Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI

To the Editor: Dobkin et al.[1] seemingly failed to detect the superiority of training on the treadmill in acute spinal cord injured (SCI) patients. This outcome is expected considering the study design. In contrast to our controlled trial,[2] both the control and the study groups were given the same large amount of specific therapy (i.e., training of upright walking). Without a proper control group, it cannot be determined whether the two procedures were better than no therapy at all.

In Dobkin et al.'s "pre-trial" group[3] (collected in the same participating clinics before onset of the trial), only 58% of the initial ASIA C and D patients reached independent walking (from table 3)[3] but 92% in the trial control (and experimental) group.[1] This highlights the significant therapeutic effect of intensive walking over ground and on the treadmill. These data also confirm the superiority of LB therapy we found with 53% comparable success of conventional but 96% of LB therapy (8/15 but 29/30 spastic patients, figure 3).[2]

The notion concerning our motor score[1] is obsolete since the maximum for both limbs is 80 (not 50), and distance to injury is larger. Our data for the first time demonstrated that aggressive task-related training, i.e., intensive upright walking with well defined rules on the treadmill (Laufband-LB-therapy, see www.meb.uni-bonn.de/wernig) or over ground (patient Z[4]), is successful.

Dobkin et al.'s study design is not practical for everyday therapy. Previous praxis found treadmill speeds between 0.1 and some 2.0 km/h effective,[2] Dobkin et al. used 3.8 km/h and above as adequate without showing an advantage. To the contrary, the robot-like moving of the limbs might hinder the patient's active contribution and jeopardize activity-related learning.[5]

With high speeds—as with over-ground walking non-ambulating ASIA B and C patients—three therapists are needed to handle a single patient instead of one to two.[2] An additional therapist may be available in well-funded trials but difficult in real-life clinical settings. The predictable consequence is a decline in compliance of patients, therapists, and financial officers.

Anton Wernig, *Bonn, Germany*

Disclosure: The author reports no conflicts of interest.

Reply from the Author: We read the comments by Dr. Wernig with interest. Drs. Wernig and Dietz[6] misrepresent the aims of the Spinal Cord Injury Locomotor Trial (SCILT).[1] SCILT is the first multicenter, randomized, parallel group, single-blinded rehabilitation trial of patients with incomplete SCI. We compared two interventions for walking in subjects who could not walk at entry—BWSTT with overground practice vs equivalent practice time for standing and conventional gait training.

Patients were consecutively recruited upon admission to six rehabilitation centers (mean 4.5 weeks after onset) and trained for 12 weeks (about 45 hours). Possibly, we provided more or less therapy than some programs, but to compare two interventions, the treatments had to be of equal intensity.[7] The Wernig study[2] has been called a controlled trial,[2,8] but in contrast to SCILT it used a convenience sample of subjects, some of whom did not have traumatic SCI.

Wernig compared results of BWSTT to selected "historic controls," which allows for bias, employed unblinded outcomes, and did not test walking speed. Wernig's design did not allow scientific conclusions about efficacy, but did stimulate the need for SCILT. Neither the Wernig, Dietz, or SCILT clinical trials were designed to test the rules of locomotion.[2]

Wernig mistakenly considers our pre-trial observations as equivalent to control data. We stated that one power analysis for SCILT was based on Functional Independence Measure locomotor (FIM-L) scores from inpatient discharges.[3] SCILT trained subjects for about 6 weeks beyond discharge, then measured outcomes at 6 months so pre-trial FIM-L is not comparable to SCILT outcomes.

Wernig also suggests that "a proper control group" may be "no therapy" at all. What value to science and patients is a trial that compares a control group seated in wheelchairs to some form of step training? The end result would only support the inferiority of inactivity to task-oriented training. Wernig and Dietz also state that SCILT subjects could walk, whereas treadmill training should only be given to those who cannot load their legs and step.[6] At entry, however, SCILT subjects had no recordable walking speed and their mean FIM-L score was 1 (unable). Wernig also believes that the BWSTT strategy was incorrect, yet both arms of SCILT had the same percentage of walkers that he reported. As an evidence-based practice, then, BWSTT is equivalent to overground training over the first 4 months after incomplete SCI. Trials of interventions for nonwalkers beyond that time are now a logical step. We must recalibrate our attachments to BWSTT,[7-9] however, during early rehabilitation.

Bruce H. Dobkin, MD, *Los Angeles, CA*

Disclosure: The author reports no conflicts of interest.

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Treadmill training after spinal cord injury: Good but not better

To the Editor: The editorial by Dr. Wolpaw highlights the significance of the first multi-randomized clinical trial (MCRCT) for neurorehabilitation after acute spinal cord injury (SCI).[1] Several therapeutic implications of the trial that were not addressed warrant discussion.

In this trial, the effect of body weight supported treadmill training (BWSTT) was compared to a control overground mobility training (CONT), not to conventional rehabilitation for individuals with incomplete SCI. A large sample of people with typical ASIA B, C, and D injuries received standing and gait training. The experimental arm received BWSTT followed by immediate practice overground. Training afforded the sensory-specific experience of walking and emphasized weight-bearing on the legs. The control group received overground standing and usual gait training. Both groups received 40 to 60 training sessions, a higher frequency than is typically provided.

The MCRCT demonstrated for the first time that ASIA C and D subjects in both groups achieved significant gains 6 months after study entry. Most subjects attained abilities sufficient for

community ambulation including a fast speed (1.0 m/s), relatively good endurance (400 m in 6 min) without walking aids, and excellent balance (54/56 Berg balance). Therefore, the trial demonstrates that aggressive rehabilitation in the early phase of SCI is likely to benefit a very high percentage of these individuals. Specifically, these results suggest that at least one h/day of weight-bearing standing and gait training should be emphasized as early as possible for up to 60 sessions, likely resulting in a progressive increase in walking speed over time, but this relationship requires further investigation.

The findings of the current clinical trial now set the minimum recovery standards by which all new treatments will be compared. Future studies may be obligated to employ a control therapy (defined by either the experimental or control arm) to ensure at least a 90% rate of locomotor recovery consistent with the present trial, each of which received substantial weight-bearing step training. The dichotomous training effects for ASIA B compared to ASIA C and D subjects in the present trial indicate that different treatment approaches are warranted for more severely injured individuals. For individuals with ASIA A and B injuries, greater supraspinal input or combination therapies may be necessary in which activity-based therapy is a catalyst for treatments such as spinal cord/muscle stimulation or pharmaceuticals.

As plasticity-inducing therapies emerge, specific activity-based therapy may enhance activation and training of the neuromuscular systems. For those persons with ASIA C and D injuries that achieved 1.0 m/s gait speed, more challenging and complex task-specific training targeting balance and adaptability requirements of community conditions may be warranted. Such training might include speed variations, quick stops/starts, obstacle and uneven terrain negotiation.

The first MCRCT for neurorehabilitation in acute SCI provides important information towards developing evidence-based practice. Future research for therapies advancing recovery after SCI should address the following questions: Which patient will benefit how much and in what way with a specific type and amount of therapy? When post-injury should a therapy (or therapies) be delivered? What therapy or combination is necessary?

H. Barbeau, M. Basso, A. Behrman, S. Harkema, *Montreal, Quebec, Canada*

Disclosure: The authors report no conflicts of interest.

To the Editor: In his editorial,[1] Dr. Wolpaw praises the conduct of a clinical trial in which Dobkin et al.[2] conclude that training on the treadmill is not more effective than conventional therapy. However, critical evaluation of their definitions leads precisely to the opposite result.

First, the use of intensive training of upright walking in non-ambulating (ASIA C) SCI patients has not been considered conventional therapy. When we and others started to train patients with SCI on the treadmill, the standard training goal for such patients was to get mobile with the wheelchair. It was unthinkable to train severe ASIA C (and D) patients for walking other than with long braces and in parallel bars. This was questioned by our early results,[3] which led NIH to propose this multicenter trial showing that task-related training (i.e., intensive upright walking) can be successful beyond previous expectations.[3] This included independent walking in near completely paralyzed patients and led NIH to propose the multicenter trial in question.[2]

We also made clear that the treadmill with harness and suspension was the most practical and safest device for an aggressive locomotor training.[3,4] In a misunderstanding of these facts, Dobkin et al. prescribed intensive walking overground for their trial control group.[2] Though they started to realize that their control was an equally trained intervention group, they state that their "results would not meet the expectation" raised by previous trials,[3] again ignoring that controls in previous trials performed true conventional therapy (which did not include such intensive walking). However, when their ignored the pre-trial group[5] is employed as baseline instead, the superiority of training on the treadmill becomes obvious and is as striking in the trial of Dobkin et al. as we have previously described.[3,4]

We would expect that an editorialist would critically investigate the matter in question and outline any discrepancies. Wolpaw's title further confuses the issue: treadmill training would be "good but not better." With such imprecision, the only therapy practical for intensive training of upright walking in severely paralyzed persons (i.e., aided training on the treadmill with low speed)[3,4] might get discredited though the results show its superiority. Walking ASIA B and C patients overground is impractical and the author should clarify this point.

Anton Wernig, *Bonn, Germany*

Disclosure: The author reports no conflicts of interest.

Reply from the Editorialist: Barbeau et al., a portion of the co-authors of the Dobkin et al study,[2] emphasize important practical implications of their study that were not fully addressed either in their article[2] or in my necessarily brief editorial.[1] As they indicate, the study shows the impressive success of very intensive standing/walking rehabilitation soon after injury, provides two benchmark regimens that can serve as controls for future evaluations of new approaches, encourages further refinement of locomotor training methods, and emphasizes the need for additional treatment methods for those most severely injured. This additional explication further establishes the importance of their study.

Dr. Wernig's objection to my editorial seems to arise from our differing definitions of conventional locomotor training. My editorial states the definition I used, which was based on the control regimen in the Dobkin et al. study itself.[2] In the study, the control (CONT) regimen consisted entirely of overground standing/stepping training. It was compared to a BWSTT regimen consisting of a combination of overground standing/walking training and treadmill training. The important point was that both groups devoted equal time to locomotor training of one kind or the other.

Thus, Dr. Wernig's distress seems to come not from any imprecision in my definition, but rather because I define a conventional locomotor training regimen as one confined to overground standing/stepping, while he defines it as simply teaching the patient how to use a wheelchair. As a result, he fears that my editorial will lead people to believe incorrectly that treadmill training provides no advantage over simply learning to use a wheelchair.

This is not a realistic fear. Both the editorial[1] and Dobkin et al.[2] emphasize the striking contrast between the good results of both the CONT and the BWSST regimens and the poor results that are described in the literature (and reflect rehabilitation closer to the wheelchair training approach). My editorial concludes that different regimens (e.g., treadmill training or similarly intensive overground standing/stepping training) can produce good results "if they are properly focused on a defined objective (i.e., restoring locomotion) and are vigorously pursued." It emphasizes the finding that, for the population studied, treadmill training was definitely effective, but at the same time, not more effective than similarly intensive overground standing/stepping training.

Furthermore, comparative studies[2,6] do not appear to support Dr. Wernig's conviction that only treadmill training is practical for ASIA B and C patients. For the individual patient, the choice of a locomotor training regimen may turn on the exact characteristics and severity of the disability, the personal preferences of patient and therapist, therapist experience and availability, and the training venue (e.g., an institution where BWSTT equipment is readily available vs a home where it is not).

Jonathan R. Wolpaw, *Albany, NY*

Disclosure: The author reports no conflicts of interest.

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Neuropsychological deficits in long-term frequent cannabis users

To the Editor: Messinis et al.[1] concluded that "heavy long-term frequent cannabis use leads to subtle deficits in specific neuropsychological domains." In the Introduction, the authors note that Pope et al.[2] did not observe consistent cognitive deficits in frequent long-term cannabis users who had undergone a 28-day abstinence period. However, Messinis et al. failed to control for length of abstinent period in their study.

It is important to control for this variable because frequent cannabis use is associated with an abstinence syndrome upon cessation of drug use,[3] and poor neurocognitive functioning[4] is a key feature of this syndrome.

On average, the cannabis users in the Messinis et al. study were abstinent for approximately 123 hours prior to neuropsychological evaluation. Note that the peak effects of the cannabis abstinence syndrome occur between 48 and 144 hours following the cessation of cannabis use.[5] It is likely that study participants in the Messinis et al. study were in the midst of cannabis withdrawal during neurocognitive testing. Therefore, the data from this study should be interpreted within the context of this important caveat.

Michael Accordino, Carl L. Hart, *New York, NY*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: We thank Drs. Accordino and Hart for their interest in our study. They raise an important issue concerning the abstinence syndrome upon cessation of cannabis use. Regarding this issue, at the time of neuropsychological assessment, approximately 80% of our sample reported that they were not experiencing any discomfort due to cannabis abstinence and we did not observe any significant withdrawal symptoms in our cannabis groups during testing. A well-controlled study by Solowij et al.[6] of long- vs short-term cannabis users showed that cognitive impairments (after a median 17-hour abstinence period) were "generally unrelated to withdrawal effects and recent use." Bolla et al.[7] reported "persistent decrements in neurocognitive performance even after 28 days of abstinence in heavy cannabis users." Controlled laboratory studies[8,9] have also shown recent cannabis use to be a minimal confounder in experienced cannabis users, as were the cannabis users in our study.

Lambros Messinis, Papathanasopoulos Panagiotis, *Patras, Greece*

Disclosure: The authors report no conflicts of interest.

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Correction

Occupational manganese neurotoxicity provoked by hepatitis C

In the Brief Communication "Occupational manganese neurotoxicity provoked by hepatitis C" by Schaumburg et al. (*Neurology* 2006;67:322–323), there was an error on page 322 regarding the whole blood manganese levels. The levels given were in units of mg/L but should have been in units of ng/mL (nanograms/milliliter).

Successful treatment of acquired idiopathic generalized anhidrosis

F. Palm, MD; C. Löser, MD; W. Gronau, MD; V. Voigtländer, MD, PhD; and A.J. Grau, MD, PhD

Hypohidrosis and anhidrosis can be caused by various diseases. Diabetes mellitus, Sjögren syndrome, pure autonomic failure, Fabry disease, Ross syndrome, thyroid dysfunction, paraneoplastic autonomic dysfunction, and congenital absence of sweat glands are possible diagnoses.[1] A less common cause of hypohidrosis/anhidrosis is the acquired idiopathic generalized anhidrosis (AIGA). Until now, 64 cases of AIGA have been reported, 62 being Japanese.[2] We here report a European patient with AIGA.

Case report. A 39-year-old white man presented with a 6-month history of progressive heat intolerance and lack of sweating except for the axillary zone and parts of his face. The patient also reported tachycardia and general fatigue. He had no history of dry mouth, dry eyes, concomitant sharp pain, or urticaria.

The patient's history and family history were unremarkable. The patient did not take any medications. Physical and neurologic examination including autonomic functional tests (heart rate variability, Valsalva maneuver, respiratory sinus arrhythmia, tilt table test) were normal. Axon reflex testing was not performed. The thermoregulatory as well as the pilocarpine sweating tests showed anhidrosis except for the axillary and periorbital zones (figure, A).

Cranial MRI, chest radiograph, and various laboratory tests (including anti-GM1 and anti-GQ1B antibodies, IgE level) revealed normal findings. A skin biopsy specimen from the sternum showed infiltration of sweat glands by CD3-positive lymphocytes (figure, C). Acquired idiopathic generalized anhidrosis was diagnosed, and methylprednisolone was administered (1,000 mg/day for 3 days IV followed by tapering oral doses for 2 weeks). One week after therapy initiation, the patient's sweat production improved. Two months later, the thermoregulatory sweating test was normal (figure, B). A repeated skin biopsy revealed no more CD3-positive lymphocyte infiltration (figure, D).

Discussion. AIGA is an uncommon cause of hypohidrosis/anhidrosis. Most of the reported cases were from Japan. Clinical features of AIGA are an acute or sudden onset of generalized anhidrosis with an onset early in life, the absence of other autonomic dysfunction, and a marked response to glucocorticoids. Concomitant sharp pain or cholinergic urticaria and elevated IgE levels have also been described in the majority of patients. These features were absent in our patient; however, the marked response to glucocorticoids and the histopathologic findings strongly support the diagnosis of AIGA.

There are three subgroups of AIGA[1]: The idiopathic pure sudomotoric failure (IPSF), sudomotoric neuropathy, and sweat gland failure. Most cases of AIGA seem to represent IPSF, as in the case of our patient. Typical histopathologic findings here include CD3-positive lymphocyte infiltrations of the sweat glands[3] and occlusion of proximal coiled ducts,[4] whereas CD3-positive lymphocyte infiltration seems to be a hallmark of IPSF. Although the etiology of AIGA is still unclear, immunologic mechanisms contribute to the disease. The facts that IPSF as a subgroup of AIGA is associated with CD3-positive lymphocyte infiltration of sweat glands and that CD3 plays an important role in the induction of cell-mediated disorders support this hypothesis. This may also explain the improvement in sweat function with corticosteroids in 78% of patients with AIGA.[2] A deficit in the muscarinic cholinergic receptor in eccrine sweat glands or interference in transmission of acetylcholine to cholinergic receptors is supposed to be involved in the pathogenesis of IPSP. This might explain the persisting sweat production of the axilla, as seen in our patient. Sweat glands of the axilla are apocrine glands and are supposed to be under adrenergic control.[2] Another explanation would be the early stage of the disease in our patient, with not all sweat glands already being involved. The possibility that the CD3 cells might be directed to some parts of the eccrine sweat gland itself has to be considered as well.

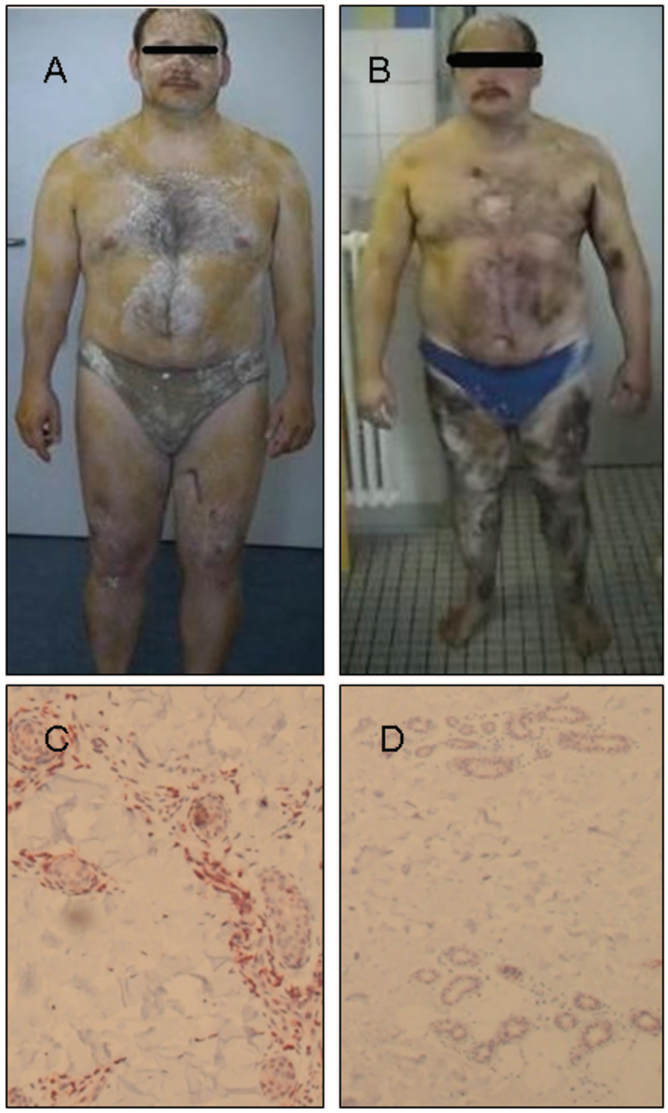

Figure. (A) Thermogegulatory sweating tests on admission (note missing blue color for anhidrotic areas). (B) Thermoregulatory sweating test after steroid treatment (note blue color for improved sweating, especially of trunk and legs). (C) Skin biopsy (CD3 stain) on admission (note lymphocyte infiltrations of the sweat glands). (D) Skin biopsy (CD3 stain) after steroid treatment.

In cases of progressive hypohidrosis/anhidrosis with no other pathologic findings, the diagnosis of AIGA should be considered. In most cases, steroid pulse therapy is effective.

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Occult celiac disease presenting as epilepsy and MRI changes that responded to gluten-free diet

Elizabeth Harper, MD; Harold Moses, MD; and Andre Lagrange, MD, PhD

Celiac disease (CD), an autoimmune disorder involving hypersensitivity to gluten, has been associated with many neurologic manifestations, most commonly ataxia and neuropathy.[1-3] We report contrast-enhancing brain lesions and epilepsy in a patient with previously occult CD that responded to a gluten-free diet (GFD).

Case report. A 30-year-old, previously healthy man presented with a 2-year history of headaches and refractory seizures with postictal right hemiparesis and aphasia. He also had a constant milder hemiparesis. A brain MRI revealed multiple contrast-enhancing lesions involving white and gray matter. Serologic testing was unrevealing. A brain biopsy showed inflammation with reactive gliosis but no microglial nodules. There was also endothelial proliferation, without vasculitis. Special stains for periodic acid-Schiff, Gomori methenamine silver, Steiner, herpes simplex virus 1 and 2, amoeba, and encephalitis panel were all negative, as were CSF cultures for viral, bacterial, and fungal organisms. Despite treatment with glucocorticoids and multiple antiepileptic drugs, his seizures persisted, and subsequent MRI over the following 10 months found the appearance and disappearance of new lesions. He then presented to our clinic for a second opinion. Past medical, family, and social history were noncontributory; a systems review revealed no fever or weight loss, but he did have chronic constipation and rash, which were exacerbated during times of increased seizures. Physical examination showed a well-nourished man with excoriated erythematous papules over his elbows, knees, and buttocks; his general medical examination was otherwise unremarkable. Neurologic examination revealed word-finding difficulty and right-sided weakness. An extensive evaluation for infectious, neoplastic, and inflammatory etiologies was negative. Notable negative studies included HIV, vitamin B_{12} and E levels, screens for collagen vascular disease, serum and CSF angiotensin-converting enzyme levels, CSF cell counts, oligoclonal banding, IgG index, cytology, and flow cytometry. CT angiogram showed no evidence for vasculitis or cerebral calcifications. Although he denied diarrhea, the patient's gastrointestinal complaints and rash prompted an evaluation for celiac disease. Antigliadin IgG and IgA antibodies as well as anti-transglutaminase and anti-endomysial antibodies were all markedly elevated. Small bowel biopsy was diagnostic of CD, and a skin biopsy was consistent with dermatitis herpetiformis. Staining of his previous cerebral biopsy for anti-transglutaminase antibodies was not available. Despite our recommendations, he refused a repeat brain biopsy to further exclude malignancy. He was instead treated with a GFD and antiepileptic medication. He has been strictly compliant with the diet and has been seizure-free for nearly 2 years, although the hemiparesis and cognitive difficulties persist. Abnormal antibody levels have normalized, as is expected with GFD compliance,[4] and the contrast-enhancing brain lesions have all resolved without recurrence (figure).

Discussion. Our patient with new-onset epilepsy and contrast-enhancing brain lesions meets the serologic and pathologic diagnostic criteria for CD. Furthermore, initiation of a GFD resulted in the clinical and radiologic resolution of the brain lesions, suggesting that the neurologic symptoms and CD were causally related.

Gastrointestinal involvement of CD may produce malabsorption and some of the neurologic manifestations of CD may be due to vitamin deficiencies.[5] However, these data have not been reproducible or conclusive. Moreover, the patient appeared well nourished, and serum albumin, hemoglobin, and vitamins E and B_{12} were all normal. To our knowledge, there is only one other report of relapsing and remitting contrast-enhancing MRI lesions associated with CD.[2] However, that patient had exclusively white matter lesions, also had oligoclonal bands in the CSF, and responded to glucocorticoids but not a GFD. It is therefore difficult to distinguish those findings from coincident multiple sclerosis in a patient with CD. In contrast, our patient's cortical involvement and seizures would be distinctly unusual for multiple sclerosis. The protracted, nearly year-long course would argue against an alternative diagnosis of acute disseminated encephalomyelitis. Finally, the contrast-enhancing white and gray matter lesions are not consistent with MRI changes due to frequent seizures.

Several series have associated CD with epilepsy,[3,5] including a child with CD whose refractory epilepsy responded to a GFD.[6] Nonetheless, other than those rare CD cases involving cerebral calcification, the potential link between CD and epilepsy remains elusive. Moreover, the pathophysiologic basis of neurologic disease and CD, if one exists, is unknown. However, recent work[7] has found deposition of anti-transglutaminase antibodies in the cerebral vessels and brain tissue of patients with gluten ataxia, thereby suggesting that the antibodies themselves may contribute to the neurologic complications of CD.

Our case of GFD-responsive CD, epilepsy, and brain MRI lesions supports the idea that CD may involve the CNS and expands the repertoire of possible neurologic complications associated with CD. Further investigation into the relationship between CD and epilepsy is warranted.

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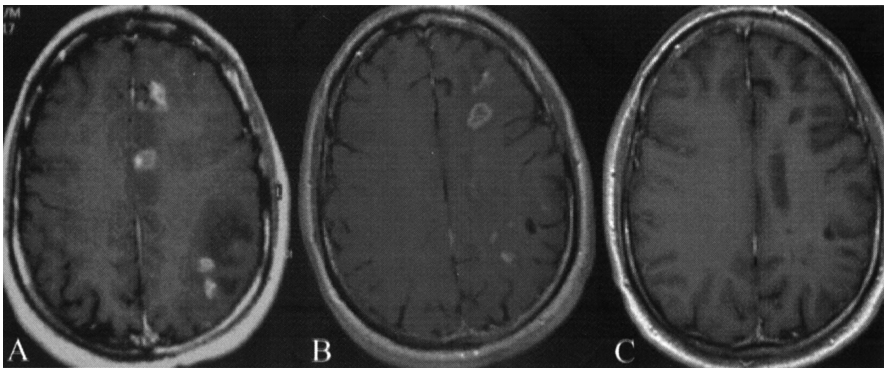

Figure. (A) T1 image showing contrast-enhancing gray and white matter lesions. (B) T1 image 2 years later, showing new contrast-enhancing lesions. (C) T1 image after 12 months on gluten-free diet, showing resolution of prior contrast-enhancing regions and no new lesions.

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Correction

There is nothing staid about STARD: Progress in the reporting of diagnostic accuracy studies

In the editorial "There is nothing staid about STARD: Progress in the reporting of diagnostic accuracy studies" by Karen C. Johnston and Robert G. Holloway (*Neurology* 2006;67:740–741), accompanying the article "The quality of diagnostic accuracy studies since the STARD statement: Has it improved?" by Smidt et al. (*Neurology* 2006;67:792–797), the pre-STARD vs post-STARD comparison was stated to be significant but the data provided demonstrated a statistically insignificant difference. The authors wish to correct the statement and apologize for the error.

Correction

CSF tau protein: A new prognostic marker for Guillain-Barré syndrome

In the Brief Communication "CSF tau protein: A new prognostic marker for Guillain-Barré syndrome" by K. Jin et al. (*Neurology* 2006;67:1470–1472), the units of CSF tau protein should be pg/mL instead of ng/mL in table 1, table 2, and figure. The authors regret these errors.

Correction

Correspondence: Neuropsychological deficits in long-term frequent cannabis users

In the reply from authors Lambros Messinis and Panagiotis Papathanasopoulos in the Correspondence concerning "Neuropsychological deficits in long-term frequent cannabis users" (*Neurology* 2006;67:1902), the second respondent's first name and surname are transposed. The author's name is Panagiotis Papathanasopoulos.