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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Small Fiber Neuropathy in Critical illness

By Russell L. Chin, MD

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

SYNOPSIS: The spectrum of critical illness polyneuropathy may include painful, small-fiber degeneration that can be readily diagnosed by punch skin-biopsy.

SOURCE: Skorna M, et al. Small-nerve-fiber pathology in critical illness documented by serial skin biopsies. *Muscle Nerve* 2015;52:28-33.

Chronic pain and sensory impairment often occur as a consequence of critical illness, and these symptoms have been viewed as part of the spectrum of critical illness polyneuropathy (CIP). To investigate the mechanism of this disorder, the investigators performed skin biopsies upon admission to the critical care unit and 10-14 days later to follow the course of any neuropathic disease.

Skin biopsies from one leg were obtained to measure intraepidermal nerve fiber density (IENFD) in 11 patients admitted to the neurocritical care unit for ischemic stroke. Nine of the patients developed sepsis or multi-organ failure during this period. Repeat skin biopsies from the opposite leg were obtained 10-14 days later. The median IENFD on admission (5.05 fibers/mm) decreased significantly to 2.18 fibers/mm ($P < 0.001$). Six patients had abnormal IENFD on final skin biopsy (two of them were already abnormal on admission). Electrodiagnostic signs of large fiber neuropathy and/or myopathy were found in six patients (54.5%) and autonomic dysfunction was found in two patients (18.2%).

■ COMMENTARY

Critical illness myopathy (CIM), CIP, and a combination of both (critical illness polyneuromyopathy) are well-recognized disorders that can develop in the setting of prolonged ventilation and neuromuscular blockade, with glucocorticoid exposure and the development of sepsis, systemic inflammatory response syndrome, or multi-organ failure. CIM (also called thick filament myopathy) may be difficult to distinguish from CIP due to the technical difficulties encountered in performing

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detailed electrodiagnostic studies in the ICU. Limb edema may prevent the detection of sensory responses and assessment of motor unit morphology, which is essential to the diagnosis of myopathy, may be limited by poor patient cooperation in the setting of encephalopathy. The presence of a pre-existing neuropathy may also cloud the assessment.[P]

Some data suggest that most patients with acquired neuromuscular disease due to sepsis have the combination of CIM and CIP and that an early drop in nerve conduction responses portends a higher mortality. Complete functional recovery (with the ability to breathe spontaneously and walk independently), however, has been reported in a majority (68%) of patients, while 28% experience chronic, severe disability. Milder residual symptoms, including hypo- and hyperesthesias, reduced or absent deep tendon reflexes, and foot drop, may be present in all patients.[2]

The pathogenesis of axonal injury in CIP is poorly understood. Injury to the microcirculation of distal nerves, causing ischemia and axonal degeneration, has been suggested. Dorsal root ganglia neurons are surrounded by fenestrated capillaries and may be exposed to neurotoxins released during sepsis or systemic inflammatory response syndrome.[3]

Skin punch biopsy is a simple, minimally invasive technique to evaluate for small fiber neuropathy, which is characterized by degeneration and loss of IENFD. It is useful in the setting of sensory symptoms without evidence of large fiber dysfunction.[2]

This study provides useful information about the chronology of critical illness neuromuscular disease in the acute stage. All of the included patients had unremarkable electrodiagnostic studies on admission, but six patients (54.5%) developed neuropathy and/or myopathy at the time of repeat testing 10-14 days later. The proportion of patients with abnormal IENFD also increased in this time frame (from two patients on admission to six patients after repeat skin biopsy).

Involvement of the small nerve fibers appears common in isolation or with large fiber neuropathy or myopathy and could be predictive of symptomatic, painful small-fiber neuropathy. ■

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ABSTRACT & COMMENTARY

The Expanding Role of Tau in Neurodegeneration: New Insights from Huntington's Disease

By Claire Henchcliffe, MD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Henchcliffe reports she is on the speakers bureau and advisory boards for Teva, IMPAX, and ACADIA; and receives grant/research support from Biogen and Kaneka.

SYNOPSIS: Although Huntington's disease (HD) is due to a triplet repeat expansion in the huntingtin gene, this study demonstrates abnormally phosphorylated tau pathology in HD brain tissue.

SOURCE: Vuono R, et al. The role of tau in the pathological process and clinical expression of Huntington's disease. *Brain* 2015;138:1907-1918.

This is a two-part study investigating the importance of the microtubule-associated protein tau (MAPT) in Huntington's disease (HD). HD is caused by CAG triplet repeat expansions in the huntingtin (HTT) gene, but variability in phenotype in individuals with similar repeat numbers has long suggested the

importance of other factors. MAPT, extensively studied in other neurodegenerative diseases such as Alzheimer's disease (AD), frontotemporal dementia, and progressive supranuclear palsy, has recently been implicated in HD. In the first part of the study, brain tissue from 16 individuals with HD from the Cambridge Brain Bank was compared with tissue from individuals with sporadic tauopathies and with healthy controls. Monoclonal antibody staining of tissue sections revealed abnormal hyperphosphorylated tau aggregates within neurons, with perinuclear, flame-shaped, or globular appearance in HD. The expected abnormal inclusions were observed in disease controls but not healthy controls. In HD, the abnormal tau inclusions were observed in the striatum, particularly putamen and nucleus accumbens, and in the cortex, particularly insular cortex. Moreover, some tau aggregates co-localized with mutant HTT aggregates. Two cases involved young patients (ages 26 years and 40 years at death), thus linking findings to presence of the disease rather than the aging process. Specific antibodies also demonstrated presence of oligomeric inclusions in HD striatum, but not cortex. Furthermore, western blot analysis of proteins isolated from brain tissue revealed an isoform profile overlapping with AD, and analysis of transcript profiles confirmed the recent report of an abnormally increased 4R:3R tau isoform ratio in HD.

In the second part of the study, tau haplotype was studied in individuals with genetically proven HD who participated in the European Huntington Disease Network REGISTRY project. This registry comprises 960 patients with HTT genotyping. Of these, 473 had clinical assessments at least a year apart involving motor, cognitive, and functional measures. Patient ages were from 48.1 (± 12.3) to 49.4 (± 12.9) years, and disease duration was from 5.3 (± 4.0) to 7.3 (± 5.0) years (patient characteristics are reported by MAPT haplotype in this article). HTT CAG repeat lengths were from 43.8 (± 3.1) to 44.9 (± 5.1). The investigators genotyped all 960 cases for MAPT haplotypes H1 (found in 60%) and H2 (found in 40%). A trend was found for decline in cognitive performance associated with the MAPT H2 haplotype that was statistically significant for verbal fluency and attention testing. Higher HTT CAG repeat number also correlated with cognitive decline in the whole group, but this finding was driven by the H2 haplotype carriers.

■ COMMENTARY

The present study adds significantly to our understanding of HD in particular, but also to neurodegenerative disorders in general. The tau protein is involved in microtubule assembly and stabilization and in axonal transport. Although well-studied in other neurodegenerative disorders, such as AD, only recently has attention been paid to a potential role in HD. As in other disorders, such as AD and Parkinson's disease, the investigators highlight that multiple mechanisms are at play in the HD pathogenic cascade. Moreover, tau now provides an important link across many disorders. These include the tauopathies, such as AD, Pick's disease, progressive supranuclear palsy, and corticobasal degeneration. In addition, the role of tau is increasingly recognized in other neurodegenerative disorders, such as Parkinson's disease in which MAPT has been associated by multiple genome wide association studies. Not only are there genetic associations, but alternative splicing leads to production of 3R and 4R isoforms (named for the numbers of microtubule binding repeat domains in each), and altered ratios of 3R:4R are associated with the tauopathies. This is now established by the present study in HD. Post-translational modification, hyperphosphorylation, adds an additional level of complexity, as does aggregation of the tau protein.

[The investigators provide independent confirmation of abnormal tau aggregates in Huntington's disease. Their characterization of tau oligomers in the putamen further strengthens the hypothesis that this is significant in pathogenesis, since oligomeric species are now thought to be most toxic to cells.]

In summary, the authors build on a recent report finding rod-like nuclear deposits of tau in postmortem brain tissue from individuals with HD, and the finding of an increased 4R:3R tau isoform ratio in HD. The investigators provide independent confirmation of abnormal tau aggregates in HD. Moreover, their characterization of tau oligomers in the putamen further strengthens the hypothesis that this is significant in pathogenesis, since oligomeric species are now thought to be most toxic to cells. Finally, using data from hundreds of HD patients in the European Huntington Disease Network REGISTRY, the association of MAPT haplotype with cognitive decline strongly suggests that the pathologic changes described have a clinical significance. This report will undoubtedly stimulate more attention to the role of tau in HD and may ultimately suggest specific interventions that will help our patients. ■

ABSTRACT & COMMENTARY

Vitamin D and Diabetic Neuropathy

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: Vitamin D deficiency may exacerbate the clinical manifestations of diabetic neuropathy, and supplementation with vitamin D3 may be beneficial.

SOURCE: Alamdari A, et al. An inverse association between serum vitamin D levels with the presence and severity of impaired nerve conduction velocity and large fiber peripheral neuropathy in diabetic subjects. *Neurol Sci* 2015;36:1121-1126.

Skeletal manifestations of vitamin D deficiency include rickets and osteomalacia in children, and osteomalacia in adults. Approximately 3% of the human genome is under vitamin D control, and at least 10 extrarenal tissues express the enzyme 1-alpha-hydroxylase, responsible for converting vitamin D to its active form. Hence, it is not surprising that extraskeletal manifestations may also occur, including muscle weakness, cancer, hypertension, cardiovascular events, schizophrenia and depression, autoimmune disorders, type 1 diabetes, multiple sclerosis, and inflammatory bowel disease. Is there an independent association between vitamin D deficiency and diabetic neuropathy as defined by electrodiagnostic studies?

[Neuropathic pain, particularly burning discomfort and hyperesthesia, was significantly improved; thus, vitamin D supplementation can be a simple addition to the treatment of painful diabetic peripheral neuropathy.]

In this case-control study, patients newly diagnosed with type 2 diabetes were recruited from the Endocrinology and Metabolism Research Center, Vali-Asr Hospital, School of Medicine, Tehran University, Iran. Exclusionary criteria comprised type 1 diabetes, neuropathy of any cause other than diabetes, cancer, and thyroid, renal, or liver disease. Insulin-requiring diabetics were not included. Nerve conduction studies (NCS) were performed on all patients with neuropathic symptoms of numbness, tingling, or pain, and included the tibial, peroneal, median, and ulnar motor nerves, and median, ulnar, and sural sensory nerves. Statistical analysis comprised the t test for continuous variables, $\chi 2$ test for categorical variables, Pearson correlation coefficients, and two multivariate linear regression analyses, with two-sided P value < 0.05 considered significant.

Sixty-two diabetic patients were recruited: 29 with normal NCS and 33 with abnormal NCS. Both groups demonstrated a similar prevalence of retinopathy, microalbuminuria, and hypertension, and comparable HbA1c and creatinine levels. Serum vitamin D level was significantly lower in the abnormal NCS group, and correlated inversely with the degree of NCS abnormality, with lower vitamin D values present in those with more profound NCS abnormalities. For every 1 ng/mL increase in serum vitamin D, the presence and severity of NCS decreased by 2.2% and 3.4%, respectively. Lower vitamin D values correlate with worsening neuropathy in diabetic patients.

■ COMMENTARY

Can vitamin D supplementation improve symptomatic neuropathy in type 2 diabetic patients with vitamin D deficiency? Among 112 such patients enrolled in a prospective, placebo-controlled, clinical trial, 57 were given oral vitamin D3 (50,000 IU weekly for 8 weeks) and 55 received placebo. Exclusionary criteria included B12 deficiency, alcohol abuse, malignancy, autoimmune disease, hyperparathyroidism, and kidney or liver failure. Statistical analysis encompassed the $\chi 2$ test, Student t and Mann-Whitney U tests, and the Spearman correlation coefficient, with $P < 0.05$ considered significant. Using nerve conduction studies, a neuropathy symptom score, and a neuropathy disability score to assess the severity of diabetic peripheral neuropathy, vitamin D supplementation both increased serum vitamin D levels and significantly improved neuropathy symptom score values, though not neuropathy disability score nor nerve conduction studies.[1] Neuropathic pain, particularly burning discomfort and hyperesthesia, was significantly improved. While awaiting confirmation from larger randomized, controlled trials, vitamin D supplementation can be a simple addition to the treatment of painful diabetic peripheral neuropathy. ■

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ABSTRACT & COMMENTARY

Cerebrospinal Fluid Tau and Amyloid-ß1-42 in Patients with Dementia

By Louise M. Klebanoff, MD

Associate Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: In patients with clinically diagnosed dementia, the CSF biomarker profile of low CSF amyloid-ß1-42, high total tau, and high phosphorylated tau was seen in the majority of patients with clinically diagnosed Alzheimer's disease. Substantial proportions of patients with non-Alzheimer's dementia were also found to have the Alzheimer's disease pathological profile. The value of CSF biomarker measurements in clinical practice is uncertain.

SOURCE: Skillback T, et al. Cerebrospinal fluid tau and amyloid-ß1-42 in patients with dementia. *Brain* 2015;138:2716-2731.

As the global population ages, Alzheimer's disease, the most common cause of dementia affecting more than 20 million people worldwide, is of increasingly critical importance to world health. The pathological signs of the disease, including neuronal and synaptic/axonal degeneration with resultant brain atrophy, the accumulation of amyloid plaques, and intranuclear neurofibrillary tangles of phosphorylated tau, have been recognized for decades. In more recent years, cerebrospinal fluid (CSF) biomarkers for Alzheimer's disease have been developed. These biomarkers include low levels of CSF amyloid-ß1-42, which correlates with greater plaque load; high levels of tau, which correlate with greater intensity of neuronal degeneration; and high levels of phosphorylated tau, which correlate with neurofibrillary tangles. In the context of a clinical presentation consistent with Alzheimer's disease, a CSF profile combining low levels of amyloid-ß1-42, high levels of total tau, and high levels of phosphorylated tau support the diagnosis with 80-93% sensitivity and 82-90% specificity when compared to controls. Other common dementing disorders, however, can overlap with Alzheimer's disease in terms of clinical presentation and CSF biomarkers. In addition, mixed syndromes are not uncommon.

Skillback et al examined CSF amyloid-ß1-42, total tau, and phosphorylated tau in patients with clinically diagnosed dementia in an effort to identify concomitant Alzheimer's disease pathology in patients without a clinical diagnosis of Alzheimer's disease. They also performed a biomarker-driven cluster analysis to test for the natural classification of study patients.

The investigators combined two sources of information for the study. They accessed a complete set of archived data of CSF biomarkers (amyloid-ß1-42, total tau, and phosphorylated tau) made in clinical practice at the Molndal site of Sahlgrenska University Hospital in Sweden that were collected between January 2004 and June 2012; this laboratory handles CSF biomarker measurements for all of Sweden. They also had clinical data from SveDen, the Swedish Dementia Registry, which covers 95% of all memory clinics and 70% of all primary care units in Sweden. When a patient is diagnosed with dementia in clinical practice, the clinical diagnosis, date of diagnosis, and Mini-Mental State Examination score is entered into the registry. The diagnosis is made on clinical grounds and ß1-42 is entered as one of the following nine categories: early-onset Alzheimer's disease (onset < 65 years of age), late-onset Alzheimer's disease (onset > 65 years of age), fronto-temporal dementia, dementia with Lewy bodies, Parkinson's disease dementia, vascular dementia, mixed Alzheimer's disease and vascular dementia, dementia not otherwise specified, or other dementias. More than 70% of the patients in the study were diagnosed by dementia specialists.

The investigators analyzed 5676 patients with complete CSF biomarker measurements obtained within 3 years of diagnosis. The combination of low levels of amyloid-ß1-42 with a pathological level of either total tau or phosphorylated tau was considered an Alzheimer's disease-like pathological profile. The investigators found that amyloid-ß1-42 was lowest in the early-onset and late-onset Alzheimer's groups and in the mixed Alzheimer's and vascular dementia group and was highest in the frontotemporal dementia group. Total tau was highest in the early-onset Alzheimer's group, followed by the late-onset group and then the mixed Alzheimer's disease and vascular dementia group; patients with Lewy body dementia and Parkinson's disease dementia had the lowest levels. Levels of phosphorylated tau and the amyloid-ß1-42:phosphorylated tau ratio showed a similar picture, with the highest levels in early onset Alzheimer's followed by late onset Alzheimer's and mixed Alzheimer's disease and vascular dementia. Patients with frontotemporal dementia had a CSF biomarker profile most distinct from patients with Alzheimer's disease.

When using established cutoffs for the measured biomarkers, patients were classified according to the presence or absence of Alzheimer's disease pathology. The biomarker profile was found significantly more in the patients with clinically diagnosed Alzheimer's disease, either late-onset, early-onset, or mixed Alzheimer's disease and vascular dementia, with more than 80% of these patients showing low levels of amyloid-ß1-42, high total tau, and high phosphorylated tau levels. However, a substantial proportion of patients without a clinical diagnosis of Alzheimer's disease also had abnormal biomarkers consistent with Alzheimer's disease pathology. More than 50% of patients clinically diagnosed with vascular dementia, dementia with Lewy bodies, and Parkinson's disease dementia had low levels of amyloid-ß1-42. More than 40% of patients diagnosed with vascular dementia and frontotemporal dementia had abnormal total tau measurements, and more than 20% of patients with vascular dementia and dementia with Lewy bodies had abnormal phosphorylated tau measurements. Therefore, CSF biomarker evidence of Alzheimer's ß1-42 disease-like pathology was found in a considerable proportion of patients without a clinical diagnosis of Alzheimer's disease.

The investigators applied cluster analysis using log (total tau) and log (amyloid-ß1-42:phosphorylated tau) to identify a division separating the subjects into two groups. The first cluster (n = 2851) contained more than 90% of the patients diagnosed with vascular dementia, frontotemporal dementia, Parkinson's disease dementia, and dementia with Lewy bodies. The second cluster (n = 2825) contained the majority of the patients with a clinical diagnosis of early-onset Alzheimer's disease (75%) and late-onset Alzheimer's disease (73%).

■ COMMENTARY

As the world's population ages and dementia becomes more prevalent, the ability to accurately diagnose dementia gains increasing importance. Once treatment interventions have been developed to alter the course of neurodegenerative conditions with associated dementia, the ability to diagnose these conditions in the preclinical stage will be essential. However, at this time, such treatment interventions are lacking.

The study by Skillback et al shows that CSF biomarkers can be obtained in a large population of patients with dementia. The study compared biomarker profiles obtained in clinical practice with patients who were clinically diagnosed to have one of nine dementing illnesses. Although certain profiles were expected, such as low amyloid-ß1-42, higher total tau, and high phosphorylated tau seen in a higher proportion of patients with clinically diagnosed Alzheimer's disease, there were still a substantial proportion of patients clinically diagnosed with Alzheimer's disease who did not have the expected biomarker profile. In addition, the Alzheimer's disease biomarker profile was seen in a substantial proportion of patients who were diagnosed with dementia not attributed to Alzheimer's disease. Since the biomarkers were obtained as part of clinical care, it is possible that the results influenced the clinical diagnosis, circular logic that the investigators readily acknowledged. Neuro-imaging and neuropathology were not included as part of the study data, also weakening the study.

At this time, CSF biomarkers can support a clinical diagnosis of Alzheimer's disease, but cannot definitively confirm the diagnosis or exclude other neurodegenerative diseases as the cause of a specific patient's dementia. CSF biomarkers may weakly correlate with disease severity, but do not provide prognostic information. It is not clear if CSF markers will predict the onset of Alzheimer's disease and other dementing illnesses in the preclinical stages; this is obviously an area for further research. However, without providing definitive diagnosis of the type of dementia, the lack of prognostic information and in the absence of proven interventions for disease prevention, should CSF biomarkers be able to diagnose dementia in the preclinical stages, CSF biomarker measurement adds little to the clinical diagnosis and management of patients with dementia. While further research on CSF biomarkers in dementia is needed, currently, obtaining CSF biomarkers should not be the part of the standard of clinical care for patients presenting with dementia. ■

ABSTRACT & COMMENTARY

Biomarkers of Intrathecal Inflammation in Multiple Sclerosis and Other Disorders

By Jai Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Perumal is on the speakers bureau for Biogen Idec, Teva Pharmaceuticals, Genzyme Corp., and Acorda Therapeutics.

SYNOPSIS: A study of intrathecal immune markers in neuro-immunological diseases revealed increased numbers of activated T and B cells in both relapsing and progressive multiple sclerosis (MS), but they were preferentially embedded in the brain tissue in progressive MS.

SOURCE: Kimori M, et al. Cerebrospinal fluid markers reveal intrathecal inflammation in progressive multiple sclerosis. *Ann Neurol* 2015;78:3-20.

In the current management of neuro-inflammatory diseases, including multiple sclerosis (MS), assessment of intrathecal inflammation in clinical practice is limited to evidence of contrast-enhancing lesions on magnetic resonance imaging (MRI) and elevated IgG index and oligoclonal bands in cerebrospinal fluid (CSF), apart from elevated cell count and protein. These markers are non-specific and do not provide further details on the underlying inflammatory processes. While elevated IgG index and presence of oligoclonal bands might help in making a diagnosis of MS, since they are static in nature, they are not helpful in monitoring response to therapy. There are little data regarding cell-specific immune markers and dynamic biomarkers of intrathecal inflammation. Knowledge of the specific immune mechanisms leading to injury in a particular disease or disease subtype, such as progressive MS, and biomarkers that allow us to monitor treatment response would ultimately lead to better treatment strategies and outcomes. They would also serve as useful tools to evaluate the efficacy of potential treatments in clinical trials, especially in early, short-duration therapeutic feasibility studies. With these goals in mind, Kimori et al sought to evaluate several CSF biomarkers and to identify and quantify cell-specific biomarkers and their primary immune-cell source. They attempted to confirm the validity of the measured biomarkers in independent cohorts of patients with neuroimmunological disorders and integrate the data to establish a biomarker profile, rather than one individual marker that would identify a disease or categorize specific disease subtypes.

This study included two cohorts of patients and eight embedded healthy controls. Each cohort included 193 patients. Cohort A was enrolled between January 2008 and 2011 and cohort B between February 2011 and January 2014, after implementation of the immunophenotyping protocol that was used to compute a biomarker profile. Subjects included patients with all types of MS (relapsing-remitting, secondary progressive, and primary progressive) and non-MS patients. Non-MS patients were categorized into either other inflammatory neurological disease (OIND) or non-inflammatory neurological diseases (NIND). OIND category included patients with cryptococcal meningoencephalitis, paraneoplastic syndrome, cyclic meningitis, Aicardi–Goutieres syndrome with central nervous system (CNS) involvement, Susac syndrome, neonatal-onset multisystem inflammatory disease with CNS involvement, Lyme disease with CNS involvement, human T-cell lymphotropic virus type 1–associated myelopathy, sarcoidosis with CNS involvement, CNS lupus erythematosus, CNS vasculitis, autoimmune lymphoproliferative syndrome with CNS involvement, and encephalitis/ventriculitis of unknown origin. The NIND group included patients with systemic Lyme disease without CNS involvement, systemic cryptococcosis without CNS involvement, epilepsy, amyotrophic lateral sclerosis, compressive myelopathy, leukodystrophy, mitochondrial disease, hydromyelia, headache/dizziness without any CNS abnormality and ischemic/gliotic white matter lesions. CSF samples were collected and subjects underwent MRI examinations. Apart from routine tests on CSF, including cell count, protein level, and electrophoresis, an electrochemiluminescent assay was developed to detect and quantify several specific immune biomarkers. Assays for immune cells, which were the sources of the biomarkers, were undertaken as well.

CD27 secreted by activated T cells significantly and reproducibly differentiated all neuroimmunological patients (MS and OIND groups) from NIND patients and healthy controls. Ratios of specific biomarkers to their cell of origin in the CSF were calculated. When compared to healthy controls, a higher ratio would suggest that the secreted biomarker marker was not from immune cells measured in the CSF but from immune cells embedded in the CNS tissue. On comparing three pairs of biomarker/immune cell of origin ratios, sCD27/T cell was significantly higher in progressive MS patients than any other group. sCD27/T cell and sCD21/B cell ratios also differentiated progressive MS from relapsing-remitting MS. These results appear to indicate that inflammation in progressive MS comes from immune cells within CNS tissue rather than active passage from systemic circulation to the CSF, as in relapsing-remitting MS. Based on the authors' model, a biomarker profile that could predict specific diagnostic categories with an accuracy > 60% could not be identified, but sCD27 was the single best predictive biomarker of active intrathecal inflammation.

■ COMMENTARY

In the management of neuroimmunological diseases, it would be invaluable to have a biomarker that can identify a specific diagnostic entity accurately and help monitor clinical course and response to treatment. Though far from perfect, contrast-enhancing lesions on MRI and elevated IgG index and oligoclonal bands are still used in confirming a diagnosis of MS, and contrast-enhancing lesions are used to monitor response to treatment. This study examined several specific CSF biomarkers with the aim of detecting a biomarker profile that would accurately predict a specific diagnosis and dynamic biomarkers that could be used to monitor

therapeutic response in clinical practice or clinical trials. Although the authors could not identify a biomarker profile that could predict disease entities with high accuracy, T cell-mediated inflammation, as measured by sCD27, seemed to be the most consistent marker of intrathecal inflammation. With regard to MS, the findings suggest that there still appears to be a significant inflammatory component in progressive MS, but it is predominantly due to embedded CNS immune cells rather than infiltration of immune cells into the CSF through a breach in the blood-brain-barrier, as seen in relapsing-remitting MS. This adds to previously published data about the different nature of inflammation in progressive MS and relative lack of efficacy of current MS therapies in this form of MS. Continued further research into potential biomarkers will hopefully provide immunological clues to better address treatment in progressive MS. ■

CME QUESTIONS

1. **Critical illness polyneuromyopathy is characterized by all of the following *except*:**
   a. Generalized weakness
   b. Muscle atrophy
   c. Cranial nerve palsies
   d. Generalized pain
   e. Associated with multi-organ failure

2. **The microtubule associated protein tau (MAPT) is associated with Huntington's disease (HD) pathogenesis. Which of the following correctly describes evidence for this association?**
   a. Existence of triplet repeat expansions in the MAPT gene in individuals with HD
   b. Presence of hyperphosphorylated tau aggregates in autopsy tissue
   c. Specificity of finding altered tau R3:R4 isoform ratio in cortical but not striatal tissue
   d. Association of the MAPT H1 haplotype with motor and cognitive decline in HD

3. **Which of the following statements about vitamin D is true?**
   a. Lower vitamin D values correlate with worsening neuropathy in diabetic patients.
   b. Higher vitamin D values correlate with worsening neuropathy in diabetic patients.
   c. Vitamin D is only important for bone health but does not affect other organ systems.
   d. To be effective, vitamin D must be given only intravenously.
   e. Oral vitamin D is not available.

4. **Which of the following is considered the cerebrospinal fluid (CSF) biomarker profile of Alzheimer's disease pathology?**
   a. Low CSF amyloid-ß1-42, low total tau, low phosphorylated tau
   b. High CSF amyloid-ß1-42, high total tau, high phosphorylated tau
   c. Low CSF amyloid-ß1-42, high total tau, high phosphorylated tau
   d. Low CSF amyloid-ß1-42, low total tau, high phophorylated tau
   e. None of the above

5. **Which of the following statements regarding cerebrospinal fluid (CSF) biomarkers in multiple sclerosis (MS) is correct?**
   a. Cell-surface markers can accurately categorize different MS sub-types.
   b. CSF biomarkers are useful in monitoring disease activity.
   c. CSF biomarkers are useful in monitoring disease progression.
   d. CSF biomarkers are useful in supporting the clinical diagnosis of MS.
   e. CSF biomarkers can help to select the type of treatment for MS patients.

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.

[IN FUTURE ISSUES]

Update on Migraines