Psychiatric Manifestations of Autoimmune Disorders

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Opinion statement

Psychiatric symptoms are common to many autoimmune disorders. Patients often will have mood disorders, anxiety, cognitive deficits, delirium, and psychosis. These symptoms may reflect the direct or indirect effect of the autoimmune disorder on the central nervous system, may be related to medications used to treat the disorder, or may be a direct psychologic impact from suffering with the autoimmune disorder. Accurately recognizing the psychiatric component and generating a differential diagnosis is a complex task for the treating physician. Treatment of the psychiatric component to the disorder often will include addressing steroid induced side effects, psychotropic medications, psychotherapy, patient and family education, and a strong physician-patient relationship.

Introduction

Patients with autoimmune disorders are prone to psychiatric conditions. Autoimmune disorders that frequently exhibit psychiatric symptoms are listed in Table 1. Central nervous system (CNS) presentations of autoimmune disturbances may include disorders of cognition, mood state, perception, or any combination of these. Fronto-subcortical tracts, especially those involving dorso-lateral prefrontal (DLPF), orbito-frontal (OF), and anterior cingulate (AC) cortices are likely to be involved. The clinical state may vary from a relatively quiet presentation of disordered executive functions, such as an inability to complete tasks requiring concentration—subtracting serial sevens or spelling "world" backwards—to a florid state of agitation and terror spurred on by visual hallucinations, thought disorder, and affective lability. In so doing, autoimmune disorders may mimic dementing processes on the one hand, and psychotic disorders, such as schizophrenia, on the other.

Autoimmune disorders affecting the CNS are best regarded as forms of delirium. This group of disorders shares the characteristics common to delirium states. Characteristics include sudden onset of symptoms, clouded or altered sensorium with or without confusion, altered function across neural structures other than cortex, CNS toxic or physiologic insult rather than tissue loss, waxing and waning symptom course, hallucinations, and often a reversible course. Therefore, the first goal of diagnosis is to recognize the symptoms that comprise the syndrome of delirium as distinct to other psychiatric diagnoses, such as the major psychotic or mood disorders. The next goal is searching for an underlying cause, in this case, consideration of a possible autoimmune disorder.

Multiple sclerosis (MS) is an autoimmune disease that may develop in genetically susceptible individuals in association with environmental factors such as being born farther from the equator. CNS inflammation, demyelination, and gliosis occur, and the disease shows a progressive course or a relapsing-remitting form. The lesions are separated in time and space. In addition to white matter gliosis that appears as plagues on magnetic resonance imaging scans, recent studies have established that Wallerian degeneration of the neural axons occurs in white matter that otherwise seems normal on magnetic resonance

Table 1. Autoimmune disorders with psychiatric symptomatology

Multiple sclerosis
Systemic lupus erythematosus
Sjögren's syndrome
Addison's disease
Temporal arteritis
Sarcoidosis
Scleroderma
Polyarteritis nardosa
Hashimoto's thyroiditis
Myasthenia gravis

imaging scans. This may account in part for variations in symptoms that may not correspond to the location of the gliotic lesions [1,2, Class II; 3, Class III].

The neuropsychiatric symptoms found in MS are as varied as the sites of the lesions. Depression is most frequently mentioned with an accepted lifetime risk of 50.3% [4••]. Prevalence studies range from 25% [5•] to 79% [6••]. Suicide risk also is greater in this group of patients. One study [7•] reported lifetime prevalence of suicidal intent as 28.6% and 6.4% already had attempted suicide. Depression, alcohol abuse, and social isolation increased the risk of suicide. Clinical neuropsychiatric studies suggest that depression in MS is multifactorial. Demyelination [8], inflammation, and neuroendocrine response [9] have been implicated. Anatomic locations in the left hemisphere—arcuate fasciculus, medial inferior prefrontal cortex, and anterior temporal cortex alterations—have been reported as linked to depression [8; 10, Class II]. Still other investigators [11] report that brain atrophy, especially central atrophy such as in the thalamus, may be more important than gliosis or other specific lesions. Fatigue is one of the most common physical symptoms of MS, and Mohr *et al*. [12] found that treating comorbid depression significantly reduced fatigue. Cognition is another area frequently affected in patients with MS. Amato *et al*. [13] found that, at the end of 10 years with the illness, 56% of patients studied showed cognitive decline. Earlier on, there were deficits in verbal memory, abstract reasoning and linguistic processes, and then later attention and/or short-term spatial memory problems emerged. He found that limitation in a patient's work and social activities were correlated with the extent of cognitive decline, independent of degree of physical disability. Other psychiatric symptoms are frequent. One report [6••] listed psychiatric symptom prevalence as anxiety 40%, irritability 35%, apathy 20%, euphoria 13%, disinhibition 13%, hallucinations 10%, aberrant motor behavior 9%, and delusions 7%.

Systemic lupus erythematosus (SLE) is an autoimmune disorder in which tissues and cells are damaged by autoantibodies and immune complexes. This abnormal immune response is likely mediated by the interactions between genetic susceptibility and environmental factors. Patients usually have fatigue, anorexia, weight loss, fever, and malaise. Arthralgias and myalgias are common, similar to intermittent arthritis. Symptoms range from mild and intermittent to persistent and severe. Pain frequently seems out of proportion to the physical findings. SLE may affect the renal, vascular, cardiopulmonary and gastrointestinal systems. The CNS frequently is involved and the presence of seizures or psychosis, including paranoia and prominent visual hallucinations without other cause, is part of the diagnostic criteria of SLE [14,15, Class III]. Neuropsychiatric symptom prevalence has been estimated as: acute confusional state 14%, psychosis 11%, mood disorder 6%, and anxiety disorder 1.5% [16]. Cognitive impairment may be mild (43%), moderate (30%), or severe (6%) with respect to relative prevalence, for a total of 79% patients having some dysfunction [17••]. Proposed mechanisms for nervous system dysfunction include defects in the blood-brain barrier that allow entry of pro-inflammatory cytokines and autoantibodies, adverse effects on blood vessels from chronic inflammation, and immune-complex–mediated damage. Other studies suggest that patients with neuropsychiatric involvement have increased rates of organ damage and a higher degree of working incapacity.

Sjögren's syndrome is a chronic autoimmune disease with peripheral and CNS involvement in which antibodies attack exocrine glands (salivary and lachrymal). It can spread to the joints, blood vessels and, rarely, the liver and kidneys. More than four million Americans are afflicted, of whom 90% are women. Average age of onset is in the late 40s. In approximately 50% of patients it is comorbid with rheumatoid arthritis, systemic lupus erythematosus, scleroderma, or polymyositis and/or dermatomyositis. The most common psychiatric abnormality in the recent literature was cognitive dysfunction, which was thought to be the most sensitive indicator of CNS involvement [18]. Proposed mechanisms include direct immune attack on the neurons in addition to small-vessel angiopathy [19]. Studies showed significant incidences of mood disorders (primarily depression) and anxiety, leading to speculation that these disorders stemmed from the reduced quality of life as a result of Sjögren's syndrome, rather than any direct pathophysiologic effect [20•,21,22•].

Addison's disease is characterized by low levels of adrenal steroids as a result of the autoimmune destruction of the adrenal cortices. The psychiatric features of Addison's disease are understandable in the context of effects of decreased levels of these circulating hormones. There is little on psychiatric complications in the recent literature, with the exception of a few case reports of patients with mood disorders, primarily depression.

Psychosis rarely is mentioned. When present, the psychologic disturbances go hand in hand with the physical features. Initially, there is fatigue, weight loss, loss of libido, and lowered stress resistance which lead to overall exhaustion. The patients often feel "down," have chronically low energy levels, do not feel like engaging in usual pleasurable activities, and tend to become withdrawn and moody. Many report memory problems and may seem to have poverty of thought. A thorough history and physical examination are essential in recognizing classically described deepening of skin color. When the degree of symptomatic skin pigmentation is slight, patients with Addison's disease may be misdiagnosed with mild forms of depression, personality disorders, or early dementia.

Temporal arteritis, or giant cell arteritis, is a systemic vasculitis of various small and large arteries that usually affects the temporal artery. It presents most often after the age of 60 years and is more common in individuals of Scandinavian descent. It is though to be an autoimmune disorder because distinctive cytokine patterns are observed. Present consensus suggest that one or more antigens residing in the arterial wall are recognized by attacking T cells. The main psychiatric symptom is cognitive deficit resulting from stroke that results from arteriovascular occlusion. One recent case report described an elderly woman with progressive cognitive decline who was diagnosed with temporal arteritis [23, Class III]. Corticosteroids improved the inflammatory response, but her cognition did not improve. She was found to have bilateral parietal infarcts secondary to bilateral internal carotid occlusion, which was thought to be from the temporal arteritis. Temporal arteritis should be considered in elderly patients who have cognitive deficits, fatigue, anorexia, and weight loss, especially if they have a fever and headaches.

Sarcoidosis is a multisystem disorder characterized by the accumulation of noncaseating granulomas and accumulations of T lymphocytes and mononuclear phagocytes with resulting lesions throughout the body. The lung is the primary target, but any part of the body can be affected. The disease can be acute or subacute and can have a waxing and waning course over many years. Although the cause is unknown, it is thought to result from an exaggerated cellular immune response to certain antigens or self-antigens. It usually occurs in individuals 20 to 40 years of age. Sarcoidosis is primarily a peripheral nervous system disease, but presents centrally in 5% of those afflicted (neurosarcoidosis). Psychosis has been described in neurosarcoidosis, but primarily in single case reports. The psychosis usually is of the paranoid type, with behavioral disturbances and cognitive impairment. Psychosis is likely the result of cellular immune activity and inflammation; therefore, long-term high-dose corticosteroids are the first line of treatment [24]. Reports suggest that the psychosis and behavioral disturbances may resolve with treatment, but cognitive impairment can remain [24]. That the cognitive impairment in neurosarcoidosis does not seem to reverse with treatment suggest a third mechanism at work, possibly causing permanent structural damage. In non-CNS sarcoidosis, depression is most commonly observed and is thought to have a psychosocial basis [25••,26].

Scleroderma, or systemic sclerosis, is another chronic multisystem disorder, in which accumulation of connective tissue causes thickening of the skin; a process that also can involve any of the visceral organs. Abnormalities of the microvasculature are common. The mechanism is thought to involve autoimmune processes, vascular endothelial cell activation, and activation of fibroblasts leading to excessive collagen buildup. Fibroblasts are in a constant state of activation as a result of stimulation by cytokines, which are released by activated T cells. The most common psychiatric symptom seen in scleroderma is depression, which is observed in up to 50% of patients [27]. One study found that 17% of patients met criteria for moderate to severe depression [28]. These studies also suggest that the depression is a result of the experience of a chronic debilitating illness rather than any direct physiologic or structural cause. One recent study reported that, in addition to depression, patients with scleroderma also scored higher than control subjects on measures of anxiety, paranoid ideation, obsessive compulsiveness, somatization, and feelings of guilt [29]. Cognitive impairment also is seen, and it has been suggested that abnormalities found in the microvasculature can lead to cerebral hypoperfusion, which may be the cause [30].

Hashimoto's thyroiditis is autoimmune hypothyroidism in which autoimmune processes gradually and often episodically cause a reduction of thyroid function. Patients report feeling weak and tired and have difficulty concentrating, poor memory, and weight gain with little appetite, all of which may mimic depression. Hashimoto's thyroiditis also is frequently misdiagnosed as dementia because of the appearance of cognitive dysfunction. The most striking psychiatric symptoms occur during periods of Hashimoto's encephalitis. This is a steroid responsive encephalopathy associated with high titers of antithyroid antibodies. Some believe that it is caused by a cerebral vasculitis secondary to autoimmune process [31]. Psychosis is not uncommon in this group. Chong reported an incidence of 38% of a group of 85 patients [32, Class III]. Psychosis in this setting usually remits with corticosteroid treatment, but has required adjunctive use of antipsychotics [33]. The early signs of Hashimoto's encephalitis may include cognitive decline, depression, psychosis that includes hallucinations, confusion, and possibly seizures. Perceptual disorders, such as paranoia or hallucinations, may be treated symptomatically with low doses of a neuroleptic agent.

Myasthenia gravis is a disease in which the destruction of nicotinic cholinergic receptors, primarily on striated muscles, occurs via autoimmunologic mechanisms. As a result, patients have increasing fatigability with exercise and recovery with rest. In many cases, thymic hyperplasia is found. Anticholinesterase drugs are the standards of drug therapy. Lishman [34] reported that emotional stress may precipitate episodes of the illness, and suggests that premorbid personality traits may influence the presentation. The fatigability, a core symptom of the illness, has made it difficult to assess degrees of cognitive impairment that, although mild, may make coping with the illness more difficult. The more sustained effort patients make to perform tasks, the more fatigued they become and the worse their performance. This circular effect has made it difficult to determine how much the fatigue may be because of peripheral mechanisms rather than CNS cholinergic involvement [35].

Treatment

Diet and lifestyle

- Avoid fatigue if possible.
- Decrease psychosocial stressors.
- Increase social support system.
- Begin a physician-instructed exercise program.

Pharmacologic treatment

- Monitor and treat steroid induced side effects.
- Limit doses of steroids if possible because psychosis generally is not seen until the daily dosage exceeds 40 mg of prednisone or its equivalent.
- Clarify delirious reactions to steroids that may be confused with primary psychiatric disorders, such as mania, depression, or psychosis.
- Consider the use of antipsychotics to treat steroid induced psychosis.
- Consider the use of antidepressants, mood stabilizers, and anti-anxiety agents when indicated.

Assistive devices

- Use of a pillbox can help maintain compliance impaired by cognitive symptoms.
- Use of case management and outreach calls to monitor treatment and psychiatric symptom progression also is helpful.

Other treatments

- Other treatments include: psychotherapy (supportive, cognitive behavioral, group); psychiatric consultation; patient and family education of disease process; and improved physician-patient relationships.

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