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INSIDE

Genetic vs Environmental Factors in the Causation of Alzheimer's Disease

ABSTRACT & COMMENTARY

Source: Pedersen NL, et al. How heritable is Alzheimer's disease late in life? Findings from Swedish twins. *Ann Neurol*. Early view online.

THE AVAILABILITY OF COMPREHENSIVE RECORDS OF PUBLIC health in Scandinavian countries is a major advantage in working out epidemiological studies. This has enabled the assessment of the role of genetics vs environmental contributions to diseases ranging from schizophrenia to Alzheimer's disease (AD). The present study of Swedish twins including many older than 80 now suggests that the genetic component of AD may be less than previously thought. The current study, which had an average of 5 years of follow-up, was notable for the large number of twin pairs older than 80. There were 297 out of a total of 662 initially enrolled. Pedersen and associates found that among 221 pairs of monozygotic twins, 21 had 1 sibling afflicted with AD and 5 had both siblings with the disease, for a concordance rate of 32.2%. The corresponding figures for 329 dizygotic twins were 42 discordant pairs and only 2 concordant pairs, for an overall concordance rate of 8.7%. They then performed structural modeling of the genetic vs environmental contributions and found that the genetic contribution to AD in the sample was 48%. This is considerably lower than the prior estimates in which the genetic risk was felt to be as high as 75%. A major difference in this study is that it was based on incident cases rather than prevalent cases, which provide only a snapshot of cases at a given time. Incident cases refer to those arising during the course of the study period. Subjects older than 80 did not have significantly greater environmental risk relative to those younger than 80.

COMMENTARY

These findings are of interest since they suggest that environmental factors may play a larger role in AD than previously suggested. Pedersen et al note that it would be important to identify further genetic factors that place individuals at risk. They, however, point out that modulation of environmental risk factors may play an equal-

VOLUME 22 • NUMBER 6 • FEBRUARY 2004 • PAGES 41-48

ly important role. These include such commonly cited risk factors as vitamin B12 deficits, elevated homocysteine, drug-induced decrements, recent head trauma, and cerebral ischemic disease. — **M. FLINT BEAL**

Melatonin Fails to Improve Sleep in Alzheimer's Disease

ABSTRACT & COMMENTARY

Source: Singer C, et al. A multicenter placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease. *Sleep*. 2003;26:893-901.

THERE ARE CONSIDERABLE ANECDOTAL DATA SUGgesting that melatonin may improve sleep. About half of patients with Alzheimer's disease (AD) experience some form of sleep disruption ranging from nighttime awakenings to complete reversal of the diurnal sleep/wake cycle. This may further impair cognitive difficulties. Singer and colleagues carried out a trial of 2 sustained-release doses of melatonin—one moderately high dose of 10 mg and one moderately low dose of 2.5 mg. These were compared to placebo in 157 individual AD patients with sleep disruption who were treated for 2 months. Singer et al, unfortunately, found no significant improvement in objective measures of sleep. Those included sleep duration, sleep maintenance, and day/night sleep ratio.

COMMENTARY

These results provide no encouragement for the use of melatonin for sleep disturbance in AD. This is a major clinical problem. At present, the only agents that have been shown to demonstrate some efficacy are more conventional sleep-inducing medications. — **M. FLINT BEAL**

Improved Cortical Metabolism in Huntington's Disease Patients Following Striatal Neural Grafting

ABSTRACT & COMMENTARY

Source: Gaura V, et al. Striatal neural grafting improves cortical metabolism in Huntington's disease patients. *Brain*. 2004;127:65-72.

THE PROSPECTS FOR THERAPY IN HUNTINGTON'S DISEASE (HD) are rapidly improving. A number of discoveries about disease pathogenesis have been made that have targeted abnormalities in gene transcription, as well as energy metabolism, as potential therapeutic targets. Nevertheless, another potential treatment is to use striatal neural grafts. HD has for 15 years been considered a disease potentially amenable to cell therapy. A characteristic of the disease is that there are reductions in glucose metabolism as assessed by positron emission tomography (PET). It is detected initially in the striatum but then progresses into the cerebral cortex as the disease worsens. The cortical hypometabolism has been attributed to dysfunction of the cortico-striato-thalamo-cortical loops induced by the striatal disease. Another possibility, however, is that it may be related directly to some loss of cortical neurons within the cerebral cortex.

The rationale for neural grafting in HD differs from that in Parkinson's disease (PD) because grafted neurons in HD have to substitute completely for degenerated cells in the striatum, whereas they are expected to provide innervation only in PD. In rodents, as well as nonhuman primates, striatal xenografts and allografts implanted into the lesioned striatum have been shown to survive, integrate into the host brain circuitry, and improve motor and

Neurology Alert, ISSN 0741-4234, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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SENIOR COPY EDITOR: Christie Messina Petrone.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to *Neurology Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

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cognitive functions. Like normal striatal neurons, grafted cells receive topographically organized cortical inputs and establish efferent projections to appropriate striatal targets. These include the globus pallidus and substantia nigra pars reticulata. Previous studies have shown that the reconstruction of neural circuitry can be physiologically active and can at least partially normalize the metabolic hypoactivity in the extrapyramidal neuronal system induced by striatal degeneration.

Gaura and associates have been studying fetal striatal allografts for many years. They carried out a pilot study, reported approximately 2 years ago in the *Lancet*. At that time, they noted that a number of patients had shown stabilization and even clinical improvement. The present report is a follow-up on these patients. They note that of the 5 patients who were initially grafted, the clinical improvement in 3 of the patients was associated with the reduction in the striatal and cortical hypometabolism. That demonstrated the grafts were able to restore function of the striatal-cortical loops. Conversely, in 2 patients who did not improve by the grafts, the striatal and cortical hypometabolism progressed over the 2-year follow-up period.

COMMENTARY

These results are very encouraging. They suggest that fetal striatal grafts can survive and function. They appear to have physiological effects that result in improved glucose metabolism that were accompanied by clinical improvements. Interestingly, the outcome of the patients with regard to both clinical improvement and clinical worsening was directly reflected by the cortical and striatal metabolism on PET scans, suggesting that this is a useful indicator for following the outcome of striatal allografts. **— M. FLINT BEAL**

Alzheimer Metal Chelator Shows Some Promise in Phase II

ABSTRACT & COMMENTARY

Source: Ritchie CW, et al. Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Abeta amyloid deposition and toxicity in Alzheimer disease: A pilot phase 2 clinical trial. *Arch Neurol*. 2003;60:1685-1691.

THE ZINC AND COPPER CHELATING COMPOUND clioquinol has been shown to reduce beta-amyloid deposits in the brain of transgenic mice and is consequently being tested as a treatment for Alzheimer's disease (AD). The compound has been found to promote solubilization and clearance of beta-amyloid in laboratory studies and may also inhibit potentially harmful copper-amyloid interactions. Clioquinol has been used as an antibacterial and antifungal agent in the past but was withdrawn from clinical use after several thousand cases of subacute myelo-optic neuropathy developed in Japan, possibly as a result of clioquinol-induced B-vitamin deficiency.

Relying on careful monitoring to reduce the risk of toxicity, Ritchie and colleagues carried out a 36-week phase II test of the efficacy of clioquinol in reducing plasma beta-amyloid levels and slowing cognitive decline in patients with moderately severe AD. The study had randomized, placebo-controlled and double-blind design and examined 36 AD patients with a mean ADAS-Cog score of approximately 26 at baseline. Despite the involvement of a relatively small number of subjects, Ritchie et al chose to stratify the subjects into 2 groups by severity of cognitive impairment for the purposes of analysis.

No significant effects on cognition were observed in the treated patients overall or in the more mildly affected group. Among the more severely affected patients (baseline ADAS-Cog score greater than 25), a statistically significant effect was seen at weeks 4 and 24 on the ADAS-Cog but not other weeks. No significant differences were seen on the Minimental State Examination at any time point. Plasma beta-amyloid levels did show change significantly with treatment, although there was wide individual variation in levels across subjects. Five serious adverse events were observed, including one case of visual changes that was considered possibly treatment related.

Ritchie et al concluded that their results were sufficiently promising to warrant further trials of clioquinol or a modified version of this compound for treatment of AD.

COMMENTARY

A phase II trial such as this is generally designed to establish proof of concept, providing minimal information on whether there is enough of a treatment effect relative to tolerance to warrant further studies. The results of this trial look respectable in terms of reduction of plasma beta-amyloid levels by clioquinol, while the primary outcome measure of cognition shows less impressive changes but noteworthy trends. Ritchie et al point out that demonstrating a comparable treatment effect with the current generation of cholinesterase inhibitors requires trials with more than 300 patients. The practicality of using a medication that was withdrawn from clinical use owing to side effects in patients with dementia is

a cause for concern. Larger studies will be needed to delineate the efficacy and safety profile of clioquinol in a more representative AD population. The use of copper and zinc chelation as a treatment for AD is novel, and the relative merits of this approach compared to other emerging techniques for altering brain amyloid burden remain to be determined. — **NORMAN R. RELKIN**

Subthalamic Stimulation and Urinary Function

ABSTRACT & COMMENTARY

Source: Seif C, et al. Effect of subthalamic deep brain stimulation on the function of the urinary bladder. *Ann Neurol*. 2004;55:118-120.

With the approval and widespread use of deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease (PD), there has been increasing awareness of non-motor effects of DBS. Recent reports have illustrated that DBS may induce mania and even impair executive function in PD, despite its often dramatic and clinically meaningful improvement in motor performance. In this elegant study, Seif and colleagues asked a simple question: does DBS alter urodynamic parameters in patients with PD? Urologic symptoms are common in PD, usually expressed as urinary urgency, increased frequency, or frank incontinence. Urodynamic studies typically show detrusor hyper-reflexia, resulting in a reduced bladder capacity and early desire to void.

Seif et al selected 16 patients with PD who had undergone bilateral STN implantation 6-29 months before. All patients experienced a significant improvement in motor disability from STN stimulation. Patients were examined 12 hours after taking their last dose of antiparkinsonian medication, in order to evaluate the effects of DBS. Two videourodynamic examinations were performed 20 minutes apart—one in the stimulation off state and one with stimulators on. These studies measured desire to void, maximum bladder capacity, detrusor pressure, and urine flow while the bladder was filled with warm isotonic saline.

In the off stimulation state, initial desire to void occurred at a bladder capacity of 135 mL, while in the on stimulation state, desire to void was noted at 199 mL. Unstable detrusor contractions were observed in 5 patients in the stimulator off state and in none when stimulators were on. The maximum capacity of the bladder was 174 mL with simulators off and 302 mL with simulators on. These changes occurred quickly, as only 20 minutes separated the stimulator off from on measurements, and were statistically significant.

COMMENTARY

This study adds another important feature to the list of symptoms improved by STN stimulation. The patients did not have symptoms of urinary distress, and none had incontinence. The effect of STN stimulation on such patients is not yet known; however, one could envision that normalizing bladder urodynamics might reduce the risk of urinary tract infections and also improve patients' comfort and quality of life.

The mechanism by which STN stimulation improves micturition is unknown. The central control of micturition is complex, involving cingulate and prefrontal cortex, the pontine micturition center, and sacral parasympathetic preganglionic neurons. Loss of dopaminergic activity in the substantia nigra leads to excitation of the STN and possibly activation of direct STN projections to the brainstem. Alternately, stimulation of the STN disinhibits thalamocortical projections to the cingular and prefrontal cortex, which might re-establish their normal role in controlling micturition. — **STEVEN FRUCHT**

Back to Basics: The Right Anti-Epileptic Drug for the Right Diagnosis

ABSTRACT & COMMENTARY

Source: Benbadis SR, et al. Idiopathic generalized epilepsy and choice of antiepileptic drugs. *Neurology*. 2003;61:1793-1795.

Benbadis and associates reviewed the medication history of patients with EEG-confirmed idiopathic generalized epilepsy (IGE). They classified patients according to the antiepileptic drugs (AEDs) used at the time of referral to their epilepsy center. They defined "adequate" or "broad spectrum" AEDs as valproic acid (VPA), ethosuximide, lamotrigine (LTG), topiramate (TPM), levetiracetam (LEV), and zonisamide. "Inadequate" AEDs for IGE included phenytoin (PHT), carbamazepine (CBZ), oxcarbazepine, gabapentin, and tiagabine. Of 58 patients, 17 (29%) were on adequate AEDs, 28 (48%) were on inadequate AEDs, and 13 (22%) were on both.

COMMENTARY

The fact that so many IGE patients (70%) were prescribed "ill-advised" AEDs (alone or in polypharmacy) for IGE at initial referral to a tertiary epilepsy center can be attributed to misdiagnosis of IGE or inappropriate AED choice despite an accurate diagnosis of IGE. In the patients in this study, Benbadis et al do not reveal how many patients had been misdiagnosed as having focal epilepsy; the criterion for referral was medically resistant epilepsy not necessarily intractable IGE (only 7 patients studied). The experience of our own epilepsy center indicates that, among patients referred specifically for presurgical evaluation of their epilepsy, approximately 10-15% are immediately ineligible because they in fact have generalized epilepsy rather than focal epilepsy.

While the issue of misdiagnosis is an important one, it can be relatively easily overcome with an open mind and appropriately scrupulous diagnostic evaluation. Inadequate knowledge of AED indications (FDA approved or "off-label") is a more difficult educational task. The problem can be divided into over-reliance and inappropriate use of older AEDs and/or lack of sufficient data to support use of newer AEDs for IGE.

We have personally been asked by a general neurologist whether we accepted the "brainwashing" by J. Kiffin Penry and others that VPA is really the agent of choice for absence and juvenile myoclonic epilepsy (JME). In that practitioner's experience, PHT and CBZ were equally effective as VPA in treating absence and JME. His experience flew in the face of well-established data that absences are worsened by CBZ in both children and adults. The clinical experience continues to mount with reports that CBZ and vigabatrin administration produced de novo absences in 3 children who only had clinical or electrographic evidence of partial epilepsy.[1] The general neurologist is, unfortunately, more comfortable with PHT, CBZ, and even phenobarbital than VPA, which helps to explain why 4 of 58 patients (7%) with IGE had never received a trial of VPA.

The flip side of the AED choice problem is that general neurologists are now presented with many AED choices (8 novel agents in the last decade). Overwhelmed by the newer AEDs and in the absence of strong evidence-based medicine, they are choosing to resort to the older agents vs nearly random usage of the newer drugs. The concept of a broad-spectrum AED (ie, one effective for both focal and generalized epilepsies) is one that has only arisen in the last 10 years. Few practitioners spoke of broad-spectrum AEDs when there was only one member of the class (ie, VPA).

We do not believe that there is a firm consensus on the drugs listed as adequate or broad spectrum. For example, there have been no published trials (controlled or not, blinded or not) to establish the efficacy of LEV for generalized epilepsy. Of the 6 references cited by Benbadis et al to support the use of LEV in IGE, one appeared in abstract form only and 3 were not peer-reviewed. As a result, at this time, we would not describe LEV as an adequate, broad-spectrum agent for IGE. By contrast, a paper by Prasad and associates[2] provides useful data about the use of LTG and TPM in treating JME. Prasad et al also point out that while PHT and CBZ can reduce generalized tonic-clonic seizures (GTCS) associated with JME, these drugs are less useful for myoclonic seizures. This raises a further issue about the end points of AED therapy. Recently, a patient presented to us with a clear electroclinical history of JME. His previous neurologist felt that he had been adequately controlled for years on PHT since it had abolished his GTCS. The patient, though, had a further improvement in quality of life when he was changed to VPA monotherapy at our center. He remained free of GTCS and also began to enjoy tennis and golf, which he had never been able to play previously because of his constant jerking.

The answer to better pharmacologic seizure control in IGE involves no more than bread-and-butter medical practice: get the diagnosis right, know your drugs, and, most important, listen to the patient. **— ANDY DEAN**

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Hepatitis C and Neuropathy

ABSTRACT & COMMENTARY

Source: Nemni R, et al. Peripheral neuropathy in hepatitis C virus infection with and without cryoglobulinemia. *J Neurol Neurosurg Psychiatry*. 2003;74:1267-1271.

Fifty-one consecutive hepatitis C patients with neuropathy were evaluated to determine whether, and by what mechanism, cryoglobulinemia was associated with peripheral neuropathy. None demonstrated other causes of neuropathy including diabetes, alcoholism, renal failure, vitamin deficiency, toxicity, thyroid disease, or neoplasia. All underwent clinical, serologic, and electrodiagnostic study, with 28 agreeing to sural nerve biopsy. Statistical analysis used X^2 testing, with Yates' correction if required, and students' *t* tests. Significance was defined by a *P* value < .01 and < .05.

Among the 25 men and 26 women, mean age was 62 years at the time of diagnosis. Forty (78%) were cryoglobulin positive (CG+), and all demonstrated mixed cryoglobulinemia, while 11 showed no cryoglobulins (CG-). Peripheral neuropathy was significantly more common in the CG+ group, whereas cranial neuropathy was more common in the CG- patients. Mononeuropathy multiplex was seen equally in both groups. CG+ patients more often had low C4 levels and rheumatoid factor positivity. Transaminase activity was increased in both. Motor and sensory nerve conduction studies were similar in both groups, with only the deep peroneal motor conduction velocity being significantly slowed in the CG+ group but not into the demyelinating range. Sural nerve biopsy findings were not significantly different in the 2 groups. Of 25 CG+ patients who underwent biopsy, axonal loss was seen in 10 (40%), epineurial vasculitis in 8 (32%), and both axonal and demyelinating changes in 7 (28%). Of 3 CG- patients who were biopsied, 2 showed epineurial vasculitis and the third, axonal loss. None of the 28 biopsies revealed primary demyelination on teased fiber preparation. Cryoglobulin positivity in hepatitis C virus (HCV) infection is associated with peripheral neuropathy. Ischemic injury, rather than direct viral invasion, is the more likely pathomechanism.

COMMENTARY

HCV, the most common cause of non-A, non-B hepatitis, is a single-stranded, enveloped RNA virus of the *Flaviviridae* family. Nine genotypes with associated subtypes exist, but genotype 1b is the culprit least treatable and most correlated with severe clinical disorders.[1] Neurologically, these include peripheral nerve vasculitis, ischemic and hemorrhagic stroke, cerebral vasculitis, myelitis, encephalitis, and, rarely, lymphoma.[2] High-risk behavior is generally necessary for contracting HCV, including exposure to blood or its products, sexual activity, and IV drug use, but household contact and perinatal exposure are also reported.[3]

Cryoglobulins, serum proteins that reversibly precipitate at low temperature, are classified as type 1 (monoclonal immunoglobulins), type II (polyclonal and monoclonal immunoglobulins), and type III (polyclonal immunoglobulins). In the absence of a lymphoproliferative disorder, types II and III are termed mixed essential cryoglobulins and are often associated with HCV infection wherein associated neurologic complications are strongest. HCV also promotes production of rheumatoid factor (RF). Cryoglobulins associated with HCV can activate complement resulting in hypocomplementemia with formation of immunoglobulin/RF cryoprecipitates that may, in turn, trigger vasculitis and its associated clinical sequelae. Treatment includes corticosteroids, immunosuppressive agents, and plasma exchange but remains challenging with frequent relapses and rare long-term remissions.[4] **— MICHAEL RUBIN**

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Lamotrigine for Sciatica

ABSTRACT & COMMENTARY

Source: Eisenberg E, et al. Lamotrigine for intractable sciatica: Correlation between dose, plasma concentration and analgesia. *Eur J Pain*. 2003;7:485-491.

Fourteen consecutive patients with sciatica were enrolled in this open-label trial of lamotrigine (LTG) to determine its efficacy in pain control and its dose response curve. Patients ranged in age from 18 to 75 and suffered from painful lumbar radiculopathy, documented by CT or MRI evidence of disc herniation, for 1-3 years. Exclusionary criteria included epilepsy and cardiac, renal, or liver dysfunction. Washout of previous analgesics for 1 week preceded a 6-week titration period, beginning at 25 mg q.d. and doubling weekly to 400 mg daily, given in divided dosage. A dose of 400 mg q.d. was then maintained for 4 weeks and subsequently discontinued. End points included a daily numerical pain scale (NPS), with the average weekly NPS serving as the primary end point. Other measurements included a visual analog pain scale (VAS) and the short form McGill pain questionnaire (SFMPQ), both performed 9 times over the 11-week study. Range of lumbar motion and the straight leg raise test using a manual goniometer, the neurological examination, and LTG blood concentrations were also performed. Statistical analysis included repeated measures ANOVA and Tukey-Kramer HSD tests, with a P value of .05 considered significant.

Of 14 enrolled patients, 13 received at least 1 week of drug, but only 7 completed the entire trial. One declined the final phase due to lack of efficacy, and 6 did not complete the titration phase due to dizziness, diarrhea (n = 1 each), or personal/nonspecific reasons. All outcome measures improved but significantly so only at the maximum dose of 400 mg, with a linear relationship seen between mean dose, plasma concentration, weekly pain score,

lumbar movement, and straight leg raise. LTG may be safe and effective for intractable sciatica in patients who tolerate the medication, but double-blinded confirmation of these findings in a larger trial will be needed first.

COMMENTARY

Approved as an anti-epileptic medication, LTG has broad-spectrum efficacy against partial, generalized tonic-clonic, and absence seizures, comparable to phenytoin and carbamazepine.[1] Low protein binding (approximately 55%) allows for few drug-drug interactions and good patient tolerance, including no interaction with oral contraceptives, make LTG an attractive alternative, save for a 0.3% risk of serious rash. Serving to stabilize neuronal membranes by acting on voltage-sensitive sodium channels, it inhibits the release of excitatory neurotransmitters, including glutamate and aspartate, and has also been shown to inhibit calcium currents in cortical neurons. Doses between 300 mg and 500 mg are recommended but may go up to 700 mg/d. About 10% of patients discontinue therapy due to adverse effects, but most commonly only rash (3%), dizziness (2.8%), and headache (2.5%) are experienced.

Attention, however, should be drawn to recently reported unusual side effects of LTG therapy in children.[2] An 8-year-old boy with myoclonic jerks developed tremor, unsteadiness, chorea, and eye movement abnormalities while starting LTG, and a 7-year-old boy with suspected absence seizures developed eye movement abnormalities and cognitive decline. In both instances, symptoms and signs resolved on stopping LTG. **— MICHAEL RUBIN**

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ED Standards For Assessment of Cervical Spine Injury Compared

ABSTRACT & COMMENTARY

Source: Stiell IG, et al. The Canadian C-spine rule versus the NEXUS low-risk criteria in patients with trauma. *N Engl J Med*. 2003;349:2510-2518.

Each year in north america more than 13 million patients at risk for cervical spine fracture after trauma are assessed in emergency departments (ED). Despite the fact that very few of these patients have a cervical spine fracture, most undergo cervical-spine radiography, a low-cost procedure that because of the high volume of its use adds substantially to health care costs. A current standard of care recommended for use by ED physicians is based on the National Emergency X-Radiology Utilization Study (NEXUS) Low-Risk Criteria (NLC)[1] The NLC rule requires cervical spine radiography for patients with trauma unless they meet all 5 of the low-risk criteria: no midline cervical spine tenderness, no evidence of intoxication, normal level of alertness, no focal neurologic deficit, and no painful distracting injuries. Studies conducted to validate these criteria indicate that the NLC rule has a high sensitivity (99.6%) but a low specificity (12.9%) for cervical spine injury.[2]

Stiell and associates, convinced that the NLC rule leads to unnecessary testing and delayed triage of patients in the ED, developed the Canadian C-Spine Rule (CCR) to assess alert, stable patients for traumatic cervical spine injury.[3] The CCR is more complex than the NLC and is based on: 1) 3 high-risk criteria (older than 65 years, dangerous mechanism of trauma, and paresthesias in extremities); 2) 5 low-risk criteria (simple rear-end motor vehicle collision, sitting position in the emergency department, ambulatory at any time, delayed onset of neck pain, absence of midline cervical spine tenderness); and 3) the ability of patients to rotate their necks.

In their current report, Stiell et al conducted a prospective cohort study in 9 EDs in Canada comparing the CCR and NLC as applied to alert patients with trauma who were in stable condition. The CCR and the NLC were interpreted by 394 physicians for patients before radiography. The purpose of the study was to prospectively evaluate the accuracy, reliability, clinical acceptability, and potential effect of the CCR and NLC on the use of ED resources. The study enrolled more than 8000 alert patients with trauma who were stable. The primary outcome measure was chosen to be any clinically important cervical spine injury. Cervical spine injury was defined as any fracture, dislocation, or ligamentous instability demonstrated by radiologic imaging. Patients who did not undergo radiologic testing in the ED were evaluated with the use of a proxy outcome assessment tool. In such patients, a study nurse contacted them by telephone and classified them as having no cervical spine injury if they met the following criteria at 2 weeks: mild or no neck pain, mild or no restriction of neck movement, neck collar not used, and a return to usual occupational activities. Patients who did not fulfill these

criteria were recalled for cervical spine radiography.

Stiell et al found that only 169 patients (2%) out of 8283 had clinically important cervical spine injuries. In 845 (10.2%) of the patients, physicians did not evaluate range of motion as required by the CCR algorithm. In an analysis that excluded such patients, the CCR was more sensitive than the NCL (99.4% vs 90.7%; $P < .0001$) and more specific (45.1% vs 36.8%; $P < .001\%$) for injury. In addition, use of the CCR vs the NLC resulted in lower rates of radiographic testing (55.9% vs 66.7%; $P < .001$). Physicians using the CCR missed one patient, but when using the NCL they missed 16 patients with important cervical spine injuries.

COMMENTARY

This study validates the high sensitivity, reliability, and clinical acceptability of the CCR. Therefore, the CCR has the potential to replace the NLC as a new standard for assessment of cervical spine injury in stable, alert patients after trauma. Use of this rule would optimize the use of radiology resources in the ED and decrease the time spent by patients in the emergency room. As Stiell et al point out, patients with possible cervical spine injuries usually are immobilized on a back board and may spend several hours awaiting radiologic testing, the delay leading to considerable discomfort and unnecessary use of space in an already crowded ED.

Stiell et al are to be congratulated for their continued efforts to standardize practice and improve the efficiency of diagnostic procedures in the ED. They previously have provided the medical community with the Canadian CT rule for patients with minor head injury.[4] The only problem with the CCR compared with the NLC appears to be the former's complexity. As Stiell et al noted, the physicians in their study appeared slightly less comfortable using the CCR compared with the NLC and, most importantly, were reluctant to assess range of motion of the neck in patients with possible cervical spine injury. Therefore, and unfortunately, it seems likely that in clinical practice, ED physicians will continue to use the simpler NLC and opt for more radiographic studies rather than for more physical examination of the patient. — **JOHN J. CARONNA AND IGOR OUGORETS**

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CME Questions

5. **The use of melatonin for sleep disturbance in AD:**
   a. shows dose-dependent improvement.
   b. is effective with 10 mg but not 2.5 mg.
   c. is effective with 2.5 mg but not 10 mg.
   d. is ineffective.

6. **The zinc and copper chelator Clioquinol has been found to alter beta-amyloid levels in the brain by:**
   a. inhibition of the enzyme beta-secretase.
   b. inhibition of the enzyme gamma-secretase.
   c. increasing solubilization of beta-amyloid.
   d. increasing amyloid-lipid interaction.

7. **Complications of hepatitis C virus and mixed essential cryoglobulinemia include:**
   a. peripheral nerve vasculitis.
   b. stroke.
   c. cerebral vasculitis.
   d. myelitis.
   e. All the above

8. **Lamotrigine:**
   a. interacts with the oral contraceptive pill.
   b. is highly protein bound (> 85%) in the serum.
   c. can be safely used at doses of 300-500 mg/d.
   d. is poorly tolerated due to a 10% incidence of rash.
   e. All the above

9. **Compared to NLC, CCR was:**
   a. more sensitive and less specific.
   b. less sensitive and less specific.
   c. less sensitive and more specific.
   d. more sensitive and more specific.
   e. None of the above

Answers: 5(d); 6(c); 7(e); 8(c); 9(d)

Readers are Invited

Readers are invited to submit questions or comments on material seen in or relevant to *Neurology Alert*. Send your questions to: Christie Petrone—Reader Questions, *Neurology Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374.

In Future Issues:

Treatment for McArdle's Disease

PHARMACOLOGY WATCH

Valacyclovir Reduces Genital Herpes Transmission

A once-a-day dose of a valacyclovir reduces the rate of transmission of genital herpes (HSV-2) from an infected partner to an uninfected susceptible partner, according to a new study. The study group included 1484 immunocompetent, heterosexual, monogamous couples in which 1 partner had symptomatic genital HSV-2 and the other was susceptible to HSV-2. The infected partners were randomized to valacyclovir 500 mg once daily or placebo for 8 months. At the end of the study period, clinically symptomatic HSV-2 infections developed in 4 of 743 susceptible partners in the valacyclovir group vs 16 of 741 in the placebo group (HR, 0.25; 95% CI, 0.08-0.75; $P = 0.008$). Overall acquisition of HSV-2, including asymptomatic infections, was observed in 14 partners in the valacyclovir group compared to 27 in the placebo group (HR, 0.52; 95% CI, 0.27-0.99; $P = 0.04$). Valacyclovir significantly cut down on viral shedding in the infected partner and also significantly cut down on the rate of HSV-2 outbreaks in the infected partner. The authors caution that 37% of couples in the study did not use condoms even though counseled to do so, and that condom use and abstinence during attacks are the most effective methods of preventing transmission (*N Engl J Med*. 2004;350:11-20).

Erythropoietin Safe for Cancer Patients?

A fascinating news item published in the December 17 issue of *Journal of the National Cancer Institute* raises the question of whether erythropoietin is safe to use in cancer patients. According to the news report, several studies suggest that many cancer cells have erythropoietin receptors that may be stimulated by erythropoietin injections. Erythropoietin is commonly given to cancer patients to treat chemotherapy-related, or cancer-related anemia. Two recent trials have shown that erythropoietin use is associated with decreased survival in some cancer patients according to the news report. Erythropoietin receptors have been found on head and neck cancer cells, prostate cancer cells, and ovarian cancer cells, as well as breast, renal, and uterine cancer cells. Preliminary data suggest that some of these cancers may actually proliferate in the presence of erythropoietin. The association between erythropoietin and decreased survival for some cancer patients needs further evaluation (*J Natl Cancer Inst*. 2003;95:1820-1821).

WHI, ALLHAT Trials Still Spur Research

It appears that 2 landmark studies have significantly changed practice patterns in this country. The Women's Health Initiative (WHI) study published in July 2002, and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) published in April 2000 both showed negative results with some of the most widely prescribed pharmaceuticals in this country. WHI suggested that combined estrogen/progesterone increases the risk of breast cancer and cardiovascular disease in postmenopausal women. Researchers from Stanford looked at prescription trends in hormone therapy from 1995 to July 2003. Annual hor-

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mone therapy prescriptions increased dramatically between 1995 in 1999 and then remained stable through June 2002. Following publication of the WHI in July 2002, prescriptions for Prempro, the combination estrogen/progesterone used in the study, declined by 56%. New prescriptions for conjugated estrogen also declined significantly. Small increases were seen with topical estrogens and low-dose estrogen preparations over the same time period (*JAMA*. 2004;291:47-53). ALLHAT was terminated early and the results released in December 1999, and published in April 2000 because early results showed that doxazosin, an alpha-blocker, was significantly inferior to diuretics with respect to preventing stroke, congestive heart failure, and a composite of other cardiovascular outcomes. The same group from Stanford reviewed alpha-blocker prescription trends from 1996 to 2002. Steady increases in alpha-blocker prescriptions were seen in between 1996 and 1999, but new prescriptions for the drugs declined 26% between 1999 and 2002. Changes in pricing, generic version, drug promotion, or competition did not have a confounding effect. The authors conclude that modest declines in alpha-blocker prescribing were seen after publication of ALLHAT (*JAMA*. 2004;291:54-62).

Alpha-Blockers Useful in BPH Treatment

Alpha-blockers are useful in treatment with benign prostatic hyperplasia (BPH). Now a new study shows that the combination of the 5-alpha-reductase inhibitor finasteride (Proscar) with an alpha-blocker may be superior to either drug alone in treating BPH. Researchers randomized 3047 men to placebo, doxazosin, finasteride, or combination therapy with the end point of clinical progression of BPH. Clinical progression was defined as an increase in the American Urologic Association symptom score of these 4 points, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection. Both doxazosin and finasteride significantly reduced clinical progression (doxazosin-39% risk reduction, $P < 0.001$; finasteride 34% risk reduction $P = 0.002$) compared to placebo. The combination of doxazosin and finasteride however resulted in a 66% risk reduction compared with placebo ($P < 0.001$). Mean follow-up was 4.5 years. The authors conclude that long-term combination therapy with doxazosin and finasteride was safe and significantly reduced the risk of clinical progression of BPH and was superior to either drug alone (*N Engl J Med*. 2003;349:2387-2398).

T4 Alone is OK for Hyperthyroidism Therapy

Hypothyroidism is one of the most common clinical disorders in general practice. Controversy about replacement therapy has raged for years regarding the need for liothyronine (T3) in addition to thyroxine (T4). A new study from Bethesda suggests that thyroxine alone is optimal therapy. In this randomized, double-blind, placebo-controlled trial, 46 hypothyroid patients were randomized to their usual dose of levothyroxine, or combination therapy in which their dose of levothyroxine was decreased by 50 µg/d, and liothyronine 7.5 µg was given twice daily for 4 months. TSH levels were followed and remained stable throughout the study. The main outcomes were scores on the hypothyroid specific health-related quality of life questionnaire, body weight, serum lipid levels, and 13 neuropsychological tests before and after treatment. After 4 months, body weight and serum lipid levels were unchanged in both groups. Quality of life scores improved in both groups (23% improvement levothyroxine group [$P < .001$], 12% improvement combination group [$P = .02$]). There is no statistical difference in neuropsychological testing between the 2 groups except for better performance in the Grooved Peg Board test in the levothyroxine group. The authors conclude combination therapy with levothyroxine plus liothyronine offers no advantage over single therapy with levothyroxine for the treatment of hypothyroidism (*JAMA*. 2003;290:2952-2958).

FDA Ban on Ephedra Awaits Final Ruling

The FDA has issued a consumer alert, banning the dietary supplement ephedra. The ban will become effective 60 days after the publication of a final rule stating that dietary supplements containing ephedra represents an unreasonable risk of illness or injury. This unprecedented move, the first time the FDA has banned a supplement, comes after several high-profile deaths linked with ephedra including professional athletes. Overall, the FDA has reports of 155 deaths associated with ephedra and more than 16,000 complaints. The drug is commonly used for weight loss and is present in many over-the-counter preparations. It is also widely used in Chinese herbal medicine practices, where it is known as Ma huang, and has been a staple of therapy for thousands of years for a variety of ailments including asthma and fever. The FDA has allowed an exemption for practitioners of Chinese medicine as long as is not used in high dose for weight loss. ■