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Clinical Criteria Identify Patients Able to Undergo LP Without CT Scan

ABSTRACT & COMMENTARY

Source: Hasbun R, et al. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med.* 2001;345:1727-1733.

THE EMERGENCY EVALUATION OF A PATIENT WITH SUSPECTED meningitis typically includes a lumbar puncture (LP) following a computed tomography (CT) scan. Imaging is intended to rule out an intracranial lesion with significant mass effect, since the pressure gradient produced by lumbar puncture may lead to the complication of downward herniation. Delay in obtaining a CT may result in a prolonged waiting time for initiation of antibiotic therapy or in the blind use of empiric antibiotics prior to lumbar puncture.

Hasbun and colleagues investigated whether a group of patients may be identified in whom lumbar puncture may be performed safely without prior CT. Hasbun et al prospectively evaluated 301 patients with suspected meningitis; 235 of these underwent CT. In 56 of the 235, the results of CT were abnormal. Mass effect was present in 11. Clinical features significantly associated with an abnormal CT were: age older than 60, immunocompromise, a history of CNS disease, history of seizure within 1 week of presentation, and neurologic abnormalities as assessed by a modified NIH Stroke Scale. These included an abnormal level of consciousness, inability to answer orientation questions, inability to follow 2 commands, gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, or abnormal language function. There were none of these findings in 96 patients, and CT was normal in 93 of these patients. The negative predictive value of these criteria was thus 97%. Of the 3 misclassified patients, only 1 had mild mass effect on CT and all 3 underwent LP without complication. Of note, papilledema, the clinical finding commonly associated with increased intracranial pressure and a danger to LP, was present in only 1 patient. Three patients with severe mass effect on CT demonstrated multiple clinical "red flags," and were deemed too unsafe for LP. Two of these soon died of herniation.

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INSIDE

The time delay for LP was 5.3 hours in patients who underwent CT and only 3 hours for those who did not have CT. There was a trend, but no statistical difference between the time from admission to the ER to the initiation of antibiotics in the 2 groups. The ultimate diagnosis was meningitis in a minority of patients, 28%. Only 6% had a pathogen identified by microbiology and most of these were nonbacterial. A large proportion of patients were immunocompromised—approximately 25%—increasing the likelihood of such diagnoses as cryptococcus, toxoplasmosis, and lymphoma. CTs were ordered by treating physicians surveyed to rule out a suspect mass lesion in 59%; as a matter of "standard of care" in 34%; and due to "fear of litigation" in 5%.

COMMENTARY

This report confirms that in the vast majority of cases, LP may be performed safely in patients suspected to have meningitis. These data convincingly show that among patients at low risk by clinical criteria, the likelihood of significant abnormalities on CT is nearly zero. In fact, if the 2 patients with abnormal CTs but no mass effect are reclassified as "safe," then the negative predictive value of these clinical criteria is greater than 99%.

The presence of CT scan abnormalities, including mild mass effect, furthermore does not preclude a safe LP. Small-volume spinal taps using smaller 22-gauge needles are likely of minimal to no risk in patients with supratentorial lesions. Indeed, it is the presence of posterior fossa masses that poses the highest risk.

These analyses may be made irrelevant in emergency rooms with easy access to a rapid CT scan. If time is of the essence, the time necessary to obtain CT may be quite brief. For example, in acute stroke patients, the "door-to-needle" time including CT may be as short as 1 hour. These data are perhaps better applied to patients who are unable to rapidly get a CT due to critical illness or complicating medical issues. Unfortunately, these patients would not be the young, neurologically normal patients whom the clinical criteria of Hasbun et al best fit. Also, the presence of a normal CT does not preclude the presence of increased intracranial pressure and does not guarantee that a herniation pattern may evolve with or without LP. **—ALAN Z. SEGAL**

Disturbed Cerebellar Functions in Patients with Essential Tremor

ABSTRACT & COMMENTARY

Source: Stolze H, et al. The gait disorder of advanced essential tremor. *Brain.* 2001;124:2278-2286.

THERE HAVE BEEN ANECDOTAL REPORTS OF A GAIT disorder characterized by an abnormal tandem gait in almost 50% of patients with essential tremor (ET) (Singer C, et al. *Mov Disord.* 1994;9:193-196). Stolze and colleagues assessed cerebellar-like abnormalities in 25 patients with ET, 8 patients with cerebellar diseases (CD) and 21 age-matched healthy controls. Tremor was rated according to the clinical scale of Fahn and associates (Fahn S, Tolosa E, Marin C. In: Jankovic J, Tolosa E, eds. *Parkinson's Disease and Movement Disorders*. 3rd ed. Baltimore, Md: Urban and Schwarzenberg; 1998:225-234.) Normal and tandem gait were studied both on a walkway and on a treadmill using a three-dimensional infrared movement analysis system.

During normal walking, ET and CD subjects showed only slight abnormalities on tandem gait. However, ET patients exhibited a broad-based ataxic and dysmetric gait that was indistinguishable from the gait in CD. The gait disorder was much more pronounced in the 15 ET

Neurology Alert, ISSN 0741-4234, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.
Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to *Neurology Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $38. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

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$279 per year.
Multiple Copies
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patients (60% of the total) who had intention tremor of the hands. Patients with gait disorder due to CD or ET were more severely disturbed in their activities of daily living than those without gait disorder.

Stolze et al conclude that their results are strong evidence for a CD in ET causing both a gait abnormality and the tremor itself.

COMMENTARY

Stolze et al found that ET patients who have a cerebellar-like intention tremor rather than predominantly postural tremor of the upper extremities are also likely to have a cerebellar-like disorder of tandem gait. At first glance this conclusion seems to be tautological, but that is not the case. The association between ET and a gait disorder has been noted by clinicians but thought to be coincidental. Since ET is hypothesized to be caused by oscillatory activity in the olivo-cerebello-rubral pathways, it seems plausible that other cerebellar motor functions could be disturbed in ET patients (Deuschl G, et al. *Brain*. 2000;123:1568-1580). In support of a cerebellar connection are case reports of the disappearance of ET after cerebellar and pontine strokes (Nagaratnam N, Kalasagail G. *J Neurol Sci.* 1997;149:195-196) and PET studies demonstrating cerebellar hyperactivity in ET (Hallett M, Dubinsky RM. *J Neurol Sci.* 1993;114:45-48).

Further clinical studies of ET patients before and after medical and surgical treatment should take an integrative approach that seeks to understand the genesis of both tremor and ataxia. **—JOHN J. CARONNA**

Variant Huntington's Disease

ABSTRACT & COMMENTARY

Source: Margolis RL, et al. A disorder similar to Huntington's disease is associated with a novel CAG repeat expansion. *Ann Neurol.* 2001;50:373-380.

HUNTINGTON'S DISEASE (HD) IS AN AUTOSOMAL dominant disorder characterized by disorders of movement, cognition, and behavior. Symptoms typically begin between the ages of 35 and 50. Affected patients typically manifest a combination of chorea, dystonia, or parkinsonism, and there is an inexorable decline with progressive dementia and behavioral disinhibition. Medium spiny projection neurons are selectively lost in the striatum, with a characteristic dorsal-to-ventral gradient of cell loss. HD was the first neurodegenerative disorder linked to expansion of polyglutamine residues (the so-called CAG repeat expansions). Over the last decade, more than 15 spinocerebellar ataxias have been linked to triplet repeat expansions, and polyglutamine repeats are now known to cause dentatorubral pallidoluysian atrophy (DRPLA), spinal and bulbar muscular atrophy (SBMA), and spinocerebellar ataxias 1, 2, 3, 6, and 7. CAG-repeat expansions result in a "gain of function" of the affected protein, with accumulation of intranuclear polyglutamine protein aggregates in selected neuronal cell populations.

The availability of a gene test for HD has profoundly changed the way neurologists evaluate HD patients and family members who are at risk for HD. Patients with more than 40 CAG repeats in the IT-15 gene (the HD gene) will develop symptoms of HD with 100% certainty if they live long enough. More than 95% of patients who have symptoms of HD and magnetic resonace imaging (MRI) consistent with the disorder are proven to have CAG repeat expansions in the IT-15 gene. However, neurologists occasionally encounter patients who look like they have HD, but in whom gene testing is normal. In this paper, Margolis and colleagues describe such a patient and pedigree, and discuss the implications for HD and other neurodegenerative conditions.

Margolis et al's pedigree is a 3-generation family with 17 affected individuals. The inheritance pattern is clearly autosomal dominant. Symptoms begin at age 35 in the youngest generation and age 45 in the oldest generation, suggesting the possibility of anticipation (ie, earlier disease onset with each succeeding generation). Early symptoms and signs include weight loss, incoordination and involuntary movements followed by depression, anxiety, irritability, and eventually profound dementia. Patients look very much like the "Westphal" variant of HD, a phenotype dominated by parkinsonism and dystonia; chorea is less prominent. MRI showed prominent striatal atrophy with flattening of the head of the caudate, moderate cortical atrophy, and preserved brainstem and cerebellar volumes. An autopsy of one patient revealed severe atrophy of the head of the caudate and putamen, severe neuronal degeneration in the striatum with a dorsal-to-ventral gradient, and occasional intranuclear inclusions.

Genetic testing for CAG-repeat expansions in the IT-15 gene (HD) were negative, and Margolis et al also excluded linkage to a locus near chromosome 20p previously linked in another HD-look-alike family. Using a new technique for detecting CAG repeat expansions, Margolis et al demonstrated a CAG-repeat expansion in affected family members of approximately 50-60 triplet

repeats. Linkage studies to identify the abnormal gene in this pedigree are ongoing.

COMMENTARY

This is an interesting and important paper. Despite a decade of investigation, several critical questions remain unanswered regarding the underlying mechanism of cell loss in HD. Polyglutamine expansion within a protein (IT-15 or the target protein abnormal in Margolis et al's pedigree) leads to a gain of function, causing aggregation of the protein within the neuron. Is the protein aggregate directly toxic to neurons, or are the neuronal inclusions an end-stage feature of the cascade? The discovery of the genes responsible for phenocopies of HD will help define the intracellular pathways responsible for the characteristic selective neuronal loss within the striatum, and will also likely suggest new targets for therapeutic approaches to interfere with these pathways. **—STEVEN FRUCHT**

Complications of Gamma Knife Surgery for Parkinson Disease

ABSTRACT & COMMENTARY

Source: Okun MS, et al. Complications of gamma knife surgery for Parkinson disease. *Arch Neurol.* 2001;58: 1995-2002.

Neurosurgery in the past 50 years has developed several intracranial procedures involving the basal ganglia and thalamus in hopes to ameliorate the crippling factors of progressive, late-stage Parkinson disease (PD). One relatively new, nonsurgical approach has consisted of using the noninvasive, radiosurgical gamma knife (GK). The GK depends on first quality, cerebral MRIs to define by cubic millimeters the fine target structures that inhabit the particular patient's thalamus and basal ganglia. From these mappings, the GK earlier directed an 8- or 4-mm collimater to control the radiation target size. A 4-mm diameter collimator has been designed to destroy just a 64 cu mm spot in the calculated thalamic or basal ganglia target. Two difficulties can occur from such steps, however. One can come immediately or the other can evolve from 1-12 months following the surgery. Unfortunately, Okun and colleagues encountered serious complications in 8 patients who underwent the GK. These all suffered distressing outcomes which appeared as follows: 1) body numbness, pseudobulbar, and laughter (1 mo); 2) hypophonia + aphasia (5 mos); 3) dysarthria, aspiration, and death (4 mos.); 4) hand weak, dysarthria (4 mos.); 5) hemiparesis (10 mos.); 6) visual field loss (3 mos, permanent); 7) hemiparesis, dysarthria (months or more).

Problems included: a) the GK lesions in the whole cohort averaged 1.5 ± 0 mm off their targeted goals; b) lesions involving functional structures adjacent to the intended target seriously affected every one of the 8 patients; and c) at best, no patient was improved more than 4 months and most were improved by a matter of weeks or none at all.

COMMENTARY

The unfortunate outcomes of this group of PD patients all come from a high-quality university medical center with excellent clinical and fundamental neurological programs. GK treatment may be favorable for cerebral neoplastic therapy, but the spatial geography of critically different functions that originate in the thalamus or basal ganglia appear too small to use isolate functional GK therapy. **—FRED PLUM**

Additional Reading

1. Lang AE. *Ann Neurol.* 2000;47 (suppl 1):S193-S202.
2. Friedman JH, et al. *Ann Neurol.* 1996;38:535-538.
3. Duma CM, Jacques D, Kopyov OV. *Neurosurg Clin N Am.* 1999;10:379-389.
4. Jankovic J. *Arch Neurol.* 2001;58:1970-1972.

Does Cigarette Smoking Protect the Appearance of Parkinson's Disease?

ABSTRACT & COMMENTARY

Source: Hernan MA, et al. Cigarette smoking and the incidence of Parkinson's disease in two prospective studies. *Ann Neurol.* 2001;50:780-786.

Persons in their late 60s who smoke heavily or even lightly may be susceptible to several illnesses, especially cancer and cerebral-cardiopulmonary illnesses. Remarkably, however, individuals who smoke cigarettes appear to suffer less risk of developing Parkinson's disease (PD) than those who never smoked. Up until 20 years ago, women may have been less scrupulously evaluated neurologically for PD,

thereby quietly overlooked it as just increasing aging. To determine the accuracy of their past and future health or illnesses, 121,700 cooperating nurses were incorporated in 1976 to a 20-year Nurses Health Study (NHS). Each member on admission submitted an immediate thorough, beginning medical profile, after which she biennially commented her own health and habits as well as other appropriate public health matters. Ten years after the NHS started, a similar Health Professionals' Follow-up Study (HPFS) was established in men in 1986. This group included 51,529 cooperating male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians. All were aged 40-75 years old at the start and provided a male's immediate health profile as well as 4 more biennial reports until 1996.

In the ultimate 20-year female group, 152 new diagnoses of PD were reported in June 1996. Eighty-six had been "never smokers," whereas 66 had been "ever (random) smokers." During the 10-year 1986-1996 decade of 51,529 HPFS, males identified 128 new diagnoses of PD. The greater incidence of PD was found to be in both genders who had never smoked. In both genders the incidence and severity of PD could be calculated in relation to the degree of smoking. Among males aged 70-74 years per 100,000 the projected PD of a "never smoker" would be 153 per cases. "Ever smokers" of the same age only developed an incidence rate of 71 per 100,000. Calculations among "never" smoking women aged 70-74 years per 100,000 indicated an incidence of 50 of PD, but only an incidence of 31 in an "ever smoker." As Hernan and colleagues put it: ultimate age-adjusted ratios (for women) for PD compared to never-smokers amounted to 0.7 for past smokers and 0.4 for current smokers. Adjusted male rate ratios for PD compared to never-smokers amounted to 0.4 for past smokers and 0.3 for current smokers.

COMMENTARY

Previous prospective studies have identified that men who never smoked have an increased incidence of PD when they pass 60 years of age. This present analysis contained a large number of relatively younger women and compared them with a somewhat older and smaller group of men. The incidence of PD in men was measurably higher than in women, but compared with age and gender, PD was much less in both women and men who smoked than didn't smoke. No satisfactory explanation explains this relationship. Also, although nonsmoking women also develop more PD than smoking women do, the expression shows the trait only after about age 65 and remains less functionally disabled in female than male PDs. **—FRED PLUM**

EBV and Risk of MS

ABSTRACT & COMMENTARY

Source: Ascherio A, et al. Epstein-Barr virus antibodies and risk of multiple sclerosis. *JAMA.* 2001;286:3083-3088.

From more than 60,000 nurses participating in the Nurses Health Study by the Harvard School of Public Health, Ascherio and colleagues identified 144 women with probable or definite multiple sclerosis (MS) and 288 matched controls, all of whom had provided blood samples. Of these, 18 cases of MS were documented to have serum collected before the onset of MS. When their serum was tested for antibodies against cytomegalovirus (CMV) and Epstein-Barr virus (EBV), they were found to have significantly higher antibody titers to EBV proteins EBNA-2 and EBNA-1 compared to controls (P = 0.01 and 0.02, respectively). Weaker elevations in antibodies against EBV were seen in 126 cases of MS with blood collected after disease onset.

Wandinger and colleagues determined the prevalence of antibodies and PCR DNA positivity to EBV, CMV, HSV-1, and HSV-2 in 108 MS patients and 163 healthy controls (Wandinger K, et al. *Neurology.* 2000;55:178-184). Serial monthly blood testing indicated frequent EBV reactivation in MS, particularly in those MS patients with more active disease (50-100%), compared to controls (17%).

COMMENTARY

The association of human herpes viruses, including EBV (HHV-5), and HHV-6 with MS has been discussed previously (Apatoff BR. *Neurology Alert*. 1999; 17:57-58). Indeed, demyelinating events have been reported in the literature with acute EBV infection and other herpes viruses over the years. The study by Ascherio et al, however, is suboptimal as a prospective study for MS because most serum samples were collected from subjects older than 40-60 years of age, when MS typically presents between the ages of 20-40. One difficulty with establishing a disease association for EBV is that this ubiquitous virus is found in more than 95% of healthy people by adulthood, with most persons being asymptomatically infected. Similarly, other systemic autoimmune disease (eg, rheumatoid arthritis) or nonspecific stress has been associated with

EBV reactivation and possibly increased antibody titers. While a causal etiology for EBV and MS cannot be made from the above studies, its association with MS and a variety of other lymphoproliferative or autoimmune disease remains of interest. Whether viral activation is a primary process in MS, or just a secondary phenomenon occurring with immune activation, will be important in the success of future therapeutic strategies. **—BRIAN R. APATOFF**

Muscle Radiography: Too Little, Too Soon

ABSTRACT & COMMENTARY

Source: Ozsarlak O, et al. Hereditary neuromuscular diseases. *Eur J Radiol.* 2001;40:184-197.

Muscle reactions to pathologic conditions are myriad and include, among others, cell death, regeneration, hypercontraction, split fibers, storage, and calcification. Clinical appreciation of these changes usually requires muscle biopsy and light or electron microscopy. Some changes, including atrophy, hypertrophy, pseudohypertrophy, and fatty infiltration, can be appreciated by computerized tomography (CT) and magnetic resonance imaging (MRI). How much information do these modalities provide and what do they add to the management of neuromuscular disease patients?

Muscle CT and MRI findings were reviewed from a large group of neuromuscular disease (NMD) patients including muscular dystrophy (Duchenne, Becker, limb girdle, facioscapulohumeral, Emery Dreifuss, congenital, merosin deficient, and myotonic), congenital myopathy, metabolic, inflammatory (inclusion body, polymyositis, and dermatomyositis), spinal muscular atrophy, and hereditary motor and sensory neuropathy. Fatty infiltration was the most common finding, falling into a variety of patterns. Central or peripheral zones of hypodensity, and generalized or diffuse patchy areas of low density (with or without preservation of peripheral fascia) were seen. None of the patterns were specific or diagnostic and all conformed to the clinical distribution of muscle abnormalities. Although not useful diagnostically, muscle radiography may assist in choosing which muscle to biopsy and in following disease progression.

COMMENTARY

Ultrasonographic examination is a relatively simpler, more time efficient, and less costly method for evaluating muscle (*Neuromusc Disord.* 1999;9:203-207). Among 100 children with suspected NMD, 66 boys and 34 girls with a mean age of 5.3 years, ultrasound had a sensitivity of 78% and specificity of 91% in detecting NMD. In the younger than 3-year-old age group, sensitivity and specificity were even greater, 81% and 96%, respectively. Muscle ultrasound is specific and sensitive for uncovering suspected NMD in children. It also appears comparable to MRI, at least with respect to examining cross-sectional area or volume (*Br J Sports Med.* 1997;31;59-64). In a study of these measurements using MRI and ultrasound in the quadriceps femoris muscle of 10 healthy volunteers, no significant differences were discerned. Presently these methods have limited usefulness in the clinical neurology setting but further advances in their methodology may prove clinically valuable. **—MICHAEL RUBIN**

IVIG for Stiff-Person Syndrome

ABSTRACT & COMMENTARY

Source: Dalakss MC, et al. High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med.* 2001;345:1870-1876.

In this randomized, double-blind, placebo controlled, crossover study, 16 patients with stiff-person syndrome, 9 women and 7 men, mean age 46 years, received 3 months of either placebo or intravenous immunoglobulin (IVIG) followed by a 1-month washout period and 3 months of the alternative therapy. None had any other neurologic disease, none were bedridden, and all were positive for circulating antibodies to glutamic acid decarboxylase (GAD65). IVIG was administered as 1 g/kg/d for 2 consecutive days, once a month for 3 months. Baseline medications were unchanged during the study and included benzodiazepines (n = 16), baclofen (n = 6), gabapentin (n = 3), and valproic acid (n = 1). Primary end points were 2-fold: first, a distribution-of-stiffness index, ranging from 0-6, reflecting stiffness in the upper or lower trunk, legs, arms, face, and abdomen. Second, change in spasm frequency, assessed using the heightened sensitivity scale, which monitors spasms following unexpected noise, visual or somatosensory stimuli, activity, stress or emotional upset, no stimuli, or nocturnal spasms. Anti-GAD65

antibody titers were measured pre- and posttreatment and patients were asked to judge their own response to treatment.

Two patients' response to treatment could not be obtained, one due to severe rash (n = 1) which precluded masking, and one due to daily fluctuations which precluded data collection. Among the remaining 14 patients, IVIG resulted in significant improvement that was lost when the placebo arm followed active treatment. Conversely, placebo, when administered first, resulted in no significant change in stiffness or spasm frequency, both of which improved when the IVIG arm of therapy was instituted. Ambulation was facilitated, falls less frequent, and household chores surmountable in 11 patients who received IVIG, and the duration of benefit lasted from 6-52 weeks. Twelve patients correctly guessed when they had received IVIG compared to placebo. GAD65 titers dropped with IVIG, and not with placebo, but titers did not correlate with disease severity, nor did reduction correlate with degree of improvement. IVIG is a safe and effective treatment for stiff-person syndrome.

COMMENTARY

In 1956, Moersch and Woltman first described 14 patients, whom they had observed at the Mayo Clinic over a 32-year period, with "progressive fluctuating muscular rigidity and spasm." They termed the disorder stiff-man syndrome, which also bears their name as eponym (Moersch Woltman syndrome) and which, in our age of political propriety, has been modified to stiff-person syndrome (although 4 of the original cases were women). Their original description has not been improved upon. However, 2 significant advances, one regarding disease pathogenesis and one regarding therapy, have occurred. Its pathogenesis remains unknown but is suspected to be autoimmune in nature, based in part on the presence of characteristic antibodies to glutamic acid decarboxylase (GAD) of various sizes, which have been reported by several groups (*N Engl J Med.* 1988;318:1012-1020; *Neurology.* 1993;43:114-120). Treatment was uniformly disappointing until diazepam was shown to be symptomatically beneficial, so dramatically in fact that it is a diagnostic criteria (*Mayo Clin Proc.* 1989;64:629-636). Presently, it appears that prolonged relief of symptoms may be obtained by IVIG infusions. Uncovering and addressing the underlying cause will be necessary before definitive treatment will be available. Meanwhile, the rare but unfortunate patient with this condition may be offered succor and solace with this safe and easily administered remedy. **—MICHAEL RUBIN**

Acute Unilateral Tongue Paralysis in Evolving GBS

CASE REPORT

A 44-YEAR-OLD MAN WITHOUT ANY SIGNIFICANT medical history awakened with left arm weakness. A few hours later he noticed left leg weakness and presented to the New York Hospital. On admission, his examination was notable for a striking left tongue deviation, left hemiparesis, proximal (MRC grade 1-2/5) more than distal (MRC 4/5) weakness in both arm and leg, and hypoflexia throughout with flexor response of the toes. A presumed diagnosis of ischemic stroke in the medullary area by the graduate staff was considered but MRI of the brain showed no abnormality.

The next day, he developed difficulty swallowing and right-sided weakness. On examination, he now had a trace of right-facial weakness, slight deviation of the uvula to the right, and a new right-arm weakness (3-4/5). He had lost all of his motor reflexes except those of the right biceps and triceps. Sensation was perfect. Nerve conduction study showed a wave (57.3) in the left peroneal nerve and a conduction block across the elbow in the left ulnar motor nerve. His CSF contained a protein of 45 and glucose of 70, with 0 WBC. A diagnosis of Guillain Barré Syndrome (GBS) was made and he was treated with IVIG.

COMMENTARY

Acute hemiparesis and unilateral tongue paresis is a rare presentation in GBS. Occasionally the peripheral Miller Fisher syndrome is mistaken as a brain stem stroke due to opthalmoparesis, but we could not find a similar case in the literature of GBS to present such a severe lingual hemiparesis that it appeared to have an upper motor neuron stroke. In retrospect, there was a subtle sign such as the evolving distribution of weakness and lack of stretch reflexes in the left limbs. Unilateral, semi-isolated tongue weakness is rare in every case. Facial nerve is the most common cranial nerve affected in GBS. In some reports, bilateral tongue weakness is reported in about 20% of the GBS patients (Winer JB, et al. *J Neurol Neurosurg Psychiatry.* 1988;51:613-618), but it is usually bilateral. In his 100 cases of tongue paralysis that Keane reported, 4 were to be from GBS, but only 1 had unilateral tongue paresis (Keane JR. *Arch Neurol.* 1996;53:561-566). **—FRED PLUM & MICHIKO K. BRUNO**

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Brief Alert

Tacrolimus for Myasthenia Gravis

Source: Evoli A, et al. Successful treatment of myasthenia gravis with tacrolimus. *Muscle Nerve.* 2002;25:111-114.

IMMUNOSUPPRESSION FOR THE TREATMENT OF MYASthenia gravis may be achieved by several agents, including prednisone, azathioprine, cyclosporine A, or mycophenolate mofetil (CellCept). This case report indicates that the new immunosuppressant, tacrolimus (FK-506), may also be beneficial.

A 56-year-old diabetic man developed myasthenia during interferon alpha 2b (Intron) therapy for hepatitis C. Diagnosis was confirmed by a decremental response on repetitive nerve stimulation testing and elevated acetylcholine receptor antibody titers. Pyridostigmine proved beneficial. Deterioration of myasthenia occurred 4 months later and cyclosporine was initiated. Prednisone and azathioprine were contraindicated due to the diabetes and hepatitis. Thymectomy followed 2 years later. Worsening renal function resulted in discontinuation of cyclosporine, and tacrolimus 2 mg b.i.d. (approximately 0.05 mg/kg) was begun for control of myasthenic symptoms. Improvement of myasthenia was seen within 2 weeks. One month later only arm fatigability and mild eye closure weakness was present. At last follow-up 15 months later, the patient was in remission.

COMMENTARY

Tacrolimus (FK506, Prograf) was approved for liver transplantation in 1994, for renal transplantation in 1997, and is also used for heart, lung, and pancreas transplants. Together with cyclosporine A and rapamycin (FKBP-12, sirolimus), it is one of a group of immunophilin-binding agents. Immunophilins are cytosolic isomerases which activate T cells and, by binding these molecules, inhibition of T cell specific kinases and phosphatases is achieved. Like cyclosporine, the target of tacrolimus is calcineurin, a calcium-calmodulin regulated, serine-threonine protein phosphatase which regulates the nuclear importation of a transcription factor, NF-AT (nuclear factors of activated T cells). NF-AT is required for cytokine gene expression and, in its absence, T cell activation is inhibited. Tacrolimus' safety profile appears similar to cyclosporine with respect to renal dysfunction, hyperglycemia, hyperkalemia, or hypomagnesemia. Hypercholesterolemia, hypertension, hirsutism, and gingival hyperplasia are less common. Favorable reviews of tacrolimus to date ensure that its use in neurological conditions is likely to increase. —MICHAEL RUBIN

CME Questions

5. Patients with essential tremor and gait disorder are likely to have all of the following *except*:
a. intention tremor of hands.
b. only postural tremor of hands.
c. only slightly disturbed normal walking.
d. abnormal tandem gait.
e. impaired activities of daily living.

6. Which of the following is *false*?
a. Most Huntington's disease patients have an expanded CAG repeat in the IT-15 gene.
b. At least 2 loci other than the IT-15 gene have been shown to cause a syndrome similar to Huntington's disease.
c. The syndrome similar to Huntington's disease is characterized by prominent chorea.
d. CAG repeat length of 41 in the IT-15 gene guarantees that an individual will develop Huntington's disease.

7. Which one of the following is correct?
a. Ultrasonographic examination of muscle is diagnostically specific.
b. CT examination of muscle is diagnostically specific.
c. MRI examination of muscle is diagnostically specific.
d. All of the above
e. None of the above

8. Stiff-person syndrome:
a. being treated with intravenous immunoglobulin is of therapeutic benefit.
b. is associated with serum GAD65 antibodies.
c. may affect women.
d. All of the above
e. None of the above

9. Tacrolimus:
a. has a similar mechanism of action as corticosteroids.
b. inhibits T cell activation.
c. enhances immunophilin activity.
d. increases calcineurin activity.
e. upregulates the nuclear importation of a transcription factor, NF-AT (nuclear factors of activated T cells).

In Future Issues:

Predictors of Functional Disability and Mortality after Status Epilepticus