Published in final edited form as:

Parkinsonism Relat Disord. 2012 December ; 18(10): 1097–1099. doi:10.1016/j.parkreldis.2012.05.025.

Limb Immobilization and Corticobasal Syndrome

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Abstract

Background—Recently, we evaluated two patients with corticobasal syndrome (CBS) who reported symptom onset after limb immobilization. Our objective was to investigate the association between trauma, immobilization and CBS.

Methods—The charts of forty-four consecutive CBS patients seen in the Mayo Clinic Alzheimer Disease Research Center were reviewed with attention to trauma and limb immobilization.

Results—10 CBS patients (23%) had immobilization or trauma on the most affected limb preceding the onset or acceleration of symptoms. The median age at onset was 61. Six patients manifested their first symptoms after immobilization from surgery or fracture with one after leg trauma. Four patients had pre-existing symptoms of limb dysfunction but significantly worsened after immobilization or surgery.

Conclusions—23 percent of patients had immobilization or trauma of the affected limb. This might have implications for management of CBS, for avoiding injury, limiting immobilization and increasing movement in the affected limb.

Keywords

Corticobasal syndrome; plasticity; immobilization

Introduction

Corticobasal degeneration (CBD) is a neurodegenerative 4-repeat tauopathy characterized by abnormal tau deposition in neurons and glia. Corticobasal syndrome (CBS) is the description for the typical clinical presentation of patients with CBD which was first described in 1968.[1] CBS is characterized by varied combinations of asymmetric parkinsonism, rigidity, cortical sensory loss, myoclonus, alien limb phenomena, apraxia, rigidity, and dystonia. CBD pathology accounts for 50% of cases of CBS.[2] Other pathologies associated with CBS include Alzheimer's disease, progressive supranuclear

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Financial Disclosures/Conflict of interests: Supported by grants P50 AG016574 and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program of the Mayo Foundation.

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palsy, frontotemporal lobar degeneration with ubiquitin- and TDP-43 positive inclusions, Creutzfeldt Jakob disease, and 3-repeat tauopathies.[3]

A number of movement disorders affecting a limb have been described after peripheral trauma to that limb,[4] although there has been no prior association between peripheral trauma and CBS. Recently, we evaluated two patients with CBS whose symptoms became apparent after limb trauma. The initial presentation of CBS appeared to be associated with casting and immobility of the affected limb. Given this observation, we assessed the frequency of immobility or casting in a CBS cohort.

Methods

This study included 44 consecutive patients with CBS who were recruited as part of the Mayo Clinic Alzheimer Disease Research Center (ADRC). Individuals participating in the ADRC typically undergo annual clinical examinations, MRI, routine laboratory tests, and neuropsychological tests. At the completion of the evaluation, a consensus committee meeting is held involving behavioral neurologists, neuropsychologists, and nurses who evaluate the subjects to assign a clinical diagnosis. All 44 patients in this study received a consensus clinical diagnosis of CBS based on published criteria.[5] The medical records of all 44 CBS patients, at the time of presentation, were reviewed with particular attention to trauma-related events. This study was approved by the Mayo Clinic IRB and informed consent was obtained from the subjects.

Results

Of the 44 consecutive CBS patients (median age, 63.5; range, 43–82), ten (23%) had procedures or significant trauma on the most affected limb within 2 years of symptom onset. The median age at onset in the subset with limb immobilization/trauma was 61 (range:53–78), 4 male, 10 right handed, and 6 had predominantly right sided symptoms. Table 1 describes the association between the immobility and presentation and the clinical and imaging features of the subjects. Six patients manifested their CBS symptoms after limb immobilization and four had pre-existing symptoms of limb dysfunction, but subjectively substantially worsened after immobilization. The first eight patients represent cases where the immobilization/trauma was time-locked to onset or marked exacerbation of symptoms in that limb. In the last two patients the relationship between the trauma/immobilization and worsening of symptoms is less clear. Pathology was available in four cases; three subjects had corticobasal degeneration and one had Alzheimer's pathology.

Discussion

After encountering two patients with the association, we found that nearly a quarter of the CBS patients in our ADRC database had experienced limb immobilization/trauma prior to or in association with worsening of CBS. All were related to the most affected limb (with no similar trauma or immobilization to other limbs).

Evidence of a preclinical CBS state has been reported by Caselli et al. They described monozygotic twins discordant for CBS.[6] While only one twin was clinically affected, both had abnormal PET scans consistent with CBS. Extrapolating this to our patients raises speculation that preclinical CBS became clinically manifest with immobilization/reduced-use/trauma.

Speculating further along these lines, note that cortical representation of body parts is substantially influenced by limb use. For example, the cortical territory of left fingers increases in size in string players compared to controls.[7] In stroke patients, the cortical

representation of the affected hand decreases in size but can be increased with constraint-induced therapy. The decrease in size is thought to be secondary to disuse. [8] During limb immobilization, the motor cortex representation size of the inactivated muscle diminishes. [9] A recent MRI study on subjects with limb immobilization demonstrated decreased cortical thickness in the primary motor and somatosensory area in the hemisphere contralateral the immobilization.[10] While in healthy individuals, function after immobilization returns, the CBS neurodegenerative process may compromise such neuroplasticity, leading to symptom onset or exacerbation.

There is somewhat of a precedent to this phenomenon among certain patients with dystonia. Thus, an underlying predisposition to dystonia may interact with environmental stress to cause dystonia, such as musician's (occupational) dystonia. Moreover, musicians with hand dystonia who switch hands playing string instruments may develop dystonia in the previously unaffected hand. In one study using magnetoencephalography, four of seven dystonic musicians demonstrated fusion of digit sensory representations of the non-dystonic hand in the "unaffected" hemisphere in addition to the expected changes in the affected hemisphere.[11] This suggested a predisposition to dystonia.

Other explanations for our findings may also be entertained. For example, CBS patients may complain of a limb problem, and be misdiagnosed and treated for another more common disease such as carpal tunnel syndrome. Similarly, patients with Parkinson's disease may be initially diagnosed with frozen shoulder, rotator cuff tear or other musculoskeletal disorder prior to the correct diagnoses being made. Another possibility is that patients with neurodegenerative disorders are at higher risk for falls with the affected limb being slow to react and protect itself.

Our study has several limitations. The study is retrospective and therefore we are unable to obtain exact temporal relationships between immobilization and development of CBS or determine the exact severity of the immobilization. Limb immobilization was not specifically asked about during the evaluation which may cause an underestimation in the number of cases. As with any neurological disease, there could be selective memory for events that are perceived as related to the disorder. Furthermore, we have no control group to assess a background frequency of limb trauma.

These unexpected findings should be pursued in a more rigorous way. A prospective design that queries a large consecutive series of CBS patients together with an appropriate control group would greatly increase confidence in the claim of a link between limb immobilization and CBS. Our observations may have important implication in management of patients with CBS. Avoiding immobilization and increasing movement in the affected limb might have some value in delaying progression of symptoms.

Acknowledgments

Supported by grants P50 AG016574 and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program of the Mayo Foundation.

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Table 1

Subject	Description	Clinical features at diagnoses	Imaging
1	Subject presented with numbness and mild difficulty using the left hand for less than 1 year and was diagnosed with carpal tunnel syndrome (EMG confirmed). After carpal tunnel release his numbness improved but left hand motor dysfunction worsened.	Parkinsonism, rigidity, with left hand fist	MRI: Mild generalized atrophy.
2	The subject underwent a right thumb arthroplasty and was casted for ten weeks. Upon removal of the cast, she immediately noted difficulty using the right hand.	Right hand apraxia, myoclonus.	MRI: Mild cerebral atrophy maximal on left. SPECT: Decreased uptake in the frontal, parietal regions, worse on left.
3	Subject was roller-blading and fell on her left knee resulting in severe thigh pain.. She developed progressive motor dysfunction of the left leg days after trauma.	Left limb apraxia, rigidity.	MRI: Symmetric frontal-parietal atrophy.
4	Subject underwent right triple arthrodesis for hindfoot valgus and hindfoot degenerative arthritis. She had right lower leg casting of 12 weeks because of a stress fracture. Almost immediately after cast removal, she presented to neurology for right leg dysfunction and falls.	Right limb rigidity, apraxia, bradykinesia.	MRI: Generalized cerebral atrophy more prominent on left. PET: Left frontal, parietal cortex hypometabolism
5	Subject developed mild motor difficulties in the right upper limb 15 months before surgery. She experienced a rotator cuff tear in the right shoulder which was surgically repaired. She was in a sling for six weeks and her motor problems were significantly worse when the sling came off.	Right limb dystonia with clenched fist, rigidity.	MRI: Generalized atrophy, worse on left. SPECT: Left frontoparietal decreased uptake
6	Subject presented with word finding difficulties and mild right lower extremity dysfunction. 18 months after symptoms started, she fractured her right fibula and was in a cast for 14 weeks. Her right side worsened after she came out of the cast.	Right limb rigidity, apraxia.	MRI: Diffuse cerebral atrophy, worse on left.
7	Two years prior to presentation the subject fractured his left scapula. Shortly after he developed progressive difficulty using his left arm.	Left limb rigidity, apraxia, dystonia	MRI: Moderate cerebral atrophy. SPECT: Right frontoparietal decreased uptake.
8	Subject underwent left foot surgery for a bunion and hammer toe. She was in a cast for about six weeks. When the cast came off, she noticed a left dysfunction.	Left limb rigidity, apraxia	MRI: Mild small vessel ischemic change. SPECT: Reduced uptake in the basal ganglia.
9	Subject presented with two years of CBS affecting his left side. He fractured his left hip. He previously was walking independently prior to the fracture. After recovery, he did not walk and became wheelchair dependent.	Left limb apraxia, increased tone and alien limb.	MRI: Moderate generalized atrophy. SPECT: Right frontoparietal decreased uptake.
10.	Subject underwent three back surgeries for spondylolisthesis. "Shortly" after a surgery complicated by a staphylococcus infection, he developed right hand incoordination.	Right limb apraxia, rigidity and cortical sensory loss.	MRI: Frontal and parietal atrophy greater on left.

SPECT=Single-photon emission computed tomography

PET=Positron emission tomography