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Monoclonal Amyloid Antibodies for the Treatment of Alzheimer's Disease: More Disappointment

ABSTRACT & COMMENTARY

By Michael T. Lin, MD

Assistant Professor of Neurology and Neurosciences, Weill Cornell Medical College

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

Synopsis: *Current trials with amyloid antibodies have not shown clinical benefit, but the results suggest that treating patients earlier in the course, or during the presymptomatic period, might be beneficial.*

Source: Doody RS, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med* 2014;370:311-321.

Salloway S, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med* 2014;370:322-333.

LAST YEAR, THE BUSINESS PRESS REPORTED THAT TWO ABETA-DIRECTED MONOclonal antibodies, bapineuzumab and solanezumab, failed to meet their primary endpoints in clinical trials for mild-to-moderate Alzheimer's disease (AD). Results from these trials are now formally reported in back-to-back articles in the *New England Journal of Medicine*. Although the overall results were negative, the trials provide information and raise

Pharmacology Watch, *Clinical Briefs* Available Online

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important questions regarding pathophysiologic mechanisms. Subgroup analyses also provide some hope that earlier intervention may prove more effective.

The two antibodies bind different portions of the Abeta peptide and recognize different populations of Abeta aggregates. Bapineuzumab binds the N-terminal portion of the Abeta peptide and recognizes both soluble aggregates (found in interstitial fluid and cerebrospinal fluid [CSF]) and fibrillar aggregates (found in plaques and blood vessel walls). In contrast, solanezumab binds the central portion of the Abeta peptide and recognizes only soluble aggregates. Because bapineuzumab recognizes a greater range of Abeta species, a priori, it might have been imagined to have greater efficacy. That did not prove to be the case. Moreover, by interacting with fibrillar Abeta deposits in blood vessel walls, bapineuzumab could potentially increase the risk of vascular leakage, resulting in edema or hemorrhage, so-called amyloid-related imaging abnormalities (ARIA). That did prove to be the case. In the bapineuzumab trials, risk of ARIA-edema increased with dose, up to 15% risk in the highest dose arm; this arm was reassigned to a lower dose by the safety monitoring committee. In contrast, the overall risk of ARIA in subjects given solanezumab was 5%, indistinguishable from the rate in placebo.

There were two bapineuzumab trials, one involving apoE4 carriers and another involving noncarriers. Both trials were randomized, double-blind, placebo-controlled, multicenter, Phase 3 clinical trials, each with more than 1000 subjects with mild-to-moderate AD. In the carrier trial, subjects were randomized to placebo or 0.5 mg/kg IV every 13 weeks for 78 weeks. In the noncarrier trial, subjects were randomized to placebo, 0.5 mg/kg, 1.0 mg/kg, or 2.0 mg/kg IV every 13 weeks for 78 weeks. As mentioned above, the 2.0 mg/kg arm was subsequently reassigned to the 1.0 mg/kg arm and followed for safety, but not efficacy. The primary endpoints were cognition (11-item AD Assessment Scale, ADAS-cog11) and function (Disability Assessment for Dementia). Secondary endpoints included amyloid imaging using the Pittsburgh B compound (PiB-PET) and CSF phosphotau concentrations. There was no difference between placebo and any active agent arm in either trial with respect to cognition or function. However, there were changes in biomarkers. In the apoE4 carrier trial, amyloid burden increased in those given placebo, but remained stable in those given the antibody. Numbers were too small to be definitive in the noncarrier trial; of note, 36% of noncarriers who participated in the PiB-PET substudy did not show abnormal amyloid burden, raising the question of whether these patients truly had AD. With respect to CSF phosphotau levels, treatment with 0.5 mg/kg reduced phosphotau in apoE4 carriers, and treatment with 1.0 mg/kg reduced phosphotau in noncarriers. CSF tau and phosphotau are currently thought of as markers of neuronal injury, akin to troponin or creatine kinase in myocardial injury. The fact that treatment reduced phosphotau without any cognitive or functional benefit raises questions about the role of tau in the pathogenesis of the disease.

There were also two solanezumab trials, EXPEDITION 1 and EXPEDITION 2, one preceding the other. Both were randomized, double-blind, placebo-controlled, multicenter Phase 3 clinical trials, each with more than 1000 subjects with mild-to-moderate AD. In both trials, subjects were randomized to placebo or 400 mg solanezumab IV every 4 weeks for 18 months. The original primary endpoints were cognition (ADAS-cog11) and function (ADCS-ADL). In a pre-specified subgroup analysis for EXPEDITION 1, a benefit of solanezumab was observed for cognition in subjects with mild AD, but not moderate AD or in all subjects combined. On the basis of this finding, and before EXPEDITION 2 was completed, the statistical analysis plan for EXPEDITION 2 was revised (and approved by regulatory agencies) so that the primary analysis population was the subjects with mild AD, and the primary cognitive endpoint was changed to the ADAS-Cog14, which is a better measure of cognitive changes in patients with mild AD. The benefit of solanezumab in mild AD in EXPEDITION 2 did not quite reach significance for ADAS-Cog14 ($P = 0.06$) or ADAS-Cog11 ($P = 0.05$), though it did just reach significance for function (ADCS-ADL, $P = 0.04$). In contrast to the bapineuzumab studies, solanezumab had no effect on amyloid burden measured by 18F-florbetapir PET, and no effect on CSF tau or phosphotau levels. There was an

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Questions & Comments
Please contact **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

increase in total CSF Abeta42 levels and plasma Abeta42 levels in subjects treated with solanezumab, suggesting engagement of target.

■ **COMMENTARY**

Both sets of studies were large, well-designed, well-executed studies. Although overall results were negative, comparing the two antibodies provides some information about pathogenesis and raises important questions. First, the discordance between plaque burden and clinical benefit (bapineuzumab reducing plaque burden but providing no benefit; solanezumab not reducing plaque burden but providing slight benefit in mild cases) reinforces current thinking that soluble Abeta aggregates may be the most pathophysiologically relevant species of Abeta. Second, the studies raise questions about the role of tau — bapineuzumab decreased CSF phosphotau levels but provided no clinical benefit, whereas solanezumab provided benefit in mild cases but did not change CSF tau or phosphotau levels. This clearly points to a gap in our understanding of AD pathogenesis. Third, the amyloid imaging data fit with other data that a substantial fraction of apoE4 negative subjects who clinically appear to have AD will be amyloid negative, suggesting that they do not suffer from AD. Understanding the cause of dementia in these individuals is an important area, and suggests that amyloid imaging should be used more routinely. Finally, the authors of both sets of studies conclude by postulating a larger benefit for anti-amyloid therapy if treatment were started earlier, before patients become symptomatic. This is reasonable, given increasing evidence from CSF studies and amyloid PET imaging that amyloid pathology can begin decades before symptoms appear. Given the slight benefit of solanezumab in mild AD and its relatively better safety profile, solanezumab has been selected as the agent for the upcoming A4 (anti-amyloid therapy in asymptomatic Alzheimer disease) trial, in which asymptomatic individuals with evidence of AD pathology as identified by amyloid imaging will be treated for 3 years to determine effect on subsequent cognitive decline. This trial represents an enormous investment of resources and currently represents the best hope for a therapeutic or preventive breakthrough. ■

Optic and Auditory Involvement in Demyelinating Neuropathy

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: *Demyelinating peripheral neuropathies may have subclinical evidence of optic nerve and auditory nerve dysfunction, only discovered by electrophysiological testing.*

Source: Knopp M, et al. Optic and auditory pathway dysfunction in demyelinating neuropathies. *Acta Neurol Scand* 2014; Feb 20. doi: 10.1111/ane.12226. [Epub ahead of print].

Are the optic and auditory pathways affected in demyelinating neuropathy? To address this question, a prospective study was undertaken at the Regional Neuromuscular Clinic, Queen Elizabeth Neurosciences Center, in Birmingham, UK, between December 2011 and June 2012. Consecutive patients were recruited, with hereditary demyelinating neuropathy, encompassing Charcot-Marie-Tooth disease type 1A (CMT1A) or hereditary neuropathy with liability to pressure palsies (HNPP), or acquired demyelinating neuropathy, encompassing chronic inflammatory demyelinating polyneuropathy (CIDP) or anti-MAG neuropathy. All underwent visual evoked potential (VEP) and brainstem auditory evoked potential (BAEP) study to assess optic and auditory nerve function in the least uncomfortable manner. Diagnosis of CMT and HNPP was based on clinical and electrophysiological grounds, and confirmed by genetic testing in all patients. CIDP patients all fulfilled the 2010 updated European Federation of Neurological Societies/Peripheral Nerve Society guidelines for CIDP diagnosis, and all responded to immunomodulatory therapy. Patients with anti-MAG neuropathy all demonstrated a monoclonal IgM paraprotein with positive anti-MAG antibodies in the setting of clinical and electrophysiological findings consistent with anti-MAG neuropathy. Statistical analysis comprised Fisher's exact tests, and Kruskal-Wallis or Mann-Whitney U-tests, with Bonferroni correction applied as warranted. $P < 0.0125$ was considered significant.

During the recruitment period, eight patients with HNPP (mean age 34 years), six patients with CMT1A (mean age 45 years), 10 patients with CIDP (mean age 60 years), and seven patients with anti-MAG neuropathy (mean age 70 years) were studied. One patient each with CMT1A and CIDP also had diabetes. Among anti-MAG neuropathy patients, 6/7 had abnormal VEP results, as did about half the CIDP and HNPP patients. Only 1/6 CMT1A patients had abnormal VEPs. BAEP testing demonstrated prolonged wave I latency, or prolonged wave I-wave III latency, in 5/7 patients with anti-MAG neuropathy, 5/10 with CIDP, 4/5 with CMT1A (one was excluded due to non-recordable responses from either side), and 2/8 with HNPP. Optic nerves are spared in CMT1A, but subclinical involvement is present in CIDP and HNPP, and particularly in anti-MAG neuropathy. Auditory nerve involvement is

infrequent in HNPP, but is seen in the majority of patients with CIDP, anti-MAG neuropathy, and CMT1A. Subclinical involvement of the optic and auditory pathways in patients already afflicted by peripheral neuropathy may compound their neurologic disability and warrants the attention of the treating neurologist.

■ **COMMENTARY**

Cranial nerves, other than the optic and auditory nerves, may also be affected in demyelinating neuropathies. Vocal cord palsy and diaphragm weakness causing respiratory failure have been reported, rarely, in patients with Charcot-Marie-Tooth. Multifocal motor neuropathy seldom involves cranial nerves but can present as ophthalmoplegia, and may cause tongue atrophy closely mimicking motor neuron disease. Although not strictly a cranial nerve, recurrent symptoms of greater occipital neuropathy developed in a father and son with HNPP when lying supine on a floor during yoga exercise. Although idiopathic CIDP may affect cranial nerves in up to 27% (ptosis, diplopia, dysarthria), it is rare in CIDP-MGUS IgM with anti-MAG antibodies, where only 1 of 29 patients was reported with facial weakness. ■

Severe Childhood Neuronopathy that Responds to Riboflavin

ABSTRACT & COMMENTARY

By Sotirios Keros, MD, PhD

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

Synopsis: *A new mutation is identified in a riboflavin transporter gene as a cause of Brown-Vialetto-Van Leare syndrome, a sensorimotor neuronopathy, which displays clinical improvement with riboflavin therapy.*

Source: Foley AR, et al. Treatable childhood neuronopathy caused by mutations in riboflavin transporter RFVT2. *Brain* 2014;137:44-56.

Brown-Vialetto-Van Leare syndrome (BVVLS), also occasionally referred to as Brown syndrome, is a rare but severe form of autosomal recessive congenital neurodegenerative disorder causing sensorimotor deficits in children. Initially described as "infantile amyotrophic lateral sclerosis of the family type" BVVLS has come to represent a constellation of symptoms that include sensorineural deafness, pontobulbar paralysis, respiratory insufficiency, and various patterns of limb weakness.

Within the past several years, three mutations in a riboflavin transporter gene (SLC52A1, SLC52A2, and SLC52A3) causing riboflavin deficiency have been discovered, with the A2 and A3 versions of the mutations (coding for human transporter proteins RFVT2 and RFVT3, respectively) linked to some patients with BVVLS. In this study, the authors perform a detailed characterization of 18 patients with newly confirmed SLC52A2 mutations, and describe clinical improvement with high-dose riboflavin therapy.

Seventy-eight patients were enrolled from 21 medical centers and fit a phenotype of sensorimotor neuropathies and cranial neuropathies, both with and without respiratory insufficiency. None of the 78 had mutations in SLC52A1 or SLC52A3. Eighteen individuals (13 probands and five family members) of the 78 had various mutations in SLC52A2, which were verified with Sanger sequencing. The age at the time of genetic diagnosis of patients ranged from 2-52 years old. Seven different missense mutations and one premature stop mutation were identified (six mutations were novel, while two were previously reported). Two of five patients had respiratory chain abnormalities (decreased complex I activity and slightly decreased complex IV activity) obtained from muscle samples. Sural nerve biopsies in six patients were consistent with a chronic axonal neuropathy, with fibrosis and degeneration but with no findings of regeneration, inflammation, or demyelination. Brain MRI was normal in all 14 patients tested. A riboflavin transport assay in an in vitro expression system revealed absent or moderately decreased transport in all seven mutations tested.

Clinically, the first abnormalities were noted in this group between 7 months and 5 years of age. The most common presenting symptom was an ataxic gait (in half the patients). Other presenting symptoms were hearing loss (n = 3), vision loss or nystagmus and ptosis (n = 3), and upper extremity weakness and respiratory failure (n = 1 each). All patients eventually developed hearing loss, and 14 of 15 were diagnosed with optic atrophy. Eleven patients had tongue fasciculations, and 13 developed respiratory insufficiency, which led to one death at age 3.5 years. A common feature of almost all patients was a rapidly progressing weakness first affecting the neck extensors, then the distal upper extremities followed by the proximal upper limbs, resulting in subgravity strength. The authors note that lower extremity weakness was mild and that all patients remained ambulatory if given neck and trunk support. Neurophysiologic testing revealed a sensory axonal neuropathy, which preceded an axonal motor neuropathy, with severity greater in the upper extremity in all patients, consistent with the clinical findings.

Sixteen patients began high-dose oral riboflavin therapy. Acylcarnitine profiles were abnormal in 10 of 17 patients tested prior to riboflavin therapy, with correction to normal in 9 of 10 after therapy. Detailed responses to riboflavin are presented for two patients. First, a 22-month-old boy who presented with a 6-month history of nystagmus, 4 months of ataxic gait, and 3 weeks of hand and bulbar weakness leading to respiratory failure and inability to swallow. During 4 weeks of riboflavin he was extubated, was able to feed, and regained upper extremity strength. A second child — whose symptoms began at age 2 with sensory ataxia, upper limb weakness, hearing loss, and vision loss, and progressed to respiratory insufficiency and inability to sit and stand by age 7 — was treated at age 10. After 3 months of riboflavin therapy, there was improvement in audiometry testing, respiratory status, and visual evoked potentials, all of which had previously been consistently declining. An additional 17 months of therapy led to increases in height and weight for the first time in 4 years, and improvements in motor function such that she could sit and stand independently.

■ **COMMENTARY**

This study adds yet another congenital neurologic disorder to the rapidly growing list of diseases that have an identified genetic etiology, with the important fact that this one comes with evidence of an effective, widely available, and safe treatment. SLC52A2 mutations are likely the most common cause of BVVLS. The patients in this report with SLC52A2 mutations had a remarkably similar phenotype, with optic atrophy, a sensorimotor neuropathy (much worse in the upper extremities and neck), hearing loss, and respiratory insufficiency. While somewhat anecdotal pending forthcoming data, it seems that high-dose riboflavin therapy can lead to substantial improvement, and might have the potential to reverse all symptoms if initiated early enough. Although BVVLS is rare, the highly specific phenotype of SLC52A2 will hopefully allow clinicians seeing young children with any of the characteristic symptoms to recognize this disorder and initiate timely empiric riboflavin therapy while waiting for genetic confirmation of the diagnosis. ■

Bevacizumab for Newly Diagnosed Glioblastoma

ABSTRACT AND COMMENTARY

By Susan C. Pannullo, MD, FAANS

Associate Professor of Clinical Neurological Surgery, Director of Neuro-Oncology, Weill Cornell Medical College

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

Synopsis: *Two recent randomized, placebo-controlled clinical trials of treatment of glioblastoma multiforme with bevacizumab have not shown superiority over standard treatment.*

Sources: Gilbert MR, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med* 2014;270:699-708.

Chinot OL, et al. Bevacizumab plus radiotherapy–temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 2014;270:370:709-722.

Glioblastoma multiforme is a frustrating and complex disease with poor survival and very limited treatment options. The standard therapeutic approach is maximal safe resection, followed by radiation therapy and systemic chemotherapy. The survival benefits of the current therapies remain poor, prompting constant attempts to add to these modest benefits through the addition of novel approaches.

A pair of articles in the February 20, 2014, issue of the *New England Journal of Medicine* present data from the Radiation Therapy Oncology Group (RTOG) 0825 trial and the Avastin in Glioblastoma (AVAglio) trial. These two Phase 3, randomized trials examined the role of bevacizumab, a humanized monoclonal antibody that targets vascular endothelial growth factor, in treatment of patients with newly diagnosed glioblastoma multiforme. Subjects in both studies received the standard 6 weeks/5 days per week of radiation therapy to a maximum of 60 Gy with concurrent oral temozolomide followed by maintenance temozolomide. Both studies randomly assigned subjects 1:1 to intravenous bevacizumab vs placebo. These trials were prompted by previous Phase 2 studies suggesting safety and efficacy of bevacizumab in patients with glioblastoma multiforme at recurrence, as well as at time of initial diagnosis.

The RTOG and AVAglio trials shared a relatively common study design. Both trials enrolled adults with newly diagnosed, histologically centrally confirmed supratentorial glioblastoma, with good performance status, stable or decreasing steroid doses, good wound healing, no postoperative hemorrhage on imaging, and adequate hematologic, hepatic, renal, and coagulation parameters. Biopsy without resection was permitted in the AVAglio study. In the AVAglio trial, bevacizumab (or placebo) was started at the same time as chemoradiation; in the RTOG study, bevacizumab infusions (vs placebo) began at week 4 of chemoradiation. There were additional minor differences in the study designs: In RTOG 0825, subjects received maintenance temozolomide for a maximum of 12 4-week cycles with q2 week bevacizumab vs placebo, while the AVAglio maintenance phase was planned for six 4-week cycles of temozolomide with concurrent q2 week bevacizumab vs placebo followed by a q3 week bevacizumab vs

placebo monotherapy phase. Both trials continued treatment until disease progression or unacceptable toxicity occurred. In the RTOG trial, the study was unblinded at time of progression and the subject could continue or start (if on the placebo arm) bevacizumab. Similarly, in AVAglio, subjects could receive salvage therapy at progression. Coprimary endpoints in both trials were overall survival and progression-free survival.

A total of 637 subjects were randomized in the RTOG study (312 to bevacizumab, 309 to placebo, with 8 excluded from each group) and 921 in the AVAglio study (458 bevacizumab, 463 placebo). Neither trial demonstrated survival advantage for "upfront" use of bevacizumab. In RTOG 0825, median survival in the bevacizumab group was 15.7 months vs 16.1 months for placebo, not statistically significant. In AVAglio, median survival was 16.8 months for the bevacizumab arm and 16.7 month for placebo.

Both trials demonstrated increased duration of progression-free survival with bevacizumab (RTOG = 10.7 months bevacizumab vs 7.3 months placebo; AVAglio = 10.6 months bevacizumab vs 6.2 months placebo). However, this parameter has been of particular debate as an outcomes measure, due to the belief that bevacizumab may produce radiographic changes on MR imaging as a result of alterations in blood-brain barrier permeability that may cause regression of tumoral gadolinium enhancement used to define tumor burden. This effect has been termed "pseudoregression" and mirrors the "pseudoprogression" that has been described as a confounder of imaging analysis in clinical neuro-oncology and a disruptor of image-based outcomes in brain tumor clinical trials.

Patients in RTOG 0825 had greater deterioration of neurocognitive measures, perceived symptom severity, and health-related quality of life in the bevacizumab-treated subjects compared with the placebo group. Interestingly, time to deterioration of several similar measures was delayed in the AVAglio trial. The AVAglio study results were notable for increased rate of adverse events, including arterial thromboembolic events, bleeding, wound healing complications, gastrointestinal perforation, and heart failure, in the bevacizumab group vs placebo.

■ COMMENTARY

Negative trials are always discouraging and disappointing, but are important nevertheless. In this orphan disease with few potential subjects, large trials are difficult to complete. Further complicating the issue of trials for glioblastoma are patient and physician biases that may encourage potential subjects to seek therapies without participation in a randomized trial. The RTOG 0825 and AVAglio studies emphasize the value of rigorously performed randomized clinical trials. Although potential subjects (and investigators) often "fear" the placebo arm as being "worse" than the study drug arm, the study drug, in the end, may be no better than the placebo. In fact, in some aspects (e.g., adverse events in the bevacizumab arm, neurocognitive function in the RTOG study), outcomes on the study drug subjects may be worse. These two trials are particularly disappointing as they cast an unfavorable light on what was thought to be a promising therapeutic approach in a devastating disease that has few treatment options and a median survival of just over 1 year. Discussions are occurring regarding plans to pool the raw data from these studies and evaluate the combined data in an additional attempt to confirm the findings and understand the discrepancies between them. In addition, examination of molecular marker subgroups may reveal a subpopulation of glioblastoma patients who would derive benefit in the future. Finally, these studies call attention to the need for refinement of imaging techniques used to evaluate response to brain tumor therapies. ■

The Importance of the CSF Specimen for Antibody Determination in NMDA Receptor Encephalitis

ABSTRACT & COMMENTARY

By Bianca D. Santomasso, MD, PhD

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Dr. Santomasso reports she is a stockholder in Novartis.

Synopsis: *The data from this large cohort of patients confirm the importance of submitting cerebrospinal fluid for assessment when NMDA receptor encephalitis is suspected.*

Source: Gresa-Arribas N, et al. Antibody titers at diagnosis and during follow-up of anti-NMDA receptor encephalitis: A retrospective study. *Lancet Neurol* 2014;13:167-177.

Since its discovery in 2007, anti-N-methyl-D-aspartate (NMDA) receptor encephalitis has entered the mainstream of neurology as an important and potentially treatable form of autoimmune encephalitis. The disorder predominantly affects young women and children, and can occur with or without tumor association (usually an ovarian teratoma in roughly half of patients). Neurologic improvement usually occurs with immunotherapy and resection of teratoma if one is present; however, relapses and refractory cases are also seen and incompletely understood.

Patients with anti-NMDA receptor encephalitis present with a subacute onset and stereotyped course characterized by psychosis, memory deficits, seizures, and language disintegration that progresses into a state of unresponsiveness, with catatonic features often associated with abnormal movements and autonomic and breathing instability. Establishing the diagnosis depends on detection of an IgG antibody targeting the GluN1 subunit of the NMDA receptor. The two principle techniques that have been used for antibody testing in this disorder are 1) immunohistochemistry of brain tissue (which produces a highly characteristic pattern of reactivity); and 2) a cell-based assay (CBA) of human embryonic kidney 293 cells expressing the GluN1 subunit of the NMDAR. It is typically thought that these two assays complement each other for laboratory quality assurance of the diagnosis. However, the authors of this study mention that reports by others have suggested that serum testing using only CBA is sufficient for the identification of NMDA receptor antibodies and the diagnosis of NMDA receptor encephalitis. Therefore, they set out to clarify the appropriate antibody testing by directly comparing the sensitivity and specificity of different NMDA receptor antibody techniques in paired serum and cerebrospinal fluid (CSF) samples.

In this study, the authors retrospectively examined a large cohort of patients and report the sensitivity and specificity of paired serum and CSF samples by immunohistochemistry-based and cell-based assays. Two hundred fifty patients with NMDA receptor encephalitis (established by antibody positivity in both immunohistochemistry and cell-based assays) were compared with 100 control patients with encephalopathy. The authors found that all patients with anti-NMDA receptor encephalitis have anti-GluN1 antibodies in the CSF (100% detectable with both techniques), but antibodies in serum are found less often: 91% with immunohistochemistry and 86% with the cell based assay, suggesting that false-negative cases can occur when only serum is used. Put another way, the diagnosis of anti-NMDA receptor encephalitis would be missed in 13% of patients if only serum and a cell-based assay were used. Using a live cell-based technique actually worsened the serum results. None of the 100 paired serum and CSF samples from control samples showed NMDA receptor antibodies with either of the techniques (specificity 100%).

The authors then went on to do quantitative studies with antibodies using antibody titers. From a smaller group of patients for whom serial clinical data (modified Rankin Score) and specimens were available, antibody titers were determined with brain immunohistochemistry and prognostic significance of these antibody titers are reported. Results from their multivariate analysis showed that patients with higher antibody titers in serum or CSF at diagnosis were more likely to have poor outcome or the presence of a teratoma or both. Additionally, patients with a tumor were more likely to have antibodies detectable in serum than those without a tumor. There was also a possible association between good clinical outcome and early decrease of CSF antibody titers during the first month of the disease, but this was not statistically significant. The change in titers in CSF correlated better with clinical relapses than that in serum, but an association between the change in antibody titers and symptoms along the course of disease in this study was not seen. By last follow-up, most patients had a decrease in their serum and CSF titers regardless of clinical outcome, with possible explanations being either a slow spontaneous fading of the immune response or a burned-out stage of the disease. For unclear reasons, after clinical recovery, 24 of 28 CSF samples and 17 of 23 serum samples from patients remained antibody positive. Finally, the authors found that the same epitope specificity (amino acid 369 of GluN1) is present in all tested patients, regardless of their clinical outcome or stage of disease.

■ COMMENTARY

The most important point to be taken from this study is that CSF antibody determination is crucial in the initial diagnostic testing for suspected cases of NMDA receptor encephalitis. Examination of serum alone is not sufficient and could lead to a delay in neoplasm diagnosis and immunotherapy initiation in up to 13% of patients. In practice, any patient presenting with suspected autoimmune encephalitis should have both serum and CSF submitted to a commercial laboratory to optimize detection of the more than 20 antibodies (including anti-GluN1) classified as pertinent to autoimmune encephalopathy, since some individual autoantibodies are more readily detected in one specimen type or by a specific assay method.

Assay methods are known to influence sensitivity and specificity. Studies that test serum with cell-based assay alone have identified anti-GNuN1 antibodies in patients with schizophrenia, Creutzfeldt-Jakob disease, Parkinson's disease, and in healthy individuals; these findings could not be reproduced in studies that used both cell-based assays and brain immunohistochemistry in serum and CSF samples. False positives resulting in misdiagnosis of a cognitive disorder as autoimmune might lead to erroneous use of potentially toxic immunotherapy.

The finding that patients with high antibody titers and little or no decrease of CSF antibodies in the first months of the disease are less likely to have a good outcome than those with low titers or a clear decrease in CSF titers is intriguing, but it needs confirmation with prospective studies. Further studies should also investigate whether the level of antibody that persists after clinical recovery predicts relapses and need for chronic immunotherapy. In the meantime, while we wait for prospective studies to

confirm CSF antibody titers as a potential prognostic biomarker, a recent large study of 577 patients suggests that clinical assessment of the patient is most important for informing clinical decisions along the course of disease.[1]

Reference

1. Titulaer MJ, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. *Lancet Neurol* 2013; 12: 157-165.

CME Objectives

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

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

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CME Questions

1. Monoclonal amyloid antibodies work via which of the following mechanisms?
   a. Bapineuzumab binds the N-terminal portion of the Abeta peptide and recognizes both soluble aggregates (found in interstitial fluid and CSF) and fibrillar aggregates (found in plaques and blood vessel walls).
   b. Solanezumab binds the central portion of the Abeta peptide and recognizes only soluble aggregates.
   c. Bapineuzumab reduces CSF levels of phosphotau, believed to be a biomarker of neuronal damage.
   d. All of the above

2. Which of the following may be affected by chronic inflammatory demyelinating polyneuropathy?
   a. The optic nerve
   b. The auditory nerve
   c. Both the optic nerve and the auditory nerve
   d. Neither the optic nor the auditory nerves

3. Which of the following is *not* a common symptom of Brown-Vialetto-Van Leare syndrome caused by SLC52A2 mutations?
   a. Spasticity
   b. Vision loss
   c. Hearing loss
   d. Upper extremity weakness

4. In spite of many new trials of novel therapy for glioblastoma multiforme, none have proven superior to standard therapy of surgical resection, maximum dose radiation therapy with concurrent temozolomide.
   a. True
   b. False

5. Which of the following statements regarding anti-NMDA receptor antibodies and NMDA receptor encephalitis is *not* true?
   a. Anti-NMDA receptor encephalitis is defined by a stereotyped clinical course and antibodies to the GluN1 subunit of the NMDA receptor.
   b. Patients with schizophrenia and Creutzfeldt-Jakob disease have GluN1-specific antibodies in their serum and CSF identical to those seen in NMDA receptor encephalitis.
   c. CSF analysis for antibodies in anti-NMDA receptor encephalitis is more sensitive than serum.
   d. Many, but not all, patients with NMDA receptor encephalitis have an ovarian teratoma.
   e. NMDA receptor encephalitis is treated with immunosuppressive agents and tumor removal when one is found.

In Future Issues:

Expanded Stroke Alert