that their series of patients showed a higher frequency of cerebral ptosis because of the prospective design of their study, we strongly suggest that some of these cases—particularly those with unilateral ptosis—may have resulted from a complete or an abortive Horner's syndrome typical for internal carotid artery dissection. Although this condition is more frequent in younger subjects than in the elderly, their favorite group of patients with ptosis and ipsilateral stroke would have needed an extensive extracranial neurovascular workup, including Doppler/duplex ultrasound or MRI/MRA. These findings in detail would help to interpret the authors' data. In contrast to this criticism, we agree with the authors about the clinical usefulness of bilateral ptosis in patients with large right hemispheric stroke, particularly as craniotomy may represent a life-saving option if malignant edematous development occurs. In this respect, we can provide further cases from a recent retrospective analysis of 14 patients with malignant middle cerebral artery infarction (six left hemispheric, eight right hemispheric). Although none of the subjects with left hemispheric stroke showed neurogenic ptosis, five of the eight patients with right hemispheric infarction had bilateral, complete ptosis in combination with rightward gaze deviation. Of these five patients, two died after cerebral herniation, two underwent successful decompressive craniotomy, and one survived after aggressive antiedematous treatment. In all patients—still awake or mildly somnolent—bilateral ptosis preceded clinical deterioration as measured by the NIH Stroke Scale and the Glasgow Coma Scale as well as signs of brainstem affection such as anisocoria by up to 18 hours. We therefore conclude that bilateral ptosis in large right hemispheric stroke is a highly predictable sign of impending herniation and therefore a useful indicator for the opportunity of early decompressive surgery at a time point when the brainstem is still intact but at risk for imminent damage, whereas unilateral ptosis is multifactorial and is not useful for the further management.

O. Lanczik, MD, K. Szabo, MD, J. Wöhrle, MD, J. Binder, MD, M. Hennerici, MD, *Mannheim, Germany*

To the Editor: The article by Averbuch-Heller et al.,¹ suggested that a complete bilateral ptosis in cases of acute large cortical stroke may be a premonitory sign of an impending herniation from midbrain compression. They noted that closed eyelids, in presence of frontalis contraction, indicates underlying ptosis and is not a sign of drowsiness.

We recently encountered a 77-year-old man who experienced a left hemispheric stroke with right hemiplegia 2 days previously. Examination showed complete bilateral ptosis with left but not right frontalis contraction (Figure). Evoking a grimace showed that the right side of the face was markedly weak. Manual elevation of right eyebrow, to check for frontalis-induced lid closure, failed to correct the ptosis.² With eyelids held open, a left gaze preference and brisk pupillary reflexes were seen bilaterally. Spontaneous movements of only the left limbs were evident. Within minutes, a CT scan was obtained, revealing left opercular stroke without midline shift or midbrain compression. Rapid neurologic improvement followed, with resolution of ptosis 1 day later and obeying simple commands 2 days later.



Figure. Complete bilateral ptosis with an asymmetric frontalis contraction opposite hemiplegia resulting in WAFFL (weak asymmetric forehead with fallen lids) sign.

An acute large hemispheric stroke may cause contralateral facial weakness resembling a peripheral seventh nerve lesion due to frontalis weakness. In this setting, frontalis contraction opposite the hemiplegia results in a WAFFL (weak asymmetric forehead with fallen lids) sign. The presence of this simple physical sign is important to recognize because herniation may follow; however, as this case demonstrates, benign outcome unaccompanied by midbrain compression can also be seen.

Kyung-Pil Park, MD, Kwang-Dong Choi, MD, *Pusan, Korea*;
Gregory Youngnam Chang, MD, *Los Angeles, CA*

Reply from the Authors: We appreciate Lanczik et al.'s interest in our article and thank them for their own observations in the field. We accept the important point that Horner syndrome is a common clinical feature of carotid dissection; however, in our group of patients with ptosis (age range, 61 to 94 years) ultrasound data (in all the survivors) did not reveal signs of dissection. Based on careful examination of the pupils and eyelids by Dr. Averbuch-Heller, we doubt that Horner syndrome was missed in our patients.

Their observation strengthens ours and suggests a new use for the sign of complete neurogenic ptosis for those centers that use a surgical approach for malignant middle cerebral artery infarctions.

With regard to Park et al., ptosis is not a feature of facial weakness and although the upper face is usually spared with central facial weakness, we agree that asymmetric frontalis contraction may sometimes be a useful sign in patients with cerebral ptosis who attempt lid opening.

Jonathan Y. Streifler, MD, *Petach-Tikva, Israel*;
R. John Leigh, MD, *Cleveland, OH*

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Diffusion abnormalities and Wernicke encephalopathy

To the Editor: Doherty et al.¹ shed new light on Wernicke encephalopathy (WE) and emphasized important but often-forgotten points on this fatal yet preventable entity. I wish to make a few relevant clinical and pathological points.

Their second case illustrates that WE is not seen only in alcoholics but also in other forms of malnutrition (e.g., thiamine deficiency). I would add other circumstances, such as (but not limited to) anorexia nervosa, peritoneal dialysis or hemodialysis,² and HIV infection,³ in which WE has occurred. In addition, I wish to emphasize that although the ocular signs are considered the hallmark of WE, it is now more recognized that the classic triad is neither consistently nor frequently encountered.⁴ I believe that every clinician should remember the many clinical circumstances in which WE may develop and that the classical clinical triad is not always present. Further, autopsy studies have shown that WE prevalence in both nonalcoholics and alcoholics far exceeds its recognition in living persons.⁴

On macroscopic examination, the involved areas are slightly shrunken and show brown discoloration due to hemosiderin deposition, typically but not limited to the mammillary bodies, and the periventricular and periaqueductal lesions often spare a slender strip of subependymal tissue.³ Microscopic sections might be needed to make the diagnosis of WE. Twenty-five percent of cases can have normal mammillary bodies on macroscopic examination, and visible hemorrhages are seen in only 5% of cases.⁵

Z. Morcos, MD, *Cleveland, OH*

To the Editor: We read with great interest the paper from Doherty et al.,¹ describing diffusion-weighted MR findings in two patients with WE. Typical MR alterations were found in both patients, including T2 hyperintensities of thalami, periaqueductal brainstem, mammillary bodies, and, in one patient, thalamic contrast enhancement.⁶ The lesions were hyperintense on diffusion-weighted images (DWI). Various contributions account for signal on DWI: reduced diffusion causes a hyperintensity, whereas increased diffusion causes a hypointensity; residual T2 contrast may variously contribute to the hyperintensity (T2-shine-through effect). Apparent diffusion coefficients (ADC) calculation allows one to separate these components and to quantify the amount of the alteration of the diffusion. ADC values were reduced in the first patient and normal in the second; the authors attribute the DWI hyperintensities in the first patient to a reduced diffusion, and in the second patient to the T2-shine-through effect.

Reduced and increased ADC values have a very different pathologic significance. Reduced diffusion generally indicates acute irreversible cellular damage. Conversely, increased ADC values are mainly due to reversible extracellular edema because the increased water content allows easier motions of the water protons. However, mixed increased and reduced ADC values were found in conditions where acute cellular necrosis and extracellular edema coexist, such as arterial ischemia.⁷

Relationships between pathology and MR findings in WE are well known.⁸ In the early phases extracellular edema predominates, leading to increased T2 signal; then alterations of the vessel wall cause a breakdown of the blood-brain barrier, allowing contrast enhancement. Neuronal necrosis occurs in later stages. The time course of DWI alterations and the relationships between pathology and diffusion alterations have not yet been investigated. In a patient with reversible WE, DWI hyperintensities of the mammillary bodies were due to a T2-shine-through effect, while ADC calculation demonstrated an increased diffusion.⁹ This suggested a prevalence of extracellular edema over neuronal necrosis. In effect, the patient completely recovered, demonstrating that no significant neuronal necrosis occurred. The patients described by Doherty et al.¹ had more advanced diseases. Reduced ADC values in the first patient suggest neuronal necrosis and may explain the only partial recovery. Normal ADC values in the second patient may be due to a nonacute neuronal damage, similarly to the arterial ischemia, diffusion alteration may disappear after the acute phase is past.

Taken together these three described cases suggest that DWI and ADC values in WE may give information on the contribution

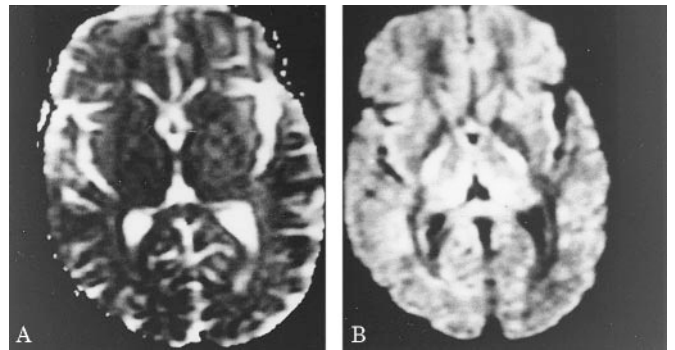


Figure. (A) DWI shows hyperintensity in the dorsomedial nuclei of the thalami without mass effect. MR of Patient 1 at the level of the basal ganglia. (B) ADC map revealed that these regions become hypointense, confirming restrictive diffusion. MR of Patient 1 at the level of the basal ganglia.

of the neuronal necrosis and of the extracellular edema in a given T2-hyperintense lesion. This information cannot be obtained in a different way and might represent a relevant prognostic factor.

M. Bergui, MD, G.B. Bradac, MD, J. Zhong, MD, *Torino, Italy*

To the Editor: Doherty et al.¹ describe two cases of WE with DWI signal changes. In the same period, three additional papers focused attention on DWI-MR changes in WE.⁹⁻¹¹ In those cases two different patterns of DWI-MR were identified with decreased or increased ADC values. We would like to document three additional patients with WE in whom DWI changes corresponded with decreased ADC map signal intensity.

We report three patients (2 women and 1 man) with a mean age of 46.6 ± 18.5 (range 34 to 68 years), with diagnoses of acute myeloid leukemia, alcoholism, and partial gastrectomy due to an adenocarcinoma. In each patient, a recent history of vomiting and nausea occurred before neurologic impairment. A confusional state, blurred vision, ophthalmoplegia, ataxia, and nystagmus were present as the most relevant symptoms. Brain MRI showed hyperintense lesions on T2-weighted images, FLAIR, and DWI that affected symmetrically both dorsal and medial nuclei of the thalamus, periaqueductal gray matter, and superior and anterior cerebellar vermis, without contrast enhancement. ADC were evaluated in abnormal lesions by visual inspection of DWI and ADC maps. In the three cases DWI abnormalities corresponded with decreased ADC values (figure).

A diagnosis of WE was made, and intravenous thiamine supplementation was administered at 100 mg/d. In all cases, neurologic improvement was rapidly achieved, except for the persistence of nystagmus.

In these three patients a restricted diffusion pattern was identified on MR, characterized by DWI-MR high signal intensity that corresponded with a decreased intensity signal on ADC maps. The present pattern is classically associated with cytotoxic edema,¹⁰ while DWI with increased ADC might represent vasogenic edema or gliosis. It remains speculative whether the restriction of diffusion may be correlated with acute or subacute microscopic changes in WE. Nevertheless, in WE vitamin B₁ deficiency is associated with intracellular and extracellular edema.¹⁰ The earliest microscopic changes are seen in the neuropil and around blood vessel walls,⁵ while in chronic lesions astrocytic proliferation occurs. In agreement with these observations, changes in DWI could represent different stages of the disease. We think that in the present cases the restriction of diffusion and the prompt improvement after thiamine administration contribute to support the hypothesis of a "reversible cytotoxic edema" that might occur before the onset of necrosis,^{1,10} thereby adding WE to the list of reversible restricted diffusion lesions.

C.A. Rugilo, M.C. Uribe Roca, M.C. Zurrú, E.M. Gatto, *Buenos Aires, Argentina*

Reply from the Authors: We thank Dr. Morcos for his comments illustrating the broad range of clinical scenarios in which WE may be encountered. Indeed, clinical diagnosis of WE can be difficult. We hope further studies of brain diffusion abnormalities will improve antemortem diagnosis in a broad range of patients.

We appreciate the discussion of DWI in light of ADC values, their meaning, and prognosis by Dr. Bergui et al. and Dr. Rugilo et al. Since submitting our initial manuscript and drafting this letter, 10 well-documented cases of diffusion abnormalities in WE have been published or brought to our attention. In all reports, thiamine therapy led to some clinical improvement, regardless of diffusion or ADC findings. In one case where ADC values were normal, thiamine therapy failed to improve memory.¹ In two of three cases of increased ADC, thiamine restitution completely reversed clinical presentations.^{9,11,12} In six cases of ADC reduction, thiamine treatments failed to reverse all the findings of WE; residual impairments included nystagmus, confabulation, or gait ataxia.¹⁰ Although ADC values may predict radiologic reversibility, they do not clearly indicate clinical reversibility.

These recent reports, regardless of ADC increases or decreases and their theoretic implications, show diffusion-weighted MRI findings aid the diagnosis of WE. Perhaps more importantly, characteristic DWI findings may indicate patients at risk of soon developing WE, as suggested by our second case.¹ DWI changes in the mamillary bodies, thalamus, periaqueductal gray, and walls of the third ventricle should prompt immediate parenteral thiamine supplementation, irrespective of clinical or ADC findings.

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Ipsilateral thalamic MRI abnormality in an epilepsy patient

To the Editor: We read with interest the article¹ that proposed to have reported for the first time a case of status epilepticus and thalamic atrophy in a 19-year-old woman following a 1-month history of repetitive complex partial seizures. Other associated findings were right cerebral hemiatrophy and contralateral cerebellar hemiatrophy. In a study by Tan and Ulrich,² the following history of seizures was reported prior to admission: 1) febrile status epilepticus, 2) hemiconvulsions lasting for several hours, 3) repetitive hemiconvulsions, and 4) severe febrile convulsions. All were diagnosed with cerebral hemiatrophy, ipsilateral thalamic atrophy, and mesial temporal sclerosis (MTS).² A more recent review of 23 patients aged 1 to 64 years with HHE demonstrated a significant relationship between cerebral hemiatrophy and thalamic atrophy.³ MRI findings in all patients revealed cerebral hemiatrophy. Eleven patients had ipsilateral MTS and ipsilateral thalamic atrophy. Nine of the 11 patients with MTS had a history of prolonged febrile seizures. We recently reported two patients with HHE, one with bilateral thalamic lesions on MRI diagnosed following febrile status epilepticus.⁴ In addition, damage to the temporal cortex, hippocampus, and thalamic structures have been demonstrated in an animal model of self-sustained status epilepticus induced by repetitive electrical stimulation of the amygdala.⁵ The possibility remains that damage to the thalamus may contribute to the progression to status epilepticus, which may be prevented by early intervention directed at the thalamocortical circuitry. To this extent, we agree with Nagasaka et al.¹ that further research is required to elucidate the role the thalamus plays in status epilepticus and other forms of intractable epilepsy.

Morris H. Scantlebury, Lionel Carmant, MD, FRCPC, *Montreal, Canada*

Reply from the Authors: Our report simply revealed reversible thalamic abnormal intensity using MRI without permanent changes, e.g., thalamic atrophy. Moreover, we demonstrated reversible cerebral abnormal intensity of right temporoparietal cor-

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tex on MRI, not cerebral hemiatrophy. Recent studies have identified thalamic abnormality in patients with epilepsy in either the interictal state or after status epilepticus both neuroradiologically and pathologically.^{6–8} The view that the thalamus plays a significant role in epilepsy is now widely accepted. We presented our case assuming that thalamic changes are a well-known fact. We did not claim that ours was the first report suggesting that the thalamus is a key site of functional abnormality in epileptic patients.

We would emphasize three points about the MRI thalamic abnormality in our patients. It 1) was reversible, 2) occurred during status epilepticus, not in the interictal state or after status epilepticus, and 3) occurred in a patient with complex partial seizures originating from parietal sensory neocortex.

Takamura Nagasaka, MD, Kazumasa Shindo, MD, Zenji Shiozawa, MD, *Yamanashi, Japan*

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Oxidative damage and cytogenetic analysis in leukocytes of Parkinson's disease patients

To the Editor: We read with interest the recent article by Migliori et al.,¹ in which oxidative damage was demonstrated in lymphocytes of untreated patients with PD. This is an intriguing finding and adds to other existing data in this disease on abnormalities detectable outside the brain of patients. The results are in line with a chronic activation status of leukocytes, as this is also indicated by, for example, higher blood concentrations of tumor necrosis factor α .² Other features of immune activation such as accelerated neopterin production or degradation of tryptophan were also described and correlate with Hoehn & Yahr stages.³ Both neopterin production and degradation of tryptophan are inducible by interferon γ and thus coincide with cell-mediated (Th-1 type) immune activation. Finally, accumulation of homocysteine was reported in the blood of patients with PD⁴ and homocysteine concentrations correlated with the degree of immune activation. Notably, changes in neopterin and homocysteine concentrations and in tryptophan degradation have also been observed in the brains of PD patients, but surprisingly, changes seen in the peripheral blood were much more significant. These data could represent an epiphenomenon, but could also indicate that immune activation outside the brain may in some way contribute to the pathogenesis of this neurodegenerative disease, the pathology of which is confined to brain tissue. Activation of immunocompetent cells such as T lymphocytes and macrophages is associated with the production of large amounts of oxidizing compounds; through this process, oxidative stress develops in the peripheral blood. There it could contribute to depletion of antioxidants, which then are also less available across the blood-brain barrier.

Friedrich Leblhuber, MD, Linz, Austria; Gabriele Neurauder, MSc, Dietmar Fuchs, PhD, Innsbruck, Austria

Reply from the Authors: In our study, the occurrence of DNA oxidative damage outside the CNS supports the hypothesis that a systemic derangement parallels neural abnormalities in patients with PD. This suggests that PD is a systemic disorder, even if the principal target of the damage is the CNS.¹ Moreover, there is evidence of immune activation in peripheral blood⁶ and in the CNS of patients with PD: glial reaction, increased expression of cytokines and components of complement have been reported in the brains of patients with PD.⁷

Safety, tolerability, and efficacy of orally administered cannabinoids in MS

To the Editor: Numerous methodologic issues require discussion with reference to the recent article¹ on cannabis in MS, in which a poorly characterized cannabis extract was studied in 16 MS patients with spasticity, and few benefited and significant side effects were reported. This contrasts dramatically with a previous double-blind study in nine subjects employing tetrahydrocannabinol (THC) 5 to 10 mg that demonstrated improvement in spasticity measures to the $p < 0.01$ level.² In fact, the material employed in the current study contained daily doses of up to 5 mg THC with 2 mg cannabidiol (CBD) and was likely inadequate to produce benefit. No dose titration was pursued.

A subsequent study in Switzerland employing a larger patient cohort with the identical extract in higher doses has provided improved results³: 57 patients in a prospective, randomized, double-blind, placebo-controlled crossover study used 15 mg THC with 6 mg CBD daily in three divided doses, demonstrating significant reductions in spasms ($p < 0.05$) and improvement in mobility, with no quantitative differences in adverse events compared to placebo. Results from a much larger study in the United Kingdom employing the same extract are pending.

Available results with another cannabis-based medicine extract (CBME) trial in the United Kingdom are even more encouraging.⁴ Large-scale phase III trials are under way in MS patients employing sublingual application of whole plant extracts containing equal proportions of THC and CBD. This oro-mucosal route of administration provides a more predictable onset of action and an improved ability for patients to titrate their own required dosages, which in the pilot study⁴ averaged 22.5 mg THC and CBD daily in

All of these findings lead to the hypothesis of immune reaction and consequent inflammation as a common mechanism contributing to the pathogenesis of neurodegeneration. This is well demonstrated in AD, where inflammatory reactions are thought to be important contributors to the neuronal loss.⁸ The deleterious effect of inflammation may be of great importance because it may point to a target for possible therapeutic intervention. However, it is not known whether inflammation and oxidative stress play a central role or only represent an epiphenomenon in neuronal death of patients with PD.

The hypothesis that oxidative stress, developing in the peripheral blood as a result of immune activation, could contribute to the depletion of antioxidants in the brain is intriguing but needs more evidence. We do know that most available natural antioxidants do not cross the blood-brain barrier.⁹

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divided doses, most often within the range of 7.5 to 40 mg of THC daily. Results to date support significant improvements in pain, spasticity, and muscular spasm attacks in MS,⁴ bladder-related symptoms, and sleep. Adverse events were characterized as predictable and well tolerated, and lowest in the 1:1 THC:CBD mixture, emphasizing the well-known tendency of CBD to counter THC-associated side effects.

These results mirror those seen in MS patients employing cannabis in medical practice. My personal experience and correspondence with approximately 100 MS patients would indicate failure of tolerability or symptomatic improvement with oral THC as Marinol[®], but marked benefit with oral, smoked, or vaporized cannabis on spasticity, hyperreflexia, appetite, sleep, neuropathic pain, and mood, but not ataxia.

We should not ignore the fact that experimental data not only document the benefit of cannabinoids in spasticity and tremor but also in the immunomodulatory aspects of MS in a chronic relapsing experimental allergic encephalomyelitis (CREAE) model,⁵ supporting the finding of an improved MRI result in one clinical cannabis patient with chronic MS not on interferon treatment.⁶

Overall, the future of clinical cannabis as a useful tool in the pharmacopia of MS treatments appears much brighter than would be evident from the preliminary results from the study by Killestein et al.¹

Ethan B. Russo, Missoula, MT

Reply from the Authors: Although we agree with Dr. Russo that there is an urgent need for more conclusive data concerning

cannabinoid therapy in MS, we would like to respond to some of the issues raised.

Dr. Russo argues that numerous methodologic issues of our study¹ require discussion: for example, the dosage, which was considered inadequate, and the absence of dose titration. Russo suggests that this might account for the discrepancy between our results and those of a previously published study.²

Obviously, we cannot exclude that our dose regimen was inadequate to produce benefit, but we were the first to apply such a high dose for 4 weeks in a relatively large MS patient group and observed a significant increase in adverse events at this dosage. In fact, as mentioned in the Methods section of our manuscript, we did pursue dose titration up to 5 mg THC twice a day. The discrepancy with the previously published study² may have many causes, including the fact that it addressed the efficacy of only a single dose of THC and not prolonged administration. In addition, this study by no means fulfilled current standards for a randomized, controlled trial (e.g., unclear randomization, no separate treating and assessing physician, no report of efficacy of masking).

Dr. Russo also highlights interesting preliminary results of recent trials that, unfortunately, cannot be considered in terms of quality of design and data, because they have not yet been published.^{3,4}

We do not ignore the possibility that cannabinoids can modulate the function of immune cells. In vitro studies unequivocally demonstrated that high doses of cannabinoids suppress immune responses.⁷ However, physiologically relevant concentrations of cannabinoids resulted in metabolic stimulation of lymphocytes⁸ and an increase in proinflammatory cytokine production⁹ rather than immunosuppression. Although several animal studies suggest that the immunosuppressive properties of cannabinoids can play a favorable role in the MS disease process,^{10,11} the compounds were used at concentrations that most likely will not be tolerated in humans. Given the nature of the disease, in our view the observation of an unspecified "improved MRI result" in a single MS patient treated with cannabis should not be interpreted as evidence for relevant immunosuppressive activity by cannabinoids in MS.

Researchers encounter a number of difficulties in designing studies that use cannabinoids. Whether the future of clinical cannabis indeed appears much brighter than would be evident from

our study can be derived only from well-designed and carefully executed clinical trials that, unlike our study, are powered for efficacy.

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Proposed diagnostic criteria and nosology of acute transverse myelitis

To the Editor: The Transverse Myelitis Consortium Working Group should be congratulated for the proposed diagnostic criteria and nosology of acute transverse myelitis (ATM).¹ However, in the differential diagnosis only scarce attention was given to fibrocartilaginous embolization from nucleus pulposus embolism (NPE), a condition that is often undiagnosed and frequently confused—clinically and pathologically—with ATM.² For instance, Bots et al.³ reexamined a teaching specimen of so-called ATM and found an acute transverse myelopathy due to NPE.

Although the exclusion criterion of <4 hours from onset to nadir would effectively exclude most vascular cases, in our review of the natural history of NPE,² we found that at least 42% of the cases had progressed for periods of ≥4 hours; furthermore, a prodromal history of intermittent back pain is not uncommon, lasting for periods of weeks to up to 4 months.⁴ The bimodal age distribution of ATM is also found in NPE, with peaks at 22 and 60 years,² with the earliest reported case in a 6-year-old girl.⁵

The distinguishing feature of NPE is the sudden onset of severe pain, localized in the neck or interscapular region in cases with cervical cord ischemia, or with back pain when the lumbosacral spinal cord is involved.^{2,6} It is conceivable that the traditional notion of the presence of pain in patients with ATM is associated with poor prognosis¹ could have resulted from inaccurate inclusion of NPE cases. It would be advisable, therefore, to add as an exclusion criterion the onset of weakness accompanied by pain.

In NPE there is usually rapid onset of weakness, from minutes to up to 48 hours,^{2,6} with no substantial recovery. The cervical/cervico-medullary cord is involved in 70% of cases, the lumbosacral and conus medullaris segments in 22%, and the thoracic cord in 8%,^{2,6} but involvement of several adjacent segments is common. According to Tosi et al.,⁶ the diagnosis of NPE can be made

accurately by MRI showing cord swelling, with increased signal on T2-weighted images, associated with a collapsed disc space at the appropriate level. A correct diagnosis of NPE may have more than academic implications considering the successful treatment of spinal cord embolism with hyperbaric oxygen (HBO) therapy in decompression sickness.^{7,8} Given the dismal prognosis of NPE, immediate treatment with HBO is probably indicated.

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Reply from the Authors: We appreciate Dr. Román's interest in our article¹ detailing the diagnosis and classification of ATM and his comments. Our primary goal was to delineate an approach to ATM; therefore, we did not describe the diagnosis and evaluation of patients with noninflammatory myelopathies. However, Dr. Román raises an important point: we may mistakenly diagnose a patient who has NPE with ATM. We believe that this is unlikely to occur for several reasons. Dr. Román and others have advanced our understanding of NPE,^{2–6,9,10} reporting that the majority of patients progress to nadir in less than 4 hours. Additionally, most patients with NPE have acellular, noninflammatory CSF and no abnormal gadolinium enhancement on spinal MRI.^{2–6} Indeed, the pathology in both humans and animals with NPE^{11–13} suggests ischemic infarction of the spinal cord rather than a primary inflammatory process. Therefore, most patients with NPE would be excluded by our criteria from a diagnosis of ATM.

We do not think that acute severe back pain is the exclusive domain of NPE; rather, we think that this symptom may occur in patients with a variety of spinal disorders, especially those with meningeal and radicular involvement. Therefore, to add acute back pain as an exclusion criterion for ATM would, in our opinion, be unfounded.

It is currently uncertain how common NPE is, though we agree that it is likely underdiagnosed. A patient with acute, noninflam-

matory myelopathy and disc space collapse at the site of deficit should be considered to have NPE, especially if there is a recent history of trauma. Even so, NPE likely represents a rare cause of acute myelopathy, and it would be misleading to say that this entity is “often” or “frequently” misdiagnosed.

Finally, there is no reported successful treatment of NPE, and hyperbaric oxygen treatment should not be considered as “indicated” treatment until studies suggest that it is effective.

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Safety, tolerability, and efficacy of orally administered cannabinoids in MS

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Neurology 2003;60;729-730

This information is current as of October 23, 2006

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