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Two Novel Neuroprotective Agents May Offer Promise for Acute Ischemic Stroke

ABSTRACTS & COMMENTARY

Sources: Paul R, et al. Src deficiency or blockade of Src activity in mice provides cerebral protection following stroke. *Nat Med* 2001;7:222-227. Marshall JW, et al. NXY-059, a free radical-trapping agent, substantially lessens the functional disability resulting from cerebral ischemia in a primate species. *Stroke* 2001;32:190-198.

Despite extensive promising data in animal research, no drug has shown benefit in humans as a neuroprotective agent in an evolving acute ischemic stroke. The experiments by Paul and colleagues, but less by Marshall and colleagues, represent important and encouraging departures from these previously failed treatment strategies. In the first report, Paul et al studied PP1, in mice, a drug that dampens the early edema and microvascular compression that accompanies the beginning abnormalities of acute stroke. The second study reports that NXY-059, a free radical spin trap agent, reduces both infarct size and clinical morbidity from stroke. Marshall et al used a primate rather than a rodent stroke model.

The brain produces vascular endothelial growth factor (VEGF) in response to ischemia and promotes vascular permeability with both cytotoxic and vasogenic brain edema. This process is mediated by the Src kinases, a family of enzymes that regulate VEGF induced vasoreactivity. Paul et al demonstrate that mice lacking the pp60 (Src) gene develop reduced infarct volumes compared to wild-type animals subjected to middle cerebral artery (MCA) occlusion. Paul et al further show that application of a Src inhibitor (PP1) reduces infarct volumes by about 70% when delivered 15 minutes after stroke. When administered up to six hours after stroke, smaller, but still impressive, 40% reductions in stroke size developed. Stroke volumes measured histologically were confirmed by MRI and clinical scales. Perhaps more importantly, mice treated with PP1 showed improved cerebral blood flow. As Paul et al and Marshall et al indicate, by inhibiting VEGF induced brain edema, PP1 likely decreased extrinsic compression of surrounding microvasculature, thereby permitting more robust flow and oxygen supply into the peri-infarct ischemic penumbra.

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Presently established approaches to the treatment of acute stroke involve either restoration of blood flow, such as with intravenous or intra-arterial tPA, or aim at neuroprotection involving agents to mitigate glutamate or NMDA receptor-associated excitotoxic cell death. PP1 represents a hybrid of these strategies, in that it reduces VEGF-associated osmotic edema and facilitates blood flow, but works on a cellular or microvascular, rather than a macrovascular, level. As such, it might extend the therapeutic window, and be helpful at time points substantially later than existing "neuroprotective" agents. Whereas the cascade of excitotic cell death may normally become irreversible after the first minutes following stroke, this novel dynamic process of edema and microvascular compression may either ameliorate the injury for six hours or even permanently reduce the size of the infarction.

It is well recognized that free radical production plays a major role in cerebral ischemia. Unfortunately, prior agents, such as Trilazad, a free radical scavenger, have failed to achieve benefit in human trials. NXY-059 and other agents known as free radical spin traps, function by a different mechanism than Trilazad. Many have shown promising data on rodent trials but not at the bedside.

Marshall et al uniquely studied NXY-059, a novel nitrone with radical-trapping properties that provide neuroprotective effects in rodents. They have now tested the agent in a MCA occlusion model of 12 marmoset monkeys. The drug was given five minutes after permanently occluding the right MCA in a dose known to be tolerable in humans. Treated monkeys showed better functional activity with their hemiparetic arm at three and 10 weeks following stroke. Even more importantly, cognitive abnormalities, such as visual-spatial dysfunction and hemineglect, improved markedly in treated animals compared with controls. Animals were asked to locate food in tubes aligned in front of them from left to right, or to reach through slots in plexiglass screens oriented toward the left, right, above, or below. On pathological study, volumes of stroke were reduced by 50% compared to controls. This occurred in both gray and white matter compartments.

As Marshall et al indicate, the drug was given immediately after stroke onset in order to establish efficacy in this primate model, rather than to prove a therapeutic window. Extensive rodent experiments have suggested that NXY-059 is effective up to five hours after stroke onset, although this may not be completely reliable extrapolated to monkeys or to humans.

If monkeys can be tested with much more sophisticated behavioral algorithms than can rodents, drug effects come much more closely to human experience in terms of the challenges faced when rehabilitating from stroke. Also interesting is that NXY-059 was protective for both gray matter (neurons) and white matter (axons). As Paul et al and Marshall et al indicate, even the most promising prior agents based on animal models have shown marked selectivity for the cerebral cortex without providing any benefit for the white matter. Human strokes are heterogeneous, affecting not only the cortex, but also subcortical white matter or deep tracts within the internal capsule and brainstem. NXY-059 may or may not, therefore, act more globally within the brain, targeting a wider variety of brain structures.

These two reports focus on finally ameliorating the post-injury size of acute cerebral infarctions due to sudden cerebral arterial thrombi or emboli. Thrombotic ischemia, depending on size of the artery and its immediately adjacent oxygen-deprived tissue, creates, within a matter of minutes, the beginning of severe pericapillary anoxia. This progressively injures capillary ependema and invokes increased osmols as surrounding cells explode into smaller molecules. Like a slow circular ripple from a relatively small ischemic center, the process swells and steadily squeezes the enlarging penumbral zone of the beginning, relatively small, infarct. For the next 48 hours or more, the ultimate damage becomes

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ever larger than the initial artery's region of supply simply because of the unyielding adjacent tissue, dural mater, and skull. Both these abstracts approach this physiological enemy of osmotic swelling and one may turn out to have considerable reduction of brain damage due to cerebral thrombosis.

Having said the above, however, the Marshall et al report possesses a serious fault. Namely, they applied their therapeutic agent within five minutes after clamping the middle cerebral artery of their monkeys. Many claims for success in stroke are based on giving animals various forms of pharmacological agents before or within a few minutes after onset. All but tPA have failed. It seems regrettable to use monkeys for an experiment that fails to provide a significant protocol that can change clinical therapy. **—alan segal**

Primary Prevention of Stroke: Fish and Aspirin Work, Vitamin E Doesn't

ABSTRACTS & COMMENTARY

Sources: Iso H, et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. *JAMA* 2001;285:304-312. Collaborative Group of the Primary Prevention Project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: A randomized trial in general practice. *Lancet* 2001; 357:89-95.

These two studies addressed the question of primary prevention of stroke and heart disease. In the first, a prospective cohort study of women in the Nurses' Health Study, almost 80,000 women aged 34-59 years in 1980 were followed up for 14 years. Women in the study were free of diagnosed heart disease, cancer, diabetes, and hypercholesterolemia, and completed a food frequency questionnaire.

Women in the study experienced 574 documented strokes, including 119 subarachnoid hemorrhages, and 62 intraparencymal bleeds. There were 303 ischemic strokes of which 264 were thrombotic (90 large-artery occlusive infarctions and 142 lacunes); 39 were embolic, and 90 were of undetermined type.

The risk of thrombotic stroke was significantly reduced by 48% among women who ate fish two to four times a week. There was no excess risk of hemorrhagic stroke with fish intake.

An inverse relationship appeared between intake of omega-3 fatty acids (fish oil) and risk of all types of stroke. Risk reduction was of borderline statistical significance for thrombotic stroke and statistically significant for lacunar infarction. Women with a high intake of omega-3 fatty acids (e.g., 15g/d of eicoapentanenoic acid) who did not use aspirin had a significant 49% reduction in risk of thrombotic stroke. The mechanism of protection may have been the action of high doses of omega-3 fatty acids to reduce blood pressure and to reduce the formation of thromboxane A2 in platelets but not the synthesis of prostaglandin I2 in vascular endothelium.

The Primary Prevention Project was a randomized, open-label clinical trial designed to test whether chronic treatment with low-dose aspirin (100 mg/d) and vitamin E (300 mg/d) reduces the frequency of major cardiovascular and cerebrovascular events. There were more than 4000 participants (57% women) aged 50 years or older (mean age 64 years) with at least one major risk factor for vascular disease. After 3.6 years the trial was stopped on the basis of evidence of an aspirin benefit in primary prevention of cardiovascular disease reported by two large trials (MRC General Practice Research Framework. *Lancet* 1998; 351:233-241. Hansson L, et al. *Lancet* 1998;351: 1755-1762). Aspirin significantly lowered the risk both for cardiovascular death by 44% and for any cardiovascular event (myocardial infarction, stroke, TIA, angina pectoris, peripheral artery disease, and revascularization procedure) by 23%. There was no major difference in type or severity of stroke between the two groups. For example, two of 16 strokes in the aspirin group and three of 24 strokes in the no aspirin group were hemorrhagic.

Bleeding complications were significantly higher in the aspirin group (1.1% vs 0.3%) but three of the four deaths caused by hemorrhage occurred in the no aspirin group.

Vitamin E showed no effect on any end point.

COMMENTARY

The Nurses' Health Study data indicate that higher consumption of fish and omega-3 polyunsaturated fatty acids reduced the risk for thrombotic stroke primarily among women not taking aspirin regularly. However, it did not increase the risk for hemorrhagic stroke. The PPD study showed that low-dose enteric coated aspirin had a protective effect in subjects with one or more cardiovascular risk factors. The fact that more than half of the patients in this series were women makes the results even more noteworthy. The higher bleeding complications in the aspirin group highlights the dangers of even low-dose coated aspirin taken chronically. This study

like a recent randomized clinical trial (The Heath Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:154-160) failed to find any beneficial effect of vitamin E.

These results enable physicians to make evidence-based recommendations to their patients with regard to diet modification and aspirin therapy for the primary prevention of cardiovascular events. **—john j. caronna**

The Short-Term Prognosis of TIA in the ED

ABSTRACT & COMMENTARY

Source: Johnston SC, et al. Short-term prognosis after emergency department diagnosis of TIA. *JAMA* 2000;284: 2901-2906.

The evaluation and treatment of patients with acute transient ischemic attacks (TIA) is variable depending upon the clinical judgement of the physicians involved. Some clinicians routinely hospitalize all TIA patients while others proceed with an outpatient evaluation. Johnston and colleagues sought to define the 90-day prognosis and risk factors for stroke after TIA in order to determine which patients needed urgent evaluation and therapy.

They studied more than 1700 patients (mean age 72) identified as having a TIA by Emergency Department (ED) physicians. Patients were followed for 90 days after presentation. Strokes, TIA, deaths, and hospitalizations for cardiovascular events were identified. Within 90 days of TIA presentation, strokes occurred in 180 patients (11%), more than half of which occurred during the first two days. Strokes were disabling in 64% and fatal in 21% of the patients.

The following factors were independently associated with an increased risk of stroke in univariate analysis: age older than 60 years, diabetes mellitus, symptom duration longer than 10 minutes, weakness or gait disturbance, and speech impairment. Symptoms of numbness were associated with reduced risk and medications taken prior to TIA did not influence prognosis. When analysis was limited to 918 patients who were not previously taking an anticoagulant or antiplatelet agent, those who initiated antiplatelet therapy (n = 775) tended to have a lower stroke risk than those not receiving prophylactic medication (n = 143) (9% vs 13%; *P* = NS). Stroke or other adverse events occurred in 25% of patients within 90 days of the index TIA and included recurrent TIA (13%), death (3%), and cardiovascular event (3%). More than 50% of adverse events occurred within the first four days.

COMMENTARY

The short-term risk of stroke and other adverse events among patients presenting to the ED with acute TIA was significant. The TIAs in this study are notable because they were both long (mean symptom duration was 207 minutes) and acute (half of the patients were symptomatic on arrival in the ED). The timing of presentation after TIA was important since more than half of strokes occurred within two days of the index TIA. This means that a patient evaluated more than two days after a TIA has already passed through the period of greatest stroke risk.

Treatment did not seem to matter much before or after TIA: patients presented with TIA who were taking prophylactic antiplatelet or anticoagulant medications, and post TIA initiated these same medications did not reduce stroke risk significantly. The present study, however, was observational and should not be used to provide data on the efficacy of medical therapies.

Johnston et al have identified risk factors that stratify TIA patients into subgroups with a low and a high short-term risk of stroke. Clinicians will find these useful in practice to select patients for acute stroke prevention interventions. **—john j. caronna**

Rivastigmine Beneficial in Dementia with Lewy bodies

ABSTRACT & COMMENTARY

Source: McKeith I, et al. Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study. *Lancet* 2000;356:2031-2036.

Dementia with lewy bodies (dlb) is considered to be the second most common form of neurodegenerative dementia after Alzheimer's disease. DLB presents in many cases with fluctuating cognitive status, parkinsonism without tremor, delusions, and/or hallucinations. It also expresses increased sensitivity to extrapyramidal side effects of neuroleptics. As yet, no medication has been specifically approved in the United States for the treatment of this condition. Over the past several years, a handful of case series and an open-label trial in Great Britain have suggested that some patients with DLB may respond to treatment with acetylcholinesterase inhibitors. Now, the first

randomized, double-blind, placebo-controlled trial of a cholinesterase inhibitor (rivastigmine) to treat DLB has been completed, with positive results.

The 23-week clinical trial involved 120 DLB patients from the United Kingdom, Spain, and Italy with mild to moderately severe dementia (MMSE > 9). The mean age of the test population was 73.9 years, with slightly more males (57%) than females. Rivastigmine 6-12 mg/d or placebo was administered over 20 weeks, followed by a three-week washout period. The primary outcome measure was scores on the Neuropsychiatric Inventory (NPI), which assesses behavioral disturbances in multiple domains based on caregiver reports. Another primary outcome was the speed of response to certain tests in a computerized cognitive assessment battery. Secondary outcome measures included clinician assessments, Mini-mental scores, and performance on various neuropsychological tests. Changes in motor function were assessed with the United Parkinson's Disease Rating Scale.

Patients treated with rivastigmine improved both in their reaction time and their behavior as measured by the NPI. Rivastigmine-treated patients tended to respond faster on neuropsychological tests than their counterparts in the placebo group, particularly on tests requiring a greater attentional component. The domains of the NPI that showed the greatest response to rivastigmine were apathy, anxiety, hallucinations, and delusions. There was a higher incidence of side effects in the rivastigmine-treated group, with gastrointestinal upset being the most common adverse occurrence. Three patients in the rivastigmine-treated group and none in the placebo group developed worsened agitation after treatment. Three weeks after discontinuing medication, rivastigmine-treated patients showed comparable reaction times and behavioral disturbances to the placebo group. No significant changes in parkinsonian symptoms were observed within the treatment group as a whole, although four patients who received rivastigmine developed tremor during the trial.

COMMENTARY

Patients with DLB may have an even greater central cholinergic deficit than Alzheimer's patients, providing a rationale for investigating the use of cholinesterase inhibitors to treat the disease. Both rivastigmine and tacrine have been previously reported to benefit DLB patients in open-label trials. The demonstration in a blinded placebo-controlled trial that rivastigmine has positive effects on DLB patients in terms of reaction time and behavior is a noteworthy finding, and represents an important step towards the possible future acceptance of this class of agents for treating DLB.

Anecdotal evidence suggests that the beneficial effect of cholinesterase inhibition in DLB is not confined to rivastigmine, but may be exhibited by other medications in this class. Presently, rivastigmine is the only cholinesterase inhibitor that has shown significant improvements in a sizable randomized, blinded, controlled trial. While these effects can be rather dramatic in some DLB patients, this study and clinical experience indicate that not every DLB patient responds to this line of therapy. It is unclear how long the benefits in responders can be expected to last, and the optimal dosing in DLB patients remains to be determined for rivastigmine or other drugs in its class.

It is important to note that patients with DLB may be exquisitely sensitive to neuroleptics, particularly high potency antipsychotics such as haloperidol, which may generate severe parkinsonism. Given the relatively benign side effect profile of acetylcholinesterase inhibitors (they do not seem to worsen parkinsonian symptoms in most cases) and the demonstrated efficacy of rivastigmine in reducing delusions and hallucinations in DLB, these agents may be a safer alternative to medications like haloperidol. Cholinesterase inhibitors tend not to be as potent in their anti-psychotic effects as neuroleptics, however, and are not likely to become first-line therapy for severe agitation or aggressive behavior. **—norman r. relkin**

Mycophenolate Mofetil: Attracting Attention

ABSTRACTS & COMMENTARY

Sources: Chaudhry V, et al. Mycophenolate mofetil: A safe and promising immunosuppressant in neuromuscular diseases. *Neurology* 2001;56:94-96. Ciafaloni E, et al. Mycophenolate mofetil for myasthenia gravis: An open-label pilot study. *Neurology* 2001;56:97-99.

Mycophenolate mofetil (mm, cellcept) is of demonstrable benefit for the prevention of renal allograft rejection, and for the treatment of Crohn's disease, systemic lupus erythematosus, and rheumatoid arthritis. It now appears promising for immune mediated neuromuscular diseases as well.

Retrospective analysis was undertaken of patients with myasthenia gravis (MG, n = 32), polymyositis (PM, n = 1), inclusion body myositis (IBM, n = 2), or chronic inflammatory demyelinating polyneuropathy (CIDP, n = 3). All had received MM 1 g twice daily for 3-36 months

(mean 12 months). MM was instituted as a steroid sparing agent (n = 26) or as an adjunct to steroids (n = 32), azathioprine (n = 8), cyclosporine-A (n = 4), methotrexate (n = 3), plasma exchange, or intravenous immunoglobulin (n = 10). Improvement of 1 grade or more on functional status or reduction of steroid dose by 10 mg or more every other day was defined as improvement.

Improvement was seen in 63% overall, 22 with MG and one each with polymyositis and CIDP, at a mean of five months of treatment (range, 2-12 months). MG nonresponders tended to have a longer history of MG (14 vs 7.5 years) and a shorter period of MM treatment (8 vs 13 months). Side effects were minor and included gastrointestinal discomfort (n = 3), diarrhea, and depressed mood (n = 1 each). MM appears to be a safe and effective immunosuppressant in the treatment of autoimmune neuromuscular diseases.

Prospectively, MM appears promising as well. Twelve MG patients, including seven with refractory MG and five treated with corticosteroids alone but requiring further immunosuppression, were given MM 1 g twice daily for six months. MG was diagnosed using standard criteria (*Neurology* 2000;55:912-913) and patients with or without thymectomy or elevated acetylcholine receptor antibodies were included. Primary end points included reduction of more than 3 points on the quantitative MG (QMG) score (*Ann NY Acad Sci* 1998;841:769-772) with reduction of more than two points on manual muscle testing (MMT), or reduction of steroid dose by more than 50% without worsening of QMG or MMT. Activities of daily living (ADL), assessed by questionnaire, served as a secondary end point.

Eight patients improved and one worsened. Of the remaining three, two improved only by QMG score and one by MMT and were thus considered unchanged by end point criteria. Improvement began by two weeks and was seen in all responders by two months. No significant side effects were noted and seven responders opted for continued MM on study completion. One did not, due to the high cost of MM. MM appears to be a useful, though expensive, adjunct in the treatment of MG and may be efficacious as sole therapy. Larger, double-blinded, placebo-controlled studies are warranted.

COMMENTARY

MM, an ester of mycophenolic acid isolated originally from penicillium culture in 1896, has antineoplastic, antibacterial, antifungal, antiviral, and, most recently discovered, immunosuppressive activity (*Am J Health Syst Pharm* 1997;54:285-294). Approved by the FDA in 1995 for the prevention of renal allograft rejection, it is currently one of the standard immunosuppressive agents following transplantation. Small case series have also shown MM to be beneficial in lupus nephritis (*J Am Soc Nephrol* 1999;10:833-839), Wegener's granulomatosis (*J Am Soc Nephrol* 1999;10:1965-1971), Takayasu's arteritis (*Ann Intern Med* 1999;130:422-426), and glomerulonephritis (*Am J Kidney Dis* 1998;31:213-217), though longer follow-up in the latter demonstrated several nonresponders and additional adverse effects (*Am J Kidney Dis* 1998;32:898-899). Autoimmune hepatitis (*J Hepatol* 2000;33:371-375) and the skin manifestations of dermatomyositis (*J Rheumatol* 2000;27:1542-1545) also respond to MM. With wider experience comes a single case report of tuberculosis reactivation (*Am J Kidney Dis* 2000;35:E12) and indications that the morbidity of cytomegalovirus (CMV) infection may be increased, although the overall incidence of CMV infection is not (*Clin Transplant* 2000;14:136-138).

One of four new xenobiotic immunosuppressive agents, including tacrolimus (FK506), sirolimus (rapamycin), and leflunomide, MM is a prodrug that is rapidly converted to its active metabolite, mycophenolic acid (MPA), following oral or intravenous administration. MPA blocks de novo purine biosynthesis by potently, selectively, and noncompetitively inhibiting inosine monophosphate dehydrogenase (IMPDH), the rate limiting enzyme that converts inosine monophosphate (IMP) to guanosine monophosphate (GMP). Guanosine triphosphate (GTP), and consequently DNA synthesis, is impaired and, as this de novo pathway operates in T and B lymphocytes, proliferation of T and B cells are selectively inhibited. In nonlymphocytic cells, a salvage pathway allows GMP synthesis via hypoxanthine-guanine phosphoribosyltransferase (*Ann NY Acad Sci* 1990;696:63-87; *Clin Transplant* 1993;7:96-112). MM is rapidly absorbed, with 94% bioavailability following oral administration, and converted to MPA which is further metabolized to inactive MPA glucuronide and excreted in the urine (*Cancer Res* 1972;32:1803-1809).

MM is generally well tolerated. In large multicenter trials, adverse effects have included gastrointestinal problems (diarrhea, abdominal pain, nausea), opportunistic infections (CMV, Herpes simplex, Herpes zoster, *Candida*, *Pneumocystis*, *Aspergillus*, Mucor), and myelosuppression (leukopenia, anemia, thrombocytopenia) (*Transplantation* 1995;60:225-232). Discontinuation of MM was necessary in 12.4% (113 patients) due to side effects, and, in the longterm, malignancies occurred more frequently in MM treated patients, albeit with an overall frequency of less than 2%. Clearly promising as a new immunosuppressant, further careful study is warranted. **—michael rubin**

Relapses and Progression of Disability in Multiple Sclerosis

ABSTRACTS & COMMENTARY

Sources: Confavreux C, et al. Relapses and progression of disability in multiple sclerosis. *N Engl J Med* 2000;343: 1430-1438; Whitaker JN, et al. Relationship of urinary myelin basic protein-like material with cranial MRI in advanced multiple sclerosis. *Arch Neurol* 2001;58:49-54.

The european database for multiple sclerosis reviewed 1844 patients with multiple sclerosis (MS) for a mean of 11 years, determining the initial course (relapsing-remitting (RR) or progressive) and subsequent course RR, secondary-progressive (SP), or primary-progressive (PP), the times of relapses, and the onset and progression of irreversible disability. Confavreux and colleagues examined landmarks of moderate to severe disability: Expanded Disability Status Scale (EDSS) score of 4 (able to walk > 500 m), EDSS of 6 (limited walking ability with unilateral support to 100 m), EDSS of 7 (ability to walk no more than 10 m with support). Of 1562 patients with a RR onset, the EDSS scores of 4, 6, and 7 were met at 11.4, 23.1, and 33.1 years after onset. The 282 patients with a progressive onset met their landmarks twice as rapidly at 0.0, 7.1, and 13.4 years ($P < 0.001$). In contrast, both groups evolved from EDSS 4 to 6 at similar times of 5.4 and 5.7 years ($P = 0.74$).

Whitaker et al measured urinary myelin basic protein (MBP)-like material in 86 RR MS patients, 259 SP MS patients without continued attacks, and 317 SP MS patients with continued attacks. Higher levels of urinary MBP had weakly significant correlations with progressive disease causing higher disability (EDSS > 5), and the volume of black hole lesions on brain MRI.

COMMENTARY

A growing understanding of the contributors to neurological disability in MS has emerged in recent years. On brain MRI and histologically, the presence of black hole formation, atrophy, and axonal loss appears to correlate with irreversible disability. The study by Confavreux et al demonstrates that more advanced, permanent neurological disability occurs with patients that have a progressive course from the onset, possibly reflecting the more destructive brain pathology occurring in this group. Thus, an early progressive course was a worse prognostic indicator than relapses. The study by Whittaker et al also supports the concept that more destructive brain injury and consequent increase in urinary MBP are seen in more advanced, progressive patterns of disease. **—brian r. apatoff**

Frequency of Specific Cancer Types in Dermatomyositis and Polymyositis: A Population-Based Study

ABSTRACT & COMMENTARY

Source: Hill CL, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: A population-based study. *Lancet* 2001;357:96-100.

Sigurgeirsson previously noted an increased association of cancer in adults who developed dermatomyositis and polymyositis (*N Eng J Med* 1992; 326:363-37). At that time, statistics were low, and specific associated cancers were not explicitly designated. This current report fills in those desired factors and provides the incidence of paraneoplastic dermatomyositis and polymyositis in patients in Sweden, Denmark, and Finland. Only patients who were in hospitals were included, reducing the overall potential association of ambulatory patients.

Based on hospital discharges from 1964-1983, 618 patients developed dermatomyositis and 914 had polymyositis. Mean age was approximately 55-57 years for cancer occurrence in each cohort. Lifetime cancer associated with dermatomyositis amounted to 198 total (32%) of which 115 developed within five years after the diagnosis of dermatomyositis. Polymyositis patients had 137 cancers, of which 95 developed after the polymyositis developed. With dermatomyositis the most frequent cancer risks consisted of ovary, lung, pancreas, stomach, colorectal cancers, and lymphomas. Polymyositis was followed by the identity of lung and bladder cancers as well as non-Hodgkins lymphoma. The risks of developing ovarian, pancreatic, and lung cancer lasted more than five years after patients who developed dermatomyositis. Within the cohort of patients suffering dermatomyositis, a number had already had a modest number of cancers within two years before the disease appeared. This especially applied to those age 45 years or older. No

patients younger than 45 years of age with polymyositis had abnormal cancer rates. The risk increased after that age, mostly within two years or less before the polymyositis appeared. A similar closeness was linked to the emergence of dermatomyositis.

COMMENTARY

Dermatomyositis and polymyositis appearing in middle aged persons provide a major warning that antibodies from systemic malignancies or other perturbed immune molecules are on the paraneoplastic loose. Admittedly, many persons with these disorders may choose rheumatologists or dermatologists to cure their disorder. Nevertheless, neurologists with strong ties to peripheral neurology may be called upon because of the muscular pain, tenderness, and swelling that may develop. This clear clinical descriptive report indicates that dermatomyositis in patients older than 50 years has a 300% cancer risk above normal while polymyositis was associated with a 30% risk. The rates would be higher had the survey included the number of patients who had cancer during the year before the skin-muscle abnormality. The report is entirely descriptive and the several types of cancer involved make it difficult to even guess the origins of the circulating paraneoplastic antigen. Unfortunately, no mention is given to what happens following the treatment of the cancer. Were there any cures of either the cancers or the paraneoplastic molecules that together or independently developed the skin and muscle antibody reactions? *Neurology Alert* awaits a modern scientific answer to this now well known problem. **—fred plum**

CME Questions

12. All of the following have been proven to promote primary stroke prevention *except*:
a. low-dose aspirin.
b. regular exercise.
c. cholesterol-lowering agents.
d. vitamin E.
e. frequent consumption of fish.

13. Patients with dementia with Lewy bodies:
a. have a dopaminergic deficit.
b. become more apathetic on rivastigmine.
c. become delirious when given acetylcholinestaerase inhibitors.
d. have less delusions and apathy on rivastigmine.

14. Mycophenolate mofetil (MM) (CellCept):
a. acts by interfering with pyrimidine synthesis.
b. is safe for use in pregnancy.
c. selectively inhibits proliferation of T and B cells.
d. is FDA approved for use in refractory myasthenia gravis.
e. is of benefit in inclusion body myositis.

15. Which factor does *not* indicate a more rapidly evolving course of severe multiple sclerosis?
a. Urinary myelin basic protein-like material
b. Expanding disability scale of 4, 6, and 7 arriving at 0.0, 7.1, and 13.4 years after onset
c. Early identified black "holes" on MRI
d. Eposidic relapses during early years of the disease

16. Risk factors associated with stroke after TIA include all of the following *except*:
a. Diabetes mellitus
b. Age older than 60 years
c. Duration longer than 10 minutes
d. Visual disturbance
e. Weakness

17. Which one of the following may offer promise in treating acute ischemic stroke?
a. Trilazad
b. NXY-059
c. All of the above
d. None of the above

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Monographs range from 25-35 Microsoft Word document, double-spaced pages. Each article is thoroughly peer reviewed by colleagues and physicians specializing in the topic being covered. Once the idea for an article has been approved, deadlines and other details will be arranged. Authors will be compensated upon publication.

As always, we are eager to hear from our readers about topics they would like to see covered in future issues. Readers who have ideas or proposals for future single-topic monographs can contact Associate Managing Editor Robin Mason at (404) 262-5517 or (800) 688-2421 or by e-mail at robin.mason@ahcpub.com. ❖

In Future Issues:

Parkinson's Disease Among Professional Welders

Update on Neurogenetic Testing

By Thomas D. Bird, MD

Editor's Note: *The molecular genetic revolution is having a major impact on the practice of neurology. This phenomenon is especially evident in the area of genetic testing for inherited diseases of the nervous system. Last year, Neurology Alert published a review of clinically available direct DNA tests for hereditary neurological diseases (see Neurology Alert January 2000 Supplement). The review listed more than 100 such disorders for which a direct DNA test is now commercially available. This review should be of considerable benefit to the busy practicing neurologist who needs quick information concerning the availability of genetic diagnostic testing for the differential diagnosis of specific patients. Metabolic and other nonDNA tests were not listed in the review, but further information about all types of genetic tests can be found at www.genetests.org. This website provides names and phone numbers of laboratories performing genetic testing as well as research laboratories that may be performing additional tests on a noncommercial (research) basis. A complementary website (www. geneclinics.org) provides clinical information and guidelines for interpreting and using DNA tests for many of the disorders listed in the table. This is a rapidly expanding field and several new tests have become available in the past year. We will briefly review them here.*

Hereditary Neuropathies

A wide range of hereditary peripheral neuropathies present as the Charcot-Marie Tooth (CMT) Syndrome with chronic, progressive, distal weakness, and sensory loss associated with depressed tendon reflexes. The conditions may be demyelinating or axonal (CMT Type 1 and Type 2, respectively). The most common form is demyelinating (CMT1A) and caused by duplication of the peripheral myelin protein 22 (PMP 22) gene. Other types with available DNA tests include hereditary neuropathy with liability to pressure palsy (HNPP), mutations in the myelin PO (MPZ) gene, and X-linked forms with mutations in the connexin 32 gene. Rare causes are point mutations in the PMP 22 gene or the Early Growth Response 2 (EGR2) gene. DNA tests for all these are now available.

Hereditary Ataxias

The autosomal dominant hereditary ataxias are referred to as Spinocerebellar Ataxias (SCA). At least 14 different subtypes have been defined on the basis of unique chromosomal loci. DNA-based tests have been previously available for SCA-1,2,3,6,7. Testing is now available for SCA-8 and SCA-10. SCA-8 is associated with a CTG repeat expansion (rather than CAG) and a relatively pure cerebellar atrophy syndrome. Testing for SCA-8 is associated with a CTG repeat expansion (rather than CAG) and a relatively pure cerebellar atrophy syndrome. Testing for SCA-8 is controversial because of decreased penetrance and because it remains unclear what is the frequency of the CTG expansion in the normal population. Positive tests for SCA-8 should be discussed with an expert in the field. SCA-10 is a dominant ataxia that is associated with seizures and is most often found in Mexican populations. SCA-10 is unique in being a penta-nucleotide repeat (ATTCT). A DNA-test for Friedreich Ataxia, the most common autosomal recessive type, is also available.

Prion Diseases

Creutzfeldt-Jacob (CJD) disease is usually sporadic and not genetic. However, a few rare families with this phenotype have a variety of mutations in the prion gene and a screening for such DNA mutations is now clinically available. The genetic prion syndromes include typical CJD (with rigidity, myoclonus, and dementia), or may be associated with ataxia (Gerstmann-Straussler-Scheinker, GSS), or may present with familial fatal insomnia (FFI).

Rett Syndrome

Rett Syndrome is an X-linked neurodevelopmental disorder affecting almost exclusively girls. It is associated with autistic features, loss of speech, microcephaly, seizures, and stereotypic hand movements. DNA-based testing can now identify a variety of mutations in the methyl CPG binding protein 2 (MECPT2) on the long arm of the X chromosome.

Additional information about the diseases can be found at www.ncbi.nlm.nih.gov/omim. Families with these disorders often require professional genetic counseling. **—tdb** (*Dr. Bird is Professor, Neurology, and Medical Genetics/Geriatric Researcher, University of Washington-VA Medical Center, Seattle, Washington.*)

Suggested Reading

1. Bird TD. Risks and benefits of DNA testing for neurogenetic disorders. *Semin Neurol* 1999;19:253-259.