Case Report

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Higher Cortical Dysfunction Resembling Corticobasal Syndrome in 2 Patients with Multiple Sclerosis

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Abstract

The cognitive dysfunction in Multiple Sclerosis is classically defined as deficits in executive function, processing speed and memory. This pattern has been termed “subcortical dysfunction”. However, a growing body of literature suggests that there is cortical disruption in patients with Multiple Sclerosis and higher cortical dysfunction may manifest as symptoms. Here is presented two patients with Multiple Sclerosis who developed symptoms suggestive of Corticobasal syndrome, a disorder of higher cortical dysfunction due to a number of different pathologic substrates.

Keywords: Multiple sclerosis; Apraxia; Aphasia; Corticobasal syndrome

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disorder affecting predominantly younger populations with a slight female predominance [1]. Despite the original descriptions indicating memory trouble and slowed processing speed as early manifestations, cognitive impairment was largely overlooked until recently. Current studies suggest that up to 60% of patients with MS will have some degree of cognitive impairment [2]. Common domains affected include complex attention, working memory, processing speed, memory, and executive function. These deficits can have a significant impact on daily life including social and work related activities [3]. The cognitive impairment in MS does not seem to be correlated with disease type (relapsing-remitting, relapsing-progressive, or primary progressive) but may be correlated with degree of brain atrophy [4,5]. The cognitive deficits in MS were initially thought to spare cortical functions such as apraxia and agnosia with MS being considered a “subcortical” type dementia. However new studies indicate that in addition to white

matter demyelination there is associated grey matter atrophy in structures such as the caudate, thalamus, and hippocampus.

Corticobasal Syndrome (CBS) is a degenerative disorder due to a variety of pathologies such as Corticobasal degeneration, Alzheimer’s disease, and Frontotemporal dementia with associated tau or amyloid deposits [6]. Clinical features are broken down into motor symptoms and higher cortical dysfunction. A variety of motor symptoms including tremor, limb rigidity, gait disturbance, dystonia, and myoclonus are common. Cortical dysfunction manifests as apraxia, alien limb phenomenon, memory loss, executive dysfunction, cortical sensory loss, and aphasia. The aphasia is classically characterized as deficits with articulation, known as apraxia of speech, along with repetition errors and agrammatic verbal output [7,8]. Diagnosis antemortem is challenging due to the wide phenotypic variability and underlying pathologic substrate.

Below is presented 2 patients who have secondary

progressive MS, both with disease duration over 10 yr that demonstrated significant cognitive impairment with prominent cortically based deficits similar to those seen in patients with CBS.

Case Presentation

Case 1: A 55 y/o right handed man initially presented to the neurology clinic in 2005 for complaints of fatigue and forgetfulness secondary to his Multiple Sclerosis. He was first diagnosed in 1996 following a presentation with weakness and ataxia. An MRI showed multiple T2 hyperintensities and his cerebrospinal fluid demonstrated oligoclonal bands. He recovered from this first event after a course of intravenous steroids and subsequently had episodes of optic neuritis and right hemiparesis over the ensuing years. He had been followed in the neurology clinic on an annual basis. On his initial presentation to the neurobehavior clinic his main complaints were keeping himself organized and ambulating. His neurologic exam was notable for a right afferent pupillary defect (APD), dysmetria of the left upper extremity, and a broad based gait. He had standardized neuropsychological testing showing mild executive dysfunction. His MRI showed global atrophy with diffuse FLAIR hyperintensities. On T1 weighted images he had several black holes and there was no evidence of contrast enhancement. The patient was switched from interferon beta-1a to interferon beta-1b for tolerability. Over the ensuing six years he continued to complain of worsening cognitive function and worsening gait disturbance. He was offered other disease-modifying agents without change in his cognitive function. He was offered natalizumab however due to potential side effects he declined. He had been taking multivitamins as well as vitamin D3 supplementation.

He was seen in clinic in 2011 for follow up and his wife reported that he had to give up driving because of disorientation on the road resulting in three accidents. He stopped going to the gym alone because he would wander off if the transportation bus was late. His exam on this visit was notable for very frequent and noticeable phonemic paraphasic errors. He had marked grammatical errors in sentence writing and he was unable to follow complex commands. He demonstrated ideomotor apraxia of both hands with intact cortical sensory modalities. On a 10-item list learning task he had a flat learning curve and spontaneously recalled 6 of the words, however recognition memory was intact. He was unable to place the hands correctly on a clock. The APD and left arm dysmetria were still present, however he now had a bilateral kinetic and postural tremor of his hands. He was

retroflexed with standing and had dystonic posturing of his right hand when walking.

One year later, his wife complained that he doesn't know what to do if she asks him to "open the refrigerator" or "hand me the spoon". She also reported that he has given up on reading because she thinks he doesn't understand the words. He had limited spontaneous speech that was circumlocutious and filled with paraphasic errors. Apraxia was still prominent, astereognosis and agraphesthesia were present bilaterally. He had a new stutter. A MoCA was attempted and he scored 6/30, gaining 1 point for naming, 1 point on drawing the clock, knowing the city, state, year, and for recalling 1 of 5 words. His general exam was notable for dystonic facial posture with reduced blink rate. His right arm was now rigid and when walking he held his right arm flexed at the elbow and slightly out away from his body. He preferred to sit on his right hand "to keep it down". MRI was obtained demonstrating multiple black holes, T2 FLAIR hyperintensities and diffuse atrophy (Figures 1 and 2). A Positron Emission Tomography (PET) scan was obtained and demonstrated "diffuse hypometabolism over the convexities with normal radiotracer distribution in the basal ganglia and thalami" (Figures 3 and 4).

Over the ensuing 2 yrs he became essentially mute and began falling backwards with difficulty sitting down into chairs. He required the use of a walker for balance and stability. He could not generate volitional eye movements in any direction. He demonstrated ideomotor and ideational apraxia and developed an upward drift of his right arm along with unilateral right sided myoclonus. His facial expression became more dystonic. In early 2015 an amyloid PET scan was obtained which was negative. In late 2015 he was placed in a nursing home due to inability to be taken care of safely at home.

Case 2: A 59 y/o woman presented to the neurology clinic to establish care for her Multiple Sclerosis. She first began having symptoms of recurrent optic neuritis in the 1980s but did not receive a diagnosis of MS until 1993 when she presented with transverse myelitis and had elevated oligoclonal bands in her cerebrospinal fluid. She subsequently developed attacks of gait disturbance and left sided hemiparesis. She had been followed at a different institution every 6 months for the previous 5 years and returned to care at this facility in 2012. At the time of her presentation to this clinic she had a baclofen pump implanted for bilateral lower extremity spasticity and was not taking immunomodulatory therapy. Her

Figure 1: T2 MRI of Case one showing atrophy and extensive confluent white matter disease

Figure 2: T2 FLAIR of case 1 demonstrating diffuse periventricular and juxtacortical demyelination.

Figure 3: FDG-PET demonstrating diffuse hypometabolism.

Figure 4: FDG-PET showing preserved metabolism in the basal ganglia and thalami.

main complaint was difficulty with memory and she was found to have deficits in retrieval memory and executive dysfunction on bedside testing. Her general neurologic exam was relatively unremarkable except for a left APD and bilateral spasticity. She was offered disease modifying therapy but declined considering she had not an attack in a few years. She was agreeable to starting vitamin D3 supplementation.

She returned for follow up 15 months later with continued complaints of memory loss but believed she had preserved independence in all of her daily functions.

On exam she was found to have marked ideomotor apraxia with impairments in demonstrating use of objects, copying gestures from the examiner and interpreting gestures from the examiner. She also struggled to select the correct tool to perform a given task, however when objects were placed in her hand she could name and use them appropriately. Her memory was impaired recalling only 5 of 10 words after a short delay. She was impaired on a clock drawing task and could not complete Trails B, with normal performance on Trails A. There was rigidity of the left arm and bilateral myoclonus. She declined immunomodulatory therapy but wanted to try

Figure 5: T2 MRI of case 2 showing atrophy, and diffuse periventricular demyelination.

Figure 6: T1 MRI of case 2 demonstrating numerous "black holes".

dalfampridine therapy. She was started on memantine for her memory loss.

At a subsequent visit 9 months later she was accompanied by her husband due to inability to navigate her way through the hospital. Her husband reported difficulty with pronouncing words describing this as stuttering to get the word out. He also felt that she didn't know how to use her fork or toothbrush. He reported that she cannot get out of her chair without his help and struggles to understand "simple concepts". On exam she was dysarthric and demonstrated apraxia of speech. She could not follow a three step command and could not repeat phrases. Her naming was impaired to moderate and low frequency objects. She had restricted saccades in the vertical plane. Ideational and ideomotor apraxia were present. When performing distal rapid alternating movements there was a decremental response on the left and she had rigidity and an updrift of the left upper extremity. MRI imaging was obtained demonstrating confluent T2 hyperintensities and atrophy (Figures 5 and 6). PET imaging was obtained demonstrating mild hypometabolism in a non-specific pattern with normal distribution in the basal ganglia. Lumbar puncture was performed with amyloid-tau index of >1 and a phosphotau level in the normal range for the lab. She was referred to the National Institutes of Health neuro-immunology section for consideration of treatment options.

Discussion

Initial descriptions of MS suggested that this chronic disease was a disorder exclusively of white matter [9]. Recent pathologic studies indicate that there is involvement of gray matter structures as well. Gray matter atrophy and lesions can occur early in the disease and may correlate with degeneration, not just demyelination [10]. A consensus panel determined that brain volume is a valuable measure and should be included in the determination of whether or not there is evidence of disease activity at follow up visits [11].

Cognitive impairment is now recognized to occur in all phases of disease and in all disease subtypes. Once thought to predominantly affect "subcortical" cognitive domains, MS can affect verbal memory mediated by hippocampus, semantic fluency mediated in the anterior cingulate and facial recognition in the fusiform gyri [12]. Higher cortical language impairment consisting of aphasia, anomia, and reduced verbal fluency has been reported [13]. A recent study correlating MRI with cognitive outcomes found that damage in the Default Mode Network containing key structures such as the posterior cingulate, medial prefrontal cortex, and the parietal lobe, was linked with overall cognitive dysfunction [14]. Whereas another study from 2016 evaluating imaging findings and neuropsychological measures demonstrated prominent deep gray matter atrophy with relative sparing of cortical volume [4]. In this group of patients with Clinically Isolated Syndrome, cognitive impairment was found in visuospatial memory

and semantic fluency when compared to healthy controls.

Both patients presented above demonstrated cognitive impairment relatively early in their disease course and it was the main functional disability as their disease advanced. Both demonstrated cortical deficits manifested by apraxia, language disturbance, executive dysfunction, memory loss, and cortical sensory abnormalities. Additionally, both patients exhibited myoclonus, tremor, dystonia, and rigidity. This constellation of symptoms is similar to that described for CBS, and has not been previously described in the MS literature. This rare syndrome is a disorder of higher cortical dysfunction that also includes an akinetic/rigid syndrome with dystonia [6]. The clinical symptoms such as aphasia, apraxia, and alien limb phenomenon, present in CBS are a result of both cortical/gray matter atrophy as well as disturbances in subcortical white matter, particularly in the corpus callosum. Atrophy in the parietal, frontal, and temporal lobes and in the caudate nucleus has been reported [15]. The differential diagnosis of CBS and includes Corticobasal degeneration, Alzheimer's pathology, Frontotemporal dementia and Progressive Supranuclear Palsy. PET imaging in this disorder demonstrates patchy hypometabolism in the frontal and parietal regions as well as reduced metabolism in the basal ganglia contralateral to the affected side and bilateral thalami [16]. Both of the patients described above had preserved FDG biodistribution in the basal ganglia and thalami. Additionally, case #1 underwent an amyloid PET which was negative and case#2 had a lumbar puncture that was not consistent with a diagnosis of Alzheimer's disease. Therefore, it is doubtful that underlying Alzheimer's pathology was the causative factor in their clinical presentations. It is plausible that this rare syndrome can manifest in patients with MS either as a result of gray matter damage or as a result of white matter damage disconnecting cortical regions. Both MS and CBS share atrophy and damage to the corpus callosum, therefore the presence of overlapping clinical features could be seen. Future studies examining higher cortical deficits, including apraxia and aphasia in patients with MS should be undertaken, ideally with pathologic correlation.

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