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# NEUROLOGY ALERT®

*A monthly survey of developments in neurologic medicine*

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## Diffusion MRI Detects Some TIAs

ABSTRACTS & COMMENTARY

**Sources:** Kidwell CS, et al. Diffusion MRI in patients with transient ischemic attacks. *Stroke* 1999;30:1174-1180; Ay H, et al. Normal diffusion-weighted MRI during stroke-like deficits. *Neurology* 1999;52:1784-1792; Marks MP, et al. Evaluation of early reperfusion and IV tPA therapy using diffusion- and perfusion-weighted MRI. *Neurology* 1999; 52:1792-1798.

Diffusion-weighted magnetic resonance imaging (dwi) is now being used routinely for the evaluation of acute stroke at many centers throughout North America and Europe. Recent studies indicate that DWI may also provide clinically relevant information about transient ischemic events (TIAs), although perhaps not in every case.

Kidwell and colleagues collected DWI data on 42 consecutive patients with TIA symptoms, and found diffusion abnormalities related to neurologic symptoms in 20 cases (48%). The TIA-associated diffusion anomalies tended to be less voluminous and less conspicuous than those typically seen in stroke patients. TIAs with positive DWI findings averaged 7.3 hours in duration, while those without DWI findings lasted a mean of 3.2 hours, suggesting that diffusion abnormalities are more likely to be observed in TIAs of longer duration. Nine of the 20 patients with positive DWI scans had follow-up studies, and nearly half of those were found to have ischemic strokes in the affected region. In the remainder, symptoms and diffusion abnormalities completely resolved, indicating that an abnormal diffusion study does not necessarily herald the later development of stroke.

Ay and colleagues studied the implications of obtaining a normal DWI in the context of stroke-like deficits. They reviewed 782 consecutive imaging studies and identified 27 cases in which the DWI was normal, despite the persistence of neurologic symptoms during the scanning period. Using all available clinical and radiologic data, Ay et al concluded that conditions other than stroke were responsible for 37% of cases, while ischemic events were the most likely etiology in the remaining 63%. The nonischemic causes included migraine, seizures, brain tumor, transient global amnesia, and psychiatric disorders. They concluded that more than half of the cases



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of stroke-like symptoms with a normal DWI will, nevertheless, have an ischemic cause for their symptoms. Ay et al suggest that absence of DWI abnormalities in a symptomatic patient should trigger a search for other causes than ischemia. Ay et al also found perfusion-weighted MRI helped to identify some patients with ischemic events who had normal DWI.

Marks and colleagues used the combination of DWI and perfusion-weighted imaging to study 12 patients receiving recombinant tissue plasminogen activator (rTPA) for treatment of acute stroke. The imaging interval between averaged three to five hours from baseline to rescanning post-rTPA. Marks et al also scanned six patients undergoing stroke who did not receive rTPA for purposes of comparison. Six patients had normalization of the perfusion scan within 24 hours, and five of those six had received rTPA. Early signs of reperfusion were seen more frequently in patients who received intravenous rTPA than those who did not. Marks et al conclude that DWI and perfusion imaging may help to guide thrombolytic therapy as well as other aspects of acute stroke management.

## COMMENTARY

DWI is sensitive to the limitations on free diffusion of water imposed by microscopic barriers in biological tissue. Freely diffusing water in CSF appears dark, while water in highly structured areas, such as white matter, often appears bright. Increased signal intensity is also observed within minutes of the onset of cerebral ischemia. Another MRI technique known as perfusion imaging (PI) is sensitive to blood flow at the capillary level. Perfusion studies can now be accomplished without injection of contrast agents in 10 minutes or less.

Large magnetic field gradients are needed to perform DWI and PI, and rapid imaging protocols such as the echoplanar technique are suitable. As such, these capabilities are not available to the thousands of neurologists using clinical scanners that are more than a few years old. This situation is likely to change as newer generations of clinical scanners are installed and older scanners are updated.

Studies of DWI in stroke and now TIA are encouraging and indicate the likelihood of an increasing clinical role in the future. The fact that not all TIAs are associated with diffusion abnormalities is hardly surprising, since some events will be too small or too transient to be detected within the resolution of these types of scans, which are typically several-fold lower in spatial resolution than standard structural MRIs. This means that clinicians do not learn that much from a negative diffusion scan, but may gain more information when the scan is positive and correlates with the neurologic symptoms. Not all diffusion abnormalities are stroke-related and, in this context, the combination of diffusion and perfusion techniques and clinical acumen may be useful in determining which events are of ischemic etiology. Serial imaging studies demonstrate that diffusion changes in the context of a TIA do not necessarily indicate irreversible ischemia. This being the case, DWI could help in acute stroke management above and beyond what can be accomplished with conventional structural MRI techniques. **—nrr**

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# Treatment of OPCA with Amantadine

ABSTRACT & COMMENTARY

**Source:** Botez MI, et al. Amantadine hydrochloride treatment in olivopontocerebellar atrophy: A long-term follow-up study. *Eur Neurol* 1999;41:212-215.

Botez and colleagues have previously reported improved results using amantadine to treat late onset heredodegenerative spinocerebellar ataxia (SCA).

The previous efforts by Boetz et al were either open or double-blinded (Botez MI, et al. *Can J Neurol Sci* 1991;18:307-311; Botez MI, et al. *J Neurol Neurosurg Psychiatry* 1996;61:259-264). Both studies showed favorable results in late-life ataxias, but not with Friedreich's ataxia. Also, however, neither trial lasted more than four months or more.

Botez et al now report an open study of outcomes from amantadine in 33 previously selected patients with SCA. Twenty-one proceeded with the trial and 12 refused treatment, apparently following the advice of other physicians. Treats and controls were relatively similar by gender, age, disease duration, and length of treatment. Apparently, no treated patient withdrew from the study.

Functional evaluations of all patients included tests of reaction time (RT) and movement time (MT) (in response to auditory or visual stimulation), using eight successive stimuli in each hand. Because of considerable geographical distances, patients were contacted monthly by telephone to determine compliance and any side effects. Initial personal examinations were followed by two direct revisits—one at a mean of 24 months and the second at 45 ± 4 months for the treated patients and ± 41 for the control patients. By the third visit, all 12 controls were symptomatically worse in both RT and MT testing. Those treated with amantadine improved in three out of four RT measurements by the 24th month visit and one of the four at the 45th week. Movement time was improved in three of four measurements on both the second (24 months) and 45th, third, final evaluation.

Botez et al indicate only the presence of mild weight loss as having affected any of the amantadine-treated group.

### COMMENTARY

This study reported meticulous care in choosing testing patients with adult-acquired SCA. Not well understood is that patients on amantadine improved their right-side bodily function more than the left. Overall quality-of-life function receives no comment, although Botez et al speculate that the effect of amantadine might be to activate cerebellar-midbrain dopaminergic pathways. Nevertheless, Botez et al cite experiments in which amantadine improves MT in mutant mice by acting as an NMDA antagonist. Whatever the mechanism, these potentially important observations deserve testing a larger cohort in a double-blind, more rigorous clinical program. Such testing must be accompanied by a broader number of quantitative motor tests, serial video-monitored changes in behavior, and reaction as to patients' general improvement. As one of our colleagues, Dr. Steven Frucht of the Columbia-Presbyterian Movement Disorders Center, advises us, amantadine may sometimes benefit multisystem atrophy and mild cases of Parkinson's disease. Could this be a factor in any of Botez's patients? **—fp**

# An Examination of Nocturnal Frontal Lobe Epilepsy

ABSTRACT & COMMENTARY

**Source:** Provini F, et al. Nocturnal frontal lobe epilepsy, A clinical and polygraphic overview of 100 consecutive cases. *Brain* 1999;122:1017-1031.

Provini and colleagues identify three different patterns of nocturnal frontal lobe epilepsy (NFLE) in 100 cases, many of which in the past have been diagnosed simply as sleep disorders. All attacks occurred during non-REM sleep. All were thought to be derived from deep frontal lobe loci and most have benefited from antiepileptic drugs. All were identified by detailed clinical and audio-video EEG sleep studies. Most subjects had onsets in infancy or adolescence, but overall onsets ranged from 1 to 64 years. Males dominated 7 to 3.

One syndrome labeled as nocturnal paroxysmal dystonia (NPD) consisted of recurrent, sudden dystonic-dyskinetic attacks interrupting sleep and lasting for less than two minutes. Abnormal EEG records were often obtainable by placing special sphenoidal or zygomatic electrodes. Paroxysmal arousal (PA) attacks consisted of stereotypic behavioral activity lasting less than 20 seconds. Suggesting their epileptic origins, abnormal EEGs accompanied the attacks and antiepileptic drugs suppressed them. Some patients were susceptible to both NPD and PA attacks. The third pattern was characterized by episodic nocturnal wanderings (ENW) by Pedley and Guilleminault (*Ann Neurol* 1977;2:30-35) and consisted of somnambulic agitation. A major factor in classifying all three of these syndromes as being epileptic is that a number of individual patients show more than one pattern and a few have suffered all three.

Genetic patterns indicated that 39 (39%) of their 100 patients had at least one first-degree relative with a primary parasomnia. Twenty-five percent had a family history of epilepsy, several with multiple sufferers. Onset age for seizures ranged from 1 to 64 years (mean 14 ± 10). Overall the 100 patients reported 20 ± 11 seizures

monthly, of which 1-20 occurred at night. Specific triggering factors were uncertain and 28% of patients had more than one nighttime seizure pattern. Altogether, 72% of patients were unaware of their nocturnal attacks; 34% had occasional attacks during wakefulness. Neurological examinations were normal in 92%, two had mental handicaps, and the remainder were trivial. Imaging results included various potential epileptogenic abnormalities in 14%. Videosomnographics, however, revealed classic motor seizures in 93%, plus seven with only one episode, but who, nevertheless, expressed classic EEG abnormalities. Other evidence of video-EEG associations are detailed in the parent article in *Brain*.

All in all, findings included the following video-EEG patterns: patients with PA, 9; with NPD, 51; and with ENW, 40. PA patients all were otherwise normal; three accepted carbamazepine, of which two became seizure-free and one reduced by 75%. Of the NPD group, 24% had a structural brain injury. Of these, 24% became seizurefree with antiepileptics and another 31% had a 50% reduction of attacks. Of the ENW group, carbamazepine halted seizures in five and reduced seizures in at least half of the other 35.

Provini et al conclude that NFLE's relation to sleep often relates to a mesio frontal epileptic focus that activates during NREM sleep. Also, k complexo may sometimes cluster to trigger the epileptic focus. The table, adapted from Provini et al's article, lists epileptic and nonepileptic differences that divide relatively benign parasomnias from those of NFLE. (*See Table 1.*)

**Table 1**

**Clinical Criteria for Parasomnia and NFLE**

| | Parasomnia | NFLE |
|---|---|---|
| Onset age | < 10 years | 14 ± 10 years |
| Family history | ± 79% | 39% |
| Frequency/month | 0-4 | ± 25% |
| Future | Ceases ± 7 years | Increases ± 20 yrs |
| Length of attack | Up to 30 minutes | 2-180 secs |
| Movement | Physiologic | Violent, consistent |
| Precipitators | Sleep-deprived; fever; Stress; alcohol/drugs | ± 0 |
| Sleep stage onset | 3-4 REM | 2 NREM in ± 60% |

### COMMENTARY

This is an important paper for the therapy programs of both epileptologists and sleep center physicians. The cohort emphasizes patients whose nocturnal behaviors consisted of more complicated activity than most uncomplicated somnambulism. The relatively few persons who had only frequently repeated, stereotypic motor arousals were designated as PA. Since these overlapped the other syndromes in certain patients and they improved with anticoagulants suggests a frontal lobe epileptic focus. Your editor suspects that the Tinuper-Lugaresi-Montagna laboratory ordinarily does not study many children with uncomplicated somnambulism. Otherwise, the contribution provides considerable interest in how to treat unusual adolescent-mature somnambulism or young children with complicated sleep behavior. **—fp**

# Cancer, Paraneoplasia, and Peripheral Neuropathy

ABSTRACT & COMMENTARY

**Source:** Antoine JC, et al. Carcinoma associated paraneoplastic peripheral neuropathies in patients with and without anti-onconeural antibodies. *J Neurol Neurosurg Psychiatry* 1999;67:7-14.

Among 422 consecutive patients with peripheral neuropathy, 26 were associated with carcinoma in the absence of tumor infiltration, drug toxicity, or malnutrition. Other known causes of polyneuropathy were excluded by blood studies including sedimentation rate, protein immunoelectrophoresis, thyroid function, vitamin $B_{12}$, and folate levels. Cerebrospinal fluid analysis excluded leptomeningeal involvement. Nerve conduction studies and needle electromyogram were performed in all 26 patients, and 18 underwent superficial peroneal nerve biopsy. Screening for onconeural antibodies comprised standard anti-Hu, anti-Ri, anti-Yo, anti-amphyphysin, and anti-CV2 immunohistochemistry and western blotting on rat brain (Moll JW, et al. *Neurology* 1995;45:1937-1941).

Of the 26 patients with cancer-associated peripheral neuropathy, seven demonstrated onconeural antibodies: six showed anti-Hu antibodies with small cell cancer of lung or prostate, and the other had anti-CV2 antibodies and a mediastinal undifferentiated carcinoma. Neuropathy in these preceded the cancer by a mean of 10 months and, in the anti-Hu group, was generally disabling and predominantly sensory, with four patients also demonstrating paraneoplastic encephalomyelitis. Mild sensorimotor neuropathy and cerebellar ataxia characterized the anti-CV2 antibody patient. None of these seven patients demonstrated inflammatory changes pathologically and none responded to immuno-

suppression, including steroids, plasmapheresis, or intravenous immunoglobulin.

Of the 19 patients without onconeural antibodies, the neuropathies and cancer types were varied and diverse, the former comprising axonal sensory or sensorimotor polyneuropathy with upper motor neuron signs (n = 4), axonal sensorimotor polyneuropathy without upper motor neuron signs (n = 7), mononeuropathy multiplex (n = 2), or demyelinating neuropathy, most often chronic inflammatory demyelinating polyneuropathy. Cancer types included, among others, carcinoma of the stomach, colon, liver, pancreas, prostate, and melanoma.

Among this antibody negative group, those with more severe polyneuropathy (n = 14) were found to have cancer by a mean of 7.8 months following onset, their neuropathy was inflammatory in nature (11 of 14), and they responded to immunosuppression in the absence of central nervous system involvement. Those less disabled from neuropathy (n = 5) fell into a slowly progressive neuropathy group, with cancer diagnosed within a mean of 8.4 years, which may indeed have been coincidental. In the absence of onconeural antibodies, a cancer workup for inflammatory neuropathy is probably unwarranted unless associated with encephalomyelitis or vasculitis.

### COMMENTARY

Antiamphyphysin antibodies, first described in women with breast cancer and stiff man syndrome, react against the nerve terminal protein, amphyphysin, found in synaptic vesicles. Among 2800 serum samples tested for onconeural antibodies, Antoine and colleagues selected five samples with antiamphyphysin activity and found that its presence is nonspecific for either tumor type or neurological syndrome (Antoine JC, et al. *Arch Neurol* 1999;56:172-177). Two patients had Lambert Eaton myasthenic syndrome (LEMS) with small cell lung cancer, a third had small cell lung cancer discovered two years following limbic encephalitis, and two had encephalomyelitis, one with ovarian, and one with breast cancer, the latter also demonstrating sensory neuronopathy. None had stiff man syndrome and three had other antibodies, including antimitochondrial (n = 2), anti-voltage-gated calcium channel (n = 2), and anti-Hu antibodies (n = 1). Among the control groups, including: 1) various cancers (lung, colon, gynecologic) but without paraneoplastic illness subjects (n = 101); 2) small cell lung cancer with paraneoplastic illness (n = 8); 3) nonparaneoplastic neurologic illness (n = 40); and 4) normals (n = 30), only three of group 2 showed anti-amphyphysin antibodies.

Unlike the majority of CNS antibody-associated paraneoplastic syndromes that appear to have a cytotoxic T-cell pathogenic mechanism, stiff man syndrome, like LEMS and myasthenia gravis, is likely antibody mediated (Dalmau JO, Posner JB. *Arch Neurol* 1999;56:405-408). **—mr**

# Preoperative Evaluation of Endarterectomy Patients

ABSTRACT & COMMENTARY

**Source:** Rothwell PM, Warlow CP. Prediction of benefit from carotid endarterectomy in individual patients: A risk-modelling study. *Lancet* 1999;353:2105-2110.

Carotid endarterectomy is the treatment of choice in patients with recently symptomatic severe carotid stenosis. Two randomized controlled trials, the European Carotid Surgery Trial (ECST) (European Carotid Surgery Trialists' Collaborative Group. *Lancet* 1991;337:1235-1243) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1991;325:445-453), showed that endarterectomy lowers the risk of major ischemic stroke by 50% over the next three years in patients with symptomatic 70-99% carotid stenosis. Nevertheless, the three-year stroke risk on best medical therapy alone is only about 20%. Therefore, surgery is not necessary and may be harmful in 80% of patients.

In fact, ECST found that surgery is harmful in patients with less than 70% stenosis (ECST Collaborative Group. *Lancet* 1998;351:1379-1387). NASCET reported a small benefit from surgery in patients with 50-69% stenosis, but no benefit in those with 30-49% stenosis (NASCET Collaborative Group. *N Engl J Med* 1998;339:1415-1425). Because of different methodologies, a 50-69% stenosis in NASCET is equivalent to a 70-80% stenosis in ECST (Barnett HJM, Warlow CP. *Stroke* 1993;24:1281-1284; Rothwell PM, et al. *Stroke* 1994;25:2435-2439).

Based on data from ECST patients with 0-69% carotid stenosis, Rothwell and Warlow developed two prognostic models (*see Table 2*), a medical model that predicted risk of major ischemic stroke on medical treatment and a surgical model that predicted risk of stroke or death within 30 days of endarterectomy. The predictive score is based on seven independent factors. Risk points were derived by rounding the hazard ratio to the nearest whole number and subtracting one. In order to identify patients most likely to benefit from endarterec-

tomy, the predictive score adds points for the presence of factors associated with a high stroke risk despite medical treatment. It then subtracts points for the presence of variables that increase operative stroke or death risk. Since the risk of stroke on medical treatment in ECST or NASCET patients with 70-99% stenosis was double the operative risk of stroke or death, surgical risk points are subtracted from the predictive score and their weighting is decreased by 50% (*see Table 2*).

**Table 2**

**Prognostic Model**

| | Hazard Ratio (95% C7) | P | Risk Points | Predictive Score |
|---|---|---|---|---|
| **Medical Model** | | | | |
| 1. Cerebral vs. ocular events | 2.45 (1.09-3.71) | 0.02 | 1 | 1 |
| 2. Irregular plaque | 2.09 (1.21-3.62) | 0.008 | 1 | 1 |
| 3. Event within past 2 months | 1.82 (1.02-3.18) | 0.04 | 1 | 1 |
| 4. Carotid stenosis | 1.30 (1.10-1.40) | 0.001 | 0-2* | 0-2 |
| **Surgical Model** | | | | |
| 5. Female | 2.05 (1.29-3.24) | 0.002 | 1 | -0.5 |
| 6. Peripheral vascular disease | 2.48 (1.51-4.13) | 0.0004 | 1 | -0.5 |
| 7. Systolic BP > 180 mmHg | 2.21 (1.29-3.79) | 0.004 | 1 | -0.5 |

*Carotid Stenosis 70-79% = 0; 80-89% = 1; 90-99% = 2.

When ECST patients in the 70-99% stenosis group were stratified using the scoring system, scores ranged from 0-5.0 (*see Table 3*). Endarterectomy was significantly beneficial in only the 16% of patients who had risk scores of 4 or more. In these patients, there was a 33% absolute reduction in the five-year actuarial risk of stroke.

**Table 3**

**Stratification of ECST Patients**

| Risk Score | Patients | | Total | Adverse Events | |
|---|---|---|---|---|---|
| | Surgery | Medical Treatment | | Surgery* | Medical** Treatment |
| 0-3.5 | 495 | 333 | 828 (84%) | 58 | 39 |
| 4.0-5.0 | 101 | 61 | 162 (16%) | 7 | 24 |
| Total | 596 | 394 | 990 (100%) | 65 | 63 |

*Operative stroke or death

**Ipsilateral major ischemic stroke

Rothwell and Warlow conclude that the use of risk-factor modeling can be used to identify patients with a high risk of stroke and a low operative risk in whom endarterectomy will be beneficial.

### COMMENTARY

The overall positive result of a multicenter clinical trial may at times obscure substantial unevenness of therapeutic effect across groups of patients. In fact, patients may appear to be homogenous, but actually have differing risks of poor outcome. Rothwell and Warlow have tried to analyze the heterogeneity of effect of endarterectomy in the ECST population by developing a predictive model to stratify patients according to both risk of stroke and of surgical complications. As they acknowledge, their predictive score needs validation by application to other data such as the NASCET results. Nevertheless, their scoring system is clear, logical, and apparently easy to apply. *Neurology Alert* thinks clinicians might well test its predictive power in their own patients. **—jjc**

# Febrile Convulsions: The Pendulum Swings

ABSTRACT & COMMENTARY

**Source:** McDonald BK, et al. Febrile convulsions in 220 children—neurological sequelae at 12 years follow-up. *Eur Neurol* 1999;41:179-186.

Febrile convulsions (fc) are the most common seizure type in humans, occurring in some 2-5% of children aged 6 months to 6 years in U.S. and European populations and in perhaps as many as 6-9% in Asian populations. The simple view that FC are without long-term sequelae and without implication for future epilepsy is rapidly changing, along with the definition of genetic and environmental factors that are associated with this seizure type (Kugler SL, Johnson WG. *Brain Dev* 1998;20:265-274).

McDonald and associates examined the risk of development of future epilepsy in 220 children with a 12-year follow-up. This study was a component of the almost 20-year-old National General Practice Study of Epilepsy (NGPSE) in the United Kingdom, which prospectively follows 1195 patients of all ages from the time of first identified seizures. Maintenance of a registry among all general practitioners in the UK with a unique study

identification number for each patient enables detailed long-term surveillance to be performed.

Of the 220 patients studied, 12 (5.9%) later developed recurrent unprovoked seizures (i.e., epilepsy) as compared to a general population lifetime incidence of 1.4%. Among the factors that seemed to be associated with increased 12-year risk of future epilepsy the presence of four or more FCs (odds ratio, OR =9.4, P = 0.015) seemed most clearly defined. Complex features, which McDonald et al consider as: 1) focal seizure at onset or post-ictally; 2) recurrent seizures during same febrile illness; or 3) convulsion lasting longer than 10 minutes, may presage future neurological deficit, but not epilepsy. For example, McDonald et al found that the presence of any complex feature does not significantly increase the 12-year risk of future epilepsy, but increases the risk of neurological deficits at 12-year follow-up by 5.1-fold (P = 0.0038). Other recent studies have stressed that focal complex febrile convulsions (CFC) may be of particular concern, with definite MRI abnormalities detected in six of 15 patients with focal CFC but in none of 12 patients with non-focal CFC (VanLandingham KE, et al. *Ann Neurol* 1998;43:413-426); however, it is not clear if the MRI abnormalities are causally related to convulsions.

### COMMENTARY

What one would really want to know is the implication of febrile seizures on the lifetime risk of epilepsy. According to the McDonald et al study, the cumulative risk of epilepsy seems to continue to increase with length of follow-up: 1.4% by two years, 3.3% by five years, 5.2% by 10 years, and 6.0% by 12 years. The lifetime risk of epilepsy in a patient with FCs, if these results are extrapolated, would translate to a risk exceeding 20%. It may be possible to define subpopulations (such as patients with > 4 seizures, or with certain genetic predisposition) that will have higher lifetime risks. In any event, it is clear that long-term follow-up of patients will be needed in order to determine minimal estimates of total lifetime risk.

Do these results have any implication to the current expectant, do-little approach to the management of FCs? Not immediately, as McDonald et al point out. A 12-year increase in risk of epilepsy from about 1% to 6% probably does not warrant the risk of a 12-year exposure to any currently available anticonvulsant. However, if genetic and clinical factors can be better defined in order to clarify "febrile convulsion syndromes," there might be certain populations of patients with especially high lifetime risks in which the need for treatment could be reconsidered. **—rt**

# Paraneoplastic Presentations of Testicular Cancer—Clinical and Immunological Characterization

ABSTRACTS & COMMENTARY

**Sources:** Voltz R, et al. A serologic marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. *N Engl J Med* 1999;340:1788-1795; Dalmau J, et al. Ma1, a novel neuron- and testis-specific protein, is recognized by the serum of patients with paraneoplastic neurological disorders. *Brain* 1999;122:27-39; Bennett JL, et al. Neuro-ophthalmologic manifestations of a paraneoplastic syndrome and testicular carcinoma. *Neurology* 1999;52:864-867.

In this study by voltz and colleagues, 13 testicular cancer patients with a syndrome of limbic and brainstem encephalitis were tested for the presence of serum antineuronal antibodies. Ten of these patients (ages 26-45) had antibody positive sera against a 40-kd protein, which were then used to identify a cDNA clone (termed Ma2) from a recombinant brain library. The expression of Ma2 is normally highly restricted to the brain and testis (2 immunologically isolated organs that do not typically express MHC antigens), and is likely to be a phosphoprotein.

The study by Dalmau and colleagues describes a related neuronal protein (Ma1) that was characterized with antibodies from four patients' sera with other tumor types (parotid, breast, colon, and large cell lung cancer) and a paraneoplastic limbic encephalitis. Three patients had brainstem and cerebellar dysfunction, and one had dysphagia and motor weakness.

In a detailed report of two cases by Bennett and associates, the patients, ages 28 and 30, presented with supranuclear gaze disorders and limbic encephalitis associated with testicular cancer. One patient had confusion, somnolence, visual and auditory hallucinations, and a vertical gaze palsy. The second had vertical diplopia that progressed to oscillopsia with dysarthria and ataxia.

### COMMENTARY

In these three related papers by investigators at

Memorial Sloan Kettering Cancer Center, a growing family of paraneoplastic antigens is further defined. Their findings have importance for clinical practice, beyond the excellent clinical characterization of this syndrome; in eight of the 10 patients studied by Voltz et al, the neurologic symptoms and signs preceded the diagnosis of testicular cancer. Thus, in male patients presenting with a limbic and brainstem encephalitis, an underlying malignancy may be diagnosed at an earlier and potentially more curable stage. The serum assay for Ma1/Ma2 is now offered as a commercial test by Athena Diagnostics (800-394-4493).

Even with apparent resection of testicular cancer, however, the neurological disorder often does not improve even with plasmapheresis or IVIG. This refractory disease process may reflect, in part, irreversible neuronal loss and gliosis, in addition to an activated T- and B-cell population directed against the Ma1 and Ma2 brain antigens. At present, our ability to diagnosis paraneoplastic diseases surpasses our ability to treat them. Although uncommon, a paraneoplastic disorder should be considered in certain patients with limbic and brainstem encephalitis not related to infection or toxic-metabolic causes. **—ba**

## CME Questions

**9. Each of the following is associated with an increased risk of stroke or death following endarterectomy *except*:**
a. female sex.
b. peripheral vascular disease.
c. uncontrolled hypertension.
d. male sex.
e. systolic hypertension more than 180 mmHg.

**10. Amantadine has recently been tested for its action on spinal cerebellar atrophy (SCA). Which one of the following statements is correct?**
a. Amantadine-receiving patients with SCA are improved in reaction time (RT) and movement time (MT) only at a 24-month therapeutic follow-up interval.
b. At the 24-month review, the SCA patients not taking amantadine are equally improved.
c. SCA patients taking amantadine improve in both RT and MT at 45 months.
d. Patients taking amantadine for 45 months are said to improve more in the right side of their bodies than the left.

**11. Abnormalities on a diffusion-weighted MRI in a patient with TIA symptoms:**
a. are an early indication of irreversible cerebral ischemia.
b. are most often observed in patients with TIAs of less than one hour duration.
c. tend to be less conspicuous and less voluminous than those seen in stroke.
d. should trigger a search for causes other than ischemia.

**12. Which one of the following statements is true?**
a. The peripheral paraneoplastic neurological syndromes likely have a cytotoxic T-cell mediated pathogenesis.
b. The central nervous system paraneoplastic neurological syndromes likely have an antibody-mediated pathogenesis.
c. Even in the absence of onconeural antibodies, a cancer workup is indicated in cases of acute inflammatory demyelinating polyneuropathy.
d. Antiamphyphysin antibodies are specific for stiff man syndrome and of an underlying lung cancer.
e. None of the above

**13. Which of the following statements is *incorrect*?**
a. Paraneoplastic limbic encephalitis usually precedes the diagnosis of cancer.
b. Paraneoplastic limbic encephalitis is only seen with testicular cancer.
c. The brain protein Ma2 is also found in the testis.
d. Plasmapheresis has not been an effective therapy in paraneoplastic limbic encephalitis.

**14. The risk of epilepsy within 12 years after febrile convulsions in childhood:**
a. is the same as in a patient without a history of febrile convulsions.
b. may be higher if there is a history of multiple (> 4) febrile onvulsions.
c. does not seem to increase beyond the risk of epilepsy at five years of follow-up.
d. is much higher if the febrile convulsions have complex features.
e. is extremely similar to the risk of neurological deficits at 12-year follow-up.

## Correction

In the article "CSF Tests for AD," in the July 1999 issue of *Neurology Alert*, Ab42 throughout the article should have been $Ab_{42}$. In the second paragraph of the commentary section, the first two sentences should read as follows: The multicenter study by Hulstaert et al provides another citation in support of the association between high CSF tau, low CSF $Ab_{42}$ levels, and AD. However, this study does little to advance the clinical use of these markers for diagnostic purposes.

In CME question number 1, Ab42 should have been $Ab_{42}$ throughout. We regret any confusion this may have caused. ❖

## In Future Issues:

Follow-up Study of Patients Treated with tPA Within Three Hours After Onset of Acute Stroke Symptoms