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INSIDE

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Ocular Myasthenia in Seniors: A Case for Treatment

ABSTRACT & COMMENTARY

By Marc Dinkin, MD

Assistant Professor of Ophthalmology, Division of Neuro-Ophthalmology, Weill Cornell Medical College

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

Synopsis: *Immunomodulatory therapy reduces the rate of conversion to generalized myasthenia gravis in seniors with pure ocular myasthenia.*

Source: Allen JA, Scala S, Jones HR. Ocular myasthenia in a senior population: Diagnosis, therapy and prognosis. *Muscle Nerve* 2009 Nov 13. [Epub ahead of print].

MYASTHENIA GRAVIS (MG) IS AN AUTOIMMUNE DISORDER THAT targets the acetylcholine receptor at the neuromuscular junction, causing fatigable weakness. Clinical presentation ranges from isolated fluctuating ptosis and strabismus (ocular myasthenia gravis [OMG]) to systemic fatigable weakness (generalized myasthenia gravis [GMG]), which may affect ambulation, swallowing and respiration. Early epidemiological studies led to the impression that myasthenia was rare after the age of 70, but more recent studies, including a prospective analysis,[1] showed that the incidence rates were actually higher in patients older than 65 and that 46.2% of patients were older than 70 years of age.

The risk of conversion of OMG to GMG is highest in the first two years after diagnosis.[2] For patients with pure OMG, the use of immunomodulatory therapy has been controversial, since the potential side effects could outweigh the benefits of ptosis and diplopia reduction. However, one retrospective analysis of 94 patients with OMG found that treatment with prednisone reduced the conversion to GMG at two years from 36% to 7%.[3] Additionally, the presence of a positive acetylcholine receptor antibody titer increased the chances of conversion from 14% to 48%. There is some evidence that seniors

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with OMG have a high rate of progression to GMG within 5 years[4] and a greater risk of respiratory crisis and death if older than 50.[2]

Allen et al have retrospectively reviewed their institution's experience with OMG in patients older than 70 years of age and found relatively bright outlook for this population. In their study, 43% of seniors with myasthenia presented with ocular symptoms only. Of these patients, only 31% went on to develop GMG over a mean follow-up period of 47 months, a smaller conversion rate than the 50% rate observed in some non-senior studies. In contrast to observations in non-senior studies,[3] the authors were not able to show that antibody status affected conversion rate to GMG.

A majority of senior patients who presented with OMG were treated with immunomodulation, mostly prednisone or azathioprine, but a good many were not treated until after they generalized. There was only an 8% rate of side effects requiring discontinuation and 49% of patients were in complete remission at the last available follow-up. Most significantly, the authors found a powerful effect of initial treatment on conversion rate to GMG in seniors with OMG (7% if treated and 46% if untreated). Furthermore, 79% of the treated patients achieved remission of the ocular symptoms, in contrast to only 5% of the untreated patients. Once untreated OMG patients generalized, the remission rate with treatment decreased to 54%. The authors also noted that in women with a second auto-immune disorder, usually thyroid disease, the rate of conversion to GMG was much higher.

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Questions & Comments

Please contact **Allison Weaver**, Managing Editor, at allison.weaver@ahcmedia.com, or (617) 629-5951.

■ COMMENTARY

Despite evidence that immunotherapy can reduce the risk of conversion to GMG in ocular myasthenics, its use has remained controversial since ocular symptoms themselves are not life-threatening. In the elderly population, practitioners may be even more judicious with the use of steroids. As this study shows, however, patients older than 70 years of age with pure OMG are likely to benefit from immunotherapy just as younger patients do. Moreover, this effect on conversion rate appears to last 4-5 years in this population. Since patients who generalized required higher doses of steroids than OMG patients who were treated initially, and enjoyed less effect on remission, a strong case for early treatment is made. Treatment's profound effect on the remission of ocular symptoms, which may be quite disabling in the elderly, buttressed that argument furthermore.

The ability of corticosteroids, not only to reduce inflammation in myasthenia gravis, but also to increase the expression of acetylcholine receptors in cultured human muscle cells was discussed. This in vitro observation may contribute to the reduction in conversion rate by early steroid treatment, but the duration of the effect in vivo remains unclear. Would patients treated with steroids for a limited time return to the non-treated rate of conversion, or would a long-lasting effect on receptor density decrease the rate?

The study is limited by its retrospective design, so that biases on who went into remission based on knowledge of treatment may have been introduced. A prospective, double-blind, placebo-controlled trial would provide stronger data but would be difficult to conduct given the positive retrospective evidence for treatment. The authors finding that acetylcholine-receptor antibody status did not affect conversion rate differs from some prior reports, but may simply reflect a sample size too small to detect such a difference. Despite these limitations, this paper provides an important description of OMG in seniors and makes a convincing argument that outcomes in this population are better than previously thought, especially in those who are treated early with immunomodulatory therapy.

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gravis in the elderly: A hospital based study. *Acta Neurol Scand* 1996;3:260-262. ■

Neuropathy in Liver Failure

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Neuropathy occurs with a high frequency in patients with end-stage liver disease, but rarely causes disability.*

Source: Cocito D, Maule S, Paolasso I, et al. High prevalence of neuropathies in patients with end-stage liver disease. *Acta Neurol Scand* DOI: 10.1111/j.1600-0404.2009.01256.x

IF YOU LOOK UP "LIVER DISEASE" IN THE INDEX OF THE two-volume classic tome, *Peripheral Neuropathy* (Dyck PJ, Thomas PK, 3rd. edition, Philadelphia: Saunders), you will find only five listings: one each for acute and chronic inflammatory demyelinating neuropathy, amyloid, Fabry's disease, and vitamin E deficiency in childhood cholestatic liver disease. The association with acute inflammatory demyelinating neuropathy is tenuous, chronic inflammatory demyelinating neuropathy in liver disease is usually mild and subclinical, Fabry's disease affects Kupffer cells to some degree but not hepatocytes, amyloid affects liver and nerve independently, and neuropathy does not occur with normal vitamin E levels. Neuropathy is clearly unusual in liver disease; but just how unusual, and what type of neuropathy does it cause?

Retrospective analysis of 83 patients with advanced liver failure awaiting transplantation, including 61 men and 22 women with a median age of 53.8 years, was undertaken to determine the presence, distribution, type, cause, and pathogenesis of neuropathy. Correlation between neuropathy, liver disease severity, and disability was also examined. Routine nerve conduction studies (NCS) and autonomic function tests were used to determine the presence of neuropathy. NCS included study of the sural and ulnar sensory nerves, and the ulnar and peroneal motor nerves. Autonomic function tests included heart-rate response to deep breathing, Valsalva maneuver, baro-reflex sensitivity, and postural blood pressure change. Disability was assessed using the Rankin scale, the Medical Research Council scale, the Sensory Sum Score scale, and the Overall Neuropathy Limitations scale. Statistical analysis included Student's t-tests and Pearson correlations.

All patients had cirrhosis, usually from viral hepatitis type C (n = 34), hepatitis type B (n = 7), alcohol abuse (n = 7), primary biliary cirrhosis (n = 5), or miscellaneous (n = 11). None had primary systemic amyloidosis, five were cryptogenic, and 14 had more than one cause. Neuropathy was diagnosed in 65% (54/83) by either nerve conduction studies or autonomic function tests. Nerve conduction studies were abnormal in 48, demonstrating sensorimotor or sensory axonal neuropathy in all but one, a patient with CIDP. Cardiovascular autonomic function tests were abnormal in 21 of 57 patients tested, including six who had normal nerve conduction studies. Neuropathy was more frequent with increased severity of liver disease, and more so in hepatitis C patients compared to other liver diseases, independent of severity of liver failure. Only Rankin and Overall Neuropathy Limitations scales were worse in neuropathy patients, compared to those without neuropathy, indicating a correlation between disability and neuropathy. Other causes for neuropathy were found in 74.5%, including diabetes, alcohol abuse, and hepatitis C infection with or without cryoglobulinemia. Peripheral neuropathy and autonomic neuropathy are common in liver failure and correlate with disease severity.

■ COMMENTARY

Neuropathy may occur following liver transplantation as well, but is rare and focal in nature.[1] Among 649 liver transplantations performed in The Department of General, Liver and Transplant Surgery at The Medical University of Warsaw, Poland, between 2000-2008, 10 patients (1.5%; five men and five women), mean age 39.3 years, developed symptoms consistent with neuropathy, including peroneal neuropathy (n = 5), arm weakness or paraesthesiae (n = 2 each), and facial nerve paralysis (n = 1). None had a prior history of neurological complaints. Iatrogenic causes predominated, including cannulation of the axillary vein or adverse effects of immunosuppression (n = 2 each), and nerve compression due to forced recumbency (n = 5). Viral infection and trauma were the cause in one patient each and all patients recovered with conservative management and physical therapy.

Reference

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Treating Multiple Sclerosis: Why Wait?

ABSTRACT & COMMENTARY

By Susan Gauthier, DO, MS

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

Synopsis: *Glatiramer acetate significantly delayed the onset of clinically definite multiple sclerosis (MS) in patients having a clinically isolated event and brain lesions consistent with MS.*

Sources: Comi G, Martinelli V, Rodegher M, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): A randomized, double-blind, placebo-controlled trial. *Lancet* 2009; 374:1503-1511

MULTIPLE SCLEROSIS (MS) IS A CHRONIC INFLAMMATORY disorder with an initial relapsing phase that eventually transitions into the secondary progressive stage causing significant ambulatory and cognitive disability. The early relapsing phase of the disease is characterized by the development of inflammatory lesions, which are easily demonstrated on MRI. Axonal degradation, which is felt to be the major cause of sustained and progressive disability, begins at the earliest stages although it becomes more prominent as the disease enters the secondary stage. All of the currently FDA-approved self-injection therapies for MS have demonstrated a beneficial effect in the relapsing phase of the disease, which is reflective of their anti-inflammatory effect; however, none have been found to be beneficial for patients with secondary progressive MS. Given the correlation of axonal injury and inflammation in MS,[1] decreasing inflammation at the earliest stages of the disease may influence the ultimate disease course. Therefore, the treatment of MS has transitioned into treating at the earliest stages.

Glatiramer acetate (GA) is the last of the four injectable therapies to be tested in patients with a clinically isolated syndrome (CIS), meaning patients with one neurological event and lesions consistent with MS on a brain MRI. In the current study by Comi and colleagues, two groups of CIS patients with unifocal neurological symptoms and at least two brain lesions (≥ 6 mm in size) were randomized to receive placebo or GA for up to 36 months. The study was powered to a primary endpoint of time to conversion to clinically definite MS (CDMS). There was a preplanned interim analysis of those randomized to the placebo arm, at which time 48% of patients had completed the study, 34% of which converted to CDMS. A 45% reduction in the risk of conversion to CDMS was found in the GA group; given the strong positive result, the study was stopped. Further evidence of a benefit was demonstrated in the 115% delay (336 vs. 772 days) in conversion to CDMS for the first quartile of patients receiving GA as compared to placebo. Secondary endpoints included various MRI metrics; new T2-hyperintense lesions, new gadolinium enhancing lesions, and new T1-hypointense lesions were all in favor of GA. There was no difference between the groups in degree of brain atrophy over time.

■ COMMENTARY

This study of GA demonstrated a similar delay in developing CDMS in patients with CIS as found in previous studies of interferon beta-1a (both IM and 22 mcg SQ formulations) and interferon beta-1b.[2-4] There were some minor differences in the study designs, although all required characteristic MS lesions on a brain MRI; thus, patients were at high risk for developing the disease. The MRI criterion in the GA study was less stringent as compared to the other CIS studies, wherein a specific location or shape was not essential; however, the lesion size was required to be larger (at least 6 mm). Interestingly, patients with gadolinium-enhanced lesions at baseline appeared to respond better to GA, which corresponds to the interferon beta-1a IM study but conflicts with the other interferon studies. Thus, the characteristics associated with a treatment response in CIS patients have yet to be identified.

Given that four studies have demonstrated a similar benefit for early treatment initiation in MS, there appears to be little reason for not treating CIS patients. The key is to ensure that patients are truly at risk for CDMS, which relates to the clinical symptoms and the proper identification of characteristic MS lesions on a brain MRI. Importantly, the long-term influence of these therapies on the course of MS has yet to be established. However, given our current understanding of the disease, early treatment can only be beneficial.

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demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med* 2000;343:898-904.
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Dissecting the Subtypes of Parkinson's Disease

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

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Dr. Henchcliffe serves on the speaker's bureau of GlaxoSmithKline, Teva Neuroscience, Boehringer Ingelheim, Novartis, and Allergan.

Synopsis: *Dementia in Parkinson's disease is associated with a non-tremor-predominant phenotype, and the MAPT H1/H1 genotype. A rapidly progressing subtype without dementia has been identified, associated with another non-motor feature, depression.*

Sources: Selikhova M, Williams DR, Kempster PA, et al. A clinico-pathological study of subtypes in Parkinson's disease. *Brain* 2009;132:2947-2957. Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain* 2009;132:2958-2969.

SELIKHOVA AND COLLEAGUES EXAMINED CLINICAL records and cerebral α-synuclein and amyloid A pathology in 242 cases with autopsy-proven Parkinson's disease (PD). They divided cases into four clinically defined groups: earlier disease onset (onset < 55 years old: EDO, 25%); onset > 55 years old that was either tremor-dominant (TD, 36%) or non-tremor-dominant (NTD, 38%); and rapid disease progression without dementia (death within 10 years of onset, 8%). Mean disease duration was not significantly different between the TD and NTD groups (13.5 years vs. 12.9 years, $p > 0.05$). However, the NTD phenotype was significantly more associated with dementia (61% vs. EDO 16% vs. TD 32%), present in 43% total, and associated with shorter duration from onset to death (13.8 ± 5.7 years vs. 17.0 ± 7.6 years). Significantly higher Lewy body scores were measured in NTD vs. EDO and TD, particularly in frontal and transentorhinal cortex. Neurofibrillary pathology was more highly represented in NTD than EDO or TD cases. Those with rapid disease progression were more likely to have the TD phenotype, but were also more likely to have been diagnosed with depression at PD onset (40%) vs. EDO (20%), TD (15%), or NTD (24%).

In the accompanying study, Williams-Gray and colleagues report five-year follow-up from a longitudinal cohort of 126 patients, together with a cross-sectional cohort of 386 cases. The importance of dementia was emphasized by its 17% incidence within the first five years from diagnosis. Baseline features of age > 72 years, difficulty copying intersecting pentagons, and impaired semantic fluency (20 words in 90 seconds) led to an odds ratio (OR) of 88 for developing dementia within five years of PD onset. Microtubule-associated protein tau (MAPT) gene alleles H1 and H2 were tested. Presence of the H1/H1 genotype resulted in an OR of 21.1 for development of dementia. The authors suggest this is likely due to an effect of genotype upon levels of tau, since in autopsy brain tissue from patients with PD or dementia with Lewy bodies (n = 61), presence of the H1 allele increased 4-repeat tau transcription by approximately 20%.

■ COMMENTARY

Parkinson's disease (PD) is both clinically and genetically heterogeneous. These two studies use different approaches to suggest how better understanding the various subtypes might be translated into the clinic to determine a more accurate prognosis. First, it has long been thought that tremor predicts a more benign course. This is challenged by Selikhova's finding of a rapidly progressing subgroup of cases, most of whom fall into the tremor-dominant (TD) category. Their data suggest that in the TD subtype, "red flags" include not only faster motor evolution and development of axial symptoms, but also older age of onset and early depression. Older-onset patients with depression may therefore warrant more careful and frequent monitoring, despite a TD phenotype. Second, dementia in PD is distressing and common, but not universal. Selikhova found that a bradykinesia (rather than tremor) -dominant phenotype was strongly associated with clinical dementia, as well as heavier cortical Lewy body load and Alzheimer's-disease-related pathology. The authors suggest this association has a biological basis, but their study does not

address what that might be. However, in the accompanying study, presence of the MAPT H1/H1 genotype was associated with more than a 20-fold increased risk of dementia. This strongly suggests a role for tau protein in the pathology underlying dementia in PD. Despite the need for caution in interpreting this finding (postmortem confirmation of diagnosis is needed), it does suggest the future possibility for adding genotyping to careful phenotypic subtyping to stratify risk for dementia in PD. ■

Pharmacokinetics of IV Immunoglobulins and Outcome in GBS

ABSTRACT AND COMMENTARY

By Norman Latov, MD, PhD

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Dr. Latov serves as consultant to Quest Diagnostics, Talecris Biotheapeutics, CSL Behring Biotherapies, Baxter Bioscience, and Octapharma AG, and owns stock in Therapath LLC.

Synopsis: *Fixed dose of IVIg may not be effective in all patients with GBS.*

Sources: Kuitwaard K, de Gelder J, Tio-Gillen AP, et al. Pharmacokinetics of intravenous immunoglobulin and outcome in Guillain-Barré syndrome. *Ann Neurol* 2009;66:597-603. Cornblath DR, Hughes RAC. Treatment for Guillain-Barré syndrome. *Ann Neurol* 2009;66:569-570.

KUITWAARD AND COLLEAGUES REVIEWED DATA FROM 174 patients with Guillain-Barré Syndrome (GBS) who had previously participated in two randomized clinical trials using intravenous gammaglobulins (IVIg). All patients were unable to walk unaided and received a standard dose of IVIg. The data analysis revealed considerable variation in the increase in serum IgG (ΔIgG) at two weeks after IVIg treatment, but the patients with a low ΔIgG recovered significantly more slowly, and fewer reached the ability to walk unaided at six months. In a multivariant analysis adjusted for other known prognostic factors, a low ΔIgG was independently associated with poor outcome. The authors suggest that patients with a small increase in serum IgG level may benefit from a higher dosage or second course of IVIg.

In an accompanying editorial, Cornblath and Hughes stress the need for improvement in the management of GBS, as at one year, 2% to 3% of those with severe GBS will have died and 15% to 18% will still have significant disability. They note the absence of studies to determine the optimal dose of IVIG in GBS, and voice support for additional clinical trials with higher, or repeat doses.

■ COMMENTARY

The preferred treatment for GBS is IVIg, although questions remain regarding the dose, timing, repeat treatment, and mechanism of action.

The findings by Kuirwaard and colleagues point to the importance of identifying biomarkers that predict response to treatment. Differences can be due to underlying disease mechanisms, or to differences in the interaction of the IVIg with the host immune system. In chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), for example, recent studies show that the response to IVIg is influenced by polymorphism in TAG-1[1] and may be associated with upregulation of the expression of Fcgamma receptor IIB on B cells.[2] Following ΔIgG in patients with GBS treated with IVIG might be such a biomarker that would help guide treatment.

Another important observation is that not all patients with GBS are the same, which puts current guidelines into question.[3] This study, as an example, provides a rationale for giving patients an additional dose of IVIg if there is a relapse or no response to the initial treatment. Restricting the treatment recommendations to patients who are no longer ambulatory, as only such patients were included in clinical trials, without comparing other time points, may also be inappropriate given our inability to identify those patients who will progress to severe disability.

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What Is Frontotemporal Lobar Degeneration? New Clues Emerge

ABSTRACT AND COMMENTARY

By Cary S. Gunther, MD, PhD and Michael Lin, MD

Dr. Gunther is a Clinical Fellow in Behavioral Neurology, Weill Cornell Medical College; Dr. Lin is Assistant Professor of Neurology, Weill Cornell Medical College.

Dr. Lin and Dr. Gunther report no financial relationships relevant to this field of study.

Synopsis: *Two studies have identified a novel inclusion found in a subset of FTLD brains and categorize the clinical entity of the behavioral variant of FTLD, based on anatomical patterns.*

Sources: Neumann M, Rademakers R, Roeber S, et al. A new subtype of frontotemporal lobar degeneration with FUS pathology. *Brain* 2009;132:2922-2931. Whitwell JL, Przybelski SA, Weigand SD, et al. Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: A cluster analysis study. *Brain* 2009;132:2932-2946.

A PAIR OF STUDIES PUBLISHED IN A RECENT ISSUE OF *Brain* attempt to further elucidate definitions and underlying pathology of frontotemporal lobar degeneration (FTLD). Neumann and colleagues identified a new pathologic subtype of FTLD. They showed that the fused in sarcoma (FUS) protein, recently identified in inclusions in familial amyotrophic lateral sclerosis, is present in FTLD cases which are negative for tau- or TDP-43 but positive for ubiquitin. FUS is normally present in most cell types, and appears to be a transcriptional activator that is involved in RNA-protein binding. It is similar in this regard to TDP-43. FUS putatively acts to transport mRNA to dendrites for local translation, thus promoting plasticity and integrity of synapses. The authors identified 15 sporadic early-onset (mean age = 38) FTLD cases, and found FUS immunoreactivity in cytoplasmic inclusions and novel intranuclear inclusions. The FUS inclusions were most numerous in hippocampal dentate fascia and were also significantly present in frontal and temporal neocortex and striatum. FUS co-localized with ubiquitin in the neuronal inclusions. FUS antibodies also stained previously undescribed glial inclusions not seen with ubiquitin staining alone. No mutation in the FUS gene was found in any of the cases. Except for brains from patients with Huntington's disease, the controls, including brains with other neurodegenerative diseases, did not show FUS inclusions, strongly associating this pathological process with an FTLD phenotype.

Whitwell et al examined the neuroanatomy of patients presenting with behavioral variant FTLD (bvFTLD). They used volumetric MRI to compare patterns of grey matter loss in 66 bvFTLD subjects against a digital atlas. Clustering the results yielded four anatomical subtypes: frontal dominant, frontotemporal, temporal dominant, and temporofrontoparietal. Interestingly, although the degree of temporal lobe atrophy observed in some cases is atypical for bvFTLD, in the temporal dominant and frontotemporal subtypes the temporal atrophy was slightly right hemisphere dominant, a distribution previously associated with behavioral presentations of FTLD. Among the four subtypes, significant differences occurred in tests of delayed recall and naming, with temporal dominant patients performing worst and frontal dominant patients performing best. There was a trend towards poorer performance on tests of executive function in frontal dominant and frontotemporal subtypes. No significant differences were measured in visuospatial abilities. Little variation occurred in the severity of behavioral disturbance or type of aberrant behaviours. Autopsy data were available for 25 of the subjects, but not uniformly distributed across the four groups. Pathological and clinical evidence of motor neuron disease was present in three subjects in frontal dominant group, while Pick's disease and progressive supranuclear palsy were present in frontotemporal and frontal dominant groups. All subjects with Alzheimer's disease pathology occurred in the temporofrontoparietal or frontal dominant groups; corticobasal and FTD-TDP-43 pathology were also seen in the temporofrontoparietal group.

■ COMMENTARY

Neumann and colleagues point out similarities between roles and structures of FUS and TDP-43 as supportive of a putative FUS role in disease. Co-localization with ubiquitin in pathological inclusions strengthens this hypothesis. However, this preliminary evidence falls short of demonstrating a causal role of FUS in FTLD. The authors note that future directions include looking for an FUS role in other TDP-43-negative ubiquitin inclusion diseases. If therapeutics are to be developed based on FUS, it will be important to elucidate the mechanism by which its solubility is altered and how

this might affect neuronal function or survival.

Whitwell and team used neuroimaging to identify four anatomical subtypes of FTLD, then sought clinical and pathological correlates to these subdivisions. The clinical syndrome of FTLD is known to be associated with variable pathology, most commonly with abnormal accumulations of TDP-43 or tau, but sometimes with AD pathology. So it stands to reason that FTLD is heterogeneous in other ways as well. Distinctions within the FTLD syndrome begin to come to light in this study, as the authors observed differences in age of onset (with the youngest onset in temporal dominant subset) and distribution of cellular pathologies across subtypes. The sample size for this study was too small to draw statistical conclusions, and longitudinal data are needed to establish whether patients with these patterns of atrophy at presentation follow divergent clinical trajectories. But this research paves the way for further clarification of FTLD into cohorts in which internally consistent disorders may occur. Ultimately, the anatomical distribution of neuronal and synaptic destruction or dysfunction produces a given phenotype, and the patterns seem associated with underlying molecular mechanisms. ■

CME Objectives

Upon completion of this educational activity, participants should be able to:

1. discuss current scientific data regarding the diagnosis and treatment of neurological disease;
2. discuss the pathogenesis and treatment of pain;
3. describe the basic science of brain function;
4. discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
5. identify nonclinical issues of importance for the neurologist. ■

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant. ■

CME Questions

30. Which of the following is NOT a correct statement based on this study on ocular myasthenia in the elderly?

a. Women with a second autoimmune disease were more likely to progress to generalized disease.
b. In senior patients, there was no significant effect of immunomodulatory treatment on conversion to generalized disease.
c. Acetylcholine receptor status did not affect conversation rate to generalized myasthenia.
d. Immunomodulatory treatment did have a significant effect on ocular symptoms in seniors with ocular myasthenia.

31. Liver failure is associated with:

a. predominantly axonal polyneuropathy.
b. predominantly demyelinating polyneuropathy.
c. both axonal and demyelinating polyneuropathy with equal frequency.
d. predominantly focal peripheral neuropathies.
e. Liver failure is not associated with neuropathy.

32. Treatment with which of the following drugs has been found to delay the development of clinically definite multiple sclerosis?

a. Interferon beta-1b
b. Glatiramer acetate
c. IM interferon beta-1a
d. SQ low-dose interferon beta-1a
e. All of the above

33. Risk for dementia in Parkinson's disease is associated with:

a. young age of onset.
b. tremor.
c. decreased cortical Lewy body burden.
d. MAPT genotype.
e. There are no identified risk factors.

34. The following statement about Guillain-Barré syndrome is true.

a. Corticosteroids are the recommended treatment.
b. IVIg is the recommended treatment.
c. All patients with GBS make a full recovery after treatment.
d. Guidelines for the treatment of GBS are based on randomized clinical trial data.

Answers: 30. b, 31. a, 32. e, 33. d, 34. b

In Future Issues:

Treatment of Traumatic Brain Injury

Clinical Briefs in
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Prevention of diabetes: The long-term outlook

Source: Diabetes Prevention Program Research Group; et al. *Lancet* 2009;374:1677-1686.

NUMEROUS RANDOMIZED CLINICAL trials show that a variety of interventions can prevent the development of type 2 diabetes (DM2) in subjects with prediabetes (i.e., impaired glucose tolerance, defined as a 2-hour post-load glucose of 140-199 mg/dL). Lifestyle interventions (i.e., intensive diet and exercise programs) are generally at least as effective as pharmacotherapy (e.g., metformin, rosiglitazone, orlistat). Some experts quibble with the term "prevent," preferring instead to indicate that our prediabetes interventions simply "delay" diabetes. Since persons at high risk for DM2 are likely to remain in a high-risk group indefinitely, the long-term picture of interventions to prevent DM2 is important.

The Diabetes Prevention Program (DPP) was one of the largest diabetes prevention trials ever performed. At 2.8 years, incidence of DM2 was reduced 58% with lifestyle, and 31% with metformin (compared to placebo). A recent report by the Diabetes Prevention Program Research Group provides a window of insight into data 10 years from the date of randomization.

Compared to placebo, subjects in the lifestyle intervention group had a 34% reduction in new onset DM2; the metformin group had an 18% risk reduction.

Follow-up of subjects enrolled in the DPP indicates a long-term risk reduction in development of DM2 attained with lifestyle or metformin intervention. Whether you call it prevention or delay, less DM2 at 10 years is a good thing. ■

Does it matter how we lower LDL?

Source: Taylor AJ, et al. *N Engl J Med* 2009;361:2113-2122.

BASED UPON A PRESUMED DIRECT relationship between LDL lowering and reduction in CV events for persons with vasculopathy, many clinicians enthusiastically embraced the combination of ezetimibe (EZT) and statins, especially when therapeutic LDL goals were difficult to attain with a statin alone. After the ENHANCE trial, which questioned the ability of EZT to effectively regress carotid atherosclerosis, clinicians began to rethink the issue, fueled additionally by disappointing data from trials of torceptrapib, an HDL-raising drug, which not only did not reduce CV events, but actually worsened CV risk, and was subsequently withdrawn from consideration for FDA approval.

A single clinical trial, the Coronary Drug Project, showed CV risk reduction with niacin in long-term follow-up. Because of adverse effects that limit more universal use of niacin, agents that were much better tolerated (like EZT) appeared to be a more suitable choice.

A clinical trial was performed to evaluate the comparative efficacy of extended-release niacin with EZT in persons with known coronary disease or with a CHD risk equivalent (e.g., DM). All subjects were already on a statin and had achieved an LDL < 100 mg/dL. Over 14 months, the performance of niacin to regress carotid intima-media thickness was significantly greater than EZT. Indeed, the incidence of CV events was significantly lower in the niacin group also (1% vs 5%).

Although EZT is effective in reducing LDL, it has not been shown to have a favorable effect upon CV or vascular surrogate endpoints; hence, its use must be reconsidered. ■

Identifying risk factors for falls in seniors

Source: Leveille SG, et al. *JAMA* 2009;302:2214-2221.

AMONG OLDER ADULTS, FALLS REMAIN in the top 10 causes of death. Risk factors for falls include vitamin D status, cognitive status, physical decline, and mobility impairment. The epidemiologic magnitude of fall risk has motivated the search for other risk factors.

Leveille et al studied a population of community-dwelling senior citizens (age > 70 years) in the greater Boston area. Each participant (n = 749) was assessed for chronic pain, and reassessed on a monthly basis for 18 months. During this interval, subjects reported 1029 falls.

Subjects were stratified into pain scores by tertile. Most pain syndromes were associated with disorders like osteoarthritis, and included individuals with a single painful area as well as multiple symptomatic sites.

There was a linear relationship between pain scores and risk for falls. Subjects with two or more painful sites had approximately 20% greater risk of falls when compared to persons without pain. Although one might think that analgesic use prompted by joint pain might explain a greater incidence of

falls, such a relationship was not demonstrable in this population.

Why pain is associated with falls is uncertain. Perhaps pain leads to deconditioning, leading to falls. There is also some support for cognitive effects of chronic pain that might lead to lesser executive alacrity, impairing the ability to respond to precipitants of a fall. It remains to be shown whether superior pain control will reduce fall risk. ■

Resistance vs aerobic exercise and COPD

Source: O'Shea S, et al. *Chest* 2009; 136:1269-1283.

COPD IS CURRENTLY THE 4TH MOST common cause of death in the United States. Other than smoking cessation, only oxygen therapy in late-stage disease has been shown to modify disease. Pharmacotherapy provides improvements in symptoms and pulmonary function tests, but has not been shown to alter disease progression.

Physical deconditioning is commonplace in COPD. Indeed, the pathologic phenomenon seen in COPD of dynamic hyperinflation — an even greater diminution in ability to utilize expiratory reserve during exercise than at rest — helps explain why COPD patients may lack enthusiasm for aerobic exercise. Resistance exercise trials indicate that COPD patients can improve muscle strength, but whether such improvements translate into incremental symptomatic benefit or ability to participate in activities of daily living is uncertain.

O'Shea et al performed a meta-analysis of 18 controlled trials employing progressive resistance exercises for COPD patients. The data show some benefits of resistance exercise in ability to rise from a sitting position and climb stairs; however, trials comparing aerobic training vs resistance training indicated more favorable outcomes for activities like cycling, and that resistance training added to aerobic training provides little if any additional benefit. Finally, studies that indicated resistance training benefits for activities of daily living were ranked as having higher risk of bias. More studies specifically addressing the effects of resistance training upon functionality in COPD are needed. ■

Breast cancer outcomes and soy intake

Source: Shu XO, et al. *JAMA* 2009;302: 2437-2443.

ESTROGEN (EST) IS FELT TO PLAY A role in the development of breast cancer (BCA), and modulation of estrogen is utilized as a treatment for BCA. Soy foods contain a large amount of phytoestrogens, which impact natural estrogen receptors. Soy components have also been shown to possess anticancer effects. Ultimately, whether dietary soy affects important outcomes like survival or progression of disease among subjects with cancers that may be estrogen-sensitive — like BCA — is critical to ascertain.

Shu et al studied data from the Shanghai Breast Cancer Survival Study, which provides a population of Chinese breast cancer survivors (n = 5042). After approximately 4 years of follow-up, the relationship between soy intake and BCA recurrence, overall mortality, and BCA-related deaths was evaluated. There was a consistent, linear, and inverse relationship between soy intake and mortality and BCA recurrence. When compared with persons in the lowest quartile of soy intake, those in the highest quartile enjoyed a 29% lower relative risk of mortality, and a 32% lower risk of BCA recurrence.

The relationship between soy intake and favorable outcomes was not altered by estrogen receptor-positive or -negative status or tamoxifen use.

Average soy intake in U.S. women (1-6 mg/day) is markedly less than Chinese women (47 mg/d). Whether incremental dietary soy increases in the U.S. population will translate into risk reduction has not been determined. ■

Oxygen therapy for cluster headache

Source: Cohen A, et al. *JAMA* 2009; 302:2451-2457.

THE PAIN OF CLUSTER HEADACHE (CLUS) is among the most severe of any clinical syndrome. The advent of triptans, especially sumatriptan injection, has restructured the landscape of CLUS management, since SQ sumatriptan has been shown to provide effective CLUS pain relief within 15 minutes. Unfortunately, since some patients with CLUS have multiple attacks per day, for multiple days, triptan dosing limitations preclude use in these high-frequency sufferers. Additionally, CLUS patients with CAD are unable to use triptans.

Another first-line CLUS treatment is high-flow oxygen (OXY). Advantageous aspects of oxygen treatment include its low adverse-effect profile, ability to be combined with other treatments, and applicability for multiple attacks within a short time frame. Despite commonplace clinical use, trial data on OXY are quite limited.

Cohen et al performed a randomized placebo-controlled study to compare 100% oxygen vs room air (both delivered at 12 L/min for 15 minutes). Study participants (n = 109) were followed for 5 years, with instructions to treat at least 4 attacks of CLUS with either OXY or placebo (room air). All subjects received indistinguishable separate tanks of 100% oxygen and room air, and were instructed to alternate tanks for sequential CLUS episodes in their home.

The primary endpoint of the study was percent of individuals pain-free at 15 minutes. OXY was much superior to air (78% vs 20% pain free). Randomized, placebo-controlled confirmation of our clinical practice supports continued appropriateness of OXY for CLUS. ■

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Dabigatran: An Oral Direct Thrombin Inhibitor

In this issue: Results from a Phase 3 study of dabigatran, intensive lipid-lowering in CVD, H1N1 vaccine dosing and efficacy, and FDA Actions.

Anticoagulation without monitoring?

Dabigatran is an oral direct thrombin inhibitor, currently being used in many countries as an alternative to warfarin. It is anxiously awaited in this country primarily because, unlike warfarin, it does not require monitoring with blood tests. The drug has been shown to be as effective as warfarin in preventing stroke in patients with atrial fibrillation (*N Engl J Med* 2009;361:1139-1151).

A new study published in December 2009 compares the two drugs in the treatment of acute venous thromboembolism. In a randomized, double-blind, non-inferiority trial, patients with acute venous thrombus embolism were given a median of 9 days of parenteral anticoagulation therapy, then were randomized to oral dabigatran (150 mg twice a day) or warfarin that was dose-adjusted to achieve an INR of 2.0-3.0. The primary outcome was 6-month incidence of recurrent symptomatic, objectively confirmed venous thromboembolism and related deaths. Of the patients randomized to receive dabigatran, 2.4% had recurrent venous thromboembolism compared to 2.1% of patients on warfarin (difference in risk of 0.4%; 95% confidence interval [CI], -0.8 to 1.5; $P < 0.001$ for the prespecified non-inferiority margin). Major bleeding episodes occurred in 1.6% of patients on dabigatran vs 1.9% of patients on warfarin. Episodes of any bleeding were 16.1% with dabigatran and 21.9% with warfarin. There was no difference in the number of deaths, acute coronary syndromes, or abnormal liver function tests between the two groups. Treatment was discontinued due to adverse events in 9% of patients on dabigatran and 6.8% of patients on warfarin. The authors concluded that for treatment of acute venous thromboembolism, a fixed dose of dabigatran is as effective as warfarin, has similar safety, but does not require laboratory monitoring (*N Engl J Med* 2009;361:2342-2352).

Physicians and patients alike in the United States have been awaiting an orally effective anticoagulant that doesn't require monitoring. Dabigatran, a direct thrombin inhibitor, may soon fill that role. The drug, which has the additional advantage of having minimal drug and food interactions, has been available in Canada and Europe for almost 2 years, and with the completion of Phase 3 trials such as this one, there is speculation the FDA may take action this year. ■

Intensive lipid-lowering and CVD

Follow-up analysis of two of the most famous lipid-lowering trials confirms that intensive lipid-lowering therapy continues to be beneficial in the longer term. The PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial, first published in 2004,

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compared moderate lipid-lowering using standard-dose pravastatin to intensive lipid-lowering with high-dose atorvastatin after acute coronary syndrome. The study showed high-dose therapy significantly reduced the occurrence of death, myocardial infarction, stroke, and unstable angina requiring hospitalization or revascularization occurring more than 30 days after the event. The new post-hoc analysis (*J Am Coll Cardiol* 2009; 54:2358-2362) followed patients for up to 2 years and showed continued benefit in reduction of the primary endpoint (16%; P = 0 .005) with high-dose therapy, as well as reduction of additional events (19%; P = 0.009).

The IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) study compared high-dose atorvastatin with usual dose simvastatin for the prevention of events subsequent to a first event. The study was published in 2005, and while not showing reduction in mortality in the 4.8 years of study, it did show a reduction in secondary cardiovascular outcomes with high-dose therapy. The new analysis looked at not only time to first event, but also second, third, fourth, and fifth events. High-dose therapy significantly reduced subsequent events by 17%-28%. The authors concluded that continued intensive statin therapy continues to be more effective than standard statin therapy, even beyond the first vascular event (*J Am Coll Cardiol* 2009;54:2353-2357).

Both these studies suggest that staying the course with intensive lipid-lowering in patients with cardiovascular disease is an effective long-term strategy. ■

H1N1 dosing and efficacy

Three recent studies in the Dec. 17, 2009, *New England Journal of Medicine* confirm that a single dose of the H1N1 vaccine is effective for most healthy adults and children age 3 and older. In the first study, 240 patients were equally divided to receive 15 µg or 30 µg of hemagglutinin antigen by IM injection. By day 21, antibody titers of 1:40 were observed in 95.0% of patients who received the 15 µg dose and 89.1% of patients who received the 30 µg dose (*N Engl J Med* 2009;361:2405-2413).

In the second study from China, antibody titers were done at 21 days after a first injection of 15 µg with or without adjuvant. A titer of 1:40 was achieved in 75% of subjects between age 3 and 11, 97.1% of subjects between age 12 and 17, 97.1% of subjects between age 18 and 60, and 79.1% of subjects age 61 and older. Alum adjuvant did not significantly raise antibody titers. Although a second injection at 21 days raised antibody titers, the authors conclude that a single dose of 15 µg induced a typically protective antibody response in the majority of subjects between age 12 and 60 (*N Engl J Med* 2009;361:2414-2423).

In the third study, standard H1N1 vaccine was compared to a MF59-adjuvanted vaccine (derived from cell culture rather than egg-based). A number of injection schedules were tested. Local reactions and muscle aches were more frequent in the MF59-adjuvanted vaccine. Although higher antibody titers were seen with the adjuvanted vaccine, significant titers were also seen within non-adjuvanted vaccine within 2-3 weeks (*N Engl J Med* 2009;361:2424-2435).

These findings confirm data previously published in the *Lancet* in the fall of 2009 confirming that one dose of the H1N1 vaccine seems adequate, although two doses may be required for younger children. Currently, the Centers for Disease Control and Prevention (CDC) recommends two doses for children younger than age 10, but the recommendations may change based on these findings.

In related news, the CDC is reporting that safety data regarding the H1N1 vaccine is "reassuring," with a rate of serious complications such as Guillain-Barré syndrome no higher than "background rates." The rate of adverse event reporting has been higher with the H1N1 vaccine compared to seasonal flu; however, most of these reports have been for mild reactions and may be attributed to the higher rate of awareness associated with the new vaccine. ■

FDA Actions

The FDA has approved the first generic version of donepezil (Aricept®) for the treatment of Alzheimer's disease. The new generic will be marketed as 5 mg and 10 mg orally disintegrating tablets, which dissolve on the tongue and do not need to be swallowed. Generic donepezil is expected to be available later this year. ■

An FDA advisory panel is recommending expansion of the indication for rosuvastatin (Crestor®) to include patients with normal cholesterol levels and no history of cardiovascular disease. The recommendation is based on the JUPITER trial, which showed a reduction in cardiovascular risk in patients with normal LDL cholesterol but high C-reactive protein who were treated with rosuvastatin. ■