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INSIDE

Biochemical Pathogenesis of Intractable Epilepsy Due to Mesial Temporal Sclerosis

ABSTRACT & COMMENTARY

Source: Eid T, et al. Loss of glutamine synthetase in the human epileptogenic hippocampus: Possible mechanism for raised extracellular glutamate in mesial temporal lobe epilepsy. *Lancet*. 2004;363:28-37.

THE CONCEPT THAT EPILEPSY ARISES FROM AN IMBALANCE between excitatory and inhibitory influences in epileptogenic tissue has become fundamental to further investigations of the pathophysiology of this disorder. The primary observation motivating the study of Eid and colleagues is that glutamate levels are elevated in patients with mesial temporal sclerosis (MTS), perhaps the most common cause of medication-resistant epilepsy. This finding emerges from in vitro and in vivo studies from rodents and humans; elevated glutamate levels are detected by microdialysis techniques in MTS patients undergoing prolonged intracranial studies in preparation for hippocampal resection.

In principle, elevated extracellular glutamate levels could result from increased glutamate synthesis, decreased glutamate catabolism (via disruption of glutamate-to-glutamine conversion by astrocytic glutamine synthetase [GlnS]), or decreased glutamate uptake by glia at the synaptic cleft. The current study serves to distinguish between the latter 2 possibilities. Eid et al studied GlnS levels in surgical and autopsy specimens from 14 epilepsy patients with MTS as compared to 15 patients with mesial temporal lobe epilepsy not due to MTS.

The main findings were as follows: (1) GlnS protein (as assessed by western blotting) was decreased by approximately 40% (P = .043) in MTS vs non-MTS controls; (2) GlnS protein was deficient in the appropriate regions of sclerosis (specifically the CA1 subfield of Ammon's horn) by immunohistochemistry; (3) GlnS enzymatic activity was decreased by 38% (P = .006) in MTS patients compared to controls; and (4) There was no significant difference in the amount of the predominant glial glutamate transporter in MTS vs non-MTS.

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COMMENTARY

Eid et al make a compelling case for the role of diminished GlnS in hippocampal sclerosis to account for increased extracellular glutamate in MTS. The GlnS detected by western blotting presumably functions normally since the total GlnS activity is decreased proportionately (40% by immunoblot, 38% by enzymatic assay). By contrast, increased glutamate is less likely to be due to defects in glial glutamate uptake.

The challenge remains to determine the cause of decreased GlnS in MTS. We are again confronted with the chicken-egg problem discussed previously by *Neurology Alert*. Does the GlnS deficiency have a genetic basis? Could a symptomatic insult, such as a prolonged febrile seizure, lead to loss of GlnS? Two studies suggest themselves that might provide clues to answering these questions. If feasible, northern blotting or in situ hybridization studies with a GlnS cDNA probe could tell us whether the loss of GlnS arises from decreased expression of the GlnS gene. Also, although it would be a heroic study to acquire sufficient numbers of patients to achieve a statistically significant result, a comparison of GlnS levels from sclerotic hippocampus to the contralateral (non-MTS) hippocampus from the same patient may help resolve the nature vs nurture question. One suspects, as in many disorders, a multifactorial process with both genetic and environmental influences.

Finally, as Eid et al mention, loss of GlnS suggests the possibility of novel therapeutic strategies to enhance GlnS expression and function. One strategy might involve the use of gene therapy to restore GlnS function in the already damaged hippocampus. Another option to exploit the current findings would be to design a pharmacological agent that could be used to abort acute seizures (particularly in the case of status epilepticus, in which such a drug might also be neuroprotective) or as a chronic anticonvulsant. — **ANDY DEAN**

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Disorders of Gait and Balance Classified

ABSTRACTS & COMMENTARY

Sources: Martin MP, O'Neill D. Vascular higher-level gait disorders—A step in the right direction? Commentary. *Lancet*. 2004;363:8; Liston R, et al. A new classification of higher-level gait disorders in patients with cerebral multi-infarct states. *Age Ageing*. 2003;32:252-258.

Martin and O'Neill called attention to and commented upon a revised classification of higher-level gait disorders (HLGD) proposed by Liston and associates.

In 1993, Nutt and associates classified gait disorders into lower, middle, and higher levels.[1] The lower level comprises peripheral musculoskeletal and sensory disorders that can be compensated for by an intact central nervous system (CNS). Middle-level disorders include hemiplegic, paraplegic, and cerebellar ataxic, parkinsonian, choreic, and dystonic gaits in which the clinical neurological deficits are consistent with the gait disorder. In contrast, higher-level gait disorders are due to disturbances of CNS sensorimotor systems that cannot be accounted for by the neurological signs. Although HLGD can be due to frontal-lobe tumors and normal-pressure hydrocephalus, the most common cause in the elderly is cerebrovascular disease.

Nutt et al subdivided HLGD into 5 categories: cautious

Table

Classification of HLGD in Patients With Cerebrovascular Disease

Type of Gait Apraxia	Site of Lesion
Ignition	SMA, BG, or connections
Equilibrium	PMA or connections
Mixed	SMA, BG, and PMA or connections

Adapted from Liston R, et al.

gait, subcortical disequilibrium, frontal disequilibrium, isolated gait ignition failure, and frontal gait disorder. They based their categories on presumed anatomical location, on clinical phenomenology, or a mixture of both.

Liston et al have proposed a simplified classification of HLGD in the context of cerebrovascular disease. They subdivided HLGD into 3 categories: ignition apraxia, disequilibrium apraxia, and mixed picture (*see Table*). To validate their classification, they analyzed the clinical features of 13 patients with HLGD and radiologically proven cerebrovascular disease. Seven patients with infarcts in the basal ganglia (BG), thalamus, supplementary motor area (SMA) and/or periventricular white matter had ignition apraxia (gait ignition failure, shuffling, freezing). Six patients with infarcts in the parietal sensory cortex and frontal primary motor area (PMA) had equilibrium apraxia (poor balance and falls). Six elderly healthy relatives served as controls. The 3 groups were distinct with respect to step length, width of base and velocity of walking.

COMMENTARY

The work of Liston et al builds upon the classification of Nutt et al and should prompt clinicians to read that excellent review of the neural control of gait and posture and its disorders. Neurologists, thus provided with an increased awareness and understanding of gait disorders, should be able to test the validity of the clinical subtypes of HLGD proposed by Liston et al in their own patients. At the present time, in the absence of effective medical or surgical treatment for HLGD due to cerebrovascular disease, even the best classification yields only a clinical distinction without a therapeutic difference. — **JOHN J. CARONNA**

Reference

1. Nutt JG, et al. *Neurology*. 1993;43:268-279.

Table

Antiepileptic Drugs for Pain

Drug	Starting Dose	Increase By	Maximum Dose
Gabapentin	300 mg/d	300 mg/d	1200 mg t.i.d.
Lamotrigine	25 mg/d	25 mg q 2 wks	250 mg b.i.d.
Oxcarbazepine	150 mg hs	150 mg q 5 d	900 mg b.i.d.
Topiramate	25 mg q.d.	25-50 mg q wk	250 mg b.i.d.
Zonisamide	100 mg hs	100 mg q 2 wk	500 mg q.h.s.

Overview of Newer Antiepileptic Drugs for Neuropathic Pain and Migraine

ABSTRACT & COMMENTARY

Source: Pappagallo M. Newer antiepileptic drugs: Possible uses in the treatment of neuropathic pain and migraine. *Clin Ther*. 2003;25:2506-2538.

SHARED PATHOPHYSIOLOGIC MECHANISMS FOR MIGRAINE, neuropathic pain, and epilepsy underscore the notion that antiepileptic drugs (AED) should be standard treatment for the former. Five new AEDs and their use in these nonepileptic painful disorders are summarized. Each shares one or more of several mechanisms of action, including sodium or calcium channel blockade, inhibition of glutamate transmission or nitric oxide formation, enhanced GABAergic or serotonergic transmission, or free-radical scavenging.

Gabapentin, in controlled clinical trials, has been demonstrably efficacious for post-herpetic neuralgia, painful diabetic neuropathy, and migraine prophylaxis. Preliminary reports in the noncontrolled setting suggest it may also be beneficial in trigeminal neuralgia and for dysesthetic limb pain and painful spasms in multiple sclerosis.

Lamotrigine was beneficial, in controlled trials, for painful HIV neuropathy, painful diabetic neuropathy, and central post-stroke pain. Results in the latter were not dramatic, and 10% (3/30) withdrew due to adverse effects, but other studies showed that tolerability was comparable to gabapentin. Open-label use of lamotrigine, in combination with other agents for migraine prophylaxis, resulted in approximately a 50% improvement, 66% in those with aura, and case reports indicate it may be useful in SUNCT—short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing.

Oxcarbazepine has no controlled trials to its credit. Open-label use has reportedly been beneficial in carbamazepine-refractory trigeminal neuralgia and gabapentin-refractory painful radiculopathy. Tolerability was comparable to carbamazepine in the former and not problematic in the latter. Its use in migraine prophylaxis has yet to be examined.

Topiramate was efficacious in the controlled setting in painful diabetic neuropathy, with 36% reporting a > 50% decrease in pain as measured by a visual analog score, compared to 21% with placebo ($P = .005$). Intercostal neuralgia and trigeminal neuralgia are other reported instances where it may be useful, although a recent controlled, crossover study in 3 patients with tic showed no benefit. Large, well-performed, controlled studies have demonstrated statistically significant benefit in migraine prophylaxis.

Zonisamide, in open-label study, has shown promise for refractory cervical or lumbar radiculopathy and, in retrospective review, in painful diabetic neuropathy (n = 30), fibromyalgia (n = 19), and pelvic pain (n = 7). Only 7% overall (n = 10) discontinued medication due to side effects. Migraine prophylaxis, in open-label study, showed an approximately 40% improvement and an even more striking 50% improvement in chronic daily headache.

Dizziness and somnolence are seen with all the newer AEDs but are dose related, and tolerance generally develops over time. Other adverse effects include fatigue, cognitive dysfunction, diplopia, nausea/vomiting, weight loss, and rash. Generally, these improve once steady-state levels are reached and do not lead to discontinuation of medication. Lamotrigine has the highest incidence of rash at 10%, less so when it is begun at a low dose and increased slowly. Although serious in only 3%, immediate medication withdrawal is necessary in all instances of rash. Overall, oxcarbazepine has the highest rate of reported adverse effects among the newer AEDs, but rash is rare, hepatic and hematologic toxicity is not a serious concern, and it is better tolerated as monotherapy. Topiramate has the highest rate of cognitive side effects (10%), again less so if started low and slow. Weight loss is an often-desired side effect, averaging 5.9 kg at 1 year and 10.9 kg in patients obese at baseline. As a sulfonamide, zonisamide has an inherent risk of rash and hematologic toxicity, but in practice this has not been a significant problem (rash incidence, 2%). It has also been used uneventfully in sulfa-allergic patients. Drug interactions are generally not a problem with 2 notable exceptions. Oral contraceptives should not be used with topiramate or oxcarbazepine due to their induction of the cytochrome P enzyme family, and lamotrigine dosage should be lowered when combined with valproic acid due to decreased clearance induced on the former by the latter. Dosages and titration schedules are tabulated in the Table.

COMMENTARY

After discussing this article with Andy Dean, our epileptologist and a *Neurology Alert* assistant editor, the following dosing suggestions are offered. Lamotrigine's initial dose and subsequent titration may be increased more rapidly in the absence of concurrent valproate use. If no valproate is on board, lamotrigine may be initiated at 50 mg/d (25 b.i.d.) and then increased by 25-50 mg/d on a weekly basis. When lamotrigine is added to valproate for migraine prophylaxis, the dosages tabulated in the Table are reasonable.

Regarding the concurrent use of oral contraceptives with topiramate or oxcarbazepine, there is some evidence to suggest that the cytochrome P isoenzyme involved is not induced until one reaches a topiramate blood level > 200/d and an oxcarbazepine blood level > 1200/d. Furthermore, no relative or absolute contraindication to contraceptive use exists for topiramate or oxcarbazepine because the induced cytochrome P increases estrogen metabolism, not progesterone. Breakthrough bleeding can be a problem, however, and an oral contraceptive with more estrogen might be warranted. Consult your gynecologist.

Lastly, topiramate and zonisamide inhibit carbonic anhydrase and thus, should be avoided when using other carbonic anhydrase inhibitors, as the combination may increase the risk of clinically significant hyperchloremic metabolic acidosis leading to osteomalacia or nephrolithiasis. — **MICHAEL RUBIN**

Vitamin D Reduces Risk of MS

ABSTRACT & COMMENTARY

Source: Munger KL, et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology*. 2004;62:60-65.

Munger and colleagues reviewed a database of 187,563 women enrolled in the Nurses' Health Study, which longitudinally surveyed participants aged 25-55. There were 173 women with probable or definite multiple sclerosis (MS). Vitamin D intake was determined through the study questionnaire and 4 1-week diet records. Blood vitamin D levels were tested and compared with other variables that might predispose to disease, such as latitude of birth and early childhood and smoking (Munger et al had reported an increased risk of MS among nurses who smoked[1]).

Women whose vitamin D intake was approximately 400 IU/day or more from supplements and food or from supplements alone had a 40% lower risk of developing MS than women who did not take the supplements.

COMMENTARY

The incidence of MS worldwide is higher in northern latitudes and lower in the equatorial regions. In addition to recognized genetic and environmental/infectious factors, one protective variable of southern climates might be increased vitamin D production from sunlight exposure. Vitamin D is now also commonly supplemented in multivitamins or with calcium, usually in postmenopausal women at higher risk for osteoporosis. While the current study indicates a preventative role for vitamin D in reducing the risk of acquiring MS, it does not address whether vitamin D supplements can alter the

course of existing MS or if vitamin D has similar preventative benefits in men. Since first-degree family members of persons with MS have approximately a 20-fold increased risk of developing MS, is it reasonable for at-risk groups to be taking vitamin D supplements?

In general, MS patients may be at higher risk of osteopenia from exposure to corticosteroids and a more sedentary lifestyle. It is reasonable to have patients on a vitamin D supplement for this health benefit alone. More needs to be understood about the immune mechanisms of MS and the immunomodulatory effects of vitamin D for broader recommendations. **— BRIAN R. APATOFF**

Reference

1. Apatoff BR. *Neurology Alert*. 2004;22:36.

Are Those White Matter Lesions in Migraine Real?

ABSTRACT & COMMENTARY

Source: Kruit MC, et al. Migraine as a risk factor for subclinical brain lesions. *JAMA*. 2004;291:427-434.

THE POSSIBLE ASSOCIATION OF MIGRAINE AND STROKE remains an active area of controversy in clinical neurology. Since migraines predominantly affect young people and the medications used can cause vasoconstriction, assessing the full vascular risk profile of migraine is important from a diagnostic and therapeutic point of view. To date, the literature is incomplete. Perhaps the best study on the subject is a case-control one from Tzourio and associates[1] suggesting that for women younger than 45, migraine with aura is only a minor stroke risk factor in association with smoking and oral contraceptive use. Adding to the complexity of the issue is presence of nonspecific white matter lesions (WML) on MRI scans of migraineurs. The reports of these findings include relatively small numbers and shed little light on the overall prevalence in migraine patients selected from the general population. Kruit and colleagues report on the results of a large Dutch population-based MRI study to look at whether migraine is associated with WML on MRI and if so, what migraine subtypes in particular, as well what regions of the brain, might be more vulnerable.

A total of 435 patients were selected for MRI scans and were subgrouped by IHS criteria accordingly: migraine with aura (n = 134); migraine without aura (n = 161); and age-matched headache-free controls (n = 140). No patients had a history of stroke or TIA. The mean age was 48, and 75% were female. Migraineurs and controls were well matched for cerebrovascular risk factors including blood pressure, smoking, diabetes, and cholesterol. Medication usage such as triptan and ergotamine were recorded as covariables. A single-blinded neuroradiologist reviewed all the MRI scans and rated the infarcts and WMLs recording number, size, and location. WMLs had to be hyperintense on all sequences and were scored with semi-quantitative measures with validated scales. WMLs were differentiated into deep WML (DWML) and periventricular WML (PVWML).

Sixty infarcts ranging in size from 2 mm to 21 mm were recorded from 31 patients. There was no difference in infarct rate between control and migraine (5% vs 8%; $P = .23$). When considering location, the migraineurs had a 7 times higher risk of posterior circulation infarct predominantly cerebellum (5.4% vs 0.7%; $P = .02$). This was largely driven by the higher prevalence of posterior circulation infarct in the migraine with aura group compared to the migraine without aura (2.2% vs 8.1%; $P = .03$). With respect to nonspecific WML, there was no difference in the distributions and severity grade between controls and migraine. Thirty-eight percent of both groups had at least 1 medium-sized WML. There was no association in WML of any kind between men and migraine. However, there was increased risk of only DWML (not PVWML) in women with migraine (odds ratio, 2.1). The risk did not vary in "with aura" or "without aura" subtypes but correlated best to migraine frequency—with more than 1 attack per month, the odds ratio was 2.6. The density of WMLs was not affected by cerebrovascular risk factors or class of medication use.

COMMENTARY

The study raises several interesting questions, and the methodology improves upon the selection biases that have compromised similar previous studies of this kind. However, as a population-based essentially retrospective study, Kruit et al should be reluctant to make statements of causality. All we now know is that in this cohort migraine with aura patients have a higher prevalence of predominantly cerebellar "infarcts," and this risk increases with increasing headache attacks. Also women with migraine have a higher prevalence of deep WMLs, and this also increases with increasing headache frequency. It is important to remember that these MRI findings were clinically silent (aside from the migraine, of course). In fact, Kruit et al's designation of the MRI changes as indeed "infarcts" might be presumptive. What we still don't know from this study is how to think of the ischemic stroke risk in migraine patients and, in general, whether this sheds further light onto the patho-

physiology of migraine. Certainly, the predominance of cerebellar MRI changes is notable given the association of cerebellar degeneration with the CANCNA1A mutation in the rare autosomal dominant familial hemiplegic migraine subtype. But the question as to whether the "infarct" changes or the WML are indeed primarily a vascular occlusive ischemic phenomenon or represent a direct neuronal apoptotic event is still unclear. The fact that there was no association with cerebrovascular risk factors argues against a vascular occlusive phenomenon. After all, this has always been the central question of migraine—vascular or neuronal. The current study helps the clinician think about his/her migraine patient who comes back from the MRI with an "abnormal" scan but does not reveal any more deeper secrets into the migraine process. **— JEFFREY REICH**

Reference

1. Tzourio C, et al. *BMJ*. 1995;310:830-833.

Table

Clinical Features of FDR's Case, GBS, and Poliomyelitis Compared

Clinical Features	FDR's Case	GBS	Poliomyelitis
Age of Onset	39 years	Mainly adults	Mainly young children
Flaccid Paralysis	Symmetric, ascending	Symmetric, ascending	Asymmetric
Progress of Paralysis	10-13 days	10-14 days	3-5 days
Facial Paralysis	Present	Common, bilateral	Rare, save in bulbar type
Bladder/Bowel Dysfunction	14 days	7-14 days	1-3 days
Numbness	Present	Common	Absent
Dysesthesia	Protracted	Protracted	Absent
Meningismus	Absent	Absent	Common
Fever	Present	Rare	Common
Recovery from Paralysis	Symmetric, descending	Symmetric, descending	Asymmetric
Permanent Paralysis	Symmetric	In about 15% of cases	In about 50% of cases

Adapted from Goldman AS, et al.

Retrospectoscope: Did FDR Have Polio or Polyneuropathy?

ABSTRACT & COMMENTARY

Soure: Goldman AS, et al. What was the cause of Franklin Delano Roosevelt's paralytic illness? *J Med Biogr*. 2003;11:232-240.

In August 1921, Franklin D. Roosevelt (1882-1945) was stricken with poliomyelitis, then also referred to as "infantile paralysis." Afterward, he made a courageous, lifetime effort to overcome the ravages of the disease. In time, he helped create a foundation to help other polio victims, and he inspired, as well as directed, the March of Dimes program that eventually funded an effective polio vaccine.

The diagnosis of polio in FDR's case has never been questioned until now. Armond Goldman, a pediatric immunologist, and associates in a new analysis of FDR's symptoms suggest that he might not have been stricken with polio but by Guillain-Barré syndrome (GBS). Goldman et al compiled all the details they could find of FDR's case and reviewed the literature to determine how common the symptoms were 80 years ago. They used Bayesian analysis to calculate the likelihood that a 39-year-old man with each of 8 symptoms would have polio or GBS (*see Table*). The latter emerged as the more likely diagnosis of FDR's paralytic illness.

COMMENTARY

In the setting of fever, FDR developed ascending, symmetrical paralysis of all 4 limbs and the facial muscles bilaterally. In addition, FDR complained of numbness and felt intense pain when anyone touched his paralyzed legs. Eventually, his paralysis slowly and partially resolved in a descending fashion. Therefore, FDR's illness more closely resembled GBS than polio.

Paralysis due to polio rarely is symmetric or ascending. Facial paralysis without involvement of other cranial nerves is rare in bulbar polio. Numbness is very rare in polio, and the pain experienced by polio patients originates in muscles (myalgias) rather than nerves (dysesthesias). Finally, a descending, symmetric recovery from paralysis as FDR experienced is rare in polio.

We will never know the cause of FDR's paralysis with certainty because the cerebrospinal fluid was not examined, and the laboratory methods now used to diagnose poliomyelitis and GBS had not been developed in 1921. If FDR did indeed have GBS, it is unlikely that his physicians would have diagnosed it since few, if any, causes of flaccid paralysis other than polio would have been considered at the time.

This paper is of both neurological and historical interest because, as noted by a commenter in *Science*, FDR's diagnosis or misdiagnosis of polio probably changed the course of history.[1] His paralytic affliction gave great impe-

tus to medical research that lead to the development of the polio vaccine, an outcome that might have been delayed had his diagnosis been GBS. — **JOHN J. CARONNA**

Reference

1. Random Samples edited by Constance Holden. *Science*. 2003;302:981.

Quetiapine for Psychosis in Parkinson's Disease

ABSTRACT & COMMENTARY

Source: Juncos JL, et al. Quetiapine improves psychotic symptoms and cognition in Parkinson's disease. *Mov Disord*. 2004;19:29-35.

VISUAL HALLUCINATIONS AND DELUSIONS ARE COMMON in patients with moderate to advanced Parkinson's disease (PD). Typically fleeting images of people, children, or animals are easily ignored; however, hallucinations often become more intense and frequent, with loss of insight. Fixed delusions, in which patients may become fearful, paranoid or even frankly psychotic, are especially problematic. Levodopa and dopamine agonists fuel hallucinations and delusions, and the treating neurologist is often faced with the difficult choice of lowering dopaminergic medications in an attempt to control hallucinations at the expense of impaired motor performance.

Fortunately, atypical neuroleptics offer an attractive option to control hallucinations in PD patients without worsening rigidity or stiffness. Recent studies have evaluated risperidone and olanzapine in hallucinating PD patients, with disappointing results—both agents reliably worsen parkinsonian symptoms and should be avoided in PD patients. Clozapine, the gold-standard atypical neuroleptic, controls hallucinations without worsening motor performance; however, the inconvenience of weekly blood tests to monitor for agranulocytosis and side effects of sedation or hypersalivation often limit the drug's use.

The present study evaluated 29 patients with PD and hallucinations who had previously failed treatment with clozapine, risperidone, and olanzapine. Using an open-label treatment arm, patients were treated with the newer atypical neuroleptic quetiapine (Seraquel). Dopaminergic therapy was kept constant for the duration of the study, and patients were slowly begun on quetiapine, increasing by 12.5-25 mg per night increments every 1-3 days, to a maximum dose of 400 mg per day. The dose was individually adjusted to achieve adequate control of hallucinations without unacceptable side effects, mirroring what is done in clinical practice. Daytime doses were added if patients experienced psychosis during waking hours. Patients were evaluated using the Unified Parkinson Disease Rating Scale, the Brief Psychiatric Rating Scale, the Neuropsychiatric Inventory, and the Clinical Global Impression Scale. Cognition was assessed, as well, using the mini-mental status exam and subtests from the Wechsler Memory Scale.

The median daily dose of quetiapine was 62.5 mg, and there was a statistically significant improvement in psychiatric rating scores, without change in baseline of the motor scores. Tests of sustained attention and memory surprisingly improved for the duration of the study (24 weeks). Except for 2 cases of symptomatic orthostatic hypotension, patients tolerated the medicine without incident.

COMMENTARY

Although limited by study design (open label, single center, flexible dosing), this elegant study confirms the Columbia experience with hallucinations in PD. Quetiapine is generally well tolerated by PD patients, and adequate control of hallucinations is generally achieved with bedtime dosing of less than 100 mg of the drug. Risperidone and olanzapine are essentially contraindicated in PD patients because they reliably worsen parkinsonism. Patients who require treatment of hallucinations are usually started on quetiapine, and the dose is titrated up until hallucinations are controlled. If adequate control is not achieved or if formed delusions become problematic and unresponsive, then our center's usual policy is to switch to clozapine. The efficacy and side effect profile of the 2 new "atypical" neuroleptics, ziprasidone and aripiprazole, are unproven in the PD population, and in this author's opinion, these agents should be used only if quetiapine and clozapine have been tried first. — **STEVEN FRUCHT**

Treatment for McArdle's Disease

ABSTRACTS & COMMENTARY

Sources: Vissing J, Haller RG. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. *N Engl J Med*. 2003;349:2503-2509; Amato AA. Sweet success—A treatment for McArdle's disease. 2004;349:2481-2482.

IN THIS SIMPLE YET ELEGANT, SINGLE-BLIND, PLACEBO-controlled, crossover study, 12 patients with McArdle's

disease were given a sucrose, or artificially sweetened placebo load, prior to aerobic exercise to determine if this might improve exercise tolerance. Average age of the 7 men and 5 women was 37 years, and all had lifelong exercise intolerance, episodic muscle cramps, and myoglobinuria triggered by exercise. Diagnosis was confirmed in all by absence of myophosphorylase staining on muscle biopsy and absence of myophosphorylase activity on biochemical muscle testing. Patients were tested after an overnight fast, with 75 g of sucrose or placebo being administered, on alternate days, by a 660 mL caffeine-free soft drink. Exercise began 30-40 minutes later, and periodic blood tests were drawn for glucose, lactose, pyruvate, ammonia, free fatty acids, and insulin measurements. Primary end points included perceived exertion level scored by the patient, each minute of exercise on a 6 (least effort) to 20 (most effort) Borg scale, and heart rate. Statistical analysis was provided by paired Student's t-test and analysis of variance, with a *P* value of .05 or less considered significant.

Borg-scale rating of effort significantly improved, and maximal heart rate significantly dropped following sucrose ingestion compared to placebo. Hyperinsulinemia and hyperglycemia followed sucrose load and remained elevated during the exercise period, whereas lactate and pyruvate increased following sucrose ingestion but fell during exercise. Free fatty acids fell, and the (expected) exercise-induced hyperammonemia was attenuated with sucrose. Sucrose ingestion prior to exercise improves exercise tolerance in patients with McArdle's disease and may prevent exercise-induced rhabdomyolysis.

COMMENTARY

Originally described in 1951, McArdle's disease is the first described metabolic myopathy resulting from a single enzyme deficiency, myophosphorylase, needed to convert glycogen to glucose-1-phosphate and lactate. Localized to chromosome 11q13, it is an autosomal recessive disorder usually resulting from a nonsense mutation at codon 49 in exon 1 (R49X), although rare mutations in the coding regions, splice junctions, and exon 2 also occur.[1]

Diagnosis of a glycogen storage myopathy can usually be made by the forearm exercise test. Following 1 minute of non-ischemic exercise (patient rapidly and vigorously opens and closes his fist), blood ammonia levels rise over the ensuing 10 minutes (indicating adequate exercise has been performed), but lactate levels do not. However, partial deficiency may result in normal lactate production, and specific enzymatic diagnosis requires muscle biopsy with myophosphorylase staining or biochemical assay to demonstrate its deficiency. — **MICHAEL RUBIN**

Reference

1. Deschauer M, et al. *Muscle Nerve*. 2003;27:105-107.

CME Questions

Please review the text, answer the following questions, check your answers against the key, and then review the materials again regarding any questions answered incorrectly. ***To receive credit for this activity, you must return a CE/CME evaluation at the end of the testing term.***

10. For patients on carbonic anhydrase inhibitors, avoid:
a. gabapentin.
b. lamotrigine.
c. oxcarbazepine.
d. zonisamide.
e. None of the above

11. A patient with multiple subcortical infarcts (BG and periventricular white matter) is likely to have all of the following except:
a. gait ignition failure.
b. shuffling gait.
c. freezing.
d. pseudoparkinsonism.
e. poor balance and falls.

12. All of the following clinical features are typical of GBS *except*:
a. flaccid paralysis.
b. numbness.
c. recovery from paralysis.
d. meningismus and fever.
e. adult onset.

13. In McArdle's disease, following the nonischemic forearm exercise test:
a. blood ammonia decreases and lactate stays constant.
b. blood ammonia increases and lactate stays constant.
c. blood ammonia increases and lactate increases.
d. blood ammonia decreases and lactate decreases.
e. blood ammonia decreases and lactate increases.

Answers: 10(e); 11(e); 12(d); 13(b)

In Future Issues: More Food for Thought?

PHARMACOLOGY WATCH

Sinus and Allergy Health Partnership Releases New Guidelines for Treatment of Bacterial Rhinosinusitis

New guidelines for the treatment of bacterial rhinosinusitis were published in the January supplement of *Otolaryngology- Head and Neck Surgery* by the Sinus and Allergy Health Partnership. The goal of the guidelines is to reduce the use of antibiotics for viral infections and to use the most appropriate antibiotic for bacterial infections. The guidelines recommend antibiotics if patients are getting worse after 5-7 days or if they are not better after 10-14 days. Patients with mild disease should be treated with cefpodoxime (Vantin), cefuroxime (Ceftin), amoxicillin, amoxicillin/clavulanate (Augmentin), or cefdinir (Omnicef). Patients with moderate disease or those with recent antibiotic exposure should receive amoxicillin/clavulanate, ceftriaxone, or one of the respiratory fluoroquinolones including gatifloxacin (Tequin), moxifloxacin (Avelox), or levofloxacin (Levaquin). The respiratory quinolones do not include ciprofloxacin. This is a follow-up to the group's first guidelines, which were published in 2000 (*Otolaryngol Head Neck Surg*. Supplement. 2004;130:1).

Steroids Not Linked to Risk of Fractures

Long-term use of inhaled steroids for the treatment of respiratory diseases or nasal steroids for the treatment of allergic rhinitis are not associated with an increased risk of fractures if they are used in normal doses, according to a study from Canada. Researchers conducted a case-control study of all elderly Québec residents who were dispensed respiratory medications and could be followed for at least 4 years from 1988 to 2001. The rate of hip or upper extremity fractures was not increased in those patients who used daily inhaled corticosteroids (RR, 0.97). The rate of upper extremity fractures increased by 12% with every 1000 µg increase in the daily inhaled corticosteroid, but the rate of hip fractures did not increase. The rate of hip fractures was only elevated with very high doses (more than 2000 µg per day) of inhaled corticosteroid. Nasal steroids did not increase the risk at any dose. The authors conclude that long-term use of inhaled and nasal corticosteroids at usual recommended doses is not associated with the risk of fracture (*Am J Resp Crit Care Med*. 2004;169:83-88).

ADT Puts Men at Risk for Osteoporosis

Men treated for prostate cancer with androgen deprivation therapy (ADT) are at risk for osteoporosis and fractures, according to a new study. One year of ADT resulted in 2-8% bone loss in the lumbar spine and 1.8-6.5% bone loss

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in the femoral neck. The study was a meta-analysis of 9 studies that included a total of 208 patients. The authors suggest that men starting ADT should be considered for bone mineral density measurement, and men at high risk should be offered a bisphosphonate (published online January 19, 2004. *Cancer*).

Study Shows Valsartan May Improve Sexual Function in Postmenopausal Women

A new study suggests that valsartan may improve sexual function in hypertensive postmenopausal women. Researchers randomized 120 postmenopausal women aged 51-55 with mild-to-moderate hypertension to valsartan 80 mg daily or atenolol 50 mg daily for 16 weeks. Doses were doubled if diastolic blood pressures remained above 90 mm Hg. The end point was a questionnaire that self-evaluated various aspects of sexual desire, orgasmic response, and coital activity. The drugs lowered blood pressure equally effectively. Women in the valsartan group noted significantly improved sexual desire (38% increase, $P < .01$), changes in behavior (45% increase, $P < .001$), and sexual fantasies (51% increase, $P < .001$). In the atenolol group, scores for sexual desire and sexual fantasies significantly worsened (18% decrease, $P < .01$, and 23% decrease, $P < .001$, respectively). The authors conclude that in the study group, hypertensive postmenopausal women in their 50s, valsartan improved some aspects of sexual function, whereas atenolol worsened it. They further speculate the drugs may have differential effects on serum hormone levels, specifically testosterone (*Am J Hyperten*. 2004;14:77-81).

New Direct-to-Consumer Pharma Advertising Rules Considered

Anyone who watched the Super Bowl can verify that direct-to-consumer advertising of prescription pharmaceuticals is big business. Now the FDA is considering tighter restrictions on the content of these ads, requiring pharmaceutical companies to highlight key risks associated with the drugs rather than listing the large number of potential side effects in small print. The guidelines encourage companies to use less cluttered formats for print ads, perhaps even using bullet points to set the import risks apart. Print ads currently contain an extensive list of side effects similar to the package insert, often in a similarly small font, frequently on a separate page from the main advertisement. The FDA is also considering changing the criteria for "reminder" ads that simply name the drug without giving the indication for its use. Currently, these ads do not require information on adverse effects and often run close to disease awareness campaigns also paid for by the drug company. These new FDA restrictions have not been finalized and are sure to be opposed by Pharma.

FDA Actions

Boehringer Ingelheim Pharmaceuticals has received FDA approval to market tiotropium bromide inhalation powder (Spiriva) for the treatment of COPD. Tiotropium, a once-daily anticholinergic agent, is indicated for the long-term maintenance treatment of bronchospasm associated with COPD.

Modafinil (Provigil) has been approved for improving wakefulness in patients with excessive sleepiness due to obstructive sleep apnea/hypopnea syndrome and shift work sleep disorder. The drug is currently approved for improving wakefulness in patients with narcolepsy.

The FDA has approved a 3-day course of azithromycin (Zithromax) for the treatment of acute bacterial sinusitis. The drug, which is dosed at 500 mg once a day, is the only 3-day regimen approved for this indication. Azithromycin is currently approved for the treatment of community-acquired respiratory infections and skin infections, as well as otitis media.

Olanzapine (Zyprexa) has been approved for maintenance treatment of bipolar disorder. The drug appears to be effective in delaying relapse into either mania or depression in bipolar patients. Olanzapine was approved in 2000 for the short-term treatment of acute mixed or manic episodes associated with bipolar disorder.

The FDA has also approved a combination of olanzapine and fluoxetine (Prozac) for the treatment of bipolar depression. The combination drug will be marketed under the trade name Symbyax. Quetiapine fumarate (Seroquel) was also recently approved for monotherapy and adjunct therapy with lithium and divalproex, for the short-term treatment of acute manic episodes associate with bipolar I disorder. ■