ity[10] might render MS trials comparing new vs presently available treatments more easily feasible.

Acknowledgment

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References

1. Nauta JJP, Thompson AJ, Barkhof F, Miller DH. Magnetic resonance imaging in monitoring the treatment of multiple sclerosis patients: statistical power of parallel-groups and crossover designs. J Neurol Sci 1994;122:6–14.
2. Truyen N, Barkhof F, Tas M, et al. Specific power calculations for magnetic resonance imaging (MRI) in monitoring active relapsing–remitting multiple sclerosis (MS): implications for phase II therapeutic trials. Multiple Sclerosis 1997;2:283–290.
3. Tubridy N, Ader HJ, Barkhof F, Thompson AJ, Miller DH. Exploratory treatment trials in multiple sclerosis using MRI: sample size calculations for relapsing remitting and secondary progressive subgroups using placebo controlled parallel groups. J Neurol Neurosurg Psychiatry 1998;64:50–55.
4. Sormani MP, Molyneux PD, Gasperini C, et al. Statistical power of MRI monitored trials in multiple sclerosis: new data and comparison with previous results. J Neurol Neurosurg Psychiatry 1999;66:465–469.
5. Pozzilli C, Bastianello S, Koudriatseva T, et al. Magnetic resonance imaging changes with recombinant human interferon b-1a: a short term study in relapsing–remitting multiple sclerosis. J Neurol Neurosurg Psychiatry 1996;61:251–258.
6. European Study Group on Interferon Beta-1b in Secondary Progressive MS. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. Lancet 1998;352:1491–1497.
7. Comi G, Filippi M, Wolinsky JS, and European/Canadian Glatiramer Acetate Study Group. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis. Ann Neurol 2001;49:290–297.
8. Sormani MP, Bruzzi P, Miller DH, Gasperini C, Barkhof F, Filippi M. Modelling MRI enhancing lesion counts in multiple sclerosis using a negative binomial model: implications for clinical trials. J Neurol Sci 1999;163:74–80.
9. Kappos L, Moeri D, Radue EW, et al. Predictive value of gadolinium-enhanced MRI for relapse rate and changes in disability/impairment in multiple sclerosis: a meta-analysis. Lancet 1999;353:964–969.
10. Rovaris M, Filippi M. Magnetic resonance techniques to monitor disease evolution and treatment trial outcomes in multiple sclerosis. Curr Opin Neurol 1999;12:337–344.

Onset of multiple sclerosis associated with anti-TNF therapy

Article abstract—Therapies aimed at inhibiting tumor necrosis factor (TNF), a proinflammatory cytokine implicated in autoimmune disease are effective, especially for rheumatoid arthritis. We report a patient with new onset MS closely associated with the initiation of anti-TNF therapy for juvenile rheumatoid arthritis. It is possible that the inhibition of TNF triggered MS in this individual.

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Tumor necrosis factor (TNF) is a proinflammatory cytokine that is involved in lymphocyte signaling and plays an important role in cell-mediated immunity. TNF has multiple effects including the induction of adhesion molecules on endothelial cells and the enhanced production of reactive oxygen species.[1] In contrast to its proinflammatory properties, TNF can also mediate T cell receptor–induced apoptosis.[2] Therefore, TNF and its receptors are involved not only in inflammation, but also in the regulation of immune activity through the elimination of autoreactive inflammatory cells.[3]

TNF is thought to be an important mediator in several autoimmune diseases including rheumatoid arthritis, ulcerative colitis, and MS.[4] Anti-TNF therapy was initially considered for the treatment of MS based on studies of experimental autoimmune encephalomyelitis (EAE) as well as human data. Increased TNF production from T lymphocytes has been associated with their ability to transfer more severe disease in an adoptive transfer model of EAE.[5] Blocking TNF with antibodies or soluble TNF receptors decreased EAE severity.[6] In humans, high levels of TNFα have been found in MS plaques and CSF.[7]

Despite these findings, anti-TNF treatments for MS worsen disease. In a trial of anti-TNF targeted therapy using a recombinant protein consisting of the TNF receptor fused to a human IgG heavy chain (lerencept), treated patients had significantly more

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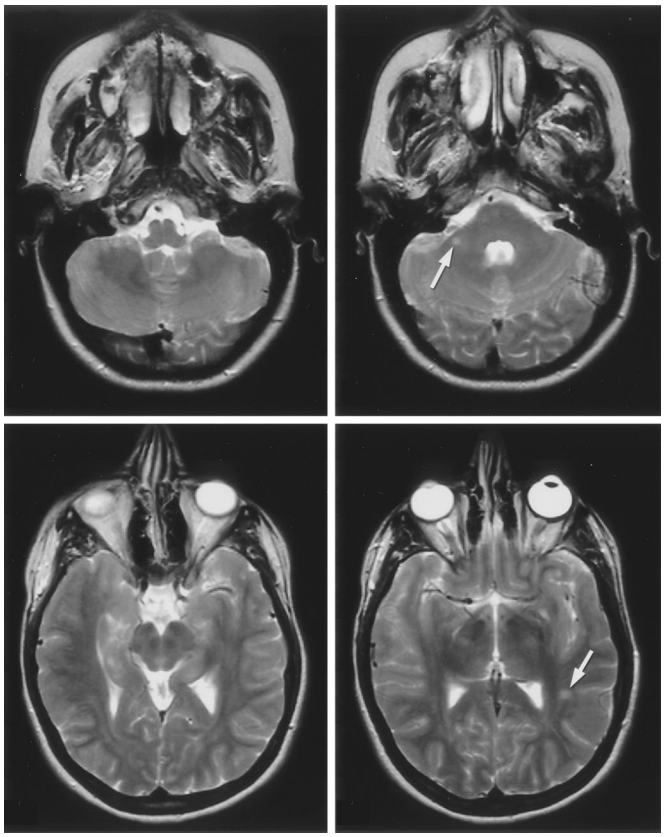

Figure 1. Axial T2-weighted MRI obtained at the time of initial presentation with optic neuritis. Arrows indicate areas of white matter hyperintensity consistent with demyelination.

ment with anti-TNF antibody in two patients with rapidly progressive MS led to a transient increase in gadolinium-enhancing lesions and no improvement in disease severity.[9] These studies suggest that anti-TNF therapy worsens MS.

Etanercept (Enbrel) is a fusion protein consisting of the extracellular portion of the human TNF receptor linked to the Fc portion of human IgG. It has become widely used in the treatment of refractory rheumatoid arthritis.[10] Several unpublished observations of presumed isolated demyelinating events and worsening of established MS disease activity in individuals treated with etanercept led to a drug warning by Immunex in October 2000. We report a patient with new-onset MS that coincided with the initiation of etanercept treatment for juvenile rheumatoid arthritis.

Case presentation. A 21-year-old woman with juvenile rheumatoid arthritis presented with a 1-week history of pain and decreased vision in her right eye. She had no previous visual symptoms or other neurologic dysfunction. She had no recent illness or travel.

She had been diagnosed with juvenile rheumatoid arthritis at age 8. Oral and IM gold, methotrexate, and sulfasalazine were only partially effective. Nine months of treatment with etanercept markedly improved her arthri-

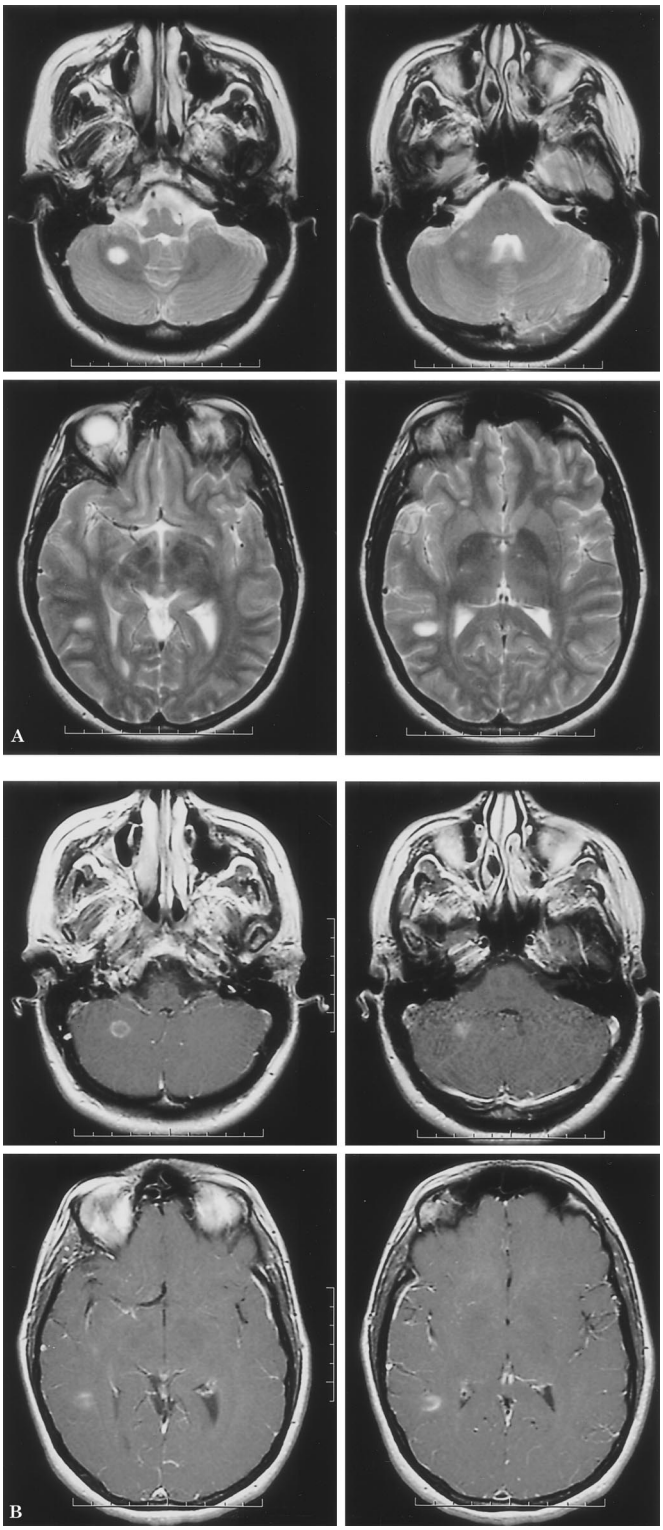

Figure 2. MRI scans obtained 2 months after presentation. There were no new complaints and the neurologic examination was normal. (A) Axial T2-weighted images reveal two new large areas of hyperintensity. (B) Axial T1-weighted images obtained after the administration of gadolinium demonstrates enhancement of these same areas consistent with active inflammation.

(Prevacid). Family history was significant for RA in her maternal grandmother. There was no family history of MS

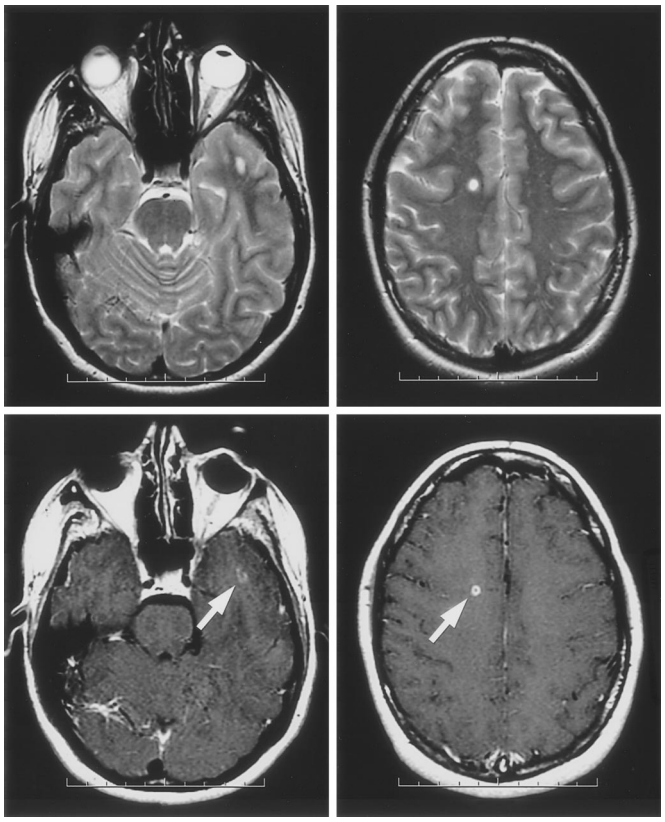

Figure 3. MRI scans performed 3.5 months after presentation and 6 weeks after discontinuing etanercept. Axial T2-weighted images show new lesions in the left temporal lobe and right frontal lobe (top row). Axial T1-weighted images obtained after contrast was given shows enhancement of these areas (bottom row).

gers and toes were noted. Visual acuity in the right eye was 20/20−2 and 20/20−1 in the left. There was a 1+ relative afferent papillary defect on the right. Disks were edematous, right greater than left. Visual fields were full to confrontation. The rest of the neurologic examination was normal.

An MRI of the brain revealed several T2 hyperintensities within the white matter including the right middle cerebellar peduncle, posterior temporal lobe, and right frontal lobe (figure 1). After contrast, two small areas of enhancement were noted high in the right frontal lobe. Spinal fluid analysis showed six white blood cells, normal protein and glucose, an elevated IgG index at 1.1 (normal range, 0.0 to 0.6) with two oligoclonal bands. Visual evoked responses showed significant slowing on the right. Brainstem auditory evoked responses and somatosensory evoked responses were normal.

After a 5-day course of high-dose IV methylprednisolone, the right eye pain resolved and vision was normal. At the time of this patient's presentation, no official warnings regarding the use of etanercept and the risk of demyelination had been reported. The patient was reluctant to stop therapy with etanercept because of the improvement in her arthritis symptoms. She continued her usual medications plus a prednisone taper.

The patient was evaluated 2 months later. There were no new symptoms. Visual acuity was 20/20 in both eyes, was normal. An MRI of the brain revealed two large enhancing lesions (figure 2). Etanercept was discontinued, and another course of high-dose steroids was initiated. She began treatment for her arthritis with leflunomide (Arava).

Six weeks later, the patient was evaluated again. She had worsening arthritis symptoms, numbness in her right foot, and dysequilibrium. Her examination revealed a new up-going toe on the right. Another brain MRI showed two new enhancing lesions (figure 3). At this time, a diagnosis of MS was made and the patient began treatment with interferon β-1a.

Discussion. Shortly after this patient presented, Immunex issued a drug warning citing observations of rare cases of demyelinating episodes including optic neuritis and transverse myelitis in patients with rheumatoid arthritis treated with etanercept. At the time of this writing, 20 to 25 cases of CNS demyelination associated with the use of etanercept have been reported to Immunex (Donald Goodkin, unpublished data, 2001).

Optic neuritis developed in this individual after using etanercept for 9 months. Cerebral MRI performed 2 months later revealed new disease activity in the absence of new symptoms. Despite discontinuing etanercept, new enhancing lesions and neurologic symptoms developed, fulfilling the criteria for clinically definite relapsing remitting MS. What role, if any, did the use of etanercept play in the onset of MS in this individual? Three possibilities exist. First, the development of MS and the use of etanercept could have been coincidental. Second, the use of etanercept could have triggered latent MS, uncovering the disease that the patient was destined to develop at some point in the future. Third, the use of etanercept could have caused MS to develop in this patient who otherwise would never have had the disease.

When patients with established MS were treated with lerencept, relapse rates increased in the first few weeks of treatment. In contrast, our patient was on therapy for 9 months before the first clinical attack. The latency period difference suggests that this patient did not have undiagnosed MS at the time etanercept treatment began.

Current guidelines are to avoid the use of anti-TNF drugs in individuals with a history of MS or demyelinating disease. The overall numbers of individuals with new-onset demyelinating events on anti-TNF therapy appears to be small, but these episodes can be clinically silent, making it difficult to assess the actual numbers of affected individuals. The risk may be higher at the initiation of therapy or alternatively could increase with cumulative exposure. In light of the case reported here, a serial MRI study designed to systematically assess the risk of developing demyelinating lesions at specific time points after the initiation of etanercept therapy appears warranted.

Patients who develop new neurologic symptoms

tored closely with frequent MRI regardless of their clinical status. Finally, all cases of new-onset demyelination should be identified and studied to determine what, if any, risk factors they share. Thorough investigations of these cases may lead to insights into the pathogenesis of MS.

References

1. Hohlfeld R. Inhibitors of tumor necrosis factor-alpha: promising agents for the treatment of multiple sclerosis? Mult Scler 1996;1:376–378.
2. Zheng L, Fisher G, Miller RE, Peschon J, Lynch DH, Lenardo MJ. Induction of apoptosis in mature T cells by tumour necrosis factor. Nature 1995;377:348–351.
3. Segal BM, Cross AH. Fas(t) track to apoptosis in MS: TNF receptors may suppress or potentiate CNS demyelination. Neurology 2000;55:906–907.
4. Raza A. Anti-TNF therapies in rheumatoid arthritis, Crohn's disease, sepsis, and myelodysplastic syndromes. Microsc Res Tech 2000;50:229–235.
5. Powell MB, Mitchell D, Lederman J, et al. Lymphotoxin and tumor necrosis factor-alpha production by myelin basic protein-specific T cell clones correlates with encephalitogenicity. Int Immunol 1990;2:539–544.
6. Selmaj KW, Raine CS. Experimental autoimmune encephalomyelitis: immunotherapy with anti-tumor necrosis factor antibodies and soluble tumor necrosis factor receptors. Neurology 1995;45(6 suppl 6):S44–S49.
7. Selmaj K, Raine CS, Cannella B, Brosnan CF. Identification of lymphotoxin and tumor necrosis factor in multiple sclerosis lesions. J Clin Invest 1991;87:949–954.
8. The Lerencept Multiple Sclerosis Study Group. TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study. The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Neurology 1999;53:457–465.
9. van Oosten BW, Barkhof F, Truyen L, et al. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. Neurology 1996;47:1531–1534.
10. Fernandez-Botran R. Soluble cytokine receptors: novel immunotherapeutic agents. Expert Opin Invest Drugs 2000;9:497–514.

Transcallosal bands: A sign of neuronal tract degeneration in early MS?

Article abstract—A pattern of injury observed in patients at high risk for MS described as transcallosal bands (TCB) is hypothesized to be the result of neuronal tract degeneration in earliest MS, extending from typical acute, focal demyelinating lesions located along the lateral borders of the corpus callosum. The TCB, a T2-hyperintense lesion traversing the corpus callosum is recognized on 3-mm thick, T2-weighted imaging, develops over months and persists over years.

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Although the principal pathology of acute MS lesions in the CNS is an inflammatory-demyelinating process, there is evidence from biochemical and microscopic analyses of brain specimens that the acute inflammatory MS lesion is also the site of early axonal injury.[1] In vivo MRS studies of early and acute lesions show reduced N-acetylaspartate and support the concept of early axonal injury in focal MS lesions.[2,3] Beyond the earliest stages of disease, for example, once a patient can be classified as in the stage of relapsing MS, the disease is characterized by diffuse and global injuries, as indicated by abnormalities of the normal-appearing white matter (NAWM),[4] and by brain and/or spinal cord atrophy.[5] Although some abnormalities in the NAWM are likely the result of microscopic or other primary focal pathology to which conventional MRI is insensitive, an alternative explanation is that these abnormalities may be the consequence of multiple focal injuries, with extension of these injury to distant sites, such as through tract degeneration.[6] Although tract degeneration is well recognized in the late stages of MS, as seen at autopsy, it has not been considered a major feature of early MS. Here we present direct imaging evidence for an injury pattern in the corpus callosum suggestive of tract degeneration emanating from focal demyelinating-like lesions at the earliest stages of MS, which we call transcallosal bands (TCB).

Methods. The TCB pattern is demonstrated based on MRI of patients enrolled in the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) trial.[7] Inclusion in the trial was based on the first occurrence of an acute, isolated neurologic syndrome consistent with demyelination, and an MRI study with a minimum of two lesions 3 mm or greater in diameter, one of which was periventricular or ovoid. The baseline and follow-up MRI protocol at 1.5 T included 1) axial intermediate and more T2-weighted classic spin-echo series with 3-mm nongapped slices, 2) a pre– and post–contrast en-

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