NEUROLOGY ALERT®

Providing Evidence-based Clinical Information for 32 Years

A monthly survey of developments in neurologic medicine

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media

INSIDE

Financial Disclosure: *Neurology Alert's* editor in chief, Matthew Fink, MD, is a retained consultant for Procter & Gamble. Peer reviewer M. Flint Beal, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Neuropathy with Hepatitis C Virus-Related Cryoglobulinemia

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: *Most patients who develop cryoglobulinemia associated with hepatitis C infection will develop symptoms and signs of a symmetric, distal sensory neuropathy.*

Source: Biasiotta A, et al. Clinical, neurophysiological, and skin biopsy findings in peripheral neuropathy associated with hepatitis C virus-related cryoglobulinemia. *J Neurol* 2014;261:725-731.

CRYOGLOBULINEMIA, ONE OF SEVERAL EXTRAHEPATIC MANIFESTATIONS OF chronic hepatitis C virus (HCV) infection, is a lymphoproliferative disorder that causes the deposition of circulating immune complexes in small- to medium-sized blood vessels, resulting in purpura, glomerulonephritis, and neuropathy, the latter usually a painful, distal, predominantly sensory polyneuropathy. Risk factors and mechanisms underlying neuropathic pain in these patients have been little studied but are now addressed.

Over a 2-year period, 74 consecutive unselected patients with HCV-related cryoglobulinemia were screened for this study. All had type II (essential mixed) cryoglobulinemia and none had oncologic or hematologic disease. Exclusionary criteria — which included cognitive impairment, non-neuropathic neurologic disease, or any condition that might cause neuropathy — resulted in the exclusion of five patients (four with diabetes,

Pharmacology Watch, *Clinical Briefs* Available Online

The June 2014 issues of *Pharmacology Watch* and *Clinical Briefs in Primary Care* are now available exclusively by e-mail or online. You can access these two valuable supplements to *Neurology Alert* at http://www.ahcmedia.com/supplements/.

VOLUME 32 • NUMBER 10 • JUNE 2014 • PAGES 73-80

NOW AVAILABLE ONLINE
www.ahcmedia.com

one with renal failure), leaving 69 for enrollment. Evaluation of all enrollees included neurologic examination, diagnosis and rating of various neuropathic pains using the Neuropathic Pain Diagnostic questionnaire and the Neuropathic Pain Symptom Inventory, respectively, and nerve conduction studies of sensory (sural, ulnar, superficial radial) and motor (peroneal, tibial, ulnar) nerves. To assess small myelinated fibers, laser-evoked-potential recordings were obtained, using a neodymium:yttrium–aluminium–perovskite (Nd:YAP) laser to stimulate the dorsum of the right foot and left hand, with recording of the N1 and N2-P2 complexes from the temporal areas. To assess C-fiber terinals, skin biopsies were obtained from the proximal thigh and distal leg. Statistical analysis included the unpaired *t* test and Mann–Whitney test, using Spearman's rank correlation coefficient for correlation analysis, with $P < 0.05$ considered significant.

Among the 69 patients, peripheral neuropathy was seen in 68% (n = 47), of which 96% (n = 45) had distal symmetric sensory polyneuropathy with the two remaining patients demonstrating mononeuropathy multiplex. Among the 45 patients with distal symmetric sensory polyneuropathy, 76% (n = 34) had both large and small fiber involvement, 15% (n = 7) had predominantly large fiber neuropathy with no pain or temperature sensation alteration, and 9% (n = 4) had a purely small fiber sensory neuropathy with pure pain and temperature involvement, abnormal laser-evoked potentials and intraepidermal nerve fiber density, and normal nerve conduction studies. Compared to patients without peripheral neuropathy, those with neuropathy tended to be older, with longer duration of HCV infection. No difference was seen for gender or duration of cryoglobulinemia. Sural sensory nerve action potential amplitude, foot laser-evoked potential amplitude, and intraepidermal nerve fiber density on skin biopsy correlated inversely with duration of HCV infection, with pain related to low laser-evoked potential amplitude, rather than sural amplitude or intraepidermal nerve fiber density. Peripheral neuropathy in HCV is related to age and duration of infection rather than to cryoglobulinemia, and pain is associated with nociceptive pathway injury.

■ COMMENTARY

Although induction therapy for mild-to-moderate chronic hepatitis C virus cryoglobulinemic vasculitis comprises pegylated interferon-α and ribavirin with boceprevir or telaprevir, severe disease, including progressive renal failure, mononeuritis multiplex, and extensive skin disease, requires additional immunosuppression. Rituximab, targeting B cells responsible for cryoglobulin production, is generally effective and well tolerated, and, combined with an optimal antiviral agent, is the recommended therapy. Adverse effects, including peripheralneuropathy or skin ulcers, may worsen with interferon therapy, and relapse of cryoglobulinemic vasculitis may presage B cell non-Hodgkin's lymphoma. Low-dose corticosteroids are usually ineffective with major organ involvement. ■

Neurology Alert, ISSN 0741-4234, is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

EXECUTIVE EDITOR: Leslie G. Coplin
MANAGING EDITOR: Neill L. Kimball
EDITORIAL DIRECTOR: Lee Landenberger

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Neurology Alert,*** P.O. Box 550669, Atlanta, GA 30355.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: leslie.coplin@ahcmedia.com
Online: www.ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $369
Add $19.99 for shipping & handling.
Online only, single user: $319
Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.
Canada
Add 7% GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of *25 AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the neurologist. It is in effect for 36 months from the date of the publication.

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

Trochlear Headache: A Rare, Specific 'Eye-strain' Headache

ABSTRACT & COMMENTARY

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Trochlear headaches should be considered in patients with new onset, constant, unilateral eye pain, especially when the pain is aggravated by eye movement.*

Source: Smith JH, et al. Clinical features and long-term prognosis of trochlear headaches. *Eur J Neurol* 2014;21:577-585.

THE TROCHLEAR NERVE (CRANIAL NERVE IV) INNERVATES A single muscle: the superior oblique muscle that depresses and adducts the eye. The tendon of the trochlear nerve sits in the trochlea, a saddle or pulley-like cartilagi-

nous structure that is located in the superomedial orbit. Inflammation of the trochlea, trochleitis, produces swelling and tenderness, presenting as a unilateral periorbital pain, a headache referable to the trochlear apparatus. Trochleitis can be idiopathic or secondary to inflammatory or autoimmune connective tissue disorders. A primary trochlear headache, not associated with inflammation, has also been described. Smith et al described 25 cases of this rare trochlear headache disorder, compiled retrospectively over 5 years (2007-2012) after diagnosis at the Mayo Clinic. The diagnosis of trochlear headache was not recognized by the referring neurologist or ophthalmologist, who reported the diagnoses of chronic migraine (n = 13), new daily persistent headache (n = 5), no diagnosis (n = 4), hemicrania continua (n = 2), and atypical facial pain (n = 1). Patients were generally female (n = 20, 80%) with a median age at diagnosis of 46 years (range 18-77). Patients had a median time from symptom onset to diagnosis of 6.7 months (range of 2 weeks to 10 years). Characteristically, the headache was a continuous, dull or achy, moderate-to-severe, periorbital (medial eyebrow, orbit, or forehead) pain that was associated with photophobia and binocular diplopia. The pain was aggravated by eye movement or reading. Almost half of individuals with trochleitis (clinically apparent trochlear edema) had an identified secondary mechanism, such as Behcet's syndrome, granulomatosis polyangiitis, lymphoma, or Tolosa-Hunt syndrome. Imaging of the trochlea tendon by contrast magnetic resonance imaging or computed tomography study of the orbits was diagnostic in all but one patient. Injection of dexamethasone/lidocaine near the trochlea usually provided symptomatic relief. At a median follow-up of 34 months (range 0-68 months), 10/25 (40%) of the cohort of patients with trochlear headache had experienced complete remission. The authors concluded that the diagnosis of a trochlear headache should be considered in patients presenting with a new daily eye pain that is aggravated by eye movements, especially while reading.

■ COMMENTARY

Unilateral periorbital pain is found with multiple headache types, but generally that pain localization is associated with migraine headaches, the most common headache type found in a neurological practice. The migraine-accompanying symptoms, as well as pain that generally switches sides or expands bilaterally, aid in making a migraine diagnosis. A less common cause of unilateral, generally side-locked, pain is cluster headaches and other trigeminal autonomic cephalgias, but these headaches are characterized by an array of distinctive dysautonomic symptoms. The International Classification of Headache Disorders, 3rd edition (beta version), published by the Headache Classification Committee of the International Headache Society (IHS), catalogues what may be misperceived as an amorphous complaint into precisely defined headache syndromes. Headache attributed to trochleitis is defined by the ICHD-3 beta as "Headache, usually frontal and/or periorbital in location, with or without eye pain, caused by peritrochlear inflammation. It is often exacerbated by downward movements of the eye."[1] Trochleitis can also trigger an episode of migraine ipsilateral to the periorbital pain. Although patients often incorrectly attribute headaches to excess use of their eyes, trochlear headaches are distinctly exacerbated by eye movement or reading. Neurologists will rarely encounter a patient with trochlear headache; unless the diagnosis is considered and review of brain imaging is focused on the area of interest, the opportunity for focused treatment of trochlear headache may be lost. ■

Reference

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013;33:629-808.

MRI as a Biomarker for Hippocampal Injury in Febrile Status Epilepticus

ABSTRACT & COMMENTARY

By Padmaja Kandula, MD

Assistant Professor of Neurology and Neuroscience, Comprehensive Epilepsy Center, Weill Cornell Medical College

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

Synopsis: *In this prospective study, the authors use brain imaging criteria to determine whether acute febrile status results in acute hippocampal injury and potentially chronic hippocampal sclerosis.*

Source: Lewis DV, et al, and the FEBSTAT study team. Hippocampal sclerosis after febrile status epilepticus: The FEBSTAT study. *Ann Neurol* 2014;75:178-185.

The interaction between prolonged febrile seizures in childhood and the development of hippocampal sclerosis has been hotly debated. In this prospective study, both the acute and long-term imaging characteristics of febrile status are compared to a cohort of controls with simple febrile seizures.

In total, 226 patients aged 1 month to 6 years, derived from three prospective studies, were included in the final

Continued on page 78

By Matthew E. Fink, MD, *Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital*

What is the Best Treatment for Cerebral Cavernous Malformations?

ABSTRACT & COMMENTARY

Synopsis: *Cerebral cavernous malformations are common lesions, often asymptomatic, with a low risk for spontaneous hemorrhage. The most effective treatment is uncertain.*

Sources: Jeon JS, et al. A risk factor analysis of prospective symptomatic haemorrhage in adult patients with cerebral cavernous malformations. *J Neurol Neurosurg Psychiatry* 2014 Mar 28; doi:10.1136/jnnp-2013-306844 [Epub ahead of print].

Poorthuis MH, et al. Treatment of cerebral cavernous malformations: A systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2014 Mar 25; doi:10.1136/jnnp-2013-307349 [Epub ahead of print].

Cerebral cavernous malformations are common brain lesions that are found in 0.5-1% of the general adult population. The natural history of these lesions is uncertain, as is the long-term risk of hemorrhage. In addition to intracranial hemorrhage, patients are also at risk for epileptic seizures and nonhemorrhagic focal neurological deficits. Two recent studies have attempted to determine the long-term risk of symptomatic hemorrhage as well as the best treatment to prevent recurrent hemorrhages.

The study by Jeon and colleagues, from the Seoul National University College of Medicine in Seoul, Korea, retrospectively studied 326 patients older than 18 years of age, seen at their center from 1998 until 2010, for a total of 410 cerebral cavernous malformations. Symptomatic hemorrhages were defined as new clinical symptoms with radiographic features of hemorrhage. The patients were divided into three groups. Type I was defined as a cavernous malformation showing acute or subacute hemorrhage. Type II was defined as a loculated hemorrhagic lesion with the typical mulberry appearance and thrombosis. Type III was defined as showing chronic resolved hemorrhage without typical mulberry appearance and a small punctate lesion surrounded by a residual hemosiderin rim. Type III was considered to be a remote hemorrhage, while types I and II were believed to be acute and subacute. One hundred seven (32.8%) and 219 (67.2%) patients, respectively, presented with hemorrhage-related symptoms and hemorrhage-unrelated symptoms. Ninety-five patients had seizures, 54 had a neurological deficit, 48 had headache or vertigo, and 22 were asymptomatic or found incidentally. Two patients died without any relationship to the cavernous malformation. Seventy-nine patients underwent surgical management with 27 undergoing surgical resection and 52 treated with gamma-knife radiosurgery. The indications for intervention were symptomatic hemorrhage in 34, intractable seizures in 26, and progressive neurological deficits in 19.

The overall rate of hemorrhage in this group was 4.46% per lesion-year. The overall annual rate of hemorrhage according to the MR appearance was 9.47% for type I, 4.74% for type II, and 1.43% for type III. There was no clinically significant difference in the rate of hemorrhage between type I and type II. Other variables that were analyzed, including female gender, age, location, multiplicity, hypertension, size, and associated venous angioma, were not significant risk factors for hemorrhage. The study authors concluded that prior symptomatic hemorrhage indicated by the MR appearance could be related to the risk of a prospective recurrent symptomatic hemorrhage in adults, but felt that this could only be confirmed with a prospective multicenter observational study.

The study by Poorthuis MHF et al attempted to analyze the relative benefits of treatment for cerebral cavernous malformations by performing a systematic review of the reported case series and a meta-analysis of those cases. The authors were able to identify 63 cohorts, involving 3424 patients. They looked at a composite outcome, consisting of death, nonfatal intracranial hemorrhage, and new or worse persistent focal neurological deficits. By combining all of the cohorts, they determined that the overall incidence for the composite outcome was 6.6 (95% confidence interval [CI], 5.7-7.5) per 100 person-years, after neurosurgical excision of the lesion and a median follow-up of 3.3 years. After stereotactic radiosurgery treatment, with a median follow-up of 4.1 years, the incidence of the composite outcome was 5.4 (95% CI, 4.5-6.4). The authors also note that patients with brainstem cavernous malformations had a higher risk of reaching the composite endpoint compared to patients with cavernous malformations in the cerebral hemispheres, whether superficial or deep.

■ **COMMENTARY**

Although these two recent studies shed some additional light on the natural history of cavernous malformations and give us some information about how treatment may affect the natural history of these lesions, we still do not know if treatment gives a long-term benefit with reduced risk of bleeding or other complications, compared to the untreated lesions. Cavernous malformations are common, and the overall risk of bleeding is quite low, in the range of 1% per year. It appears that the risk of recurrent hemorrhages is higher in the first 2-3 years, but this information is not validated, and it is not clear if interventional therapies, such as surgical excision or stereotactic radiosurgery, will improve the long-term outcome compared to the natural history. A prospective randomized trial will have to be initiated to answer these questions with any certainty. ■

Cerebrovascular Consequences of Beta-Amyloid Deposition

ABSTRACT & COMMENTARY

Synopsis: *Beta-amyloid deposition, as documented by PET amyloid imaging, correlates with increasing arterial stiffness and may explain some of the relationship between vascular disease and Alzheimer's disease.*

Source: Hughes TM, et al. Arterial stiffness and beta-amyloid progression in nondemented elderly adults. *JAMA Neurol* 2014;71:562-568.

It has been known for many years that cardiovascular risk factors, particularly hypertension, are related to the cognitive impairments and pathological features of Alzheimer's disease. In addition, there is a link between chronic hypertension and the development of white matter hyperintensities in the brain, which are then associated with progressive cognitive impairment during aging. Additional evidence has implicated the development of arterial stiffness in the pathogenesis of the aging brain, the development of cerebrovascular disease, and impaired cognitive functioning in the elderly. At the current time, positron emission tomography (PET) imaging, using a beta-amyloid radiolabeled isotopes such as the Pittsburgh compound B, has demonstrated that more than half of non-demented older adults > 80 years of age have a significant deposition of A-beta in the brain. Other than the known risk factor of APOE-4 positive genotyping and aging, other risk factors are poorly understood and not identified. However, the effects of high blood pressure may be evaluated with the measurement of arterial stiffness, measured as higher pulse-wave velocities in the brain. The authors of this study recruited participants who were originally involved in the Ginkgo Memory Study to undergo PET scanning for A-beta, as well as testing of arterial stiffness using a noninvasive and automated waveform analyzer of pulse-wave velocity.

Pulse-wave velocity was measured in the central (carotid-femoral) vascular bed, as well as the peripheral vascular bed as measured in the femoral-ankle distribution and the brachial-ankle vascular beds. This was calculated as the distance in centimeters between arterial sites of interest over time, in seconds, that the pressure waveforms traveled from the heart to the respective arterial sites. The more rapidly the wave forms traveled down the vascular tree, the more arterial stiffness was present in that vascular bed. These measurements were then correlated with the presence of A-beta on PET scanning and the development of A-beta deposition on repeated measures.

Eighty-one non-demented individuals who were ≥ 83 years participated in this study. The main outcome measures were the change in A-beta deposition over 2 years and the presence of peripheral pulse-wave velocity changes in the central and peripheral vascular beds.

At baseline, 48% of the elderly patients had significant A-beta deposition demonstrated by PET scan, and on 2-year follow-up this number increased to 75%. Brachial-ankle peripheral wave velocities were significantly higher among A-beta positive participants at baseline and at follow-up. Femoral-ankle peripheral wave velocities were only higher among the A-beta positive participants in follow-up. Each standard deviation increase in central stiffness of the carotid-femoral and heart-femoral vascular beds was linked with increases in A-beta deposition on repeat study after 2 years.

■ **COMMENTARY**

This intriguing study shows a possible mechanism for the relationship between Alzheimer's disease and vascular risk factors, such as hypertension. The change

See Stroke Alert, page 78

Continued from page 77

in arterial stiffness, as demonstrated by measurements of pulse wave velocity in this study, may be the mechanism by which A-beta effects blood vessels and may be one mechanism to explain the development of amyloid angiopathy. It is difficult to distinguish A-beta deposition, demonstrated by PET scanning, from amyloid plaques in the brain parenchyma, compared to deposition of A-beta in the walls of blood vessels, but arterial stiffness measurements may identify which patients are developing significant amyloid angiopathy, as opposed to traditional Alzheimer's disease. Randomized trials of treatment are being developed using this measurement as a biomarker for possible amyloid angiopathy, but confirmation of this correlation will ultimately depend on examination and correlation of pathology in those patients who are followed to death and undergo postmortem examination. In the meantime, the measurement of arterial pulse-wave velocity appears to be a valid and noninvasive way to measure the effects of both high blood pressure as well as amyloid deposition on the brain arteries. ■

Continued from page 75

analysis. Febrile status in this study was defined as status epilepticus lasting 30 minutes or longer or repetitive febrile seizures lasting at least 30 minutes without resumption of consciousness. All patients were imaged with 1.5 T MRI within one week of febrile status. Hippocampal T2 signal scores (0-normal,1-equivocal, 2-mildly abnormal) were assigned by two blinded experienced neuroradiologists. T2 scores ≥ 2 were considered a definite abnormality. Radiographic criteria for hippocampal sclerosis required hippocampal atrophy and T2 scores ≥ 2. In addition, hippocampal volumes and ADC maps were also incorporated in the study. Patients with normal MRI hyperintensity, volume, and ADC maps with either febrile status or simple febrile seizures served as controls.

Of 226 patients, 22 had acute T2 hyperintensity and increased hippocampal volume on MRI. ADC maps were available on 13 of 22 patients and showed that the mean ADC for the hyperintense hippocampi was lower than matched contralateral hippocampi. Follow-up MRI was performed 1 year later on 14 of the 22 patients with initial abnormal hippocampal signal. Ten of 14 patients met formal criteria for hippocampal sclerosis. Twelve of 14 patients showed reduced hippocampal volume. In contrast, follow-up MRI of 116 children without acute hyperintensity (initial normal MRI) showed abnormal T2 signal in only one patient (following another episode of febrile status). In addition, compared to controls with simple febrile seizures, febrile status epilepticus patients with initial normal acute MRI had abnormally low right to left hippocampal volume ratios, smaller hippocampi initially, and reduced hippocampal growth suggesting subtle hippocampal injury.

■ COMMENTARY

The results of this study suggest that T2 hyperintensity after febrile status likely reflects acute injury, which then evolves to radiographic hippocampal sclerosis. Impaired hippocampal growth, 1 year after febrile status, in initially normal imaging suggests a possible biomarker of subtle injury. Although MRI may potentially identify those febrile status patients ultimately at risk for long-term hippocampal injury, this does not confirm definite pathologic injury. That is not to say that the initial results of this prospective study are not promising. However, further conclusions should be tempered until additional follow-up imaging can be performed to determine what proportion of these febrile status patients ultimately develop medically refractory temporal lobe epilepsy. ■

Pesticides and Development of Alzheimer's Disease — New Evidence

ABSTRACT & COMMENTARY

By Richard S. Isaacson, MD

Associate Professor of Neurology (Education), Weill Cornell Medical College

Dr. Isaacson reports that he is a scientific advisor/consultant for Novartis and Accera.

Synopsis: *A new case-control study finds that increased levels of dichlorodiphenyldichloroethylene (DDE), which is the metabolite of the pesticide dichlorodiphenyltrichloroethane (DDT), are associated with an increased risk for Alzheimer's disease. In addition, carriers of an APOE4 ε4 allele may be more susceptible to the effects of DDE.*

Source: Richardson JR, et al. Elevated serum pesticide levels and risk for Alzheimer disease. *JAMA Neurol* 2014;71:284-290.

THE SEARCH FOR ANY OF THE MYRIAD OF POTENTIAL "CAUSES" of Alzheimer's disease (AD) has continued in the right direction with the recent article by Richardson and colleagues from Emory University's Alzheimer's Disease Research Center and the University of Texas Southwestern Medical School's Alzheimer's Disease Center. While the etiology of AD is yet unknown, it is highly likely that a combination of genetic, environmental, and lifestyle factors influence a person's risk. Richardson et al have expanded on their past pilot work to find the most definitive proof of an association between pesticide exposure and the development of AD.

Over the last decade, great progress has been made in determining modifiable and non-modifiable risk factors involved in the development of AD, as well as pharmacogenomics and nutrigenomic considerations for AD management.[1] While APOE4 is the most commonly known and most well-understood gene associated with late-onset AD, and Presenilin-1, Presenilin-2, and amyloid precursor protein gene mutation are the most common for early-onset cases (comprising ~6% of total AD cases), more than 10 genes now have been found to be involved in the development of AD. In addition, a variety of epigenetic mechanisms play a role, including changes in the expression of thousands of genes and upregulation of several pathologic pathways (e.g., beta-amyloid deposition, tau hyperphosphorylation, inflammation, oxidative stress, and energy metabolism).[2]

The objective of the Richardson study was to further investigate the potential role of serum pesticide levels and to determine whether the apolipoprotein E (APOE) genotype modifies an association. Past epidemiological research has suggested that exposure to pesticides is associated with AD, and a prior pilot study (n = 20) found that serum levels of DDE were elevated in AD patients.

In this two-site, case-control study consisting of 86 AD cases and 79 controls, serum levels of DDE were measured and degree of cognitive impairment was assessed via Mini-Mental State Examination (MMSE) scores. While DDE was detected in 70% of controls and 80% of AD cases, mean DDE levels were 3.8-fold higher in the AD cases. MMSE scores were significantly lower in the highest DDE-tertile. A significant interaction between serum DDE levels and APOE status was also found, compared with those without an ε4 allele. Since serum DDE levels did not differ by genotype, this suggested a functional interaction.

■ COMMENTARY

Although further research is warranted, the mechanistic explanation of why pesticide exposure (DDT/DDE) would increase AD risk is rooted in their propensity to increase amyloid precursor protein. From a practical clinical perspective, it is unclear at this time whether to suggest to patients at risk for AD to avoid potential exposure to DDT. It is important to note that in the United States, the Environmental Protection Agency banned the use of DDT in 1972 due to safety concerns; however, many other countries throughout the world continue to allow DDT. The impact of DDT on AD risk is still a consideration due to an exceptionally long half-life (8-10 years) and additional exposure from food imports from abroad where DDT is still used, or from legacy contamination of soil and waterways in the United States. While it is unclear whether recommending that patients at risk for AD preferentially select organic foods, this recommendation may deserve consideration in certain circumstances (balanced by a generally increased cost of organic food). Additionally, from a diagnostic perspective, elevated levels of DDE and APOE ε4 allele positivity may in the future lead to earlier identification of some cases of AD. ■

References

1. Oboudiyat C, et al. Alzheimer's disease: Pathophysiology and targeted therapeutic approaches. *Sem Neurol* 2013;33:313-329.
2. Mastroeni D, et al. Epigenetic mechanisms in Alzheimer's disease. *Neurobiol Aging* 2011;32:1161-1180.

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.

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Scan the QR code at the right or log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME Questions

1. Peripheral neuropathy in chronic hepatitis C virus infection is associated with increasing age and duration of infection.
a. True
b. False

2. Trochlear headaches are associated with which of the following?
a. Lacrimation
b. Bilateral retro-orbital pain
c. Pain with sneezing
d. Pain with eye movement downward in adduction
e. Ptosis

3. In the FEBSTAT study, all of the following characteristics define hippocampal sclerosis *except*:
a. hippocampal atrophy.
b. hippocampal hyperintensity.
c. T2 scores ≥ 2.
d. hippocampal edema.

4. According to the study by Richardson et al, which statement regarding Alzheimer's disease (AD) is incorrect?
a. The metabolite of DDT, dichlorodiphenyldichloroethylene (DDE), is only found in the serum of patients with AD.
b. Patients with AD generally have higher levels of DDE than do patients without AD.
c. AD patients with APOE ε4 allele positivity and DDE in the serum had lower MMSE scores than those with APOE ε3 alleles.
d. It is not known if AD can be prevented or delayed by avoiding all foods that have been exposed to DDT.

5. Which of following statements is *not* true regarding cerebral cavernous malformations?
a. Cerebral cavernous malformations are common in the healthy adult population.
b. Cerebral cavernous malformations commonly bleed and commonly re-bleed.
c. Epileptic seizures are a common manifestation of cerebral cavernous malformations.
d. Stereotaxic radiosurgery is an unproven therapy for cerebral cavernous malformations.

6. Which of the following is *not* true regarding A-beta deposition in the brain?
a. A-beta deposition is documented by PET and correlates with the development of dementia.
b. A-beta deposition may be present in non-demented elderly patients.
c. Vascular stiffness is increased in patients with A-beta deposition in the brain.
d. All patients with A-beta deposition in the brain have Alzheimer's disease.

In Future Issues:

Update on Parkinson's Disease