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ABSTRACT & COMMENTARY

Continuous EEG Monitoring in Critically Ill Patients Is Associated With Reduced Hospital Mortality

By Peter B. Forgacs, MD

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

SYNOPSIS: In this retrospective cross-sectional study involving more than 7 million critically ill adult patients from the National Inpatient Sample database, researchers showed that the use of continuous electroencephalography is associated with lower in-hospital mortality.

SOURCE: Hill CE, Blank LJ, Thibault D, et al. Continuous EEG is associated with favorable hospitalization outcomes for critically ill patients. *Neurology* 2019;92:e9-e18. doi:10.1212/WNL.0000000000006689.

Continuous electroencephalography (cEEG) monitoring has been used increasingly to monitor brain function of patients admitted to intensive care units (ICUs). cEEG offers real-time, noninvasive, and direct assessment of ongoing brain activity. Therefore, it plays a unique and well-established role in diagnosing ongoing or fluctuating functional cerebral disturbances, such as seizures/status epilepticus (including seizures without overt clinical symptoms) and encephalopathies, in the detection of delayed cerebral ischemia after subarachnoid hemorrhage and in assessment of prognosis after severe brain injuries, including post-cardiac arrest hypoxic brain injury. However, the relationship between the use of cEEG and hospital outcomes, including mortality, is not well-characterized.

Hill et al designed this study to characterize the association between cEEG use and outcomes for specific diagnostic categories using administrative claims data recorded between 2004 and 2013 in the National

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Inpatient Sample. More than 7 million critically ill patients were identified in the database. Over 10 years, cEEG use increased more than 10-fold, but cEEG remains underused; overall, only 0.3% of the critically ill patients included in the study underwent cEEG monitoring at any point during their hospitalization.

Importantly, while patients in the cEEG cohort appeared to be more ill with higher comorbidity scores, more frequent palliative care consultation, and longer length of stay, cEEG use was associated with decreased in-hospital mortality (22.8% of cEEG cohort vs. 27.8% for no cEEG). In subgroups divided by diagnosis, a similar relationship between cEEG use and mortality was observed in patients with subarachnoid or intracerebral hemorrhage (26.3% vs. 54.0%) and altered levels of consciousness (21.5% vs. 28.3%), but no significant correlation was found in patients with seizures/status epilepticus (18.2% vs. 19.8%). The authors postulated that patients who had a lethal primary diagnosis leading to status epilepticus did not benefit from further monitoring. The use of cEEG was associated with an increase in total cost of hospitalization and longer length of stay. Patients admitted to large or urban teaching hospitals located in the Northeast or Midwest were more likely to undergo cEEG monitoring than patients who were admitted to non-teaching or rural hospitals or in other regions of the country.

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Hill et al documented that the use of cEEG in critically ill patients is strongly associated with decreased in-hospital mortality, but it remains underused based on data from an administrative claims database. Despite the demonstrated benefit in reduced mortality in ICU patients, many barriers hinder the wider implementation of cEEG monitoring in critically ill patients. The overwhelming majority of U.S. hospitals with ICUs currently do not have the infrastructure to perform cEEG studies. Despite the 10-fold increase in cEEG use over the nine-year period analyzed in this study, within the 3,054 unique hospitals involved, 93.9% never used cEEG. Major barriers to more widespread use of cEEG include the cost of acquiring and maintaining EEG equipment and providing 24-hour availability of technologists and specialized neurologists.

The scarcity of cEEG use among all hospitals represents a limitation in the interpretation of the study results. It is possible that the observed mortality benefit is related to unmeasured characteristics of the hospitals with cEEG availability (i.e., the differences in management strategies in larger volume, urban hospitals in academic centers). These hospitals also are more likely to have dedicated neurocritical care units with specialized teams using advanced therapeutic approaches and technologies. Other limitations include similarities to all studies using claims databases and the dependence of the study on billing codes used for administrative purposes; it cannot be determined if coding practices may have influenced the results. Finally, long-term functional outcomes, such as level of independence and quality of life, could not be assessed in this study; such measures are just as important for patients and caregivers as in-hospital mortality.

Nevertheless, the Hill et al study strongly highlights the potential benefits of continuous neurological monitoring of electrical brain activity in critically ill patients. Further prospective studies should aim to assess the value of conventional and newer electrophysiological brain monitoring techniques in all ICU patients, similar to cardiac monitoring in intensive care settings worldwide. Many new technologies offer cost savings in cEEG monitoring. More affordable, fast, secure, and reliable remote access of studies may allow physicians to cover multiple lower-volume hospitals at the same time. In addition, many ongoing studies use a limited number of EEG channels and easily apply electrode caps to assess the accuracy of simpler techniques in acute and intensive care settings. Furthermore, automatic seizure detection algorithms and newer visualization methods using quantitative EEG features may allow quick bedside assessment of large segments of EEG data by nurses or other ICU staff.

In the future, deep learning algorithms using artificial intelligence may offer automated assessment, further decreasing the cost of monitoring and analyzing large amounts of data. Hospitals with ICUs currently not equipped to perform cEEG studies should be encouraged to implement neurological monitoring capabilities to expand these benefits to all critically ill patients. ■

ABSTRACT & COMMENTARY

Rituximab for CIDP Associated With Systemic Immune Disorders

By Michael Rubin, MD

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Dr. Rubin reports he is a consultant for Merck Sharp & Dohme Corp.

SYNOPSIS: Rituximab has been used "off label" for the treatment of primary chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with variable reports of success. These authors reported a high rate of response in patients who developed CIDP in the setting of other systemic immune-mediated disorders.

SOURCE: Roux T, Debs R, Maisonobe T, et al. Rituximab in chronic inflammatory demyelinating polyradiculoneuropathy with associated diseases. *J Peripher Nerv Syst* 2018;23:235-240.

Intravenous immune globulin (IVIG), plasma exchange (PLEX), and glucocorticoids are the pillars of treatment for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), but each has its advantages and disadvantages. IVIG may lead to improvement more rapidly than steroids but it is expensive, sometimes limited in supply, and is less likely to result in remission, with a response rate of 40-60%. PLEX also may lead to more rapid improvement than steroids and has a response rate of up to 80%, but it is invasive, expensive, not as widely available, and venous access may be problematic. Steroids are inexpensive and readily available, but are fraught with significant side effects and have a response rate of 54-63%. Rituximab has been suggested as an alternative to prednisone as an immune modulator for treatment of CIDP.

This was a retrospective study of all CIDP patients in the database of Pitié-Salpêtrière Hospital, Paris, treated with rituximab between January 2004 and December 2016. Patients with anti-MAG antibodies were excluded. All received standard treatment (corticosteroids, IVIG, PLEX) for CIDP but additionally received rituximab, either because they had an insufficient response to or continued dependence on first-line CIDP treatment, or had an associated autoimmune or hematological condition requiring rituximab. Rituximab 375 mg/m^2 usually was administered twice, two weeks apart (n = 11), with two patients receiving it weekly for four weeks, and nine patients receiving it monthly for four or six months. One lupus patient received it every three months for three years. Patients were seen in follow-up every four to eight weeks, and response to rituximab was defined as a five-point increase in the Medical Research Council (MRC) sum score, a one-point decrease in the Overall Neuropathy Limitations Scale (ONLS) score, discontinuation of first-line treatment(s), or an increase of at least one week in the interval between courses of IVIG or PLEX compared to the dependence threshold. Response was considered significant if it was maintained for at least two consecutive visits. Additionally, electrodiagnostic (EDX) studies were performed prior to and between five and nine months following the first rituximab infusion, with improvement defined as disappearance of conduction block in at least one site or two nerves showing decreased distal motor latency, improved motor conduction velocity by at least 10 m/s, or improved motor amplitude, with no nerve showing worsening. Worsening EDX was defined as at least one new site of conduction block or two nerves showing increased distal motor latency, slowed motor conduction velocity by at least 10 m/s, or decreased motor amplitude. Statistical analysis comprised Student's t test, χ^2 test, and the Shapiro-Wilk test, with significance set at $P < 0.05$.

Twenty-eight CIDP patients (12 men and 16 women) with a mean age of 66 years received rituximab. Eighteen patients had the common form of CIDP, seven had sensory CIDP, and three had Lewis-Sumner syndrome (multifocal acquired demyelinating sensory and motor neuropathy, MADSAM). All but one had an associated disease, either B-cell malignancy (n = 13), monoclonal gammopathy of undetermined significance (MGS, n = 7), or an autoimmune process, including rheumatoid arthritis or lupus (n = 1 each), anti-neurofascin 155 antibodies (n = 3), or anti-SSA/anti-SSB antibodies (n = 2). Thirteen (46%) received rituximab because of an insufficient response to CIDP first-line treatment, eight (29%) because of treatment dependence, and seven (25%) for hematological disease. Overall, within a median of six months, 21 patients (75%) responded to rituximab, with 11 demonstrating improved clinical scores, 10 decreasing their dependence threshold, and seven of the latter improving both. Of these 10, six were able to discontinue their first-line treatment, and four increased their inter-treatment interval by a median of three weeks (one to six weeks). Typical CIDP responded best (83%) vs. 43% of sensory CIDP and 67% of Lewis-Sumner disease, a statistically significant difference. Rituximab resulted in no major adverse events and appeared to improve clinical

response and decrease dependence on first-line agents in CIDP patients with associated hematological or autoimmune disease.

■ COMMENTARY

Patients with CIDP represent a significant clinical and economic burden. Neuropathic pain, back pain, and osteoarthritis requiring opioids, antidepressants, and anticonvulsants are more frequent, as are hospitalizations, physician office visits, and outpatient prescriptions. Mean total costs increase by a factor of six, with therapy accounting for more than 50% of mean total costs.[1] Additions to the therapeutic armamentarium against CIDP, including rituximab, are to be welcomed. ■

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ABSTRACT & COMMENTARY

Amyloid-ß Pathology Induced by Contaminated Cadaver-Derived Growth Hormone

By Brian Andersen, MD, PhD, and Matthew E. Fink, MD

Dr. Andersen is Chief Resident in Neurology, New York Presbyterian Hospital, Weill Cornell Medical College. Dr. Fink is Louis and Gertrude Feil Professor and Chair, Department of Neurology, Weill Cornell Medical College.

Dr. Andersen and Dr. Fink report no financial relationships relevant to this field of study.

SYNOPSIS: Cadaveric pituitary-derived growth hormone that previously was known to transmit Creutzfeldt-Jakob disease (CJD) also contains ß-amyloid. Growth hormone vials from cases associated with amyloid plaques in CJD patients cause amyloid plaque formation and cerebral amyloid angiopathy when injected intracranially into mice.

SOURCE: Purro SA, Farrow MA, Linehan J, et al. Transmission of amyloid-ß protein pathology from cadaveric pituitary growth hormone. *Nature* 2018;64:415-419.

Iatrogenic exposure to prion proteins can occur through medical or surgical interventions and result in fatal prion disease after incubation for decades. Thousands of children diagnosed with short stature between 1958 and 1985 were injected with cadaveric human growth hormone (c-hGH). Batches of c-hGH were contaminated with prion proteins from patients who died from Creutzfeldt-Jakob disease (CJD), resulting in iatrogenic transmission of CJD in more than 200 patients to date. Cases associated with c-hGH continue to rise because of the prolonged incubation period.[1] Intriguingly, examination of postmortem brain tissue from these tragic cases of CJD has raised concerns of potential transmissibility of Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA).

In 2015, investigators reported unexpected pathologic findings in the brains of eight patients, ages 36-51 years, who recently had died from c-hGH-induced CJD. In addition to CJD pathology, four contained severe gray matter amyloid β (Aβ) pathology; two others had focal Aβ plaques. Three of these eight patients also had widespread vascular amyloid deposition, fulfilling diagnostic criteria for CAA. Genetic testing found no AD susceptibility mutations. In contrast, 19 age-matched patients from a series of patients who died from other prion diseases (sporadic and variant CJD or inheritable prion diseases) showed no amyloid pathology. These researchers hypothesized that misfolded Aβ from patients with AD and/or CAA had contaminated batches of c-hGH and that native Aβ in young patients had been seeded to misfold.[2] Soon after, several groups reported cerebral hemorrhages from CAA in young patients, decades after dural grafts were placed.[3-5]

Purro et al first characterized many batches of c-hGH that had been safely stored by Public Health England. All patients who developed CJD received c-hGH from a batch that was isolated by the Hartree-modified Wilhelmi procedure (HWP).[1] Remarkably, Aβ and tau levels within the HWP-derived vials were comparable to levels found in the brains of patients with AD, despite storage at ambient temperature for decades. Aβ and tau were undetectable in c-hGH vials extracted by other methods.[6]

Knock-in mice expressing human amyloid precursor protein gene were used for transmission experiments. Mice were injected intracerebrally with saline, recombinant hGH, brain homogenate from AD patients, or from two archival vials of c-hGH isolated by HWP. By four months of age, mice injected with Aβ-containing c-hGH vials developed CAA, and to a lesser extent, Aβ plaques

in gray matter. Mice injected with brain homogenate from AD patients developed robust CAA and AD pathology. Notably, no plaques developed in mice injected with saline or recombinant hGH at four months of age.[6]

■ COMMENTARY

These findings provide additional evidence for "seeding" activity as a potential mechanism of disease progression in AD and CAA. First, the authors add to a well-established body of evidence that Aβ can participate in seeding — aggregates of Aβ induce pathologic conformational change in normally folded forms of Aβ, exponentially propagating plaque formation.[7] The potential for seeding of Aβ plaques after storage of vials for decades at ambient temperature is especially provocative. However, the connection between seeding of plaques, neuronal dysfunction, and AD has not been established. To begin, Aβ plaque burden, while part of the neuropathologic diagnosis of AD, does not correlate with memory impairment in AD.[8] Rather, soluble Aβ oligomers contribute more directly to neuronal dysfunction and clinical impairment.[9,10] Previous work has demonstrated that plaques are diverse in aggregate composition and only sometimes are accompanied by Aβ oligomers.[10] In addition, the authors did not find tau aggregates in the brains of c-hGH-induced CJD patients (although an analogous study on CJD from c-hGH from France did).[11] Given the six patients who died from c-hGH-induced CJD with Aβ plaque deposition in gray matter succumbed prematurely from a more severely dementing disease, it is unknown if AD eventually could have developed through contaminated Aβ seeding.

In contrast, vascular Aβ plaques were induced more robustly by injection of c-hGH into the mice in this study. Since CAA is diagnosed pathologically, clear demonstration of vascular Aβ plaque was sufficient for the diagnosis of iatrogenic CAA. Purro et al demonstrated the potential of Aβ-contaminated batches of c-hGH to cause CAA and some pathologic features of AD; however, gray matter plaque formation does not equate to AD.

With the memory of c-hGH-induced CJD in more than 200 patients worldwide and hundreds of thousands of patients with AD and CAA, the authors argued for the evaluation of the risks of iatrogenic transmission of CAA and possibly AD through surgical instruments by measurement of Aβ. Aggregates or plaques are unlikely to be resistant to current sterilization methods, but testing has not been conducted to confirm effectiveness. With a long disease incubation period in CAA and AD, young patients who undergo neurosurgical procedures may be at risk for development of disease decades after surgery. ■

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ABSTRACT & COMMENTARY

Predicting the Risk of Mild Cognitive Impairment Using Imaging Biomarkers

By Makoto Ishii, MD, PhD

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

SYNOPSIS: In this population-based study, researchers used imaging biomarkers of amyloid and neuronal injury to estimate an absolute risk of mild cognitive impairment in the elderly.

SOURCE: Petersen RC, Lundt ES, Therneau TM, et al. Predicting progression to mild cognitive impairment. *Ann Neurol* 2018; Dec. 6. doi.org/10.1002/ana.25388. [Epub ahead of print].

Alzheimer's disease (AD) is recognized to be a continuum that begins years to decades before the mild cognitive impairment (MCI) with a preclinical stage, where amyloid-β and tau pathologically accumulate prior to any significant cognitive decline. Importantly, it is now possible to identify individuals in vivo with preclinical AD using biomarkers of amyloid-β (A) by cerebrospinal fluid (CSF) or positron emission tomography (PET) and measures of neuronal injury (N) by CSF, ^{18}F-fluorodeoxyglucose (FDG) PET, or MRI. This has led to an AD biomarker-based staging of cognitively unimpaired individuals based on normal (-) or abnormal (+) levels of A and N, with the A+N+ group having an elevated risk of progression to cognitive impairment. Despite the advances in AD biomarker-based staging, the absolute risk of cognitive impairment for the elderly patient with these biomarkers is not clear, which makes it difficult to use these biomarkers in clinical practice. Therefore, Petersen et al set out to determine the role of imaging biomarkers in predicting progression to cognitive impairment.

Study participants were part of the Mayo Clinic Study of Aging, a longitudinal, population-based study of residents of Olmsted County, Minnesota. All participants were cognitively unimpaired and 70 years of age or older at the baseline visit. Each participant was evaluated clinically approximately every 15 months, with the clinical diagnosis of cognitively unimpaired, MCI, or dementia determined by consensus based on previously established criteria. Amyloid PET imaging was performed using Pittsburgh Compound-B. 3T MRI was performed, and a composite AD-characteristic cortical thickness measure averaging entorhinal, inferior temporal, middle temporal, and fusiform gyri thickness was obtained. Cutoffs for each imaging biomarker were determined based on recent analysis, and individuals were placed into one of four groups: A-N-, A+N-, A-N+, and A+N+.

Out of 763 cognitively unimpaired participants at baseline, 26% were A-N-, 15% were A+N-, 30% were A-N+, and 28% were A+N+. Both A+ and N+ were associated with older age, and men were more likely to be N+. Over a median follow-up of four years, 159 (22%) individuals progressed to MCI (n = 152) or dementia (n = 7). Overall progression rates (events per 100-person years with 95% confidence interval [CI]) were 2.4 (95% CI, 1.8-3.2) at age 75 and 6.5 (95% CI, 5.5-7.6) at age 85. Based on biomarker status, the progression rates at age 75 years were highest for the A+N+ group at 3.9 (95% CI, 2.7-5.7), intermediate for A+N- at 2.3 (95% CI, 1.4-3.7) and A-N+ at 2.3 (95% CI, 1.5-3.4), and lowest for A-N- 1.1 (95% CI, 0.7-1.9). At age 85, the progression rates increased for all groups, with the highest rate in the A+N+ group at 8.9 (95% CI, 6.8-11.5) followed by intermediate rates for both the A+N- and A-N+ groups, and lowest for A-N- group at 2.6 (95% CI, 1.5-4.3). Using the A-N- group as a reference, the relative rate for A+N+ was 3.5 (95% CI, 2.1-6.2), A+N- was 2.0 (95% CI, 1.1-3.9), and A-N+ was 2.0 (95% CI, 1.2-3.6). Male sex and having a high school education or less increased the relative risk (RR, 1.2; 95% CI, 0.9-1.7 for male sex and RR, 1.3; 95% CI, 1.0-1.9 for high school education). Using biomarker status, age, sex, and education level, the investigators calculated an estimated risk of progression to MCI/dementia in five and 10 years. For example, a cognitively unimpaired 75-year-old A-N- woman with some college education was estimated to have a 6% chance of becoming cognitively impaired within five years; however, this increased to 19% if she was A+N+.

■ COMMENTARY

The findings of this study are of great interest, as it is becoming clear that for an AD intervention to be most effective it will need to be implemented as early as possible. As expected, A+N+ individuals had the highest risk of progression. Interestingly, participants with only one positive biomarker (A+N- or A-N+) yielded a similar intermediate risk for developing cognitive impairment. This result differs from other studies that found no significant risk for A-N+. Any discrepancy could be caused

by differences in the biomarkers used for neuronal injury. Although amyloid biomarkers are relatively well-established, the best biomarker for neuronal injury is less clear with a range of modalities. Even when one uses the same modality such as structural MRI, the analyses often differ as one study may focus on hippocampal volumes while others, including this study, may use a composite of cortical thickness from various brain regions. Therefore, a uniformed "best" approach to measuring neuronal injury needs to be established.

A major strength of this study is the relatively large sample size and population-based design, which minimizes any potential referral bias. However, a limitation of the study is that all participants were from one county in Minnesota. It is not clear if the results from this study can be extrapolated to other communities because of differences in race/ethnicity, local environmental effects, or other unforeseen factors. Therefore, similarly designed population studies are needed in other communities to verify and validate these findings. Furthermore, future studies using additional factors strongly associated with AD, including genetic (APOE genotype) and vascular risk factors, would further help stratify the risk of developing cognitive impairment. Despite any limitations, this important study brings us closer to being able to predict the risk of cognitive impairment for any given patient in the clinic. ■

ABSTRACT & COMMENTARY

Thinking Outside of the 'Alpha-Synuclein Box': A Critical Role of Tau in Lewy Body Disorders

By Claire Henchcliffe, MD, DPhil

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Dr. Henchcliffe reports she is a consultant for Amneal Pharmaceuticals, Prevail Therapeutics, and US WorldMeds, and receives grant/research support from Biogen.

SYNOPSIS: Neocortical tau pathology was associated with worse antemortem cognition in this large study of Parkinson's disease dementia and dementia with Lewy bodies. Regional brain variations correlated with specific cognitive domains.

SOURCE: Coughlin D, Xie SX, Liang M, et al. Cognitive and pathological influences of tau pathology in Lewy body disorders. *Ann Neurol* 2018; Dec. 14. doi: 10.1002/ana.25392. [Epub ahead of print].

This sophisticated analysis of alpha-synuclein and tau pathology in Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), often termed "alpha-synucleinopathies," suggests an important role for tau protein as a contributor to cognitive deficits. Tissue was characterized histologically from 55 brains of individuals with PDD or DLB from the Penn LBD autopsy cohort. Cases were categorized as medium-to-high AD pathology (SYN+AD, n = 20) or no to low-level AD pathology (SYN-AD, n = 35) according to ABC scoring (Aβ amyloid Thal phase; Braak tau phase; CERAD plaque score). In examining antemortem clinical characteristics of the two groups, later age at onset with faster progression to clinical dementia and death was seen in the SYN+AD group (onset 69 ± 6.2 years; dementia 73.2 ± 6.7 years; death 77 ± 8.7 years) compared with the SYN-AD group (onset 61.8 ± 9.8 years; dementia 72.5 ± 6.3 years; death 78 ± 6.1 years). DLB was more common than PDD in the SYN+AD group compared with the SYN-AD group (60% vs. 20%).

Coughlin et al used digitized histology methods to generate scores on tissue sections for percent area occupied of immunoreactivity for tau, Aβ, and alpha-synuclein. The authors analyzed more than 900 slides comprising tissue from neocortical areas chosen for their roles in cognition (mid-frontal gyrus, superior temporal gyrus, angular gyrus), in addition to entorhinal cortex and putamen. In the SYN+AD group, greater tau and Aβ burden was found in neocortical regions when compared with the SYN-AD group.

Interestingly, greater alpha-synuclein burden also was demonstrated in neocortical regions (but not entorhinal cortex nor putamen) in the SYN+AD group compared with the SYN-AD group. Moreover, the alpha-synuclein neocortex:putamen ratio was higher in the SYN+AD group compared with the SYN-AD group. SYN and tau pathology independently associated with temporal cortex, in contrast with a relatively higher burden in the mid-frontal gyrus in AD. Antemortem neuropsychological testing comprised the Mini-Mental Status Exam, the Dementia Rating Scale-2, semantic category fluency testing, and the Boston Naming Test. The SYN+AD group performed worse on the Boston Naming Test, but not significantly on other measures. However, there were a number of interesting correlations of regional tau measures of percent area occupied with specific testing,

including category fluency with the mid-frontal gyrus ($r = -0.45$; $P < 0.001$) and the Boston Naming Test with the superior temporal gyrus ($r = -0.45$; $r = -0.68$; $P < 0.001$). This did not hold for alpha-synuclein or β amyloid pathology.

■ COMMENTARY

This important report once again highlights the heterogeneity of PDD and DLB, two of the so-called alpha-synucleinopathies. The authors nicely suggested how non-alpha-synuclein pathology can go some way toward explaining differences between individual patients in terms of symptoms, signs elicited in clinical testing, and clinical trajectory. This study is highly innovative, leveraging a great amount of data collected and using digital pathology to demonstrate the association of specific cognitive deficits with tau pathology in specific and relevant brain regions. In contrast, β amyloid did not show regional associations. The regional deposition of tau in PDD and DLB also seemed to differ with that in AD samples studied for comparison, raising questions about what processes cause this difference. In the cases defined as SYN+AD, not only was there more neocortical tau, there also was more neocortical alpha-synuclein (and at a higher level relative to alpha-synuclein pathology in the putamen). Could this simply be a reflection of "overall worse" pathology in these cases, or could pathophysiological processes be in place that mean one protein could drive damage and deposition in the other? Although this speculation is interesting, an important consideration now is how to make this information actionable and clinically useful. Getting outside of the "alpha-synuclein box" may trigger broader consideration in the debate on diagnosis. Importantly, it also could stimulate improved clinical trials and new therapeutic development for the devastating consequences of these categories of dementia. ■

CME QUESTIONS

1. **Continuous electroencephalography monitoring in critically ill patients is associated with an almost 20% reduction in in-hospital mortality risk.**
   a. True
   b. False

2. **Treatments for chronic inflammatory demyelinating polyradiculoneuropathy may include which of the following?**
   a. Intravenous immune globulin
   b. Plasma exchange
   c. Rituximab
   d. All of the above

3. **Based on the recent findings from the Mayo Clinic Study of Aging, which of the following would *not* increase the risk for developing cognitive impairment in the elderly?**
   a. High school or lower education
   b. Positive amyloid imaging but no evidence of neuronal injury
   c. Negative amyloid imaging but evidence of neuronal injury
   d. All of the above will increase the risk for developing cognitive impairment

4. **How does tau pathology associate with cognition in the alpha-synucleinopathies, Parkinson's disease dementia (PDD), and dementia with Lewy bodies (DLB)?**
   a. Tau pathology is associated preferentially with cognitive decline in DLB but not in PDD.
   b. The presence of Alzheimer's disease pathology, including tau deposition, is associated with more aggressive disease and faster onset of dementia in PDD and DLB.
   c. Tau pathology burden overall, but not regionally, associates with greater cognitive deficits in PDD and DLB.
   d. Individuals with more rapid cognitive decline in DLB and PDD are more likely to have tau but not alpha-synuclein pathology in the neocortex.

[IN FUTURE ISSUES]

Update on Multiple Sclerosis