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INSIDE

PML Complicating Treatment with Natalizumab (Tysabri) for MS

ABSTRACTS & COMMENTARY

By Brian R. Apatoff, MD, PhD

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Dr. Apatoff is on the speaker's bureau of Biogen and Teva.

Synopsis: *These 2 cases demonstrate a tragic complication of natalizumab therapy in this promising novel immune modulatory therapy, and the difficulties of predicting late stage drug failures in the difficult and costly process of drug development.*

Sources: Langer-Gould A, et al. Progressive Multifocal Leukoencephalopathy in a Patient Treated With Natalizumab. *N Engl J Med*. 2005;353:375-381; Kleinschmidt-DeMasters BK, et al. Progressive Multifocal Leukoencephalopathy Complicating Treatment With Natalizumab and Interferon Beta-1a for Multiple Sclerosis. *N Engl J Med*. 2005;353: 369-374.

TWO CASE REPORTS OF PROGRESSIVE MULTIFOCAL LEUKOENcephalopathy (PML) complicating treatment of multiple sclerosis (MS) with natalizumab were studied in a phase III clinical trial that had led to the early FDA approval on the basis of one year safety-efficacy data. Natalizumab is a monoclonal antibody against an alpha-4 integrin adhesion molecule on lymphocytes that prevents normal attachment on the vascular endothelium of the blood brain barrier and limits trafficking into the central nervous system. It was shown to be highly effective in phase II and phase III clinical trials in reducing clinical and MRI measures of MS disease activity (see *Neurology Alert*. February, 2005)

The first patient was a 45-year-old man with relapsing-remitting MS diagnosed in 1983, treated interferon beta-1a since 1998, who was treated with monthly infusions of natalizumab for 28 months. The first PML lesion seen on MRI was thought to be indistinguishable from a MS lesion, but PML

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was confirmed ultimately by brain biopsy. The patient deteriorated quickly, becoming quadraparetic and minimally responsive despite treatment with corticosteroids, IVIG, and cidovir. Three months after discontinuing natalizumab, he developed changes thought to be consistent with an immune-reconstitution inflammatory syndrome. Two additional months after treatment with cytarabine, his condition had improved.

The second patient was a 46-year-old woman diagnosed with relapsing-remitting MS in 1999, treated with weekly interferon beta-1a since 2000, and then treated with 37 monthly doses of natalizumab. She developed a rapidly progressive right hemiparesis and aphasia that was treated with IV corticosteroids. PML was confirmed on autopsy.

COMMENTARY

These 2 cases demonstrate a tragic complication of natalizumab therapy in this promising novel immune modulatory therapy, along with the difficulties of predicting late stage drug failures in the difficult and costly process of drug development. PML is typically a consequence of profoundly impaired cellular immunity, such as seen in AIDS, leukemia, or chronically immunosuppressed organ-transplant recipients. The only effective treatment for PML is immune-reconstitution, for example, with strong anti-retroviral therapy, in the case of HIV infection, to allow for recovery of T-cells.

Questions remain about the potential use of natalizumab in the future, given that the drug was shown to be safe and highly effective in clinical trials in which several hundred patients were dosed. Could the drug be used with relative safety, with more limited dosing regimens of possibly 12 months, since both PML cases were treated for over 2 years before their adverse event was detected? However, a third case of PML occurred in a patient that received just 8 doses of natalizumab for Crohn's disease, but who was on additional immunosuppressives including azathioprine (*N Engl J Med*. 2005; 353:362-368). Both MS cases of PML were detected in a clinical trial combining natalizumab and interferon beta-1a, but none in a monotherapy trial for MS with natalizumab alone. Did interferon beta-1a increase the relative risk of acquiring PML, possibly inducing mild lymphopenia, or by additional reduction of T-cells trafficking across the blood-brain barrier? If the drug is allowed to be given in limited dosing regimens, for example in patients with severe MS refractory to other treatments, could it be re-dosed after an acceptable period of time to allow for immune recovery? These and other complicated questions will be addressed by the FDA in the months ahead. .■

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Review: Treatment of Inflammatory Neuropathies

ABSTRACT & COMMENTARY

Michael Rubin, MD

Professor of Clinical Neurology, NewYork-Presbyterian Campus

Dr. Rubin is on the speaker's bureau for Athena Diagnostics and does research for Viatris.

Synopsis: *Neuropathies with IgM monoclonal gammopathy may respond to various chemotherapeutic agents, although the long-term effects are unknown.*

Source: Finsterer J. Treatment of Immune-Mediated, Dysimmune Neuropathies. *Acta Neurol Scand*. 2005;112: 115-125.

IMMUNE-MEDIATED, INFLAMMATORY NEUROPATHIES may be acute or chronic and occur with an incidence

of 2-4/100,000 worldwide. All are potentially treatable, and a timely review of this topic is presented.

Guillain-Barre syndrome (GBS) may involve the myelin (acute inflammatory demyelinating polyradiculoneuropathy) or the axon (acute motor axonal neuropathy, acute motor and sensory axonal neuropathy, AMAN and AMSAN, respectively) and, in two-thirds of cases, is preceded by *C. jejuni*, cytomegalovirus, Epstein-Barr, or *M. pneumoniae* infection. When the autonomic nervous system is the primary target, acute pandysautonomia results, while Miller Fisher syndrome comprises ophthalmoplegia, ataxia, and areflexia. Clinical trials have demonstrated that plasma exchange and intravenous immune globulin (IVIG, 0.4 mg/kg/day for 5 days) are equally efficacious for moderate or severe disease, including acute pandysautonomia. No convincing evidence justifies the administration of oral or intravenous corticosteroids, even in combination with IVIG. Interferons are of no proven benefit, and may even trigger GBS.

Chronic inflammatory demyelinating polyneuropathy (CIDP) includes several entities whose treatment differs. Classic, idiopathic CIDP is an acquired, immune mediated, symmetric neuropathy causing proximal and distal weakness with sensory impairment. By definition, it progresses over at least 8 weeks, thereby differentiating it from the more acute GBS, which nadirs by 4 weeks. Controlled clinical trials have proven the efficacy of oral prednisone, plasma exchange, and IVIG for the majority of CIDP patients. For the one-third that do not respond, cyclophosphamide, cyclosporine, or etanercept (Enbrel) may be beneficial, but azathioprine, methotrexate, and mycophenolate mofetil (CellCept) are not. Interferons are under investigation, but do not look promising. Rituximab, a monoclonal antibody against CD20, has shown promise in individual case reports.

Up to 22% of CIDP patients demonstrate a monoclonal gammopathy, IgM, IgG, or IgA, having no autoantibody activity and not associated with underlying hematologic malignancy. Termed CIDP with monoclonal gammopathy of undetermined significance (MGUS), its treatment is identical to idiopathic CIDP, as it responds to corticosteroids, plasma exchange, and IVIG. Azathioprine may be used as a steroid-sparing agent, but is contraindicated together with allopurinol.

CIDP develops in 17% of diabetics, and electrodiagnosis of CIDP in these patients is challenging, given the frequent presence of underlying diabetic polyneuropathy. Progressive symmetric or asymmetric motor and sensory neuropathy, despite good diabetic control, and in the presence of elevated cerebrospinal fluid protein, should alert the physician to possible concomitant CIDP. CIDP diabetics respond best to corticosteroids, and less often to plasma exchange or IVIG, compared to idiopathic CIDP.

Multifocal motor neuropathy with conduction clock (MMNCB) is a slowly progressive disorder predominantly affecting young adults, resulting in asymmetric weakness in the distribution of individual nerves, usually worse in the distal arms, and often mimicking motor neuron disease. Unlike CIDP, cerebrospinal fluid protein is usually normal, as are sensory nerve conduction studies, and patients do not respond to corticosteroids or plasma exchange. IVIG is the controlled-trial-proven treatment of choice for 80% of cases, with refractory patients responding to cyclophosphamide or rituximab, and perhaps interferon-beta. Mycophenolate mofetil appears ineffective.

Multifocal-acquired demyelinating sensory and motor neuropathy (MADSAM or Lewis-Sumner syndrome) presents as a mononeuropathy multiplex, affecting both motor and sensory fibers in an asymmetric pattern, with a laboratory profile and therapeutic response pattern similar to CIDP. It may indeed simply be asymmetric CIDP. Sensory impairment and elevated cerebrospinal fluid protein in up to 80%, distinguish it from MMNCB, a critical distinction as one-third of MADSAM patients respond to corticosteroids. IVIG benefits two-thirds. MADSAM with axonal, rather than demyelinating features is designated MASAM (multifocal acquired sensory and motor neuropathy), and also responds well to IVIG.

DADS denotes distal-acquired demyelinating sensory neuropathy, and presents with prominent sensory symptomatology, while affecting both sensory and motor fibers. As distinct from CIDP, IgM kappa monoclonal gammopathy is present in nearly two-thirds, of which 67% have anti myelin-associated glycoprotein (MAG) antibodies. Response to immunomodulating therapy is poor in those with gammopathy. DADS without gammopathy respond to corticosteroids, IVIG, or plasmapheresis.

Paraproteinemic neuropathies may be associated with underlying hematologic malignancy, and treatment of the neuropathy is directed at the underlying condition. Among others, these include Waldenstrom's macroglobulinemia, which may rarely be

associated with a painful sensory axonal neuropathy, possibly due to underlying vasculitis. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) is associated with a monoclonal lambda sclerotic plasmacytoma in over 95%, and dramatically responds to thalidomide, itself neurotoxic. Mixed cryoglobulinemia may be associated with polyneuropathy, and rituximab shows promise for its treatment. GALOP (gait ataxia and late-onset polyneuropathy) demonstrates a monoclonal IgM-kappa protein and specific IgM binding to the central nervous system white matter antigen, galopin. IVIG is beneficial.

COMMENTARY

Rituximab (Rituxan) is the first monoclonal antibody approved by the FDA for cancer therapy, and may also be effective in autoimmune diseases. Genetically engineered, it is a human-mouse chimeric monoclonal antibody, containing human heavy-chain and light-chain constant-region sequences and murine variable-region sequences (*Annu Rev Med*. 2004;55;477-503). CD-20, a 35-kDa transmembrane lymphocyte antigen involved in cell-cycle progression and differentiation, is its target, and accounts for rituximab's specificity. It is present exclusively on B cells, from pre-B cells to activated B cells, but not differentiated plasma cells. B cells are depleted, but antibody production is maintained. Hematopoietic stem cells replenish normal peripheral B cells within 3-12 months post therapy.

Rituximab is relatively well tolerated, with the majority of adverse events being infusion-related and including fever and chills, with occasional dyspnea and hypotension, the latter sporadically mandating interruption of infusion and resumption at a slower rate. Rarely, death or tumor lysis syndrome encompassing acute renal failure, electrolyte abnormalities, and hyperuricemia are seen, particularly in the presence of a higher tumor burden. Mucocutaneous reactions are exceedingly rare and include Stevens-Johnson syndrome, toxic epidermal necrolysis, and paraneoplastic pemphigus.

Rituximab is efficacious for malignant, as well as non-malignant conditions, including autoimmune hemolytic anemia, refractory immune thrombocytopenia, refractory thrombotic thrombocytopenic purpura, rheumatoid arthritis, and systemic lupus erythematosus. Case reports suggest its may be beneficial for autoimmune neuropathy. Multiple sclerosis appears to be its next stop.

Genetic Predictors of AED Dosing

ABSTRACT & COMMENTARY

By Barry Kosofsky, MD

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Dr. Kosofsky reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Synopsis: *This report provides evidence of a drug target polymorphism in epilepsy patients predictive of their maintenance dose of AEDs.*

Source: Tate SK, et al. Genetic Predictors of the Maximum Doses Patients Receive During Clinical Use of the Anti-Epileptic Drugs Carbamazepine and Phenytoin. *Proc Natl Acad Sci*. 2005:102;5507-5512.

Anti-epileptic drugs (AEDs) are the mainstay in the treatment of epilepsy. Phenytoin and carbamazepine, specifically, are very effective, yet sometimes a challenge to dose accurately in patients with epilepsy, in part because of the narrow therapeutic index of phenytoin and the auto-induction of metabolism of carbamazepine. There is also high individual variability in the required maintenance dosage. Moreover, an acceptable balance between the effective maintenance dose and associated adverse drug reactions can be difficult to achieve. As a result, identifying an acceptable dose and regimen for such AEDs often involves trial and error, which can delay achieving therapeutic efficacy. This impedes prompt adequate control of seizures. Theoretically, genetic diagnostic testing may reduce this delay by offering individualized ways to predict the maximum dose of AEDs for each patient based on genetic predispositions for drug metabolism. This retrospective report investigates this theoretical concept in epilepsy patients who were treated with carbamazepine and/or phenytoin. The genetic targets of investigation for this study were the variant alleles in the phenytoin metabolic pathway, the CYP2C9 alleles 1, 2, 3, as well as the variants of the SCN1A gene. This encodes voltage-sensitive sodium channels, the main therapeutic target of both carbamazepine and phenytoin efficacy. Variations of these genes were investigated in 425 patients taking carbamazepine and 281 patients taking phenytoin.

This report indicates that the CYP2C9*3 allele is significantly associated with the highest plasma levels of

phenytoin. Individuals with 0, 1, or 2 copies of the CYP2C93 allele require significantly lower amounts of phenytoin (354mg, 309mg, and 250mg, respectively) as their maximum daily maintenance dose. Recent evidence indicates that individuals with allele 3 have a significant reduction in phenytoin clearance, compared to those with alleles 1 and 2.

Furthermore, variants of SCN 1A were found to have a significant association with maximum doses of both phenytoin and carbamazepine. Overall, individuals with AA, AG, and GG genotypes averaged maximum doses of 373mg, 340mg, and 326mg of phenytoin, respectively and 1313mg, 1225mg, and 1083mg of carbamazepine, respectively. Clinically, this finding suggests the target dose that would be well tolerated is lower in the presence of the GG allele.

Additional molecular genetic insights were reported in this study. The SNP7 polymorphism in the SCN1A gene can influence alternate splicing of exon 5N. Of note, seizures are known to up-regulate exon 5N inclusion in SCNIA a rodent model. Tate and colleagues report significantly higher levels of SCN1A with exon 5N in the cadaveric brain tissue of epilepsy patients (~12.6 %), compared to that of Parkinson's patients (9.5 %). Furthermore, among epilepsy patients, a more detailed genetic analysis based on the SCN1A gene showed differences in patients who underwent surgery for intractable epilepsy. Brain tissue resection showed that the amount of SCN1A copies with exon 5N was significantly upregulated in the temporal lobe, compared to the hippocampus in individuals with the GG genotype vs other patients with AG and AA genotypes. While the clinical significance of the difference in the presence of exon 5N in extra-hippocampal temporal cortical regions vs hippocampus is unclear, these findings provide evidence of a genetic component related to the SCN1A gene in contributing to the epilepsy in humans.

COMMENTARY

While these novel findings are intriguing, they probably will not substantially alter our current practice of dose escalation until seizures are well controlled in the absence of clinical toxicity. The maximum recorded doses of these medications imply that a maximum tolerated dose and/or a satisfactory efficacy in preventing seizures is associated with CYP2C9 genotypes.

This paper reveals 2 interesting associations with the G allele of the SCN1A gene; an association with decreased AED doses required for both phenytoin and carbamazepine, and a correlation of increased exon 5N copies in the temporal lobes vs hippocampus of patients with epilepsy who required surgical resection of those structures for intractable epilepsy.

In summary, the findings clearly demonstrate that the CYP2C9 3 and the G allele of SCN1A are associated with lower AED doses for efficacy. Additionally, the G allele of SCN1A is associated with intractable epilepsy. While the direct clinical correlates are yet to be determined, and the specific role of the exon 5N copies of SCN1A in epilepsy are as yet unknown, the evidence provided implies that genotyping may eventually serve as an essential clinical tool in the diagnostic, therapeutic, as well as prognostic components involved in our approaches to epilepsy.

Transient Ischemic Attack: Short-Term and Long-Term Risk Factor for Stroke

ABSTRACT & COMMENTARY

By Dana Leifer, MD

Associate Professor of Neurology, Weill Medical College of Cornell University

Dr. Leifer reports no consultant, stockholder, speaker's bureau, research, or other financial relationship related to this field of study.

Synopsis: *Patients who have had a transient ischemic attack have not only a high short-term chance of ischemic stroke but also a long-term risk of vascular events over 10 years or more.*

Source: van Wijk I, et al. Long-Term Survival and Vascular Event Risk After Transient Ischaemic Attack or Minor Ischaemic Stroke: A Cohort Study. *Lancet*. 2005;365: 2098-2104.

ALTHOUGH THE SYMPTOMS OF TRANSIENT ISCHEMIC attack (TIA) are often minor and fleeting, several studies have demonstrated that TIAs should be taken seriously and evaluated quickly because of the short-term risk of potentially devastating ischemic stroke. Johnston and colleagues reported that, in a cohort of 1707 TIA patients, 5.3% had a stroke within 48 hours and an additional 5.3% had a stroke between 2 and 90 days after the presenting TIA (*JAMA*/. 2000;284:2901-2906). Moreover, Rothwell and colleagues demonstrated in a study incorporating results from 2 population-based studies and 2 randomized clinical trials that 15% to 26% of stroke patients had a preceding TIA. Of the patients who had a TIA, 17% occurred on the day of the stroke, 9% on the day before the stroke, and an additional 19% between 2 and 7 days before the

stroke (*Neurology*. 2005;64:817-820).

In addition, multiple studies have indicated that 35% to 67% of ischemic episodes producing only transient signs and symptoms are actually associated with evidence of acute infarction, when MRI studies with diffusion-weighted imaging (DWI) is performed. A recent report by Ay and colleagues studied a group of 87 patients with transient ischemic symptoms, of whom 36 had DWI-positive infarcts. They suggest that transient symptoms (less than 24 hours in duration) with a DWI-positive infarct may represent a particularly unstable problem, with an 8.3% risk of stroke during the admission for the transient symptoms (*Ann Neurol*. 2005;57:679-686). In contrast, none of their patients with TIA and normal DWI had a stroke before discharge from the hospital. Only 1.3% of a control group of patients with clinical stroke syndromes, who had symptoms lasting longer than 24 hours, had a second stroke while hospitalized.

Taken together, these studies strongly suggest that rapid evaluation and treatment of patients with transient ischemic symptoms is appropriate in an attempt to reduce the short-term risk of stroke. Furthermore, a MRI to screen for DWI-positive lesions may be useful to identify high-risk patients.

A recent paper by van Wijk and colleagues (*Lancet*. 2005;365:2098-2104) provides additional information about the natural history of TIA and minor ischemic stroke over the long-term. They followed 2447 patients with TIA or minor ischemic stroke who had been enrolled in the Dutch TIA trial (DTT). This trial compared 30 mg of aspirin daily to 283 mg for up to 4 years. After the end of the DTT, patients resumed standard medical care. van Wijk et al now report that the 10-year risk of vascular events was 35.8% for TIA patients and 47.8% for patients with minor stroke. They do not report whether any of the TIA patients had DWI-positive infarcts on MRI.

van Wijk et al do report the time course of events for stroke and TIA patients combined, but not for TIA patients alone. The annual risks of stroke and other vascular events declined from 4.6% and 2.4%, respectively, in the first year, to approximately 1.0% and 2.5%, respectively, in the third year. The rates then gradually rose to about 2% and 5%, respectively.

The results suggest that the relative risk of recurrent stroke and other vascular events changes over time. The risk of stroke is greatest at first, then declines, and then after the first 3 years increases slowly. The risk of over vascular events also declines over the first 3 years, and then gradually increases and becomes greater than the risk of stroke.

van Wijk et al do not provide a definitive explanation for these results, but they do propose several plausible hypotheses. They suggest that the decreased risk in the first 3 years could reflect antiplatelet therapy and better control of risk factors during the trial, and increased risk after 3 years could reflect changes in management and in closeness of follow-up after the end of the Dutch TIA trial (DTT). Stabilization of plaque that caused the initial ischemic event could also explain the drop in stroke rate over time, whereas the increased rate of other ischemic events could reflect progression of underlying atherosclerosis.

In any case, ongoing efforts to manage vascular risk factors such as hypertension, diabetes, and hypercholesterolemia appear to be important for years after a TIA or minor stroke. Each of these risk factors was found to be associated with a significantly increased risk of major vascular events in general, and hypertension and diabetes were also associated with a significantly increased risk of stroke in particular.

In conclusion, there is now evidence not only that prompt evaluation of patients with transient ischemic syndromes is needed to attempt to reduce the incidence of stroke acutely, but also that ongoing follow-up is important and should focus on risk factor management to reduce the chance of ischemic events of all types in the long run. ■

Fleur du Mal: IRIS in AIDS-Related PML

ABSTRACT & COMMENTARY

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Dr. Caronna reports no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study.

Synopsis: *Better understanding of the mechanisms of the IRIS may enable prevention or cure of this severe, sometimes fatal complication of HAART.*

Source: Vendrely A, et al. Fulminant Inflammatory Leukoencephalopathy Associated With HAART-Induced Immune Restoration in AIDS-Related Progressive Multifocal Leukoencephalopathy. *Acta Neuropathol*. 2005;109:449-455.

THE CLINICAL INTRODUCTION OF COMBINATION anti-retroviral treatment, also called highly

active anti-retroviral therapy (HAART), has dramatically reduced morbidity and mortality in human immune virus (HIV) infected patients. HAART-induced immune restoration has improved survival in AIDS patients with progressive multifocal leukoencephalopathy (PML),[1] and has become standard therapy for AIDS-related PML. Nevertheless, PML can develop in AIDS patients while on HAART.[2] In some PML patients with prolonged survival, neurological and radiological signs may not improve or may even worsen despite good virological and immunological response to HAART.[2,3] In rare instances, immune reconstitution inflammatory syndrome (IRIS) causes acute deterioration of both clinical and radiologic features. A recent case of IRIS in a patient with AIDS-related PML led us to review the case report by Vendrely and colleagues.

A 52-year-old man, HIV positive for 16 years, began HAART (lopinavir boosted by ritonavir, lamivudine and zidovudine, then didanosine) 4 weeks after hospital admission for confusion, aggressiveness, and aphasia. Initial MRI showed nonenhancing T1 hypointense and FLAIR hyperintense lesions in the left hemisphere consistent with PML. CSF tests were negative for pathogens, including PCR for JC virus.

One month later, in the setting of a reduced viral load and a strong immunological response to treatment, his neurological condition worsened. A second brain MRI showed an increase in the size and number of lesions, and enhancement of all lesions. Stereotactic biopsy of a lesion showed severe inflammation and demyelination. He was treated with high doses of corticosteroids without improvement and died 3 months later of sepsis.

At postmortem examination, multiple demyelinating lesions were found in the subcortical areas of the cerebral and cerebellar hemispheres. Most were small and discrete but some were large, confluent, and necrotic. Microscopic examination showed lesions characteristic of PML, with an intense inflammatory reaction and abundant swollen oligodendrocytes containing JC virus. No other infectious agent could be identified. The intense perivascular inflammation correlated topographically with the areas of contrast enhancement noted antemortem on MRI. In addition to the inflammatory PML changes, there were other white matter lesions that did not contain JC virus and were typical of acute disseminated encephalomyelitis (ADEM), a nonspecific immune complication of many causative factors.

COMMENTARY

IRIS is an acute, symptomatic, or paradoxical deterioration of a preexisting infection that is temporally related to the recovery of the immune system. There are 4 diagnostic criteria:

1. Patient with AIDS
2. HAART-induced decrease in HIV viral load and increase in CD4 + T lymphocytes
3. Symptoms consistent with inflammation who appeared on HAART
4. No other infectious or toxic explanation for symptoms

IRIS results from the response of a newly reconstituted immune system to infectious antigens already present before antiretroviral therapy was started. In the case of PML reported by Vendrely et al, paradoxical clinical and radiological deterioration was associated with accentuated JC virus infection and acute leukoencephalitis. They hypothesized that the neuropathological changes they observed may have been due to an imbalance of the CD8+ to CD4+ T cell ratio, with massive infiltration of the brain by CD8+ cytotoxic cells in the absence of sufficient CD4+ cells.

IRIS has been described in a wide variety of infections, including mycobacterial, herpes zoster, hepatitis C and B, CMV retinitis, cryptococcal meningitis, pneumocystis carinii pneumonia, and others,[4] and is likely to become more common as improved retroviral therapy prolongs the survival of AIDS patients.

Neurologists who are involved in the care of AIDS patients should be aware of this often fatal complication of antiretroviral treatment for which no prevention or cure exists. ■

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A New Cause of Treatment-Responsive Limbic Encephalitis

ABSTRACT & COMMENTARY

By M. Flint Beal, MD

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Dr. Beal reports no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study.

Synopsis: *A new from of limbic encephalitis is reported, characterized by neuropil antibodies. Patients show an excellent response to immunotherapy or tumor resection.*

Source: Mayberg HS, et al. Deep Brain Stimulation for Treatment-Resistant Depression. *Neuron*. 2005;45:651-660.

Limbic encephalitis is a rare paraneoplastic illness characterized by symptoms of severe short term memory loss, or more extensive symptoms with confusion, seizure, and occasional psychosis. Previously, 2 groups of patients have been identified. The first of these include patients who have neuronal antibodies which have been identified as Hu, Ma2, or CV2/CRMP5. These antibodies produce strong immunostaining of hippocampus neurons. These patients usually have underlying tumors. It is associated particularly with small cell lung carcinoma, non-small cell lung carcinoma, testicular tumors, and thymoma. These patients frequently show increased signal in the medial temporal lobe, with T2 MRI imaging. Reposes to treatment, which are either resection of the tumor or immunosuppressants, are rare, except for patients with testicular tumors and Ma2 encephalitis. The clinical course is typically progressive.

A second group of patients was identified who have antibodies to voltage gated potassium channels (VGKC). These patients have antibodies that show mild staining of hippocampal neurons. CSF abnormalities are infrequent. They frequently show hyponatremia. The brain MRI also tends to show increased T2 signal in the medial temporal lobe. They frequently respond to treatment with corticosteroids, intravenous gamma globulin, and plasma exchange. Relapses may occur but are typically treatable.

The present report is that of a new form of limbic encephalitis. The patients had Sera and CSF that contained an antibody that reacted not as in most previously described paraneoplastic syndromes, with the nucleus or cytoplasm, but instead with the neuropil of the hippocampus or the cerebellum. In only one patient was an intracellular antibody identified. Unlike patients who have antibodies against VGKC, 5 of the 6 patients described had tumors. The tumors included a mediastinal teratoma, thymoma, thymic carcinoma, thyroid cancer, and an ovarian teratoma. In addition, they all showed CSF pleocytosis and intrathecal synthesis of the antibody. All, except for the patient who had the intracellular antibody, made a nice recovery with treatment of the tumor, immunosuppression, or both. The patients showed dramatic clinical and neuroimaging responses. Two patients who had neurological relapses improved with further immunotherapy. Brain MRI and PET imaging studies complemented each other in showing temporal lobe abnormalities; however, there was no overlap between the 2 studies in 50% of the patients, suggesting that both studies were needed. The antibody titres decrease or disappear over months.

COMMENTARY

The present report broadens the spectrum of limbic encephalitis. Mayberg and colleagues have identified a new group of patients who show an excellent response to treatment. The nature of the antibodies remains to be determined. The finding of CSF abnormalities, oligoclonal bands, and abnormalities in the hippocampus on MRI and PET imaging suggest the possibility of limbic encephalitis with novel neuropil antibodies. Thorough investigation of these patients in warranted, since they show an excellent response to therapy.

CME Question

5. Intravenous immune globulin (IVIG) is very beneficial for all the following *except*:

a. chronic inflammatory demyelinating polyneuropathy (CIDP).
b. acute inflammatory demyelinating polyradiculoneuropathy.
c. multifocal motor neuropathy with conduction clock (MMNCB).
d. multifocal acquired demyelinating sensory and motor neuropathy (MADSAM or Lewis-Sumner syndrome).
e. distal acquired demyelinating sensory neuropathy (DADS) with gammopathy.

6. In order to make a diagnosis of IRIS in a patient with AIDS, all of the following must be present?

a. HAART-induced decrease in HIV viral load
b HAART-induced increase in CD4+ cells
c. Onset of symptoms after HAART begun
d. A diagnosis of PML
e. Exclusion of a new infection

Answers: 5. (e); 6. (d)

In Future Issues:

A Step Toward Restorative Therapy in Parkinson's Disease

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Beta-Blockers May Be Useful for Noncardiac Surgery

High risk patients benefit from perioperative beta-blockers when undergoing major noncardiac surgery according to new study. Researchers from Tufts University reviewed the records of 782,969 patients in 2000 and 2001 at 329 hospitals throughout the United States. Patients were graded with the Revised Cardiac Risk Index (RCRI), which takes into account high-risk surgery, ischemic heart disease, cerebrovascular disease, renal insufficiency, and diabetes. The RCRI is graded on a 0-5 point scale, with 5 representing the highest risk. High risk surgery included all intrathoracic, intraperitoneal, and superinguinal vascular procedures. Patients with contraindications to beta blocker therapy were excluded. Over 660,000 patients had no contraindications to beta-blockers, and 120,338 patients received beta-blocker treatment during the first 2 hospital days. The relationship between perioperative beta-blocker treatment and the risk of death varied directly with cardiac risk. Patients with an RCRI of 0 or 1 were found to have no benefit from beta-blocker treatment, whereas for patients with an RCRI of 2, 3, or 4, or more the adjusted odds ratio for death in the hospital, were 0.88 (95% CI, 0.80, 0.80-0.98), 0.71 (95% CI, 0.63 - 0.80) and 0.58 (95% CI, 0.50-0.67), respectively. The authors conclude that perioperative beta-blocker therapy is associated with a reduced risk of in-hospital death among high-risk patients undergoing major noncardiac surgery. They also noted that there was no benefit for low risk patients (Lindenauer PK, et al. Perioperative Beta-Blocker Therapy and Mortality After Major Noncardiac Surgery. *N Engl J Med*. 2005;353:349-361). An accompanying editorial points out that perioperative beta-blocker therapy has been somewhat controversial because of conflicting data in recent years. The current study shows an apparent benefit in high-risk patients, but they also look forward to the results of 2 ongoing randomized trials that will help clarify the role of beta-blockers for low-risk and intermediate-risk patients (Poldermans D, et al. Beta-Blocker Therapy in Noncardiac Surgery. *N Engl J Med*. 2005;353:412-414).

Promising New Weight Loss Drug?

More data shows that topiramate (Topamax) is associated with weight loss and, in this latest study, may also lower blood pressure in obese, hypertensive patients. In a study from Norway, 531 obese patients with hypertension were randomized to placebo, topiramate 96 mg/day, or topiramate 192 mg/day. All patients received the same diet, exercise, and behavioral modification advice. Patients were followed for 28 weeks. Mean weight loss was 1.9% for placebo and 5.9% and 6.5% for the 96 mg and 192 mg doses, respectively ($P < 0.001$ for each compared with placebo). Diastolic blood pressure was reduced 2.1, 5.5, and 6.3 mm Hg, respectively ($P < 0.015$ vs placebo). Systolic blood pressure was reduced 4.9, 8.6, and 9.7 mm Hg, respectively (P = NS). Paresthesia occurred in 33% of the active treat-

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ment group. The authors conclude that topiramate produced clinically relevant effects in reducing body weight and BP, with generally mild to moderate adverse effects (Tonstad S, et al. Efficacy and Safety of Topiramate in the Treatment of Obese Subjects with Essential Hypertension. *Am J Cardiol.* 2005;96:243-251).

Treating Shift-Work Disorder

Modafinil (Provigil) may be of some value for people with excessive sleepiness associated with shift-work sleep disorder. Researchers from Harvard randomized 209 patients with shift-work sleep disorder to receive either 200 mg of modafinil or placebo before the start of each shift. Modafinil resulted in modest improvement in nighttime sleep latency (1.7 ± 0.4 vs 0.3 ± 0.3 minutes, respectively; $P = 0.002$). More patients also had improvement in their clinical symptoms based on multiple objective tests and patients diaries (74% vs 36%, respectively; $P < 0.001$). Patients taking modafinil also had reduction in frequency and duration of lapses in attention during nighttime testing of performance, and proportionally fewer patients reported having had accidents or near accidents while commuting home (both $P < 0.001$). These benefits, however, were mild, and patients treated with modafinil continued to have excessive sleepiness and impaired performance at night. The authors conclude that modafinil 200 mg at the beginning of a shift may improve shift-worker's performance as compared to placebo, although the benefit is modest (Czeisler CA, et al. Modafinil for Excessive Sleepiness Associated with Shift-Work Disorder. *N Engl J Med*. 2005;353:476-486). An accompanying editorial urges caution when interpreting these results and suggests "the current study does not adequately assess the clinical value of this particular drug in shift-work sleep disorder, nor does it justify writing more prescriptions for modafinil." The authors do note that up to 20% of workers in industrialized nations are shift-workers and calls for "further scientific studies to address in a cohesive manner the serious health and safety issues that surround us by virtue of us having become, to a large extent, a shift-working society" (Basner RC. Shift-Work Sleep Disorder--The Glass is More Than Half Empty. *N Engl J Med*. 2005;353:519-521).

Another Flu Vaccine Shortage?

With the flu season looming, Chiron Corp. is again having difficulty with flu vaccine production. Last year the company found contamination at its Liverpool production plant, a situation that cause severe shortages of vaccine in the United States. This year, the company has discovered contamination at a German plant and is stating that it can only provide vaccine for the US market. The German plant was primarily the source of the Begrivac flu vaccine, which was sold on the world market. The company is making "substantial progress" in fixing problems at the Liverpool plant where the US vaccine is made. Meanwhile, Acambis plc is working on a universal flu vaccine that could offer permanent protection against all types of influenza. The company hopes to generate a universal vaccine that would not require annual changes in formulation and would protect against both influenza A and B including avian strains. The company, however, states that it may require years of clinical trials before earning approval. Fears of avian influenza pandemic have prompted the French company Sanofi-Aventis to work on a vaccine for the avian H5N1 strain that has killed millions of birds and 50 people in Asia. Preliminary results are promising, however, full-scale production could take months, according to Anthony Fauci, MD, Director of the National Institute of Allergy and Infectious Diseases.

FDA Actions

The FDA has approved the first of the new class of drugs for the treatment of insomnia characterized by difficulty with sleep onset. Takeda Pharmaceutical's ramelteon (Rozerem) is a selective agonist at 2 melatonin receptors in suprachiasmatic nucleus, receptors that are thought to regulate circadian rhythm and sleepiness. Recently marketed sleeping medications target GABA receptors (ambien, lunesta) and, although these drugs are associated with less addiction and sleep latency then benzodiazepines, they are still designated as Schedule IV drugs. Ramelteon has shown no evidence of abuse or dependence potential and will, therefore, be marketed as a unscheduled drug. It is also approved for long-term use and has not been associated with memory impairment or impairment of motor ability. The most common adverse events associated with ramelteon were somnolence, fatigue and dizziness (> 2% over placebo).

Plan B, Barr Pharmaceutical's "morning-after pill" is being considered for over-the-counter approval by the FDA. The issue has become a political hot potato, and even briefly held up the Senate's confirmation of Lester Crawford, MD, as Commissioner of the FDA. It is expected that decision will be made by September. ■