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Can tPA be Used Safely for Acute Ischemic Stroke in Your Emergency Room?

ABSTRACTS & COMMENTARY

Sources: Albers GW, et al. Intravenous tissue-type plasminogen activator for treatment of acute stroke: The Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *JAMA* 2000;283:1145-1150; Katzan IL, et al. Use of tissue-type plasminogen activator for acute ischemic stroke: The Cleveland area experience. *JAMA* 2000;283:1151-1158.

With fda approval of intravenous (iv) tissue plasminogen activator (tPA) in 1996, therapy for acute ischemic stroke moved out of the era of therapeutic nihilism and potentially became a treatable medical emergency. However, with limitations such as a three-hour time window and 10-fold increased risk of intracerebral hemorrhage (ICH) over placebo, this drug has been met with much skepticism and reluctance by the broad neurological community. Among all stroke patients presenting to emergency rooms (ERs) in the United States, only about 2-6% of these receive tPA. This figure rises to only about 10% among the minority of patients who present within three hours. tPA is more likely to be used in academic "stroke centers" than in the community. Recent reports published in the *Journal of the American Medical Association* (*JAMA*) suggest that limiting tPA use in this manner may be justified.

Since publication of the National Institute of Neurological Disorders and Stroke (NINDS) trial (*N Engl J Med* 1995;333:1581-1587), several groups have reported on the routine use of tPA in practice and have shown comparable outcomes and intracerebral hemorrhage (ICH) rates. Most of these studies, however, involved doctors with prior or current experience in acute stroke clinical trials. Albers and colleagues report on one such study. All 83 centers in the STARS study were simultaneously participating in ATLANTIS, a study of tPA in the three- to five-hour time window (which, of note, showed lack of efficacy). In STARS, of the 389 patients enrolled, there was a symptomatic ICH rate of 3.3%, half that of NINDS (6.4%). Protocol violations (previously shown to increase the risks of tPA by as much as fourfold) occurred in 34.7% of patients and were not associated with more hemorrhages. Among 13 patients with symptomatic ICH,

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five hemorrhages (3.9%) occurred in patients with protocol violations compared with eight (3.1%) among patients without violations. The most common protocol violations were treatment beyond the three-hour window and the use of additional anticoagulants within the first 24 hours. Interestingly, even among these experienced investigators, the "door to needle" time was inversely proportional to the time from symptom onset. Patients presenting close to the three-hour limit were given tPA within minutes. By comparison, those presenting within the first hour were treated up to two hours later, perhaps reflecting a feeling of a luxury of time. Such a luxury does not exist. Subgroup analysis of the NINDS data has shown that the majority of benefit of tPA was seen among patients treated in the 0- to 90-minute time range.

Katzan and colleagues report on data from 3948 strokes at 29 hospitals in Cleveland, reflecting heterogeneous experience from a moderate-sized metropolitan area. Among 70 patients who received tPA, there was a symptomatic hemorrhage rate of 15.7% (nearly 3 times that of NINDS and 5 times that of STARS). In-hospital mortality was 15%, significantly higher than that of matched patients seen within three hours who did not receive tPA (7.2%). Protocol violations occurred in half of the tPA-treated cases, but, as in STARS, these did not significantly affect ICH rates. The overall use of tPA was low. It was given in only 1.8% of all strokes presenting during the one-year study period (10.4% for patients arriving within three hours). It is not clear from Katzan et al's data why so many potentially eligible patients were not treated.

COMMENTARY

What explains the unexpectedly high hemorrhage rates in the Cleveland community study? Protocol violations common to less experienced operators (such as excessively dosing tPA in cardiac quantities) do not appear to be the explanation. Unfortunately, the nature of Katzan et al's data limits further insights. Baseline stroke severity (e.g., in the form of NIH Stroke Scale measurements) is known to affect ICH risk but these data are only available in a minority of the Cleveland patients. Early computerized tomography (CT) changes (such as hypodensity affecting more than one-third of the middle cerebral artery [MCA] territory) are also associated with ICH risk, but no radiological data are presented. Also, because these data analyze only end points such as ICH and in-hospital mortality, we may be missing important clinical benefits such as neurological improvement or reduced long-term disability. Finally, the Cleveland numbers are small, reflecting only 70 tPA-treated cases with 11 hemorrhages, compared with 389 treated patients in STARS and 312 in the NINDS trial.

These data have led to a call by some for centralization of stroke care in major centers akin to a trauma-care network. Time is of the essence, however, and travel can be cumbersome. Perhaps better education of local community practitioners would allow safe administration of this efficacious drug. **—azs**

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Can Lacunar Infarcts be Caused by Carotid Stenosis?

ABSTRACTS & COMMENTARY

Sources: Overell JR, et al. Association between carotid disease and ipsilateral lacunar stroke. Poster 187, p. 60. Abstract from the 25th International Stroke Conference, February 2000; Inzitari D, et al. Risk factors and outcome of patients with carotid artery stenosis presenting with lacunar stroke. *Neurology* 2000;54: 660-666.

Lacunar strokes have traditionally been considered to arise from microcirculatory disturbances at the level of the small perforating arteries. Published literature does not support extracranial carotid disease as an

etiological factor. However, two recent reports indicate that ipsilateral carotid stenosis may be a contributing factor in producing a significant subset of lacunar strokes.

Overell and colleagues report on 98 patients presenting with clinical or neuroimaging (CT/MRI) evidence of unilateral subcortical disease and a single stenotic carotid artery. Sixty-four patients had carotid stenosis ipsilateral to their stroke, compared to 34 who had a contralateral stenosis. Lacunes had a chi-square association of $P < 0.003$ with the ipsilateral strokes. These data suggest that lacunes could be a manifestation of symptomatic carotid stenosis.

Inzitari and associates also examine the relationship between carotid artery stenosis and lacunar stroke. A total of 43% of patients in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) group had lacunar strokes as their entry event, defined by their clinical syndrome. The majority of these were confirmed on neuroimaging. Infarctions in the deep subcortical internal carotid artery border zone territory were not classified as lacunes. Patients with lacunar strokes tended to have lesser degrees of carotid stenosis. However, among patients with the most severe degrees of carotid stenoses (70-99%), one-third presented with a lacune. The benefit of carotid endarterectomy (CE) for patients with a lacune as their qualifying event was a 35% stroke risk reduction at three years. This reduction is several orders of magnitude lower than what is reported among patients presenting with a cortical hemispheric stroke (61%). Both Overell et al and Inzitari et al nevertheless conclude that CE is indicated for patients with ipsilateral carotid stenosis and a corresponding lacune. They suggest that stroke in these patients is due to small emboli from stenotic carotid lesions lodging in the deep penetrating arteries.

COMMENTARY

These data demonstrate that emboli and low flow may be alternative pathophysiologic mechanisms in lacunar stroke. Subcortical areas such as the anterior limb of the internal capsule and the caudate head are in a border zone between the deep and cortical perforating branches of the anterior and middle cerebral arteries. Strokes in these territories may thus be hemodynamic insults mediated by severe carotid stenosis.

The alternative mechanism as speculated by the NASCET investigators is artery-to-artery embolism from the carotid to a penetrating artery.

Given these possibilities, a carotid evaluation should be strongly considered in the investigation of what has, until now, been largely believed to be a local microcirculatory disease. **—ak & azs** (*Dr. Ayeesha Kamal is a Chief Resident of Neurology at New York Presbyterian Hospital.)*

Electrical Brain Stimulation and Epilepsy—Fighting Fire with Fire

ABSTRACT & COMMENTARY

Source: Velasco M, et al. Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. *Epilepsia* 2000;41(2): 158-169.

Deep brain stimulation has improved selected movement disorders, and vagal nerve stimulation has been found to ameliorate refractory epilepsy. These favorable results have now encouraged a growing interest in using direct brain stimulation to prevent the onset and spread of seizures. Although preliminary investigations in animal models are going on, Velasco and colleagues have investigated the effect of subacute temporal lobe electrical stimulation in 10 patients. Four men and six women between 11-35 years old underwent intracranial monitoring with depth and subdural electrodes to determine the location of epilepic foci prior to temporal lobectomy. After tapering off antiepileptic medications, patients were monitored over two to three weeks to characterize seizures and determine the outcome of subacute stimulation. All patients had complex-partial seizures and seven suffered from secondary general attacks as well. Velasco et al applied electrical stimulation consisting of biphasic current pulses at a rate of 130 per second to contiguous pairs of depth and subdural contacts nearest to the region of seizure onset.

Stimulation intensities used were 5-10% of the intensity typically required to evoke an epileptiform afterdischarge. Stimulation continued for 23 hours each day. The remaining hour was used to record EEG. Following the monitoring period, patients underwent temporal lobectomy. The resected tissue did not show any pathological changes related to stimulation when compared to unstimulated tissue.

Subacute stimulation produced a marked response in seven patients. In every such patient, no seizures occurred after the first week of stimulation. Interictal discharges also decreased over the course of stimulation and the frequency of interictal spikes declined 10-fold after two weeks. Patients who best responded to subacute stimulation had electrode contacts located in or on the hippocampal formation. In the five patients with the fastest and most complete antiepileptic response, contacts were located in either

the anterior hippocampus or the anterior parahippocampal gyrus. Over the course of stimulation, Velasco et al noted that the background surface EEG of responders progressively normalized. Two patients with electrode contacts either in the medial hippocampus or the anterior perforate space had an initial improvement in seizure frequency that reversed when stimulation was interrupted. After stimulation restarted, both patients became seizure free. One patient had electrode contacts in the white matter and did not respond to stimulation.

COMMENTARY

The results of the study by Velasco et al provide compelling evidence that direct brain stimulation may become an effective treatment for patients with refractory epilepsy. Nevertheless, many questions remain before the clinical use of direct brain stimulation can be fully assessed. At present, its capacity for long-term success remains unknown, nor do we know whether any reduction of antiepileptic drugs can be taken safely. Furthermore, the behavioral effects of chronic direct hippocampal stimulation remain unknown. With growing interest in the anticonvulsant effects, neurologists can expect to hear more of direct brain stimulation in the treatment of epilepsy. **—fal**

Sedation for MRI in Children

ABSTRACT & COMMENTARY

Source: Lawson GR. Controversy: Sedation of children for magnetic resonance imaging. *Arch Dis Child* 2000;82: 150-154. Subsequent commentary by R.J. Bray.

Magnetic resonance imaging (mri) of the brain is among the most commonly ordered of neurological tests. Performance of a useful MRI study requires that a patient be as still as possible for periods of 15 minutes or more; logistically, this means that most children aged 1-7 years needing these studies will also need some degree of sedation and, thus, will be exposed to some degree of risk. The article by Lawson and commentary by Bray highlight British views on this problem. There seems to be a consensus among physicians that young children require deep rather than conscious sedation due to the relatively high failure rate of the latter. Somewhat surprisingly, British and American guidelines for MRI sedation differ with respect to the need for patient monitoring by an anesthesiologist; British guidelines oppose the administration of deep sedation without an anesthesiologist present, while American guidelines permit this. Clearly, the need for an anesthesiologist would increase the cost of MRI, but would it necessarily make the procedure safer?

According to available American data (Cotè CJ, et al. *Anesthesiology* 1995;83:183) for the last 28 years, there were 52 sedation-related deaths among patients younger than 21 years of age, 22 of which involved patients younger than 4 years old. Fourteen of these deaths occurred in the context of radiological studies. Among the 52 deaths, 38 were associated with drug overdosage, and 25 had inadequate monitoring, presumably factors that might be greatly reduced if an anesthesiologist were present. Unfortunately, the denominators in these studies are unknown, so no incidences can be computed.

COMMENTARY

The issue of MRI sedation in children is one that a practicing child neurologist would be likely to face on a daily basis. Given this challenge, it is somewhat surprising that the literature carries little objective information about the problem. Much more work will need to be done in order to define optimal sedation protocols and to define subgroups at high risk for complications from a specific sedative.

Neurology Alert suggests that pediatric, anesthesiological, radiological, and neurology societies should work together to develop rational guidelines for the administration and monitoring of MRI sedation in children. If possible, a highly-trained practitioner (anesthesiologist or nurse anesthetist) should be available to monitor the patient and intervene as necessary. Monitoring should include both pulse oximetry and some measurement of chest movement. **—rt**

Parkinsonism Due to Predominant Involvement of Substantia Nigra in Japanese Encephalitis

ABSTRACT & COMMENTARY

Source: Pradhan S, et al. Parkinsonism due to predominant involvement of substantia nigra in Japanese encephalitis. *Neurology* 1999;53:1781-1786.

In this paper, pradhan and colleagues report their finding of a new clinicopathologic pattern for

Japanese encephalitis (JE). JE is the most common endemic encephalitis seen in Southeast Asia and India. The virus usually affects the thalamus, brainstem, anterior horn cells, and cerebral cortex, but may also affect the basal ganglia and cerebellum. While prior reports had shown occasional involvement of the substantia nigra, Pradhan et al recognized a new pathologic pattern that selectively involved the nigra, sparing all other brain regions.

Of the 52 patients they encountered with JE over a period of six years, five patients shared a strikingly similar clinical and radiologic phenotype. All of these patients were young (ages 7-16), and all presented with a prodrome of encephalitis (fever, headache, altered level of arousal, and seizures). On examination during their acute illness, upbeating nystagmus and opsoclonus were accompanied by severe parkinsonism, with prominent cogwheeling, tremor, and rigidity. Cerebrospinal fluid analysis revealed a mild leukocytosis with mild elevation in protein and normal glucose. The diagnosis of JE was secured by demonstrating at least a four-fold rise in serum antibody titers to the virus. Despite the severe nature of their illness, three of five patients recovered completely at one-year follow-up, and two other patients were recovering when seen two months after their acute illness.

The most striking feature of these patients was the appearance of their magnetic resonance imaging (MRI) scans. In all five patients, the substantia nigra appeared hyperintense on T2-weighted images and hypointense on T1 views. There was no enhancement with contrast, and no lesions were seen in any other areas of the brain.

COMMENTARY

There has long been heated debate whether Parkinson's disease (PD) is predominantly genetic or if it is related to environmental exposure to toxins or viral agents. Viral agents are unlikely to be responsible for the vast majority of PD or parkinsonism. Nevertheless, the discovery of a viral agent with selective propensity for the substantia nigra could have profound implications for understanding the selective vulnerability of this target cell population.

The 1918 epidemic of postencephalitic parkinsonism demonstrated that environmental agents may cause parkinsonism. Although the virus responsible for this epidemic has never been identified, other viruses have been reported to have selective affinity for the substantia nigra, including human immunodeficiency virus (HIV) and coxsackie viruses. With this report, Pradhan et al have added JE to this list. Although neurologists in the United States are unlikely to encounter patients with JE, these patients are relevant even in a major city. This was demonstrated last summer with the outbreak of a rare but devastating viral encephalitis that produced movement disorders in some of its victims. **—steven frucht, md**

Occipital Plagiocephaly: Flat-Out Controversial

ABSTRACT & COMMENTARY

Source: Miller RI, Clarren SK. Long-term developmental outcomes in patients with deformational plagiocephaly. *Pediatrics* 2000;105:E26.

Occipital plagiocephaly (op) is a complex abnormality in head shape involving unilateral or bilateral occipital flattening and some degree of axial asymmetry of the skull base. It is one of the most common abnormalities of skull shape seen in children and although its true incidence is unknown, it is probably quite high, for as many as 14% of adults show morphometric evidence of skull base anterior-posterior asymmetry (Rekate HL. *J Neurosurg* 1998;89:24-30). The unifying mechanism of OP appears to be an asymmetry of axial forces on the pliable infant skull. It may be due to abnormalities of brain shape, unilateral lambdoid craniosynostosis, and, most commonly, asymmetry of external compressive forces on the skull. The incidence of OP has apparently risen dramatically over the past decade, widely attributed in large part to the April 1992 recommendations by the American Academy of Pediatrics that infants avoid a prone sleep position in order to reduce the incidence of sudden infant death syndrome (Turk AE, et al. *J Craniofac Surg* 1996;7:12-18).

Recently, it has become clear that only a small fraction of patients with OP have craniosynostosis. In the series of 115 OP patients reported by Mulliken and colleagues (Mulliken JB, et al. *Plast Reconstr Surg* 1999; 103:371-380), only a single patient had lambdoid craniosynostosis; the remainder of the cases were deformational. This has motivated a sea of change from surgical to nonsurgical management of this condition. The most widely nonsurgical therapy is helmet therapy, particularly dynamic orthotic cranioplasty helmet (or "DOC banding"; Littlefield TR, et al. *J Craniofac Surg* 1998;9:11-17). These helmets are applied to

infants between 6 and 18 months of age, are worn almost continuously for (on average) four to six months, and are effective in complete or near-complete correction of cranial asymmetry.

A major point of controversy is whether OP is associated with any significant medical complications. Theoretical complications of OP include dental malocclusion, orbital dystopia with resulting accommodative errors, and increased intracranial pressure, none of which has been proven (Rekate HL. *J Neurosurg* 1998;89:24-30). Many physicians (and insurance companies) have thus regarded OP as an essentially cosmetic problem. Miller and Clarren now report that developmental difficulties are dramatically increased in children with OP, furthering the controversy.

Miller and Clarren performed a retrospective record review of 254 patients with OP evaluated at a single craniofacial surgery program over an 11-year period (1980-1991). Among these patients, 181 were located, and 63 of these agreed to telephone interview in order to determine developmental outcome some 10-20 years after diagnosis of OP, compared to siblings with normal head shape. A major finding of this study is that 25 of 63 (40%) of children with OP were sufficiently developmentally delayed to require special services (special education; or speech, occupational, or physical therapy) as compared to seven of 91 (8%) of sibling controls. This increased relative risk of development was more marked in males with OP—almost 10-fold as compared to sibling controls. Interestingly, the use of helmet therapy did not influence the incidence of developmental delay (11/27 [41%] in the helmet group and 14/36 [39%] in the nonhelmet group).

COMMENTARY

The main issue raised by this study is clear: does early skull molding lead to subtle brain dysfunction or is OP simply an early sign of subtle brain dysfunction? The lack of significant difference between the helmet-treated and nontreated groups suggests that either correction of the molding does not influence developmental outcome or the mean age at helmet intervention (about 6 months) is already too late to make a difference. Clearly, a child who is delayed in getting up from a supine to a sitting position (for whatever reason) is plausibly at increased risk of developing OP. A prospective study of the influence of helmet treatment on long-term developmental outcome that uses quantitative and standardized neuropsychological test results will be needed to settle this issue. Also, are the delays seen transient or enduring? If the latter proves to be true, do not be surprised to see more babies crawling about with helmets on. **—rt**

Multiple Sclerosis and Antiphospholipid Syndrome Are Not Always Easy to Differentiate

ABSTRACTS & COMMENTARY

Sources: Cuadrado MJ, et al. Can neurologic manifestations of Hughes (antiphospholipid) syndrome be distinguished from multiple sclerosis? Analysis of 27 patients and review of the literature. *Medicine* 2000;79:57-68; Kovacs B, et al. Transverse myelopathy in systemic lupus erythematosus: An analysis of 14 cases and review of the literature. *Ann Rheum Dis* 2000;59:120-124.

Cuadrado and colleagues retrospectively reviewed 27 consecutive patients at a London hospital with an initial diagnosis of clinically probable or definite multiple sclerosis (MS), who were referred over a two-year period to a lupus unit to exclude underlying collagen-vascular disease. All 27 patients were women, with a mean age of 38 years (range 18-45), and a mean duration of MS diagnosis of 57 months (range 7-72). Anticardiolipin antibodies of IgG and IgM were detected in 74% and 78% of patients, respectively. Lupus anticoagulant was positive in seven of 21 patients tested.

Of the 27 patients, 16 were thought to have a primary antiphospholipid syndrome (APS) whose initial clinical involvement was largely cerebral or cerebellar. The remaining 11 patients had secondary APS associated with systemic lupus erythematosus (SLE), and were more likely to present with myelopathy and optic neuropathy. During follow-up, 19 of 27 (70%) patients developed some other SLE- or APS-related features, including photosensitivity, hair loss, arthralgias, livedo reticularis, venous thrombosis, or miscarriages.

Blinded review of brain MRIs were not thought to be significantly different from a control group of MS patients, with 14 patients demonstrating the majority of lesions in the white matter, but nine patients showed damage in both the white and grey matter, and four patients with a normal MRI. Analysis of cerebrospinal fluid (CSF) was performed in only six patients; oligoclonal bands (OCBs) were found in four patients, all of whom had APS secondary to SLE.

Treatment included warfarin, aspirin, and prednisone, with secondary APS patients typically doing worse.

Kovacs and colleagues described 14 patients presenting with transverse myelopathy (TM) from a population of 600 SLE patients at two Philadelphia hospitals. In seven of 14 patients (50%), TM was an initial symptom of SLE. Optic neuritis also occurred in four of 14 patients. In their series, 55% of patients tested positive for anticardiolipin antibodies or lupus anticoagulant. CSF typically showed a pleiocytosis and elevated protein, but OCBs were not described. Patients were treated with intravenous (IV) methylprednisolone and cyclophosphamide or plasmapheresis, with complete to partial recovery in only five patients (36%).

COMMENTARY

These two papers address a significant concern for the neurologist constructing a differential diagnosis in patients presenting with possible MS. The presence and significance of anticardiolipin antibodies in demyelinating disease has been studied in previous reports, most recently by Karussis and associates (Karussis D, et al. *Ann Neurol* 1998;44:629) and D'Ohlaberriague and associates (D'Ohlaberriague L, et al. *Neurology* 1998; 51:1376). For example, Karussis et al found low to significant titers of IgG and IgM antibodies in up to 20 of 100 of MS patients with classic brain MRIs and clinical presentations, more commonly with myelopathy, optic neuropathy, and headache. CSF OCBs were detected in only three of 20 patients.

The distinction between MS and APL syndromes is more than an academic issue, since clinical management will differ between the two disorders. The MS patient would typically be treated with interferon-beta or glatiramer acetate, whereas the APL syndrome might require therapy with antiplatelet or anticoagulant agents (or even plasmapheresis in the case of fulminant catastrophic APL syndrome). Patients should have a careful evaluation for any clinical signs or symptoms of systemic collagen-vascular disease. It is well described in the literature that many MS patients can have a slightly elevated ESR, ANA, ACE, or ACLA (see *Neurol Alert*). Indeed, a few of the patients described by Cuadrado et al may fall into this category. Low titers of anticardiolipin antibodies, particularly IgM, are common and are not thought to have much pathogenic significance, while high titers of IgG may be relevant. A careful medical history (e.g., for thrombosis or fetal loss), other subtle findings of systemic disease, consistently abnormal serologies, atypical lesion localization on MRI, and negative CSF OCBs may help guide an accurate diagnosis and optimal management. **—bra**

Neurotherapeutic Briefs

3,4 DAP for LEMS

Source: Sanders DB, et al. A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome. *Neurology* 2000;54:603-607.

Though yet to be fda approved, 3,4-diaminopyridine (DAP) appears to be safe and effective for Lambert-Eaton myasthenic syndrome (LEMS). Twenty-six LEMS patients were enrolled in this prospective, randomized, two-arm, parallel-treatment trial comparing DAP 20 mg tid (n = 12) vs. placebo (n = 14) for six days, followed by open-label DAP for as long as there was symptomatic improvement. Diagnosis was established by demonstrating proximal muscle weakness associated with characteristic electromyographic abnormalities (i.e., small-amplitude compound muscle action potentials [CMAP] that drop still further on low-frequency repetitive stimulation but increase at least twofold after maximal voluntary contraction). Exclusionary criteria included cardiac arrhythmia; seizures; renal, hepatic, or hematologic disease; and all female patients practiced contraception while on the drug. Quantitative myasthenia gravis (QMG) score, a functional assessment of involved muscle groups, was the primary end point, with the average summated CMAP amplitude of three intrinsic hand and foot muscles (abductor digiti minimi, abductor pollicis brevis, and extensor digitorum brevis) serving as secondary end points. Wilcoxon's rank sum test provided statistical analysis.

Compared to baseline, at the end of the six-day blinded phase significant improvement in QMG scores and average summated CMAP amplitudes occurred in the DAP arm, with no significant change seen in the placebo group. On open label, 24 of 25 patients who continued on DAP improved, with the optimal response seen at 30 to 40 mg/day. One patient with recurrence of LEMS discontinued DAP, but without return of weakness. Side effects included mild perioral tingling and acral paresthesia, but no hematologic, renal, hepatic, or cardiac

complications were seen.

COMMENTARY

Until FDA approval, DAP may be obtained for compassionate use from Jacobus Pharmaceutical Company, Inc. (which provided the DAP for this study), in Princeton, NJ (fax: 609-799-1176). **—mr**

Avonex for ALS

Source: Beghi E, et al. A randomized controlled trial of recombinant interferon beta-1a in ALS. *Neurology* 2000; 54;469-474.

Hoping that interference with immune mechanisms would have an effect on amyotrophic lateral sclerosis (ALS), 61 patients were enrolled in this double-blind, randomized, placebo-controlled study of recombinant interferon beta-1a (Avonex), administered subcutaneously tid for six months. Multiple measures of disease progression and disability, including the ability to swallow, self-feed or walk unassisted, Medical Research Council scale of muscle strength, Norris scale, bulbar scores, spirometric forced vital capacity, and electrodiagnostic studies showed no difference between the two treatment groups. Sadly, treatment for ALS must look elsewhere, but why does it take five pages to say so? **—mr**

IVIG for Chronic Sensory Ataxic Neuropathy

Source: Takeuchi H, et al. Immunoglobulin therapy for idiopathic chronic sensory ataxic neuropathy. *Neurology* 2000; 54:1008-1010.

Chronic sensory ataxic (large-diameter fiber) neuropathy may occur as a consequence of toxic (pyridoxine, cisplatinum), nutritional (vitamin E deficiency), or infectious disorders (tabes, herpes zoster), malignancy (*Ann Neurol* 1977;2:7-19), Sjogren's syndrome (*Neurology* 1989;39:390-394), monoclonal gammopathy (*Ann Neurol* 1985;18:655-659), or as a form of chronic inflammatory demyelinating polyneuropathy (*J Neurol Neurosurg Psychiatry* 1992;55:677-680). The last responds to immunosuppressive therapy, including plasma exchange and azathioprine, though not prednisone (*Muscle Nerve* 1992;15:255-256). It appears that intravenous immunoglobulin therapy (IVIG) may also be beneficial for the idiopathic form. Four women, ages 45 to 63 years, with idiopathic chronic sensory ataxic neuropathy of 1.5 to 15 years duration, with normal cerebrospinal fluid protein and cell count, and without evidence of malignancy or other cause of neuropathy, were treated in an open trial with IVIG, 2 gm/kg over five days. All improved remarkably after a single course, with three requiring additional courses to maintain improvement. Double-blind studies ought be next. **—mr**

CME Questions

11. Occipital plagiocephaly:

a. is usually a consequence of occult craniosynostosis.
b. is best managed surgically in most cases.
c. has been clearly associated with medical complications, including dental and visual difficulties.
d. may be associated with developmental delays, especially in boys.
e. has been decreasing in incidence over the past decade.

12. Which of the following is *false*?

a. Anticardiolipin antibodies occur in demyelinating conditions of the CNS.
b. Fetal loss and thrombosis are associated with the antiphospholipid syndrome.
c. Anticardiolipin antibodies do *not* occur in transverse myelopathy or optic neuropathy.
d. Systemic manifestations collagen-vascular disease do *not* always precede neurologic symptoms.
e. Brain MRI scans in the antiphospholipid syndrome may be similar in appearance to MS.

13. Which of the following answers is *false*?

a. Electrodes were best placed in the anterior parahippocampal gyrus.
b. Stimulation lasted 23 hours a day.
c. Patients remained off anticonvulsants.
d. Stimulation intensity was 50% of that required to induce seizures.

14. Cerebral lacunes ipsilateral to a stenotic carotid artery are equal to or more than approximately what percentage as frequent than on the nonstenotic carotid artery hemisphere?

a. 0%.
b. 25%.
c. 50%.
d. 100%.

In Future Issues: Cerebral White Matter Lesions in Aging and Dementia