

**Rare Neuroimmunologic Disorders Symposium, 8/21/04**  
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**Immunopathogenesis of TM and Depression:**  
**What Listening to Patients Taught Us About These Diseases**

Cytokines are chemical messengers that transmit signals between cells of the immune system sometimes across great distances, which are analogous to neurotransmitters that convey messages between neighboring neurons. Surprisingly, recent studies have shown that neurons respond to cytokines and are thereby capable of “listening in” on the broadcast messages of the immune system when it is activated. There has been a growing excitement regarding recent explorations of the role of cytokines in depression.

Contemporary studies of affective disorders are confounded by the diagnostic heterogeneity that results from DSM-IV criteria. The work done at Johns Hopkins on Post-Stroke Depression in the Department of Psychiatry in the 1980’s, led by Dr. Bob Robinson working with Dr. John Lipsey and others, established the existence of lesion models of depression. At the time, this work supported the heretical notion that mood disorders could result from insults to the brain. Such a model, where subjects with depression share a similar physiological etiology for their mood dysregulation, offers a possible solution to the problem of diagnostic heterogeneity.

With this in mind, we have embarked on the study of Multiple Sclerosis (MS) as a model of depression, motivated in part by the fact that MS has the highest rate of comorbid depression of any medical or neurologic disease (i.e. 60% lifetime rate following diagnosis with MS). Dr. Peter Rabins at Johns Hopkins in the 1980’s pioneered the exploration of the epidemiology of depression in MS patients. Research has demonstrated suicide (which is motivated by depression in the vast majority of cases) is the third leading cause of death across all age ranges in patients attending outpatient MS clinics. There is a lack of correlation between depression and physical disability but a strong correlation between depression and periods of exacerbation in MS patients. Research evidence such as this suggests that the depression in MS results from the effects on the brain of immune system activation.

Dr. Doug Kerr founded the only center in the world for the care and research of patients with an autoimmune condition called Transverse Myelitis (TM) at Johns Hopkins Hospital. Through a collaborative effort between the department of Psychiatry and Neurology, we have begun research on this poorly understood ailment. TM is a unique model of depression, and by paying attention to the suffering of patients afflicted with this disease we have been led to novel insights about the possible role of cytokines in the pathophysiology of depression.

TM is a focal disorder of the spinal cord in which an immune-mediated process results in neural injury and varying degrees of weakness, sensory loss and autonomic dysfunction. Although TM exists on a continuum of CNS inflammatory disorders that includes MS, Neuromyelitis Optica (NMO), and Acute Disseminated Encephalomyelitis (ADEM), virtually nothing is known about the immune derangements present in TM patients. Work done in collaboration with Dr. Kerr, Ms. Krishnan and their group in Neurology has demonstrated that depression occurs at a rate in TM that is at least as great as that found in MS, does not correlate with physical disability, and results in a rate of suicide greater than that found in any other disease reported to date. Taking depression as a possible marker for brain involvement

in TM, investigation of the cognitive performance of TM patients revealed similar deficits as found in MS controls.

Because TM patients, by definition, do not have gross lesions seen by MRI in their brains, we speculated that cytokines might be involved in mediating a distributed signal from the spinal cord lesion that affects regions of the brain important for mood regulation. We have found selective and dramatic elevations in CSF Interleukin-6 (IL-6) levels in TM patients. IL-6 is a protein cytokine that transmits messages between immune cells. IL-6 produces its effects on CNS cells by binding to specific receptors on neurons and their support cells called glia.

We have found that CSF levels of IL-6 in TM patients strongly predicts their clinical outcome and may be etiologically related to tissue injury leading to clinical disability in TM. We further showed through lab work done on animal models of TM that elevated levels of IL-6 were necessary and sufficient for spinal cord injury mirroring that found in TM patients. This establishes a causative role for IL-6 in mediating the spinal cord injury seen in TM. Based on this work, investigations of novel, rational therapeutics for TM patients are already under way in the Johns Hopkins TM Center.

The hippocampus is one of the few regions of the brain where new neurons are manufactured throughout life, in a process called neurogenesis. We found that IL-6 causes a dramatic reduction in hippocampal neurogenesis. This fits with both the finding that patients with major depression experience a 20% hippocampal volume loss, and the more recent observation that antidepressants stimulate hippocampal neurogenesis. Antidepressant behavioral responses in animals have been shown to depend on this ongoing neuronal production.

This line of investigation has led us to a plausible model of depression, involving IL-6 and the production of new cells in the hippocampus, to account for the specific changes that take place in the brain as a result of immune activation. This model could account for the pathophysiology of depression in autoimmune diseases.