Title

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Journal

American Journal of Geriatric Psychiatry, 24(2)

ISSN

1064-7481

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Publication Date

2016-02-01

DOI

10.1016/j.jagp.2015.04.007

Peer reviewed

HHS Public Access

Author manuscript

Am J Geriatr Psychiatry. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

Am J Geriatr Psychiatry. 2016 February ; 24(2): 107–116. doi:10.1016/j.jagp.2015.04.007.

Frontotemporal Dementia and Psychiatric Illness: Emerging Clinical and Biological Links in Gene Carriers

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Abstract

Objective—To describe psychiatric presentations in individuals with genetic mutations causing frontotemporal dementia (FTD).

Design—Case descriptions from five carriers of FTD-related gene mutations with symptoms associated with non-neurodegenerative psychiatric disease.

Setting—A comprehensive research program investigating genetic and non-genetic FTD at the University of California, San Francisco Memory and Aging Center.

Participants—Three probands and two non-proband gene carriers.

Measurements—Medical history and neurological examination, neuropsychological testing, MR and/or PET imaging, and a genetic analysis to screen for dementia-related mutations. Genetic status was unknown at the time of initial evaluation.

Results—The chosen cases are illustrative of the variety of presentations of psychiatric symptoms in FTD-gene carriers. In some cases, a non-neurodegenerative psychiatric illness was diagnosed based on specific symptoms, but the diagnosis may have been inappropriate based on the overall syndrome. In other cases, symptoms closely resembling those seen in non-neurodegenerative psychiatric illness did occur, in some immediately preceding the development of dementia, and in others, developing a decade prior to dementia symptoms.

Conclusions—Psychiatric symptoms in FTD gene carriers can be very similar to those seen in non-neurodegenerative psychiatric illness. Psychiatric symptoms with atypical features (e.g., late-life onset, insidiously worsening course) should prompt careful assessment for neurodegenerative disease. Guidelines for such an assessment should be established.

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No Disclosures to Report

Keywords

frontotemporal dementia; C9ORF72; psychiatric disease

OBJECTIVE

Frontotemporal dementia (FTD) is a neurodegenerative disease that causes changes in socioemotional behavior. The symptoms can overlap with those of psychiatric disorders, leading to erroneous diagnoses.[1–8] Better knowledge about the features that lead clinicians to attribute behavioral changes to non-neurodegenerative psychiatric syndromes could aid in early diagnosis of FTD.

Most data on psychiatric diagnoses in FTD come from retrospective studies in patients who have already received an FTD diagnosis.[7] It has been difficult to identify the reasons for the prior psychiatric diagnoses because detailed clinical and/or research data were not collected when symptoms began. Recent developments in the genetics of FTD offer an opportunity to revisit this issue. Because individuals who have FTD-related genetic mutations can be identified before they develop symptoms, these patients offer an opportunity to characterize psychiatric symptomatology during the earliest phases of illness. FTD gene carriers exhibit a high rate of psychiatric symptomatology, such as delusions and hallucinations, and have a high prevalence of psychiatric diagnoses in their families.[9–11] While prior reports have highlighted psychiatric features, the degree to which the symptoms in such cases mimic typical non-neurodegenerative psychiatric illness has not been well characterized.

We describe five individuals with disease-causing FTD mutations who received psychiatric diagnoses. These cases illustrate a variety of clinical presentations that led to psychiatric diagnoses and highlight the significant overlap in symptomatology that can occur between FTD and psychiatric disorders. In addition, they suggest neurodegenerative diseases may lead to psychiatric symptoms through multiple biological mechanisms.

METHODS

Subjects

Patients were referred to the University of California, San Francisco Memory and Aging Center (UCSF) to participate in ongoing, longitudinal research on aging and neurodegenerative disease, and informed consent was obtained for their participation. Participants were not known to have an FTD-associated mutation at the time of their initial clinical assessment. During the research evaluation, mutations were identified in a laboratory specialized in FTD genetics. Based on the clinical presentations of patients being evaluated in the research program, it became clear that multiple types of psychiatric symptoms were present, with varying relationships to the other symptoms of neurodegenerative disease. The cases presented here were chosen as exemplars of three types of “psychiatric” presentation.

RESULTS

Case 1

Ms. A, a 62-year-old, right-handed woman was referred for evaluation of 18 months of progressive cognitive and personality change, lack of empathy, and poor planning. At age 60, she displayed obsessive behavior, including rigid adherence to brushing her teeth after every meal, repeatedly organizing household items, and checking her email compulsively. She was evaluated by a community physician and diagnosed with obsessive-compulsive disorder (OCD). Over the next two years, she became more withdrawn, apathetic, and exercised poor judgment. She lost money in an email scam and posted a profile of herself on an Internet sex site. She made inappropriate political and racial remarks in public. She ate ravenously by shoveling food into her mouth. She became fixated on having three meals each day, sometimes eating immediately after a meal to satisfy the schedule.

Ms. A's family history included FTD in her sister and bipolar illness in her mother. Her 60-year-old sister was diagnosed at UCSF with behavioral variant FTD (bvFTD) that began at age 50. At the time of evaluation, she spent hours transferring individual leaves into a bucket, wore layers of clothing in 38°C heat, and began hoarding. A second sister, still independent in her 50s, was also seen at the UCSF with personality and behavior changes and hoarding behavior.

On exam, Ms. A was alert and cooperative but made inaccurate or vague statements. She had a tendency to move her mouth repetitively, had a fixed, open-eyed stare, square-wave jerks, and mild slowing of vertical saccades. She had mild cogwheel rigidity in the right hand and a mild action tremor. On cognitive testing, she scored 27/30 on the Mini Mental State Exam (MMSE) but otherwise performed normally.

The MRI revealed mild-to-moderate frontal and anterior temporal lobe atrophy (figure 1). Her amyloid-PET scan was negative, and her FDG-PET scan indicated relatively symmetric and mild medial-greater-than-lateral bifrontal hypometabolism. Genetic testing revealed a chromosome 9 open reading frame 72 (*C9ORF72)* expansion mutation.

Case 2

Mr. M, a 60-year-old, right-handed man was referred for evaluation of hallucinations and delusions beginning at age 58. He began talking to himself and yelling out of the car in response to auditory hallucinations. Over the next few months, his hallucinations increased, hearing voices from other continents that spoke to him through his hearing aid and eyeglasses. He believed that his home and work were bugged with audio and video devices and covered the mirrors in his house to avoid being observed. Mr. M would occasionally hide in the closet or look for nearby weapons because he believed the Mafia was coming to steal his firearms. He also came to believe he was a "sex god" and went to his neighbors' homes believing they wanted to have sex with him. He additionally believed his neurologist had been killed and replaced by an imposter.

By age 60, Mr. M's delusions and hallucinations had become much less prominent. He became apathetic and developed a voracious appetite, often eating any object in sight,

including an embroidered piece of the tablecloth. He required assistance in nearly all activities of daily living.

Mr. M had a family history of dementia. His mother had a Parkinsonian dementia, with symptoms of social withdrawal, forgetfulness, and wandering beginning in her late 50s. His maternal grandfather had cognitive impairment with an unknown age of onset and died of colon cancer at age 81, and his maternal great-uncle was diagnosed with dementia in his 70s.

On neurological exam at age 60, Mr. M had bradyphrenia, utilization behavior, and effortful speech. He had marked hypomimia, cogwheel rigidity in the arms, bradykinesia, fasciculations in all four limbs, mild weakness, a postural tremor, and slowed gait with en-bloc turning. He scored 19/30 on the MMSE and showed impairment in memory, language, executive function, affect recognition, and calculations.

The MRI at age 60 showed moderate bilateral frontal and parietal atrophy notably in the medial frontal lobes (figure 2). Mild cerebellar vermis and bilateral caudate atrophy was also noted. He was diagnosed with FTD with motor neuron disease (FTD-MND). Genetic testing revealed a *C9ORF72* expansion mutation. He passed away two months later, and the autopsy revealed FTLD-TDP, Type-B pathology.

Case 3

Mr. R was a 55-year-old, right-handed man who began having trouble keeping a job and started living on the streets or with friends and family by age 40. At age 51, he was incarcerated for trespassing related to a delusion that he knew a prominent celebrity. He also had auditory hallucinations, including hearing the celebrity's voice, but recognized these voices were not real. He developed spontaneous screaming and was diagnosed with schizophrenia while in prison and started on ziprasidone. After release, he developed further bizarre behavior, including urinating on himself. He began to abuse alcohol and drugs. By age 53, he developed a shuffling gait and left-sided stiffness, holding his hand against his body. He wandered and had periods of inappropriate laughter. By age 54, he had developed markedly reduced speech output, slurred speech, and significant trouble walking.

Mr. R's family history was significant for dementia on his maternal side and in his siblings. His mother died of dementia at age 70, his maternal grandparent died of dementia at an unspecified age, his 57-year-old sister was living with amnestic mild cognitive impairment, and a second sister died after a three-year course of cognitive decline that began with primary progressive aphasia. This sister was shown to have dual FTLD and Alzheimer's disease pathology at autopsy.[12]

By age 55, Mr. R was mute and unable to follow commands. He was wheelchair bound with little use of his limbs. His behavioral symptoms resolved and he stopped taking antipsychotics. On exam, he had dystonia of the left elbow, wrist, fingers, and both legs. Passive movement of the arms resulted in a coarse tremor more prominent on the left. Mild spontaneous movement in his right hand was appreciated.

His MRI at age 55 showed diffuse atrophy with a right-greater-than-left frontal predominance (figure 3). He was diagnosed with corticobasal syndrome with behavioral features. Genetic testing revealed a progranulin (*GRN)* p.M1L mutation in him and other family members.

Case 4

At the age of 53, Ms. G had her first episode of mania, which developed over several days and was characterized by accelerated thinking and her head “full of ideas.” She had poor sleep and many grandiose ideas, including starting a new business, a new religion, and changing United States voting procedures. She talked about these ideas to work colleagues. Over several weeks, she became overly familiar with strangers, occasionally hugging them. The problems escalated, resulting in hospitalization. Ms. G improved on lithium treatment and was able to return to work after a few weeks. She was diagnosed with bipolar disorder but had no prior history of manic or depressive symptoms. She remained stable for several years on valproic acid and was referred to UCSF at age 63 because her husband felt her cognition remained below her premorbid baseline.

Ms. G’s family history was notable for dementia in her mother and psychiatric illness in her sister. Her mother, living at 84, developed memory difficulties by age 81 when she began repeating herself. Ms. G had a sister who was diagnosed with bipolar disorder in her 20s and died at age 61 of unclear etiology. She was noted to have personality changes prior to her death and became passive.

Ms. G’s neurological exam was largely unremarkable. She was noted to pause while thinking but did not exhibit excessive word-finding trouble. Ms. G scored 28/30 on the MMSE and showed verbal-memory impairment and very mild executive dysfunction. The MRI showed mild global atrophy with a slightly posterior predominance and bilateral hippocampal atrophy (figure 4). She was diagnosed with mild cognitive impairment.

By age 65, she was still working but had developed a strange affect. During the neurological examination, she was overly casual and inappropriate when discussing her sexual abilities with her husband. She showed decreased strength in her left anterior tibialis, brisk reflexes, and a fine postural tremor. Concern was raised for a foot drop and an upper motor neuron syndrome. There were no fasciculations or muscle atrophy. On cognitive testing, she scored 29/30 on the MMSE and showed impaired phonemic fluency.

At age 68 Ms. G was diagnosed with amyotrophic lateral sclerosis (ALS) by an outside neurologist. A limited home visit confirmed she was wheelchair bound, had profound muscle atrophy, and swallowing difficulty. Genetic testing revealed a *C9ORF72* expansion mutation.

Case 5

Mr. T was a 57-year-old, left-handed man with cognitive and emotional complaints. At age 44, he ended a relationship with his girlfriend, became engaged to another woman, and had several, short sexual interludes. He felt “revved up” and “out of control,” needed less sleep, and wrote a book. He described an episode of going to a movie and feeling “intoxicated” by

the experience. He left the theatre feeling outside of his body. He hit another car on his drive home but did not realize until the other driver tracked him down and put him under citizen's arrest. His mood returned to baseline after this episode, and he felt afraid of how he had been feeling. No prior hypomanic or manic episodes were reported.

By his UCSF evaluation at age 50, Mr. T reported changes to his memory and was evaluated for depression. In the five years prior, Mr. T had changed jobs twice and was fired most recently after an affair with a coworker. Mr. T had moved out of his house due to marital problems related to viewing pornography and masturbation. He claimed that these had been lifelong activities and the marital turmoil was related to his wife's changes, not his own. Mr. T was seen for a follow-up research visit at age 57. He reported no change to cognition or personality but felt depressed because of his ailing marriage.

Mr. T's family history was significant for dementia in his maternal lineage and schizophrenia in two brothers. His mother was diagnosed with Pick's disease with onset in her 50s, including memory problems, excessive alcohol consumption, eating to the point of choking, and odd behavior, such as driving her neighbor's car without permission. She died at age 75. Two maternal uncles died of dementia, one in his 40s, the other in his 60s. His maternal grandmother died at 59 of dementia. She was described as moody and had her nursing license revoked. There was no known family history of suicide. Mr. T had five siblings: a brother in his 50s with schizophrenia diagnosed in childhood—chronically psychotic with auditory hallucinations and delusions—and another brother aged 53 with schizophrenia. One of Mr. T's sisters became overwhelmed with work and had a history of both alcohol and cocaine abuse.

Mr. T's neurological exam at age 50 was unremarkable. He showed a flat affect and sometimes appeared sad or angry and was self-deprecatory. He scored 30/30 on the MMSE, showed impairment in executive function and non-verbal memory, and endorsed 24/30 on the Geriatric Depression Scale (GDS). His MRI showed no atrophy.

Mr. T's neurological exam at age 57 was again unremarkable. He scored 29/30 on the MMSE, showed impairment in executive function, and endorsed only three GDS items. His MRI showed subtle posterior-frontal atrophy (figure 5). Genetic testing revealed a *C9ORF72* expansion mutation.

DISCUSSION

All of the cases had early psychiatric symptomatology followed in four of five by a neurodegenerative process. Yet, the cases differed in the degree to which their presentation mimicked typical non-neurodegenerative psychiatric disorders.

Early symptoms in Case 1 included rigid adherence to routines leading to a diagnosis of OCD. Yet, in contrast to the symptoms in typical OCD,[13] they developed late in life, were not distressing to the patient, and occurred in the setting of a loss of empathy and emotional detachment. Thus, the diagnosis of OCD may never have been appropriate, and other symptoms eventually raised concern for a neurodegenerative etiology. In cases 2 and 3, a psychiatric diagnosis is reasonable to consider because they met DSM-V criteria for

schizophrenia.[13] Cases 4 and 5 showed transient mood symptomatology that would not normally trigger concerns for neurodegenerative disease. Except for the presence of a strong family history suggestive of FTD and relatively late age of onset, the episodes appeared typical. While it can be argued that the psychiatric presentation in Cases 4 and 5 were not related to their genetic status, the fact that these symptoms developed relatively late in patients carrying FTD-causing mutations, and the high frequency of bipolar disorder and schizophrenia in some of these families (and others in the literature),[14] should prompt consideration of a causal relationship between the mutations and the reversible psychiatric symptoms.

What clinical features should lead a clinician to consider neurodegeneration in patients presenting with psychiatric symptoms? One potential factor could be the age of onset. First symptoms of schizophrenia occur after age 40 in about 27% and after age 60 in 12% of those afflicted.[15] Similarly, first onset of mania after age 40 occurs in about 22% of cases.[16] Thus, development of these symptoms late in life is unusual, but clear evidence that these presentations represent a distinct pathophysiological entity is still lacking. Studies attempting to identify other features that differentiate late-versus-early-onset bipolar disorder and schizophrenia have only found relatively subtle differences, including less severe psychopathology in late-onset disorders.[17] Findings on cognitive assessment have been variable, with some studies finding less cognitive impairment[17] and others finding more cognitive impairment[18] in late-onset compared with younger-onset patients. Some studies have found a lower incidence of family history of psychiatric disease in late-onset cases.[19] Although several reports have indicated that “neurological illness” is more common in late-life psychiatric disease, this includes a variety of causes such as cerebrovascular disease, and the syndromes are sometimes described with vague terms such as “organic brain syndrome.”[20,21] Longitudinal studies have indicated that patients with late-life schizophrenia[22] or “mild behavioral impairment”[23] have a high incidence of dementia on follow-up, but these analyses did not identify specific predictors of this outcome. Thus, while there are indications that a subset of patients with late-onset psychiatric symptoms may have neurodegenerative disease, the available studies do not provide guidance on how to identify them.

Recent reviews have suggested some “red flags” that should raise suspicions for an FTD diagnosis, including cognitive dysfunction, in particular aphasia or executive dysfunction, lack of distress in the setting of mood or anxiety disorders, progressive impairment, lack of treatment response, and unusual psychiatric features, such as compulsions without obsessions, sustained manic states without grandiosity or euphoria, or schizophrenia without complex delusions or hallucinations.[8,24] These criteria seem reasonable and are relevant to some of our cases, for instance, Case 1 who showed lack of distress and compulsions without obsessions. Cases 2–4 appear to have been more typical, and the sensitivity of these criteria may not have been adequate to identify them in the earliest phases of illness. Family history of dementia, motor neuron disease, and parkinsonism are also relevant, as would be any signs of motor neuron disease or parkinsonism on examination. In addition, given the relatively low incidence of family history of psychiatric disorders in studies of late-life psychiatric disease, a strong family history of psychiatric disease as well as

neurodegenerative disease in a patient whose psychiatric symptoms develop late in life may be an indicator of neurodegenerative etiology.

If neurodegenerative disease is being considered, how should this be assessed? Screening all psychiatric patients for FTLD-related mutations is not likely to be productive. Among three recently-published studies that screened cohorts with schizophrenia for *C9ORF72* mutations, only two patients were identified.[14,25,26] Symptom onset in most of these patients was at the typical age for schizophrenia, leaving open the question of whether focusing on late onset cases would yield a different result. Brain imaging has a clear role in the assessment of neurodegenerative disease, but its role in psychiatric assessment is not defined. Routine imaging in psychiatric patients is not standard practice, and there are no guidelines indicating when it should be done.[27,28] Prior studies indicate that when atypical features such as the “red flags” highlighted above prompt brain imaging,[29] the likelihood of abnormal findings including brain atrophy is increased.[30] In patients being assessed for dementia, atrophy patterns typical of FTD can be detected on visual inspection,[31,32] but they are not always noted by radiologists.[31] Studies have indicated that radiologists are more likely to make a specific diagnosis if they are provided with details on the clinical question.[33] Thus, in psychiatric patients where neurodegenerative disease is being considered, provision of clinical details to the radiologist may be helpful. Neuroradiological and neurological consultation should be considered. For the patients whose atrophy is too subtle to be identified by eye, quantitative assessment may ultimately be fruitful as quantification of brain structure and function is becoming increasingly fast and reliable.[34,35]

Cases 4 and 5 suggest the possibility that neurodegenerative diseases may be associated with an earlier period of destabilized synaptic and neurotransmitter function that presents as a psychiatric disorder (figure 6).[36] The diagnostic considerations in atypical psychiatric syndromes could/should be extended to psychiatric syndromes that respond to treatment. It is notable that Case 4, who only had mild, stable cognitive symptoms at her first UCSF evaluation, already had significant brain atrophy. While the mechanisms by which FTD-associated mutations cause disease are still being determined, it is clear that they disrupt cell function in ways that can cause subtle structural and functional changes.[37–43] Mutation-based animal models of FTD have demonstrated subtle morphological changes in neurons, such as decreased synaptic density, altered spine morphology, and altered synaptic vesicle content,[40,41,44,45] as well as changes in physiological functions, such as excitatory post-synaptic potentials[41,44] and long-term potentiation.[45] These findings can be demonstrated in mice with behavioral abnormalities, such as anxiety and altered social interaction, months before neuropathological abnormalities develop.[41] In some cases, they are reversible.[45] Continued study of these types of changes may reveal markers that could be detected in humans using imaging, gene expression, protein quantification, or other biological variables. Beyond FTD, this phenomenon may extend to other genetic neurological disorders, including Huntington’s disease and spinocerebellar ataxias, where cases of psychiatric illness preceding motor symptoms have been described.[46,47]

The cases discussed here were chosen to illustrate the variety of psychiatric symptoms that can occur in FTD, and to highlight the limitations in our current assessment strategies. They reinforce the growing awareness among clinicians that neurodegenerative diseases such as

FTD can present with psychiatric symptoms that are very similar to those associated with other etiologies. Reliable criteria for identifying when such symptoms are due to neurodegenerative disease are needed and will only be identified with prospective studies that utilize formal, standardized psychiatric assessments in cohorts of patients who carry FTLD-associated mutations, as well as cohorts with late-life and/or atypical psychiatric syndromes. Appropriate studies in mutation carriers are underway.

Acknowledgments

Support for this project was provided by grants P01AG019724 P50AG023501, AG045333, AG032306, AG045390, and NS092089 from the NIH National Institute on Aging. We would like to thank Alyssa Caplan for her assistance on this project.

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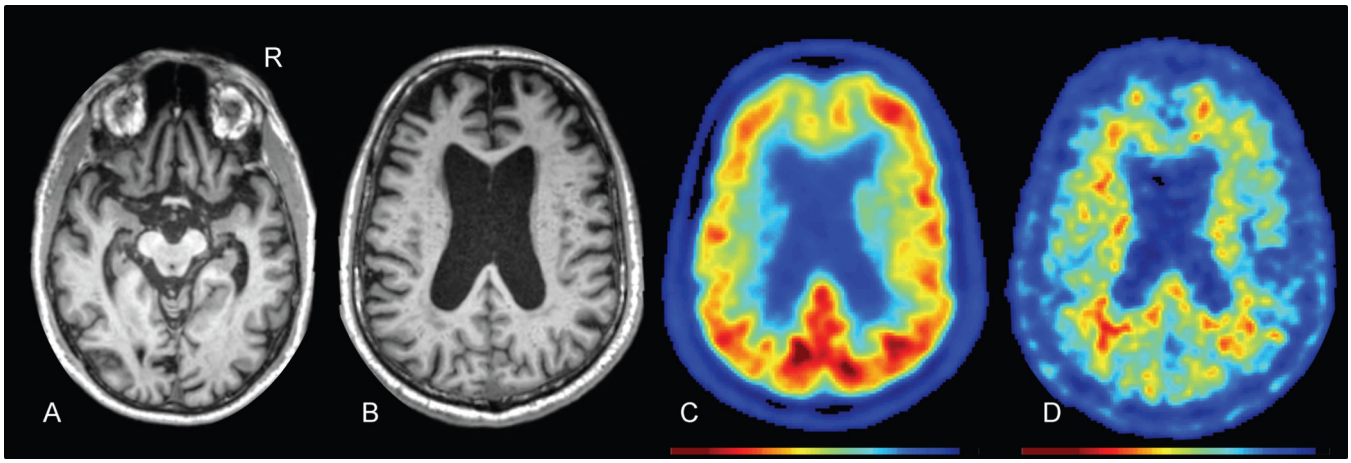

Figure 1.

(A and B) T1-weighted 3T MRI of Case 1, indicating (A) mild to moderate anterior temporal lobe and (B) frontal lobe atrophy. (C) FDG-PET with bifrontal hypometabolism (pons-normalized; SUVR=0.1–2.5). (D) Amyloid-PET negative for amyloid binding (cerebellum-normalized, SUVR=0.1–3.0).

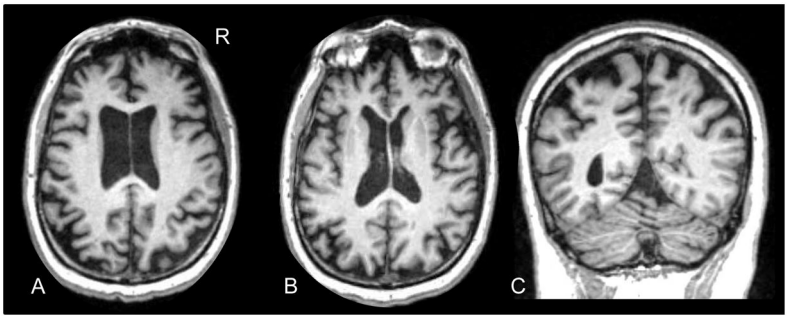

Figure 2.

T1-weighted 3T MRI of Case 2, showing moderate bilateral parietal lobe and bi-frontal lobe atrophy, notably in the medial-frontal areas (A and B). Mild vermian (C) and caudate atrophy (B) was also noted.

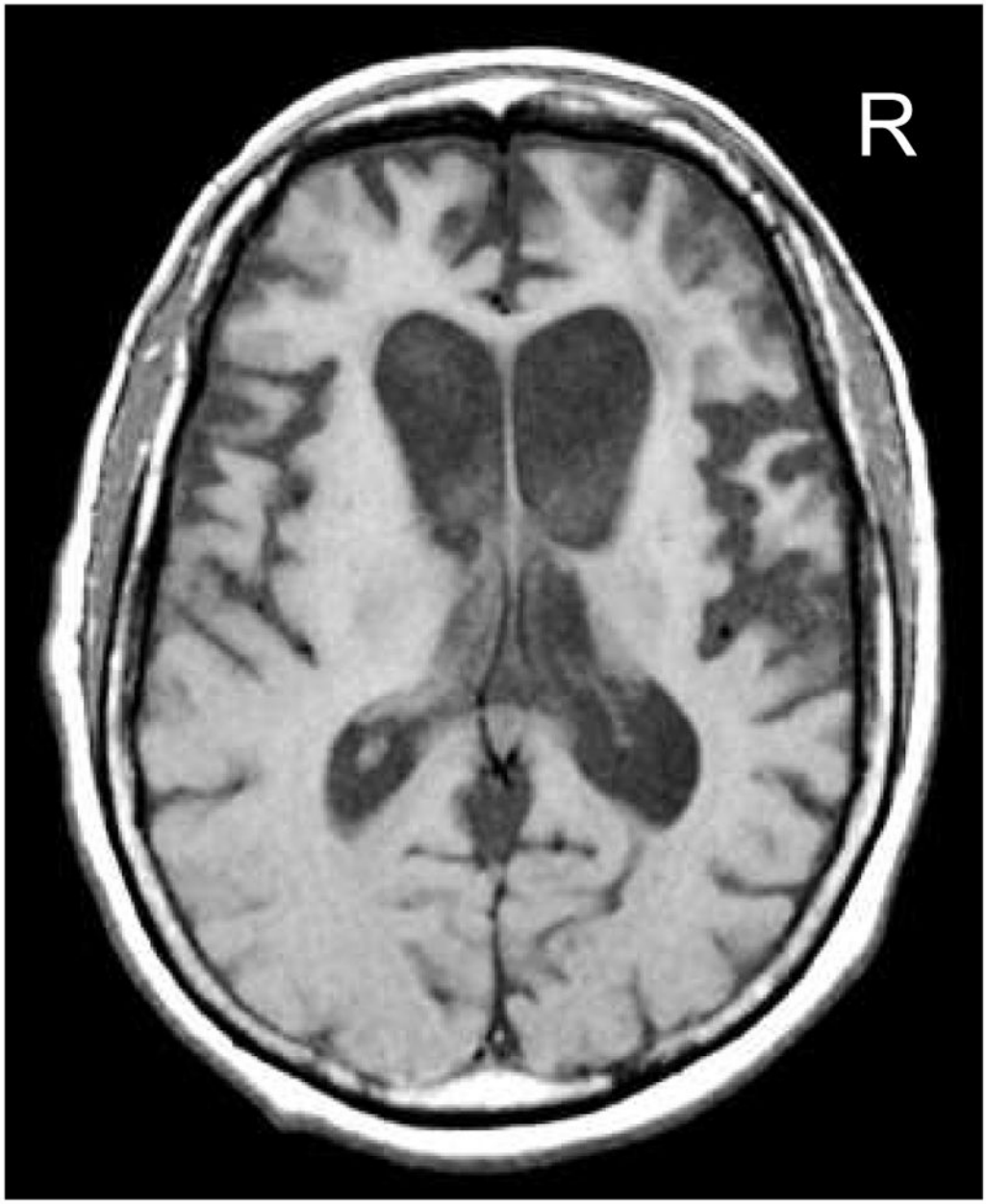

Figure 3.
T1-weighted 1.5T MRI of Case 3, showing diffuse atrophy with right-greater-than-left frontal predominance.

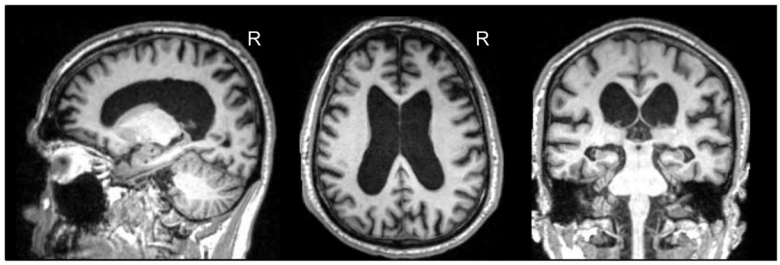

Figure 4.

T1-weighted 3T MRI of Case 4, showing mild global atrophy with slight posterior predominance and bilateral hippocampal atrophy.

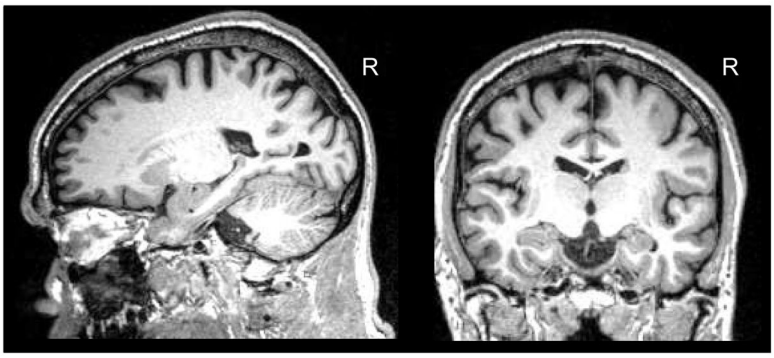

Figure 5.
T1-weighted 3T MRI of Case 5, showing possible posterior-frontal lobe atrophy.

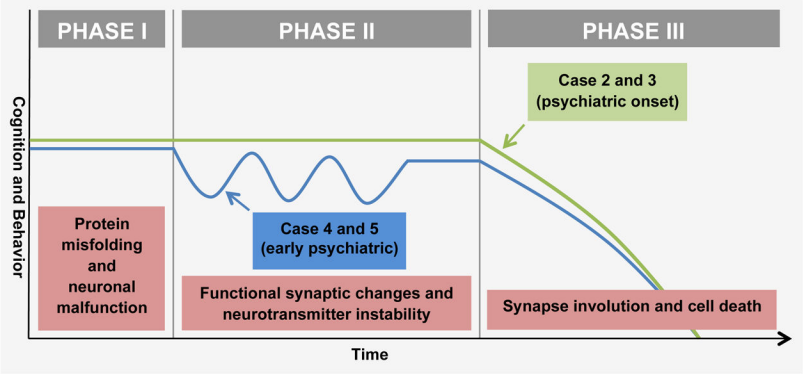

Figure 6.

Depiction of possible biological changes and corresponding symptomatology. Cases 2 and 3 present psychiatric disease in phase III as an early sign of cell death, whereas cases 4 and 5 present phase-II isolated psychiatric disease and relative recovery during functional synaptic changes and neurotransmitter instability, followed by later phase-III neurodegenerative decline.