

1-1-2015

Why is Alzheimer's disease confused with other dementias?

DURSUN AYGÜN

İBRAHİM LEVENT GÜNGÖR

Follow this and additional works at: <https://journals.tubitak.gov.tr/medical>



Part of the [Medical Sciences Commons](#)

Recommended Citation

AYGÜN, DURSUN and GÜNGÖR, İBRAHİM LEVENT (2015) "Why is Alzheimer's disease confused with other dementias?," *Turkish Journal of Medical Sciences*: Vol. 45: No. 5, Article 4. <https://doi.org/10.3906/sag-1405-47>

Available at: <https://journals.tubitak.gov.tr/medical/vol45/iss5/4>

This Article is brought to you for free and open access by TÜBİTAK Academic Journals. It has been accepted for inclusion in Turkish Journal of Medical Sciences by an authorized editor of TÜBİTAK Academic Journals. For more information, please contact academic.publications@tubitak.gov.tr.

Why is Alzheimer disease confused with other dementias?

Dursun AYGÜN*, İbrahim Levent GÜNGÖR

Department of Neurology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

Received: 14.05.2014 • Accepted/Published Online: 29.08.2014 • Printed: 30.10.2015

Abstract: Alzheimer disease (AD) is the most common cause of dementia. The cardinal manifestation of AD is progressive loss of memory. However, there are some nonamnestic presentations of AD, also called atypical AD. Symptoms of AD can sometimes start suddenly. In the presence of atypical symptoms or sudden onset, it may be difficult to distinguish AD from other dementias. We would like to discuss the confusing features of atypical AD that mimic other dementias. In this review, the literature associated with confusing features of AD, suggesting other dementia syndromes, is reviewed. In addition, a case of semantic dementia (SD) with the complaint of forgetfulness previously diagnosed as AD is presented together with clinical and radiological clues of the differential diagnosis of dementia syndromes. As in our representative SD case, a careful clinical history, a detailed mental evaluation, and neuroimaging will overcome this difficulty in diagnosis.

Key words: Alzheimer disease, dementia, atypical presentations, true diagnosis

1. Introduction

Alzheimer disease (AD) is the most common cause of dementia, accounting for about 60%-70% of all cases (1). AD has been commonly defined as a progressive amnestic neurodegenerative disorder followed by other cognitive and behavioral changes that impair activities of daily living (2). Patients with AD typically present with progressive forgetfulness. However, some clinical variants of AD like posterior cortical atrophy (PCA) and frontal-variant AD (also called atypical AD) may not emerge with the typical amnestic syndrome (3). The initial symptoms of these variants of AD may be language impairment and behavioral disturbances such as mood disorders, visual hallucinations, and personality changes. In fact, the first patient described by Alois Alzheimer in 1906 also had atypical symptoms, dominantly personality changes (4,5). Symptoms in AD can sometimes start suddenly. In the presence of atypical symptoms or sudden onset, it may be difficult to distinguish AD from other dementias. Atypical presentations of AD have also been described in some neuropathological studies (6–8). On the other hand, amnesia may be prominent even in patients with histopathologically diagnosed frontotemporal dementia (9). Semantic dementia (SD) may also cause severe hippocampal atrophy, just as in AD (10). In addition, it has been shown that the specific pathological findings of AD can also be present in some SD patients (11). Here, a case

of SD previously diagnosed as AD is presented together with clinical and radiological clues of the differential diagnosis of dementia syndromes.

A 60-year-old, right-handed male patient was admitted with the complaint of forgetfulness. From his past medical history, it was learned that he had closed his grocery store 4 years earlier because of the difficulty in shopping, and later he experienced forgetfulness and difficulty in recognizing family members and friends from time to time. These complaints increased steadily. The patient more recently exhibited mild irritability and aggressive and sexually inappropriate behaviors. It was learned that the patient had not exhibited address mixing, inability to find directions, or getting lost finding foreign or known addresses of their family members. The patient's speech was fluent with limited vocabulary and grammatical with some paragrammatic errors including perseverations. Spatial attention (clock drawing) and configuration (copying) were normal. Visual naming was mildly impaired. Recognition was impaired; he had prosopagnosia and agnosia. Understanding, category and phonetic fluency, naming in the mind, attention, abstraction, and problem solving were severally impaired. Reading and writing could not be evaluated, because he was illiterate. He had a partially preserved memory for recent events. Long-term episodic memory was impaired. There were no signs of parkinsonism. Other neurological

* Correspondence: daygun@omu.edu.tr

examination findings was normal. He had compulsive and stereotypic behaviors. Routine blood tests including complete blood count, serum biochemistry, renal and liver function tests, thyroid functions, and serum vitamin levels were normal. Structural cranial magnetic resonance imaging (MRI) demonstrated bilateral (but more prominent on the left) severe anterior-inferior temporal cortical atrophy, and perisylvian and hippocampal atrophy (Figures 1A–1D).

2. Discussion

2.1. The typical and atypical symptomatology of AD

The typical symptomatology in AD is characterized by progressive memory impairment, accompanied by loss of other cognitive functions including visuospatial and speech functions, which may not be associated with systemic diseases or neuropsychiatric disorders (12). The brain imaging and other biomarkers should support the diagnosis of AD (12). Thus, the typical initial presentation of patients with AD is episodic memory deficit, followed by language, visuospatial, and executive impairments. These aspects of

AD have been clearly defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association for clinical diagnosis (13). However, neuropathological examination still remains the gold standard for definitive diagnosis of AD (14). AD can be categorized into early (age of <65 years) and late (age of >65 years) onset groups, and 95% of patients are over 65 years (15). Most early-onset AD patients present with nonamnestic syndromes, called atypical forms of AD. In a recent study, it was reported that 22%–64% of early-onset AD patients have predominantly a nonamnestic syndrome, presenting with deficits in language, visuospatial abilities, praxis, or other nonmemory cognition (16). In the series of Galton et al. (6) including 180 patients, 14% presented with atypical forms of AD.

2.2. Other dementia syndromes showing pathological findings of AD

It is known that patients with PCA characterized by progressive disturbances in visuoperceptual and spatial

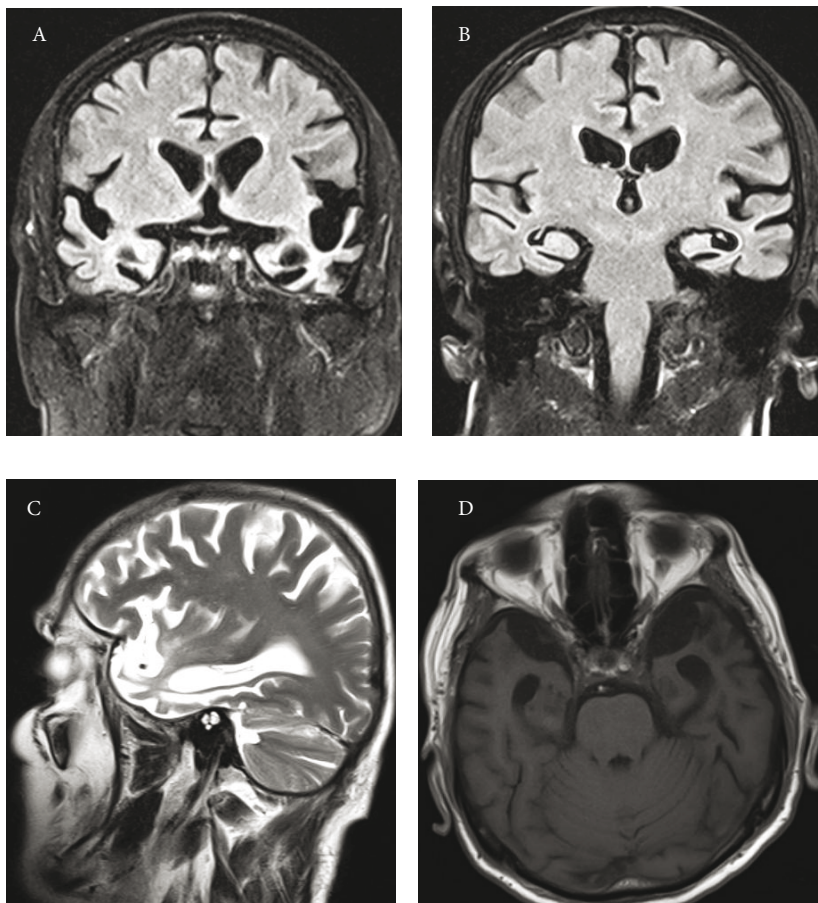


Figure 1. Coronal fluid attenuated inversion recovery (A, B), T2-weighted sagittal (C), and T1-weighted axial (D) cranial MRI images show bilateral (left-prominent) anterior-inferior temporal cortical atrophy and perisylvian and hippocampal atrophy.

abilities have AD pathology (8). Similarly, some SD patients may show pathological findings of AD (11). In addition, it has been reported that clinical pictures that can be caused by AD pathology, such as corticobasal syndrome (CBS), frontal-variant AD, PCA, and logopenic variant primer progressive aphasia (PPA), may present with behavioral changes (17). Alladi et al. (8) reported that 2 of the 19 cases of PPA caused by AD pathology fulfilled the criteria for SD. Ten of 19 patients with PPA in the study of Alladi et al. developed prominent memory impairment in the late stages of the illness (8).

2.3. Other causes of dementia mimicking AD

More importantly, any toxic, systemic, traumatic, ischemic, paraneoplastic, autoimmune, or neurodegenerative damage of the brain areas associated with episodic memory, like the hippocampus, may lead to episodic memory impairment and may mimic AD. In this paper, we report a SD case previously diagnosed as AD. It has been reported that patients with semantic variant PPA (SD) generally have a progressive and multimodal loss of semantic knowledge, especially conceptual knowledge, characterized by losing the meanings of the words (also called a “loss of memory for words”), together with retained syntax and fluency of speech (18). The word comprehension and naming performance of these patients is very poor (5,18). SD also causes different forms of agnosia such as impairments in

object and face recognition in advanced stages (18,19). Prosopagnosia is also familiarity-dependent in SD (20). Since SD patients have difficulty in recognizing/identifying familiar people, they may be misdiagnosed with AD. Our patient had difficulty in recognizing/identifying family members and friends. Although SD patients may exhibit nonspecific memory loss, which does not reflect a true amnesia, their episodic memory is relatively preserved, particularly for autobiographical events (20). On the other hand, it has been reported that as the disease progresses, episodic memory may also become impaired (21). Additionally, it has been reported that SD patients typically have very well-preserved perceptual and spatial abilities, with normal cube copy and clock drawing (5). In our case, spatial attention (clock drawing) and configuration (copy) tests were normal, in discordance with AD. SD patients may have early behavioral and personality changes such as disinhibition, irritability, and increased social attention seeking (18). Our patient had irritability and aggressive and sexually inappropriate behaviors. SD patients have bilateral involvement (cortical atrophy or decreased metabolism) in the anterior temporal lobes in the early stages of the disease, more marked on the left side as in our case (22). However, as the disease progresses, the fusiform gyrus, temporal pole, anterior hippocampus, and amygdala are also involved in SD (23). Galton et al.

Table. The differences between AD and other types of dementia.

Characteristics	AD	Other dementias (ODs)
Chief presenting symptom	Forgetfulness	Others: e.g., behavioral disturbance, difficulty in speaking
Age of onset	95% of patients over 65 years	Lower than AD (e.g., FTLD)
Sex	Female > male	Male > female (e.g., DLB)
Prevalence	60%-70% of all dementia cases	<40% of all dementia cases
Onset	Insidious	Sudden (e.g., MED)
Average time for survival	AD > ODs (from 3 to 9 years for AD) (24)	Lower than in AD
Time course of cognition	Gradual decline	Stepwise decline (e.g., MED)
Family history	<40%	50% (e.g., FTLD)
Main cognitive dysfunction	Memory loss (episodic)	Others: e.g., executive dysfunction, language impairment, semantic knowledge loss
Visuoperceptual skills	Impaired	Preserved (e.g., FTLD)
Prosopagnosia	Absent	Present (e.g., SD)
Noncognitive signs	Mood swings, depression	Parkinsonism (e.g., DLB)
CSF findings	Amyloid β 1-42 ⁺ , p-tau, t-tau	14-3-3 protein (e.g., CJD)
Brain regions involved	Hippocampus, temporoparietal lobes	Anterior temporal lobes (e.g., SD), frontotemporal lobes (bvFTD)
AChe inhibitor drugs	Effective	Noneffective (e.g., FTLD)

FTLD: Frontotemporal lobar degeneration; DLB: dementia with Lewy bodies; MED: multi-infract dementia; CSF: cerebrospinal fluid; bvFTD: behavioral variant frontotemporal dementia; CJD: Creutzfeldt–Jakob disease; SD: semantic dementia; AChE: acetylcholinesterase.

(6) reported a patient with an initial SD diagnosis and pathological findings of AD. Their patient had some impairments in incomplete drawings assessing perceptual functions (6). Probable AD with aphasia was diagnosed in that patient because of the presence of impairment in visuoperceptual skills.

We think that the cause of cognitive dysfunction in our representative case is SD, because of the partially preserved memory for recent events and normal spatial attention and configuration, which are discordant with AD. The patient's age at onset of symptoms was under 65 years, whereas in 95% of patients with AD, age at onset is over 65 years (15). In addition, his speech was fluent with perseverations and

he had disinhibited, compulsive, and stereotypic behaviors. The disturbance in recognizing family members of the patient was not associated with memory loss and even may be attributed to prosopagnosia, familiarity-dependent in SD. The Table summarizes the differences between AD and other types of dementia 1, 15, 24.

In conclusion, AD can be infrequently misdiagnosed as other dementias due to atypical presentations or the presence of amnesic features in non-Alzheimer dementias. Nevertheless, a careful clinical history, a detailed mental evaluation, and neuroimaging evaluation will overcome this confusion.

References

1. Fratiglioni L, Winblad B, Strauss E. Prevention of Alzheimer's disease and dementia. Major findings from the Kungsholmen Project. *Physiol Behav* 2007; 92: 98–104.
2. Querfurth HW, LaFerla FM. Alzheimer's disease. *N Engl J Med* 2010; 362: 329–344.
3. de Souza LC, Bertoux M, Funkiewiez A, Samri D, Azuar C, Habert MO, Kas A, Lamari F, Sarazin M, Dubois B. Frontal presentation of Alzheimer's disease. *Dement Neuropsychol* 2013; 7: 66–74.
4. Maurer K, Volk S, Gerbaldo H, Auguste D and Alzheimer's disease. *Lancet* 1997; 349: 1546–1549.
5. Harciarek M, Kertesz A. Primary progressive aphasia and their contribution to the contemporary knowledge about the brain-language relationship. *Neuropsychol Rev* 2011; 21: 271–287.
6. Galton CJ, Patterson K, Xuereb JH, Hodges JR. Atypical and typical presentations of Alzheimer's disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases. *Brain* 2000; 123: 484–498.
7. Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. *Lancet Neurol* 2011; 10: 785–796.
8. Alladi S, Xuereb J, Bak T, Nestor P, Knibb J, Patterson K, Hodges JR. Focal cortical presentations of Alzheimer's disease. *Brain* 2007; 130: 2636–2645.
9. Graham A, Davies R, Xuereb J, Halliday G, Kril J, Creasey H, Graham K, Hodges J. Pathologically proven frontotemporal dementia presenting with severe amnesia. *Brain* 2005; 128: 597–605.
10. La Joie R, Landeau B, Perrotin A, Bejanin A, Egret S, Pélerin A, Mézenge F, Belliard S, de La Sayette V, Eustache F et al. Intrinsic connectivity identifies the hippocampus as a main crossroad between Alzheimer's and semantic dementia-targeted networks. *Neuron* 2014; 81: 1417–1428.
11. von Gunten A, Bouras C, Kövari E, Giannakopoulos P, Hof PR. Neural substrates of cognitive and behavioral deficits in atypical Alzheimer's disease. *Brain Res Rev* 2006; 51: 176–211.
12. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guide lines for Alzheimer's disease. *Alzheimers Dement* 2011; 7: 263–269.
13. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* 2007; 6: 734–746.
14. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. *Lancet* 2006; 368: 387–403.
15. Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants and strategies toward intervention. *Dialogues Clin Neurosci* 2009; 11: 111–128.
16. Mendez MF. Early-onset Alzheimer's disease: nonamnesic subtypes and type 2 AD. *Arch Med Res* 2012; 43: 677–685.
17. Duker AP, Espay AJ, Wszolek ZK, Rademakers R, Dickson DW, Kelley BJ. Atypical motor and behavioral presentations of Alzheimer disease: a case-based approach. *Neurologist* 2012; 18: 266–272.
18. Kertesz A, Jesso S, Harciarek M, Blair M, McMonagle P. What is semantic dementia?: a cohort study of diagnostic features and clinical boundaries. *Arch Neurol* 2010; 67: 483–489.
19. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998; 51: 1546–1554.
20. Irish M, Addis DR, Hodges JR, Piguet O. Considering the role of semantic memory in episodic future thinking: evidence from semantic dementia. *Brain* 2012; 135: 2178–2191.
21. Matuszewski V, Piolino P, Belliard S, de la Sayette V, Laisney M, Lalevée C, Pélerin A, Viader F, Eustache F, Desgranges B. Patterns of autobiographical memory impairment according to disease severity in semantic dementia. *Cortex* 2009; 45: 456–472.

22. Diehl J, Grimmer T, Drzezga A, Riemenschneider M, Förstl H, Kurz A. Cerebral metabolic patterns at early stages of frontotemporal dementia and semantic dementia. A PET study. *Neurobiol Aging* 2004; 25: 1051–1056.
23. Mion M, Patterson K, Acosta-Cabronero J, Pengas G, Izquierdo-Garcia D, Hong YT, Fryer TD, Williams GB, Hodges JR, Nestor PJ. What the left and right anterior fusiform gyri tell us about semantic memory. *Brain* 2010; 133: 3256–3268.
24. Helzner EP, Scarmeas N, Cosentino S, Tang MX, Schupf N, Stern Y. Survival in Alzheimer disease: a multiethnic, population-based study of incident cases. *Neurology* 2008; 71: 1489–1495.