Amyloid-PET Positive Patient with bvFTD: Wrong Diagnosis, False Positive Scan, or Co-pathology?

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Practical Implications

"Positive amyloid PET does not exclude FTD pathology in the diagnostic workup of dementia patients"

CASE REPORT

A 65-year-old man was referred to a local memory clinic with memory complaints but clinical assessment found no abnormalities. When he presented two years later to our clinic social disinhibition, reduced empathy, poor judgment and hoarding had become obvious. He showed no insight. He had ischemic heart disease and was on preventive treatment. His mother died aged 97 suffering from dementia. Neurological examination was normal. During neuropsychological examination he exhibited verbal and behavioral disinhibition, inattention, emotional blunting and unconcern. He had prominent difficulties in abstraction, set shifting and sequencing with significant impact on memory tests (table1). A clinical diagnosis of behavioral variant FTD (bvFTD) was made. MRI (figure A) showed right more than left-sided temporal atrophy, bilateral frontal and milder parietal atrophy. Fluorodeoxyglucose (FDG)-PET (figure B) demonstrated fronto-temporal hypometabolism. Metabolism in the posterior cingulate was normal. He was homozygous for the *APOE* ε4 allele and negative for the *C9orf72* expansion and mutations in *MAPT, GRN, PSEN1, and APP*. [18F]-Florbetapir PET (figure C) revealed increased tracer binding in all cortical regions corresponding to a centiloid value of 74%.

Over the subsequent 3 years his behavior deteriorated (table1) and formal neuropsychological assessment was no longer possible. He became incontinent without concern, developed grasp reflexes, and parkinsonism. He died aged 74 years, 9 years after clinical onset.

The brain showed considerable atrophy, neuronal loss and gliosis in the temporal neocortex and amygdala with sparing of the hippocampus. Features were less prominent in the frontal cortex. The basal ganglia showed severe compromise of perforating arteries with calcification. The globus pallidus showed a lacunar infarct. All neocortical regions and subcortical grey matter contained diffuse subpial and perivascular amyloid plaques but fewer neuritic and cored plaques. The occipital cortex showed a few cored plaques and severe amyloid angiopathy which was mild elsewhere, affecting mostly leptomeningeal vessels. Tau-related pathology was severe in CA1 and CA2 sectors and entorhinal cortex; the neocortex only showed few pre-tangles and tangles, scattered threads and deposits in a few neuritic plaques with more prominent changes in the temporal and parietal lobes. A few tau deposits in neurons and subpial astrocytes were seen in the basal ganglia. Abnormal TDP-43 deposits consisted of neuronal cytoplasmic inclusions and dystrophic neurites (DN), which showed similar density in the hippocampus (dentate gyrus) and amygdala while DN were more prominent in the temporal neocortex. TDP-43 related pathology was noticeable but milder in the frontal neocortex (figures 1D-H).

Pathological features were in keeping with FTLD-TDP type A, Braak neurofibrillary tangle stage 2, (0-6) [1], CERAD neuritic plaque score B (sparse) [1], Thal phase 5 (Aβ plaque score 0-5) [1], Braak synuclein stage 0 and severe small vessel disease in the basal ganglia. LATE-NC stage 3 was considered in the differential diagnosis but felt to be unlikely given, the extent of TDP-43 in the temporal and frontal neocortex, mild AD changes, absence of hippocampal sclerosis and lacunar infarcts being uncommon.

DISCUSSION

As we previously reported [2], this patient presented with a clinical and neuropsychological syndrome of bvFTD, but further investigations revealed conflicting results (MRI brain and FDG-PET in support, Florbetapir-PET against). We now report autopsy findings showing co-existent TDP-43 type A and AD pathologies and cerebrovascular disease in the context of *APOE* ε4 homozygosity.

Amyloid-PET imaging is becoming a standard clinical investigation. Recent studies [3] document a frequent change of the clinical diagnosis when PET findings and clinical diagnosis appear to be incongruent. A diagnosis of bvFTD may be changed to AD when amyloid-PET is positive, a decision supported by cases diagnosed with bvFTD but found to have AD at post-mortem [4]. There may, however, be coexistent-pathology or the scan report could be wrong (e.g. incorrect interpretation of off-target binding [5]). Patients with genetic or autopsy proven FTD are often "amyloid-positive" in CSF or PET or show amyloid pathology at post-mortem [6]. In patients with a clinical diagnosis of FTD who are *APOE* ε4 carriers, amyloid-PET scan is positive in 19% at age 60 and 43% at age 80 [7].

Using an evidence-based approach [4] our patient's probability of having AD given a positive amyloid-PET, low pre-PET clinical probability of AD, his age and *APOE* ε4 positivity is only 0.2. Our patient's load of AD neuropathological change was associated in 60% of patients in the National Alzheimer's Coordinating Center Data Set with a CDR sum of boxes score=0 but 12% had a CDR sum of boxes score>12 [1] demonstrating the variable clinico-pathological relationships. According to the Vascular cognitive impairment neuropathology guidelines [8] there was <45% predictive probability that vascular pathology contributed to his cognitive impairment given his age. Whilst the finding of TDP-43 type A pathology raises the question of LATE-NC, his clinical phenotype, age, MRI brain, FTD-PET and distribution and severity of TDP-43 pathology were in keeping with FTLD.

This case emphasizes the importance of integrating clinical evaluation, patterns of brain atrophy and FDG-PET hypometabolism, potential genetic etiologies, pre-test probability of amyloid positivity and variability of clinico-pathological relationships before final diagnosis.

Appendix 1 – Authors

Name	Location	Role	Contribution
Tobias Langheinrich, MD	Cerebral Function Unit, Manchester	Consultant neurologist	Design and conceptualization of case report, data collection and analysis, drafted the manuscript for intellectual content
Dr Kobylecki, PhD	Manchester Centre for Clinical Neurosciences	Consultant neurologist	Acquisition and interpretation of data; drafting and revision of manuscript
Dr Jones, MD	Cerebral Function Unit, Manchester	Consultant neurologist	Interpreted the data; revised the manuscript for intellectual content
Dr Thompson, PhD	Cerebral Function Unit, Manchester	Consultant neuropsychologist	Interpreted the data; revised the manuscript for intellectual content
Dr Snowden, PhD	Cerebral Function Unit, Manchester	Professor of neuropsychology	Acquisition and interpretation of data; drafting and revision of manuscript
Dr Hinz, PhD	University of Manchester	Senior lecturer in functional imaging	Acquisition and interpretation of data; revised the manuscript for intellectual content
Dr Pickering-Brown, PhD	University of Manchester	Professor of neurogenetics	Acquisition and interpretation of data; revised the manuscript for intellectual content

Dr Mann, PhD	University of Manchester	Professor of neuropathology	Acquisition and interpretation of data; drafting and revision of manuscript
Dr Roncaroli, PhD	University of Manchester	Clinical chair in neuropathology	Acquisition and interpretation of data; drafting and revision of manuscript
Dr Herholz, MD	University of Manchester	Professor in clinical neuroscience	Acquisition and interpretation of data; drafting and revision of manuscript
Dr Gerhard, MD	University of Duisburg- Essen, Germany	Consultant neurologist	Acquisition and interpretation of data; drafting and revision of manuscript

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Figure

MRI brain, FDG-PET brain, Florbetapir PET, and histological slides with amyloid, tau and TDP pathology
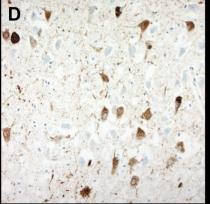
A: MR and PET scans were obtained 3 years after clinical diagnosis.

Coronal T1 MRI (in radiological orientation) showing right more than left temporal, bilateral frontal and milder parietal atrophy. B: color coded 3-dimensional stereotactic surface projection (3D-SSP) maps of FDG-PET demonstrating fronto-temporal hypometabolism and preservation of posterior cingulate/precuneus (color bar indicating z-values of hypometabolism,top: medial projection, bottom: lateral projection; R: right hemisphere, L: left hemisphere). C: standardized uptake value ratios (SUVR) compared to cerebellum of Florbetapir PET revealing increased tracer binding in all cortical regions. D: the fusiform gyrus shows severe atrophy (haematoxylin-eosin, x20); E: Aβ peptide positive diffuse and neuritic plaques are shown in the occipital grey matter (immunoperoxidase, x20). F: neurofibrillary tangles and neuropil threads in the entorhinal cortex (immunoperoxidase, phosphorylated tau, x20). G: TDP43 inclusions are documented in the dentate gyrus of hippocampus (immunoperoxidase, x40) and H: frontal lobe (immunoperoxidase, x40).
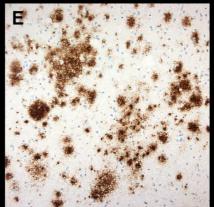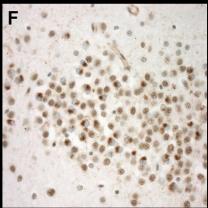
Table

Time points in months and age of patient when neuropsychological tests were performed; raw scores and z-scores of forward and reverse digit span, MMSE, animal and FAS fluency; note decline in fluency, MMSE and reverse digit span with maintained forward digit span; [1]https://doi.org/10.4306/pi.2014.11.1.39; [2]https://doi.org/10.1186/1471-2318-5-7; [3]https://doi.org/10.1093/arclin/14.2.167; [4]locally developed visual episodic memory test: mean (SD): Immediate recall: 10(0.8); Immediate recognition: 18(1); Delayed recall: 9(1.6); Delayed recognition: 18(0.7); note superior but not normal recognition performance; [5]locally developed delayed face recall and recognition test; superior but not normal recognition; of note patient was distracted by 'choice' figures and made frequent references to his personal relationship to them; also patient had difficulty recognizing faces on the face identification part of the test; [6]locally developed verbal episodic memory test; striking features of patient's recall included misconstruction errors, intrusion errors, interference between the stories and a tendency to relate the story to his personal experience; note better cued than free recall; following a delay cued recall was similar; of note during the delayed performance the patient was distracted by his mobile phone, making comments about his mobile phone throughout.
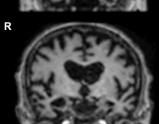
Time point (age) / Test	0 months (67)	14 months (68)	19 months (68)	27 months (69)	39 months (70)
Digit span forward (f) **Digit span reverse (r)[1]** **Raw score (z-score)**	f 7 (-0.23) r 3 (-1.56)	f 7 (-0.23) r 4 (-0.92)	f 6 (-0.63) r 4 (-0.92)	f 6 (-0.63) r unable	f 6 (-0.63) r unable
MMSE[2] **Raw score (z-score)**	26/30 (-1.3)	27/30 (-0.8)	20/30 (-4.3)	14/30 (-7.3)	17/30 (-5.7)
Category (animals) fluency **Letter (FAS) fluency[3]** **Raw score (z-score)**	Animals 14 (-0.6) FAS 21 (-1.2)	Animals 11 (-1.3) FAS 20 (-1.3)	Animals 3 (-3.1) FAS 7 (-2.3)		
Visual object memory[4] **Raw score (z-score)**	Immediate recall 7/20 (-3.8) Immediate recognition 16/20 (-2) Delayed recall 2/20 (-4.4) Delayed recognition 15/20 (-4.3)				
Memory for faces[5] **Raw score (median/range)**	Delayed recall 1/10 (7/5-9) Delayed recognition 6/10 (9/9-10)				
Story memory[6] **Raw score (median/range)**	Immediate free recall 1/10 (9/9-10) Immediate cued recall 5/10 (10/9-10)				

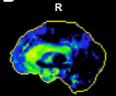| | Delayed free recall 3/10 (9/6-10)

Delayed cued recall 4/10 (10/8-10) | | | | |
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