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Clinical course of neuropathologically confirmed frontal-variant Alzheimer's disease

Kirsten I Taylor, Alphonse Probst, André R Miserez, Andreas U Monsch and Markus Tolnay*

SUMMARY

Background A 66-year-old man presented with a 3-year history of personality changes marked by increasing apathy, social withdrawal and deficits in complex attention, and a 1-year history of progressive memory problems and difficulties in planning and carrying out complex tasks.

Investigations Three neuropsychological examinations over 2 years, neurological examination, routine laboratory tests, brain MRI, single-photon emission CT scan, genetic analyses, and neuropathological examination.

Diagnosis A clinical diagnosis of frontal-variant frontotemporal dementia was superseded by postmortem neuropathological evidence, which established a diagnosis of frontal-variant Alzheimer's disease.

Management The patient and his spouse were referred for counseling, and the patient was referred for follow-up examinations.

KEYWORDS Alzheimer's disease, behavioral disturbances, cognitive functioning, frontal-variant Alzheimer's disease, frontal-variant frontotemporal dementia

CME

KI Taylor is a Marie Curie Fellow at the University of Cambridge, Cambridge, UK, AU Monsch is Professor and Director of the Memory Clinic, A Probst is Professor and M Tolnay is Professor and Director, Department of Neuropathology, all at the University Hospital Basel, Basel, Switzerland, and AR Miserez is Professor at the University of Basel and Director at the Research Laboratories of diagene, Reinach, Switzerland.

Correspondence
*Department of Neuropathology, University Hospital Basel, Schoenbeinstrasse 40, CH-4031 Basel, Switzerland
mtolnay@uhbs.ch

Received 16 July 2007 **Accepted** 30 November 2007 **Published online** 19 February 2008
www.nature.com/clinicalpractice
doi:10.1038/ncpneuro0746

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Learning objectives

Upon completion of this activity, participants should be able to:

1 Identify the hallmark postmortem pathognomonic findings for Alzheimer's disease (AD).
2 Describe the clinical features of frontotemporal dementia (FTD).
3 List the core diagnostic criteria for frontal variant (fv)FTD.
4 Describe the distinguishing features between fvFTD and fvAD.
5 List the treatment options for AD and FTD.

Competing interests

The authors declared no competing interests. Désirée Lie, the CME questions author, declared no relevant financial relationships.

THE CASE

A 66-year-old man was referred by his primary care physician to a university hospital memory clinic because of insidious onset of gradually progressive personality changes during the preceding 3 years. The patient reported a lack of drive and problems with his memory and spatial orientation. His spouse noted his increasing apathy, indifference, social withdrawal, anxiety, difficulty with planning and carrying out complex tasks, and progressive forgetfulness during the past year. His medical history was notable for an episode of depressed mood following retirement from work 5 years previously, a partial thyroidectomy for struma, and diagnosis of diabetes mellitus type II 1 year before presentation. His family history was

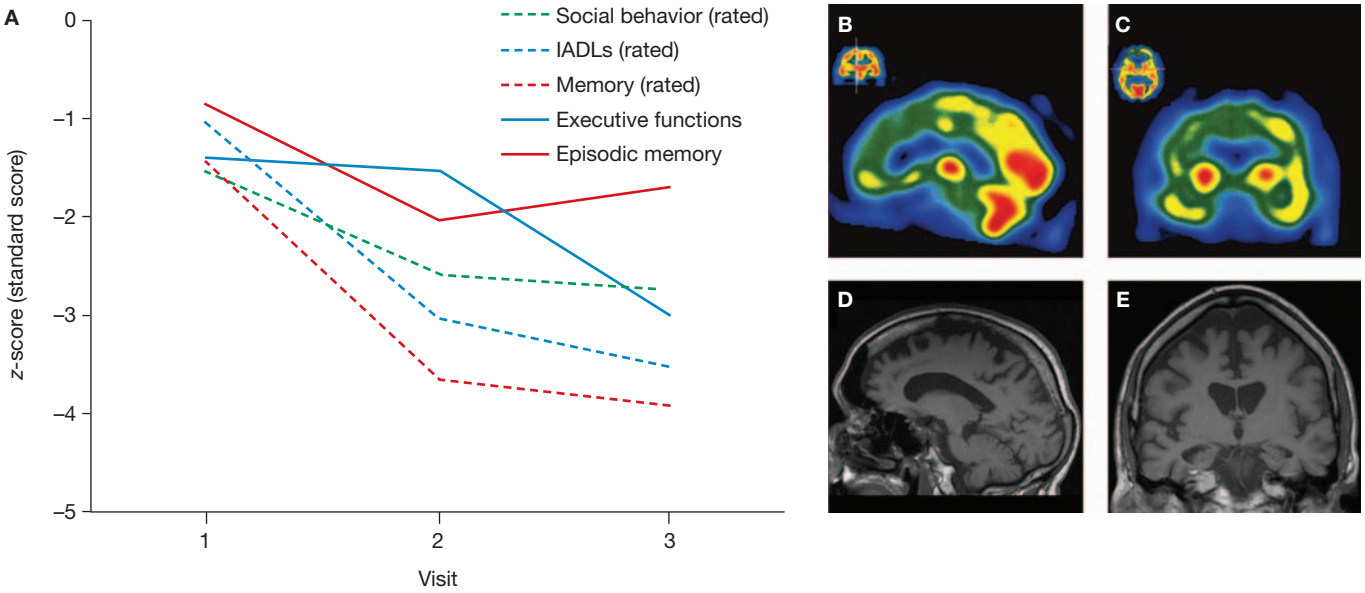

Figure 1 Clinical course of a patient with neuropathologically diagnosed frontal-variant Alzheimer's disease. (**A**) Summary of results of neuropsychological tests performed at three visits over 2 years. Social functioning, frontal lobe functioning (as reflected by IADLs), and memory were rated by the patient's spouse; executive functioning (mean performance on divided attention and alternating attention, letter and figural fluency, and Stroop tasks) and episodic memory functioning (mean performance on verbal learning and free recall, and visuospatial free recall tasks) were measured. All results are shown as *z*-scores, or standard scores, where negative values indicate a worse score relative to demographically matched control groups. (**B**) Sagittal and (**C**) coronal SPECT images at the time of the patient's presentation showed severe regional hypoperfusion in both frontal lobes. (**D**) Sagittal and (**E**) coronal T1-weighted MRI scans 2 years after presentation illustrated marked atrophy in the frontal lobes and, to a lesser extent, in anteromedial temporal regions including the hippocampi. Abbreviations: IADLs, instrumental activities of daily living; SPECT, single-photon emission CT.

positive for dementia—his father and both paternal aunts were diagnosed with neuropathologically unconfirmed Alzheimer's disease (AD), and his mother with a dementia syndrome of presumed vascular origin.

Neurological examination of the patient revealed abnormally brisk patellar and radial reflexes. The patient had no extrapyramidal signs. His blood pressure was elevated and measured 183/116 mmHg in his right arm and 180/115 mmHg in his left. Comprehensive laboratory tests, including measurement of thyroid-stimulating hormone, were normal. His apolipoprotein E (*APOE*) genotype was ε3/ε4. The patient scored three points on the Hachinski Ischemic Scale—indicating a nonvascular origin of his symptoms—and his test results were within normal limits on the Geriatric Depression Scale (GDS; 2 out of 15) and Mini Mental State Examination (MMSE; 28 out of 30). The Nurses' Observation Scale for Geriatric Patients (NOSGER) confirmed the anamnestic report of impaired social behavior, mood, and basic activities of daily living (ADLs), but not the reported memory problems or poor instrumental ADLs, which are associated with executive dysfunction (see Supplementary Table 1 online). Neuropsychological examination revealed intact orientation to time and space. The patient showed severe deficits on the divided attention and alternating attention subtests of the Tests for Attentional Performance battery. Of all other frontal lobe functions tested (digit span; Corsi block-tapping; Trail Making Test Parts A and B; letter, category, and design fluency; and Stroop test), only Stroop test performance was slightly impaired. Verbal episodic learning and memory were normal (German version of the California Verbal Learning Test; Consortium to Establish a Registry for AD [CERAD] neuropsychological battery). Language (reading, writing, comprehension, verbal production, naming; CERAD), visuoconstructive (CERAD subtest) and gnostic (object and famous face identification) functions as well as praxis (examination according to Goldenberg) were intact (Figure 1A). T1-weighted MRI scans showed pronounced bilateral enlargement of the lateral ventricles and marked bilateral frontal atrophy (data not shown), and single-photon emission

CT (SPECT) showed substantial frontal lobe hypoperfusion (Figure 1B,C). A diagnosis of frontal-variant frontotemporal dementia (fvFTD) was made.[1,2]

At follow-up 1 year later, the patient's spouse reported that he now showed a complete lack of drive and insight into his condition. GDS (3 out of 15) and MMSE (27 out of 30) scores were normal. According to the NOSGER, his mood had improved, social behavior and ADLs had declined, and, notably, memory functioning and instrumental ADLs were now impaired. He showed no signs of disturbing behavior. Neuropsychological tests revealed that verbal and figural memory performance were now impaired (Figure 1A). The diagnosis of fvFTD was confirmed.

At the third and final examination 1 year later, the patient's spouse reported that he hardly spoke, was extremely passive, completely emotionally blunted, highly distractible and forgetful, and had poor grooming behavior. His spouse had to ration his food intake when he had a bout of uncontrolled eating several months previously, and his libido was highly variable. The patient complained merely of an increased forgetfulness. His GDS was normal (2 out of 15), and his MMSE score indicated mild impairment (25 out of 30). According to the NOSGER, only ADLs and mood had declined since the last examination. Neuropsychological testing showed marked decrements in frontal lobe functioning (Figure 1A). T1-weighted MRI scans showed severe cortical atrophy affecting primarily frontotemporal regions (Figure 1D), and, to a lesser extent, anteromedial temporal regions including the hippocampi (Figure 1E). The diagnosis of fvFTD was maintained.

The patient died from respiratory insufficiency resulting from bronchopneumonia 5 years after presenting to the memory clinic. An autopsy revealed arteriosclerotic changes to large vessels and biventricular myocardial hypertrophy, but no myocardial infarct. The fresh brain weight was lower than normal at 1070 g (normal weight ~1250 g). Gross brain examination revealed severe bilateral atrophy focused in the frontal lobes (shown in the right hemisphere in Figure 2A–C). Pigmentation in the substantia nigra was slightly reduced.

Histological and immunohistochemical examination included (among others) hematoxylin and eosin, Holmes–Luxol, and Gallyas silver staining as well as tau, β-amyloid, α-synuclein, ubiquitin, and transactive response DNA-binding protein-43 (TDP-43) immunohistochemistry. Hematoxylin and eosin staining revealed microvacuolation, neuronal cell loss, and astrogliosis centered in

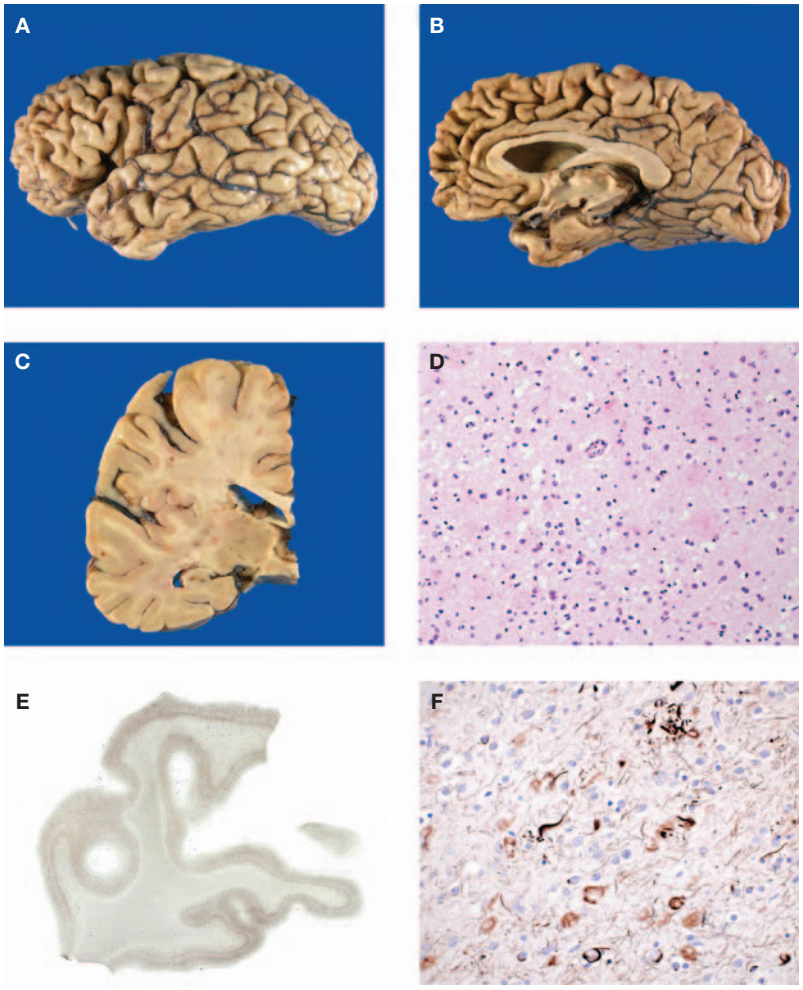

Figure 2 Neuropathological findings of frontal-variant Alzheimer's disease. (**A**) Lateral aspect of the right hemisphere shows severe frontal lobe atrophy in middle and superior frontal gyri, moderate atrophy of the orbital gyri, and preservation of the parietal, temporal, and occipital lobes. (**B**) Medial surface of the right hemisphere shows severe atrophy of the cingulate, subcallosal, superior frontal, and infracallosal gyri, as well as moderate atrophy of the temporopolar gyri. The posterior limit of the frontal atrophy is relatively sharp. Note also the thinning of the anterior and middle third of the corpus callosum and the enlarged anterior horn of the lateral ventricle. (**C**) Coronal view of the right hemisphere shows that whereas the entorhinal cortex, anterior hippocampus, amygdala, and striatum appear moderately atrophic bilaterally, the coronal section through the posterior thalamus illustrates the normal appearance of the hippocampus and parahippocampus gyrus at this posterior level, as well as the normal appearance of the parietal and temporal lobes. (**D**) Frontal cortex showing details of layers II and III. Note prominent microvacuolation and astrocytic gliosis as well as senile plaques (purple spots with central core). Section stained with hematoxylin and eosin, magnification ×100. (**E**) High densities of Gallyas-positive neurofibrillary lesions (dark dotted material in the frontal cortical ribbon). Magnification ×100. (**F**) At higher magnification there are abundant ghost tangles (brown color), neurofibrillary tangles (NFT), neuropil threads, and neuritic plaques (black color). Magnification ×200.

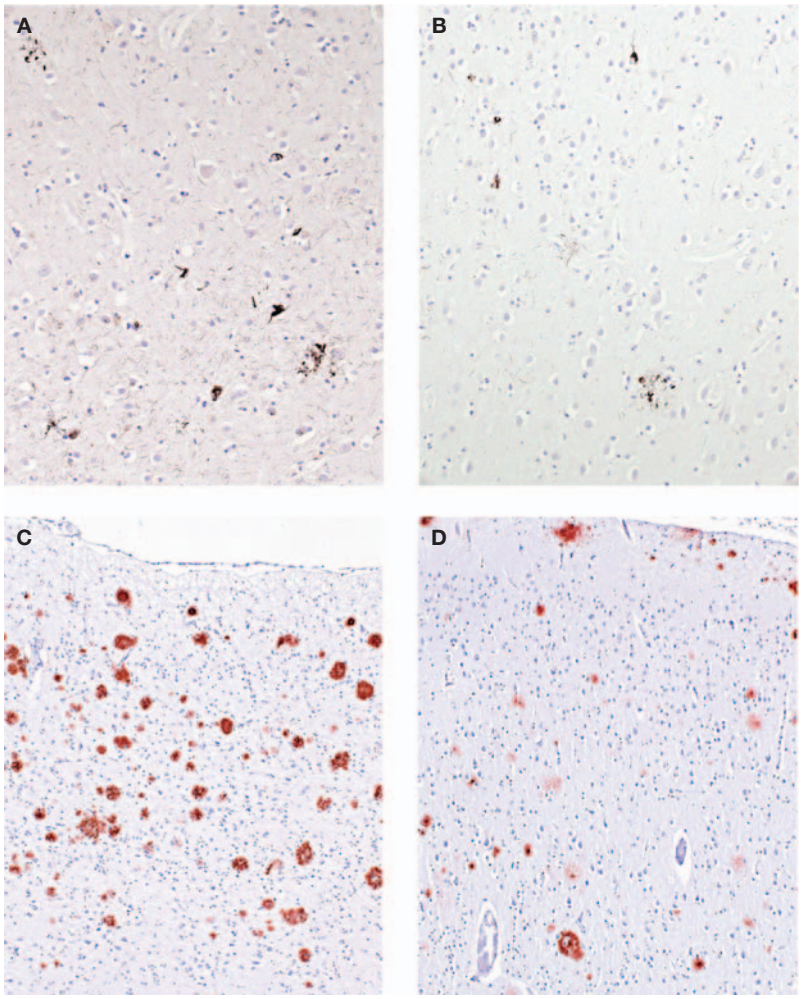

Figure 3 Neurofibrillary tangle and neuritic plaque load in various brain regions of a patient with frontal-variant Alzheimer's disease. (**A**) In contrast to the frontal cortex (Figure 2E,F), in the parietal cortex there are considerably fewer Gallyas-stained neurofibrillary tangles, neuropil threads, and neuritic plaques. Magnification ×120. (**B**) Only scattered neurofibrillary tangles and neuritic plaques are observed in the occipital cortex. Magnification ×120. (**C**) β-Amyloid immunostaining in the frontal cortex revealed a substantially higher number of senile plaques than in the occipital cortex (**D**). Magnification ×50 (C and D).

layers II and III of the frontal cortex (Figure 2D). Surprisingly, however, further neuropathological examination revealed the hallmark signs of AD, but atypically distributed. Most notably, the frontal cortex showed a high density of neurofibrillary tangles (NFTs), ghost tangles (approximately 80% of the NFTs), neuropil threads and neuritic plaques (Figure 2E,F). The entorhinal cortex and hippocampus subregions CA1 and CA4 also contained numerous NFTs, but the density of ghost tangles in these areas was lower than in the frontal cortex. The temporal isocortex and parietal cortex contained considerably fewer NFTs than the frontal cortex (Figure 3A) and comparatively fewer ghost tangles (<5% of NFTs). Only scattered NFTs were found in the occipital cortex (Figure 3B). Densities of senile plaques (β-amyloid deposits) in various cortical areas (Figure 3C,D) were highest in the frontal cortex. No TDP-43 immunoreactive inclusions were present in the frontal cortex or the dentate gyrus granule cells. A few Lewy bodies and Lewy neurites were found exclusively in the substantia nigra pars compacta and some lower brain stem nuclei, consistent with subclinical Parkinson's disease. A primary neuropathological diagnosis of frontal-variant AD (fvAD) was made.[3]

We investigated with comprehensive sequencing analyses genes related to frontotemporal dementia (FTD) that encode presenilin 1 (*PSEN1*) and the microtubule-associated protein tau (*MAPT*).[4,5] In *PSEN1*, no mutations were found in the coding regions associated with FTD,[4] nor were functionally significant mutations found in the noncoding regions. In exon 9 of *MAPT*, silent mutations at amino acid positions 544 (Arg544Arg, A>G, heterozygous) and 572 (Asn572Asn, T>C, heterozygous), as well as mutations in noncoding regions, were found, all of which were single nucleotide variants with no known pathogenetic significance.[4,5] On the basis of the results of the neuropathological examination, we did not investigate genes associated with frontotemporal lobar degeneration with ubiquitin-positive inclusions, such as the valosin-containing protein, charged multivesicular body protein 2B, or the progranulin genes.

DISCUSSION OF DIAGNOSIS

FTD is a clinically and pathologically heterogeneous group of neurodegenerative diseases presenting in the presenium, typically in individuals between the ages of 45 and 65 years. Roughly 20–40% of patients with FTD have a family history of the disorder. fvFTD is the most common form of FTD and is characterized by gradual and progressive changes in personality, which can take disinhibited or apathetic forms.[6]

The present patient fulfilled four of the five core diagnostic criteria for fvFTD of the Lund–Manchester group (i.e. all but disturbing social manners) and displayed all features of a simplified set of diagnostic criteria (Boxes 1 and 2).[1,2] The prevailing clinical picture was of an apathetic variant of fvFTD (pronounced apathy, mental inertia and rigidity, and perseverative tendencies).[7] During the course of the disease, the

Box 1 Clinical criteria for the diagnosis of frontotemporal dementia.

Core diagnostic features

- Insidious onset and gradual progression
- Early decline in social interpersonal conduct
- Early impairment in regulation of personal conduct
- Early emotional blunting
- Early loss of insight

Supportive diagnostic features

Behavioral disorder

- Decline in personal hygiene and grooming
- Mental rigidity and inflexibility
- Distractibility and impersistence
- Hyperorality and dietary changes
- Perseverative and stereotyped behavior
- Utilization behavior

Speech and language

- Altered speech output: aspontaneity and economy of speech; press of speech
- Stereotypy of speech
- Echolalia
- Perseveration
- Mutism

Physical signs

- Primitive reflexes
- Incontinence
- Akinesia, rigidity and tremor
- Low and labile blood pressure

Investigations

- Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia or perceptuospatial disorder
- Electroencephalography: normal on conventional electroencephalogram despite clinically evident dementia
- Brain imaging (structural or functional): predominant frontal or anterior temporal abnormality

Box 2 Clinical criteria for the diagnosis of the behavioral presentation of frontotemporal dementia.

1 Behavioral or cognitive deficits develop that are manifested by early and progressive change in personality that are characterized by difficulty in modulating behavior, often resulting in inappropriate responses or activities.

2 The deficits outlined in (1) cause significant impairment in social or occupational functioning and represent a considerable decline from a previous level of functioning.

3 The course of disease is characterized by a gradual onset and continuing decline in function.

4 The deficits outlined in (1) are not due to other nervous system conditions (e.g. cerebrovascular disease), systemic conditions (e.g. hypothyroidism), or substance-induced conditions.

5 The deficits do not occur exclusively during a delirium.

6 The disturbance is not better accounted for by a psychiatric diagnosis (e.g. depression).

patient showed increasing mental rigidity, inflexibility and distractibility, a decline in grooming behavior, a change in eating habits, and an increasingly economical speech output progressing towards mutism. Neuropsychologically, the patient presented with marked disturbances in frontal lobe functioning, which deteriorated over time, and brain imaging showed marked frontal lobe hypoperfusion (SPECT) and frontal lobe atrophy (MRI).

Surprisingly, neuropathological examination revealed the hallmark signs of AD, but they were atypically distributed. Most notable were the severe tau pathology and high number of ghost tangles in the frontal cortex, an expression of neuronal cell death presumably pointing to a long-standing pathology in this case. Moreover, as in typical AD, the entorhinal cortex, the hippocampus and the temporal cortex were also affected, but to a lesser extent than the frontal cortex. The neuropathological findings were, therefore, consistent with the behavioral and cognitive impairments and a with diagnosis of fvAD.[3]

Atypical fvAD, where the brunt of AD pathology is found in the frontal lobes, can present with a dementia syndrome more consistent with fvFTD than AD, as illustrated by the present case. A retrospective analysis of

Clinical features	AD	Present patient (fvAD)	fvFTD
Genetic predisposition			
Family history	Positive for AD	Positive for AD	Positive for FTD
APOE genotype	*APOE* ε4 allele frequent	One *APOE* ε4 allele	*APOE* ε4 allele rare
Presenting symptoms	Episodic memory impairment	Changes in personality and social behavior	Changes in personality and social behavior
Episodic memory	Impaired	Impaired	Typically spared
Atrophy revealed by MRI	Anteromedial temporal and temporoparietal lobes	Frontal lobes	Frontal and anterior temporal lobes
Hypoperfusion revealed by SPECT	Temporoparietal lobes	Frontal lobes	Frontal or frontotemporal lobes

Figure 4 Selected key clinical features of a patient with autopsy confirmed fvAD that overlap with those features typical of AD and fvFTD. The patient displayed some features consistent with AD (overlap indicated in yellow) and some features consistent with fvFTD (overlap indicated in dark blue). Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; FTD, frontotemporal dementia; fvAD, frontal-variant Alzheimer's disease; fvFTD, frontal-variant frontotemporal dementia; SPECT, single-proton emission CT.

this patient's clinical presentation and course, however, revealed clinical signs of AD. First, the patient had a strong family history of AD,[8] and he carried one *APOE* ε4 allele, as do 50–60% of patients with AD.[9] While his cognitive frontal lobe symptoms were consistent with both sporadic AD and fvFTD, he also developed impairments in episodic memory and everyday memory functioning (Figure 1A). Episodic memory impairments may occur in fvFTD,[10,11] but are considered uncommon.[1,2,12] Moreover, a retrospective study of patients with neuropathologically confirmed fvAD also noted poor functioning of their episodic memory.[3] Thus, we suggest that the co-occurrence of the following clinical signs may indicate a clinical diagnosis of fvAD in patients presenting with a fvFTD syndrome: first, signs of a genetic predisposition for AD, including a positive family history and the presence of an *APOE* ε4 allele; and, second, impaired episodic memory performance (Figure 4). It remains to be established whether cerebrospinal fluid biomarkers or novel *in vivo* amyloid imaging procedures (e.g. Pittsburgh compound B) might also aid the differential diagnosis of fvAD and fvFTD.

TREATMENT AND MANAGEMENT

Although the patient in this case was treated conservatively with counseling, pharmacotherapy can be considered in cases of fvAD and fvFTD. In typical AD, treatment with acetylcholinesterase inhibitors and/or *N*-methyl-D-aspartate receptor antagonists positively affects cognitive, behavioral and everyday functioning.[13,14] On the other hand, behavioral symptoms associated with fvFTD have been successfully treated with selective serotonin reuptake inhibitors (SSRIs). A study of the SSRI paroxetine in 10 patients with FTD, however, found that paroxetin had no effect on behavioral symptoms and, importantly, reportedly decreased memory functioning.[15] Although the status of the serotonergic system in FTD and fvAD most likely differs, a conservative therapeutic approach to treating fvAD would contraindicate the use of SSRIs. Instead, atypical serotonergic agents, such as trazodone, which improves behavioral disturbances in apathetic and disinhibited forms of FTD,[16] might be indicated if they are well tolerated.

CONCLUSIONS

FvAD is a rare form of AD which can masquerade as an fvFTD syndrome. The present longitudinal clinical data show, however, that fvAD may be distinguished from fvFTD by the co-occurrence of signs of a genetic predisposition for AD and episodic memory impairments early in the course of the disease. In the present case, neither MRI nor SPECT imaging differentiated fvAD from fvFTD, and the diagnosis of fvAD was made only at autopsy. Although the condition is rare, the identification of fvAD has significant therapeutic consequences because such patients may benefit from combination therapy with acetylcholinesterase inhibitors, *N*-methyl-D-aspartate receptor antagonists and atypical serotonergic agents. The neuropathological examination of these patients is critical to further our understanding of the pathology and clinical phenotype of this AD variant.

Supplementary information in the form of a table is available on the *Nature Clinical Practice Neurology* website.

References

1 McKhann GM *et al.* (2001) Clinical and pathological diagnosis of frontotemporal dementia: report of the work group on frontotemporal dementia and Pick's disease. *Arch Neurol* **58:** 1803–1809
2 Neary D *et al.* (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* **51:** 1546–1554
3 Johnson JK *et al.* (1999) Clinical and pathological evidence for a frontal variant of Alzheimer disease. *Arch Neurol* **56:** 1233–1239
4 Mendez MF and McMurtray A (2006) Frontotemporal dementia-like phenotypes associated with presenilin-1 mutations. *Am J Alzheimers Dis Other Demen* **21:** 281–286
5 Gasparini L *et al.* (2007) Frontotemporal dementia with tau pathology. *Neurodegener Dis* **4:** 236–253
6 Neary D *et al.* (2005) Frontotemporal dementia. *Lancet Neurol* **4:** 771–780
7 Snowden JS *et al.* (2001) Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *J Neurol Neurosurg Psych* **70:** 323–332
8 Gatz M *et al.* (2006) Roles of genes and environments for explaining Alzheimer disease. *Arch Gen Psych* **63:** 168–174
9 Corder EH *et al.* (1993) Gene dose of apolipoprotein E ε4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261:** 921–923
10 Caine D *et al.* (2001) Severe anterograde amnesia with extensive hippocampal degeneration in a case of rapidly progressive frontotemporal dementia. *Neurocase* **7:** 57–64
11 Graham AJ *et al*. (2005) Pathologically proven frontotemporal dementia presenting with severe amnesia. *Brain* **128:** 597–605
12 Knibb JA *et al.* (2006) Frontotemporal dementia. *Curr Opin Neurobiol* **19:** 565–571
13 Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD005593. doi:10.1002/14651858.CD005593
14 McShane R *et al.* Memantine for dementia. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD003154. doi:10.1002/14651858.CD003154.pub5
15 Deakin JB *et al.* (2004) Paroxetine does not improve symptoms and impairs cognition in frontotemporal dementia: a double-blind randomized controlled trial. *Psychopharmacol* **172:** 400–408
16 Huey ED *et al.* (2006) A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. *Neurology* **66:** 17–22

Acknowledgments

The authors thank Prof Dr Stefan Kneifel for the SPECT analysis and Professor Christophe Büla for the helpful discussion. KI Taylor was supported by the Swiss Foundation for Ageing Research (financed by the Loterie Romande) and the Swiss Alzheimer's Association. Désirée Lie, University of California, Irvine, CA, is the author of and is solely responsible for the content of the learning objectives, questions and answers of the Medscape-accredited continuing medical education activity associated with this article.

Competing interests

The authors declared no competing interests.