Correspondence

Efficacy of levodopa therapy on motor function after posteroventral pallidotomy for Parkinson's disease

To the Editor: We read with interest the article by Uitti et al. on the efficacy of levodopa therapy on motor function in 41 patients with complicated PD submitted to microelectrode-guided pallidotomy.[1] The authors found no significant change in the latency, duration, or magnitude of clinical response after administration of an acute challenge of levodopa. However, it is difficult to understand how the magnitude of the clinical response remained unchanged after surgery. This pharmacologic parameter is defined as the difference between basal "off" and best "on" Unified Parkinson's Disease Rating Scale (UPDRS) motor scores. Many reports confirm that pallidotomy provides marked contralateral amelioration of parkinsonian symptoms, and after surgery patients reported less recognizable "on-off" fluctuations.

Current ideas about the pathophysiologic basis of motor fluctuations suggest that the magnitude of the motor response is the key factor in the development of the wearing-off phenomenon.[2] The improvement in motor fluctuations after pallidotomy is most likely due to a reduction in the magnitude of the motor response as a result of reduced severity of the parkinsonian signs and symptoms in the operated side. Indeed, Uitti et al. noted that the mean motor "off" score after pallidotomy was improved by 10 points (48.7 versus 38.6). The best motor "on" score was also improved, although to a lesser degree (24.6 versus 20.1). Despite this improvement in both scores, the magnitude of the motor response should be reduced after surgery because the degree of improvement in the "off" score is bigger than that obtained in the best "on" score. Other groups, despite methodologic differences, have found a significant reduction in the magnitude and an increase in the duration of the clinical benefit after acute levodopa and apomorphine challenges.[3-5]

We evaluated six patients with PD who underwent pallidotomy. The magnitude was reduced by 30% and the duration of either levodopa or apomorphine effect was 40% longer.[6] Merello et al. recently reported similar results although they did not specifically evaluate the magnitude of the response.[5] More recently, we have extended our results to a group of 14 patients submitted to deep brain stimulation of the subthalamic nucleus or internal globus pallidus, obtaining similar results, although the changes were more pronounced in these patients, probably because of the bilateral nature of the surgical intervention.[7] In our experience, pallidotomy and deep brain stimulation shift the pharmacologic response profile to a pattern more characteristic of less advanced parkinsonian patients. These changes may account for the "disappearance" or lack of perception of motor fluctuations leading to a less difficult drug management.

G. Linazasoro, J.A. Obeso, A. Gorospe, M.C. Rodríguez, J. Guridi, E. Ramos, *San Sebastián, Spain*

Reply from the Authors: We appreciate the interest expressed by Linazasoro et al. in our article.[1] They indicate that "it is difficult to understand how the magnitude of the clinical response remained unchanged after surgery." We agree with this statement but believe it to be true. We performed our analyses to examine the issue of levodopa's impact on motor function in the face of elimination or reduction of levodopa-related side effects (dyskinesias) following pallidotomy.

Linazasoro et al. state that the magnitude of the clinical response is a "pharmacologic parameter defined as the difference between basal "off" and best "on" UPDRS motor scores." This may be one definition, but we believe that other definitions give other reflections of the true magnitude of the clinical response. Linazasoro et al. conclude that in our series "the magnitude of the motor response should be reduced after surgery because the degree of improvement in the "off" score is bigger than that obtained in the best "on" score." In other words, if the postoperative reductions in UPDRS motor scoring are greater for the "off" state than the "on" state, efficacy of levodopa is reduced. We believe that comparisons of preoperative "off" and postoperative "off" scores (and similarly "on" scores) actually address the effects of surgery rather than levodopa effects. We believe that "short duration" levodopa effects are tied to the "off" and "on" scores immediately surrounding the time of levodopa administration. The absolute differences in UPDRS scoring, related to levodopa use, need to be considered in their own context—i.e., the "on" state, representing a percentage change from "off," is a more accurate reflection of the magnitude of levodopa response.

There are several important details regarding the UPDRS motor score: 1) the rating scale ordinal subscores are not linear—for example, the difference between a bradykinesia or rigidity score of 1 and 2 is not the same as between 2 and 3; 2) the summed scores for an individual patient are not linear—for example, the difference between a motor score of 5 and 6 may not be equivalent to the difference in motor scores of 45 and 46; 3) summed scores among a series of patients are not linear; and 4) the nature of the range of subscores (0–4) gives rise to potential for a "ceiling effect." Consequently, use of absolute value changes, and to a lesser extent, percentage changes, may be problematic.

Using the suggested definition, a change of 10 UPDRS points from "off" to "off" (preoperative to postoperative) or "off" to "on" would be equivalent regardless of the context. For example, if Patient 1 has an "off"/"on" score of 80/70 with treatment, this would be equivalent to Patient 2 with an "off"/"on" of 20/10. In contrast, we believe that the effects of levodopa need to be considered in the context of the patient's "off" state when levodopa is administered and the effect ("on") expressed as a percentage change in UPDRS scoring. Hence, the magnitude of the treatment effect producing the "on" state was 10/80 or 12.5% in Patient 1 and 50% in Patient 2. This is the methodology employed routinely when reporting changes following pharmacologic therapy used for motor dysfunction in PD. It is interesting to note that in assessing the effects of pallidotomy in PD, Linazasoro et al. have written elsewhere[8] that "more objective assessment of the effects of pallidotomy" can be gleaned by separate analysis of movements at individual joints, for example, rather than the total motor score. In describing this approach in 1996, exclusively percentage improvements were employed rather than absolute differences (as now suggested in their definition of the magnitude of clinical response as it relates to pallidotomy). They reported that objective, timed measurements following pallidotomy "showed minor (less than 20 percent) improvement," whereas isolated analysis of rigidity (presumably using the UPDRS motor score) showed reduction of 84% and arm bradykinesia improved by 54%. They concluded that "large changes in motor function in specific tasks or in specific parts of the body can be concealed if the usual Parkinson's disease rating scales are employed (in total)." We agree with their previous conclusions regarding the usefulness of reporting percentage improvements as being most reflective of the true magnitude of a treatment's efficacy.

Additionally, we wish to comment on two of the studies Linazasoro et al. cite as showing a "significant reduction in the magnitude (of response) after acute levodopa administration."[4,5]

The study of nine patients reported by Skalabrin et al.[4] used a different methodology, as pointed out. Skalabrin et al. evaluated patients with motor UPDRS scoring in an "off" state and at 2-hour intervals thereafter following a single morning dose of levodopa. In contrast, our protocol scored 41 patients at 0, 30', 60', 90', 120', 180', 240', 300', and 360' following levodopa administration. We suspect that our methodology may have recovered a more optimal best "on," as we found that most patients experienced the lowest UPDRS motor score between 60' and 90' (rather than 120'). In any case, the absolute values of UPDRS motor scores were not supplied in the Skalabrin article. However, our estimates from their figure 1 were: preoperative "off"/"on" = 44/25 and postoperative "off"/"on" = 38.5/21. Using the definition suggested in the letter, the levodopa effect would be reduced in this series because the "off" change (preoperative to postoperative) of 6.5 was greater than the "on" change of 4. Using our calculations, the levodopa effect would be: 44→25 = 43% improvement ("off"→"on") preoperatively and 38.5→21 = 45% postoperatively. (Skalabrin et al.'s study is similar to our experience[1]: levodopa effect—49% improve-

ment ["off" to "on"] preoperatively and 48% postoperatively.) This would appear to be the same conclusion drawn by Skalabrin et al., as they state that "the mean best motor UPDRS score was approximately one half the mean worst score both preoperatively and postoperatively." They go on to comment in their discussion that pallidotomy "did not impair any motor responses to levodopa," with this being reiterated further by their choice for the article's running title: "Pallidotomy improves levodopa motor responses." Consequently, we believe that the Skalabrin et al. study is similar to ours (although they were not able to report statistically significant improvements postoperatively, probably because of small sample size) in documenting preserved levodopa efficacy.

The study by Merello et al.[5] is quite different in methodology in that it addressed duration and latency of levodopa effects immediately after surgery. However, they did report contralateral UPDRS motor scores preoperatively as 31.6→15.5 ("off"→"on") and postoperatively 20.1→10 ("off"→"on"). This would conform to reduced efficacy of levodopa by the Linazasoro et al. interpretation (as $31.6 - 20.1 = 11.5 > 15.5 - 10 = 5.5$). By our definition, the efficacy of levodopa in reducing the contralateral motor score is 51% preoperatively and 50% postoperatively. Merello et al. also conclude that pallidotomy "exerted influence of L-dopa effect by enhancing the magnitude of response and ameliorating dyskinesia on an asymmetric basis." We cannot find statements by either Skalabrin et al.[4] or Merello et al.[5] that there is a significant reduction in the magnitude of response after acute levodopa administration following pallidotomy. We cannot comment on levodopa efficacy following bilateral deep brain stimulation of the subthalamic nucleus or internal segment of the globus pallidus but defer to Linazasoro et al. given their experience.[7]

We agree with Linazasoro et al.'s main conclusion that pallidotomy shifts the pattern of levodopa response to that of less advanced parkinsonian patients. It is clear that varying definitions of the magnitude of response after levodopa administration lead to varying interpretation of the data (which we both agree upon). Whereas speculation concerning explanations of the pathophysiology of motor fluctuations are important to consider, we believe that the data support the contention of maintained efficacy of levodopa in PD following pallidotomy. Interpretation of these findings, in the face of reduced levodopa-induced dyskinesias, is certainly complicated and beckons for explanations that conform to the data rather than theoretical expectations.

Ryan J. Uitti, MD, Robert E. Wharen, Jr., MD, Margaret F. Turk, MSN, *Jacksonville, FL*

References

1. Uitti RJ, Wharen RE, Turk MF. Efficacy of levodopa therapy on motor function after posteroventral pallidotomy for Parkinson's disease. Neurology 1998;51:1755–1757.
2. Nutt JG, Holford N. The response to levodopa in Parkinson's disease imposing pharmacological law and order. Ann Neurol 1996;39:561–573.
3. Verhagen L, Mouradian MM, Chase TN. Altered levodopa dose-response profile following pallidotomy. Neurology 1996;46(suppl):S58.004.
4. Skalabrin EJ, Laws ER, Bennet JP. Pallidotomy improves motor responses and widens the levodopa therapeutic window in Parkinson's disease. Mov Disord 1998;13:775–781.
5. Merello M, Nouzeilles MI, Cammarota A, Pikielny R, Leiguarda R. Clin Neuropharmacol 1998;21:135–138.
6. Linazasoro G, Obeso JA, Gorospe A, et al. The mechanism of action of pallidotomy in Parkinson's disease: clinical and pharmacological response. Soc Neurosci Abstracts 1995;21:1981.
7. Obeso JA, Linazasoro G, Gorospe A, Rodríguez MC, Lera G. Complications associated with chronic levodopa therapy in Parkinson's disease. In: Olanow CW, Obeso JA, eds. Dopamine agonists in early Parkinson's disease. Kent: Wells Medical, 1997:11–36.
8. Obeso JA, Linazasoro G, Rothwell JC, Jahanshahi M, Brown R. Assessing the effects of pallidotomy in Parkinson's disease. Lancet 1996;347:1490. Letter.

A tentative interpretation of electromyographic regional differences in bulbar- and limb-onset ALS

To the Editor: Cappellari et al.[1] address the interesting problem of regional differences of denervation in ALS. The authors present the results of 36 ALS patients; needle EMG data were studied in cranial-innervated, paraspinal, and limb muscles for the presence of fibrillation. Presence of fasciculation potentials (FPs), as well as a qualitative classification of motor unit potentials morphology and of the recruitment under voluntary contraction, were given.

However, some important methodologic issues are lacking. We are not told if they consider fibrillation and sharp-waves to be the same, how many different sites were sampled in each muscle, and the criteria for presence of spontaneous activity. Furthermore, they do not specify the muscle chosen when studying the tongue, in which spontaneous activity is particularly difficult to record because of patients' inability to inactivate the voluntary motor units.

They conclude that the spontaneous activity is much more common in limb muscles than either paraspinal or cranial-innervated muscles, even for bulbar-onset patients. The same was observed for qualitative muscle analysis. A nerve length-dependent susceptibility was claimed to justify the observations.

We did a similar study in the last 55 ALS patients (13 bulbar-onset) consecutively diagnosed in our laboratory and followed in our department. By the time of the neurophysiologic study the mean evolution time was 17 months. In all of these patients, other clinical conditions were ruled out and the follow-up confirmed the typical disease evolution toward a definite diagnosis by El Escorial criteria.[2] Conduction velocities were normal. In each patient, two or three (in bulbar-onset patients) cranial-innervated muscles (masseter, genioglossus, or sternocleidomastoid) and two muscles in each limb (first dorsal interosseous, biceps, tibialis anterior, and gastrocnemius or vastus medialis) were sampled in at least four different sites. Even the presence of scarce fibrillation or sharp-waves (FIBS-SW) was accepted as meaning active denervation. FPs were also recorded. We observed no FIBS-SW in cranial-innervated muscles but rare FPs and complex repetitive discharges were recorded in these muscles in bulbar-onset patients. Two bulbar-onset patients had no FIBS-SW elsewhere, five had FIBS-SW in upper limbs, and six in lower limb muscles. All lower limb–onset patients had FIBS-SW in lower-limb muscles. In 3 out of 19 upper-limb–onset patients, who had a short evolution, no FIBS-SW were observed. In those 16 with FIBS-SW, these potentials were observed equally in upper and lower limb muscles. One patient who presented with paraspinal weakness had no FIBS-SW in those muscles, but active denervation was confirmed in the four limbs. FPs were more frequent in slightly denervated muscles with no FIBS-SW[3] and FIBS-SW were more frequent in more severely denervated muscles.

Our results agree with the authors' assertion of a nerve-length susceptibility to denervation in ALS. However, in our experience, the presence of FIBS-SW in cranial-innervated muscles is a rare event only observed in patients with a long evolution time. The absence of FIBS-SW should not preclude the neurophysiologic diagnosis of ALS in bulbar-onset patients.

Mamede de Carvalho, MD, Carla Bentes, MD, *Lisbon, Portugal*

Reply from the Authors: We appreciate the interest of Drs. de Carvalho and Bentes in our article.[1] The methodologic issues lacking in the original report, due to the space limitations of the "Brief Communication" format, are as follows:

Fibrillation potentials and positive sharp waves have the same significance as electrophysiologic markers of active denervation. Positive sharp waves are considered fibrillation potentials blocked at the recording site by a traumatic lesion of the membrane of the denervated muscle fibers due to the intramuscular electrode placement.[4]

We have examined at least two areas in each muscle, positioning the needle in four different directions. According to the Mayo Clinic guidelines,[5] active denervation is characterized by the unequivocal evidence of fibrillation potentials that are persistent (over 1–2 second duration) and present in at least two sites of the muscle.

Spontaneous activity is difficult to assess in the tongue muscles owing to the difficulty in relaxing the tongue. We usually insert the needle electrode in the lateral sides of the tongue, asking the patient to relax as much as possible. If there is any doubt in distinguishing between fibrillation and voluntary motor unit action potentials, we adopt a less invasive technique, reach-

ing the genioglossus muscle through the floor of the mouth to overcome aversion against direct needle insertion into the tongue.[6]

Alberto Cappellari, MD, Sergio Barbieri, MD, Vincenzo Silani, MD, *Milan, Italy*

References

1. Capellari A, Brioschi A, Barbieri S, Braga M, Scarlato G, Silani V. A tentative interpretation of electromyographic regional differences in bulbar- and limb-onset ALS. Neurology 1999;52:644–646.
2. Brooks BR, World Federation of Neurology Sub-Committee on Motor Neuron Diseases. El Escorial WFN criteria for the diagnosis of amyotrophic lateral sclerosis. J Neurol Sci 1994;124:965–1085.
3. Lambert EH. Motor neuron diseases: research on amyotrophic lateral sclerosis. In: Norris FH, Kurland LT, eds. Contemporary neurology symposia. Vol. 5. New York: Grune and Stratton, 1967:135–153.
4. Eisen A, McComas AJ. Motor neuron disorders. In: Brown WF, Bolton CF, eds. Clinical electromyography. 2nd ed. Boston: Butterworth-Heinemann, 1993;427–450.
5. Electromyography and Clinical Neurophysiology Laboratory. Manual of techniques in motor and sensory clinical neurophysiology. Rochester, MN: Mayo Clinic, February 1989.
6. Finsterer J, Fuglsang-Frederiksen A, Mamoli B. Needle EMG of the tongue: motor unit action potential versus peak ratio analysis in limb and bulbar onset amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 1997;63:175–180.

Creatine monohydrate increases strength in patients with neuromuscular disease

To the Editor: We read with interest the article on creatine monohydrate (CM) treatment in neuromuscular disease by Tarnopolsky and Martin.[1] The article reports that CM has therapeutic potential for various neuromuscular diseases. The study also suggests that creatine administration improved motor behavior and prolonged survival in the SOD (G93A) transgenic mouse, an animal model of ALS.[2] We have encountered several patients with refractory polymyositis or inclusion body myositis (IBM) who did not respond to high doses of corticosteroids, other immunosuppressants, plasma exchange, and high-dose immunoglobulin therapy. Among them, CM treatment attenuated hyperCKemia but did not enhance muscle strength in one patient with IBM. We would like to present such a patient and pose several questions concerning CM administration.

A 51-year-old Japanese woman noticed muscle weakness in the lower extremities. One month later, she was no longer ambulatory and developed muscle weakness in the upper extremities. Her mother had died of malignant lymphoma and her sister has had Hashimoto thyroiditis. Neurologic examination revealed muscle weakness in the upper (Medical Research Council [MRC] 3/5) and lower (MRC 2/5) extremities, predominantly in the proximal portion. Muscle stretch reflexes were normal. Serum creatine kinase (CK) increased to 10,044 (normal $<$ 189 IU).

Electromyography disclosed myopathic changes. Muscle biopsy indicated IBM. Pulse methylprednisolone and plasma exchange were performed. However, muscle weakness deteriorated (MRC 2/5 in the upper limbs and 1/5 in the lower limbs) and dysphagia presented. Treatment with high-dose IV immunoglobulin did not ameliorate motor deficits, although serum CK dropped to 6,564 IU. Two months later, she had respiratory failure. Our patient received total doses of 75 g CM (101% pure, Wako Pure Chemical Industries, Japan) by oral administration for 11 days. Immediately after CM treatment, serum creatine levels were increased from 1.5 to 3.2 (normal 0.4 to 0.9 mg/dL), but serum creatinine remained low at 0.1 mg/dL. Serum CK was decreased to 2,444 IU. Serum aldolase and myoglobin were reduced 149.0 to 23.8 (normal 1.2 to 7.6 IU/L) and 1,200 to 493 (normal $<$ 61 ng/mL), respectively. However, CM administration did not potentiate motor function, such as MRC of the four extremities and bulbar and respiratory function.

Tarnopolsky et al.[1] indicate that short-term administration of CM increased muscle strength approximately 10% in their patients. CM failed to recover muscle weakness in our patient whereas the serum levels of CK, aldolase, and myoglobin were reduced markedly. The question is whether those enzymes were altered in their patients with inflammatory myopathies or whether this treatment had favorable effects in their three patients with IBM. Our patient is currently given 60–75 g CM/month. They conclude that further long-term study is warranted. If they have such preliminary data, we would like to know how doses and duration of CM are administered in their long-term trial or whether long-term treatment with CM exerts more powerful effects on muscle strength.

Oral administration of creatine protected against motoneuron degeneration in G93A transgenic mice.[2] Our preliminary results also suggest that CM therapy delays progression of wobbler mouse motoneuron disease. Note that CM treatment had symptomatic effects in the authors'[1] patients with spinal muscular atrophy or other neuropathic disorders. They speculated that CM supplementation could have more benefits in lower intramuscular creatine storage, such as muscular dystrophy and inflammatory myopathy. Thus, CM therapy is promising in several neuromuscular diseases. Long-term trials of CM or creatine may be worthwhile in patients with refractory inflammatory myopathies and motoneuron disease.

Ken Ikeda, MD, PhD, Masao Kinoshita, MD, Yasuo Iwasaki, MD, Nobuo Wakata, MD, *Tokyo, Japan*

Reply from the Authors: We thank Ikeda et al. for their interesting comments on our article.[1] We have now followed close to 70 patients with a variety of neuromuscular disorders for more than 6 months who continue to take CM at between 3 and 5 grams per day. We have followed serum CK in these individuals and have not seen a positive nor a negative treatment effect on CK concentration. The mechanism behind the serum CK drop in the patient with possible IBM that was presented by the authors was cotemporal with CM administration; however, the mechanism is unclear. In fact, we have been concerned about the possibility that creatine supplements may increase serum CK activity due to an upregulation of enzyme activity.[3] We tested this in healthy young males and females and found no effect on CK activity. In a pathologic situation, creatine has been shown to improve intercellular calcium handling in mdx skeletal muscle cells[4]; thus, it is possible that a reduction in Ca^{++} activated proteases may decrease sacrolemmal damage.

The case presented by Ikeda et al. is unusual for IBM in that the CK was markedly elevated (10,044) and that weakness progressed to be both severe and generalized, also affecting respiratory and pharyngeal muscles. To determine whether the drop in CK was in fact the natural history of this disorder or was a result of the creatine administration would require withdrawal of treatment with judicious following of strength and CK activity.

We agree with the authors that long-term randomized double-blind crossover studies need to be performed to fully evaluate the potential efficacy and safety issues around this form of therapy. Data from animal models[2,4] suggest that creatine may be an adjunctive therapy in certain neuromuscular disorders and preliminary evidence[1,5] in humans supports the animal data.

Direct muscle biopsy results have demonstrated a reduction in phosphocreatine concentration in patients with mitochondrial cytopathy, inflammatory myopathies, and muscular dystrophy.[6] These individuals are those most likely to benefit from a creatine supplementation strategy.

Mark Tarnopolsky, MD, PhD, Joan Martin, MSc, *Hamilton, Canada*

References

1. Tarnopolsky M, Martin J. Creatine monohydrate increases strength in patients with neuromuscular disease. Neurology 1999;52:854–857.
2. Klivenyi P, Ferrante RJ, Matthews RL, et al. Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. Nat Med 1999;5:347–350.
3. Mihic S, MacDonald JR, McKenzie S, Tarnopolsky MA. Acute creatine loading increases fat-free mass, but does not affect blood pressure, plasma creatinine or CK activity. Med Sci Sports Exerc 2000 (in press).
4. Pulido SM, Passaquin AC, Leijendekker WJ, Challet C, Wallimann T, Rüegg UT. Creatine supplementation improves intracellular Ca^{2+} handling and survival in mdx skeletal muscle cells. FEBS Lett 1998;439:357–362.
5. Tarnopolsky MA, MacDonald J, Roy B. A randomized double blind trial of creatine monohydrate in patients with mitochondrial cytopathies. Muscle Nerve 1997;20:1502–1509.
6. Tarnopolsky MA, Parise G. Direct measurement of high energy phosphate compounds in patients with neuromuscular disease. Muscle Nerve 1999;22:1228–1233.

The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease

To the Editor: The interesting finding by Delacourte et al.[1] that neurofibrillary tangles seem to spread through the brain along a stereotypical, sequential, hierarchical pathway is not the first time that this phenomenon has been noted. In a multivariate analysis of the brains of 45 people with dementia dying of AD and 12 age-matched normative controls, my laboratory found that the hippocampus is affected by neurofibrillary degeneration (NFD) before any parts of neocortex, and that the histopathologic lesions of AD then progress through the other temporal gyri, followed by frontoparietal and cingulate regions, and involve the sensorimotor and visual cortices only very late in the disorder.[2] We speculated that this gradual mode of spread through the brain favors a progressive neuron-to-neuron dissemination of some etiologic trigger.

It is comforting that the French workers a decade later have confirmed with the paired helical filament-tau stain our original morphometric findings based on the anomalous dichroism and yellow-green birefringence of tangles when viewed under polarized illumination with Congo red staining.

Melvyn J. Ball, MD, FRCP (C), *Portland, OR*

Reply from the Authors: Anti-tau and anti-Aβ are immunochemical markers that help to describe the natural and molecular history of sporadic AD. Using biochemical approaches to quantify insoluble Aβ and tau pathology in the different brain areas from a large panel of nondemented and demented patients followed prospectively, we described the biochemical pathway of NFD and amyloid deposition in aging and AD.[1] As mentioned in our article, our data agree with several neuropathologic studies, especially that of Fewster et al.,[2] who described a progressive neuron-to-neuron spreading of NFD from the hippocampus to the temporal cortex, the association brain areas, and ending in the sensorimotor and visual cortices. Our results also agree with those of Price et al.,[3] who observed that the amounts and extent of amyloid deposits and NFD in the brain can be important at the preclinical stages of AD.

In the complex and controversial world of Alzheimer research, similar conclusions brought by two different approaches (neuropathologic and biochemical) should be interpreted as good news. They present solid data that should be taken into account by those who want to develop realistic models of the pathogenesis of AD.

Together, these data describing the morphologic and biochemical changes in the aging human brain demonstrate important physiopathologic events that explain the features of sporadic AD pathogenesis: 1) the constitutive vulnerability of the hippocampal region to NFD in aging; 2) the diffuse and widespread amyloid burden or APP dysfunctions that strike first the most vulnerable brain area—the hippocampal region; and 3) the extension of NFD to other brain areas in a chain reaction between neuronal populations, via their main connections (figure). This neuronal chain reaction of degeneration is an important physiopathologic feature of sporadic AD showing that each cofactor involved in the dynamic of NFD progression is potentially a therapeutic target.

André Delacourte, PhD, *Lille, France*

References

1. Delacourte A, David JP, Sergeant N, et al. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 1999;52:1158–1165.
2. Fewster PH, Griffin-Brooks S, MacGregor J, Ojalvo-Rose E, Ball MJ. A topographical pathway by which histopathological lesions disseminate through the brain of patients with Alzheimer's disease. Dementia 1991; 2:121–132.
3. Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol 1999;45:358–368.

Bilateral infarction in the territory of the anterior cerebral arteries

To the Editor: We read with interest the article by Minagar and David[1] on bilateral infarction in the territory of the anterior cerebral arteries (ACA). Their patient presented with akinetic mutism and quadriparesis for 2 weeks. He showed some recovery of speech, but his motor function remained severely impaired. As stated, it may initially be difficult to delineate the exact cause of the motor dysfunction based only on clinical presentation and an early CT scan. Neurophysiologic assessment may provide localizing information by testing the functional integrity of efferent pathways. Valls-Solé and Chamorro[2] studied three patients with

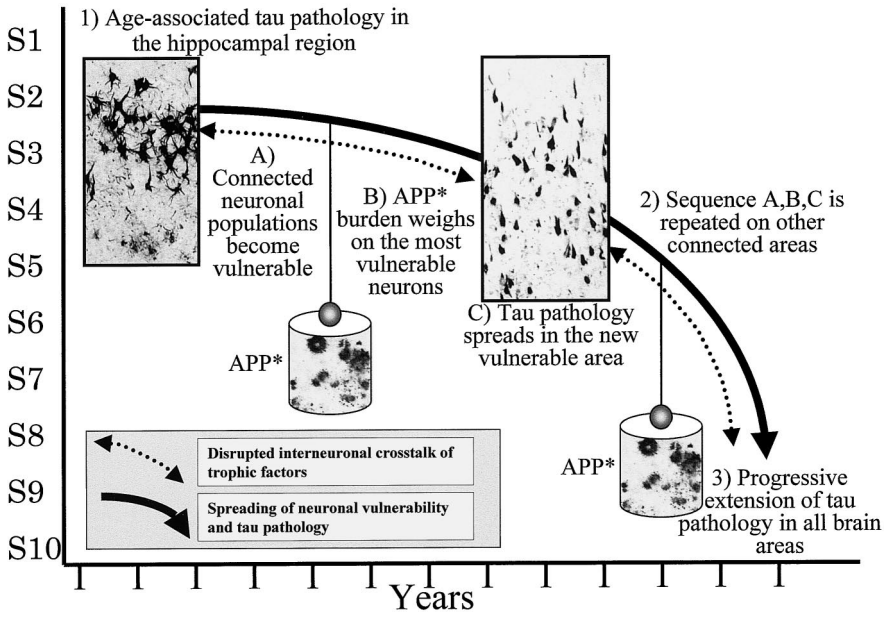

Figure. Spreading of neurofibrillary degeneration (NFD) in sporadic AD: putative mechanisms. S1 to S10: Different stages of tau pathology in aging and AD.[1] 1) There is a constitutive vulnerability of the hippocampal region to tau pathology in aging, as demonstrated by neuropathologic and biochemical observations. The dynamic of spreading of tau pathology is fueled by three basic mechanisms: A) degenerating neurons from the hippocampal region are no longer able to exchange trophic factors with connected neuronal populations, which, in turn, will also become vulnerable; B) APP dysfunctions of AD (loss or gain of function of APP or Aβ neurotoxicity), represented as APP, are a general burden weighting first on the most vulnerable populations; C) consequently, tau pathology will extend to the new vulnerable neuronal populations that may be located in other brain regions. 2) Progressively, processes A, B, and C will affect other brain areas S4, S5, S6, . . . , like a chain reaction. Along with this sequence of dysfunctions, other cofactors could work in synergy to speed up the dynamic of tau pathology spreading, such as* APOE *ϵ4, microglial reaction, and oxidative stress. 3) Finally, all brain areas will be affected by tau pathology. Clinical AD will be observed when compensation by neuronal plasticity is overcome (generally stage 7).*

unilateral ACA infarction using transcranial magnetic stimulation. Although none of their patients was able to move the affected contralateral extremities, the central conduction time was normal to the upper limb, indicating a premotor lesion. On the contrary, responses were absent in the lower limb, thereby localizing the lesion to the corticospinal pathway. Recently, we reported motor evoked potentials in a patient with a bilateral frontomesial lesion including the supplementary motor areas (SMA) due to meningioma who underwent surgery.[3] On clinical examination, the patient was alert, but did not move spontaneously. However, he was able to move his hands on command. Neurophysiologic examination indicated integrity of the corticospinal tract to thenar and tibialis anterior muscles bilaterally, thereby suggesting a premotor lesion to both upper and lower extremities. Although the presence of motor evoked potentials after acute insults to the brain is usually considered to signify good functional outcome, our patient did not show improvement in motor performance. This is in agreement with the lasting motor deficit encountered in the patient of Minagar and David.[1]

Markus Kofler, MD, *Zirl, Austria*

Reply from the Authors: We welcome the neurophysiologic observations made by Kofler,[3] who also quotes Valls-Solé and Chamorro,[2] differentiating loss of motor performance due to corticospinal interruption from that caused by damage to the SMA or premotor cortex in patients with ACA infarction. Neither evoked potential nor transcranial electrical stimulation was performed in our patient.[1]

Brickner[4] and Penfield[5] originally investigated the role of SMA and premotor cortex in planning, setting, initiation, and execution of voluntary movements and speech. Later, the existence of somatotopy in the human SMA, first suggested by Talairach and Bencaud,[6] was confirmed by subdural stimulation in epileptic patients undergoing presurgical evaluations. However, neurophysiologic studies of corticospinal tracts and SMAs have not been performed in patients with bilateral ACA territory infarct previously, which makes Kofler's experience[3] noteworthy.

We hope that in the future observations using this method will be applied systematically to study paralysis in patients with unilateral or bilateral ACA territory infarcts. If Kofler's findings[3] are reproducible, transcranial electrical stimulation could become useful for localization as well as prediction of functional outcome in this group of patients.

Alireza Minagar, MD, Noble J. David, MD, *Miami, FL*

References

1. Minagar A, David NJ. Bilateral infarction in the territory of the anterior cerebral arteries. Neurology 1999;52:886–888.
2. Valls-Solé J, Chamorro A. Transcranial cortical magnetic stimulation in patients with anterior cerebral artery infarct. Muscle Nerve 1997;20: 1075–1076. Abstract.
3. Kofler M, Morota N, Deletis V. Preserved motor evoked potentials fail to predict functional outcome in quadriplegia because of bilateral lesions of the supplementary motor areas. Am J Phys Med Rehabil 1999;78:66–72.
4. Brickner RM. A human cortical area producing repetitive phenomena when stimulated. J Neurophysiol 1940;3:128–130.
5. Penfield W, Welch K. The supplementary motor area of the cerebral cortex: a clinical and experimental study. Arch Neurol Psychiatry 1951; 66:289–317.
6. Talairach J, Bencaud J. The supplementary motor area in man. Int J Neurol 1966;5:330–347.

Corrections

In the editorial "To test or not to test? That is the question" by Holloway and Feasby (1999;53:1905–1907), reference 10 in the table (p. 1906) should be reference 12. It is correctly cited in the text. The authors apologize for the error.

In the article "ACTH versus vigabatrin in infantile spasms: A retrospective study" by Cossette et al. (1999;52:1691–1694), the statistical method used to evaluate the differences between both groups should have been the Fisher exact test rather than the chi-square test (owing to the small number of individuals in certain groups). This renders the differences in relapse rates not statistically significant, with p values at 3, 6, and 12 months of 0.11, 0.10, and 0.17, respectively. The authors emphasize that they did not suggest that vigabatrin is superior to ACTH, but is their drug of first choice because of its more favorable side-effect profile when used over a 12-month period for the control of infantile spasms. The authors apologize for the error.

In the article "ACTH versus vigabatrin in infantile spasms: A retrospective study" by Cossette et al. (1999;52:1691–1694), the statistical method used to evaluate the differences between both groups should have been the Fisher exact test rather than the chi-square test (owing to the small number of individuals in certain groups). This renders the differences in relapse rates not statistically significant, with *p* values at 3, 6, and 12 months of 0.11, 0.10, and 0.17, respectively. The authors emphasize that they did not suggest that vigabatrin is superior to ACTH, but is their drug of first choice because of its more favorable side-effect profile when used over a 12-month period for the control of infantile spasms. The authors apologize for the error.

Neurology 2000;54;539
DOI 10.1212/WNL.54.2.539