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INSIDE

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Peer reviewer M. Flint Beal, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company having ties to this field of study.

Moving in the Right Direction: Deep Brain Stimulation for PD

ABSTRACT & COMMENTARY

By Melissa J. Nirenberg, MD, PhD
Assistant Professor, Neurology and Neuroscience, Weill Cornell Medical College
Dr. Nirenberg reports no financial relationship relevant to this field of study.

Synopsis: *Deep brain stimulation of the subthalamic nucleus improved "off" motor symptoms and quality of life in advanced Parkinson's disease, but was associated with an increased rate of serious adverse events.*

Source: Deuschl G, et al. A Randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2006;355:896-908. Erratum in: *N Engl J Med*. 2006;355:1289.

DEEP BRAIN STIMULATION (DBS) OF THE SUBTHALAMIC NUCLEUS (STN) is an FDA-approved treatment for advanced Parkinson's disease (PD), but there is a need for additional large, randomized, controlled trials to clarify the safety and efficacy of this procedure. In this study, an unblinded, randomized-pairs design was used to compare STN DBS with medical management alone. Subjects (n = 156) were recruited from 10 academic medical centers in Germany and Austria, and then enrolled in pairs (78 pairs), with one subject randomly assigned to bilateral STN DBS (plus medications) and the other to best medical therapy. Study subjects were < 75 years old, diagnosed with idiopathic PD for at least 5 years, experiencing disabling motor symptoms or dyskinesias, and did not have dementia, major psychiatric illness, or contraindications to surgery. Surgical techniques were based on the protocol of the enrolling institution. Primary end points were the changes in quality of life on the Parkinson's Disease Questionnaire (PDQ-39), and the severity of motor symptoms in the "off" state (after 12 hour medication withdrawal) on the Unified Parkinson's Disease Rating Scale part III (UPDRS III). Secondary end points included changes in self-reported activities of daily living scores (UPDRS part II and Schwab and England Disability Scale).

Six months after enrollment, an intention-to-treat analysis showed that subjects who received DBS had 1) a greater improvement in PDQ-

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39 quality of life scores in 50/78 pairs ($P = 0.02$) and 2) a greater improvement in motor scores on the UPDRS-III during medication withdrawal in 55/78 pairs ($P < 0.001$). The DBS group, as a whole, had a mean improvement of 25% in the PDQ-39, with benefits in mobility, activities of daily living, emotional well-being, stigma, and bodily discomfort; they did not show improvement in social support, cognition, or communication. The DBS group also had a 41% improvement in the mean UPDRS-III motor scores 12 hours after medication withdrawal. In contrast, the mean PDQ-39 and UPDRS-III scores were unchanged in the medical management group. Activities of daily living scores on the UPDRS-II during medication withdrawal showed a 39% improvement in the DBS group, compared with a 5% worsening in the non-DBS group. Serious adverse events were significantly more common in the DBS group (13% vs 4%, $P < 0.04$), and included a fatal intracerebral hemorrhage during surgery and a suicide 5 months after randomization.

COMMENTARY

DBS is a highly effective intervention for advanced PD that can improve cardinal motor symptoms (tremor, rigidity, and bradykinesia) and reduce disabling motor complications, such as dyskinesias and end-of-dose "wearing off." Selection of appropriate surgical candidates is critical, since the procedure does not help midline symptoms such as postural instability, and can worsen non-motor symptoms such as cognitive impairment. Adverse events include not only expected problems such as stroke and infection, but also neuropsychiatric disorders and suicidality.

The results of this study add to a growing body of literature supporting the role for STN DBS in carefully selected patients with advanced PD. They show that DBS can improve quality of life and "off" motor disability in relatively young, non-demented patients whose symptoms are poorly controlled with medications alone. Study limitations include the relatively brief follow up time and the lack of blinded raters; several of the authors also had financial ties to Medtronic, Inc., which makes the DBS hardware. Future studies are needed to clarify the ideal patient characteristics, surgical techniques, and timing of surgical intervention, so that physicians will be able to provide patients with individualized, evidence-based treatment recommendations. ■

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Creutzfeldt-Jakob Disease: How to Best Diagnose It

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Medical College, Cornell University

Dr. Safdieh reports no financial relationships relevant to this field of study.

Synopsis: *Sporadic Creutzfeldt-Jakob disease (CJD) has multiple subtypes, and the subtype has an effect on the sensitivity of commonly utilized diagnostic tests in the workup of CJD.*

Sources: Head MW, Ironside JW. Sporadic Creutzfeldt-Jakob disease: Further twists and turns in a convoluted protein. *Brain*. 2006;129:2238-2240.

As a group, prion diseases are relentlessly progressive and ultimately fatal neurodegenerative diseases. However, the time course, symptomatology, and sensitivity of diagnostic studies vary between different patients affected with the sporadic form of Creutzfeldt-Jakob disease (sCJD). It seems that there are multiple clinical variants of sCJD, and the clinical manifestations depend both on the configuration of the abnormal prion protein and the prion protein gene. There are 2 physiochemical forms of the abnormal prion protein known as type 1 and type 2. These 2 types are distinguished by their N-terminus and by their gel mobility of the prion after treatment with a proteolytic enzyme, proteinase K.

Codon 129, of the prion protein gene, plays a key role in determining the clinical form as well. Patients may be homozygous for methionine, homozygous for valine, or heterozygotes. A classification system pro-

posed by Gambetti contains 6 subtypes of sCJD: MM1, MV1, VV1, MM2, MV2 and VV2.[1] An alternative classification system proposed by Collinge further subdivides the MM1 group into short and long duration subtypes based on chemical properties. In the paper by Cali and colleagues,[1] a series of experiments were performed suggesting that differentiation of the MM1 subgroup is not justified. They argue that the subdivision proposed by Collinge was an artifact of laboratory conditions, specifically pH.

The article by Collins and colleagues[2] is a prospective study over a 10-year period, with a total of 2451 patients with definite sCJD, all from Europe or Australia.[2] The study assessed the influence of age at onset, duration of illness, prion protein gene codon 129 polymorphism, and molecular subtype (type 1 or type 2) on the diagnostic sensitivity of EEG, brain MRI, and CSF 14-3-3 assay. EEG was considered positive when it contained sustained periodic sharp wave complexes typically seen in sCJD. Brain MRI was considered positive when high signal was present in the putamen and caudate nucleus on T2-weighted images. Overall, the median age of onset of CJD was 67 years. VV1 patients were significantly younger at onset. The median duration of illness was 5 months. Two-thirds of patients had the more common MM genotype, and two-thirds of the prion proteins were type 1.

Overall, the CSF 14-3-3 assay was the most frequently positive investigation, with 88.1% sensitivity. However, it was much less sensitive in the uncommon MV2 and MM2 subtypes. Overall sensitivity of EEG was 58.4%. The EEG was most sensitive in MM1 subtype patients, with sensitivity of 72.8%. This is the most common subtype of sCJD. Sensitivity of EEG decreased significantly over the duration of the disease. Additionally, older patients more frequently demonstrated positive EEG findings. Positive MRI was seen in only 39.1% of cases where the test was done. The likelihood of a positive MRI was higher in MV and VV subtypes, in contrast to EEG. However, Head and colleagues acknowledge that this may be an underestimate of MRI sensitivity given recent advances in technology, especially diffusion-weighted imaging.

COMMENTARY

As with most neurological disorders, the diagnosis of CJD is usually made at the bedside with a comprehensive neurological history and examination. Because of the rarity of this disease, the utility of diagnostic tests has not been well established. The study by Collins et al is the largest to date, and it sheds light on the sensitivity of the 3 most commonly used diagnostic tests in the evaluation of CJD. Clearly, the CSF 14-3-3 protein assay is highly sensitive. The study does not address the specificity of this protein assay, which is not as high as the sensitivity. However, in the proper clinical context, a positive CSF 14-3-3 protein is quite helpful. EEG is more sensitive early in the course of CJD. As the disease progresses, the periodic sharp wave complexes in the EEG become less frequent as the overall pattern of EEG becomes slower and more disorganized. The sensitivity of MRI in this study is quite low. However, with newer technology, it is likely that the sensitivity of MRI will be higher. Additionally, in the less common and less clinically characteristic VV2 and MM2 subtypes, MRI demonstrates higher sensitivity. These subtypes have traditionally been more difficult to diagnose, and it seems that the diagnosis may become easier with modern, high-field MRI imaging.

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2. Collins SJ, et al. Determinants of diagnostic investigation sensitivities across the clinical spectrum of sporadic Creutzfeldt-Jakob disease. *Brain*. 2006;129:2278-2287.

New Oral Agent for Multiple Sclerosis Shows Benefit

ABSTRACT & COMMENTARY

By Brain R. Apatoff, MD, PhD

Director, Multiple Sclerosis Clinical Care and Research Center, Department of Neurology and Neuroscience, NewYork-Presbyterian Hospital, Cornell Campus

Dr. Apatoff is on the speaker's bureau for Biogen and Teva.

Synopsis: *Fingolimod, a novel immunomodulating agent that can be taken orally, reduces the number of clinical relapses and MRI lesions in patients with multiple sclerosis.*

Source: Kappos L, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl J Med*. 2006;355:1124-1140.

In this phase II clinical trial, 281 patients with multiple sclerosis (MS) from centers in Europe and Canada were randomized to treatment with the immune modulator, fingolimod, at a dose of 1.25 mg or 5.0 mg daily, or to a placebo, once daily for 6 months. The baseline characteristics of the patients were similar in all 3 groups — mean age was approximately 38 years, mean disease duration was 8.5 years, and mean EDSS score was 2.5. The majority of patients had relapsing-remitting MS, with a small percentage (approximately 10%) categorized as secondary progressive MS.

Patients were monitored with blinded, monthly clinical assessments and brain MRI scans for 6 months. At the end of 6 months, 255 patients completed the core study. For the primary end point, the median total number of gadolinium-enhancing lesions on MRI was lower with fingolimod 1.25 mg (1 lesion, $P < 0.001$) and fingolimod 5.0 mg (3 lesions, $P < 0.006$) than with placebo (5 lesions). The annualized relapse rate in the placebo group was 0.77, compared with a rate of 0.35 in the 1.25 mg fingolimod group ($P < 0.01$) and a rate of 0.36 in the 5.0 mg fingolimod group ($P < 0.01$).

In a blinded extension study, patients in the placebo group were randomly assigned to one of the fingolimod doses for months 7 through 12. For the 227 patients completing the extension phase, there was a sustained benefit in the original fingolimod groups, and reductions in the clinical measures and brain MRI activity of patients who switched from placebo to fingolimod.

Adverse events included nasopharyngitis, dyspnea, headache, diarrhea, and nausea. Asymptomatic elevations of liver enzymes were seen in 10-12% of fingolimod patients vs 1% of placebo patients. Fingolimod was also associated with a transient reduction in heart rate and a slight decrease in the forced expiratory volume in one second. There was one case of posterior reversible encephalopathy syndrome (PRES) in the 5 mg. per day fingolimod group.

COMMENTARY

Fingolimod is derived from a fungus that has been used in Chinese traditional medicine for thousands of years. Its lymphopenic effect has been shown to be caused by its blockade of sphingosine-1-phosphate receptors (S1P) that are expressed on T-lymphocytes and regulate lymphocyte migration. The S1P receptor is necessary for extravascular lymphocytes to migrate from lymph nodes and enter the vascular compartment and, ultimately, the central nervous system compartments. Thus, fingolimod's ability to induce lymphopenia results from T-cell sequestration rather than the cytotoxic effects seen with other immunosuppressive drugs. Because the S1P receptor is also expressed in cardiac and pulmonary tissue, some adverse effects were seen on heart rate and pulmonary function. The presence of S1P receptors in the brain may also explain the case of PRES that was observed in the high-dose fingolimod group.

This proof of concept study shows that oral fingolimod causes a significant and relatively rapid reduction of disease activity based on brain MRI lesions and clinical relapse rate. A larger, long-term Phase III study is being organized in the United States, and will hopefully provide more complete safety and efficacy data for this promising, novel, immune-modulating drug. ■

"Why Do I Hear a Heartbeat in My Ear?"

ABSTRACTS & COMMENTARY

By Dara G. Jamieson, MD

Associate Professor, Clinical Neurology Director,
Weill Medical College, Cornell University

Dr. Jamieson is a consultant for Boehringer Ingelheim and Merck, and is on the speaker's bureau for Boehringer Ingelheim, Merck, Ortho-McNeil, and Pfizer.

Synopsis: *Pulsatile tinnitus is usually due to an ipsilateral venous anomaly that can be diagnosed with CT angiography and venography in most cases.*

Sources: Krishnan A, et al. CT arteriography and venography in pulsatile tinnitus: Preliminary results. *AJNR Am J Neuroradiol*. 2006;27:1635-1638; Doshi J, et al. Objective pulsatile tinnitus: A video clip demonstration of the condition. *Laryngoscope*. 2006;116:1926.

Tinnitus is a common, annoying condition that can be pulsatile or non-pulsatile. While most tinnitus has a benign etiology, pulsatile tinnitus, due to vibrations of turbulent flow reaching the cochlea, may indicate a potentially concerning vascular lesion. Non-vascular causes are rare, and include idiopathic intracranial hypertension, skull base meningoceles, and medication. Multiple imaging modalities are often needed to distinguish between benign vascular etiologies such as an audible intracranial bruit and a more concerning condition such as a vascular malformation. Four vessel catheter angiography is the most sensitive modality to diagnose a dural arteriovenous malformation producing subjective auditory symptoms. Magnetic resonance studies, magnetic resonance imaging, magnetic resonance angiography, and magnetic resonance venography are used to look for carotid artery disease, cerebral venous disease, and idiopathic intracranial hypertension. A patient with pulsatile tinnitus and a retrotympanic mass may be screened with a CT scan of the temporal bone, looking for a cholesteatoma or glomus tumor. Ideally, imaging would involve a single study.

In the paper by Krishnan and colleagues, CT angiography and venography (CTA/V) was used prospectively to evaluate pulsatile tinnitus in 16 patients who had normal otological examinations and no middle ear mass. Arterial or venous localization was predicted using ipsilateral carotid artery or jugular vein compression. Both arterial and venous phases were obtained with a single acquisition after injection of non-ionic contrast, followed by imaging using a CT scanner, with sections from the vertex to C6 level. All images were reconstructed using standard bone

reconstruction algorithms. Coronal reformations through the temporal bone, as well as coronal and sagittal reformations through the carotid artery bifurcations and posterior fossa venous sinuses, were generated.

The study included 9 women and 7 men ranging in age from 27 to 73 years. Only one had tinnitus that could be heard on auscultation. Six patients had presumed venous origin of the tinnitus based on neck compression, and 2 had obliteration of tinnitus on internal carotid artery compression. Five patients had entirely normal CTA/V studies. Six patients had strongly dominant venous systems, with all but one of these patients reporting tinnitus on the side of the dominant transverse and sigmoid sinus. An extremely thin sigmoid plate between the dominant transverse sinus and the ipsilateral mastoid complex was seen in 3 of these 6 patients. One patient, with a decade of tinnitus, noted resolution of symptoms after surgical repair of a diverticulum of the right transverse sinus extending into the mastoid complex. Other findings which lateralized to the side of the tinnitus were a dominant venous system, with a high-riding jugular bulb in one patient and external carotid stenosis in another patient. Mastoid air cell opacification was noted contralateral to the tinnitus in one patient.

Different CT settings can be used to evaluate pulsatile tinnitus. Bone window settings can be used to assess the temporal bone and middle ear on axial images and coronal reformations. An aberrant internal carotid artery can be diagnosed, with a vascular window setting to evaluate carotid stenosis, looking for a small patent luminal diameter on axial images. This same window setting can be used to evaluate for an empty sella and small ventricles, as found in idiopathic intracranial hypertension. The vascular window can be formatted to evaluate the venous system, including the dural venous sinuses. While dural arteriovenous fistula may be detected on CTA/V, the technique is not as sensitive as conventional angiography.

All the patients in this series who had lesions that could potentially account for tinnitus symptoms had venous etiologies, such as venous sinus dominance, transverse sinus stenosis, and venous diverticulum. The significance of the dominance of the venous sinus system in pulsatile tinnitus is unclear, as approximately 59% of the population has a dominant right venous system. Krishnan et al are conducting a study on the use of CTA/V in asymptomatic individuals, compared to patients with pulsatile tinnitus.

Krishnan et al conclude that the single CTA/V study of the middle and inner ear and of the vascular structures may replace multiple other imaging modalities used to evaluate a patient with pulsatile tinnitus. But, when a dural arterial venous malformation is suspected, CTA/V may not replace conventional angiography.

Doshi and colleagues report on a 72-year-old woman who sustained a small dural venous tear during the resection of a petrous meningioma. Two months later, she developed ipsilateral pulsatile tinnitus, with otoscopic evaluation revealing a tympanic membrane pulsating synchronously with her arterial pulse. CT showed opacified mastoid air cells, and surgical exploration found an iatrogenic communication between the upper end of the craniotomy and the mastoid air cells. The pulsatile tinnitus completely resolved with bio-glue repair of the defect. Doshi et al present a real time visual demonstration of the pulsating tympanic membrane through a non-pneumatic otoscopy at www.laryngoscope.com. ■

Safety of Long-Term Combined Immunosuppression in Myasthenia Gravis

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, NewYork-Presbyterian Hospital, Cornell Campus

Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.

Synopsis: *Long-term treatment of myasthenia gravis with combined immunosuppressive therapy is generally safe and effective.*

Source: Rozsa C, et al. Safety of long-term combined immunosuppressive treatment in myasthenia gravis — analysis of adverse effects of 163 patients. *Eur J Neurol*. 2006;13:947-952.

Prospective, open, long-term observation (mean 19 months, range 6-65 months) of 163 myasthenia gravis (MG) patients was undertaken to determine the safety of enduring combined immunosuppressive therapy. Diagnosis of MG was based on the presence of typical fluctuating muscular symptoms, combined with a decremental response on repetitive nerve stimulation testing, with or without acetylcholine receptor antibody positivity. Immunosuppressive therapy, azathioprine 1.0-2.5 mg/kg daily, combined with alternate day methylprednisolone 1-1.5 mg/kg, to a maximum of 100 mg, was administered only to generalized myasthenics who did not respond to cholinesterase inhibitors, or to those with a history of crisis. Patients were seen every 3 months, underwent clinical and laboratory assessment, and completed a detailed questionnaire. Chi-square and Mann-Whitney tests were used for statistical analysis.

Sixty-one percent of patients experienced adverse effects from medication; overall, in 52%, these were steroid-related and, in 20%, azathioprine-related. Among patients with adverse effects, 67% were due solely to

steroid, 15% to azathioprine, and 18% to both. Azathioprine was discontinued in 10, due to neutropenia, hepatotoxicity, or severe joint pains (2 each), pancytopenia, vomiting, allergic skin reaction, or severe axonal polyneuropathy (one each). Steroids were discontinued in only 1 patient, due to bleeding duodenal ulcer. Osteoporosis with vertebral compression (n = 4) or hip fracture (n = 1) did not mandate medication withdrawal. Steroid induced myopathy or psychiatric complications were not observed. Cancer caused death in 3 patients (colon in 2, and endometrial in one), cardiac disease in 4, and pulmonary embolism and iliac artery thrombosis in one each. Long-term immunosuppressive therapy was deemed safe and rarely required interruption of treatment. Adverse effects appeared to correlate with disease severity at onset of treatment.

COMMENTARY

Prolonged treatment of generalized MG for up to 2 years (88-104 weeks) with tacrolimus, 2-4.5 mg/day, also appears safe and effective (*J Neurol Neurosurg Psychiatry*. 2005;76;448-450). Among 12 MG patients, 3 men, 9 women, aged 4-31 years, steroid dose could be reduced in 7 (58%) and Activities of Daily Living score improved in 8 (67%). Eight patients experienced side effects, mostly minor and not requiring discontinuation of treatment. Severe headache and eye pain was seen in one, for which tacrolimus was stopped for 7 weeks and then restarted. Infection was not observed.

The Pathology of Essential Tremor

ABSTRACT & COMMENTARY

By John J. Caronna, MD

Vice-Chairman, Department of Neurology, Cornell University Medical Center, Professor of Clinical Neurology, NewYork-Presbyterian Hospital

Dr. Caronna reports no financial relationships relevant to this field of study.

Synopsis: *Patients with essential tremor may have degenerative changes in the Purkinje-dentate-thalamic pathways.*

Source: Louis ED, et al. Essential tremor associated with pathologic changes in the cerebellum. *Arch Neurol*. 2006;63:1189-1193.

Essential tremor (ET) usually is a monosymptomatic disorder, although the manifestations of the tremor may be varied. Essential tremor can affect arms, head, eyelids, lips, voice, jaw, tongue, trunk, and legs. In some patients with typical ET, clinicians have described signs of cerebellar dysfunction, such as dysmetria and ataxia, but the association has been thought to be coincidental.[1,2] The histopathological characteristics of the brain in cases of ET have remained unclear. In a previous report, Louis and colleagues[3] reported the pathologic findings in 10 patients with ET. ET patients could be divided into 2 groups: those with brainstem Lewy bodies (n = 6) and those with mild cerebellar changes (n = 4). Now, they've reported a case of ET in which cerebellar involvement was marked. The patient, a 90-year-old woman, had a 30-year history of ET, characterized by head tremor and gradually, worsening action tremor of both arms. There were no clinical signs of Parkinsonism or cerebellar disorder.

At postmortem examination, there were mild degenerative changes in the cerebellar cortex (segmental loss of Purkinje cells, torpedoes, and Bergmann gliosis), as described previously.[3] There were previously unreported extensive changes in the dentate nucleus that included marked neuronal loss, with atrophy of the remaining neurons, microglial clusters, and pallor of the dentate hilum. These changes were absent in 3 control subjects who were older than 90 years of age and 3 who were ages 85 to 90 years old. The brain of the patient with ET had no Lewy bodies and only mild changes of Alzheimer disease.

COMMENTARY

ET is hypothesized to be caused by oscillatory activity in a cerebellum-dentate-brainstem pathway. Clinical studies[1] have associated ET with higher-level gait disorders in the elderly.[4] PET studies have demonstrated increased cerebellar activity in ET patients.[5] Louis and colleagues have studied pathological specimens in the Essential Tremor Centralized Brain Repository at Columbia University to describe the cerebellar features of ET. The present report extends those findings. The neurons of the dentate nucleus receive synaptic input from Purkinje cells. Efferent fibers leave the dentate nucleus via the hilum, exit the cerebellum through the superior cerebellar peduncle, and pass rostrally in the brainstem to synapses in the contralateral ventrolateral nucleus of the thalamus. Therefore, patients with lesions in this pathway, whether in the cerebellum, dentate nucleus, or brainstem, could be expected to have some type of tremor, either that associated with essential tremor or a more cerebellar-like intention tremor. Such patients also would be expected to benefit from deep brain stimulation in the region of the ventrolateral nucleus of the thalamus. Louis et al have promised to continue to catalogue and describe the pathological changes in cases of essential tremor; therefore, one can look forward to future publications in which further clinicopathological correlations are provided.

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Severe Tongue Protrusion in Dystonic Syndromes

ABSTRACT & COMMENTARY

By Claire Henchcliffe

Assistant Professor, Department of Neurology, Weill Medical College, Cornell University

Dr. Henchcliffe is on the speaker's bureau for GlaxoSmithKline, Teva/Eisai, and Boehringer Ingelheim.

Synopsis: *Severe tongue protrusion dystonia is disabling and occasionally life-threatening, and may suggest either a secondary cause or particular heredodegenerative diseases.*

Source: Schneider SA, et al. Severe tongue protrusion dystonia: Clinical syndromes and possible treatment. *Neurology*. 2006; 67:940-943.

This case series of 8 patients (6 men, 2 women, age range 18-62 years) describes rare examples of severe tongue protrusion dystonia, with text accompanied by startling videotaped examinations (available as supplemental material at www.neurology.org). Patients comprised a heterogeneous group of pre-existing dystonic syndromes due to pantothenate kinase-associated neurodegeneration (PKAN) (n = 3), neuroacanthocytosis (n = 1), postnatal ischemic encephalopathy (n = 1), Lesch-Nyhan syndrome (n = 1), presumed tardive dystonia (n = 1), and generalized non-DYT1 familial dystonia (n = 1). Life-threatening exacerbations in 2 required intubation and intensive care management; one had choking and respiratory compromise as a result of tongue protrusion, and a second required intubation after tongue biting led to almost complete severance of the anterior tongue. In a third case (neuroacanthocytosis), tongue thrusting was severe enough to perforate the lower lip. Self-mutilation was also observed in 3 patients (PKAN, Lesch-Nyhan, neuroacanthocytosis). Botulinum toxin injections of the genioglossus muscle were successful in 2 patients. However, increasing toxin dose led to side effects of dysphagia and respiratory difficulties in one patient, resulting in hospitalization. One patient with PKAN underwent bilateral pallidal deep brain stimulation, with partial benefit for generalized dystonia, and complete resolution of tongue protrusion dystonia. A second patient (postnatal ischemic encephalopathy) also obtained marked benefit from this surgery; interestingly, in the context of a brain MRI revealing bilateral globus pallidus atrophy.

COMMENTARY

Tongue protrusion dystonia rarely presents in such severe forms as described here. As Schneider and colleagues report, however, it may lead to movement disorder emergencies, requiring endotracheal intubation and intensive care. Symptoms were disabling to patients, and distressing enough that the accompanying videotape is actually accompanied by a warning to viewers. Despite being purely descriptive, given the paucity of literature regarding this pattern of dystonia, the present article is of much interest. Of the 8 cases, only one had primary generalized dystonia, and the remainder had secondary dystonia or heredodegenerative diseases. Previous reports also describe tongue protrusion dystonia in Wilson disease,[1] neuroferritinopathy,[2] and other conditions. Its occurrence in the setting of generalized dystonia in the clinic should, therefore, prompt work up, including brain imaging, a blood smear, testing for Wilson disease, and genetic testing in the appropriate context. There is scant information in the literature on management of this condition. Medications seem to be of limited use, although clonazepam and tetrabenazine (not yet available in the United States) were of help in some cases. Schneider et al suggest considering local injections of botulinum toxin into the genioglossus muscles, although potential complications include dysphagia and difficulty breathing (occurring in one of the 2 cases receiving botulinum toxin injections in this series). As more patients undergo deep brain stimulation for generalized dystonia, it will be helpful to see whether tongue dystonia responds as well as in the 2 cases described here. ■

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CME Questions

18. In advanced Parkinson's disease, subthalamic nucleus deep brain stimulation has been associated with all of the following EXCEPT:

a. reduced motor disability.
b. improved quality of life.
c. improved activities of daily living scores.
d. reduced number of serious adverse events.

19. Which of the following diagnostic studies is the most sensitive in the diagnosis of sporadic CJD?

a. Brain MRI
b. CSF 14-3-3 assay
c. EEG
d. CSF protein level
e. Head CT

20. Pulsatile tinnitus:

a. is all in the patient's head.
b. is due to non-vascular causes more frequently than vascular causes.
c. is rarely if ever amenable to surgical treatment.
d. may be efficiently evaluated with CT angiography and venography.
e. never necessitates evaluation with conventional angiography.

21. Long-term treatment of generalized myasthenia gravis:

a. is usually safe and effective.
b. may include tacrolimus.
c. may include steroid therapy.
d. may include azathioprine.
e. All the above

22. All of the following pathological findings are associated with essential tremor EXCEPT:

a. brainstem Lewy bodies.
b. cerebellar atrophy.
c. loss of Purkinje cells.
d. cerebral amyloid angiopathy.
e. atrophy of the dentate nucleus.

Answers: 18. (d); 19. (b); 20. (d); 21. (e); 22. (d)

CME Objectives

The objectives of *Neurology Alert* are:

• To present the current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;

• To discuss the pathogenesis and treatment of pain;

• To present basic science lessons in brain function;

• To discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs; and

• To discuss nonclinical issues of importance to neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness. ■

Announcement

The 12th Annual "Clinical Neurophysiology: Principles and Practice" December 27, 28, 29, 2006, New York City, Presented by the Cornell University Medical College Department of Neurology. Contact: Fatima Castro, Department of Neurology, The New York Hospital Cornell Medical Center, 525 East 68th Street, Rm. K-615, New York, NY 10021; Telephone (212) 746-2320; Fax: (212) 746-8984. Email: frcastro@med.cornell.edu

The 3rd Annual Update Symposium on Clinical Neurology and Neurophysiology, Feb. 19-21, 2007, Tel Aviv, Israel. Presented by Weill Cornell University Medical College Department of Neurology and Tel Aviv Medical Center. Information: www.neurophysiologysymposium.com ■

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In Future Issues:

New Guidelines for TIA Management

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Wait and See Prescriptions for Treatment of Otitis Media

Wait and see prescriptions (WASP) is a new concept for the treatment of otitis media in children. Children with otitis media frequently improve without antibiotics, and antibiotic overuse may be avoided with WASP, where prescriptions are given to parents but only filled if symptoms persists or worsen after 48 hours. This approach was evaluated in a recent study from the University of Oregon. In an urban, emergency room setting, 283 children with acute otitis media were randomized to WASP or standard therapy with an antibiotic. Sixty-two percent of parents in the WASP group did not fill their prescriptions, while 13% of parents in the standard therapy group did not fill theirs ($P < .001$). There was no statistically significant difference in the frequency of subsequent fever, otalgia, or unscheduled visits for medical care between the 2 groups. Very sick or toxic children were excluded from the study.

The authors conclude that wait-and-see prescriptions substantially reduce unnecessary use of antibiotics in children with acute otitis media (*JAMA*. 2006;296:1235-1241). In an accompanying editorial, Paul Little, MD, from University of Southampton in England, discusses how wait-and-see prescriptions for otitis media have been adopted by many northern European countries. He praises the current study because it was done in the emergency room setting where there is no ongoing relationship with a physician, and the chance for poor outcomes may have been higher. He also states that "If parents are given clear information about the timing of antibiotic use and specific guidelines for signs and symptoms that should trigger reassessment, delayed prescribing probably has its place, should be acceptable to parents, appears reasonably safe, and provides a significant step in the battle against antibiotic resistance" (*JAMA*. 2006;296:1290-1291).

New Hope for Macular Degeneration?

Two studies in the October 5th *New England Journal of Medicine* evaluate a new treatment for macular degeneration. Ranibizumab is a recombinant, humanized, monoclonal antibody Fab that neutralizes all active forms of vascular endothelial growth factor A (VEGF-A), which has been implicated in promoting neovascularization. Administration of the drug involves a monthly intravitreal injection. In the first study, 716 patients were enrolled and randomized to 2 different doses of ranibizumab or sham injections. In both the low-dose and high-dose ranibizumab (0.3 mg and 0.5 mg, respectively), loss of visual acuity was significantly slowed compared to sham injections ($P < 0.001$ for both doses), and visual acuity actually improved by 15 or more letters in 25% of the 0.3 mg group and 34% of the 0.5 mg group, as compared to 5% of the sham injection group ($P < 0.001$ for both doses). The benefit

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

in visual acuity was maintained for 24 months. Side effects were uncommon (*N Engl J Med*. 2006; 355:1419-1431).

In the second study, ranibizumab (0.3 mg or 0.5 mg) was compared to verteporfin photodynamic therapy. Significantly more patients lost fewer than 15 letters in the ranibizumab group vs verteporfin group (96.4% vs 64.3%, P <0 .001 for each comparison). Visual acuity improved by 15 letters or more in both ranibizumab groups (35.7% for 0.3 mg group and 40.3% for 0.5 mg group) vs 5.6% for the verteporfin group (P < 0 .001 for each comparison). Mean visual acuity increased in both ranibizumab groups, and decreased significantly in the verteporfin group. Side effects were uncommon in both groups.

The authors conclude that ranibizumab is superior to verteporfin for treatment of neovascular age-related macular degeneration (*N Engl J Med*. 2006:355:1432-1444). An accompanying editorial (*N Engl J Med*. 2006;355:1493-1495) and perspective (*N Engl J Med*. 2006;355:1409-1412) raise a fascinating ethical and economic issue regarding this issue.

Ranibizumab was recently approved by the FDA for use for macular degeneration under the trade name Lucentis (Genentech). The wholesale cost for the 0.5 mg monthly injection is $1950. Prior to the approval of ranibizumab, many ophthalmologists began compounding bevacizumab — a closely related monoclonal antibody also manufactured by Genentech and marketed under the trade name Avastin for the treatment of colorectal cancer — and using it as an intravitreal injection. The drug is formulated as an intravenous formulation, and the use of bevacizumab for macular degeneration is off label, but the drug seems to be effective based on several case studies. There is also a chance that bevacizumab may last longer in the eye since it is a much larger molecule. The cost of a single injection is also between $20 and $50. The economics alone make this issue of interest; however, it is unlikely that Genentech will intentionally undermine its own drug with a less expensive alternative, so we may not see company-sponsored studies on the use of bevacizumab for macular degeneration anytime soon.

Can Cialis be Used for Edema?

Erectile dysfunction drugs have significant effects on pulmonary vasculature, as evidenced by the recent approval of sildenafil for pulmonary hypertension. A new study suggests that tadalafil (Cialis) may be effective for preventing high-altitude pulmonary edema. In a small study from Europe, 29 adults with a history of high-altitude pulmonary edema were randomized to tadalafil 10 mg, dexamethasone 8 mg, or placebo twice daily during ascent and stage to 4559 m (14,000 feet). Two participants in the tadalafil group dropped out early because of acute mountain sickness but, of the remainder, high-altitude pulmonary edema developed in 7 of 9 participants receiving placebo, 1 of 8 adjustments receiving tadalafil, and none of the 10 participants receiving dexamethasone (P = 0.0074 for tadalafil, P < 0.001 for dexamethasone).

The authors conclude that both dexamethasone and tadalafil decrease pulmonary artery pressures and reduce the incidence of high-altitude pulmonary edema in patients at risk, although dexamethasone may be somewhat more effective (*Ann Int Med*. 2006;145:497-506).

FDA Actions

Novartis is warning doctors about the risk of congestive heart failure associated with its anticancer drug imatinib (Gleevec). The company is sending a letter to US and Canadian physicians as a result of an article in *Nature Medicine* that reported 10 patients had developed cardiotoxicity associated with use the drug (*Nature Medicine*. 2006;12:908-916). Patients with a history of high blood pressure, diabetes, or a history of heart disease may be particularly at risk.

Once a day amoxicillin is a reasonable alternative to twice a day dosing for children with strep pharyngitis, according to a new study. In 652 children with pharyngitis, researchers compared 750 or 1000 mg (depending on weight) once daily doses vs twice-a-day standard dosing. Failure rates by culture were 20.1% in the once daily group and 15.5% in the twice daily group; however, failure rates were lower in the once daily group at 28 days. There were no significant differences in adverse events (*Pediatric Infect Dis J*. 2006;25:761-767).

Mirtazapine may be a safe antidepressant for pregnant women. In 77 live births exposed to mirtazapine in the first trimester, there were 2 major malformations, a rate that is not significantly higher than chance. The drug was associated with a higher rate of preterm birth and spontaneous abortion, as noted with other antidepressants (*J Clin Psychiatry*. 2008:67:1280-1284). ■