The Neuropsychiatric Interface in Multiple Sclerosis and Three Neurodegenerative Disorders

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ABSTRACT

MS can present with a number of different symptoms, some of which may mirror other neurologic and psychiatric disorders. As a result, detection of other disorders in patients with MS can be difficult. We describe 3 patients with confirmed MS, who subsequently were diagnosed with a second neurodegenerative disease similar in presentation to MS. We present cases of MS and Huntington's Disease, Primary Progressive Aphasia, and parkinsonism to highlight the overlap in psychiatric symptoms in relatively rare comorbid diagnoses.

INTRODUCTION

Depression and anxiety are among the most frequently occurring emotional symptoms experienced by patients with multiple sclerosis. It is reported that more than 50 percent of patients with MS also have depression[1]. This is about three times higher than in the general population. Anxiety disorders are reported to be experienced by approximately 36 percent of patients with MS[1]. The pathophysiology of depression and anxiety in MS is not well understood but there is evidence that some might be due to lesions in the brain, specifically frontal regions[2]. It has also been proposed to reflect disease activity, likely in part as a result of axon demyelination, and as a result of a more generalized inflammation[1]. However, some symptoms of depression and anxiety still within the context of adjustment disorder that are not accounted for in the above statistics. Many patients have reactions that include symptoms of depression and anxiety when diagnosed with the disease or as the disease progresses.

Current estimates suggest that as many as 40 to 65% of patients with MS also experience cognitive problems. Most specifically, patients often demonstrated difficulty with recent memory, information processing speed, and sustained attention[3]. These difficulties often present in the early stages of MS and typically worsen over the course of the disease[3, 4]. The extent and nature of the deficits often depend on lesion burden, overall brain atrophy, as well as brain localization. It is also common for cognitive difficulties in the early stages of MS to be attributed to depression rather than an independent concern to be addressed.

We describe 3 cases, all with confirmed MS and treated accordingly. Each patient developed symptoms that were initially were understood in the context of MS, but progressed beyond the evidence from MRIs and with relatively rapid onset. Through the use of intensive neurological workups, ultimately, each patient was diagnosed with a second, separate and distinctive neurodegenerative disorder. We present the cases to highlight the overlap in symptoms, rarity of comorbidity of the diagnoses with complicated neuropsychiatric presentation, and the need for an integrated interdisciplinary approach toward treatment that includes neurology, behavioral medicine/psychology and psychiatry.

Cases

Case 1

This is the case of a married Caucasian woman in her forties with relapsing remitting MS and Huntington's Disease (HD). The patient was diagnosed with relapsing remitting MS in 2001 with symptom onset approximately 2 years prior. An MRI completed 7 months later indicated no definite new T2 lesions. Over the course of approximately 10 years, the patient's MS remained relatively stable, treated with interferon beta-1a and monitored by periodic MRI. Ibeta-1a was continued as her MS remained clinically stable. Continuous contact with various providers including her neurologist, psychologists, and allied health care providers led to a heightened level of concern regarding increases in apparent MS symptom presentation (i.e., gait abnormalities, tremor, mood fluctuations) without corroborating evidence of disease activity as indicated on imaging.

She was treated for depressed mood beginning in early 2011, including 20 mg citalopram per day and monthly outpatient psychotherapy appointments. She noticed significant reduction in symptoms of irritability and subjective feelings of sadness that remained stable. In late 2012, clinical manifestations related to MS and MRI lesion burden remained mild. At that time she noted a subacute decline in cognitive functioning, particularly executive functioning, accompanied by irritability and mild motor disturbances, which were described as not bothersome. Specifically, she noted sudden onset trouble concentrating, which she first noted at work.
She reported over the period of a weekend she was unable to perform her work, and keep up with tasks. She stopped working the following week in 2012. She had increasing difficulty with daily tasks like planning dinner and managing bills. She began to have word finding problems and short term memory difficulties. Formal neuropsychological evaluation indicated significant cognitive impairments in the domains of information processing speed, memory, and attention, which were consistent with cognitive deficits typical of MS. More specifically, the sudden onset was thought possibly to represent an MS relapse, but MRI did not reveal any lesion activity. There was some correspondence in changes noted between images (in white matter of left temporal lobe) and the cognitive findings of greater verbal than visual memory impairment. However, the extent of cognitive decline was greater than would be expected for a single focal change in that area.

In addition to the significant cognitive decline, the patient also began to experience increased depressive symptoms that were not as responsive to the citalopram as in the past. A trial of 75 mg venlafaxine XR was initiated. This failed and after 3 months, she was returned to citalopram at an increased dose of 40mg. At that time the patient disclosed the details of HD in her family that she had gathered from her paternal aunt. It was determined that some of her recent difficulties could be attributed to HD and she agreed to genetic testing. The results indicated that the patient had one allele in the normal range and one allele in the affected/reduced penetrance range, 38 repeats

Case 2

This is the case of a twice divorced Caucasian woman in her sixties who sought care because of persistent headaches and neck pain following a motor vehicle accident in 2004. MRI of cervical spine in 2005 showed a disc bulge at C5-6 without cord lesions. MRI of the brain in 2006 showed at least 10 small T2 hyperintensities in the subcortical and periventricular white matter. In 2008 she developed numbness and paresthesias of both feet that spread over the course of one week up to the waist. There was no associated neck or back pain, L'hermittes phenomenon, motor impairment, gait impairment, or bowel or bladder symptoms. At that time, blood studies were unremarkable. She denied any significant difficulties with mood; however her sister reported an increase in irritability and "moodiness," which was not previously present. Several months later she developed what she described as painless blurred vision. A brain MRI showed several new lesions with 1-2 GdE foci. Cerebrospinal fluid (CSF) showed RBC of 0/uL, WBC of 0/uL, glucose 69 mg/dL, protein 41 mg/dL, IgG index 0.8 (high), positive oligoclonal bands, and normal cytology. In September 2008, VEP showed P100 latencies of 106 msec OD and 135 msec OS, leading to the diagnosis of MS. She began glatiramer acetate in 2009.

In 2010, MRI revealed 19 or 20 multiple small T2 lesions, an increase over the 7 or 8 in 2009. She continued on glatiramer acetate and was scheduled for follow-up in 6 months at which time, she reported having some hesitation and slurring of speech, word finding problems, instances of using the wrong word (e.g. "breast" instead of "breathe of fresh air"), increased irritability, and depressed mood. Over the course of 2 years her speech difficulties worsened and she reported an increasing frequency of "my brain gets ahead of my talking", using the wrong word, and found that it was interfering with her work as a substitute teacher. She reported increased frustration with her inability to function at work the way she had liked, leading to increases in depressive symptoms, but declined psychopharmacologic interventions.

In early 2012 she returned for follow-up appointment with her sister who reported worsening of word mixing, (e.g "no" and "yes", "right" and "left."). She noted that the patient was able to type and text messages better than she was able to speak. The overall neurological exam was similar to the previous exam 6 months prior; however the dysarthria had worsened and was reported to be the most bothersome symptom. This also marked the first indication of a component of expressive dysphasia, suggestive of a possible cerebral process. Her sister noted that the patient's mood had become more irritable and that she was demonstrating increased apathy. A brain MRI indicated multiple scattered white matter lesions around the ventricles which appear to be similar in number and configuration when compared to previous study. There were no enhancing lesions, and the brainstem and cerebellum appeared normal.

She denied having any trouble with her memory although third party reports indicated that she had been misplacing important items (e.g. bank card, keys, and phone). She was able to function independently at home, but had stopped working entirely as a result of her speech difficulties. The results of cognitive assessment supported the reported difficulty with memory and concentration. She was seen by a cognitive neurologist and evaluated for her 2 year history of progressive dysarthria followed by word finding difficulty as independent of her MS. It was determined that her symptoms were consistent with progressive aphasia. The patient did not wish to pursue additional treatment and wished to transfer care to clinic closer to home.

Case 3

This is the case of a Caucasian man in his late thirties presenting due to vision changes and an abnormal MRI to be evaluated for the possibility of MS. clinic finding words and memory problems. The patient's wife reported that approximately 18 months prior, the patient was in his usual state of health. She noted that he had some trouble with his short-term memory and that his mood was becoming increasingly irritable. He was seen by a psychiatrist and diagnosed with major depressive disorder and treated with 20 mg citalopram per day. After several months, his mood improved modestly, but he continued to have progressing memory difficulty beyond the cognitive slowing associated with a major depressive episode. The psychiatrist recommended he be evaluated by neurology when an MRI indicated multifocal periventricular ovoid lesions and at least 4 enhancing lesions. There were also two cerebellar hemispheric lesions. CSF showed RBC 31 uL, WBC 2 uL, glucose 57 mg/dL, protein 21 mg/dL, IgG index 1.41 (high), positive oligoclonal bands, and normal cytology. The patient was diagnosed with MS and treated with IV methylprednisolone. He was then started on started on interferon beta-1a. Over the course of the next three months, the patient reported continued decline in cognitive ability and significant depressive symptoms. He completed neuropsychological testing that suggested deficits on memory tasks, specifically that his immediate and delayed recall of verbal and visuospatial information. In addition, his visual scanning/sequencing was considerably slower than expected, his timed word fluency was constricted, and he completed measures of attention/concentration or working memory well below expectation.

Over the course of the next 2 years, he was followed in an MS specialty clinic for an atypical form of multiple sclerosis that primarily affected his vision and memory. For the first year, he and his wife reported that he was stable with the exception of worsening cognitive symptoms, very prominent abulia, but no other typical MS related symptoms. His mood was mostly stable with periods of increased irritability not reporting to last more than a few days, which he continued to treat with citalopram 40mg. Over 6 months he developed an intermittent rest tremor in his right hand that disappeared with action. Retrospectively, his wife also noticed that his facial expressions had decreased significantly and there was the presentation of a tremor in his legs when standing. Handwriting had become very difficult to read and his voice had softened. He developed asymmetric rest tremor, bradykinesia and rigidity, consistent with idiopathic Parkinsonism. His profound neurologic deterioration, physically, cognitively, and emotionally was consistent with MS, dementia and parkinsonism. Genetic testing for PINK mutation was negative, ruling out one form of early onset Parkinsonism, yet he continued to undergo clinical decline and was becoming much more dependent on his wife for care. An MRI of the brain indicated widespread focal demyelinating lesions and breakthrough disease in the form of multiple gadolinium enhancing lesions. He was changed to natalizumab and also started carbidopa-levodopa for parkinsonian symptoms. He stabilized with the exception of increasingly irritable mood.

Over the course of the next 12 months, his wife reported symptoms of disinhibition (e.g. inappropriate noises). He continued to exhibit parkinsonism features with hypomimia, hypophonia, bradykinesia and rigidity, all of which were worse on the left side. He then presented as nonfocal and more animated, which was attributed to progression of frontal lobe degeneration. He developed near daily urinary incontinence and relied on his wife assistance with many of his tasks of daily living. His mood had improved and he remained on citalopram 40mg. On his last visit to the clinic he was more responsive and engaged. His wife reported that he was stable and planned to continue current treatment regimen.

Discussion

The comorbidity of MS and one of the other 3 neurodegenerative diseases discussed in this paper is rare. The early presentation of overlapping psychiatric symptoms further complicates the diagnostic picture. Psychiatric symptoms are often initially treated as independent problems and when a diagnosis of MS is suspected or confirmed, these symptoms are often attributed to disease or to adjustment to the disease. In addition, if cognitive symptoms worsen with disease progression it is similarly explained as typical for the disease. However, this may not be directly as result of MS (as in these 3 cases) and complete, reliable and comprehensive psychosocial and medical history is ideal.

Psychiatric symptoms were present in each of these cases. However, behavioral medicine integration was only present with the patient with Huntington's disease. The other two cases had contact with psychology and neuropsychology services through independent outside providers and had records forwarded for treatment by neurology teams, often limiting the availability for direct consultation between providers. Behavioral medicine as part of a care team can be especially helpful with assessing the emotional and cognitive symptoms in relationship with neurological symptoms, and developing a treatment strategy that is informative to the other disciplines while considering the needs of the patient. This can lead to a faster and more accurate diagnostic picture and provides a framework for treatment as symptoms change in a timely manner.

Table Disease	Neurological Symptoms	Emotional Symptoms	Cognitive Symptoms
Multiple Sclerosis[1,2,3,4,5,6]	Balance problems, blurred vision, dysarthria, fatigue, numbness, spasticity, tremor	Anxiety, apathy, depression, irritability	Attention problems, bradyphrenia (executive process slowing), short term memory problems
Huntington's Disease[7,8]	Chorea, general restlessness, lack of coordinated movements, rigidity, slowed saccadic eye movements	Anxiety, apathy, blunted affect, depression, obsessions & compulsions, psychosis	Episodic, procedural, short term, and working memory deficits, dementia
Parkinsonism[9,10,11,12]	Balance problems, bradykinesia, fatigue, rigidity, speech difficulty, tremor	Anxiety, blunted affect, depression, irritability, psychosis, visual hallucinations	Attention problems, bradyphrenia, working memory problems
Primary Progressive Aphasia (Nonfluent-agrammatic)[13,14,15,16]	Dysarthria, speech difficulties, errors in speech sounds	Anxiety, blunted affect, irritability, personality changes	Attention problems, judgment problems, multitasking problems, difficulties with problem solving, dementia

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