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Positive Florbetapir PET Amyloid Imaging in a Subject with Frequent Cortical Neuritic Plaques and Frontotemporal Lobar Degeneration with TDP43-Positive Inclusions

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Abstract

Abnormal neuronal accumulation and modification of TAR DNA binding protein 43 (TDP-43) have recently been discovered to be defining histopathological features of particular subtypes of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), and are also common in aging, particularly coexisting with hippocampal sclerosis and Alzheimer's disease (AD) pathology. This case report describes a 72 year old Hispanic male with no family history of neurological disease, who presented at age 59 with obsessive behavior, anxiety, agitation and dysphasia. Positron emission tomography (PET) imaging using the amyloid ligand ¹⁸F florbetapir (Amyvid) was positive. Postmortem examination revealed frequent diffuse and neuritic amyloid plaques throughout the cerebral cortex, thalamus and striatum, Braak stage II neurofibrillary degeneration and frequent frontal and temporal cortex TDP-43-positive neurites with rare nuclear inclusions. The case is unusual and instructive because of the co-existence of frequent cortical and diencephalic amyloid plaques with extensive TDP-43-positive histopathology in the setting of early-onset dementia and because it demonstrates that a positive cortical amyloid imaging signal in a subject with dementia does not necessarily establish that AD is the sole cause.

Keywords

Alzheimer's disease; frontotemporal dementia; neurofibrillary degeneration; neuritic amyloid plaques

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Competing interests

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Background

Frontotemporal lobar degenerations (FTLD) are a group of heterogeneous neurodegenerative disorders that represent the second most common cause of early-onset dementia following AD [1, 2]. These conditions most commonly present with abnormal behavior and/or progressive aphasia typical of a frontotemporal dementia (FTD) syndrome, occasionally with accompanying clinical and/or pathological findings of motor neuron disease. The clinical diagnosis is challenging and autopsy studies indicate that the cause of FTD is sometimes AD rather than FTLD [3, 4]. Intraneuronal accumulation of TAR DNA binding protein 43 (TDP-43), with or without mutations of the progranulin (*GRN*) gene or hexanucleotide expansion in chromosome 9 open reading frame 72 (*C9orf72*), are a common subtype of FTLD [5]. It has been reported that TDP-43 histopathology is detected in 25% to 50% of AD cases and that the phenomenon more frequently accompanies AD cases with a severe clinical phenotype, severe AD histopathology, longer disease duration and hippocampal sclerosis (HS) [6]. When coexisting with AD pathology, TDP-43 pathology is most often limited to the mesial temporal lobe whereas in FTLD-TDP it is more widely distributed throughout the temporal and frontal neocortex. In this case report we present a 72 year old Hispanic male with early-onset frontotemporal dementia and positive PET amyloid imaging with ^{18}F florbetapir [7, 8], found at autopsy to have FTLD-TDP.

Material and Methods

Subject recruitment and amyloid imaging

The subject was recruited for a Phase III clinical trial of ^{18}F florbetapir (Amyvid), a ligand recently approved by the US Food and Drug Administration (FDA) for the estimation of β -amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease or other causes of cognitive impairment. Florbetapir image acquisition methodology for this study has been previously described [7, 8]. Briefly, 11 months prior to death, a 10-min PET acquisition was conducted approximately 50 min after administration of 370 MBq (10 mCi) ^{18}F florbetapir. For deciding whether a scan was on the whole positive or negative, five board-certified nuclear medicine physicians were selected as readers and underwent a detailed training program [8].

Neuropathological methods

The subject was autopsied and the brain sampled according to the protocol for the clinical trial [7, 8] as well as for complete neuropathological examination using the standard methods of the Brain and Body Donation Program at Banner Sun Health Research Institute, Sun City AZ which has been approved by the Institutional Review Board of Banner Health[9]. The staining done for the clinical trial was limited and predominantly directed at documenting the presence or absence of amyloid plaques. For the detailed neuropathological examination, multiple brain regions were microscopically examined, including frontal, parietal, temporal and occipital lobes of the cerebrum, all major diencephalic nuclei and major subdivisions of the brainstem and cerebellum. For clinical trial documentation of the presence of amyloid plaques, a modified Bielschowsky silver stain and A β immunohistochemistry (4G8, Covance, Emeryville, CA) were performed on paraffin-

embedded sections. The neuropathological examination slide set included staining of formalin-fixed paraffin-embedded sections with hematoxylin and eosin, and identification of amyloid plaques, neurofibrillary tangles and glial tauopathies on 80 µm-thick, large-format (3 x 5 cm) formalin-fixed sections using two enhanced silver stains, the Gallyas and Campbell-Switzer methods [10], for tangles and plaques, respectively, as well as the Thioflavin S fluorescent stain for amyloid. The distribution of amyloid throughout the brain was staged using the Campbell-Switzer stain, as originally done by Thal [11], neuritic plaques were graded as recommended by CERAD [12] and neurofibrillary degeneration was staged by the original method of Braak, in thick sections using the Gallyas method [10]. In addition, primary antibodies against phosphorylated tau protein (ptau, clone AT8; Research Diagnostics) and TDP-43 phosphorylated (pTDP-43) at residues 409 and 410 [13] were used for immunohistochemistry on large format formalin-fixed, free-floating sections.

Genetic testing

Genotyping of DNA extracted from cerebellum was performed at the University of Pennsylvania Center for Neurodegenerative Disease Research (CNDP). The G₄C₂ hexanucleotide repeat region in *C9orf72*, as well as coding regions in *MAPT*, *GRN*, *VCP*, *CHMP2B*, and *TARDBP*, all genes that have been associated with FTD, were characterized by PCR as previously described [14, 15].

Results

Clinical Summary

This 72 year old man died with a clinical diagnosis of frontotemporal dementia. According to family members, symptoms had first been noticed 13 years earlier, at age 59, with personality changes, including becoming obsessive and fixated on single ideas. The available private medical records date from about 7 years prior to his death, at which point he had been symptomatic for about 6 years. On examination at that time he had fluent speech but word-finding and comprehension difficulty as well as echolalia. He had difficulty following commands and frequently gave answers that were unrelated to the questions. He exhibited poor judgment, anxiety and agitation. He was incontinent of urine on occasion. He scored 11/30 on the Mini Mental State Examination (MMSE), recalling none of 5 words after a 5 minute delay. On motor examination he had normal muscle tone, no atrophy and 5/5 muscle strength. He had prominent apraxia, diffuse bradykinesia and tardive dyskinesia with jaw tremor. The diagnostic impression was of FTD, possible Pick's disease, tremor disorder (TD) and parkinsonism. He was treated with risperidone and divalproex sodium for his anxiety and agitation and with sertraline for depression. In subsequent years he became delusional with nonsensical speech. He was admitted to a residential memory care center. While living there he exhibited socially inappropriate behavior and because of this had to be admitted on at least one occasion to a mental health facility for acute treatment. Additionally, he developed swallowing difficulties. A fluoro-dexoxyglucose PET scan done approximately a year before death revealed diminished metabolism in the temporal lobes; there was severe atrophy of both frontal and temporal lobes. The cause of death was listed as heart failure. The time elapsed between imaging and death was 11 months.

There was no significant substance abuse history and no family history of dementia or parkinsonism. His father had a history of stroke while his mother had liver cancer and his brother had multiple myeloma. Post-mortem genetic screening did not identify any pathogenic mutations in *C9orf72*, *GRN*, *MAPT*, *TARDBP*, *CHMP2B*, or *VCP*.

Florbetapir PET Scan

A representative view of the florbetapir PET scan is shown in Figure 1B-C. The image was rated visually positive by all five nuclear medicine physician readers. The cerebellum was used to subtract non specific binding (Fig 1C). Tracer activity appeared greatest in posterior regions of the brain, i.e., precuneus, occipital cortex, posterior cingulate and parietal cortex. However, the CT scan (Fig 1A) shows significant atrophy in the frontal and temporal regions which may contribute to the appearance of less activity in these regions.

Gross Postmortem Findings

The brain weighed 874 grams in the fresh state. The dura was normal and the leptomeninges showed mild fibrotic changes. The cerebral convexities had a normal gyral pattern and there were no focal lesions present. There was asymmetrical gyral atrophy, with severe gyral atrophy of the left frontal lobe and moderate gyral atrophy of the right frontal lobe (see Figure 2). The left temporal lobe showed severe gyral atrophy, particularly of the anterior part, while there was moderate gyral atrophy of the right lobe. The right parietal lobe and paracentral areas showed moderate gyral atrophy while other areas were normal in appearance. The base of the brain showed mild to moderate patchy atherosclerosis of the vessels of the circle of Willis. The mammillary bodies showed moderate to marked atrophy and light brownish discoloration. The uncus showed moderate to marked atrophy. The cerebellum was externally unremarkable. The brainstem showed moderate atrophy of the basal pons and of the medulla. Cerebral slices showed no focal lesions and the white matter had a normal appearance. There was severe dilatation of the left lateral ventricle and the third ventricle; the right lateral ventricle showed moderate dilatation. The basal ganglia showed moderate bilateral atrophy while the thalamus and subthalamic nucleus were unremarkable. The left amygdala, head and body of the hippocampus and the parahippocampal gyrus showed very severe atrophy whereas on the right side these changes were moderate. The substantia nigra was normally pigmented on both sides. Respective axial and parasagittal slices of the brainstem and cerebellum were unremarkable.

Microscopic Findings

Paraffin-embedded, H & E-stained sections showed moderate to marked gliosis of upper neocortical layers in the frontal and temporal lobes. The amygdala and entorhinal cortex showed very marked fibrillary gliosis with frequent hypertrophic astrocytes and marked tissue rarefaction. The hippocampal CA1 region showed focally marked gliosis without appreciable neuronal loss. There was mild to moderate patchy gliosis in the caudate nucleus and putamen and moderately frequent mineralized blood vessels in the globus pallidus. The mammillary body was unremarkable while there was marked gliosis of the hypothalamus and medial thalamus. The subthalamic nucleus was unremarkable. The substantia nigra and locus ceruleus were not depleted of pigmented neurons; Lewy bodies and neurofibrillary

changes were not present. Remaining sections of the cerebellum, brainstem and cervical spinal cord were unremarkable except for mild to moderate patchy loss of Purkinje cells from the superior vermis of the cerebellum. Large-format, H & E-stained sections showed no significant cerebral white matter rarefaction. There were no infarcts anywhere in the brain.

Sections stained with Gallyas, Campbell-Switzer, Thioflavin S, Bielschowsky and A β immunohistochemical methods showed, in all neocortical areas, uniform and very frequent densities of diffuse amyloid plaques while neuritic and cored plaques were patchy in distribution, ranging from sparse to frequent (Figure 3). Amyloid plaques were also present at frequent densities within the putamen and thalamus but were absent from the substantia nigra and cerebellum (Thal amyloid phase 3). Neurofibrillary tangles were absent from the cerebral cortex, rare within the amygdala and CA1 region of hippocampus and frequent within layer II of the entorhinal cortex as well as within the transentorhinal region (Braak neurofibrillary stage II, Figure 4). Amyloidotic blood vessels were absent from all brain regions.

Immunohistochemical staining for phosphorylated TDP-43 protein revealed positive tissue elements within the cerebral cortex, striatum, amygdala and hippocampal formation. In the cerebral cortex the predominant features were relatively long neurites present at moderate to frequent densities in layer II with sparse densities in other cortical layers. The fibers were of a caliber and configuration suggestive of dendritic branches and many showed frequent spines along their length (Figure 5). Some of the fibers were focally thickened into fusiform or bulbous shapes and some had kinked segments or a tortuous course, occasionally forming tight intertwined knots. Also present at moderate to frequent densities were small solid circular neuropil profiles consistent with cross-sections of the fibers described above or with enlarged presynaptic terminals as well as thin-caliber, short fibers resembling neuropil threads, which were present at moderate densities. Some of the threads had a tortuous or coiled course. Perikaryal neuronal cytoplasmic inclusions were rare to sparse, mostly within layer II. These were within small granular neurons and were circular in shape or wrapped partially around the nucleus in crescentic or comma shapes. Very rare threadlike intranuclear inclusions were also present in the same neuronal population. The amygdala showed features similar to the cerebral cortex, with high densities of very short thickened fibers in the superficial layers near the surface of the ambient and semilunar gyri. Also within the amygdala were moderately frequent neuronal perikaryal inclusions within medium-sized to larger neurons. The CA1 region of hippocampus and the entorhinal cortex showed features similar to the cerebral cortex but at lower densities. In the caudate nucleus and putamen the thicker fibers were rare to sparse while the neuropil threads and neuronal perikaryal inclusions were sparse to moderate. The hypothalamus had similar TDP-43-immunoreactive features as the striatum. Overall, the TDP-43 histopathology was most consistent with Type C [16].

Discussion

Amyloid imaging promises to become a remarkable tool for the clinical evaluation of AD [7, 8, 17-19] and offers a new opportunity to identify asymptomatic, amyloid-positive subjects

for testing anti-amyloid therapeutic agents. However, because neuritic amyloid plaques may be seen at autopsy in clinically normal individuals and concurrent with other dementing diseases, a positive amyloid scan should be interpreted with caution, since this does not exclude a concurrent cause of dementia.

In this report we present a subject who presented with early-onset dementia and was found to have a positive cortical amyloid scan. Prior to amyloid imaging, the clinical evaluation had indicated the presence of frontotemporal dementia. The amyloid scan was not available to the attending physicians because this was a blinded clinical trial but it is possible that, had it been available, clinicians might have considered AD in a differential diagnosis, as the syndrome of FTD may be present in subjects with pure AD pathology [4]. The fluoro-deoxyglucose PET scan showed decreased uptake predominantly in the temporal lobes and therefore was inconclusive in this respect. The florbetapir signal was most prominent in the parietal and occipital lobes including the posterior cingulate gyrus and precuneus. However, it is difficult to determine whether the relatively decreased (but still positive) signal in the frontal and temporal regions was due to dilutional effects of cerebral atrophy.

At autopsy there were frequent amyloid plaques throughout the cerebral cortex as well as the putamen and thalamus but the distribution and density of neurofibrillary tangles and associated neurites was consistent only with Braak Stage II, which, in both National Institute on Aging AD classification schemes since 1997, has not been thought to be sufficient as a cause of dementia [20-22]. The major cause of dementia in this subject was most probably FTLTDP as the characteristic histopathology of this disorder was present at high densities in both frontal and temporal cortex as well as in the mesial temporal lobe, striatum and hypothalamus. The possibility that this case might represent primarily AD with concurrent but subordinate TDP-43 pathology is unlikely due to the low Braak tangle stage and because in such cases the TDP-43 involvement is usually limited to the mesial temporal lobe and/or is absent or present at relatively low densities in the frontal and/or temporal neocortex [23-25].

The case is unusual and even rare when set against the entirety of elderly dementia. We have searched our database for similar cases and have found that, out of 775 cases of dementia that received a neuropathological examination, only 3, of which the reported case is one, had a concurrence of a neuropathological diagnosis of FTLTDP with ubiquitinated inclusions (FTLTDP-U; not all archived cases have had TDP-43 staining done) and a similar level of AD. When set against all cases of FTLTDP-U, however, this amount of AD histopathology is not uncommon (3 out of 13 cases). However, as our program is set in a retirement community from which most of the volunteer research subjects are drawn (mean age at death is 83), the percentage of FTLTDP-U subjects in a younger dementia population is likely to be considerably higher and thus the likelihood will be greater of encountering cases similar to the one presented here. About 15% of FTLTDP cases are autosomal dominant inherited disorders, most of which are due to mutations in *MAPT* or *GRN* or to expansion in *C9orf72*, and a minority to mutations in *CHMP2B*, *VCP*, and *TARDBP* [26]. We tested for, and excluded, mutations in all six genes. In addition, immunohistochemical staining for phosphorylated tau protein indicated that a tau mutation was not likely.

Amyloid imaging is not intended to provide a diagnosis, but is intended to provide information regarding one potential underlying pathology as an aid to diagnosis. Amyloid imaging should be interpreted in the context of a full diagnostic evaluation, including as needed other imaging and biomarker tests and clinical/phenotype evaluation. In the current case, the patient's presentation was consistent with an FTD diagnosis, although the FDG PET scan was inconclusive. The florbetapir amyloid PET scan was positive, but atypical in that activity was more prominent in posterior regions and atrophy could be seen on both PET and CT in frontal and anterior temporal regions. On autopsy there was evidence of amyloid pathology as well as widespread TDP pathology.

We conclude that this case demonstrates that a positive cortical amyloid imaging signal in a subject with dementia does not necessarily establish that AD is the sole or primary contributor to cognitive impairment. While this situation might previously been hypothesized based on the neuropathology literature, this is the first confirmation and as such serves to inform clinicians using amyloid imaging as an aid in their diagnostic process.

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Figure 1. CT (A) and PET-Florbetapir (B-C) images of subject brain

Representative axial, sagittal and coronal views (left to right) showing, on CT, atrophy in frontal and temporal regions while on florbetapir-PET there is dense amyloid binding in precuneus, occipital and parietal regions plus nonspecific binding in pons. Bottom row is a SUVr image normalized to whole cerebellum and aligned in MNI brain atlas space, which show areas of relative uptake.

Figure 2. Gross postmortem views of subject brain

Superior (A), inferior (B), left (C) and right (D) views had a normal gyral pattern without any focal lesions. The frontal and temporal lobes showed asymmetric gyral atrophy, marked on the left, moderate on the right. The parietal lobes showed moderate gyral atrophy whereas the occipital lobes were relatively spared. Coronal sections at the level of the hippocampus (E) showed severe atrophy of the left hippocampal formation, parahippocampal gyrus and amygdala, with accompanying marked and moderate dilatation of the left and right lateral ventricles, respectively.

Figure 3. Staining for amyloid plaques in cortical regions of interest

The precuneus (A) and lateral occipital cortex (B), stained with the Campbell-Switzer silver stain, showing frequent amyloid plaques. In (B) as well as generally throughout the cerebral cortex, diffuse plaques were frequent while neuritic and cored plaques had a patchy distribution, ranging from sparse to frequent. The middle temporal gyrus is seen in C) and (D), stained with the Thioflavin S stain for amyloid and showing, in this particular field of view, moderate to frequent neuritic plaques.

Figure 4. Staining for neurofibrillary tangles in layer II of the entorhinal cortex

The entorhinal cortex stained with (A) Gallyas silver stain and (B) phosphorylated tau protein, immunostain against clone AT8 showing frequent neurofibrillary tangles and dystrophic neurites within layer II of the entorhinal cortex.

Figure 5. Phosphorylated TDP-43 protein staining

Phosphorylated TDP-43 was present at sparse to moderate frequencies in the cerebral cortex, striatum, amygdala and hippocampal formation (A-C are from amygdala; D-F are from cerebral cortex). Perikaryal neuronal inclusions are shown in the amygdala (A-C), and long neurites with frequent synaptic spines are shown in neocortical layer II (D-F).