Correspondence

Clinical utility of surface EMG: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

To the Editor: I read with interest the report of the AAN Therapeutics and Technology Assessment (TTA) Committee on the clinical utility of surface electromyography (EMG).[1] Although the review dealt comprehensively with most possible indications, I was surprised to find no discussion of the use of surface EMG in the investigation of sleep disorders (apart from citations 79 and 81, quoted to illustrate EMG activity of breathing in general).

Surface EMG has been routinely used in polysomnography for more than 30 years. Submental and anterior tibial EMG are routinely recorded, and intercostal and arm EMG are monitored in some laboratories. Surface EMG plays a vital role in the staging of sleep, specifically in the determination of skeletal muscle atonia associated with REM sleep.[2] This is particularly essential when a multiple sleep latency test is used for the diagnosis of narcolepsy. It is helpful in detecting arousals, especially from REM sleep.[3] It is fundamental to the diagnosis of a number of neurologic motor disorders of sleep, including REM sleep behavior disorder[4] and periodic limb movement disorder.[5] In addition to polysomnography, surface EMG of leg muscles is monitored in the suggested immobilization test for restless legs syndrome.[6]

Thus, the diagnosis of sleep disorders should be added to the list of accepted indications for surface EMG recordings.

Michael H. Silber, MB, ChB, *Rochester, MN*

To the Editor: I disagree with the opinion of the TTA Subcommittee concerning the use of surface EMG for evaluating low back pain.[1] The Subcommittee appears to consider surface EMG as a generic technology applied in a universal manner by all researchers, practitioners, and product developers. One cannot assume technologic homogeneity, as other well-accepted evaluative procedures such as electrocardiography and nerve conduction velocities also rely on surface sensors. Was the Subcommittee's mission statement to consider surface EMG as a way to document pain or was it to evaluate the diagnostic capabilities of the surface EMG techniques themselves?

Surface EMG measures muscle activity; it reports nothing about pain. There is no "gold standard" for measuring pain. Differences often exist between *perceptions* of pain and objective pathology. The Subcommittee seemed focused on a presumed association between muscle fatigue and back pain. One must first establish the presence (or absence) of muscle dysfunction before suggesting any possible correlations to self-reported pain.

Tissue trauma can result in a reduction of the force-generating capability of muscle and alter neural recruitment patterns. It can cause swelling, pain, discoloration, and altered proprioceptive relays.[7] I work with a surface EMG model called Muscle Pattern Recognition (MPR) (MPR Health Systems, Inc., Culver City, CA) that assesses multiple ratios of recruitment patterns between pairs of different combinations of muscles during a series of defined movements. By comparing recruitment *patterns* against those of a normative database for identical movements, MPR has isolated regions of hypokinesia (weakness), hyperkinesia (spasm), and the compensating interactions between these regions as manifestations of muscle impairments.[8,9] Using this technology, we are now correlating subjects' regions of pain to their surface EMG patterns. No load, nonfatiguing, static end-of-motion postures eliminate effort or motivational contamination. Initial classification accuracy (1995 to 1996) was 88%.[8] Current specificity and sensitivity is 90%.

Ratio-metric mathematical analysis of muscle recruitment patterns is a scientifically validated procedure.[10,11] My colleagues and I strongly believe that surface EMG can appropriately assess muscle impairment. Our ongoing clinical experiences show impressive correlations to subjects' self-reported pain. I am disappointed that the Subcommittee did not review the articles cited above and that their conclusions did not consider objective measures of impairment. We feel ratiometric surface EMG analysis is an innovative and appropriate tool for assessing neck and back soft tissue injuries.

Alan J. Goldman, MD, *Santa Ana, CA*

To the Editor: We read with interest the report on the clinical utility of surface EMG.[1] We are delighted to have one of our articles[12] selected in this important review on the judgment on the reliability issue of using surface EMG in low back pain assessment. It is necessary to point out that the reliability results mentioned in the article by Pullman et al.[1] were from another article.[13] Furthermore, the Pearson's *r* value for median frequency slope was quoted as 0.39 to 0.55, which is based on one of the back muscles (iliocostalis lumborum) investigated. It should be pointed out that Pearson's *r* value of another muscle, multifidus (0.77 to 0.87) was not mentioned in the review article. Because the report will be treated as one of authoritative reference in the field of EMG investigation, we are in a position to make clear the above points to the readers of *Neurology*.

Joseph K.-F. Ng, MPhtySt, *Hong Kong;* Carolyn A. Richardson, PhD, Gwendolen A. Jull, MPhty, FACP, *Queensland, Australia*

To the Editor: In this review, Pullman et al.[1] report on the clinical utility of surface EMG in neuromuscular disorders, low back pain, and disorders of motor control.[1] Reviewing the literature, they conclude that surface EMG is unacceptable as a clinical tool in the diagnosis of neuromuscular disease and low back pain. They consider it acceptable for kinesiologic analysis of movement disorders; for differentiating types of tremor, myoclonus, and dystonia; and for evaluating gait and posture disturbances and psychophysical measures of reaction and movement time.

We fully agree that, at the current time, surface EMG is not established in clinical routine for diagnosing neuromuscular disorders. The authors apparently missed a point that we believe to be important. When comparing needle with surface EMG it is often disregarded that, although both methods look at electrophysiologic muscle activity, they see different things. Needle EMG (NEMG) records single MUAPs, whereas surface EMG records the interference pattern of multiple firing fibers. This provides important clues to muscle activity during exercise. There is yet another difference between NEMG and surface EMG, which we believe to be important: needle EMG can be interpreted without auxiliary tools, because the patterns are usually recognizable visually. To obtain conclusive data from surface EMG, sophisticated computer algorithms are necessary.[14] These introduce new linear and nonlinear variables, which are still poorly understood in their implications and clinical relevance.

Because it is noninvasive, surface EMG can be used to record electrophysiologic muscle activities during exercise.[15] This is not possible with needle EMG. In a recent study, we found totally different frequency characteristics in diaphragmatic surface EMG during fatiguing contractions before and after specific inspiratory muscle training.[16] We attributed this to changes in the central activation pattern rather than to fiber hypertrophy alone. Regarding diagnosis of neuromuscular diseases, Huppertz et al.[17] showed surface EMG and needle EMG to be of similar validity, using high spatial resolution surface EMG, a new and sophisticated recording and analysis technique.

We think that the development of new technologies in electrophysiology, e.g., for analyzing surface EMG, should be encouraged. Accepting modern computer-aided techniques will be inevitable. This will provide new variables to which we will have to become accustomed. With them, surface EMG will become an equal complementary rather than a rival tool of needle EMG.

H. Lahrmann, MD, MSc, U. Zifko, MD, W. Grisold, MD, *Vienna, Austria*

Reply from the Authors: We appreciate Dr. Silber's comments and agree that surface EMG is useful in the evaluation and diagnosis of sleep disorders. Sleep studies are important neurologic

tests that rely on multiple physiologic monitoring methods, of-which respiratory, extraocular, chin, and limb surface EMG are of paramount importance. Under the section on kinesiology and disorders of motor control, it was our intent to evaluate the many kinesiologic and noninvasive physiologic methods that legitimately utilize surface EMG. Although we did not specifically highlight sleep studies, we did mention the use of surface EMG for the measurement of breathing and tried to give representative examples of its use in the references, two of which related to sleep analyses.[18,19]

We find Dr. Goldman's comments interesting. We considered pain assessment a key issue and determined that pain and muscle fatigue or other quantifiable markers of muscle physiology are not clearly linked for many reasons. As stated in the TTA report,[1] muscle fatigue, spectral shifts in motor unit activity, and discriminant analyses at different levels of recruitment are variably affected by motivation, stress, muscle soreness malingering, and other biases.[20-22] These factors render surface EMG problematic and unreliable for assessing muscle impairment, much less so in correlation with pain.

We agree with Dr. Goldman's statement that surface EMG "reports nothing about pain" and therefore find his subsequent arguments difficult to understand. References 7–9 in his letter do not provide class I evidence or any additional information not covered in the TTA assessment on spectral changes and recruitment analysis. Reference 10 (a 1½ page abstract) reports on one monkey's changes in muscle recruitment patterns after space flight and has nothing to do with pain or muscle injury. Reference 11 (a study in a rat) notes that surface EMG amplitude changes modulate between different tasks with a hysteresis effect. No specific mention of "ratio-metric mathematical" analysis is offered in references 10 or 11, making it difficult for us to believe it is a clinically "scientifically validated" procedure.

Seth L. Pullman, MD, FRCPC, Douglas Goodin, MD,
Michael Rubin, MD, FRCPC

References

1. Pullman SL, Goodin DS, Marquinez AI, Tabbal S, Rubin M. Clinical utility of surface EMG. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2000;55:171–177.
2. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles, CA: Brain Information Service, Brain Research Institute, 1968.
3. Bonnet M, Carley D, Carskadon M, et al. EEG arousals: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992;15:173–184.
4. Olson EJ, Boeve BF, Silber MH. REM sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. Brain 2000;123: 331–339.
5. The Atlas Task Force. Recording and scoring leg movements. Sleep 1993;10:748–759.
6. Montplaisir J, Boucher S, Nicolas A, et al. Immobilization tests and periodic leg movements in sleep for the diagnosis of restless legs syndrome. Mov Disord 1998;13:324–329.
7. Herring SA. Rehabilitation of muscle injuries. Med Sci Sports Exerc 1990;22:453–456.
8. Edgerton VR, Wolf SL, Levendowski DJ, Roy RR. Evaluating patterns of EMG amplitudes for trunk and neck muscles of patients and controls. Int J Rehab Health 1996;2:1–18.
9. Edgerton VR, Wolf SL, Levendowski DJ, Jennich RI, Roy RR. EMG activity in neck and back muscles during selected static postures in adult males and females. Physiother Theory Pract 1997;13:179–195.
10. Hodgson JR, Bodine-Fowler SC, Roy RR, et al. Changes in recruitment of rhesus soleus and gastrocnemius muscles following a 14 day space flight. Physiologist 1991;34:102–113.
11. Hutchison DL, Roy RR, Hodgson JA, Edgerton VA. EMG amplitude relationships between cat soleus and medial gastrocnemius during various motor tasks. Brain Res 1989;502:223–244.
12. Ng JK-F, Richardson CA, Jull GA. Electromyographic amplitude and frequency changes in the iliocostalis lumborum and multifidus muscles during a trunk holding test. Phys Ther 1997;77:954–961.
13. Ng JK-F, Richardson CA. Reliability of electromyographic power spectral analysis of back muscle endurance in healthy subjects. Arch Phys Med Rehabil 1996;77:259–264.
14. Webber CL Jr, Schmidt MA, Walsh JM. Influence of isometric loading on biceps EMG dynamics as assessed by linear and nonlinear tools. J Appl Physiol 1995;78:814–822.
15. Yan K, Fang J, Shahani B. An assessment of motor unit discharge patterns in stroke patients using a surface electromyographic technique. Muscle Nerve 1998;21:946–947.
16. Lahrmann H, Wild M, Wanke T, Zwick H, Grisold W. Frequency spectrum of diaphragmatic surface EMG changes after training. Clin Neurophysiol 2000;11:8s.
17. Huppertz HJ, Disselhorst-Klug C, Silny J, Rau G, Heimann G. Diagnostic yield of noninvasive high spatial resolution electromyography in neuromuscular diseases. Muscle Nerve 1997;20:1360–1370.
18. Jeffries B, Brouillette RT, Hunt CE. Electromyographic study of some accessory muscles of respiration in children with obstructive sleep apnea. Am Rev Respir Dis 1984;129:696–702.
19. White JE, Drinnan MJ, Smithson AJ, Griffiths CJ, Gibson GJ. Respiratory muscle activity during rapid eye movement (REM) sleep in patients with chronic obstructive pulmonary disease. Thorax 1995;50: 376–382.
20. Abraham WM. Factors in delayed muscle soreness. Med Sci Sports 1977;9:11–20.
21. Bansevieius D, Westgaard RH, Jensen C. Mental stress of long duration: EMG activity, perceived tension, fatigue, and pain development in pain-free subjects. Headache 1997;37:499–510.
22. Biedermann HJ. Comments on the reliability of muscle activity comparisons in EMG biofeedback research with back pain patients. Biofeedback Self Regul 1984;9:451–458.

Diagnosis of Creutzfeldt–Jakob disease: Effect of clinical criteria on incidence estimates

Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt–Jakob disease

To the Editor: Brandel et al.[1] described the effect of different clinical criteria on incidence estimates for sporadic Creutzfeldt–Jakob disease (CJD): accepting either 14-3-3 protein positivity in CSF or an EEG showing periodic complexes as one of the criteria for suspected CJD in either the French or European criteria resulted in a slight increase in estimated incidence. They also compared test performance characteristics of different traditional diagnostic criteria for CJD, but did not compare modifications incorporating 14-3-3 protein results. Therefore, I analyzed the authors' results to calculate gain in diagnostic certainty and other performance characteristics[2,3] attributable to incorporation of 14-3-3 protein results into the French or European criteria for probable CJD (additional information can be found on the *Neurology* Web site; go to www.neurology.org). Inclusion of 14-3-3 protein results improved sensitivity, without a loss of specificity, for both the French and European criteria. Because the false negative rate decreased markedly, both the predictive value of a negative test and gain in diagnostic certainty for a negative test improved significantly.

I evaluated two possible further modifications of the criteria, which differ in the weight given to the 14-3-3 protein results: in one, 14-3-3 protein results are considered to be of equal importance to the combination of typical EEG findings *plus* at least two of four specified clinical features, whereas in the other, 14-3-3 protein results replace the previous requirements for typical EEG results plus at least two of four clinical features. Both performed better in this sample than either the original criteria or the previous modification incorporating 14-3-3 protein results (additional information can be found on the *Neurology* Web site; go to www.neurology.org). The excellent estimated performance of the second variation is undoubtedly overestimated, because it is dependent in part on the observed perfect specificity of the 14-3-3 protein assay, which has not been the case in other samples. The point is not to suggest a specific modification, but to indicate that various modifications of existing criteria are possible, and that different modifications incorporating CSF 14-3-3 protein results may produce different performance characteristics.

The article by Zerr et al.[4] suggests a specific modification of CJD criteria. However, the modification presented is confusing, as it appears to suggest that both periodic complexes on EEG and 14-3-3 proteins in CSF are required for a diagnosis of probable CJD (see the Appendix). This was presumably not the authors' intention because they state that sensitivity was improved. To increase sensitivity, criteria have to be made more inclusive rather than more exclusive. Requiring both periodic complexes on EEG and 14-3-3 proteins in CSF for a diagnosis of probable CJD could increase specificity, but would not increase sensitivity (as

confirmed in the authors' table 3). Suggested amended criteria are listed (see the Appendix).

Further studies are needed to evaluate and verify the performance of clinical diagnostic criteria for CJD incorporating 14-3-3 protein results. Nevertheless, it appears that the incorporation of 14-3-3 protein results into clinical diagnostic criteria for probable CJD can significantly improve performance characteristics. Other modifications may produce further improvements.

Douglas J. Lanska, MD, MS, MSPH, *Tomah, WI*

Reply from the Authors: Dr. Lanska discusses the impact of inclusion of 14-3-3 protein test on the clinical diagnostic criteria for probable CJD. The inclusion of 14-3-3 test into the clinical diagnosis of CJD was shown to improve the sensitivity of the clinical diagnosis and to have an impact on incidence estimates for sporadic CJD.[4,5] Our study has shown that in the differential diagnosis of CJD, the sensitivity and specificity of the detection of 14-3-3 proteins in the CSF is higher (94% and 84%) than using the detection of periodic sharp- and slow-wave complexes (PSWC) in EEG (sensitivity 66%, specificity 74%). Because the 14-3-3 test is not available in many countries at the moment, it seems not feasible to use this test only for the diagnosis of probable CJD, but we suggest including the 14-3-3 test into the diagnostic criteria for CJD in addition to EEG. Based on our analysis, the diagnosis of probable CJD requires a combination of neurologic signs and either the detection of PSWC in EEG or 14-3-3 proteins in the CSF. It seems that Dr. Lanska misinterpreted this message. Our analysis was based on the data from the European CJD surveillance study, and previously established diagnostic criteria by Masters et al.[6] were used in this surveillance system. The duration of dementia was not limited by these criteria. The European study group agreed to limit the disease duration for the diagnosis of possible CJD in order to exclude other neurodegenerative diseases from this diagnostic category. Our analysis was based on data collected in the framework of this study. In our study, we could show patients with the clinical diagnosis of possible CJD (duration less than 2 years and two of four clinical features), who had detectable 14-3-3 levels in the CSF, in fact had CJD. The modification of the criteria was the upgrading of the possible cases with 14-3-3 in the CSF to the category probable. Based on the data analyzed in our study, the limitation of the duration of dementia for those patients who had 14-3-3 proteins in the CSF was unavoidable. There are no data at the moment to perform a further modification as proposed by Dr. Lanska, but surely there is need to conduct further studies to simplify the criteria.

Inga Zerr, MD, Sigrid Poser, MD, *Göttingen, Germany*

Appendix

Modified diagnostic criteria for sporadic probable Creutzfeldt–Jakob disease

Zerr et al.

Progressive dementia with at least two of four clinical features:

1. Myoclonus
2. Visual or cerebellar signs
3. Pyramidal or extrapyramidal signs
4. Akinetic mutism

Periodic sharp and slow-wave complexes in EEG
14-3-3 proteins in CSF and duration of <2 years

Suggested amended criteria, Lanska

Progressive dementia with duration <2 years
At least two of four clinical features:

1. Myoclonus
2. Visual or cerebellar signs
3. Pyramidal or extrapyramidal signs
4. Akinetic mutism

At least one of two laboratory features:

1. Periodic sharp and slow-wave complexes in EEG
2. 14-3-3 proteins in CSF

Additional material related to this letter can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the May 22 issue to find the title link for this article.

References

1. Brandel J-P, Delasnerie–Lauprêtre N, Laplanche J-L, Hauw J-J, Alpérovitch A. Diagnosis of Creutzfeldt–Jakob disease: effect of clinical criteria on incidence estimates. Neurology 2000;54:1095–1099.
2. Connell FA, Koepsell TD. Measures of gain in certainty from a diagnostic test. Am J Epidemiol 1985;121:744–753.
3. Lanska DJ. Diagnosis of thymoma in myasthenics using anti-striated muscle antibodies: predictive value and gain in diagnostic certainty. Neurology 1991;41:520–525.
4. Zerr I, Pocchiari M, Collins S, et al. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt–Jakob disease. Neurology 2000;55:811–815.
5. Budka H, Aguzzi A, Brown P, et al. Neuropathological diagnostic criteria for Creutzfeldt–Jakob disease (CJD) and other human spongiform encephalopathies (prior diseases). Brain Pathol 1995;5:459–466.
6. Masters CL, Harris JO, Gajdusek DG, Gibbs CJJ, Bernoulli C, Asher DM. Creutzfeldt–Jakob disease: patterns of worldwide occurrence and significance of familial and sporadic clustering. Ann Neurol 1979;5:177–188.

Onset seizures independently predict poor outcome after subarachnoid hemorrhage

To the Editor: Butzkueven et al.[1] report that seizures at the onset of subarachnoid hemorrhage are a predictor of poor outcome. Their definition of the seizure was ". . . repetitive rhythmic jerking, with or without preceding tonic spasm . . . with or without loss of consciousness. These were usually described by relatives, ambulance personnel, nurses, or doctors."

We raise the possibility that some of the reported seizure activity was repetitive or fragmentary extensor posturing mistaken for seizures by physicians or other health care providers. We have observed this in our own practice on several occasions and it is also described in the emergency medicine literature.[2] Medical personnel must keep in mind that all abrupt motor activities in the presence of a neurologic disorder or injury do not represent seizure activity. The presence of extensor ("decerebrate") posturing in acute subarachnoid hemorrhage has been shown to correlate with a worse outcome.

J. Stephen Huff, MD, Andrew D. Perron, MD, *Charlottesville, VA*

Reply from the Author: Drs. Huff and Perron raise the question of misclassification of extensor posturing as a seizure in patients with a subarachnoid hemorrhage. We were aware of this important point. Our case ascertainment was based on chart review, and this method is clearly limited by the clarity of the description in the notes. We do, however, feel that the misclassification rate was low because identified putative seizure records were reviewed by three of the authors, one of whom is an epileptologist. The onset seizure rate in our subarachnoid hemorrhage cohort was 7.8%, which is in the middle of the range of previously reported incidence figures (4 to 16%).[3,4] Extensor posturing is most likely to occur in patients with low Glasgow Coma Scale (GCS) scores, but we did not find any association between onset seizure and either GCS score or duration of loss of consciousness. Only nine of our 32 patients with onset seizure had a GCS score of less than 10. It is for this reason that the multivariate regression statistic was able to identify onset seizure as a risk factor for poor prognosis independent of the GCS score. Furthermore, onset seizures were found to be an independent, strong risk factor for later seizures, but initial GCS score was not.[1] If the original events had been misclassified, this would be a most unlikely result.

Helmut Butzkueven, FRACP, *Melbourne, Australia*

References

1. Butzkueven H, Evans AH, Pitman A, et al. Onset seizures independently predict poor outcome after subarachnoid hemorrhage. Neurology 2000; 55:1315–1320.

2. Haines SJ. Decerebrate posturing misinterpreted as seizure activity. Am J Emerg Med 1988;6:173–177.
3. Sundram MB, Chow F. Seizures associated with spontaneous subarachnoid hemorrhage. Can J Neurol Sci 1986;13:229–231.
4. Hasan D, Schonk RSM, Avezaat CJJ, Tanghe HLJ, van Gijn J, van der Lugt PJM. Epileptic seizures after subarachnoid hemorrhage. Ann Neurol 1993;33:286–291.

The Goltz–Ferrier debates and the triumph of cerebral localizationist theory

To the Editor: I read with interest the article by Tyler and Malessa.[1] It must be emphasized that the concept of "localization" so aptly presented by Ferrier not only served as an impetus to neurosurgical and neurologic diagnosis and treatment, but also placed in a dark shadow the fact that the brain can adapt to and recover from major injury. Functional MRI has provided striking evidence that a variety of behaviors can be maintained despite brain injury resulting from cerebral infarction and other causes.

The classical studies by Ramon y Cajal of the CNS response to injury cast in the stone the belief that the CNS is incapable of recovering from injury. This concept has had a crippling effect on research in neurorehabilitation, and we are just now recovering from many years of indifference by neurologists.

Unfortunately, the "phenomenon of restitution" supported by Goltz was also cast into the background as the concept for cortical localization presented by Ferrier was accepted. In the 21st century, the ability of the brain to recover from injury by reorganizing itself and even generating new cells will be disclosed.

Jack H. Petajan, MD, PhD, *Salt Lake City, UT*

Reply from the Authors: We appreciate Dr. Petajan's interest in our recent article.[1] From a modern perspective, it is clear that localizationist and holistic views should be considered complementary rather than antagonistic approaches to understanding brain function. Localizationist theory paved the way for the development of modern neurosurgery, and we continue to use many of its tenets in the clinical arena on a daily basis. The meticulous neurohistologic studies of Ramon Y Cajal were instrumental in the establishment of the "neuron doctrine."[2] The idea that neurons formed the fundamental and discrete cytologic units of the CNS, as opposed to being part of a vast interconnected reticulum or net, provided additional scientific support for conceptions of a hard-wired nervous system that might some day be deciphered as easily as an electrical circuit diagram. Despite its obvious utility, the limits of localizationist theory for truly understanding brain function was apparent to such astute 19th and early 20th century clinicians as Hughlings Jackson, Henry Head, and Pierre Marie. The work of Karl Lashley and Kurt Goldstein made it apparent that strict localizationism was particularly deficient in explaining many disorders of higher cognitive function (reviewed in Finger[3]). At the same time, modern research in neuroscience has expanded dramatically on the seminal studies by Ramon y Cajal of degeneration and regeneration in the nervous system, and has revealed a degree of neuronal plasticity that would have amazed Ramon y Cajal. It is however, patently unfair to state that Ramon y Cajal cast in stone the belief that the CNS is incapable of recovering from injury. Even a cursory reading of his magnum opus on degeneration and regeneration of the nervous system[4] reveals his interest in identifying and circumventing factors that limited effective regeneration in the CNS. The capacity of neurons to alter aspects of their function, chemical profile, and structure is now an essential component of modern theories of learning and memory, pain, epileptogenesis, and restitution of function following neural injury. New neuroimaging techniques have provided us with wonderful tools to visualize the complex and wonderfully choreographed interplay between diverse brain regions in the integrative action of the nervous system. I can only hope, like Dr. Petajan, that these discoveries will yield wonderful fruit as they make their way into practical application in the field of neurorehabilitation.

Kenneth L. Tyler, MD, *Denver, CO*

References

1. Tyler KL, Malessa R. The Goltz–Ferrier debates and the triumph of cerebral localizationist theory. Neurology 2000;55:1015–1024.
2. Shepherd G. Foundations of the neuron doctrine. New York, NY: Oxford University Press, 1991.
3. Finger S. Holism and the critics of cortical localization. In: Origins of neuroscience, New York, NY: Oxford University Press, 1994:51–62.
4. Ramon y Cajal S. Degeneration and regeneration of the nervous system [May RM, translator]. London, UK: Oxford University Press & Humphrey Milford, 1928.

Exacerbation of juvenile myoclonic epilepsy with lamotrigine

To the Editor: Biraben et al.[1] reported seven patients with juvenile myoclonic epilepsy (JME) myoclonus exacerbated by treatment with lamotrigine (LTG), four of whom were taking LTG monotherapy. As a result of this observation, they raised concerns about the rationale of using LTG in the treatment of JME.

Because of possible weight gain, hair loss, and menstrual irregularities with valproic acid (VPA) treatment,[2] we have used LTG as a first-line therapy in women with JME. Our positive experience with the drug contrasts that reported by Biraben et al.

Retrospectively, 24 patients with an established diagnosis of JME were identified. Diagnosis was established by clinical history of sporadic generalized tonic-clonic (GTC) seizures, morning myoclonic jerks, and an EEG with generalized 3 to 4 Hz polyspike, slow-wave complexes. The age range was from 15 to 53 years, with a mean of 32 years. Twenty-one of the 24 patients were women. Patients had been taking LTG therapy for an average of 23 months, ranging from 9 to 37 months. The mean dosage was 310 mg/d, ranging from 150 to 600 mg/d. In most patients, the target dosage was empirically set at 300 mg/d, with some patients requiring higher doses to achieve seizure or myoclonus control. Lower doses were kept in case of adverse effects.

Only two of the 24 patients (8.33%) developed a dramatic exacerbation of myoclonus, leading to LTG therapy discontinuation. An additional two patients had a mild increase in morning myoclonus, but it was tolerable and transient (<2 months' duration). Other adverse effects included mild anxiety (4/24), mild transient rash (2/24) (which was managed by dose reduction), and dizziness (1/24).

Seizure control was excellent (seizure free) in 21/24 patients, and sporadic GTC seizures continued in 2/24 patients. In one patient, the occurrence of sporadic seizures was attributed to poor compliance with therapy.

Other investigators have reported similar positive experience with the use of LTG for treatment of JME.[3,4] The differences in the reported experience with LTG in JME may be due to a recruitment bias. Biraben et al.[1] mentioned that their patients were likely medication resistant, referred to a tertiary center; whereas in our center we see a more balanced population in terms of the spectrum of seizure severity.

We agree that further studies are needed to establish the degree of efficacy and tolerability of LTG in the treatment of JME patients. We believe that in light of certain side effects that VPA treatment presents to the female patient, LTG should be considered as an alternate option. Our experience suggest that exacerbation of myoclonus is seen in a small number of patients.

Enrique J. Carrazana, MD, Steve D. Wheeler, MD, *Miami, FL*

Reply from the Authors: The interesting letter by Carrazana and Wheeler on the use of LTG in JME indicates the efficacy of this antiepileptic drug in certain forms of the disease, a finding also reported by Buchanan.[4] This observation is not in contradiction with the exacerbation it caused in our patients because JME is most certainly a heterogeneous entity. Firstly, it is known that a variable percentage of patients with JME do not respond to VPA. Fernando–Dongas et al.[5] suggested that these patients could have partial epilepsy. Secondly, in certain patients, neuropsychological tests demonstrate a frontal dysfunction not found in others.[6] Finally, from a genetic point of view, two disease-related loci have been identified on two different chromosomes: 6 and 15.[7,8] Our patients were referred to a tertiary center because of their difficult management, and thus might constitute a particular subgroup of JME; this particular phenotype might also be more frequent in our recruitment. Keeping in mind this variability, and

owing to the fact that no simple test has been developed to identify these patients, we believe it most important to emphasize the need for utmost prudence when using LTG in patients with JME.

A. Biraben, MD, H. Allain, MD, PhD, J.-M. Scarabin, MD, S. Schück, MD, G. Edan, MD, *Rennes, France*

References

1. Biraben A, Allain H, Scarabin JM, Schück S, Edan G. Exacerbation of juvenile myoclonic epilepsy with lamotrigine. Neurology 2000;55:1758.
2. Isojarvi JIT, Laatikainen TJ, Pakarinen AJ, Juntunen KT, Myllyla VV. Obesity and endocrine disorders in women taking valproate for epilepsy. Ann Neurol 1996;39:579–584.
3. Timmings PL, Richens A. Efficacy of lamotrigine as monotherapy for juvenile myoclonic epilepsy. Epilepsia 1993;34(suppl 2):160.
4. Buchanan N. The use of lamotrigine in juvenile myoclonic epilepsy. Seizure 1996;5:149–151.
5. Fernando–Dongas M, Radtke R, VanLandingham K, Husain A. Characteristics of valproic acid resistant juvenile myoclonic epilepsy. Seizure 2000;9:385–388.
6. Devinsky O, Gershengorn J, Brown E, Perrine K, Vazquez B, Luciano D. Frontal functions in juvenile myoclonic epilepsy. Neuropsychiatry Neuropsychol Behav Neurol 1997;10:243–246.
7. Durner M, Sander T, Greenberg D, Johnson K, Beck–Mannagetta G, Janz D. Localization of idiopathic generalized epilepsy on chromosome 6p in families of juvenile myoclonic epilepsy patients. Neurology 1991;41:1651–1655.
8. Elmslie F, Rees F, Williamson M, et al. Genetic mapping of a major susceptibility locus for juvenile myoclonic epilepsy on chromosome 15q. Hum Mol Genet 1997;6:1329–1334.

Correction

Chenodeoxycholic treatment of cerebrotendinous xanthomatosis
The reply to the letter "Chenodeoxycholic treatment of cerebrotendinous xanthomatosis" by Samenuk et al. (*Neurology* 2001;56:695–696) was erroneously listed as a "Reply from the Authors." Dr. Gerald Salen, who authored the reply, was not an author of the original article but is a professor of medicine at the GI Research Laboratory, VA Medical Center, East Orange, NJ.