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Wernicke-Korsakoff Syndrome: Diagnosis and Pathogenesis

ABSTRACT AND COMMENTARY

By Louise M. Klebanoff, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Wernicke-Korsakoff syndrome, consisting of the triad of mental status changes, ocular motility abnormalities, and ataxia, in the setting of thiamine deficiency, remains a clinical diagnosis.*

Source: Wijnia JW, Oudman E. Biomarkers of delirium as a clue to diagnosis and pathogenesis of Wernicke-Korsakoff syndrome. *Eur J Neurol* 2013;20:1531-1538

WERNICKE-KORSAKOFF SYNDROME IS AN EXAMPLE OF DELIRIUM-RELATED cognitive impairment, with an initial state of delirium subsequently progressing to chronic cognitive impairment. This neuro-psychiatric syndrome, caused by thiamine deficiency, is characterized by acute mental status changes, ocular motility abnormalities, and ataxia. In autopsy-confirmed cases, mental status changes are reported in 82% of cases. However, the complete triad of mental status changes, ocular motility abnormalities, and ataxia is present in only 16%. The diagnosis can be missed due to the lack of the clinical triad as well as the difficulty in distinguishing this acute encephalopathy from other causes of encephalopathy, including the delirium associated with alcohol withdrawal. In developed countries, the

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vast majority of cases of thiamine deficiency are associated with alcohol abuse.

Wernicke's encephalopathy is due to brain lesions caused by high metabolic demands on already depleted vitamin B1 (thiamine) stores. In neuronal and glial cells, thiamine is converted to thiamine pyrophosphate, which is necessary for several biochemical pathways in the brain. With thiamine deficiency, the earliest biochemical change is a decrease in a-ketoglutarate-dehydrogenase activity (a-KGDH) in astrocytes. Activated microglia is a pathological feature of thiamine deficiency and, based on rat models, has been suggested as a contributing cause of the neurological impairment seen in this condition. Thiamine deficiency can lead directly to cellular energy deficit, focal acidosis, regional increase in glutamate, and ultimately cell damage and death. In the early phase of the condition, these deficits are potentially reversible if the thiamine deficit is corrected. For this reason, early identification of Wernicke's encephalopathy can allow for correction of thiamine deficiency and prevention of cell death and ultimately cognitive impairment.

In an effort to identify the main biomarkers of delirium in Wernicke-Korsakoff syndrome and related conditions, the authors reviewed articles describing possible underlying causal mechanisms in delirium and alcohol withdrawal delirium published between January 1997 and December 2012. From an initial pool of 1400 articles, they identified five studies related to delirium with alcohol withdrawal and another 22 studies related to delirium of other causes.

Several potential biomarkers showed strong relationships with delirium. Lower cerebrospinal fluid levels of neuronal-specific enolase, an enolase-isoenzyme normally present in neuronal and neuroendocrine tissue, were associated with the occurrence of delirium. Higher median levels of S100B were found in blood samples of patients following an episode of delirium when compared with levels taken during delirium or in patients without delirium. Catecholamine metabolites were found to be elevated in certain patients with delirium. Mean homovanillic acid levels were higher in Alzheimer's patients with delirium when compared with age- and gender-matched non-delirious controls. Plasma levels of MHPG were found to be higher preoperatively in patients who subsequently developed postoperative delirium when compared to those who did not. Patients with delirium demonstrated higher levels of cerebrospinal fluid lactate when compared to patients with dementia. Tissue counts of CD68-positive cells and of human leukocyte antigen DR-positive cells, which in postmortem studies are markers of microglial activation, were found to be significantly elevated in delirious patients when compared with controls.

When focusing exclusively on delirium in Wernicke-Korsakoff syndrome, the potential biomarkers were further reduced. Only brain tissue cells counts of CD68-positive cells in an animal model of Wernicke-Korsakoff syndrome, high cerebrospinal fluid lactate levels in six children with Wernicke's encephalopathy, and low MHPG concentrations in patients with long-standing Korsakoff syndrome could be identified.

It remains undetermined if these biomarkers provide an objective measure of disease pathophysiology in delirious patients. They may reflect an underlying general medical condition, a non-specific state of increased arousal, or other traits that may increase the risk of developing delirium but are not necessarily causative.

■ COMMENTARY

Delirium is a common neurological syndrome; however, the pathophysiology of underlying biomechanisms of delirium remains poorly understood. Wernicke-Korsakoff syndrome represents a unique form of delirium, progressing to chronic cognitive impairment if the underlying thiamine deficiency is not corrected. Microglial proliferation caused by thiamine deficiency is a possible underlying pathological mechanism.

Due to the difficulty in diagnosing the condition, identification of biomarkers could enhance early diagnosis and increase the potential for therapeutic intervention. Although the biomarkers identified may have an association with delirium, evidence for causality is lacking. Additional investigation, including prospective and longitudinal studies of patients with thiamine deficiency and Wernicke-Korsakoff syndrome, is needed. ■

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Hyperkalemic Periodic Paralysis

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: *Hyperkalemic periodic paralysis has now been well characterized — clinically, physiologically, and genetically.*

Source: Charles G, et al. Characterization of hyperkalemic periodic paralysis: A survey of genetically diagnosed individuals. *J Neurology* 2013:260:2606-1613.

First described in 1951 and now classified as one of the autosomal dominant, voltage-gated, sodium channelopathies, hyperkalemic periodic paralysis (hyperPP) is a rare disorder (1:200,000 persons) affecting men and women equally, causing episodic, painless muscle weakness. To better define — or refute — previously accepted epidemiological, clinical, diagnostic, and therapeutic aspects of hyperPP, review of a large cohort of genetically confirmed cases was undertaken.

Members of multiple organizations were surveyed, including the Periodic Paralysis Association; the Periodic Paralysis News Desk; and the Universities of Ulm (Germany), Rochester (New York), Southwestern Texas, Pierre et Marie Curie (France), and University College, London, England. Surveys comprised multiple-choice questions, offering abundant space for patients' personal comments, with criteria for inclusion requiring patients ≥ 18 years of age with a genetically confirmed diagnosis of hyperPP. Statistical analysis comprised chi-square computations, with Bonferroni correction as needed.

Among 137 responses, 94 (68.6%) possessed the requisite eligible mutation. Men and women were approximately equally distributed (53.3% vs 46.7%), with an age range of 19-84 years (median 46 years). Thyroid dysfunction was a significantly associated comorbidity (20.2%, $P < 0.0001$), with a non-significant trend found for cardiac arrhythmias (9.6%, $P = 0.04$). On average, 19.4 years and four different health care professionals were required until a correct diagnosis was obtained. Although onset in the first decade is usually expected, 25% had their initial attack during their teenage years. Attacks were more often reported in the morning (55.8%), during sleep (45.3%), or on waking (43%), with only 29.1% and 19.8% reporting attacks in the afternoon or evening, respectively. Attack frequency varied from 1-3 per month (29.9%) to weekly (20.7%) to 2-6 per week (24.1%), lasting 2 days (22.2%), 30-60 minutes (21%), or 15-30 minutes (13.6%), with 22.9% stating it lasted over a week. Surprisingly, respiratory symptoms were reported in 26.1%, facial weakness in 62%, inability to speak in 2.2%, and 7 and 2 patients, respectively, reporting bladder or bowel incontinence. Among the 55.8% with myotonia, progressive myopathy was reported in 37.5%, compared to 33.3% of those denying myotonia. HyperPP triggers included cold temperature (75.8%), rest following exercise (67%), fatigue or stress (47.3%), alcohol (45.1%), hunger (42.9%), potassium in food, specific foods or drinks, or changes in humidity (35.2% each), oversleeping (34.1%), pregnancy (27.9% of females), illness (27.5%), menstruation (18.6% of females), medication (16.5%), or potassium supplements (14.3%). Prodromal symptoms the day prior to an attack comprised fatigue, weakness, irritability, or restlessness (38.6%), with sweating, myalgia, stiffness, weakness, restlessness, tingling, and/or numbness more immediately preceding the attack (85.7%), usually by 20 minutes, but occasionally up to several hours. Typically, attacks were described as stiffness followed by weakness, and affected areas included the arms and hands (> 80%) as often as thighs and calves. Most attacks were described as mild (43.3%), but 15.6% were felt to be severe ("cannot speak or call for help"). Following attacks, most reported fatigue, weakness, clumsiness, or irritability, symptoms not previously noted in the literature. Muscle pain was experienced during an attack in 41.3% and in 62% following the episode, with only 26.1% denying muscle pain entirely. Between attacks, most felt well with mild or no symptoms, but 12.4% did report impairment of daily activities. Attacks increased in frequency with aging, more so earlier in life, as did muscle stiffness during attacks prior to adulthood, whereas muscle weakness during attacks tended to decrease in severity. By age 40 years and above, 84.6% reported fixed muscle weakness between attacks. Long-term treatment regimens for most patients included a combination of medication (hydrochlorothiazide, mexiletine, or flecainide), and medium-sized, carbohydrate-rich meals, usually 3-5 per day, with a carbohydrate rich snack every 2-3 hours, comprising candy, sugar, bread, or pasta. Strategies to mitigate acute attacks comprised staying warm, eating sweets, drinking water, or doing gentle exercise, but 36% were only occasionally able to abort an attack, if at all, despite best efforts. Liquid and solid carbohydrates were equally efficacious and usually took effect within an hour.

■ COMMENTARY

For the first time, a mitochondrial disorder has now been reported in association with periodic paralysis in a patient with acute episodes of limb weakness, identical to periodic paralysis and responsive to acetazolamide, with no

Stroke Alert: A Review of Current Clinical Stroke Literature

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

New Oral Anticoagulants Poised to Alter Approach to AF

Source: Ruff CT, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomized trials. *Lancet Neurology* 2013; http://dx.doi.org/10.1016/S0140-6736(13)62343-0.

FOUR NEW ORAL ANTICOAGULANTS (DABIGATRAN, RIVAROXABAN, apixaban, and edoxaban) have been studied in individual clinical trials, and, compared to warfarin, have been shown to be equal or better in the prevention of cardioembolic stroke in the setting of atrial fibrillation, with a reduced frequency of intracranial bleeding.[1-4]

Ruff and colleagues performed a meta-analysis of Phase 3, randomized trials in patients with atrial fibrillation, comparing all four of these new anticoagulants with warfarin, and analyzed outcomes in 71,683 participants in 48 trials. The main outcomes studied were stroke and systemic embolic events, ischemic stroke, hemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial hemorrhage, and gastrointestinal hemorrhage, and the authors calculated relative risks (RRs) and 95% confidence intervals for each outcome.

New oral anticoagulants significantly reduced stroke or systemic embolism by 19% compared to warfarin (RR = 0.81), driven primarily by a reduction in hemorrhagic stroke, and also resulted in a reduction in all-cause mortality (RR = 0.90), with an increase in gastrointestinal hemorrhage. These new medications had a favorable risk-benefit profile, with significant reductions in stroke, intracranial hemorrhage, and mortality, with a similar rate of major bleeding as for warfarin. ■

References

1. Connolly SJ, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-1151.
2. Patel MR, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-891.
3. Granger CB, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-992.
4. Giugliano RP, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093-2104.

recognized channelopathy mutation, but with mitochondrial DNA mutations previously associated with Leigh syndrome and MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes). (*Neurology* 2013;81;1-9). In cultured primary fibroblasts and cybrid cells, these mutations resulted in complex V and I defects and in oxidative stress. Understanding the mechanistic link between the ionic disturbance at the cell membrane level and the mitochondrial defect will require further study. ■

Iatrogenic Fungal Meningitis: Lessons Learned?

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *An outbreak of fungal meningitis and paraspinal infections occurred over the past year due to contaminated methylprednisolone injections.*

Sources: Smith RM, et al. Fungal infections associated with contaminated methylprednisolone injections. *N Engl J Med* 2013;369:1598-1609. Chiller TM, et al. Clinical findings for fungal infections caused by methylprednisolone injections. *N Engl J Med* 2013;369:1610-1619.

IN SEPTEMBER 2012, CASES OF FUNGAL MENINGITIS STARTED emerging in Tennessee. The first cluster of cases, eight in total, all received epidural steroid injections at the same ambulatory surgical center. Upon investigation, it was determined that all vials of methylprednisolone used in these patients had been purchased from a single compounding pharmacy in Massachusetts. In response, the Centers for Disease Control (CDC) and Prevention and FDA requested a list of all clinical facilities that had ordered the same lot numbers of methylprednisolone from this compounding pharmacy. Cases of fungal meningitis in patients who received injections using these lots of steroid then started becoming apparent in other states, sparking a serious concern of widespread national epidemic. Epidemiologic investigation by the CDC determined that 13,534 patients were potentially exposed to the contaminated steroid — 89% through epidural, spinal, or paraspinal injection, and 11%

through peripheral-joint or other injection.

The pathogenic organism implicated in the development of fungal meningitis in these patients was found to be *Exserohilum rostratum*, an environmental mold. A total of 749 patients developed fungal infection in 20 states. The *E. rostratum* organism was difficult to culture, with only 20% of cases actually being culture positive. Median age of infected patients was 64 years old. Of the 749 infections, 31% had meningitis only, 20% had meningitis and concomitant paraspinal infection, and 4% had peripheral joint infection. Forty patients had strokes, mostly in the posterior circulation and in association with meningitis. A total of 61 patients (8%) died from complications of the fungal infection. More than 90% of affected patients were not known to be immunosuppressed.

The median time from steroid injection to presentation of infection was 47 days, although cases of stroke tended to present sooner than paraspinal infections. Most patients with meningitis presented with headache (88%); fever was less common (31%). Most patients with paraspinal infections presented with back pain (63%), making it difficult to diagnose, as many of the patients had back pain as the initial indication for the injection. Mean CSF cell count among all cases was 83, mean glucose was 53, and mean protein was 84. Overall attack rate was 5.5 cases per 100 exposed persons.

■ COMMENTARY

This series of infections raises a number of important issues. First and foremost, clinicians must be careful to order medications from reputable pharmacies. The fact that a compounding pharmacy produced steroid contaminated with fungus that was injected into more than 13,000 patients is a clear indication that we need better regulatory control over compounding pharmacies. That said, for neurologists who are more likely to recommend epidural injections than perform them, the main issue that arises from this case is the question of whether many of these patients actually needed the injections in the first place. It reminds us that all invasive procedures, even "routine" and "minor" ones like epidural steroid injections come with inherent risk and patients should be carefully selected. The American Academy of Neurology practice parameter on lumbar epidural injections made a level B (good evidence) recommendation that epidural injections showed *no impact on average impairment of function, need for surgery, or pain relief after 3 months*. A level C (weak evidence) recommendation suggested that these injections may result in limited improvement for 2-6 weeks post-procedure. Risks and benefits must always be taken into account. The fact is that most patients with radicular syndromes would do just fine without these injections, and we should use the available practice parameters to best select patients for these spinal injections. ■

Optic Disc Cupping and Cognitive Decline: Three-year Prospective Study Demonstrates Association

ABSTRACT & COMMENTARY

By Marc Dinkin, MD

Assistant Professor of Ophthalmology, Weill Cornell Medical College

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

Synopsis: *This long-term epidemiological study shows an association between glaucoma and Alzheimer's disease. Cup to disc ratio, but not elevated intraocular pressure, is a risk factor for dementia.*

Source: Helmer C, et al. Is there a link between open-angle glaucoma and dementia: The three-city–Alienor cohort. *Ann Neurol* 2013;74:171-179.

From a neurologist's perspective, glaucoma is the mirror image of pseudotumor cerebri, with both diseases leading to optic atrophy due to pressure on one side of the optic nerve head. However, since neuronal degeneration in glaucoma typically occurs over decades, and may occur even in the absence of elevation in intraocular pressure (IOP), the disease is perhaps most similar to Alzheimer's disease (AD). Indeed, multiple studies have shown areas of overlap between the two diseases – diffusion tensor imaging has shown a loss of cortical white matter along the optic radiations in glaucoma patients,[1] while optical coherence tomography (OCT) has demonstrated retinal nerve fiber layer (RNFL) thinning in AD patients.[2]

The evidence linking one disease to the other has so far been conflicting, with two case-control studies demonstrating an increased risk of glaucoma in AD patients,[3,4] while several studies based on review of hospitalization records were negative.[5] The case-control studies were problematic in that the diagnosis of glaucoma could have been artifactually increased due to visual field defects secondary to the posterior cortical atrophy that may occur in some AD patients, while the negative studies, which depended on hospitalization records, may have missed either the diagnosis of AD, glaucoma, or both in some patients, since the rate of missed diagnosis of these conditions in the inpatient setting is high.

Helmer and colleagues aimed to settle the issue, with a prospective, epidemiological study, following a group of patients from one French city over a three-year period. Unlike prior studies addressing the AD-glaucoma link, pa-

tients were all actively screened for both AD and glaucoma at baseline and then again at 3 years. The results were impressive, with 17.5% of the 29 patients who developed AD at some point over the 3 years also receiving a diagnosis of glaucoma vs only 4.5% of the non-demented patients. Additionally, those patients who began the study with a diagnosis of glaucoma were four times as likely to develop AD, even when adjusting for age, sex, family history of glaucoma, education, and apolipoprotein ε4 status. Interestingly, an increased vertical cup to disc ratio (vCDR) of ≥ 0.65 and a small minimal rim to disc ratio (mRTDR), both predisposed to the development of dementia, while elevated IOP ≥ 21 and taking IOP-lowering drops did not.

■ **COMMENTARY**

This appears to be the first study in which a large cohort of patients were actively screened for both glaucoma and AD over several years, in search of an association. The results suggest that similar vulnerabilities of neuronal populations, perhaps determined by genetics or prior environmental exposures, may underlie the neurodegeneration in both glaucoma and AD, with the identity of the degenerating cell population determined by a secondary factor, such as elevated IOP in glaucoma patients. The finding that markers of neurodegeneration (such as a large vCDR) correlated with the risk of dementia, while elevated IOP did not, is consistent with that hypothesis. The lack of correlation of interocular cup to disc asymmetry (≥ 0.2) with dementia also supports a link through a factor predisposing to neurodegeneration, as cases with monocular or asymmetric cupping are more likely to result from a specific ocular factor.

A second interpretation of the results is that one disease actively predisposes to the other. AD, for example, has been shown to be associated with a low cerebrospinal fluid pressure,[6] which in turn would cause a higher translaminar pressure differential across the optic nerve head. It may be that this difference in pressure (whether it results from high IOP or low intracranial pressure) predisposes to glaucoma.

The study is limited by the relatively low number of patients diagnosed with glaucoma in the cohort, and also by the lack of OCT data to corroborate and quantify the degree of glaucoma. Furthermore, although lumbar puncture is not necessary for the diagnosis of AD, it would have been interesting to measure the opening pressure in the AD patients to see if low measurements correlated with the incidence of glaucoma. Cerebrospinal fluid analysis for AD biomarkers such as β-amyloid1-42 (Aβ1-42), total tau protein (T-tau), and hyperphosphorylated tau would have been useful as well, as an association with glaucoma would have pointed to their role in both diseases.

While one pathological study that showed retinal degeneration in postmortem retinas of AD patients failed to show any neuritic plaques,[7] more recently curcumin angiography has allowed in vivo visualization of retinal Aβ plaques in transgenic mouse models of AD,[8] suggesting a primary degeneration of retinal neurons that could include the ganglion cells. This has been corroborated by OCT studies that have shown increased atrophy of the RNFL in AD patients. In light of this, it is possible that the results of the current study were confounded by a prior misdiagnosis of glaucoma based on AD-associated structural changes in the optic disc, especially since the definition of glaucoma in this study did not require an elevation in IOP. Of course, an alternative interpretation is that the association between glaucoma and AD demonstrated in this study explains the RNFL thinning previously demonstrated in AD patients.

Despite many remaining questions, this study makes an impressive statement on a powerful relationship between two of the most common neurodegenerative diseases in the world. The findings have significant implications for population screening of both diseases, and may even be relevant to future avenues of therapy. Further research will hopefully illuminate the cause and effect relationships subserving the observed association in this study, bringing us closer to a true understanding of both of these potentially devastating neurological conditions. ■

References

1. Michelson G, et al. DTI parameters of axonal integrity and demyelination of the optic radiation correlate with glaucoma indices. *Graefes Arch Clin Exp Ophthalmol* 2013;251:243-253.
2. Kirbas S, et al. Retinal nerve fiber layer thickness in patients with Alzheimer disease. *J Neuroophthalmol* 2013;33:58-61.
3. Bayer AU, et al. High occurrence rate of glaucoma among patients with Alzheimer's disease. *Eur Neurol* 2002;47:165-168.
4. Tamura H, et al. High frequency of open-angle glaucoma in Japanese patients with Alzheimer's disease. *J Neurol Sci* 2006;246:79-83.
5. Kessing LV, et al. No increased risk of developing Alzheimer disease in patients with glaucoma. *J Glaucoma* 2007;16:47-51.
6. Wostyn P, et al. More advanced Alzheimer's disease may be associated with a decrease in cerebrospinal fluid pressure. *Cerebrospinal Fluid Res* 2009;6:14.
7. Blanks JC, et al. Retinal ganglion cell degeneration in Alzheimer's disease. *Brain Res* 1989;501:364-372.
8. Koronyo Y, et al. Alzheimer's disease in the retina: Imaging retinal aβ plaques for early diagnosis and therapy assessment. *Neurodegener Dis* 2012;10:285-293.

Brain Volume Abnormalities in Lesch-Nyhan Disease

ABSTRACT & COMMENTARY

By Sotirios Keros, MD, PhD

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

Synopsis: *Subjects with Lesch-Nyhan disease and Lesch-Nyhan variant have significant reductions in brain size in the basal ganglia as well as several cortical areas.*

Source: Schretlen DJ, et al. Regional brain volume abnormalities in Lesch-Nyhan disease and its variants: A cross-sectional study. *Lancet Neurol* 2013;12:1151-1158.

Lesch-Nyhan disease is an X-linked recessive disorder caused by mutations that cause hypoactivity of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT). This defect in HGPRT activity results in the overproduction of uric acid which then leads to hyperuricemia, tophi, and gout. Most children with the classic form of Lesch-Nyhan disease present in the first year of life with neurodevelopmental delays, and typically go on to develop mental retardation, self-injurious behaviors, and both pyramidal and extra-pyramidal motor disabilities such as dystonia, choreoathetosis, ballismus, dysarthria, hypotonia, and spasticity. Less severe mutations result in a Lesch-Nyhan "variant," which is notable for the absence of self-injury and is otherwise a less severe phenotype that correlates with enzyme activity.

The neurological symptoms in Lesch-Nyhan disease are diverse, and likely are a result of dysfunction in several different brain regions or circuits. Previous work has concentrated on the basal ganglia, revealing dysfunction of dopaminergic basal ganglia pathways. However, basal ganglia abnormalities do not fully explain the spectrum of symptoms seen in Lesch-Nyhan disease.

In this study, the authors used voxel based morphometry on brain MRIs obtained from subjects with classic Lesch-Nyhan disease (n = 21), Lesch-Nyhan variant (n = 17), and healthy controls (n = 33) using either a 1.5 tesla or 3.0 tesla MRI machine. The analysis was performed using the VBM8 toolkit of the SPM8 software package using manual alignment to the anterior commissure posterior commissure line. Diagnoses were confirmed with either fibroblast testing of HPRT enzyme activity or with genetic analysis of the HPRT1 gene. Subjects underwent examination by a specialist in movement disorders as well as cognitive testing by a neuropsychologist. Additionally, informants such as a family member or caregiver were asked to rate each subject's behavior, adaptive functioning, and personality.

Compared to healthy controls, those with Lesch-Nyhan disease had lower IQ scores (KBIT-2 score of 54 vs 112) and higher BFM dystonia scale ratings (73 vs. 1.4), while subjects with Lesch-Nyhan variant had intermediate values (KBIT-2 of 85; BFM of 24). The total brain volume of Lesch-Nyhan patients was 20% less than controls and 14% less in variant disease. Brain volume measurements in the classic disease, variant disease, and controls was (in cm^3) 1003, 1077, and 1267, respectively. Grey matter volumes were 601, 611, and 724, while white matter volumes were 402, 466, and 543. In all cases, the disease group values were statistically significant with respect to controls. Total brain volume to total intracranial volume ratio was identical in all three groups.

Grey matter reductions were most prominent in the caudate, thalamus, and anterior putamen, with the general basal ganglia structures in classic Lesch-Nyhan approximately 75% as large as controls and 85% of controls for variant disease. However, significant reductions were also found in several cortical areas within the temporal and frontal lobes. These areas included the left and right dorsolateral prefrontal cortex, left inferior frontal gyrus, left and right orbital frontal cortex, right and left amygdala, right and left hippocampus, right and left parahippocampal gyrus, and left middle temporal gyrus. In addition, reductions were found in the anterior cingulate cortex and the cingulate gyrus. In all cases, the sizes of these structures in variant disease was intermediate between the classic form and controls. However, the primary regions where classic disease differed from variant disease were the cingulate gyrus, ventral striatum, and orbitofrontal cortex. No differences between any groups were seen in the parietal and occipital lobes. In addition, no brain regions were larger in Lesch-Nyhan patients compared to controls. Basal ganglia size was strongly correlated to dystonia severity in both classic and variant disease.

■ COMMENTARY

This study, which represents the largest analysis of brain volumes in Lesch-Nyhan disease, confirms that the effects of HPRT deficiency are not limited to the basal ganglia and nigrostriatal pathways and demonstrates abnormalities in areas previously not known to be affected. The fact that brain-to-intracranial volume ratios were similar also strongly implies that this disorder is developmental in nature rather than degenerative. It still remains unclear why certain structures and brain regions are affected while others are spared. Do all the observed affected structures depend on HPRT activity for optimum development? Or rather, perhaps only a subset of brain structures are directly affected by HPRT deficiency, and all connections to these structures also suffer, such that the collection of deficits observed reflect all the connections within the affected circuit.

The variant form of the disease exhibits less severe brain volume reductions than the classic form, and this is congruent with the intermediate phenotype seen in the variant form. However, one key distinction between the classic and variant form is the self-injurious behavior. As the authors point out, this study may give some clues as to the anatomic origin of this phenomenon. The greatest differ-

ences seen between the classic and variant form were in the cingulate, as well as the ventral striatum and orbitofrontal cortex. The cingulate is known for its involvement in negative emotions, such as fear and anxiety, while the ventral striatum orbitofrontal cortex pathway has previously been suspected to contribute to self-injury. This study further implicates these areas and will hopefully lead to advances in determining underlying anatomical structures involved in self-injury in Lesch-Nyhan and other neuropsychiatric diseases. ■

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

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

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CME Questions

1. Which of the following statements is *false* regarding Wernicke-Korsakoff syndrome (WKS)?

a. WKS is a delirium attributed to thiamine deficiency.
b. The most common cause of thiamine deficiency in North America is alcoholism.
c. There are several biomarkers that can confirm the diagnosis of WKS.
d. In children, low levels of CSF lactate have been found in WKS.
e. It is unusual to find the classic WKS triad of ocular motility abnormalities, mental status changes, and ataxia at the time of presentation.

2. Which statement is *false* regarding hyperkalemic periodic paralysis?

a. Thyroid dysfunction is a significantly associated comorbidity.
b. Twenty-five percent of patients have their initial attack during their teenage years.
c. Attacks are more often reported in the morning than in the afternoon or evening.
d. Bladder or bowel incontinence never occur during attacks.
e. Muscle pain is commonly experienced during or following an episode.

3. Which of the following statements about a recent outbreak of iatrogenic fungal meningitis is *false*?

a. Most cases were introduced via epidural and paraspinal steroid injections.
b. The organism involved was a rare environmental mold that contaminated a compounding pharmacy facility.
c. Iatrogenic fungal meningitis is not a concern for neurologists.
d. Epidural spinal steroid injections are not of proven value for the relief of radicular pain.

4. Which of the following statements is *true* regarding Alzheimer's disease and glaucoma?

a. Glaucoma may cause Alzheimer's disease.
b. Alzheimer's disease may cause glaucoma.
c. A common neuropathology may underlie the causes of Alzheimer's disease and glaucoma.
d. There is no relationship between glaucoma and Alzheimer's disease.

5. Lesch-Nyhan disease is a degenerative disease that results in a reduction of the size of several brain areas.

a. True
b. False

6. The new oral anticoagulants (dabigatran, rivaroxaban, apixipan, and edoxaban) compare favorably to warfarin in terms of stroke prevention, mortality, and bleeding complications.

a. True
b. False

In Future Issues:

Update on Movement Disorders

Dear *Neurology Alert* Subscriber:

This issue of your newsletter marks the start of a new continuing education semester**.**

Neurology Alert, sponsored by AHC Media, provides you with evidence-based information and best practices that help you make informed decisions concerning treatment options and physician office practices. Our intent is the same as yours — the best possible patient care.

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On behalf of AHC Media, we thank you for your trust.

Sincerely,

Lee Landenberger
Continuing Education Director
AHC Media