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Case Report / Olgu Sunumu

Corticobasal Syndrome as Alzheimer's Disease Subtype: A Case Report

Alzheimer Hastalığı Alt Tipi Olarak Kortikobazal Sendrom: Olgu Sunumu

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Abstract

Typical Alzheimer's disease (AD) is a chronic neurodegenerative disease centered on progressive amnestic disorder. However, it may present atypically with various non-amnestic clinical profiles of other focal cortical dementia syndromes depending on the brain areas affected. One of these atypical forms is corticobasal syndrome (CBS), which is not included in the AD diagnostic criteria published by the National Institute of Aging and Alzheimer's Association in 2011 and the International Working Group 2 in 2014, but is well known by behavioral neurologists. This paper presents the case report of a 61-year-old male patient with asymmetric parkinsonism, myoclonus, pyramidal findings, primitive reflexes, and cranial imaging findings evaluated as CBS and cerebrospinal fluid biomarkers compatible with AD pathology. CBS, which is not included in the current diagnostic criteria, but is known to be associated with AD pathology in a considerable number of cases, should not be ignored in the new AD diagnostic criteria to be determined in the future.

Keywords: Atypical Alzheimer's disease, corticobasal syndrome, Alzheimer's disease diagnostic criteria

Öz

Tipik Alzheimer hastalığı (AH), merkezini progresif amnestik bozukluğun oluşturduğu, kronik nörodejeneratif bir hastalıktır. Bununla birlikte etkilenen beyin alanlarına bağlı olarak diğer fokal kortikal demans sendromlarının çeşitli amnestik olmayan klinik profilleri ile atipik olarak ortaya çıkabilir. Bu atipik formlardan birisi, Ulusal Yaşlılık Enstitüsü–Alzheimer Derneği'nin 2011 yılında ve Uluslararası Çalışma Grubu 2'nin 2014 yılında yayınladığı Alzheimer Hastalığı Tanı Kriterleri'nde yer almayan ancak davranış nörolojisi uzmanlarınca iyi bilinen kortikobazal sendromdur (KBS). Bu çalışmada asimetrik parkinsonizm, miyokloniler, piramidal bulgular, ilkel refleksler ve kraniyal görüntüleme bulguları ile KBS olarak değerlendirilen ve beyin omurilik sıvısı biyobelirteçleri AH patolojisi ile uyumlu olan altmış bir yaşındaki bir erkek hasta anlatılacaktır. Mevcut tanı kriterleri içinde yer almayan, ancak azımsanamayacak sayıda olgu AH patolojisi ile ilişkili olduğu bilinen KBS'nin gelecekte belirlenecek yeni AH tanı kriterlerinde göz ardı edilmemesi gerekmektedir.

Anahtar Kelimeler: Atipik Alzheimer hastalığı, kortikobazal sendrom, Alzheimer Hastalığı Tanı Kriterleri

Introduction

Typical Alzheimer's disease (AD) is a chronic neurodegenerative disease in which progressive amnesia is the core feature, while impairment in other cognitive functions and personality changes often emerge later. However, the disease may present atypically with various non-amnestic clinical profiles of other focal cortical dementia syndromes depending on the brain areas affected. Apart from typical amnestic AD, language disorders [logopenic variant of primary progressive aphasia (lvPPA)], visuospatial disorders [posterior cortical atrophy (PCA)], behavioral/executive dysfunctions [frontal variant (fvAH)], and atypical AD groups presented with Down syndrome have also been included in the AD diagnostic criteria published by the National Institute of Aging and Alzheimer's Association (NIA-AA) in 2011 and the International Working Group (IWG-2) in 2014 (1,2). However, another clinical profile that has been shown to carry AD pathology with cerebrospinal fluid (CSF) biomarkers in clinical practice and postmortem examinations is corticobasal syndrome (CBS), which is not among the atypical AD presentations contained within the scope of the NIA-AA and IWG-2 diagnostic criteria (3).

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CBS is a relatively rare syndrome with an insidious onset, involving the cortex and extrapyramidal areas, and clinically manifesting asymmetric extrapyramidal findings and cortical findings, such as apraxia, alien hand syndrome, cortical sensory defect, and myoclonus, while it frequently occurs between the ages of 50 and 70. Most patients develop a frontal type of dementia, also known as executive disorder. In an autopsy series performed in relation to this syndrome, the most common pathology was corticobasal degeneration (CBD); however, it has been shown that AD is the second most common pathology, with rates varying from 23% to 50% (3,4). Moreover, in an autopsy series of 34 cases of atypical AD from Cambridge, CBS accounted for 18% of the group, while fvAH accounted for only 6% (5). However, while much rarer atypical AD variants, including fvAH, find their place in the diagnostic criteria, CBS is not defined as a subtype, which could lead to the possibility of CBS presentation being correlated with AD. As such, the condition may be overlooked and the cause-oriented treatments that could be available in the near future will not be selected for these patients.

In this case report, a patient with CBS whose CSF biomarkers were compatible with the pathology of AD is discussed in view of highlighting which features could suggest atypical AD.

Case Report

A 61-year-old right-handed, secondary school graduate male patient was admitted due to forgetfulness that began six years earlier. Specifically, the patient presented with subject and question repetitions and complained of losing his personal belongings. It was subsequently determined that the issues of the slowing down of walking and movements, tremors in the right hand while resting, falling out of bed at night, and having difficulty in finding words had emerged two years earlier. The patient's medical history was unremarkable except for the presence of benign prostatic hyperplasia. The grandparents of the patient's mother and father were siblings. Except for his mother, who was diagnosed as having AD in her seventies, he had no family history of neurological disease.

The patient, whose spatial and temporal orientation was limited in his neurological examination, spoke slurredly and could carry out some of the single-step orders. Slow vertical and horizontal saccades were observed during the eye movements. There was distal dominant paresis in the right upper extremity, as well as moderate bradykinesia, myoclonus, bilateral Babinski positivity, and a global increase in deep tendon reflexes. Myerson's reflex, jaw reflex, bilateral grasping, palmomental, and Hoffmann reflexes were positive. The patient walked unsupported and slowly, with an anteflexed posture with small steps and less swinging of his right arm. On cortical sensory examination, the two-point separation was 15 mm on the right index finger and 8 mm on the left. He often gave astereognostic answers when he felt with his right hand but less frequently when he felt with his left hand. He had ideomotor apraxia on both sides, most prominently in the right upper extremity. The patient's mini mental state examination (MMSE) score was 11/30. Here, he lost five points in space orientation, three points in time orientation, one point in recording, two points in attention, three points in recall, one point in sentence repetition, two points in three-digit command, and one point each in writing and copying figures.

In his neuropsychological evaluation, the patient's orientation to personal and non-personal information and to time and space was distorted. His simple attention, working memory, mental naming, semantic information processing and ability to maintain attention, planning, conceptualization and abstraction skills, ventral and dorsal tract functions, and structuring skills were severely impaired. He also presented with simultanagnosia and acalculia. Anomia was observed in low-frequency words during the confrontation naming assessment for language functions. His single-word comprehension was also slightly impaired. While his comprehension was preserved for "yes-no" questions, the fact that most of the grammatical questions were answered incorrectly indicated that the patient's comprehension of grammatically complex sentences was impaired. In addition, it was observed that the patient had difficulty in remembering proper names. Furthermore, during the Pyramid and Palm Trees Test, it was observed that the patient had difficulty in semantic information processing. There was also deterioration in repetition ability, but it was thought that this situation might be related to a working memory problem. The presence of word-finding difficulty was reflected in the patient's spontaneous speech. There was a secondary type of deterioration in memory, while the recording process was preserved.

The patient's complete blood count was unremarkable, except for mild thrombocytopenia in the laboratory examinations. The biochemical test results, thyroid function test results, erythrocyte sedimentation rate, and vitamin B12 and folate levels were within normal limits, while the anti-human immunodeficiency virus and syphilis antibody testsresults were negative.

A cranial magnetic resonance imaging (MRI) examination revealed bilateral symmetrical atrophy in the frontal regions and prominent bilateral atrophy in the temporoparietal regions on the left. Atrophy was also present in the hippocampal and parahippocampal regions. Triventricular hydrocephalus was also observed and the pericallosal angle was narrowed (Figure 1).

The brain fluorodeoxyglucose positron emission tomography (FDG-PET) examination revealed bilateral asymmetric frontoparietal (prominent on the left) hypometabolism and hypometabolism in the thalamus with basal ganglia on the left (Figure 2).

In the CSF examination, there were no cells on direct examination. The CSF biochemistry and CSF cytology examinations were normal, and the oligoclonal band was negative. The amyloid beta 1–42 level was 295 pg/ml (<813), the phosphorylated tau level was 52 pg/ml (>52), and the total tau level was 506 pg/ml (>375).

No mutations were found in the presenilin 1, presenilin 2, and amyloid precursor protein genes, which were searched for genetic etiologies.

In the nerve conduction and needle electromyography examinations performed following the detection of pyramidal findings in the patient's neurological examination, no issue suggesting motor neuron disease was found. Electrophysiological examination of the patient revealed polyneuropathy in which sensory and motor fibers were affected. Vasculitis markers, protein and urine electrophoresis and immunoelectrophoresis were performed for the etiology of the detected polyneuropathy and the results were within normal limits.

The patient was initially diagnosed as having CBS with asymmetric parkinsonism, myoclonus, pyramidal findings, primitive reflexes, and cranial imaging findings. Following this, the patient was diagnosed as having CBS with motor variant atypical AD based on CSF biomarkers that are compatible with AD pathology, and was followed up with oral memantine therapy.

Discussion

AD is one of the well-defined underlying pathologies of CBS. In a series where the postmortem pathologies of 21 patients diagnosed as having CBD in the antemortem period were examined, CBD pathology was found in only five patients, while the pathology was AD in five patients, progressive supranuclear paralysis in six patients, Parkinson's disease in two patients, and frontotemporal lobar degeneration in three patients (6). As the results of many similar studies and those for the patient in the present case study demonstrate, it is valuable to investigate the presence of AD pathology in patients presenting with CBS with positive CSF biomarkers or amyloid-PET indicators. Considering the tau and amyloid-targeted therapies that are currently under examination in clinical trials, determining the underlying pathology is more important than academic curiosity, paving the way for a cure for patients with CBS.

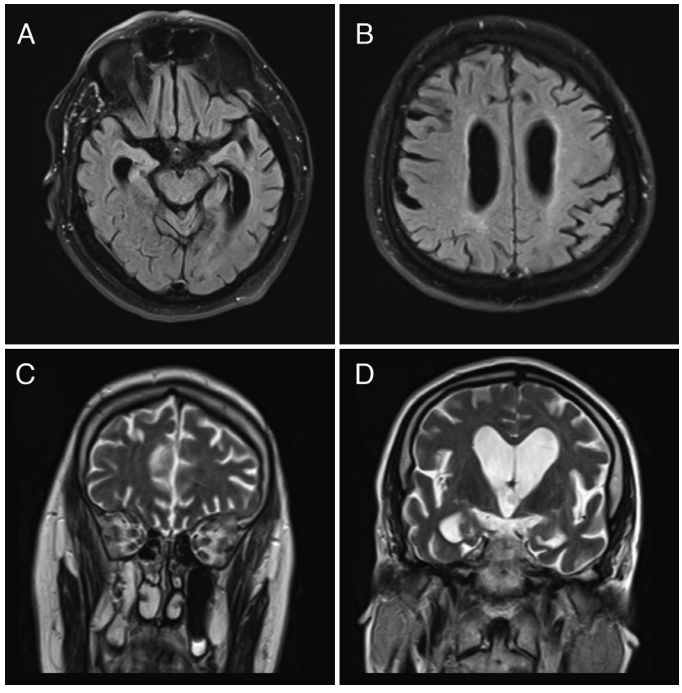

Figure 1. (A) Asymmetrical atrophy in the hippocampal and parahippocampal regions, which is more prominent on the left in the fluid-attenuated inversion recovery axial images of the cranial magnetic resonance imaging of the patient. (B) Enlargement of the sulci consistent with atrophy in the left parietal region. (C, D) While bilateral symmetrical atrophy can be seen in the frontal region in T2 coronal images, prominent bilateral asymmetric atrophy can be seen in the temporoparietal regions on the left

Patients with CBS with underlying AD pathology (CBS-AD) and patients with CBS with underlying CBD pathology (CBS-CBD) were compared in case series and case reports that aimed to examine the factors that might predict the pathology of AD. It was shown that findings such as memory deficit, low MMSE score, epileptic seizure, visuospatial disorder, and absence of extremity rigidity could predict the pathology of AD (7,8,9). In patients with CBS, low amyloid levels, high phosphorylated tau and total tau levels among CSF findings, posterior lateral temporal atrophy in cranial MRI, temporoparietal hypometabolism in brain FDG-PET scans, and amyloid load in amyloid-PET scans were found to be compatible with AD (7). Sha et al. (10) defined two clinical subtypes accompanying CBS in their proposed modified CBS criteria: (I) frontal variant CBS (fvCBS) and (II) temporoparietal variant CBS (tpvCBS). While fvCBS is characterized by non-fluent PPA and dvFTD features, with one or more of the executive disorder features dominant in the cognitive profile, tpvCBS is characterized by lvPPA and PCA (Balint and/or Gerstmann syndrome) features, with memory impairment dominant in the cognitive profile. The authors determined the amyloid positivity to be 17% in fvCBS and 69% in tpvCBS. Thus, it can be argued that the tpvCBS subtype among patients with CBS suggests atypical AD, much like the lvPPA subtype among patients with PPAs suggests atypical AD.

The presented patient fulfills the core CBS criteria with a progressive disease course and findings of asymmetric parkinsonism, myoclonus, and asymmetric cortical sensory defects. The patient also fulfilled the tpvCBS subtype of the modified CBS criteria, with severe visuospatial disorder, simultanagnosia, acalculia, and anomia. The left parietal hypometabolism findings in the FDG-PET examination supported the diagnosis of tpvCBS, and the low amyloid, high phosphorylated tau and total tau levels

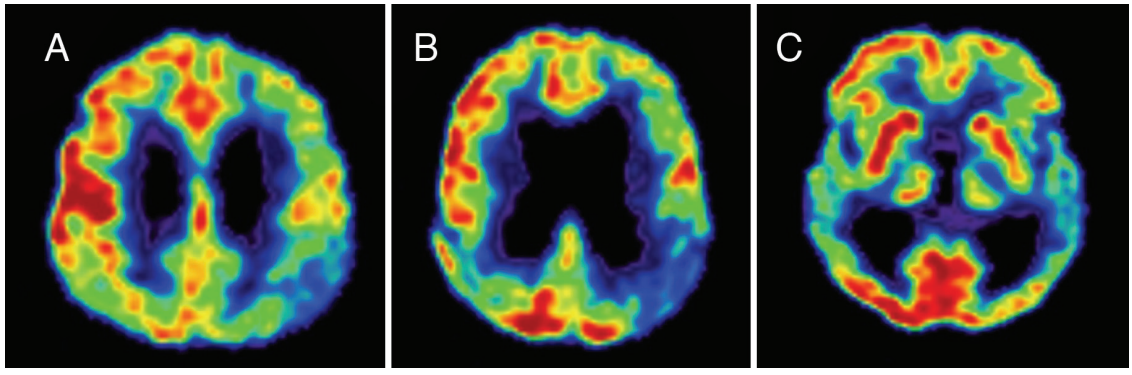

Figure 2. In the brain fluorodeoxyglucose positron emission tomography examination, bilateral asymmetric (prominent on the left) frontoparietal hypometabolism was observed (A, B) along with hypometabolism in the basal ganglia and thalamus on the left (C)

in CSF [A+T+(N+)] confirmed that this syndrome was associated with AD (11).

It is known that focal cortical dementia syndromes, including CBS, are significantly associated with AD pathology. In an autopsy study, Alladi et al. (5) classified focal cortical dementia syndromes from strongest to weakest according to their relationship with AD pathology as follows: PCA, mixed aphasia, non-fluent aphasia, CBS, frontal variant, and semantic dementia. As noted above, clinically and pathologically, the underlying AD pathology in CBS is not to be underestimated. Despite this, while even the frontal variant, which is reported to be seen less frequently among atypical presentations, was included in the NIA-AA and IWG-2 diagnostic criteria, CBS was not. We believe that this may result in the underlying AD pathology being overlooked by clinicians who clinically diagnose CBS, and could present a problem in terms of follow-ups and possible new treatment opportunities.

In conclusion, we believe that CBS, which is not included in the current diagnostic criteria but is known to be associated with AD pathology in a substantial number of patients, should not be ignored in the new AD diagnostic criteria determined in the future. As such, clinicians will be more careful in assessing a possible AD pathology when evaluating the patient, and this patient group could also benefit from the treatments to be developed for AD.

Ethics

Informed Consent: Informed consent forms were obtained from all healthy volunteers.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.U.D., B.S., B.B., H.A.H., H.G., Concept: F.U.D., B.S., H.G., Design: F.U.D., B.S., B.B., H.A.H., H.G., Data Collection or Processing: F.U.D., B.S., B.B., H.A.H., H.G., Analysis or Interpretation: F.U.D., B.S., B.B., H.A.H., H.G., Literature Search: F.U.D., B.S., B.B., H.A.H., H.G., Writing: F.U.D., B.S., B.B., H.A.H., H.G.

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