AMERICAN HEALTH CONSULTANTS® A Medical Economics Company

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

New MRI Technology Provides Insights into Multiple Sclerosis

ABSTRACTS & COMMENTARY

Sources: Van Walderveen MAA, et al. Development of hypointense lesions on T1-weighted spin-echo magnetic resonance images in multiple sclerosis. *Arch Neurol* 1999;56:345-351; Filippi M, et al. Comparison of MS clinical phenotypes using conventional and magnetization transfer MRI. *Neurol* 1999;52:588-594; Filippi M, et al. Magnetization transfer imaging of patients with definite MS and negative conventional MRI. *Neurol* 1999;52:845-848; Sailer M, et al. Quantitative MRI in patients with clinically isolated syndromes suggestive of demyelination. *Neurol* 1999;52:599-606; Edwards SGM, et al. Infratentorial atrophy on magnetic resonance imaging and disability in multiple sclerosis. *Brain* 1999;122:291-301; Stevenson VL, et al. Primary and transitional progressive MS: A clinical and MRI cross-sectional study. *Neurol* 1999;52:839-845.

Conventional mri of the brain is sensitive in detection of MS lesions and is the most important paraclinical measure of disease activity. Surprisingly, several previous studies have shown limited correlation between clinical disability in MS and MRI findings. Recently, several new MRI techniques with potential for higher pathologic specificity have been used to monitor MS, including magnetization transfer (MT) MRI, diffusion-weighted (DW) MRI, and magnetic resonance spectroscopy. In standard MRI, increased signal on T2-weighted images reflects increased water content that occurs in a range of pathology, from early inflammation and edema to severe demyelination with axonal loss. This may be one reason hyperintense signal on T2 MRI does not correspond closely to clinical disability.

Van Walderveen and colleagues, in their study of 38 MS patients over an average of 40 months, focused on the accumulation of hypointense lesions on T1-weighted MRI ("black holes," which indicate areas of axonal loss and tissue matrix destruction) and the development of disability in MS. Such black hole formation on T1 MRI appeared to correlate with a new enhancing lesion rate and initial T1 lesion load, suggesting that certain patterns of MS are prone to develop destructive lesions. The hypointense T1 lesion load at the end of the study period correlated with clinical disability better than the T2 lesion volume.

Volume 17 • Number 9 • May 1999 • Pages 65-72

INSIDE

In addition to gross MS pathology with cystic degeneration, microscopic damage has been shown histologically to occur in normal appearing white matter (NAWM), and is not detected by conventional MRI. The process, nevertheless, also may contribute to brain atrophy and MS disability. In MT MRI, a low MT ratio indicates a reduced capacity of macromolecules to exchange magnetization with surrounding water molecules, reflecting damage to the myelin or axonal membranes. Filippi and colleagues performed conventional MT MRI on 11 patients with clinically definite MS or laboratory supported MS with positive CSF findings and negative brain images. Six of the 11 patients, however, expressed MRI lesions in the cervical or thoracic spinal cord. Compared with control subjects, the MS patients had significantly lower MT ratios in the pons, cerebellum, and periventricular regions ($P < 0.0001$). In a second study, Filippi et al used MT MRI in a variety of MS clinical phenotypes. Patients with secondary progressive (SP) MS had significantly lower MT ratios that corresponded more accurately to clinical disability than did T2 lesion load. Patients with primary progressive MS had a lower MT peak height consistent with diffuse white matter pathology not revealed on T2-weighted imaging.

Dousset and colleagues performed serial MT-MRI studies in four MS patients for 9-12 months (Dousset V, et al. *Neurol* 1998;51:1150-1155). Monitoring 15 new lesions, 13 had a marked decrease in the MT ratio for two months after the onset of the lesion, followed by a variable increase. Two other lesions showed a progressive decline in the MT ratios suggesting continuing demyelination and tissue destruction.

Goodkin and colleagues performed a more comprehensive analysis of 22 relapsing remitting (RR) MS patients and 11 normal controls over 12 months (Goodkin DE, et al. *Neurol* 1998;51:1689-1697). In 129 new lesions identified in 11 patients, there were differences in the MT ratios that preceded by months the new gadolinium-enhanced lesion formation in NAWM. Residual abnormalities beyond two months were more evident on MT and proton density MRI, consistent with irreversible tissue damage.

Most patients present with an RR course and subsequently enter a secondary progressive (SP) phase with or without relapses. However, 10% of patients have a primary progressive (PP) course from onset. A multi-center European MRI study (Stevenson et al) was performed on 158 PP MS patients, 33 with transitional progressive MS (TP MS, a progressive course with a significant relapse at some point in the disease). The SP and TP MS patients had significantly more lesions in the spinal cord than PP patients. There was a correlation of Expanded Disability Status Scale Scores (EDSS) in the PP and TP MS patients with brain and spinal cord atrophy, but not lesion load.

A longitudinal, quantitative MRI study was performed by Sailer and colleagues at Queen Square, London, in 58 patients with their first attack of MS, with a follow-up five and 10 years later. The total initial lesion volume on T2-weighted MRI correlated significantly ($P = 0.0001$) with the 10-year lesion volume and EDSS. Sailer et al concluded that the initial brain MRI strongly predicted the subsequent development of clinically definite MS and future level of disability. Thus, a high lesion load on an initial MRI would imply a poor prognosis and would support early immunodulatory treatment intervention to slow new lesion formation and minimize long-term disability.

Recognizing that brain atrophy may provide an important index of fixed neurological dysfunction, Edwards and colleagues determined the infratentorial volumes on MRIs from 21 RR and 20 SP MS patients. The volume of the C1-C3 cervical spinal cord correlated with a composite spinal cord disability score derived from the EDSS as well as disease duration ($P < 0.01$). There was also a weak correlation with the Scripps Neurological Disability Rating score with the cerebellar ($P < 0.01$) and brain stem ($P < 0.05$) volumes.

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

VICE PRESIDENT/ GROUP PUBLISHER: Donald R. Johnston.
EXECUTIVE EDITOR: Glen Harris.
ASSISTANT MANAGING EDITOR: Robin Mason.
COPY EDITORS: Neill Larmore, Michelle Moran, Holland Johnson.

GST Registration Number: R128870672.
Second class postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Neurology Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $33. 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.

Subscriber Information

Customer Service: 1-800-688-2421.

Customer Service E-Mail Address:
customerservice@ahcpub.com

Editorial E-Mail Address: neill.larmore@medec.com

World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
$199 per year (Student/Resident rate: $100).

Multiple Copies
1-9 additional copies: $100 each. 10 or more copies: $60 each.

Outside the United States
$229 per year plus GST (Student/Resident rate: $110 plus GST).

Accreditation

American Health Consultants is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor CME for physicians. American Health Consultants designates this CME activity for 20 credit hours of Category 1 of the Physician's Recognition Award of the AMA. This CME activity was planned and produced in accordance with the ACCME Essentials.

Questions & Comments

Please call **Robin Mason,** Assistant Managing Editor, at (404) 262-5517 or **Neill Larmore** at (404) 262-5480 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

American Health Consultants does not receive material commercial support for any of its continuing medical education publications. In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, a statement of financial disclosure of editorial board members is published with the annual index.

COMMENTARY

The imprecise correlation of burden of disease on brain MRI with neurological disability may be related to the pathological heterogeneity of T2-weighted lesions. The series of MRI studies reviewed above document the lack of specificity of T2-weighted MRI for reversible demyelination vs. permanent axonal loss. The greater sensitivity of MT MRI will aid in assessing demyelination, axonal loss, and early pathology in "normal" white matter. New measures of brain atrophy may correspond more accurately to neurologic disability. Investigators at the Cleveland Clinic have developed an index of brain atrophy, brain parenchymal fraction (BPF), which may serve as a sensitive, early marker of MS-related disease activity. Treatment with interferon beta-1a after one year was shown to stabilize the reduction in the BPF (RA Ruddick, personal communication). It is expected that such MRI technology will improve our ability to test drug efficacy in slowing progression of the disease. **—ba**

Interferon for Chronic Demyelinating Motor Neuropathy

ABSTRACT & COMMENTARY

Source: Martina ISJ, et al. Chronic motor neuropathies: response to interferon-ß1a after failure of conventional therapies. *J Neurol Neurosurg Psychiatry* 1999;66:197-201.

In this prospective, open-label, preliminary study, interferon beta-1a (INF-beta-1a) was administered to three patients with multifocal motor neuropathy (MMN) and one with chronic inflammatory demyelinating polyneuropathy (CIDP). All had been previously unresponsive, over the course of 7-9 years, to conventional therapy including prednisone, plasma exchange, intravenous immunoglobulin, or cyclophosphamide. Patients were treated with interferon beta-1a subcutaneously three times weekly at a dose of 6 million IU for six months, with an option to continue for another six months if clinical improvement occurred. Primary end points included the nine-hole peg test, 10 meters walking test, and the modified Rankin scale, while the secondary end point was a modified Medical Research Council (MRC) sumscore. Statistical analysis included conventional linear and linear spline regression.

MRC subscore and time required to perform the nine-hole peg test improved significantly in all patients, and time to walk 10 meters was significantly reduced in all patients by three months. These changes, however, did not necessarily reflect clinically significant improvement, as the modified Rankin score improved in only two patients at six months. Improvement of conduction block on nerve conduction studies was demonstrated only in the CIDP patient, and anti-GM1 titres, present in three patients at entry, remained unchanged. INF-beta-1a was well tolerated with flu-like symptoms, fever, sweats, and injection site erythema disappearing by two months. INF-beta-1a may be somewhat beneficial for acquired, chronic, refractory, demyelinating forms of neuropathy. Controlled double-blind studies are the appropriate next step.

COMMENTARY

At least 12 functional forms of interferon a (IFN-alpha) exist in humans, synthesized predominantly by lymphocytes. This compares to only one antigenically distinct IFN-beta, synthesized by fibroblasts. Both IFN-alpha and IFN-beta, however, operate through a common pathway involving two IFN receptor subunits, two Janus tyrosine kinases (JAK), two signal transducers and activators of transcription (STAT), and the interferon regulatory family (IRF) transcription factor p48 (Stark GR, et al. *Annu Rev Biochem* 1998;67;227-264). As a first step in the signaling pathway, IFN receptors are dimerized by IFN at the cell membrane, resulting in initiation of the intracellular tyrosine phosphorylation cascade and phosphorylation of STATs. These STATS, in turn, dimerize and become activated for transport into the nucleus where they stimulate transcription by binding to specific DNA sequences. Other pathways also appear to be activated by IFN-alpha and IFN-beta but their physiological roles remain unclear.

Antiviral, antiproliferative, and immunomodulatory functions are induced by interferons. Antiviral mechanisms of IFN action include the dsRNA-dependent protein kinase pathway (affects transcription and translation), the 2-5A synthetase system (cleaves single-stranded RNA), and the Mx protein pathway of IFN-inducible GTPases, which interferes with viral replication at the level of viral transcription (Meurs E, et al. *Cell* 1990;62:379-390; Carroll SS, et al. *J Biol Chem* 1996;271:4988-4992). Cancer suppression is affected by IFN through its inhibition of cell growth, which varies with cell type, and through its control of apoptosis. Immunomodulation is predominantly stimulated by IFNg with IFN-alpha and IFN-beta playing more restricted roles, directed largely at resistance to viral infection. All IFNs regulate the expression of major histocompatability complex (MHC) proteins, particularly class I proteins

which promote CD8+ T-cell responses, whereas IFNg is unique in its ability to induce MHC class II proteins, thereby enhancing CD4+ T-cell responses. Macrophage activation is another IFNg-unique activity, not provided by IFN-alpha and IFN-beta. All IFNs may regulate humoral immunity directly at the B-cell level, including B-cell development and proliferation, immunoglobulin (Ig) secretion, and Ig heavy-chain switching.**—mr**

Sleep Disorders and Anxiolytics Increase the Risk of Traffic Accidents

ABSTRACT & COMMENTARY

Source: Teran-Santos J, et al. The association between sleep apnea and the risk of traffic accidents. *N Engl J Med* 1999; 340:847-851.

Based on simulated driving tests, obstructive sleep apnea has been thought to increase automobile accidents by as much as two- to three-fold when compared with healthy persons (Aldrich MS. *Sleep* 1989;12:487-494). Teran-Santos and colleagues approach the problem directly, selecting all inter-urban highway drivers involved in traffic accidents and brought to a regional Spanish hospital for immediate treatment. Patients without known chronic illnesses or traffic accidents during the past two months were selected as controls for each above patient involved in a traffic accident. Subjects were questioned for personal habits, diseases, medication, past accidents, and possible causes of drowsiness. Histories of sleep apnea were scaled and tested technically and by low-level nocturnal polygraph. More detailed maneuvers were applied when considered desirable.

Outcomes of 102 case patients and 152 matched controls were compared. Persons who had a clinically abnormal apnea-hypopnea ratio more than 10 had a traffic accident adds rate 4.1 greater than normals. Those who additionally had consumed alcohol on the accident day increased the rate to 11.2.

Psychoactive drugs have often been blamed as contributing to at least 10% of all fatalities in road traffic accidents (De Gier JJ. Maastricht:University of Limburg, Institute for Human Psychopharmacology, 1993). Alcohol carries the greatest dangers, but other psychoactive drugs also may contribute. Barbone and colleagues report from an area in Scotland that 1731 out of 19,386 drivers involved in accidents between August 1, 1992, and June 30, 1995, at least sometimes used a psychoactive drug (Barbone F, et al. *Lancet* 1998;352:1331-1336).

To be specific: on any given accident day, an average of 189 of the users were taking tricyclic antidepressants, 84 serotonin-reuptake inhibitors, 235 benzodiazepines, and 47 other psychoactive drugs. Only benzodiazepines increased the risk ratio compared to nondrugged drivers' rate. Overall, adds ratio was 1.62, but the rate was measurably higher in persons younger than 40 years (3.42). Add a positive alcohol test and the odds ratios climbed to 9.55 (n = 4). Barbone et al refer to two reports providing similar results (Ray WA, et al. *Am J Epidemiol* 1992;136:873-883; Hemmelgarn B, et al. *JAMA* 1997;278:27-31).

COMMENTARY

Most studies that identify a relationship between sleep apnea syndromes and traffic accidents reflect the airway-pulmonary obstructive type rather than a faulty central regulation of breathing during sleep. Nevertheless, many neurologists who participate in providing polysomnographic sleep studies or even hear complaints of hypersomnia must warn their patients against driving when feeling drowsy. The dangers of alcohol and anxiolytics must be emphasized. As the data show, these same attitudes must hold for young persons, especially those who combine benzodiazepines with alcohol and sleep deprivation. Therapy that can help outpatients prevent brain trauma is far greater than trying to restore them from traumatic brain injury. **—fp**

New PET Technique Provides New Clues to Autism

ABSTRACT & COMMENTARY

Source: Chugani DC, et al. Developmental changes in brain serotonin synthesis capacity in autistic and non-autistic children. *Ann Neurol* 1999;45:287-295.

Autism, as noted in a recent *Neurology Alert*, remains a puzzling disorder continuing from infancy. Although some groups have reported small changes in brain structure (Plum F. *Neurol Alert* 1998;16:89-91), others have failed to detect functional changes using quantitative MRI (Piven J, et al. *Neurology* 1997; 49:546-551). Conventional neurological investigations fail to explain the profound symptoms in these children. Using a new PET technique that enables the study of

brain serotonin synthesis capacity, Chugani and associates now report direct evidence for significant abnormalities in the development of serotonin synthesis capacity in autistic patients.

PET has evolved into a technique that can be used quantitatively to probe various neurochemical systems. The recent development of (11C)-alpha-methyl-tryptophan [(11C)-AMT] has enabled the study of serotonin (5-hydoxytryptamine) synthesis in humans (Nishizawa S, et al. *PNAS* 1997;94:5308-5313). (11C)-AMT uptake directly reflects serotonin synthesis capacity, i.e., it reflects the maximal rate at which serotonin could be synthesized if all tryptophan taken up were to be converted to serotonin. (11C)-AMT uptake is not a direct measure of serotonin synthesis rate, since there are multiple metabolic pools for tryptophan and other potential rate-limiting steps of serotonin synthesis (e.g., tryptophan hydroxylase).

Chugani et al examined whole brain serotonin synthesis capacity in 30 autistic patients, eight normal siblings of autistic patients, and 16 children with epilepsy. The youngest patient in the study was a 3-month-old epileptic infant, demonstrating applicability of the technique to young infants. Chugani et al found a decline in serotonin synthesis capacity among nonautistic children (control or epileptic) from age 2 to age 15, at which point synthesis capacity approaches adult values. As compared to either control group or epileptic patients, autistic patients: 1) show a significantly smaller increase (relative to normal adult values) in serotonin synthesis capacity during childhood and, 2) fail to show the age-related decreases in serotonin synthesis capacity seen in nonautistic children. In short, serotonin synthesis capacity seems to have lost most of its "developmental dynamism" in the autistic patient.

COMMENTARY

The study by Chugani et al provides further evidence for abnormalities in serotonergic systems in autism, which Cook (Cook EH. *Synapse* 1990;6:292-308), had already suspected. The study suggests a defective developmental regulation of development and attrition of serotonergic mechanisms in autism. Indeed, the results concur with more recent findings by Cook et al (Cook EH, et al. *Mol Psychiatry* 1997;2:247-250), that certain poorly transcribed polymorphisms in a serotonin transporter frequently affect autistic families. The finding suggests a possible molecular basis for the differences seen in (11C)-AMT PET.

Differences in serotonin synthesis capacity between autistic and nonautistic children appear most marked during infancy. Hopefully, (11C)-AMT PET may identify that the defect exists in infancy in high-risk families before a clinical diagnosis is established (often not made until age 2). Unfortunately, it is not yet clearly established if the changes seen in autistic patients are entirely specific for that disorder. Serotonin reuptake inhibitors (SRIs) are already being given increasingly to both adults and children with autism (McDougle CJ, et al. *Arch Gen Psychiatry* 1996;53[11]:1001-1008 and 1998; 55:633-641; Fatemi SH, et al. *J Autism Dev Disord* 1998; [Aug 28]:303-307). Whether this improves the person's development or adult life is unclear.

This was a cross-sectional study and "developmental changes" were inferred by examining serotonin synthesis capacity measurements among different patients of different ages. It would be valuable to follow a cohort of autistic patients over time in order to examine developmental differences in serotonin synthesis capacity in a given patient. Autism is a syndrome not yet identified as a specific disease. If, however, similar abnormalities in serotonin synthesis capacity were found in different autistic patients, heredity would be a likely common denominator of the disease. **—rt**

Seeing and Treating Cholinergic Deficits in AD

ABSTRACTS & COMMENTARY

Sources: Imbimbo BP, et al. Efficacy and safety of epistigmine for the treatment of patients with AD. *Neurology* 1999;52(4):700-708; Kuhl DE, et al. In vivo mapping of cerebral acetylcholinesterase activity in aging and AD. *Neurology* 1999;52(4):691-699.

Alzheimer's disease (ad) progresses slowly, necessitating many years to fully assess the efficacy of new treatments. One small step consists of the outcome of a randomized trial of epistigmine, yet another acetylcholinesterase inhibitor (AChEI) being tested for ameliorating AD-related dementia. Epistagmine given 15 mg tid previously showed marginal improvement in AD patients, but failed to produce a significant change in global function (Imbimbo BP, et al. *Alz Dis Assoc Disord* 1998:12:313-322). In a new study involving 463 AD patients, treatment with placebo was compared to either 15 mg or 20 mg epistigmine tid. The effects were comparable to those of the previous study, but the higher dose significantly improved activities of daily living over a 24-week period, apparently the first reported improvement in instrumental activities by a drug of this

class. A similar dropout rate occurred between epistigmine- and placebo-treated patients. A low rate of gastrointestinal side effects with epistigmine was nearly comparable to that of placebos. Unfortunately, 6.2% of patients treated with 20 mg tid of epistigmine developed neutropenia, which Imbimbo and colleagues acknowledge will limit the drug's clinical use.

Cholinergic therapy is an established treatment for AD, but the exact mechanisms of its beneficial effects are not completely understood. Accordingly, optimal candidates for such drugs cannot be identified in advance. To clarify this issue, Kuhl and colleagues developed a PET technique similar to that first proposed by Irie and colleagues in 1994 (Irie T, et al. *Nucl Med Biol* 1994;21:801-808) for mapping brain acetylcholinesterase in the brains of living subjects. The radioligand used was N [11C] methylpiperidin-4-yl propionate, a highly selective substrate for the AchE enzyme that enters the brain after intravenous injection. Kuhl et al studied 26 normal controls and 14 patients with AD. They correlated their findings with other PET measures of cholinergic terminal density and glucose metabolism. The [11C]PMP PET results agreed reasonably well with postmortem data on the distribution of cholinergic activity in normals and AD patients, and changed in the expected manner when physostigmine was administered. Kuhl et al speculate that the [11C]PMP PET technique may prove valuable in identifying responders to cholinergic therapies, thereby facilitating other aspects of drug development and use.

COMMENTARY

Two AChEIs (tacrine, donepezil) are already FDA approved for treating symptoms of AD. Last year, *Neurology Alert* reported the positive results of Phase III clinical trials of metrifonate, an irreversible AChEI, which showed comparable efficacy to the tacrine and donepezil (Relkin, NR. *Neurol Alert* 1998;16:84-85). All human studies with metrifonate were stopped voluntarily by Bayer, Inc. when a small fraction of patients developed unexpected muscle weakness. Rivastigmine, a chemically unrelated AChEI that requires twice-daily dosing, has shown comparable efficacy to other agents in its class and is currently used to treat AD patients in Europe. Rivastigmine has yet to receive approval for use in the United States. Other cholinesterase inhibitors like galanthamin are currently under large-scale study in Europe and the United States.

The positive effects of epistigmine on the performance of daily activities and the low incidence of gastrointestinal side effects represent potential selling points. The negative problems include a three-time-daily dosing and the drug's dose-dependent neutropenic effect. It seems unlikely that epistigmine will replace drugs like donepezil, which can be dosed once daily with comparable efficacy and greater safety. The data on epistigmine corroborate the cognitive benefits of cholinergic therapy for AD, and may provide modest improvements in daily function when receiving this type of medication.

The direct clinical applicability of the [11C]PMP PET technique is questionable in light of the complexity, expense, and limited availability of quantitative PET. The real value of this method would appear to be as an investigational tool. Although cholinergic deficiency is well-documented as a biological correlate of AD, the benefits of cholinergic therapy are inconsistent across both symptoms and patients for unexplained reasons. A specific and quantitative in vivo measure of central acetylcholinesterase activity could assist in the further development of cholinergic therapies. By more directly measuring the brain's response to these agents, the [11C]PMP PET method could facilitate dose finding and other aspects of new drug development. **—nrr**

Age-Related Prognosis in Benign Astrocytoma

ABSTRACT & COMMENTARY

Source: Shafqat S, et al. Age-dependent rate of anaplastic transformation in low-grade astrocytoma. *Neurology* 1999; 52:867-869.

It's well known that the prognosis of fibrillary astrocytomas depends significantly on patients' ages and the histopathologic interpretation of their tissue. Shafqat and colleagues cite sources indicating that the incidence of low-grade astrocytomas maximizes at about 34 years of age, whereas anaplastic astrocytomas top at about 41 years of age and glioblastomas at about 53 years of age. Against this background, they suggest that age of onset importantly influences both the initial form of these tumors and their resistance to future anaplasia.

From a cohort of 276 patients biopsied at Mass General Hospital [MGH] between 1981-1995, the records of 24 cases fulfilled the following: 1) all had low-grade fibrillary astrocytomas, free of oligodendroglia; 2) the tumor occupied a single cerebral hemisphere; 3) tumors were biopsied within six months after first symptom;

and 4) all tumors transformed into high-grade, malignant glioma judged by either second biopsy (n = 14) or clinical/imaging signs (10).

As expected, time from initial biopsy of fibrillary astrocytoma to convert to malignant anaplasia shortened as the age of first symptoms increased. Shafqat et al present a table and scatter plot diagram identifying each patient's age of onset and malignant transformation of the tumor. Specific breakdowns of risk into ages were consistent with the literature. Seven patients younger than 25 at onset had a 49-month average between first diagnosis of malignancy and a total of 60 months from first diagnosis until death. Those aged from 25-44 years at onset averaged 49 months to transformation and 43 months until death; nine patients older than 44 at onset averaged 7.6 months to develop anaplasia and on average died at 13.6 months after first biopsy. Out of the 24 reported patients, four have survived: three younger than 45 years, and one older.

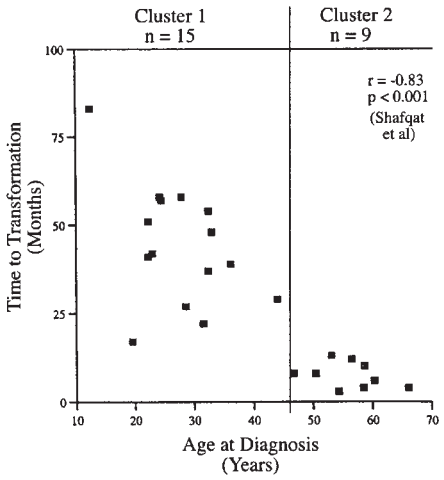
COMMENTARY

This report provides useful information about the lifetime biology of nonanaplastic fibrillary astrocytomas. I, however, find two omissions that would increase the value of the report. One is that only patients whose tumors have undergone anaplastic regrowth are cited. *Neurology Alert* wishes that all cases of fibrillary astrocytomas from MGH, including those who have not transformed, would likely have identified a larger cohort of patients. This would possibly have strengthened survival statistics of the younger than 45 years of age cohort, thereby improving possible prognoses to patients and families. I can recall two patients who first suffered a low-grade, resected astrocytoma during their early 20s, then remained disease-free until their late 50s. At that time, they developed fatal glioblastomas in the same areas occupied by their previous astrocytomas.

A second comment has to do with Shafqat et al's printed scattergraph, here modified by *Neurology Alerts* placing of a perpendicular line to divide the independent ages and prognoses of two clusters. The P value given in the upper right quarter describes Shafqat et al's original linear values of age/transformation as calculated by a Pearson correlation coefficient. A quick glance, however, indicates no overlapping of patients between Cluster 1 and Cluster 2 in years of onset, and of time from initial diagnosis to malignant development. Our accompanying table illustrates that the average patient in Cluster 2 showed a six-fold rapidity between the first diagnosis of astrocytoma and transformation into anaplastic malignancy. Time to death in Cluster 2 patients was one-fourth that of Cluster 1 [P < 0.01-6 ANOVA]. **—fp**

Figure

Age at Diagnosis and Time to Transformation



	Cluster 1	Cluster 2
Mean age at diagnosis (yrs)	27.6 ± 7.6	56.0 ± 5.7
Mean time (mos) to transformation	44.2 ± 17	7.5 ± 3.6
Overall time to death (survivors deleted)	58 mos (n = 12)	14 mos (n = 8)

$P < 10^{-6}$ ANOVA

Adapted from Shafqat S, et al. Age-dependent rate of anaplastic transformation in low-grade astrocytoma. *Neurology* 1999;52:867-869.

Brief Alert

Tourette Syndrome: Don't Spare the Pimozide

Source: Tourette Syndrome Study Group. Short term versus longer term Pimozide therapy in Tourette's Syndrome: A preliminary study. *Neurology* 1999;52:874-877.

Pimozide is a potent neuroleptic widely used for more than a decade to treat vocal and motor tics in Tourette Syndrome (TS). Considering the potential long-term risks of neuroleptics, is it rational to treat only when tics are out of control, discontinuing treatment once tics disappear? The Tourette Syndrome Study Group (TSSG) suggests not.

The TSSG examined 10 patients with TS who had achieved stable tic control with Pimozide. Six were

maintained on the medication and four were withdrawn over a 12-day period. The patients withdrawn from Pimozide relapsed and regained their prominent tics within a median of 37 days and a maximum of about 90 days. The end point of the continuation group for more treatment was 239 days. Two treated patients dropped out at 0 and 210 days arbitrarily. Four, however, lasted ± 100, 90, and 235 days. The results differed at the P = 0.02 level.

The TSSG advocates long-term (up to 12 months or more) Pimozide therapy in stabilized patients. Although Pimozide has a theoretical risk for tardive dyskinesia, two prior studies by Mesulam and colleagues (Mesulam MM, et al. *Neurology* 1987; 37:1828-1833) and Regeur and colleagues (Regeur L, et al. *J Neurol Neurosurg Psychiatr* 1986;49:791-795), each involving about 60 patients with TS on long-term Pimozide therapy, reported that not a single case of tardive dyskinesia was observed. **—r t**

Letter to Readers

This issue promises a new subsection for *Neurology Alert*. As we all know, journals dedicated to clinical neurology become rapidly obese just as their contents take a progressively shorter time during which new data make the old obsolete.

This issue of *Neurology Alert* introduces two of several changes that will be included in this and future issues. Just as these last 10 years have been rightly designated the "Decade of the Brain," neurologists must realize that the coming millenium will begin with the "Century of the Brain." Neurology has passed the divide of being a descriptive discipline into an action discipline, exposing the roots of neurological development and lifetime durability as well as finding the cell-molecular steps necessary to prevent limited growth of the nervous system. Particular attention will address genetic or acquired illnesses that presently interfere with life-long healthy neurological capacity.

Pursuing the above goals, your editor will make every effort to identify and explain dependable reports concerning new diseases or other factors that adversely affect the human nervous system, and, whenever possible, therapy will be emphasized. (This is obviously central to our present goals.)

Beyond the above, we plan to list within every volume new gene discoveries that affect the nervous system and, when possible, will briefly describe its produced protein and putative disease mechanism. Where possible, commercial laboratories that can identify the gene abnormality for diagnosis will be included. A second novelty that also will be updated annually will consist of a glossary of new pharmaceutical products aimed at neurological disorders. Currently estimated, neutrally reported advantages, costs, and sources will be provided.

A third step will briefly describe important advances in fundamental neuroscience that bring promise for future therapy of serious neurobiological disorders presently considered incurable. Under no circumstances, however, will we reduce our devotion to assist clinical practicing neurologists.

Thank you for your interest. —Fred Plum, MD ❖

CME Questions

21. Please choose the answer that best completes the following statement: "Positron Emission Tomography with (11C)-alpha-methyl-tryptophan ([11C]-AMT-PET)

a. enables a direct noninvasive measure of serotonin synthesis.
b. cannot be performed in children younger than 1 year of age.
c. can be used to measure serotonin synthesis capacity.
d. shows little differences between normal children and normal adults.
e. shows greater differences between autistic children and normal adults (as compared to normal children and normal adults).

22. Fibrillary astrocytomas may have which of the following characteristics?

a. A peak incidence in persons younger than 25 years of age
b. May at onset involve both cerebral hemispheres
c. Show a sharp predisposition to early malignancy in patients older than 50 years
d. Have longest average rates to recurrence in persons between 35-50 years

23. Acetylcholinesterase inhibitors used in the treatment of AD:

a. are well tolerated but have no measurable benefits.
b. can improve cognition but not activities of daily living.
c. can improve activities of daily living but not cognition.
d. can improve cognition and activities of daily living.

24. Which of the following MRI techniques appears to be a less specific indicator of clinical disability?

a. Magnetization transfer (MT) MRI
b. Standard T2 MRI
c. Proton Density MRI
d. T1-weighted MRI

In Future Issues:

Future Uses of Neuronal Regeneration