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Tremor and Other Hyperkinetic Movements

Case Reports

The Progression of Posterior Cortical Atrophy to Corticobasal Syndrome: Lumping or Splitting Neurodegenerative Diseases?

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Abstract

Background: Posterior cortical atrophy is a clinical syndrome that is characterized by the progressive loss of visuospatial integration and is associated with neurodegenerative conditions.

Case Report: We describe a 60-year-old female with simultanagnosia, oculomotor apraxia, and optic ataxia for which she received an initial clinical diagnosis of posterior cortical atrophy. Three years later, she developed Balint's syndrome, Gerstmann's syndrome, left alien hand syndrome, smooth asymmetric (left) rigidity, cortical sensory loss, and spontaneous myoclonic jerks of the left arm, which suggested a final diagnosis of corticobasal syndrome.

Discussion: This case report indicates that corticobasal syndrome may present with visuospatial deficits.

Keywords: Posterior cortical atrophy, corticobasal syndrome, SPECT (Single Photon Emission Computed Tomography), magnetic resonance imaging, Alzheimer's disease

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Introduction

Posterior cortical atrophy (PCA) is a neurodegenerative syndrome that is characterized by the progressive decline of multiple cognitive functions, such as visuoperceptual and visuospatial skills, and arises from the dysfunction of parieto-occipital regions.[1] Age at onset is typically between 50 and 65 years, and patients usually first present to ophthalmologists with difficulties in fine vision tasks distinguishing lines and reading texts, judging distances, identifying static objects within the visual field, or problems with stairs and escalators.[2] After ophthalmologic consultation, and sometimes after receiving unnecessary medical procedures, such as cataract surgery, patients are sometimes referred to psychiatrists for evaluations for depression, anxiety, or malingering, which are frequently thought to be responsible for the complaints.

The symptoms typically progress over a brief time span, and careful neuropsychological evaluation often reveals signs of cognitive decline that are not only related to visuospatial abilities but also include ideational and ideomotor apraxia, dyscalculia, problems with spelling, and memory deficits. Although physical examination does not reveal signs of dysfunction in other systems of the central nervous system, the occurrences of extrapyramidal signs, myoclonus, and grasp reflex are reported in most cases of PCA; these symptoms occur with prevalences similar to those observed in typical Alzheimer's disease (AD).[3] The pathologic substrates of PCA include AD (62%) in the majority of cases, dementia with Lewy bodies (10%), corticobasal degeneration (CBD) (22%), prion disease, and subcortical gliosis.[1,2]

Corticobasal syndrome (CBS) is a clinical phenotype that may be associated with a variety of neurodegenerative diseases.[4] CBS is characterized by asymmetric presentation of two of the following signs 1) limb rigidity or akinesia, 2) limb dystonia, and 3) limb myoclonus, plus two of the following signs 4) orobuccal or limb apraxia, 5) cortical sensory deficit, and 6) alien limb phenomena.[4] Cases of CBS that also present with a complex visuospatial disorder, such as Balint's syndrome (simultanagnosia, optic ataxia, oculomotor apraxia), that is present from early onset have also been reported.[5,6] In this report, we describe a case of PCA that developed to CBS over a span of 3 years.

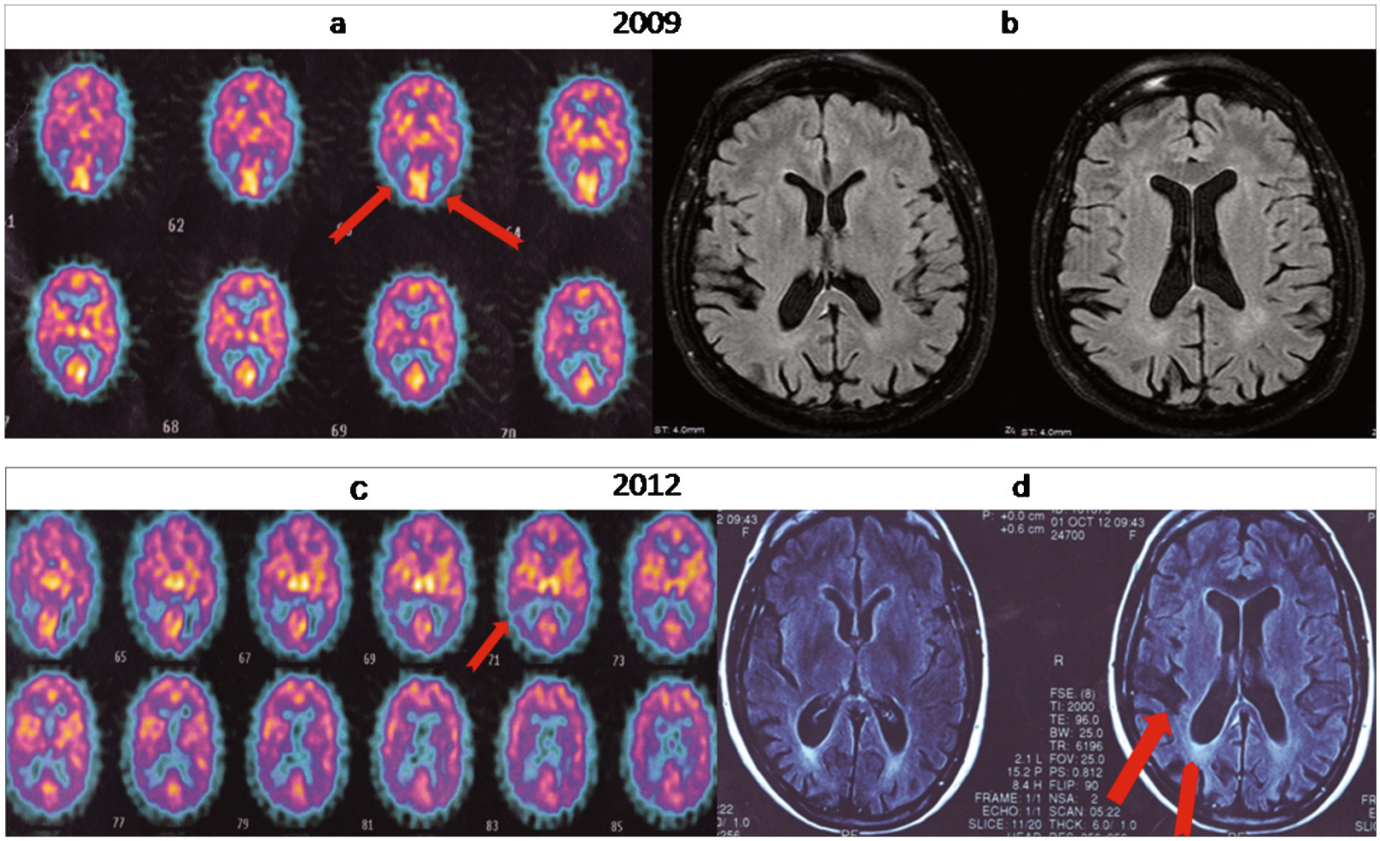
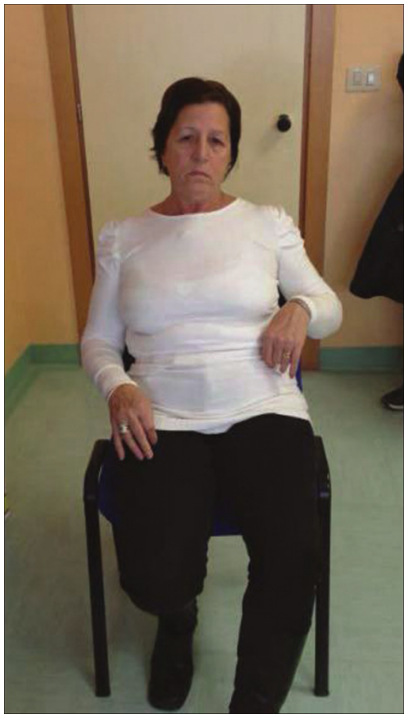


Figure 1. **Brain Scans and Imaging.** In 2009, a perfusional ^{99m}Tc-ECD-SPECT brain scan of the patient revealed bilateral hypoperfusion of the visual association cortices (arrows) (A). Brain magnetic resonance imaging revealed hyperintensities of the optical radiations and bilateral parieto-occipital atrophy (B). In 2012, ^{99m}Tc-ECD-SPECT revealed an area of perfusional deficit within the post-central right lobule (arrow) (C). MRI revealed atrophy of the post-central parietal lobule (thick arrow) and increased and asymmetric dilatation of the posterior horn of the right lateral ventricle (small arrow) (D).

Case report

A 60-year-old right-handed female presented to our outpatient memory clinic for evaluation in late 2009. She claimed to have developed difficulties in the performance of complex visual tasks such as locating items or orienting herself in familiar surroundings. She had contacted several ophthalmologists, but all consultants had excluded ocular diseases. She finally sought neurological consultation on advice from her general physician and on the general complaint of depressive symptoms and memory deficits. The patient could not finely locate items in her visual field and encountered great difficulties in the performance of domestic work. Her physical examination revealed intact extrinsic eye movements on voluntary command (pursuit and saccades), normal intrinsic ocular motility, and the absence of pyramidal, extrapyramidal, cerebellar, and sensory signs. She was unable to move her view toward specific visual objects in her peripheral field upon request (oculomotor apraxia) or to reach out and touch objects with either arm by visual guidance (optic ataxia). She could not recognize more than one item at a time (simultanagnosia) when tested with the Cookie Theft Picture from the Boston Diagnostic Aphasia Examination.[7] Extensive neuropsychological examination revealed deficits on the Clock Drawing Test,[8] Trail Making Tests A and B,[9] and the Stroop Test.[10] Her corrected Mini Mental State Examination (MMSEc)[11] score was 26/30. Verbal and autobiographic memories were normal at that time.[12] Brain magnetic resonance imaging (MRI) revealed posterior cortical atrophy, enlargement of the posterior horns of the lateral ventricles, and hyperintensities in the optical radiations. An assessment of brain perfusion with ^{99m}Tc-ECD (Ethyl Cysteinate Diolef)-SPECT revealed complete obscuration of the visual association areas within both occipital regions (Figure 1A,B). A dopamine transporter (DaT) scan revealed a normal representation of dopaminergic nerve terminals within the basal ganglia. Ultimately, a diagnosis of PCA was made according to established criteria,[1,2] and the patient began treatment with rivastigmine (4.6 mg/day). This treatment was subsequently slowly titrated up to 9.5 mg/day in the belief that she might have been affected by the posterior variant of AD. The patient was included in a periodic program of visits to our memory clinic, and she attended our outpatient laboratory twice a year in the following years. Two years later, on her first visit in 2011, she exhibited mild progressive worsening of her cognitive deficits with short-term memory involvement. Neurological



Video 1. **Posterior Cortical Atrophy: Corticobasal Syndrome at its Final Presentation.** The video demonstrates the patient's left alien hand phenomenon, oculomotor apraxia, right–left confusion, finger agnosia, and ideomotor apraxia. Denomination and vision of single elements were intact. The video shows the patient being asked to repeat "Oggi è una bella giornata di sole (Today is a beautiful sunny day)" to evaluate prosody and intonation; "Quante dita vedi (How many fingers do you see?)" while the examiner was showing two fingers of his right hand to evaluate elementary vision; "Che cosa è un gatto? (What category does a cat belong to?)" to evaluate semantic language; "Mostrami la tua mano destra (Show me you right hand)" to evaluate the recognition of the right and left sides; "Per favore, conti usando le dita della mano (Please, count using your fingers)" to assess finger agnosia; and "Per favore, faccia il segno della croce (Please, make the sign of the cross)" to evaluate ideomotor apraxia.

examination at that time revealed persistence of Balint's syndrome and the appearance of a Gerstmann's syndrome (finger agnosia, acalculia, dysgraphia, and right–left disorientation). In 2012, she slowly developed a complex movement disorder that included left alien hand syndrome, smooth asymmetric (left) rigidity, cortical sensory loss, and spontaneous myoclonic jerks of the left arm. MRI at that time revealed increased atrophy of the right post-central parietal lobule with enlargement of the posterior horn of the right lateral ventricle, and an overwhelming absence of perfusion of brain ^{99m}Tc-ECD-SPECT within that area (Figure 1C,D). Extensive neuropsychological testing revealed severe ideomotor apraxia and deficits in working memory, planning, naming, and the abstract conceptualization of time. She also presented with a deficit of immediate verbal recall and inattention. Her MMSEc score was 14/30. CBS was the final diagnosis on the basis of recently established diagnostic criteria.[4] Video 1 illustrates the patient's syndrome.

Discussion

Several clinical syndromes can be caused by different underlying neuropathologies. PCA and CBS share similar pathogenetic mechanisms, and the same neuropathologic conditions might underlie both conditions, albeit in different proportions. PCA might be associated with AD, CBD, or Lewy body disease (LBD).[1,2,6,13,14] CBS can originate from AD, CBD, frontotemporal lobar degeneration, progressive supranuclear palsy, or Creutzfeldt–Jacob Disease.[15] There are currently no methods to ascertain the underlying pathology while the patient is alive, with the exception of the assessment of amyloid burden with Pittsburg compound B (PiB) positron emission tomography. Several distinctive clinical signs and symptoms have been suggested to predict both of these histopathologies,[16] and diagnostic protocols may be supported by searches for biomarkers via analyses of cerebrospinal fluid (CSF), MRIs, and the study of brain metabolism with scintigraphic methods.

In CBS, episodic memory complaints and poor performance in orientation memory testing seem to predict AD pathology, whereas behavioral symptoms, such as non-fluent language disturbances, apraxia, and utilization behavior, are associated with CBD pathology.[16] Mixed phenotypes are more difficult to categorize and may either arise from mixed pathologies or represent unique evolutions of neurodegenerative conditions. The features of different neurodegenerative diseases, such as AD and LBD, have been found to coexist in the brains of both clinically probable AD and mild cognitive impairment patients.[17] One case of alien hand syndrome with pathologically proven AD has been described.[18] The patient reported herein presented with pure Balint's syndrome, which strongly suggested the PCA variant form of AD. This hypothesis was further strengthened by the appearance of memory defects a short time later. Unfortunately, the pharmacologic response to rivastigmine was lacking. Imaging analysis at that time revealed a dysfunction of the visual association cortex that was consistent with the patient's inability to detect and reach objects in the peripheral visual field. The later involvement of the post-central right lobule was more consistent with CBS. Whether this complex syndrome arose from a variant form of AD or from CBD is unclear. The early appearance of memory and visuospatial deficits at presentation is suggestive of AD pathology.[16] In contrast, the presence of inattention and executive dysfunction in the very early stages and the long-term sparing of the hippocampi are suggestive of CBD pathology.[16] The lack of data from CSF analyses due to the patient's refusal to submit to lumbar puncture did not allow the collection of further information about the underlying pathology. Moreover, the current diagnostic criteria for PCA and CBS did not improve the accuracy of the diagnosis. These diagnostic criteria are based on clinical signs and symptoms that are not informative about the actual underlying degenerative condition,[4,16] and show poor clinicopathological correlations.[15] These issues are concerns for a number of applications. First, these criteria do not allow for the prediction of the clinical course of the neurodegenerative condition with any reliability, and clinicians should be careful to avoid categorizing such rare variants at presentation and incorrectly informing the relatives and the

patient about future outcomes. Second, the clinical diagnostic criteria are not applicable to investigations that require direct consideration of the underlying pathology such as clinical trials of disease-modifying drugs. Third, these criteria do not allow for the proper and disease-targeted management of symptoms. Fourth, these criteria do not consider atypical forms of either AD or CBD, such as mixed or focal presentations. Complex and mixed neurodegenerative diseases might present with symptoms of each of the underlying conditions that exhibit different burdens and speeds of progression. The empowerment of histopathology-targeted diagnostic protocols for neurodegenerative diseases is highly desirable and should be achieved using disease-specific biomarkers. Until markers suitable for scintigraphic assessments of either taupathies or synucleinopathies are developed, brain PET scans utilizing either ^{11}C-PiB or ^{18}F-labeled radioligands should be performed whenever possible and used as AD diagnostic tools for all patients who are affected by rare, bridging variants of complex conditions that couple dementia and movement disorders. The diagnostic algorithm should include a complete blood examination and metabolic or perfusional brain scintigraphy. CSF analysis for β-amyloid fragments and tau, phospho-tau and 14-3-3 proteins can be performed, but only after acquiring informed consent. This study demonstrates that the rare and complex clinical syndromes that arise from variants of common diseases or from mixed neurodegenerative disorders might have distinct and unpredictable clinical courses.

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