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Journal

Neurocase, 28(1)

ISSN

1355-4794

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Publication Date

2022-01-02

DOI

10.1080/13554794.2021.1936072

Peer reviewed

Published in final edited form as:

Neurocase. 2022 February ; 28(1): 19–28. doi:10.1080/13554794.2021.1936072.

Clinical, neuroimaging, and neuropathological characterization of a patient with Alzheimer's disease syndrome due to Pick's pathology

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Abstract

The most common neurodegenerative syndrome associated with Pick's disease pathology (PiD), a type of frontotemporal lobar degeneration, is behavioral variant frontotemporal dementia (bvFTD), which is characterized by profound changes in social behavior. However, in rare cases, PiD can manifest as an Alzheimer's disease-type dementia featuring early impairment of episodic memory. We describe the longitudinal cognitive and socioemotional changes as well as the structural imaging and neuropathological findings of a patient who presented with late-onset AD-type dementia with PiD. The patient showed slowly progressive episodic memory impairment, followed by executive dysfunctions and changes in social behavior, but preserved visuospatial, language, and motor functions. Consistent with this clinical profile, gray matter atrophy and underlying PiD were most predominantly found in anterior temporal and frontal lobe regions of the salience and semantic-appraisal networks, with relative sparing of language-related temporal lobe structures and parietal areas involved in visuospatial functioning. Our findings from this patient presenting with memory complaints suggest that early bvFTD-like social symptoms such as loss of empathy and disinhibition as well as slow disease progression and paucity of motor symptoms are key clinical features suggestive of a frontotemporal lobar degeneration pathology like PiD. This case report may help improve the ability of clinicians and clinical researchers to predict the pathology of patients with atypical presentations of AD, which will ultimately be critical for enrollment of patients into disease-modifying clinical trials targeting the underlying proteinopathy.

Keywords

Alzheimer's disease; Pick's disease; Frontotemporal lobar degeneration; Memory; Social functioning

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Disclosure statement: No potential conflict of interest was reported by the authors.

Introduction

In 1892, Arnold Pick first described the clinical symptoms and neuroanatomical changes of a patient with Pick's disease who presented with aphasia and frontotemporal lobar atrophy (Pick, 1892). However, the microscopic features, which include Pick bodies (round, neuronal, cytoplasmic inclusions) and Pick cells (ballooned neurons) (Cairns et al., 2007; Munoz et al., 2003), were delineated nearly 20 years later by Alois Alzheimer (Alzheimer, 1911). Pick's disease was used for many years as an umbrella term for all frontotemporal lobar degeneration (FTLD) syndromes and pathologies. Today, however, the term refers to a well-defined pathological entity constituting one specific neuropathological subtype of the FTLD spectrum (Mackenzie et al., 2010): FTLD-tau, Pick's disease subtype (PiD).

PiD typically causes marked gyral atrophy in the frontotemporal lobe referred to as "knife-edge" atrophy (Ball, 1979; Perry et al., 2017). The pathology affects brain circuits that are critical for memory, language, and social functioning, including the anterior temporal lobe (hippocampus, amygdala), anterior insula, medial and lateral frontal lobe, as well as subcortical regions such as the basal ganglia and thalamus (Graham et al., 2005; Munoz-Garcia & Ludwin, 1984; Perry et al., 2017; Rankin et al., 2011; Rohrer et al., 2011; Tsuchiya et al., 2001; Whitwell et al., 2011). In the vast majority of cases, PiD causes FTD syndromes, most frequently behavioral variant frontotemporal dementia (bvFTD) and nonfluent variant primary progressive aphasia (nfvPPA) (Caplan et al., 2018; Choudhury et al., 2020; Hodges et al., 2004; Josephs et al., 2006). FTD patients with PiD frequently show early social symptoms such as loss of empathy (Perry et al., 2017; Rankin et al., 2011), slow disease progression, absence of motor symptoms until late disease stages, and lack of family history of dementia (Josephs et al., 2006; Kertesz, McMonagle, Blair, Davidson, & Munoz, 2005; Miller, 2013; Perry et al., 2017; Yokota et al., 2009).

Previous studies have reported cases with early memory loss and underlying PiD (Graham et al., 2005; Munoz-Garcia & Ludwin, 1984; Tsuchiya et al., 2001), and some case series suggest that in 2–8% of patients PiD manifests as Alzheimer's disease-type dementia (AtD) (Hodges et al., 2004; Mendez, Mastri, Sung, & Frey, 1992; Risse, Raskind, Nochlin, Sumi, & Lampe, 1990). A very recent case series in 21 autopsy-confirmed PiD cases suggests that amnestic presentations are even rarer, with less than 1% (1 of 21 patients) showing early and focal memory impairment (Choudhury et al., 2020). Yet, none of these studies showing PiD manifesting as AtD have provided a thorough description of the cognitive performance over time as well as the corresponding neuroanatomical and neuropathological changes of autopsy-confirmed cases. Such knowledge is critical for improving the ability of clinicians and clinical researchers to predict the molecular pathology of individual patients, which in turn has important implications for enrollment of patients into clinical trials that are now being conducted for both FTLD-tau and FTLD-TDP (Khouri et al., 2021; Tsai & Boxer, 2016). In this report, we provide an in-depth analysis of clinical, neuroanatomical, and pathological features of a patient with clinical AtD due to PiD to elucidate the key features of this rare clinical-pathological entity.

Clinical history

The patient was a right-handed man with a history of hyperlipidemia, bilateral hernia repairs, coronary stent replacement, tonsillectomy and ulcers, and smoking. He had a bachelor's degree in marine engineering and naval architecture. For most of his career, he worked in the computer industry as a networking specialist and customer support manager. He retired at the age of 68, which was unrelated to any changes in his cognition or behavior.

He was first seen at the UCSF Memory and Aging Center at the age of 77, with mildly progressive memory loss as a first symptom beginning at least three years prior at age 74. Specifically, his wife noticed that he had difficulties remembering conversations and upcoming plans and that he forgot things such as why he went into a room. The patient was aware of the changes in his memory and reported having difficulties remembering recent events, conversations and plans, and that he frequently misplaced objects. He denied any difficulties with planning or organizing but admitted to mild trouble with multitasking. His wife reported that he had become more irritable, particularly when he drove. She also mentioned that his social and interpersonal skills had always been a weakness; however, she hadn't noticed any significant changes in his personality in the past 10 years. At the age of 77, two months before his first visit, the patient had an episode where he lost his car. According to his wife, he was somewhat confused and not himself during that whole day. For instance, earlier in the day he could not find his symphony tickets and seemed confused about where he had put them and became agitated when he was not able to find the tickets. She said that after the concert he could not remember the program he had seen at the symphony, whereas in the past he could easily describe what happened at a concert. Besides this one day, she did not note any days when he was particularly confused or different than his usual. On neurological examination, he was well groomed and somewhat quiet but very cooperative. Speech was fluent. Apart from a mild action tremor in the left hand, his motor examination was normal. His physical examination remained relatively normal until his last evaluation at our center. After this visit, based on the memory complains and impaired verbal episodic memory and executive functions on neuropsychological testing, the patient received a diagnosis of mild cognitive impairment (MCI).

At his second visit at the age of 78, the patient and his wife reported that his memory had worsened and that he needed to write things down more and relied on his wife to remind him of what he needed to do. He was more comfortable in a familiar environment and felt easily disoriented. His wife noticed that he seemed more absent in their relationship and that he communicated less. She complained of him not wanting to talk about changes and felt that he was not engaged as much in family activities, in conversations or in plans for the future. She had concerns that he was depressed, though he insisted that his mood was good. He became irritable, short-tempered, and defensive. He started to order many items like watches and clocks from catalogues. The patient was also known to have a lifelong pornography addiction that he no longer hid. There was also a decline in his ability to manage his finances and deal with daily problems. On neurological examination, the patient had decreased vibration, proprioception, and pinprick in the lower limbs. Because of the progressive changes in episodic memory and executive functioning, the functional decline, as well as the volume loss and vascular changes found on the MRI (see neuroimaging section), the

patient received a clinical diagnosis of mixed dementia (AD and vascular disease). Based on the information available, the clinicians presumed that the clinical syndrome was caused by underlying AD pathology, thus treatment with a cholinesterase inhibitor was recommended.

At his third visit when the patient was 79 years old, his wife reported that his memory and executive functions had worsened over the past year, that he frequently repeated himself, forgot conversations and events, was less organized and less able to multitask. He had become harsher and more irritable and showed social disinhibition (e.g. he booed a performer at a café) and apathy. Moreover, his wife described his driving as impulsive. He could still perform chores around the house and work on his truck, handled his own medications and paid the bills. However, he sometimes left the stove on and left doors unlocked. He took Aricept for three months and did not notice any improvement on the medication, thus it was discontinued. During the neurological examination, the patient told the same stories more than once. He showed rapid forgetting for events, he was somewhat irritable and defensive. He could not recall the name of his sister who died in childhood and confused his daughters with his granddaughters. He had difficulty performing the Luria three-step task and had troubles with tandem walking.

At his last visit at the age of 80, his wife reported increasing behavioral changes. He became more frustrated with his symptoms and insisted on doing his finances and other bookkeeping tasks although he made frequent mistakes. He had frequent constant bouts of anger and got easily frustrated with people who attempted to correct him. At that time, he was not taking Aricept or Citalopram although they were on his prescribed medication list. His neurological examination was normal except for decreased vibration sensations in his toes bilaterally, which was no change compared to his prior visits. As in the previous year, the patient repeated himself multiple times and told the same stories during the course of the examination. This time, however, he was also somewhat irritable and defensive and at one point hit the table with his fist and yelled at the examiner.

At age 81, the patient moved to a higher-level care facility with some memory support. In the following years, the patient gradually became weaker, both physically and mentally, and stopped recognizing his wife and children. He became very passive and unresponsive and died at the age of 86.

Neuropsychological evaluations

Neuropsychological assessments were performed in four consecutive years between the age of 77 and 81 (Table 1). For all tests scores, the following cutoffs were used to assess whether a score was in the normal or impaired range: a score ≤ 5^{th} %ile = significant impairment, a score between 6^{th} and 8^{th} %ile = borderline impairment, and a score > 8^{th} %ile = normal range. A decline of 1.5 SDs or more between two test scores was considered clinically significant progression. The patient showed severe behavioral symptoms including anger and verbal aggressiveness during his last neuropsychological evaluation, thus testing had to be discontinued and only a subset of the tasks of the neuropsychological battery could be administered (Table 1).

Global cognition: At his initial visit, the 77-year old patient scored 28 out of 30 on the Mini-Mental State Examination (MMSE) (Folstein, Robins, & Helzer, 1983). His Clinical Dementia Rating (CDR) (Morris, 1993) score was 0.5, showing that his functional status in six domains, including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care, rated by his wife, corresponded to MCI stage. In the following three years, the patient's general cognitive functioning progressed slowly, his MMSE score dropped to a mildly impaired score of 25 between the first and last visit. Consistent with that, his CDR score increased from 0.5 to 1, which corresponds to mild dementia stage.

Episodic memory:

Verbal: The patient showed a very consistent pattern of verbal episodic memory impairment on the 9-word version of the California Verbal Learning Test (CVLT) (Libon et al., 1996) in each year, with significant impairment on learning, short delay free recall, and long delay free and cued recall of the word list. No intrusions (incorrect recall of words that had not appeared in the word list) and perseverations (immediate repetitions of prior responses) were observed. Performance on recognition was relatively preserved at each evaluation, he correctly recognized 9 out of 9 words from the list in each year but showed a significantly increased number of false positive answers.

Visual: Compared to the patient's significantly diminished verbal episodic memory, scores on visual episodic memory varied between normal and significantly impaired over the years. Specifically, performance on the delayed recall of the Benson Figure (Possin, Laluz, Alcantar, Miller, & Kramer, 2011) was borderline in the first and last year, normal in the second year, and significantly impaired in the last year. Except for the last visit, recognition of the figure was intact.

Executive functions and attention: In the first year, rapid word retrieval on the Stroop color-naming condition (state the color of the ink of blocks of letters) was significantly impaired, which suggests that the patient had diminished information processing. In addition, he was disproportionately slow when he had to inhibit an automatic reaction on the Stroop interference condition (state the color of the ink instead of reading a word). Significant impairment was also observed on generation of novel phonemic (D-words) and semantic (animals) material. While his ability to solve five arithmetic problems was intact in the first two years, he had significantly diminished scores (3 out of 5) at his third and last visit. Scores on echoic memory, working memory, set shifting, and generation of visuospatial material (Designs, 5 filled dots) (Delis, 2001) were within the lower normal to average range. Except for significant worsening on Stroop color naming, none of the scores in the executive function and attention domain showed clinically significant progression over the four-year disease course.

Language: At each neuropsychological assessment, the patient had fluent and grammatically correct speech and showed no word-finding difficulties. Performance on all speech and language tasks was in the normal range, including confrontational naming on the Boston Naming Test (BNT), single-word comprehension (PPVT-R) (Dunn, 1981),

comprehension of syntactically complex sentences (BDAE) (Goodglass & Kaplan, 1983), repetition of short phrases and sentences (BDAE) (Goodglass & Kaplan, 1983), verbal agility (BDAE) (Goodglass & Kaplan, 1983), and reading of regular and irregular words (WRAT-4) (Wilkinson & Robertson, 2006). No clinically significant changes were observed across the different visits.

Visuospatial: Visuospatial functioning also remained intact across the four visits. In each year, the patient correctly copied the Benson Complex Figure (Possin et al., 2011) and had preserved space perception on the Number Location task of the Visual Object and Space Perception (VOSP) battery (Warrington & James, 1991).

Mood and behavior: There were no signs of depressive symptoms on the self-report Geriatric Depression Scale (GDS) (Yesavage et al., 1982), with scores ranging between 1 and 5 across the different years. According to the neuropsychologist examining the patient in the first year, the patient showed no behavioral symptoms such as disinhibition, apathy, social inappropriateness, agitation, or lack of social engagement during testing. However, in the following years, he displayed increasing behavioral disturbances during testing, including agitation, disinhibition (e.g., singing during test performance), social inappropriateness, perseverations, and motor stereotypies. At his last visit, the patient was verbally aggressive and screamed at the neuropsychologist who administered the tests, thus the testing had to be discontinued.

Social functions: After diagnosis, the patient was enrolled in different research studies conducted at the UCSF Memory and Aging Center. Social function testing was performed in one of the projects, thus the data was not available to the clinicians who saw and diagnosed the patient. Face perception and affect naming on the Comprehensive Affective Testing System (CATS) (Froming, Levy, Schaffer, & Ekman, 2006) were normal at each evaluation. However, his wife reported on the Interpersonal Reactivity Index (IRI) (Davis, 1983) that the patient had reduced ability to take other people's perspectives and show empathic concern for others. In years two and three, she additionally indicated that he demonstrated more self-centered emotional reactivity than in the past.

In summary, the neuropsychological profile was characterized by normal global cognition and significant impairment on learning and retrieval of verbal episodic information, executive functioning (information processing, inhibition, verbal fluency), and social cognition (empathic concern, perspective taking). Follow-up testing revealed slow cognitive progression, including mild worsening on general cognitive functioning, verbal episodic memory, executive functions (processing speed, calculations), and social cognition (emotion regulation). Speech and language, visuospatial functions, and mood were unaffected across all evaluations. Table 2 provides a timeline showing which symptoms required for diagnosing bvFTD and AD according to the mostly used clinical criteria were present at each visit.

Neuroimaging

Structural magnetic resonance imaging (MRI): The patient received a structural MRI scan at another hospital two months before his first visit at the UCSF Memory and Aging Center. A T1-weighted spin echo sequence was performed on a GE Genesis Signa 1.5T scanner, with parameters as follows: 24 sagittal slices, 5-mm thick, skip = 6 mm; repetition time = 567 ms; echo time = 11 ms; flip angle = 90°; field of view = 192 × 320 mm^2; voxel size = 0.5mm x 0.5mm x 6 mm; matrix size = 512 × 512. The MRI was visually reviewed at the first visit and was rated to show left greater than right atrophy predominantly in the mesial temporal and also in the frontoparietal lobe, as well as mild to moderate degree of subcortical ischemic white matter changes.

For this report, to statistically quantify the patient's atrophy pattern against a healthy comparison group, the structural MRI scan was used to create a voxelwise W-score map. The T1-weighted image was preprocessed in Statistical Parametric Mapping (SPM)12 (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing included segmentation into gray matter, white matter, and cerebrospinal fluid segments, warping with the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) method (Ashburner, 2007), normalization to MNI space, modulation, and smoothing with an 8-mm FWHM isotropic Gaussian kernel. The smoothed gray matter image was compared to 534 healthy older controls (age range 44–99; M±SD: 68.7±9.1; 232 male/302 female) from the UCSF Hillblom Aging Network. Specifically, a W-map was calculated by first performing voxelwise regressions in SPM12 on the nuisance factors age, sex, total intracranial volume (TIV), and magnet field strength in the control sample to derive beta maps estimating each factor's effect on the gray matter probability images. Next, a voxelwise W-map was calculated on the patient's normalized, modulated, and smoothed gray matter probability image according to the following formula: W-score = (actual voxel intensity – expected voxel intensity) / standard deviation (SD), where actual is the gray matter probability at a given voxel and expected refers to the predicted gray matter at the same voxel using the beta weights from the four nuisance covariates (age, sex, TIV, magnetic field strength). SD refers to the voxel's SD of the residuals observed in the control group. Thus, the W-score for a voxel represents where that voxel falls on a normal probability distribution of gray matter volume after the 4 nuisance factors are taken into account (La Joie et al., 2012; Ossenkoppele, Pijnenburg et al., 2015). W-scores have a mean=0 and SD=1 (like z-scores) and negative values indicate below average gray matter volume. We considered voxels with a score < −1.5 SDs (<7^{th} %ile) below the average of the control group as clinically abnormal. Compared to the healthy control group, the patient showed left worse than right volume loss predominantly in frontotemporal and subcortical regions, including the hippocampus, amygdala, temporal pole, anterior insula, anterior (ACC) and middle cingulate cortex, prefrontal and orbitofrontal (OFC) cortex, thalamus, and basal ganglia (putamen, caudate, nucleus accumbens) (Figure 1A, Table 3).

Computed tomography (CT): Because the patient had a syncope at the age of 84 (after his last visit at UCSF), a non-contrast CT scan was performed at the emergency room of another hospital. The CT scan was reviewed for this report and was found to show the

typical knife-edge cortical atrophy associated with PiD, most predominantly in the frontal lobe (Figure 1B).

Genetic testing

The patient had no family history of dementia. He was negative for the eight main autosomal dominant causing genes for AD and FTLD: *APP, PSEN1, PSEN2, MAPT, GRN, C9orf72, FUS,* and *TARDBP*. He was heterozygous for the extended *MAPT H1/H1* inversion polymorphism. His apolipoprotein E (APOE) genotype was *E2/E3*.

Neuropathology

The brain weighted 1380 grams. Gross atrophy was primarily found in bilateral, left greater than right, frontotemporal regions, including the mesial temporal lobe (Figure 2). This is consistent with the patient's early and pronounced verbal episodic memory impairment, executive dysfunctions, and changes in social behavior. On microscopic examination, superficial vacuolation, astrogliosis, and neuronal loss was more prominent in the left than right hemisphere and was most predominantly seen in the ACC and the C1 region of the hippocampus. The neuropathological involvement of the ACC may explain the significantly diminished verbal fluencies in the absence of language deficits on neuropsychological testing and the apathy reported by the wife. Phospho-tau immunohistochemistry revealed severe PiD (Pick bodies and ballooned Pick cells) (Mann, South, Snowden, & Neary, 1993) in frontotemporal regions, including the middle frontal gyrus and the dentate gyrus of the hippocampus, which was the primary pathological diagnosis. Vascular brain injury, which included old microinfarcts in the putamen and superior frontal sulcus, white matter rarefaction of vascular etiology in the parietal lobe, and an old territorial ischemic infarct in the right parietal lobe contributed to the clinical manifestation. Besides progressive worsening on calculation abilities, which were more likely caused by executive dysfunctions than reflecting acalculia, the patient did not present with clinical symptoms that were suggestive of parietal damage such as impaired visuospatial functions, diminished echoic memory, or apraxia. This indicates that vascular parietal pathology had low, if any, impact on the patient's clinical symptom profile. In addition, there were two incidental diagnoses presumed to have contributed little, if at all, to the patient's clinical deficits: (1) mild arteriolosclerosis, and (2) low degree of Alzheimer's disease neuropathological changes (Braak Stage 1), with presence of beta-amyloid plaques (Thal Amyloid Plaque Phase 1) but absence of neuritic plaques (CERAD Neuritic Plaque Score absent).

Discussion

This report comprehensively described a 77-year old patient with a 12-year history of slowly progressive memory loss, followed by executive dysfunctions and changes in social behavior, but with preserved visuospatial, language, and motor functions, as well as underlying PiD. Based on the patient's early and progressive impairment of episodic memory, he was clinically diagnosed with late-onset AtD. Genetic testing was negative for the main AD- and FTD-causing genes. Consistent with the clinical presentation, visual evaluation of the MRI showed predominant mesial temporal atrophy, which pointed to an underlying AD pathology. However, retrospective statistical quantification of the patient's

atrophy pattern revealed volume loss in regions of the salience (SN) and semantic appraisal (SAN) networks, which suggests an underlying FTLD pathology. A CT scan that was performed after the patient's visits at UCSF showed knife-edge atrophy in the frontal lobes, which is typical for PiD. Consistent with that and the patient's early changes in social behavior, the ACC, which is a hub region of the SN, was one of the most affected regions by PiD.

The patient was 77 years old when he first presented with memory complaints at the UCSF Memory and Aging Center. Though the age of symptom onset in patients with underlying PiD has a wide range, the average onset reported in group studies is around 60 years (Choudhury et al., 2020; Hodges et al., 2004). This shows that compared to published group averages, our patient had a late onset of episodic memory impairment. In addition, amnestic presentations of PiD as found in our patient are extremely rare, with a recent case series study showing that only one of 21 patients with autopsy-confirmed PiD had an amnestic presentation (Choudhury et al., 2020). Thus, the old age of the patient and the predominant memory impairment at his first evaluation may explain why the patient was clinically diagnosed with AD and not with an FTLD syndrome such as bvFTD.

Clinico-anatomical correlations

The first symptom of the patient, which was noticed by his wife at the age of 74, was loss of episodic memory, including substantial impairment on learning, retrieval, and rapid forgetting of verbal information. This suggests that the disease started in the left mesial temporal lobe, which was supported by structural imaging showing that the most pronounced atrophy was found in the left hippocampus. Visuospatial memory was less affected and was in the borderline range. Evidence from neuroimaging and human lesion studies shows that encoding, storage, and retrieval of episodic memories is supported by the default-mode network (DMN) (Buckner, 2004; Greicius, Krasnow, Reiss, & Menon, 2003; Maguire & Mummery, 1999). Specifically, previous research has shown that episodic memory is mediated by the medial temporal subsystem of the DMN, which includes the mesial temporal lobe (hippocampus, parahippocampal gyrus, entorhinal cortex), retrosplenial cortex, ventral medial prefrontal cortex, and posterior inferior parietal lobe (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). In addition, other studies have emphasized the importance of particularly the lateral and anterior frontal lobe for episodic memory, for use for strategies during encoding, tagging of events with contextual information, as well as search and monitoring during retrieval (Davidson, Troyer, & Moscovitch, 2006; Fletcher & Henson, 2001). The patient's W-map showed substantial damage to bilateral, left greater than right, mesial temporal (hippocampus, entorhinal cortex) and lateral frontal lobe, which is consistent with the proposed link between episodic memory and frontotemporal circuits.

Executive dysfunctions are early key symptoms of patients with both AtD due to underlying AD pathology (=typical AD) and FTLD syndromes, particularly bvFTD, and include impaired working-memory, verbal and nonverbal fluency, inhibition, set-shifting, and processing speed (Collette, Van der Linden, & Salmon, 1999; McPherson, Fairbanks, Tiken, Cummings, & Back-Madruga, 2002; Ossenkoppele, Cohn-Sheehy et al., 2015; Torralva,

Roca, Gleichgerrcht, Bekinschtein, & Manes, 2009). Previous studies have linked these functions to fronto-subcortical circuits (Heyder, Suchan, & Daum, 2004). Our patient had early executive dysfunctions in most of these domains and bilateral damage to the dorsolateral prefrontal cortex, striatum, and thalamus, which are the key regions of this fronto-subcortical loop (Alexander, DeLong, & Strick, 1986)

Though patients with typical AD often show neuropsychiatric symptoms such as apathy, depression, and anxiety (Spalletta et al., 2010), they usually maintain intact socioemotional functions, including empathy, emotion reading, and personality traits like interpersonal warmth (Rankin et al., 2006; Shany-Ur et al., 2012; Sollberger et al., 2009). This stands in contrast to the clinical presentation of our patient, whose wife reported reduced empathic concern for others and perspective taking abilities at the first visit three years after symptom onset. Early social symptoms such as loss of empathy are also frequently seen in bvFTD patients with underlying PiD. Previous research has shown that loss of empathy corresponds to atrophy in regions of the SN (Seeley et al., 2007) and SAN (Yeo et al., 2011), including the anterior insula, ACC, amygdala, temporal pole, and OFC (Cerami et al., 2014; Rankin et al., 2006). The patient had atrophy in each of these regions, which may have contributed to the early informant-reported loss of empathy. At the age of 78, the patient's wife also reported changes in emotion regulation, she noted that the patient showed more self-centered emotional reactivity. This aspect of social function has been associated with neurodegeneration to right mesial and lateral temporal lobe regions, including the hippocampus and temporal pole (Sturm et al., 2013), structures that were early and severely affected in our patient.

Disinhibition is one of the key diagnostic features of bvFTD (Rascovsky et al., 2011) but it occurs only in subsets of patients with AD (Mega, Cummings, Fiorello, & Gornbein, 1996; Spalletta et al., 2010). Neuroimaging and human lesion studies have linked disinhibition to the ventromedial and lateral OFC (Eslinger & Damasio, 1985; Hornak, Rolls, & Wade, 1996; Rosen et al., 2005). Previous research has shown that the medial OFC is involved in evaluating reward value, while the lateral OFC primarily evaluates reinforcers that have a valence related to punishment (Kringelbach & Rolls, 2004). Our patient exhibited profound atrophy in both medial (reward) and lateral (punishment) aspects of the OFC, and in subcortical structures of the reward network, including the caudate and nucleus accumbens (Yeo et al., 2011). Consistent with these neuroanatomical changes, at four years of disease duration, the patient showed social disinhibition and socially inappropriate behavior during his visits and in his real life. At the same time, neuropsychological testing also revealed early and profound disinhibition on the Stroop interference condition.

Apathy is a common neuropsychiatric symptom of both AD and bvFTD (Ducharme, Price, & Dickerson, 2018; Mega et al., 1996; Rosen et al., 2005). Previous studies suggest that apathy consists of three subcomponents with partially distinct underlying neuronal substrates and that degradation in each of these circuits can contribute to apathy (Massimo et al., 2015; Robert et al., 2009). (1) Impaired executive functions (e.g. planning, setshifting) can cause apathy because of difficulties with formulating and carrying out multi-step goals and actions, which corresponds to damage to the dorsolateral prefrontal cortex (Ber et al., 2006; Massimo et al., 2009; Zamboni, Huey, Krueger, Nichelli, & Grafman, 2008).

(2) Reduced initiation and ability to generate or activate actions, which is mediated by dorsomedial frontal areas, including the ACC and midcingulate cortex (Ber et al., 2006; Rosen et al., 2005; Zamboni et al., 2008). (3) Diminished motivation and emotional responsiveness due to altered personal evaluations of semantic entities caused by damage to fronto-subcortical reward-circuits, including the OFC and basal ganglia (Rosen et al., 2005; Zamboni et al., 2008). The patient showed impaired executive functions and reduced initiation during the generation of verbal material within the first three years since symptom onset. In addition, neuroimaging analysis revealed atrophy in each of the three circuits, and neuropathological examination demonstrated that the ACC was the most severely affected among these regions, with more than 50% loss of neurons.

Conclusions

This report of a rare 77-year old patient presenting with AtD due to underlying PiD suggests that clinical AD caused by PiD features symptoms that are often seen in patients with underlying AD pathology (memory loss, executive dysfunctions, apathy). In addition, both the clinical history and social function testing showed early bvFTD-like changes in social behavior, including loss of empathy and disinhibition, which point to an underlying FTLD pathology. Consistent with these social symptoms, retrospective statistical quantification of the patient's atrophy pattern revealed volume loss in the SN and SAN, showing that the clinical manifestations in neurodegenerative diseases depend on the particular networks affected and are not a reflection of the underlying neuropathological signature. Our findings suggest that a reliable clinical history and formal social function testing may help clinicians and clinical researchers to accurately predict an underlying FTLD pathology. Overall, this report highlights the importance of combining longitudinal cognitive assessments, including standard neuropsychological and socioemotional measures, and quantitative approaches to measure brain volume loss on an individual patient level to elucidate the key clinical and neuroanatomical features of rare clinical-pathological entities.

Acknowledgments

Funding: This work was supported by institutional NIH grants (P01AG019724, P50AG023501). LTG is supported by the NIH (K24AG053435) and GT is supported by the Swiss National Science Foundation (P300P1_177667).

References

Alexander GE, DeLong MR, & Strick PL (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annual Review of Neuroscience, 9(1), 357–381.

Alzheimer A. (1911). Über eigenartige krankheitsfälle des späteren alters. Zeitschrift Für Die Gesamte Neurologie Und Psychiatrie, 4(1), 356.

Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, & Buckner RL (2010). Functional-anatomic fractionation of the brain's default network. Neuron, 65(4), 550–562. [PubMed: 20188659]

Ashburner J. (2007). A fast diffeomorphic image registration algorithm. NeuroImage, 38(1), 95–113. [PubMed: 17761438]

Ball M. (1979). Topography of pick inclusion bodies in hippocampi of demented patients. Journal of Neuropathology & Experimental Neurology, 38(6), 614–620. [PubMed: 230324]

Ber IL, Guedj E, Gabelle A, Verpillat P, Volteau M, Thomas-Anterion C, . . . Lacomblez L. (2006). Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia. Brain, 129(11), 3051–3065. [PubMed: 17071924]

Buckner RL (2004). Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. Neuron, 44(1), 195–208. [PubMed: 15450170]

Cairns NJ, Bigio EH, Mackenzie IR, Neumann M, Lee VM, Hatanpaa KJ, . . . Halliday G. (2007). Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: Consensus of the consortium for frontotemporal lobar degeneration. Acta Neuropathologica, 114(1), 5–22. [PubMed: 17579875]

Caplan A, Marx G, Elofson J, Lis C, Grinberg L, Miller B, & Rosen H. (2018). A case of semantic variant primary progressive aphasia with pick's pathology. Neurocase, 24(2), 90–94. [PubMed: 29508660]

Cerami C, Dodich A, Canessa N, Crespi C, Marcone A, Cortese F, . . . Cappa SF (2014). Neural correlates of empathic impairment in the behavioral variant of frontotemporal dementia. Alzheimer's & Dementia, 10(6), 827–834.

Choudhury P, Scharf EL, Paolini MA, Graff-Radford J, Alden EC, Machulda MM, . . . Boeve BF (2020). "Pick's Disease: Clinicopathologic Characterization of 21 Cases." Journal of Neurology, 267(9), 2697–2704. [PubMed: 32440921]

Collette F, Van der Linden M, & Salmon E. (1999). Executive dysfunction in alzheimer's disease. Cortex, 35(1), 57–72. [PubMed: 10213534]

Davidson PS, Troyer AK, & Moscovitch M. (2006). Frontal lobe contributions to recognition and recall: Linking basic research with clinical evaluation and remediation. Journal of the International Neuropsychological Society, 12(2), 210–223. [PubMed: 16573855]

Davis MH (1983). Measuring individual differences in empathy: Evidence for a multidimensional approach. Journal of Personality and Social Psychology, 44(1), 113–126.

Delis D, Kaplan E, & Kramer J. (2001). Delis-kaplan executive function scale (D-KEFS): Examiner's manual. San Antonio: The Psychological Corporation.

Ducharme S, Price BH, & Dickerson BC (2018). Apathy: A neurocircuitry model based on frontotemporal dementia. Journal of Neurology, Neurosurgery, and Psychiatry, 89(4), 389–396. doi:10.1136/jnnp-2017-316277 [doi] [PubMed: 29066518]

Dunn L. (1981). 1981: Peabody picture vocabulary test-revised. circle pines, MN: American guidance service.

Eslinger PJ, & Damasio AR (1985). Severe disturbance of higher cognition after bilateral frontal lobe ablation: Patient EVR. Neurology, 35(12), 1731–1741. [PubMed: 4069365]

Fletcher PC, & Henson RN (2001). Frontal lobes and human memory: Insights from functional neuroimaging. Brain, 124, 849–81. [PubMed: 11335690]

Folstein MF, Robins LN, & Helzer JE (1983). The mini-mental state examination. Archives of General Psychiatry, 40(7), 812–812. [PubMed: 6860082]

Froming K, Levy M, Schaffer S, & Ekman P. (2006). The comprehensive affect testing system. Psychology Software, Inc, Gainesville, FL.

Goodglass H, & Kaplan E. (1983). Boston Diagnostic Aphasia Examination (BDAE). Philadelphia: Lea & Febiger.

Graham A, Davies R, Xuereb J, Halliday G, Kril J, Creasey H, . . . Hodges J. (2005). Pathologically proven frontotemporal dementia presenting with severe amnesia. Brain, 128(3), 597–605. [PubMed: 15634737]

Greicius MD, Krasnow B, Reiss AL, & Menon V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. Proceedings of the National Academy of Sciences of the United States of America, 100(1), 253–258. [PubMed: 12506194]

Heyder K, Suchan B, & Daum I. (2004). Cortico-subcortical contributions to executive control. Acta Psychologica, 115(2–3), 271–289. [PubMed: 14962404]

Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, Bak TH, . . . Halliday GM (2004). Clinicopathological correlates in frontotemporal dementia. Annals of Neurology, 56(3), 399–406. [PubMed: 15349867]

Hornak J, Rolls E, & Wade D. (1996). Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. Neuropsychologia, 34(4), 247–261. [PubMed: 8657356]

Josephs KA, Petersen RC, Knopman DS, Boeve BF, Whitwell JL, Duffy JR, . . . Dickson DW (2006). Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. Neurology, 66(1), 41–48. [PubMed: 16401843]

Kertesz A, McMonagle P, Blair M, Davidson W, & Munoz DG (2005). The evolution and pathology of frontotemporal dementia. Brain, 128(9), 1996–2005. [PubMed: 16033782]

Khoury R, Liu Y, Shehryar Q, & Grossberg GT (2021). Pharmacotherapy for Frontotemporal Dementia. CNS drugs, (35), 425–438. [PubMed: 33840052]

Kringelbach ML, & Rolls ET (2004). The functional neuroanatomy of the human orbitofrontal cortex: Evidence from neuroimaging and neuropsychology. Progress in Neurobiology, 72(5), 341–372. [PubMed: 15157726]

La Joie R, Perrotin A, Barre L, Hommet C, Mezenge F, Ibazizene M, . . . Chetelat G. (2012). Region-specific hierarchy between atrophy, hypometabolism, and beta-amyloid (abeta) load in alzheimer's disease dementia. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 32(46), 16265–16273. [PubMed: 23152610]

Libon DJ, Mattson RE, Glosser G, Kaplan E, Malamut BL, Sands LP, . . . Cloud BS (1996). A nine —word dementia version of the california verbal learning test. The Clinical Neuropsychologist, 10(3), 237–244.

Mackenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, . . . Holm IE (2010). Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: An update. Acta Neuropathologica, 119(1), 1. [PubMed: 19924424]

Maguire EA, & Mummery CJ (1999). Differential modulation of a common memory retrieval network revealed by positron emission tomography. Hippocampus, 9(1), 54–61. [PubMed: 10088900]

Mann DM, South PW, Snowden JS, & Neary D. (1993). Dementia of frontal lobe type: Neuropathology and immunohistochemistry. Journal of Neurology, Neurosurgery, and Psychiatry, 56(6), 605–614. [PubMed: 8509772]

Massimo L, Powers JP, Evans LK, McMillan CT, Rascovsky K, Eslinger P, . . . Grossman M. (2015). Apathy in frontotemporal degeneration: Neuroanatomical evidence of impaired goal-directed behavior. Frontiers in Human Neuroscience, 9, 611. [PubMed: 26617508]

Massimo L, Powers C, Moore P, Vesely L, Avants B, Gee J, . . . Grossman M. (2009). Neuroanatomy of apathy and disinhibition in frontotemporal lobar degeneration. Dementia and Geriatric Cognitive Disorders, 27(1), 96–104. [PubMed: 19158440]

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, … & Phelps CH (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, 7(3), 263–269.

McPherson S, Fairbanks L, Tiken S, Cummings JL, & Back-Madruga C. (2002). Apathy and executive function in alzheimer's disease. Journal of the International Neuropsychological Society, 8(3), 373–381. [PubMed: 11939696]

Mega MS, Cummings JL, Fiorello T, & Gornbein J. (1996). The spectrum of behavioral changes in alzheimer's disease. Neurology, 46(1), 130–135. [PubMed: 8559361]

Mendez MF, Mastri AR, Sung J, & Frey WH (1992). Clinically diagnosed alzheimer disease: Neuropathologic findings in 650 cases. Alzheimer Disease and Associated Disorders, 6 (1), 35–43 [PubMed: 1605942]

Miller BL (2013). Frontotemporal dementia. Oxford University Press.

Morris JC (1993). The clinical dementia rating (CDR): Current version and scoring rules. Neurology, 43 (11), 2412–2415.

Munoz-Garcia D, & Ludwin S. (1984). Classic and generalized variants of pick's disease: A clinicopathological, ultrastructural, and immunocytochemical comparative study. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 16(4), 467–480.

Munoz DG, Dickson DW, Bergeron C, Mackenzie IR, Delacourte A, & Zhukareva V. (2003). The neuropathology and biochemistry of frontotemporal dementia. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 54(S5), S24–S28.

Ossenkoppele R, Cohn-Sheehy BI, La Joie R, Vogel JW, Möller C, Lehmann M, . . . Gorno-Tempini ML (2015). Atrophy patterns in early clinical stages across distinct phenotypes of A lzheimer's disease. Human Brain Mapping, 36(11), 4421–4437. [PubMed: 26260856]

Ossenkoppele R, Pijnenburg YA, Perry DC, Cohn-Sheehy BI, Scheltens NM, Vogel JW, . . . Rosen HJ (2015). The behavioural/dysexecutive variant of alzheimer's disease: Clinical, neuroimaging and pathological features. Brain, 138(9), 2732–2749. [PubMed: 26141491]

Perry DC, Brown JA, Possin KL, Datta S, Trujillo A, Radke A, . . . Rabinovici GD (2017). Clinicopathological correlations in behavioural variant frontotemporal dementia. Brain, 140(12), 3329–3345. [PubMed: 29053860]

Pick A. (1892). Uber die beziehungen der senilen Hirnatrophie zur Aphasie. Prag Med Wochenschr, 17, 165–167.

Possin KL, Laluz VR, Alcantar OZ, Miller BL, & Kramer JH (2011). Distinct neuroanatomical substrates and cognitive mechanisms of figure copy performance in alzheimer's disease and behavioral variant frontotemporal dementia. Neuropsychologia, 49(1), 43–48. [PubMed: 21029744]

Rankin KP, Mayo MC, Seeley WW, Lee S, Rabinovici G, Gorno-Tempini ML, . . . DeArmond SJ (2011). Behavioral variant frontotemporal dementia with corticobasal degeneration pathology: Phenotypic comparison to bvFTD with pick's disease. Journal of Molecular Neuroscience, 45(3), 594. [PubMed: 21881831]

Rankin KP, Gorno-Tempini ML, Allison SC, Stanley CM, Glenn S, Weiner MW, & Miller BL (2006). Structural anatomy of empathy in neurodegenerative disease. Brain : A Journal of Neurology, 129(Pt 11), 2945–2956. [PubMed: 17008334]

Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, . . . Miller BL (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain : A Journal of Neurology, 134(Pt 9), 2456–2477. [PubMed: 21810890]

Risse SC, Raskind MA, Nochlin D, Sumi SM, & Lampe TH (1990). Neuropathological findings in patients with clinical diagnoses of probable alzheimer's disease. The American Journal of Psychiatry, 147(2), 168. [PubMed: 2301654]

Robert P, Onyike C, Leentjens A, Dujardin K, Aalten P, Starkstein S, . . . Drapier D. (2009). Proposed diagnostic criteria for apathy in alzheimer's disease and other neuropsychiatric disorders. European Psychiatry, 24(2), 98–104. [PubMed: 19201579]

Rohrer JD, Lashley T, Schott JM, Warren JE, Mead S, Isaacs AM, . . . Warrington E. (2011). Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. Brain, 134(9), 2565–2581. [PubMed: 21908872]

Rosen HJ, Allison SC, Schauer GF, Gorno-Tempini ML, Weiner MW, & Miller BL (2005). Neuroanatomical correlates of behavioural disorders in dementia. Brain, 128(11), 2612–2625. [PubMed: 16195246]

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, . . . Greicius MD (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. The Journal of Neuroscience, 27(9), 2349–2356. [PubMed: 17329432]

Shany-Ur T, Poorzand P, Grossman SN, Growdon ME, Jang JY, Ketelle RS, . . . Rankin KP (2012). Comprehension of insincere communication in neurodegenerative disease: Lies, sarcasm, and theory of mind. Cortex, 48(10), 1329–1341. [PubMed: 21978867]

Sollberger M, Stanley CM, Wilson SM, Gyurak A, Beckman V, Growdon M, . . . Rankin KP (2009). Neural basis of interpersonal traits in neurodegenerative diseases. Neuropsychologia, 47(13), 2812–2827. [PubMed: 19540253]

Spalletta G, Musicco M, Padovani A, Perri R, Fadda L, Canonico V, . . . Palmer K. (2010). Neuropsychiatric symptoms and syndromes in a large cohort of newly diagnosed, untreated patients with alzheimer disease. The American Journal of Geriatric Psychiatry, 18(11), 1026–1035. [PubMed: 20808086]

Sturm VE, Yokoyama JS, Seeley WW, Kramer JH, Miller BL, & Rankin KP (2013). Heightened emotional contagion in mild cognitive impairment and alzheimer's disease is associated with temporal lobe degeneration. Proceedings of the National Academy of Sciences of the United States of America, 110(24), 9944–9949. [PubMed: 23716653]

Torralva T, Roca M, Gleichgerrcht E, Bekinschtein T, & Manes F. (2009). A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. Brain, 132(5), 1299–1309. [PubMed: 19336463]

Tsai R, & Boxer LA (2016). Therapy and clinical trials in frontotemporal dementia: past, present, and future. Journal of Neurochemistry, 138, 211–221. [PubMed: 27306957]

Tsuchiya K, Ikeda M, Hasegawa K, Fukui T, Kuroiwa T, Haga C, . . . Yagishita S. (2001). Distribution of cerebral cortical lesions in pick's disease with pick bodies: A clinicopathological study of six autopsy cases showing unusual clinical presentations. Acta Neuropathologica, 102(6), 553–571. [PubMed: 11761716]

Warrington EK, & James M. (1991). The visual object and space perception battery. Bury St Edmunds: Thames Valley Test Company.

Whitwell JL, Jack CR, Parisi JE, Knopman DS, Boeve BF, Petersen RC, . . . Josephs KA (2011). Imaging signatures of molecular pathology in behavioral variant frontotemporal dementia. Journal of Molecular Neuroscience, 45(3), 372. [PubMed: 21556732]

Wilkinson GS, & Robertson GJ (2006). WRAT 4: Wide range achievement test; professional manual Psychological Assessment Resources, Incorporated.

Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, . . . Buckner RL (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. Journal of Neurophysiology, 106(3), 1125–1165. [PubMed: 21653723]

Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, & Leirer VO (1982). Development and validation of a geriatric depression screening scale: A preliminary report. Journal of Psychiatric Research, 17(1), 37–49. [PubMed: 7183759]

Yokota O, Tsuchiya K, Arai T, Yagishita S, Matsubara O, Mochizuki A, . . . Terada S. (2009). Clinicopathological characterization of pick's disease versus frontotemporal lobar degeneration with ubiquitin/TDP-43-positive inclusions. Acta Neuropathologica, 117(4), 429–444. [PubMed: 19194716]

Zamboni G, Huey ED, Krueger F, Nichelli PF, & Grafman J. (2008). Apathy and disinhibition in frontotemporal dementia: Insights into their neural correlates. Neurology, 71(10), 736–742. [PubMed: 18765649]

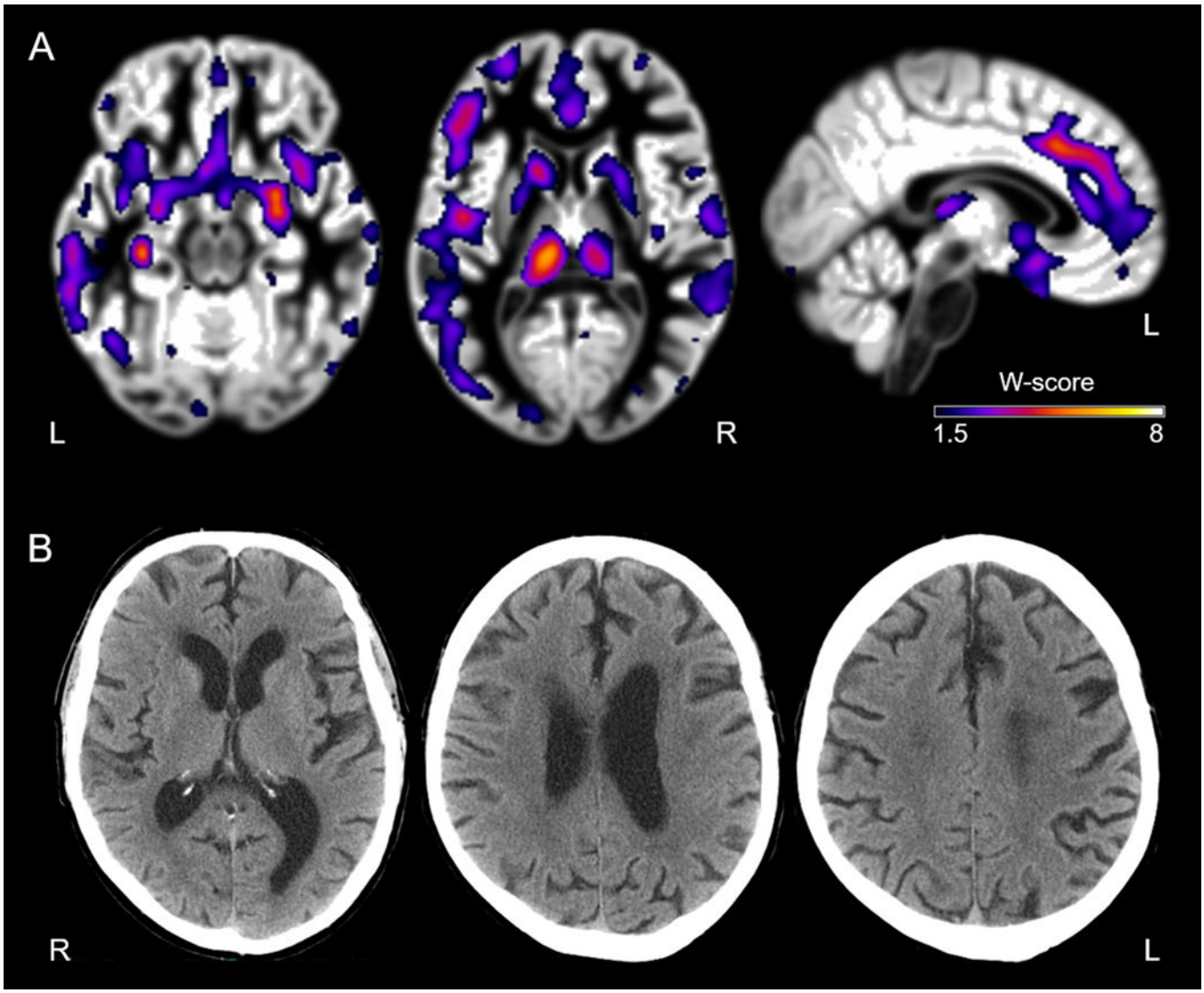

Fig. 1.

Neuroimaging revealed frontotemporal, knife-edge atrophy when the patient was 77 years old. (A) The images show reduced gray matter volume in the mesial temporal lobe, anterior insula, ACC, prefrontal cortex, OFC, thalamus, caudate, and putamen. The threshold for the W-map was set at $W < -1.5$. (B) The CT scan shows knife-edge cortical atrophy.

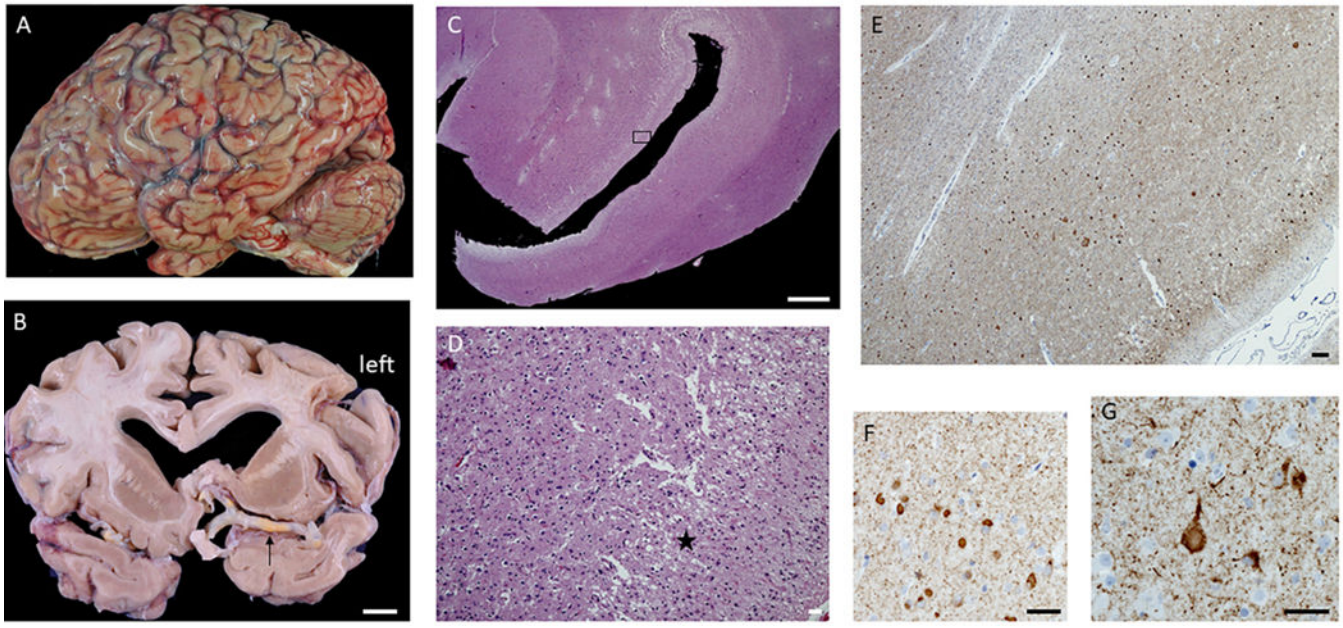

Fig. 2.

Gross and microscopic features of the case. A) Gross picture of the left side of the brain. Note the atrophy in the frontal lobe. B) Coronal cut of the brain at the level of the optic chiasm. Note the asymmetric pattern of atrophy, greater on the left side. The arrow points to atherosclerosis in the middle cerebral artery. C) Histological picture of the anterior cingulate cortex (ACC) stained with hematoxylin and eosin. Note the superficial vacuolation and gliotic aspect and subcortical enlargement of the perivascular space. D) Enlargement of the boxed area in C. The star points to the area with superficial vacuolation, which is characteristic of FTLD. E) Microscopic aspect of the ACC immunostained against phospho-tau (CP-13 antibody), showing tau pathology throughout the cortical thickness, but more pronounced in layer 2. F) and G) enlargements of (E) illustrating Pick's bodies (F) and ballooned neurons (G), both hallmarks of FTLD-tau, Pick's type. Scale bars: (B) 1 cm, (C) 1 mm, (D) 20 μm, (E) 50 μm, (F,G) 10 μm.

Table 1.

Standard neuropsychological and socioemotional test scores of the patient at four consecutive visits. All scores represent raw scores (percentiles). Bold text indicates that the patient scored in the clinically impaired range (≤5th %ile).

Tests (maximum score)	Year 1 (age=77)	Year 2 (age=78)	Year 3 (age=79)	Year 4 (age=80)
Global cognition				
MMSE total score (30)	28	28	27	**25**
MMSE missed items	memory, attention	memory, orientation	memory	memory, WORLD
CDR total score (3)	0.5	0.5	0.5	**1**
CDR sum of boxes (18)	2	4	4	8
Episodic memory				
Verbal (CVLT-SF)				
Learning total (36)	**20** (< 1st %ile)	**15** (<1st %ile)	**17** (< 1st %ile)	**14** (< 1st %ile)
30'' (9)	**3** (<1st %ile)	**3** (<1st %ile)	**3** (<1st %ile)	**1** (<1st %ile)
10' (9)	**1** (<1st %ile)	**1** (<1st %ile)	**1** (<1st %ile)	---
10' recognition (9)	9 (72th %ile)	9 (72th %ile)	9 (72th %ile)	---
10' recognition false positives	**3** (<1st %ile)	**2** (<1st %ile)	**2** (<1st %ile)	---
Visual (Modified Benson Figure)				
Delayed recall (17)	7 (6th %ile)	9 (20th %ile)	**5** (1st %ile)	7 (6th %ile)
Recognition (yes/no)	Yes	Yes	Yes	No
Executive functions/attention				
Span of digits forward (9)	7 (43rd %ile)	6 (17th %ile)	7 (43rd %ile)	---
Span of digits backward (8)	4 (12th %ile)	**3** (2nd %ile)	**3** (2nd %ile)	---
Modified Trails speed (lines/min)	15/min (11th %ile)	**9/min** (4th %ile)	13/min (8th %ile)	---
Modified Trials errors	2	1	1	---
Stroop Naming correct/errors (126)	**56**/0 (4th %ile)	**44**/0 (< 1st %ile)	**32**/0 (< 1st %ile)	---
Stroop Inhibition correct/errors (77)	**18**/0 (< 1st %ile)	**8**/0 (< 1st %ile)	---	---
Design Fluency	6 (10th %ile)	7 (17th %ile)	8 (25th %ile)	6 (13th %ile)
Phonemic Fluency (D-words)	**8** (4th %ile)	**9** (6th %ile)	**9** (6th %ile)	---
Semantic Fluency (animals)	**12** (3rd %ile)	**8** (<1st %ile)	**11** (2nd %ile)	---

Tests (maximum score)	Year 1 (age=77)	Year 2 (age=78)	Year 3 (age=79)	Year 4 (age=80)
Calculations (5)	5	5	**3** (<1st %ile)	**2** (<1st %ile)
Language				
BNT Confrontation Naming (15)	14	14	15	---
PPVT-R Word Comprehension (16)	16	16	15	---
BDAE Sentence Comprehension (5)	5	5	5	---
BDAE Verbal Agility (6)	---	6	6	---
BDAE Repetition (5)	5	5	5	---
WRAT-4 Reading Regular Words (70)	59	60	64	---
WRAT-4 Reading Irregular Words (6)	6	6	6	---
Visuospatial				
Modified Benson Figure copy (17)	14 (11th %ile)	15 (35th %ile)	16 (68th %ile)	16 (68th %ile)
VOSP Number Location (10)	10 (79th %ile)	10 (79th %ile)	9 (55th %ile)	---
Social				
CATS Face Matching (12)	11	12	12	---
CATS Affect Matching (16)	13	15	13	---
IRI Empathic Concern (28)	**13**	**14**	**10**	---
IRI Perspective Taking (28)	**7**	**7**	**7**	---
IRI Personal Distress (28)	15	**22**	**21**	---
Mood				
Geriatric Depression Scale (30)	2 (62th %ile)	2 (62th %ile)	1 (74th %ile)	5 (28th %ile)

MMSE=Mini-Mental State Examination, CDR=Clinical Dementia Rating, BNT=Boston Naming Test, PPVT=Peabody Picture Vocabulary Test, BDAE=Boston Diagnostic Aphasia Examination, WRAT=Wide Range Achievement Test, VOSP=Visual Object and Space Perception Battery, CATS=Comprehensive Affect Testing System, IRI=Interpersonal Reactivity Index.

Table 2:

Timeline of symptoms of bvFTD and AD over the course of four years.

	Year that symptoms first appeared based on neuropsychological assessment and/or clinical history			
BvFTD (Rascovsky et al., 2011)	**1**	**2**	**3**	**4**
Early behavior disinhibition				
Early loss of sympathy or empathy				
Early loss of apathy or inertia				
Early perseverative, stereotyped or compulsive/ritualistic behavior				
Hyperorality and dietary changes				
Executive dysfunctions with relative sparing of memory, visuospatial functions				
Amnestic AD (McKhann et al., 2011)				
Impairment in learning and recall of recently learned information				
Executive, visuospatial or language deficits or behavior changes				

Table 3.

Regions where the patient demonstrated significant atrophy compared to a sample of 534 healthy controls. Only regions with a W-score < −3 are shown.

Brain region	Peak MNI coordinates			W-score
	x	y	z	
Left hippocampus	−27	−35	−6	−8.48
Right hippocampus	27	−8	−23	−4.48
Right amygdala	26	−6	−17	−4.77
Left amygdala	−27	−5	−20	−4.73
Right entorhinal area	27	2	−17	−5.05
Left entorhinal area	−26	−2	−18	−4.26
Left middle temporal gyrus	−63	−29	−9	−1.54
Right middle temporal gyrus	68	−36	−11	−3.96
Right temporal pole	35	8	−21	−4.59
Left temporal pole	−41	5	−23	−3.49
Left ACC	−5	30	32	−4.54
Right ACC	6	39	23	−3.43
Left middle cingulate gyrus	−5	20	36	−4.88
Right middle cingulate gyrus	5	14	38	−3.55
Right anterior insula	38	14	−11	−4.55
Left anterior insula	−33	18	−6	−4.32
Left middle frontal gyrus	−42	12	33	−4.26
Right middle frontal gyrus	33	54	21	−3.21
Left OFC	−33	21	−11	−3.73
Right OFC	35	20	−14	−3.04
Left precentral gyrus	−47	5	39	−3.54
Left thalamus	−11	−27	6	−7.23
Right thalamus	12	−27	8	−4.57
Left putamen	−20	8	−3	−6.49
Right putamen	27	−8	−8	−5.39
Left caudate	−12	14	−2	−6.16
Right caudate	9	9	−5	−4.31
Right nucleus accumbens	9	8	−8	−5.35
Left nucleus accumbens	−12	8	−9	−4.72
Left angular gyrus	−47	−56	45	−6.06

ACC=Anterior cingulate cortex, OFC=orbitofrontal cortex.