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INSIDE

Parkinson's Disease—A New Mutation Leads to Potential New Insights Into Disease Pathogenesis

ABSTRACT & COMMENTARY

Synopsis: *The findings also support further investigations with agents, which may modify mitochondrial function, and exert antioxidative effects such as coenzyme Q10.*

Source: Valente EM, et al. Hereditary Early-Onset Parkinson's Disease Caused By Mutation in PINK1. *Science*. 2004:304:1158-1160.

PARKINSON'S DISEASE IS A PROGRESSIVE NEURODEGENERATIVE illness that affects about 1 million people in North America. Although environmental risk factors have received considerable attention, the importance of genetics to understanding susceptibility to Parkinson's disease is increasingly recognized. Familial forms of Parkinson's disease are rare, and account for less than 10% of cases. However, the identification of single gene mutations have led to new insights which have implicated both abnormal protein aggregation as well as oxidative damage in disease pathogenesis. The present report is that of a new form of hereditary early-onset autosomal recessive Parkinson's disease, which is caused by mutations in PINK1 (PTEN)-induced kinase 1. Valente and colleagues identified 2 homozygous mutations affecting the PINK1 kinase domain in 3 consanguineous PARK6 families. A truncating nonsense mutation and a missense mutation were found in a highly conserved amino acid. Valente et al demonstrated that PINK1 was localized to mitochondria, and that mutations in the kinase resulted in a reduction in mitochondrial membrane potential, as well as increased vulnerability to apoptosis induced by inhibitors of the proteasome. These findings are, therefore, the first direct evidence linking a nuclear encoded protein, which is localized to mitochondria to Parkinson's disease pathogenesis. These findings correlate with a large body of other evidence suggesting that mitochondrial dysfunction contributes to Parkinson's disease. The models of Parkinson's disease produced by MPTP and rotenone both specifically inhibit complex 1 activity of the electron transport gene.

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Genetic studies have also implicated oxidative stress in Parkinson's disease pathogenesis. Mutations in DJ-1 cause autosomal recessive early-onset Parkinson's disease. DJ-1 is a protein that participates in the oxidative stress response. Mutations in the protein render cells more vulnerable to oxidative damage. It is known that oxidative damage leads to crosslinking of proteins such as a-synuclein. A-Synuclein is both oxidatively modified as well as nitrated in Parkinson's disease. Dopamine can also generate the highly reactive dopamine quinones which can form adducts with proteins such as a-synuclein and crosslink them, facilitating their aggregation. Inhibition of complex 1 may also impair the ubiquitin proteasome protein degradation pathway by causing oxidative damage to proteins, perhaps including components of proteasomes.

COMMENTARY

Converging evidence implicates both protein aggregation as well as oxidative damage in mitochondrial dysfunction in Parkinson's disease pathogenesis. It is likely that these factors may interact. The discovery of the mutations in PINK1 provide further evidence that mitochondrial dysfunction might play a key role in disease pathogenesis. What the normal function of PINK1 is within mitochondria however, remains to be determined. It is not known what its substrates are or how it directly affects mitochondrial function. Nevertheless, the discovery of this mutation may lead to improved animal models, as well as novel insights into Parkinson's disease pathogenesis. The findings also support further investigations with agents, which may modify mitochondrial function, and exert antioxidative effects such as coenzyme Q10. — **M. FLINT BEAL**

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What's the Cause of Normal Aging?—Part 2

ABSTRACT & COMMENTARY

Synopsis: *These findings are amongst the most direct data to date that oxidative damage plays a critical role in normal human aging.*

Source: Lu T, et al. Gene Regulation and DNA Damage in the Aging Human Brain. *Nature.* 2004;429(6994):883-891.

In the present report, Lu and colleagues examined postmortem frontal cortex samples taken from normal donors 26-106 years of age. They analyzed 30 samples in all, with Affeymatrix gene arrays, to determine how gene expression changed with age. Compared with people younger than 42, Lu et al found that in people older than 76, about 4% of the genes were differentially expressed in the frontal cortex. Many of these were downregulated, including genes involved in synaptic plasticity, long-term potentiation, and microtubular function. Another group of genes which were downregulated were those involved in mitochondrial function. Genes, which were upregulated included chaperones, antioxidant enzymes, and DNA repair genes.

Due to the induction of DNA repair mechanisms, Lu et al examined whether the gene expression changes were tied to DNA damage. They isolated genomic DNA under conditions to prevent in vitro oxidation and incubated it with enzymes that specifically excised damaged bases, particularly 8-oxoguanine. In using real time polymerase chain reaction, they were able to identify and quantify stretches of damaged DNA by their failure to amplify. Lu et al found that there was increased DNA damage in the genes, which were downregulated. This was particularly true in the promoter regions. This may be the case since they are not subject to transcription coupled repair, the major repair mechanism in neurons. Of 30 promoters examined, many showed an age-related

increase in DNA damage by age 40, and all genes showed damage by 70. Lu et al then examined the effects of direct oxidative damage to the promoter regions in cultured human neuroblastoma cells in primary human cortical neurons treated for their mild oxidative stress. Again, they found that the genes that were downregulated in aging were damaged to a greater extent than genes that did not change in aged brain. Lastly, they examined whether a reduction in expression of some mitochondrial genes, that Lu et al observed in the aging brain, could induce DNA damage. They found that the decreases in the expression of these genes using siRNA, created oxidative damage to DNA.

COMMENTARY

These findings are amongst the most direct data to date that oxidative damage plays a critical role in normal human aging. — **M. FLINT BEAL**

US Map of Deaths from Stroke in Children Similar to that Seen for Adults

ABSTRACT & COMMENTARY

Synopsis: *In the case of this paper, the impact reaches beyond pediatrics, and makes implications about potential contributing factors to adult stroke mortality as well.*

Source: Fullerton HJ, et al. Pediatric Stroke Belt: Geographic Variation in Stroke Mortality in US Children. *Stroke*. 2004;35(7):1570-1573.

For approximately the past half century, it has been noted that adults, both black and white, living in the Southeastern United States, had an excess stroke mortality, relative to those living in other areas of the country. The region has thus been dubbed the "Stroke Belt". This excess mortality has been variably attributed to 1, or a combination of, risk factors, particularly dietary fat intake and hypertension, but these seem to explain only part of the story. The current study was undertaken to help elucidate whether other variables, particularly those that are not considered traditional atherosclerotic stroke risk factors, might contribute. Fullerton and colleagues evaluated the geographic variation in stroke mortality in children, a population for whom hypertension, smoking, hypercholesterolemia, etc, have been shown to play little part in stroke risk. Given this, pediatric stroke mortality should not cluster geographically, as does that of adults, unless factors aside from these are at play.

Using the National Center for Health Statistics' death certificate data, for both ischemic infarct and hemorrhage similar to those used in earlier adult studies, Fullerton et al evaluated the rates of death from childhood stroke throughout the United States from 1979 to 1998. They found that children in the Stroke Belt did have an increased relative risk (RR) of death from stroke when compared to their peers in other portions of the country (RR, 1.21, 95% CI, 1.12-1.29; $P < 0.0001$; similar to the RR of 1.20 in adults).

Some of the increased mortality risk could be accounted for by race. However, even after adjustment for ethnicity, the relative risk in the Stroke Belt remained significantly elevated in white children (RR, 1.10, CI, 1.01-1.19, $P = 0.03$) and trended toward significance in blacks (RR, 1.12, CI, 0.99-1.27, $P = 0.07$). The increased risk occurred at all ages from infancy through late adolescence, and as in adults, applied to both genders.

Fullerton et al conclude that their findings support the hypothesis that the disproportionately high risk of death from stroke seen in the Southeastern area of the United States must be caused by mechanisms common to both ischemic and hemorrhagic stroke, and that are in effect throughout life from infancy to adulthood. The underlying risk factors causing this Stroke Belt may do so by contributing to either an increased incidence and/or an increased case fatality rate. As atherosclerotic stroke risk factors (smoking, hypertension, etc) have been shown not to play a significant etiologic role in pediatric stroke on the population level, they are unlikely to be a significant cause of the Stroke Belt. Fullerton et al also point out that there is evidence in the literature suggesting that those born in the Stroke Belt region are at higher risk than those who move into the region from elsewhere. Thus it is the location of ones birth, rather than that of the community in which one is reared, that is more strongly associated with one's geographic stroke mortality risk.

Whether these cryptic risk factors reflect any environmental factors, and if so which, remains to be elucidated. Fullerton et al point out that the Stroke Belt is shifting westward, prompting others to suggest that environmental factors are an unlikely explanation for the existence of a Stroke Belt. Indeed, several studies have shown that in recent years this concentration of stroke deaths has dissipated somewhat in the deep South, but

has spread westward across the Mississippi to encompass much of the KS/OK/TX region, and has even skipped to include non-adjacent regions such as the Pacific Northwest. Certainly, changes in contaminants caused by changes in regional industry, environmental policies, or geographic movement of infectious agents, could cause slow shifts such as these, as could socioeconomic factors and changes in access to and quality of health care, among other factors.

COMMENTARY

This is the latest of several important publications by Dr. Fullerton and her colleagues, at The University of California at San Francisco, describing details of the epidemiology of pediatric stroke during the last 2 decades of the 20th century. This body of work is a welcome contribution to the underserved and important field of pediatric neurovascular medicine. In the case of this paper, the impact reaches beyond pediatrics and makes implications about potential contributing factors to adult stroke mortality as well. — **SUSAN E. SNYDER**

Susan E. Snyder, MD, Phd, is a resident of Pediatric Neurology at New York Presbyterian Hospital, Cornell Campus.

New Concern About Old Drugs

ABSTRACTS & COMMENTARY

Synopsis: *These papers and the accompanying editorial by Rascol bring attention to a known but under-recognized complication of ergot derivatives.*

Sources: Rascol O, et al.New Concerns About Old Drugs: Valvular Heart Disease On Ergot Derivative Dopamine Agonists as an Exemplary Situation of Pharmacovigilance. *Mov Disord.* 2004;19:611-613; Horvath J, et al. Severe Multivalvular Heart Disease: A New Complication of the Ergot Derivative Dopamine Agonists. *Mov Disord.* 2004;19:656-662; Agarwal P, et al. Diagnosis and Management of Pergolide-induced Fibrosis. *Mov Disord.* 2004;19:699-704.

THE ERGOT DOPAMINE AGONIST PERGOLIDE MESYLATE is commonly prescribed to treat Parkinson's disease and restless leg syndrome. Like its ergot-agonist cousins, parlodel and cabergoline, anti-migraine ergots ergotamine and methysergide, and the appetite suppressants fenfluramine and dexfenfluramine, rare cases of retroperitoneal or pleural fibrosis have been reported following exposure. Cases of fenfluramine-induced valvulopathy generated intense media scrutiny, ultimately leading to the removal of these diet drugs from the market.

The current papers, all contained within the June issue of *Movement Disorders*, address ergot-agonist induced fibrosis affecting retroperitoneal, pleural, and cardiac valvular structures. Horvath and colleagues report 4 Parkinson's disease patients, 3 treated with pergolide and 1 with cabergoline. All 4 developed multivalvular heart disease after treatment that ranged from 16 months to 5 years. The doses of agonist employed were high but not outside the recommended limits. Thickening and leaflet retraction of the tricuspid and mitral valve were documented by echocardiography in all cases, and pathologic examination in 1 patient revealed typical ergot-induced fibrotic valvular degeneration. Two patients who discontinued the drug experienced marked improvement in their echocardiograms.

The second paper, authored by members of the Columbia University Movement Disorders Group, reports 2 patients treated with pergolide, 1 of whom developed retroperitoneal fibrosis and the other pleural fibrosis. Comparison of these cases to 24 other reported cases in the literature revealed several important trends. Patients developed fibrotic complications on a wide range of pergolide doses, from 1 mg/d to 7 mg/d, after receiving the drug for 11 months to 8 years. In at least 6 patients, the erythrocyte sedimentation rate was elevated from 40 to 127 mm/h. Chest radiographs were abnormal in most patients with pulmonary fibrosis, and abdominal CT was abnormal in patients with retroperitoneal fibrosis. Four patients received steroids, with dramatic improvement in fibrosis within weeks.

COMMENTARY

These papers, and the accompanying editorial by Rascol, bring attention to a known but under-recognized complication of ergot derivatives. Beyond the obvious medico-legal implications, the principle questions facing neurologists are as follows: Should patients taking ergots be screened for this rare complication with imaging studies? If so, which imaging studies are appropriate (echocardiogram vs CT scan);[1] can patients be safely treated with these drugs as long as appropriate surveillance takes place?; or should these drugs be removed from the armamentarium?

As described in the editorial, there are no ready answers for these questions. For patients with Parkinson's disease or restless leg syndrome, the decision to begin or continue pergolide must be tempered by the

fact that there are other treatments that are available that do not appear to incur this risk (pramipexole, ropinirole, levodopa, etc). Unless a patient cannot tolerate these other alternatives, it is currently our practice to switch patients from pergolide to another drug. Screening for asymptomatic patients exposed to pergolide is a more difficult issue, complicated by the fact that many patients will not have had a pre-treatment echocardiogram for comparison. Screening tests should be ordered in patients who develop new symptoms that might suggest a fibrotic process, and the drug should be immediately discontinued. A course of steroids seems reasonable before embarking on a resection or valve replacement. In those patients who decide to continue the drug, serial imaging is warranted. — **STEVEN FRUCHT**

Stroke Prevention Strategies Are Successful

ABSTRACTS & COMMENTARY

Synopsis: *The good news from OXVS is that community-wide risk factor modifications and preventive treatment are worth the effort, and that further reductions in stroke incidence are possible with more widespread stroke prevention programs.*

Sources: Rothwell PM, et al. Change in Stroke Incidence, Mortality, Case-Fatality, Severity, and Risk Factors in Oxfordshire, UK From 1981 to 2004 (Oxford Vascular Study). *Lancet.* 2004;363:1925-1933. Feigin V, et al. How to Study Stroke Incidence. *Lancet.* 2004;363:1920-1921.

ROTHWELL AND ASSOCIATES SOUGHT TO DETERmine whether implementation of preventive strategies in an aging population can offset the predicted rise in stroke incidence. They reported a population-based incidence study of Transient Ischemic Attack (TIA) and stroke that analyzed changes in rates, outcomes, and risk factors in Oxfordshire, United Kingdom over 20 years. They compared the results of the Oxfordshire Community Stroke Project[1,2] (OCSP) of 1981-1984 with the present findings in the same community of the Oxford Vascular Study (OXVASC) of 2002-2004.

In OXVASC there were 476 patients with stroke or TIA, of which 262 strokes and 93 TIAs were initial events. Compared to the OCSP data, age-adjusted and sex-adjusted incidence of first-ever stroke fell by almost one-third; for primary intracerebral hemorrhage, incidence declined by more than one-half, but for subarachnoid hemorrhage, incidence was unchanged. Although 28% more initial strokes were expected in 2002-2004, compared to 1981-1984 due to demographic changes, namely a 33% increase in those aged 75 or older, the observed number fell (262 vs 286).

The incidence of disabling or fatal stroke declined, but there was no change in the core fatality rate (17.2% vs 17.8%). Age- and sex-adjusted relative risk did not change. Comparison of premorbid risk factors revealed substantial decreases in the proportion of smokers, mean total cholesterol, and mean systolic and diastolic blood pressures. In contrast, there were major increases in premorbid treatment with antiplatelet, antihypertensive, and lipid-lowering drugs.

COMMENTARY

Dr. Rothwell, with his associate Dr. Warlow, previously analyzed the heterogeneity of the effect of endarterectomy in the European Carotid Surgery Trial (ECST) population.[3,4] The result was a predictive model that allowed clinicians to stratify patients according to risk of stroke and likelihood of surgical complications.

In editorial comments, Feigin and Vander Hoorn characterize Rothwell and associates' present report as a "state-of-the-art" study that makes an important contribution to knowledge about the epidemiology of stroke. Above all, Rothwell et al provide welcome evidence that preventive strategies can reduce the incidence of stroke at the community level. Although Rothwell et al did not prove that the decline in stroke incidence was a direct result of changes in stroke risk factors, the size of the changes is consistent with such an effect. Furthermore, the measured increase in the use of preventive medications would be expected to produce a significant reduction in stroke incidence.

Rothwell et al noted a decline in the incidence of major stroke and incident fatal stroke but not in the case fatality of incident stroke. This finding can be explained by the fact that despite all the recent advances in acute stroke management, only 56% of acute stroke patients in Oxfordshire were hospitalized, and those who were admitted to hospital, were not cared for in dedicated stroke units.

Nevertheless, the good news from OXVS is that community-wide risk factor modifications and preventive treatments are worth the effort, and that further reductions in stroke incidence are possible with more widespread stroke prevention programs. — **JOHN J. CARONNA**

References

1. Bamford J, et al. *J Neurol Neurosurg Psychiatry.* 1990;53:16-22.

2. Dennis MS, et al. *Stroke.* 1989;20:333-339.
3. Rothwell PM, et al. *Lancet.* 1999;353:2105-2110.
4. *Neurology Alert.* 1999;17:93-94.

Transient Global Amnesia: Unlocking an Ischemic Etiology

ABSTRACT & COMMENTARY

Synopsis: *Treatment of TGA patients with antiplatelet treatment is likely warranted, particularly if there are underlying vascular risk factors.*

Source: Sedlaczek O, et al. Detection of Delayed Focal MR Changes in the Lateral Hippocampus in Transient Global Amnesia. *Neurology.* 2004:62:2165-3170.

Transient global amnesia (TGA) presents with acute and profound memory loss, but is nevertheless a benign condition that generally does not recur. It has been postulated that TGA may be explained by hippocampal venous congestion, occurring during valsalva maneuver, sexual activity, or excessive exercise. Ischemic lesions in the hippocampus have been demonstrated inconsistently on MRI with diffusion-weighted imaging (DWI), with the majority of reports showing negative findings. In the study of Sedlaczek and colleagues, using sequential DWI imaging, a much higher frequency of hippocampal ischemic lesions is demonstrated in individuals with images delayed 24-48 hours after symptom onset.

In 26 of 31 cases, small DWI-positive hippocampal lesions were observed on 48 hour scans. In 23 cases, there was a corresponding reduction in the absolute diffusion coefficient (ADC), confirming an ischemic etiology. Lesions were left sided in 15, with 6 right and 5 bilateral. Scans at 24 hours showed the lesion in 23 patients, but 11 of these could only be seen retrospectively. Hyperacute scans showed a lesion in only 2 patients. None of the scans showed signs consistent with venous stasis or thrombosis.

An embolic etiology could only be identified in one-fourth of patients, while 50% had more than 1 vascular risk factor. Sedlaczek et al identify a "watershed zone" within the hippocampal blood supply where the superior and inferior hippocampal arteries meet. This area corresponds to the CA1 sector of Sommer, which is the most susceptible portion of the hippocampus to O_2 deprivation. Sedlaczek et al postulate that high metabolic demand, such as during exercise, might produce hypoperfusion in patients with existing microvascular changes in this region.

COMMENTARY

There have been many postulated, and unconfirmed, etiologies for TGA including migraine, seizure, and transient ischemic attack (TIA). These data suggest that TIA may be the most compelling of these theories. It has been well documented that DWI imaging may be positive in TIA, even when neurologic symptoms are fleeting. Many questions still remain unanswered however. Why do TGA associated DWI abnormalities appear on delayed but not hyperacute MRI scans? If there is truly an underlying vascular abnormality, why doesn't TGA recur more frequently in susceptible individuals? As suggested in the editorial accompanying Sedlaczek's report, treatment of TGA patients with antiplatelet treatment is likely warranted, particularly if there are underlying vascular risk factors. — **ALAN Z. SEGAL**

Lidocaine Patch for Diabetic Neuropathy

ABSTRACT & COMMENTARY

Synopsis: *Evidence suggests that Erythropoietin acts by stimulating neuroprotective pathways, including the protein kinase B cascade and the transcription factor nuclear factor-kB pathway, to activate antiapoptotic and antioxidant factors.*

Source: Barbano RL, et al. Effectiveness, Tolerability, and Impact on Quality of Life of the 5% Lidocaine Patch in Diabetic Neuropathy. *Arch Neurol.* 2004;61:914-918.

Fifty-six patients with painful diabetic neuropathy of at least 3 months duration, volunteered for this open-label, flexible-dosing, 3-week study evaluating the effectiveness and tolerability of the 5% lidocaine patch. All patients rated their average daily pain as at least 4 out of 10 on the Brief Pain Inventory (BPI), were on a stable analgesic regimen for at least 1 week prior to the baseline visit, and demonstrated hemoglobin A1C less than 13. Exclusionary criteria included any other concomitant more painful condition, open skin lesions interfering with placement of the lidocaine patch, prior treat-

ment with, or allergy to, topical lidocaine, alcoholism, suicide attempts or intent, and treatment with class 1 anti-arrhythmic agents. Treatment allowed for up to 4 patches to be placed over the entire painful area, if possible, for 18 hours of the day, with 6 hours off, for a period of 3 weeks. Evaluations included daily patient Brief Pain Inventory (BPI) ratings, short-form McGill Pain Questionnaires (MPQ), sleep quality assessments, Beck Depression Inventory scores, and Profile of Mood States mood scores. Change in mean-daily-pain diary rating was the primary outcome measure, with secondary outcome measures including the BPI, MPQ, quality of life, and safety and tolerability. Statistical analysis used a 2-way, repeated-measures analysis of variance and the McNemarr test, with $P < 0.05$ considered significant.

Significant improvement was seen in both primary and secondary outcome measures. Thirty-seven patients (66%) achieved at least 30% pain reduction over 3 weeks, 23 (41%) appreciating greater than 50% pain reduction. Sleep quality, BPI rating, Beck Depression Inventory scores, and Profile of Mood-States mood scores also improved. Among 28 patients treated an additional 5 weeks, 3 were able to completely discontinue concomitant analgesic medication (gabapentin, amitriptyline) and 4 maintained reduced dosage. Pain or burning at the application site was the only adverse effect deemed related to the study drug, and no systemic adverse events were reported. Painful diabetic neuropathy responded to the 5% lidocaine patch in this flexible-dosing, open-label study. Controlled trials are warranted to confirm this result.

COMMENTARY

Given the limited success of available treatments for painful diabetic neuropathy, newer agents are ever being sought. Erythropoietin, a renal cytokine crucial to erythropoiesis, is also produced in the nervous system, possibly functioning as a neuroprotective agent. In streptozocin-induced diabetic rats, intra-peritoneal administration of erythropoietin has recently been shown to protect from, and reverse, experimental diabetic neuropathy, improving nerve conduction velocity, motor evoked potentials, Na/K ATPase activity, and pain thresholds, while preventing cutaneous nerve fiber loss (*Proc Natl Acad Sci USA*. 2004;101;823-828). What can it do for man? Evidence suggests that it acts by stimulating neuroprotective pathways, including the protein kinase B cascade and the transcription factor nuclear factor-kB pathway, to activate antiapoptotic and antioxidant factors (*N Engl J Med.* 2004;350;2516-2517). Human clinical trials should begin forthwith. We impatiently await the results. — **MICHAEL RUBIN**

Leflunomide Peripheral Neuropathy

ABSTRACT & COMMENTARY

Synopsis: *Leflunomide's immunomodulatory activity derives from its action as a competitive inhibitor of the rate-limiting enzyme necessary for pyrimidine synthesis.*

Source: Bonnel RA, et al. Peripheral Neuropathy in Patients Treated With Leflunomide. *Clin Pharmacol Ther.* 2004;75:580-585.

Following its FDA approval and marketing release for rheumatoid arthritis (RA) in 1998, leflunomide has been associated with 80 cases of new onset-peripheral neuropathy. Most patients were treated for RA (n = 57) but also included were those with psoriatic arthritis (n = 2), undifferentiated connective tissue disease, dermatomyositis, or polyarthritis (n = 1, each), as well as 18 with unstated disease. Sixteen patients had other risk factors for neuropathy, including diabetes, prior chemotherapy known to be associated with neuropathy (cisplatin, chloroquine, isoniazid), spinal stenosis, or hypothyroidism. Daily dose never exceeded the recommended range of 10-20 mg. Symptoms began 3 to 1126 days following onset of therapy and included distal numbness, tingling, burning, cold, or weakness. Onset did not correlate with age, gender, or dose. Electrodiagnostic studies, reported in 46% (n = 37) indicated axonopathy (n = 12), demyelinating, or mixed neuropathy (n = 2 each). Sensory neuropathy was the predominant feature in 13, with sensorimotor neuropathy documented in 9 and motor neuropathy in 1. Sural nerve biopsy performed in a single patient showed only axonal loss without vasculitis. Improvement or recovery followed medication withdrawal and occurred more rapidly when medication was stopped within, rather than beyond, 30 days of symptom onset (median time, 135 days vs 755 days, respectively), but was not associated with age, sex, daily dose, or duration of treatment. Post-marketing analysis has revealed an adverse event with leflunomide not reported among the 816 patients involved in its pre-marketing clinical trial. In this event,

neurologists should be forewarned and should recommend immediate discontinuation of the medication.

COMMENTARY

Leflunomide's immunomodulatory activity derives from its action as a competitive inhibitor of the rate-limiting enzyme necessary for pyrimidine synthesis. This activity has similar efficacy to, and complements, the anti-purine synthesis effect of methotrexate, resulting in potentially additive anti-proliferative activity and benefit in rheumatoid arthritis. A77 1726, the active metabolite of leflunomide, accounts for 95% of drug levels in the blood, is highly protein bound, and has a half-life of 15 to 18 days, requiring up to 2 months to achieve steady-state levels. Enterohepatic recirculation further enables drug levels to be detected even 2 years after discontinuation of treatment.

Hepatotoxicity is the most serious adverse effect, with 5% demonstrating elevated liver enzymes, usually less than twice the normal. However, 15 deaths have resulted from hepatic failure or associated illness, leflunomide being possibly implicated in 10. Weight loss, diarrhea, hypertension, alopecia, pancytopenia, and interstitial pneumonitis are also reported. Peripheral neuropathy now must also be added to the list. Its etiopathogenesis remains unknown but vigilance is warranted (*N Engl J Med* 2004;350:2167-2179). — **MICHAEL RUBIN**

CME QUESTIONS

6. **Side effects of the new anti-rheumatoid arthritis drug, leflunomide, include**
   a. weight loss and diarrhea
   b. hypertension
   c. pancytopenia
   d. peripheral neuropathy
   e. All the above

7. **The Oxford Vascular Study results indicate that treatment can reduce the incidence of all of the following except:**
   a. any ischemic stroke.
   b. fatal stroke.
   c. cerebral hemorrhage.
   d. subarachnoid hemorrhage.

8. **Treatment for painful diabetic neuropathy at this time includes all the following except**
   a. gabapentin
   b. amitriptyline
   c. 5% lidocaine patch
   d. erythropoietin
   e. all the above may be used

Answers: 6. (e); 7. (d); 8. (d)

In Future Issues:

Pregnancy and Multiple Sclerosis: Predictors of Postpartum