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NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

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Neuroscience Today: Early Education Tomorrow?

ABSTRACTS & COMMENTARY

Sources: Gould E, et al. Learning enhances adult neurogenesis in the hippocampal formation. *Nat Neurosci* 1999;2:260-265. van Praag H, et al. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* 1999;2:266-270. Eriksson PS, et al. Neurogenesis in the adult human hippocampus. *Nat Med* 1998;4:1313-1317. Wickelgren I. Nurture helps mold able minds. *Science* 1999;283:1832-1834.

New remarkable findings in basic neuroscience promise future opportunities to treat damaged brains and lengthen the life of the chronically stimulated ones (McKay RD. *Nat Med* 1999;5:261-262). Until a few years ago, neuroscience dogma had clung to the principle that human, postnatal brains could not generate new neurons, much less accept neuronal transplants. Between 1975-1985, evidence that the human olfactory receptor system turned over its neurons at a rate of about two weeks was almost completely ignored (Kaplan MS, Hinds JW. *Science* 1977;197:1092-1094). Similar inattention was directed at observations made by McKay that premordial granular cells in the cerebellum and the hippocampus apparently generated new neurons in experimental mammals. The success of transplanting fetal nigral cells from human fetuses into Parkinsonian striatums broke the ice of wide ignorance, but only recently has the evidence proved that:

1) continuous hippocampal neurogenesis occurs normally throughout human life;

2) neurogenesis increases in nonprimate animals at a rate greatly accelerated by optimal environments and stimulating the species by appropriate problem-solving tasks;

3) the human brain contains stem cells that have the capacity not only to generate progenitor central nervous system neurons but, given the appropriate environment, hematopoeitic cells as well (McKay).

Gould and associates (*Proc Natl Acad Sci USA* 1998;95:3168-3171) have identified newly produced hippocampal cells in monkeys and, most recently, van Praag and associates from the Sahlgrenska Hospital in Goteborg, Sweden, along with Eriksson and associates from Fred Gage's laboratory at the Salk Institute, have made a similar

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discovery in humans. The Gould et al primate study brings out evidence that granular precursor cells in the dentate gyrus of the hippocampus constantly and normally produce new mature neurons at a relatively steady state. Neurogenesis and differentiation of neurons measurably declined, however, when the animals were exposed to regulated degrees of acute psychosocial stress (similar responses to stress have been identified in hippocampal regions in rodents). Eriksson et al describe findings in five humans dying of cancer who were free of severe brain disease, but steadily generated new hippocampal granular neurons. Evidence is that hippocampus neurogenesis is not related to those patients because of their cancer; rather, the cohort was chosen because at present neurogenesis can only be identified by scheduled future brain biopsy or permission for autopsy within a few years.

The technical approach for identifying the above depends on marking granulomatous stem cells in the hippocampus with the stable thymidine analog, bromodeoxyuridine (BrdU). The BrdU enters the DNA of hippocampal stem cells that subsequently divide into neurons carrying permanent DNA markers. Such cells can be identified almost indefinitely throughout the recipient's natural life. Eriksson et al's paradigm consisted of infusing BrdU into five patients with malignant systemic cancers, none of whom showed evidence of involvement of the brain. The patients were expected to die within a measurable time, which actually ranged from 16-781 days following systemic BrdU injection. Intensity of stained (progeny) neurons was greatest in patients dying at 16 and 136 days after injection, but the other three also demonstrated newly engendered hippocampal neurons, the latest being 781 days after the initial injection. The subventricular zone adjacent to the caudate nucleus did not generate BrdU neurons, but did generate round-to-oval progenitor neurons, presumably as the cells migrated closer to the olfactory system.

Although not conducted in humans, the two index articles by van Pragg et al and Gould et al report that hippocampal neurogenesis as much as doubled in rodents put to enriching or associative-learning tasks. Presumably, the increased neuronal numbers contributed to the memory of the rewards gained by learned activity.

In an additional report by Young and associates (Young D, et al. *Nat Med* 1999;5:448-453), they report that rodents, a species that has consistently anticipated the finding of brain regeneration in higher mammals, reduce potential apoptosis in post-traumatic hippocampus when enriched by environment in situ neurogenesis depends.

COMMENTARY

These experimental findings in the hippocampus of lower level mammals and humans imply that this structure normally generates throughout adult life new granular neurons that may closely contribute to processed learning and memory. Furthermore, evidence gained from trained rodents suggests that stimulating the animal accelerates the genesis of new cells and new memories, and also may reduce traumatic induced apoptosis. Carrying such a possibility into clinical action, these favorable events especially occur in young animals. A "News Focus" article in *Science* by Ingrid Wickelgren reports that underprivileged children who receive systematic lessons in language and enrichment in complex problems suitable to their age (i.e., as young as 6 months) later attain IQ values far higher than those possessed by their parents as well as by other neighborhood children. The report provides evidence from many other sources which indicate that the younger children start and the more persistently that they are taught appreciably raises their later intelligence. This conclusion suggests that early, sustained stimulation of an infant's/child's hippocampus, the smarter and more capable their futures are likely to be. Only a few months ago, *Neurology Alert* (Plum F. *Neurol Alert* 1998;16:94-95) abstracted a study from *Neurology* (De Ronchi D, et al. *Neurology* 1998;50:1231-1238) that linked early senile dementia to a lack of sufficient childhood education to gain literacy. Hopefully, knowing the scientific data abstracted in

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these present reports may stimulate neurologists to lead their communities to emphasize the value of environmental and educational programs for all children aged 2 years or older. It appears that such a step will pay off with enriching hippocampal activity, thereby reducing the number of unemployed or the incidence of late dementia in the society. Who knows, such early teaching of the child's mind might reduce its seeming intoxications with violence. **—fp**

Aphasiology

ABSTRACTS & COMMENTARY

Sources: Thulborn KR, et al. Plasticity of language-related brain function during recovery from stroke. *Stroke* 1999;30: 749-754; Heiss W-D, et al. Differential capacity of left and right hemispheric areas for compensation of poststroke aphasia. *Ann Neurol* 1999;45:430-438.

Functional brain imaging techniques are helping to advance our knowledge of the brain's language networks and are providing new insights into the surprising degree of plasticity the brain sometimes demonstrates after damage to its eloquent areas.

Thulborn and colleagues used anatomic, metabolic, and functional magnetic resonance imaging (fMRI) techniques to study two patients with aphasia who ultimately recovered a significant degree of language function. One 45-year-old right-handed man suffered a dense expressive aphasia secondary to a left middle cerebral artery infarct. The other, a 34-year-old right-hander, awoke from epilepsy surgery with a severe receptive aphasia despite intraoperative electrocorticographic localization of Wernicke's area 2 cm from the site of resection. These patients were compared to six healthy right-handed control subjects who underwent fMRI activation during a sentence reading and comprehension task. The recovery of language in the patient with expressive aphasia was paralleled by an increasing degree of activation of the right-sided homolog of Broca's area, with continued left-sided dominance of Wernicke's area. The partial resolution of the other patient's receptive aphasia was associated with right-sided dominance of activation in Wernicke's area. The apparent redistribution of function to the right hemisphere in these two cases began within days of the injurious events and continued over the subsequent several months. In light of these findings, Thulborn et al assert that functional neuroimaging may be essential in testing the efficacy of stroke interventions, in order to distinguish apparent therapeutic efficacy from spontaneous mechanisms of recovery.

Results similar to the above were obtained by a team of German researchers, Heiss and colleagues, who carried out cerebral blood flow activation studies using positron emission tomography (PET) in 23 right-handed aphasic stroke patients and 11 normal controls. The infarct site was frontal in seven cases, temporal in seven, and subcortical in nine patients. Subjects were asked to perform a word repetition task during PET scans carried out two and eight weeks after the stroke in the aphasic group. Aphasics who could not comply with the task demands were excluded. Analysis of task-related blood flow changes was performed, focusing on 14 regions in the left and right hemispheres with speech-related functions. Aphasics with frontal and subcortical strokes improved substantially, while patients with temporal infarcts improved less. As in the case of the expressive aphasic studied by Thulborn et al, recovery in the frontal and subcortical groups associated with language-related activation of the right inferior frontal gyrus and left superior temporal gyrus. Patients with temporal lobe strokes improved only in their word comprehension ability and showed activation of the right superior temporal gyrus and left-sided Broca's area. Heiss et al conclude that right hemisphere language structures play an important role in recovering language after stroke, and preserving and/or reintegrating Wernicke's area is essential to recover language after left temporal lobe infarction.

COMMENTARY

These studies by Thulborn et al and Heiss et al used quite different functional brain imaging methods, but yielded remarkably similar results concerning the role of the right hemisphere in recovery from aphasia. The serial nature of the observations and the temporal association between recovery of language and recruitment-specific subregions of the right hemisphere provide some of the most convincing evidence to date that reorganization of functional language networks begins within days of a stroke and continues for months following the acute brain injury.

The inference by Heiss et al that the integrity of Wernicke's area is the critical determinant of the degree of recovery of language after stroke is not proven by their data. The inclusion criteria used by Heiss et al preclude drawing such conclusions, since they excluded patients who were initially unable to perform the word repetition task satisfactorily, thereby creating a selection bias relating to severity of the aphasia. It would be more prudent to conclude that location of stroke, not simply infarct volume, influences the extent of recovery of language function after stroke.

The assertion by Thulborn et al that functional brain imaging is essential to testing putative stroke interventions is debatable. Although brain imaging is likely to play an important role in assessing the efficacy of future neuroprotective and thrombolytic therapies, good study design should permit medication effects to be distinguished from spontaneous recovery without necessarily resorting to the expense and technical difficulty of obtaining functional brain images. There are many other potential applications for the paradigms used in these studies, however, particularly in the context of neurosurgical planning for epilepsy and brain tumor surgery. **—nr**

Post-Whiplash Pain

ABSTRACT & COMMENTARY

Source: Obelieniene D, et al. Pain after whiplash: A prospective controlled inception cohort study. *J Neurol Neurosurg Psychiatry* 1999;66:279-283.

Whiplash injury, a condition almost always reflecting an acute neck muscle sprain, carries in most western European and North American countries a measurable risk of chronic disability characterized by neck pain, emotional disturbance, and financial litigation. In Lithuania, an impoverished Baltic country of about 3.5 million functioning under the shadow of Russia, a different response is encountered.

Schrader and colleagues, from Lithuania, reported in the *Lancet* (Schrader H, et al. *Lancet* 1996;347:1207-1211; Plum F. *Neurol Alert* 1996;14:92-93) the results of a historically conducted study of 202 persons with presumed whiplash recorded on police records of rear-end automobile crashes. The cohort reported no greater incidence of chronic head or neck pain when compared to a randomly identified control group. The same investigators, headed by Obelieniene, now report the results of a more recent prospective study of 210 persons involved in rear-end car accidents. They compared the injured against 210 persons randomly chosen and free of injuries. The subject groups were matched for age, gender, and a variety of education and/or employment patterns. Average collision speed of the damaging car was estimated at about 25 mph. Questionnaires were obtained on subjects following the accident on an average of 7 days, 2 months, and 1 year for all whiplash persons. Controls answered at the first and last question time. Participation was, remarkably, 94% in the injured and 92% in the controls. Ninety-eight (47%) of the injured group described either headache, neck pain, or both. Among the injured, no neck pain lasted more than 17 days (median 3 days) and no headache lasted more than 20 days (median 4.5 hours).

At the time of one year follow-up, no difference in symptoms or employment separated the accident cohort from the controls in incidence of headache, neck pain, or both. Obelieniene et al conclude, "In a country where there is no preconceived notion of chronic pain...symptoms after an acute whiplash are self-limiting (and) brief." **—fp**

The Neurology of Neurofibromatosis

ABSTRACT & COMMENTARY

Source: Creange A, et al. Neurological complications of neurofibromatosis type 1 in adulthood. *Brain* 1999;122:473-481.

Between 1995 and 1997, prospective evaluation of 158 neurofibromatosis type 1 (NF1) patients (138 persons > 18 years, 20 children) was performed to determine the neurologic morbidity and prognosis of NF1 in adults. Diagnosis was established using NIH criteria and required two or more of the following characteristics, including: 1) six or more cafe-au-lait spots; 2) two or more neurofibromas or one plexiform neurofibroma; 3) axillary or inguinal freckling; 4) optic pathway tumor; 5) two or more Lisch nodules [pigmented iris hamartomas]; 6) distinctive osseous lesions (e.g., sphenoid dysplasia); or 7) a first-degree relative with NF1 (*Arch Neurol* 1988;45:575-578).

Overall, 55% (n = 87) demonstrated one or more neurological complications, most frequently headache (18%), followed by optic pathway tumor (12.6%). Hydrocephalus (usually due to idiopathic aqueductal stenosis), epilepsy (cryptogenic, or secondary to subdural hematoma, meningioma, or hamartoma in one each), or malignant peripheral nerve sheath tumor (the only neurological cause of death in this series) was seen in approximately 4% each, whereas cerebral tumor (glioma or meningioma) and intraspinal neurofibroma were seen in roughly 3% and 2%, respectively. Two adults had a meningocele and one each had a lacunar infarct (aged 19 years) and progressive spastic paraparesis (onset at age 35 years). Significantly, no adult patient required treatment for optic pathway tumor or brainstem glioma due to their nonprogressive nature, suggesting that repetitive ophthalmological and neurological examinations, rather

than neuroimaging studies, may be effective in the follow-up care of these patients. Furthermore, other than four malignant peripheral nerve sheath tumors and one meningioma, life-threatening complications occurred only during childhood, again mitigating the perceived need for frequent radiologic imaging in NF1 adults.

COMMENTARY

Most correctly identified with Quasimoto, the Hunchback of Notre Dame, and incorrectly with John Merrick, the Elephant Man (who probably had an unrelated disorder termed hemihypertrophy-nevi-hamartoma, or Proteus syndrome, named for the Greek god with protean guises), NF1, peripheral NF, or von Recklinghausen syndrome, should perhaps be more rightfully identified with the teacher (Rudolf Virchow) than the pupil (Tibbles JR, Cohen MM. *BMJ* 1986;293:683-685; Morse RP. *Arch Neurol* 1999;56:364-365). Dominantly inherited and traced to a gene at chromosome 17q11.2 coding for neurofibromin, this protein is a modulator of Ras-mediated signal transduction, specifically p21ras, a growth-stimulating protein, suggesting that one of neurofibromin's functions is to suppress tumor growth. Ras activity, controlled by a regulated GDP/GTP cycle, mediates its proliferative effects by activating a cascade of kinases including Raf, MEK, and ERK1/2, and responds to diverse stimuli, including peptide growth factors, cytokines, and hormones (Vojtek AB, et al. *J Biol Chem* 1998;273:1925-1928). Mutations that activate Ras are present in an estimated 30% of all tumors, most frequently lung, colon, thyroid, and pancreatic carcinomas, but even this may be an underestimation of its role in human malignancy, as mutation is unnecessary for chronic Ras upregulation (Clark GJ, Der CJ. In: Dickey BF, Birnbaumer L, eds. *GTPases in Biology*. Berlin: Springer Verlag; 1993:259-288). Up to half of NF1 cases are due to spontaneous new mutations, usually paternal in origin, with a mutation rate 100 times greater than other genes, and with deletions, point mutations, and insertions all described (Jadayel D, et al. *Nature* 1990;343:558-559; Wallace MR, et al. *Nature* 1991;353:864-866; Wu BU, et al. *Am J Med Genet* 1995;59:528-535). NF1 demonstrates variable expressivity both between families and within families but its penetrance is 100% after age 5 years. Presently, recommendations of the American Academy of Pediatrics include annual physical and eye examinations during the school years including blood pressure measurements, a preschool audiologic evaluation, and careful follow-up to monitor for the development of scoliosis, rapid enlargement, or pain due to neurofibromas (Committee on Genetics, AAP. *Pediatrics* 1995;96:368-372).

NF2 or acoustic NF, diagnosed either by the presence of bilateral vestibular schwannomas or by unilateral schwannoma and a first degree relative with NF2, is due to mutation at chromosome 22q12.2, resulting in inactivation of the gene for neurofibromin 2, termed schwannomin, or "merlin" for the first letters of moesin-, ezrin-, and radixin-like proteins, which share significant homology to the NF2 gene product, and adding -in for protein (Trofatter JA, et al. *Cell* 1993;72:1-20). Merlin, a novel member of the ERM (ezrin, radixin, moesin) family of actin-associated, cytoskeleton-membrane linker proteins, inhibits cell growth when overexpressed in cell lines and, thus, may also act as a tumor suppressor, possibly by altering cytoskeletal function by interfering with F-actin organization, cell spreading, and cell attachment (Gutmann DH, et al. *Hum Mol Genet* 1999;8:267-275).

Molecular testing for NF2 is recommended for all persons at risk and, if positive, baseline MRI of the entire neuraxis with follow-up imaging every three years if initially negative (Harsh GR, et al. *Arch Otolaryngol Head Neck Surg* 1995;121:590-591). Mutation analysis is available for both NF1 and NF2, with a 70% and 60% detection rate, respectively, in known familial cases, but DNA testing is not useful for the isolated NF1 or NF2 patient with no detectable mutation (Karnes PM. *Mayo Clin Proc* 1998;73:1071-1076). Clinical screening of family members is necessary in these instances. Prenatal diagnosis is possible by linkage analysis only in the presence of several affected family members.

Other variants of neurofibromatosis have been proposed, including NF3 (overlapping NF1 and NF2), NF5 (segmental NF involving the midline and one arm but sparing head and neck structures), NF6 (cafe-au-lait spots only), and NF7 (late onset NF) but these have not been definitively recognized and their molecular biology is not well understood. **—mr**

The Hyperdense MCA Sign on CT Revisited

ABSTRACT & COMMENTARY

Source: Manelfe C, et al. Association of hyperdense middle cerebral artery sign with clinical outcome in patients treated with tissue plasminogen activator. *Stroke* 1999;30:769-772.

A hyperdense middle cerebral artery (mca) on CT scan was first identified as a marker of thrombus in the MCA in 1983 (Gacs G, et al. *Stroke* 1983;14:756-762). Although the hyperdense MCA sign

has a high specificity for MCA occlusion, its sensitivity is low, and false positive signs, usually bilateral, have been noted in patients with calcific atherosclerotic cerebrovascular disease or a high hematocrit (Tomsick TA, et al. *Neuroradiology* 1989;31:312-315). Previous studies have associated the hyperdense MCA sign with severe neurological deficit and poor clinical outcome, but the number of patients has been small (Moulin T, et al. *Neurology* 1996;47:366-375).

The present study was aimed at determining the frequency of the hyperdense MCA sign, its association with stroke severity and early ischemic changes on CT, its relevance to clinical outcome, and the efficacy of intravenous (IV) recombinant tissue plasminogen activator (rtPA) in stroke patients with this radiologic sign.

Manelfe and colleagues analyzed data from more than 600 patients who received either rtPA or placebo in the ECASS I trial (Hacke W, et al. *JAMA* 1995;274:1017-1025). CT scans were obtained within six hours from onset of symptoms. Functional outcomes were assessed at day 90 using the modified Rankin and Scandinavian Stroke Scales. A high-density MCA sign was noted in 107 out of 603 patients (18%) on the baseline CT. This sign of MCA thrombus persisted in 56 of 106 patients (55%) on a subsequent CT on day 1, but in only 22 of 86 patients (26%) on a CT scan at one week.

Patients with a high-density MCA sign had a more severe neurological deficit ($P < 0.0001$) and more commonly had cerebral edema or mass effect on the baseline CT ($P < 0.0001$). This sign of MCA thrombus on the baseline CT was significantly associated with a poor clinical outcome at day 90 on univariate analysis: 84% of patients with a high-density MCA were dependent or dead at that time compared with only 62% of patients without the sign ($P < 0.0001$). Nevertheless, the high-density MCA sign had no independent prognostic value in a logistical model that took into account among others: age, initial severity of the neurological deficit, and changes on the baseline CT scan.

Among the 107 patients with a high-density MCA sign, 46 patients who received rtPA had a better neurological recovery than the 61 who received placebo ($P = 0.03$). Mortality at day 90 was not significantly greater in the rtPA group.

COMMENTARY

This analysis of ECASS I patients with a hyperdense MCA sign yielded interesting results. Manelfe et al found that the sign related to the severity of initial clinical neurological deficits and to ischemic changes on CT demonstrating the specificity of the sign for MCA occlusion. Nevertheless, CT evidence of MCA thrombosis did not, by itself, indicate a poor prognosis and did not rule out a favorable response to IV rtPA. Some clinicians have questioned the efficacy of IV thrombolytic therapy in patients with proximal cerebral artery occlusions compared with the results in those who have only distal branch occlusions (Caplan LP, Grotta J. *N Engl J Med* 1997;337:1309-1312; Caronna, JJ. *Neurol Alert* 1998;16:35). In fact, ECASS I patients with a CT sign of MCA thrombosis who received IV rtPA did not have an increased mortality and had a better neurological recovery than those who received placebo.

A hyperdense MCA sign on CT scan remains an important sign that may aid the clinician in reaching an etiological diagnosis in a stroke patient. Nevertheless, it does not have independent prognostic significance and its presence should not affect a decision to use thrombolytic therapy. **—jjc**

Generalized Periodic Epileptiform Discharges—To Treat or Not to Treat?

ABSTRACT & COMMENTARY

Source: Husain AM, et al. Generalized periodic epileptiform discharges: Etiologies, relationship to status epilepticus, and prognosis. *J Clin Neurophysiol* 1999;16(1):51-58.

Few studies have investigated the underlying mechanisms and clinical importance of periodic epileptiform discharges, whether lateralized (PLEDs), bilateral independent (BiPEDs), or generalized (GPEDs). Conflicting statements have frequently resulted in hesitation to treat GPEDs as epileptic events, unless prompted by the clinical behavior of the patient.

Husain and colleagues review the etiologies and clinical course of 25 patients who demonstrated GPEDs on EEG. Patients with lateralized or bilateral independent PEDs were excluded. Despite the small number of patients, the lack of reference to the immediate cause of death, or the effect of treatment, the study offers some useful observations.

As the table indicates, age older than 70 years and the presence of GPEDs following anoxia strongly predicted death. Among the 25 patients, eight were found to be in status epilepticus (SE), which was defined as: 1) recognition of unambiguous electrographic seizure patterns; 2) tonic-clonic activity during the EEG; or 3) electrographic or clinical improvement following administration of an antiepileptic medication—surprisingly offered

a somewhat better prognosis. Half of the eight SE patients survived compared to five of the 17 non-SE patients. Examining outcomes in the entire group of 25 patients, six of nine survivors had a history of seizures whereas the remaining three did not. In contrast, of the 16 nonsurvivors, only four had a history of seizures.

Table

Outcome by Age, Etiology, and the Presence of SE in 25 Patients with GPEDs

		n	Outcome	
Age	Older than 70 years	8	8 died	(100%)
	Younger than 70 years	17	8 died	(47%)
Etiology	Anoxic encephalopathy	10	9 died	(90%)
	Toxic-metabolic encephalopathy	7	4 died	(43%)
	Primary neurological diseases (seizures, stroke, hemorrhage, head trauma)	8	3 died	(37%)
Status Epilepticus	Present	8	4 died	(50%)
	Absent	17	5 died	(29%)

Husain et al also attempt to identify EEG features that might foretell the presence of SE. They describe a statistically significant correlation ($P < 0.05$) between the presence of SE and with increasing GPED amplitude, duration, and with higher inter-GPED amplitude on EEG. Closer examination of the data, however, reveals that these EEG features have a low predictive value. For instance, a GPED amplitude greater than 100 µV (62.5% of SE patients) has a positive predictive value for the presence of SE equal 44% only. Similarly, the positive predictive value for a GPED duration of more than 0.4 seconds (62.5% of SE patients) is only 41.66%, and for an inter-GPED amplitude equal to or greater than 35 µV (50% of the SE patients) is only 66%.

COMMENTARY

This study has serious limitations: small numbers, retrospective design, and lack of information on immediate cause of death or quality of outcome. Nevertheless, it describes one of the few available attempts to study the clinical usefulness of GPEDs in predicting SE and outcome. It may turn out that the presence of seizures or even SE confers a relatively favorable overall prognosis, which cannot be explained completely by age range, or less grave underlying comorbid condition. The reasons for the improved survival in patients with SE are unclear. It may be that the absence of seizures is a marker for more extensive neuronal damage or dysfunction. Alternatively, the presence of seizures and SE may have resulted in more aggressive treatment that improved survival. The question of whether to treat GPEDs as seizures or as SE remains open. An additional prospective study needs to answer this question and that of the eventual quality of life following GPEDs. **—fl, aristea s. galanopoulou, solomon l. moshé** (*Dr. Galanopoulou is EEG Fellow, Department of Neurology, Montefiore Medical Center-Albert Einstein College of Medicine, Bronx, NY. Dr. Moshé is Professor and Director, Pediatric Neurology and Clinical Neurophysiology, Department of Neurology, Montefiore Medical Center-Albert Einstein College of Medicine, Bronx, NY.*)

Brief Alert

PENS for Low Back Pain

Source: Ghoname EA, et al. Percutaneous electrical nerve stimulation for low back pain. *JAMA* 1999;281:818-823.

Percutaneous electrical nerve stimulation (PENS) therapy uses an acupuncture-like needle positioned in soft tissues or muscle to electrically stimulate dermatomal areas that correspond to levels of

radicular pathology. In this single-blind, sham-controlled, cross-over study, 29 men and 31 women, mean age 43 years, with stable low back pain (LBP) for at least three months and radiologically confirmed lumbosacral degenerative disc disease, were randomized to one of four treatment groups: sham-PENS, PENS, transcutaneous electrical nerve stimulation (TENS), and flexion-extension exercises. Exclusionary criteria included acute sciatica, drug or alcohol abuse, long-term opioid use, previous use of alternative therapies (e.g., acupuncture), and pending litigation. All patients underwent all four therapies in one of four different, computer-generated sequences. Each treatment was administered three times weekly for 30 minutes for three weeks. A week-long respite was inserted before advancing to the next modality. End point measures included visual analog scores (VAS) for pain, physical activity level, sleep quality, analgesic use, global patient assessment questionnaire, and Health Status Survey Short Form (SF-36). Standard statistical testing provided analysis of the data.

VAS pain score and daily nonopioid analgesic use significantly dropped, and level of physical activity, sleep quality, and sense of well-being significantly improved with PENS but not with the other treatment modalities. These findings were confirmed on the SF-36 scoring. PENS is better than TENS or exercise in providing relief for long-term LBP. **—mr**

CME Questions

25. Which of the following statements is true?
a. Sham-percutaneous electrical nerve stimulation (PENS) is no better than true percutaneous electrical nerve stimulation (PENS) for relief of low back pain
b. True PENS is no better than transcutaneous electrical nerve stimulation (TENS) for relief of low back pain
c. Percutaneous electrical nerve stimulation (PENS) is no better than flexion-extension exercises for relief of low back pain
d. Percutaneous electrical nerve stimulation (PENS) is significantly better than TENS or flexion-extension exercises for relief of low back pain

26. Recovery of language in a right-handed patient after a left hemisphere stroke:
a. is always greater in the case of frontal rather than temporal infarcts.
b. requires that both Wernicke's and Broca's areas be preserved.
c. has been linked to recruitment of right hemisphere language areas.
d. has been shown to depend on nonlanguage-related areas of the left hemisphere.

27. In a society with little tolerance for somatic disability attributed to minor accidents, post-whiplash symptoms of headache, neck pain, or other somatic disturbances appear to last no longer than:
a. 12 months.
b. 6 months.
c. 3 months.
d. 1 month.

28. Neurofibromin:
a. is localized to chromosome 17q11.2.
b. is a modulator of Ras-mediated signal transduction.
c. mutates 100 times more frequently than most other genes.
d. function appears to be that of tumor growth suppression.
e. All of the above

29. All of the following statements are true *except*:
a. The hyperdense MCA sign has a high specificity, but low sensitivity for MCA occlusion.
b. The bilateral hyperdense MCA sign may be due to calcified atherosclerosis.
c. The hyperdense MCA sign does not predict response to IV rtPA.
d. The hyperdense MCA sign always indicates a poor outcome.
e. The hyperdense MCA sign may not be seen on later CT scans taken after day 1.

30. Which of the following statements is true about the findings of recent studies being done on humans and experimental animals?
a. Adult human brains do not normally generate new brain neurons after age 12 years.
b. Structured teaching of children between ages 2-5 may significantly and permanently increase their I.Q.
c. Brain stem cells are rare and explicitly targeted at specific areas of the organ.
d. Brain stem cells are not capable of generating progenitor cells for other tissues of the body.

31. The most reliable predictor of a fatal outcome in patients with generalized epileptiform discharges (GPEDs) on EEG is/are:
a. high amplitude and duration of the GPED bursts on EEG.
b. age older than or equal to 70 years.
c. presence of status epilepticus clinically or electrographically.
d. a and b
e. b and c

32. Which of the following statements is correct?
a. Not all aphasics developed increased functional activity in the undamaged right hemisphere.
b. Patients suffering from expressive aphasia improved more than those with receptive aphasia.
c. Increased functional activity in the right temporal lobe was consistently associated with improved sensory aphasia.
d. PET scanning is essential for judging rehabilitation efforts following acute stroke.

In Future Issues:

The Incidence of Cognitive Impairment in Coronary Artery Bypass Patients