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The GGGGCC Repeat Expansion in *C9ORF72* in a Case with Discordant Clinical and FDG-PET Findings: PET Trumps Syndrome

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Abstract

A hexanucleotide repeat expansion in the chromosome 9 open reading frame 72 (*C9ORF72*) gene was recently discovered as the cause underlying frontotemporal degeneration (FTD) and/or amyotrophic lateral sclerosis (ALS) linked to chromosome 9 (c9FTD/ALS). In this atypical case of c9FTD/ALS, the proband presented with amnestic mild cognitive impairment which evolved into Alzheimer's disease (AD)-type dementia and later developed ALS. Fluorodeoxyglucose-positron emission tomography of the brain demonstrated mild hypometabolism involving the medial frontal and lateral temporal lobes, left more so than right, which progressed over time. He

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Dr. Adeli - nothing to disclose
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Dr. Knopman serves as Deputy Editor for Neurology®; has served on a data safety monitoring board for Eli Lilly and Company; has served as a consultant for Elan/Janssen AI; is an investigator in clinical trials sponsored by Elan/Janssen AI, Baxter International Inc., and Forest Laboratories, Inc.; and receives research support from the NIH (R01 AG011378 [Coinvestigator], P50 AG016574 [Coinvestigator], U01 AG006786 [Coinvestigator], AG029550 [Coinvestigator], AG032306 [Coinvestigator], and U01 096917 [Coinvestigator]).
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was subsequently confirmed to have the *C9ORF72* expansion. This report highlights the need to consider mutations in the FTD-associated genes when a familial disorder is suggested and neuroimaging studies reveal findings atypical of an AD pathophysiological process despite the typical anterograde amnestic syndrome.

Keywords

Frontotemporal degeneration; amyotrophic lateral sclerosis; motor neuron disease; Alzheimer's disease; TDP-43; *C9ORF72*; c9FTD/ALS

INTRODUCTION

The frontotemporal lobar degenerations (FTLD) comprise a clinically and pathologically heterogenous group of disorders associated with degeneration of the frontal and/or anterior temporal lobes (McKhann et al., 2001). Behavioral variant frontotemporal dementia (FTD), the most common clinical syndrome of the FTLDs, is typically characterized by progressive changes in personality, behavior, insight, judgment, reasoning abilities, or language, with relative perseveration of episodic memory (Rascovsky et al., 2011). There is growing awareness of the overlapping syndromes of FTD, motor neuron disease, parkinsonism, corticobasal syndrome, and progressive supranuclear palsy syndrome (Josephs, 2008). The clinical and pathological overlap of FTD with amyotrophic lateral sclerosis (ALS) is exemplified in the multiple kindreds with FTD and/or ALS associated with deposition of 43 kDa transactive response DNA-binding protein (TDP-43) in the ubiquitinated inclusions (Arai et al., 2006; Hosler et al., 2000; Morita et al., 2006; Neumann et al., 2006). The most common genetic cause known to date in kindreds whose members have developed FTD and/or ALS was recently identified to be a hexanucleotide repeat expansion (GGGGCC) in the chromosome 9 open reading frame 72 (*C9ORF72*) gene (DeJesus-Hernandez et al., 2011; Renton et al., 2011). These cases are now collectively referred to as c9FTD/ALS (Boeve et al., 2012; DeJesus-Hernandez et al., 2011; Murray et al., 2011).

As genetic testing has expanded to include cases outside of the typical FTD and/or ALS phenotype, atypical cases are being increasingly identified (Khan et al., 2012), although many are lacking with detailed longitudinal characterization. We report detailed longitudinal clinical, neuropsychological, and neuroimaging findings of a proband of a small kindred with the *C9ORF72* mutation who initially presented with amnestic mild cognitive impairment which evolved to Alzheimer's disease (AD)-type dementia and was later followed by the development ALS. This report extends the clinical phenotype associated with the *C9ORF72* expansion.

METHODS

Subjects

The subject underwent a clinical evaluation at our institution and was then enrolled in the Mayo Alzheimer Disease Research Center – a Mayo Foundation Institutional Review Board-approved program. The subject and his wife provided written consent for participation. All additional data from affected relatives were collected and analyzed.

Clinical and Neuropsychological Data

His neurological and neuropsychological data were reviewed. Neuropsychological testing was performed using standard measures (Fields, Ferman, Boeve, & Smith, 2011). Index Scores were converted to Mayo Older American Normative Studies (MOANS) age-adjusted

scaled scores (mean of 10 and standard deviation of 3) (Ivnik et al., 1992; Ivnik, Malec, Smith, Tangalos, & Petersen, 1996; Lucas et al., 1998; Machulda et al., 2007; Pedraza et al., 2010). Clinical diagnoses were based on published criteria for mild cognitive impairment (MCI), FTD, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS) (Brooks, Miller, Swash, & Munsat, 2000; McKhann et al., 1984; Neary et al., 1998; Rascovsky et al., 2011; Petersen et al., 2001).

Neuroimaging

MRIs were performed either at 1.5 Tesla or 3 Tesla (GE Healthcare). At 1.5 Tesla, a 3D high resolution spoiled gradient recalled acquisition in steady state (SPGR) and at 3 Tesla magnetization prepared rapid gradient echo acquisition were used for the high resolution T1 weighted images. A fluid attenuated inversion recovery (FLAIR) sequence was performed at both 1.5 and 3 Tesla.

All positron emission tomography (PET) scans were acquired using a PET/computed tomography scanner (DRX; GE Healthcare) operating in 3-dimensional mode. A computerized tomography image was obtained for attenuation correction. The subject was injected with both 11C-Pittsburgh compound B (PiB) (average, 715 MBq; range, 713–718 MBq) and 18F-fluorodeoxyglucose (FDG) (average, 564 MBq; range, 449–691 MBq). The images were acquired on the same day, one hour apart. Following a 40-minute PiB uptake period, a 20-minute PiB scan was obtained. PiB PET acquisition consisted of four 5-minute dynamic frames. Following a 40-minute FDG uptake period, an 8-minute FDG scan was obtained. Image acquisition consisted of four 2-minute dynamic frames. Standard corrections were applied, and standard acquisition and vendor reconstruction parameters were used. FDG-PET scans were processed using CortexID software (GE Healthcare). The activity in each FDG-PET data set was normalized to the pons and compared with an age-segmented normative database, yielding 3-dimensional z-score metabolic maps. The uptake on PiB-PET was calculated using an averaged multiregional cortical to cerebellar ratio described previously (Lowe et al., 2009), with a ratio below 1.5 being considered "PiB-PET negative."

Genetic Analyses

Genomic DNA (gDNA) was extracted from peripheral blood samples using standard procedures. The gDNA was screened for the presence of the expanded hexanucleotide repeat in *C9ORF72* using the repeat primed PCR method as previously described. (DeJesus-Hernandez et al., 2011) Genetic analysis and DNA sequencing for *C9ORF72, MAPT*, and *PGRN* were performed as previously described (DeJesus-Hernandez et al., 2011). Apolipoprotein E (ApoE) genotyping was performed as previously described (Tsai et al., 1994).

RESULTS

Clinical, Neuropsychological, and Neuroimaging Data

The proband began experiencing mild forgetfulness of recent events and difficulty recalling names at age 67 without any additional cognitive deficit or change in behavior. He had been started on donepezil and memantine without any significant benefit. His parent had been diagnosed with Parkinson's disease at age 70 years. There was no additional family history of neurologic or psychiatric disease.

On our first encounter with the proband at age 70, he expressed frustrations over short term memory, and his wife corroborated problematic forgetfulness for details of recent events and upcoming appointments. He had a total score of 32 out of 38 on the Kokmen Short Test of

Mental Status (STMS) (Kokmen, Naessens, & Offord, 1987) with one out of four objects recalled after a five minute delay. He had dysnomia on confrontation naming, but otherwise language evaluation was within normal limits. He demonstrated preserved recognition of famous faces, but had difficulty stating their names. He had mild distal sensory loss to vibration in stocking distribution and hyporeflexic Achilles tendon reflex bilaterally. Motor and cerebellar examinations were normal. Neuropsychological assessment showed weakness in verbal retention on serial list learning with an adequate learning curve (Figure 1). Executive functioning was above average. Based on his clinical presentation and his performance on neuropsychological testing, he was diagnosed with amnestic MCI, realizing that his delayed recall for paragraphs and figures was relatively preserved. MRI of the brain showed mild generalized cortical atrophy which was slightly more apparent in the medial frontal regions, as well as more obvious hippocampal atrophy, more pronounced on the left (Figure 2). FDG-PET showed mild asymmetric hypometabolism involving the mesial and dorsolateral frontal and temporal lobes, left much more so than right (Figure 3).

Over the subsequent years his short-term memory difficulties dominated his symptomatology. At the age of 73 years, he developed mild apathy, but other changes in behavior and personality were absent. He started to have mild navigational problems when driving. He noted mild clumsiness involving his left leg without associated weakness, numbness, or cramps. His examination revealed a score of 26 out of 38 on STMS with most prominent difficulties on delayed recall and mild difficulties on tests of attention and construction. He had mild spasticity, mild hyperreflexia, and decreased alternating motion rates of the left lower limb. There was no evidence of parkinsonism, weakness, or fasciculations. Neuropsychological assessment demonstrated a marked decline in learning of paragraph length information as well as visually presented information (Figure 1). There was relative preservation of verbally learned material on delayed recall, as compared with visually presented information for which there was zero percent retention. There was a marked decline in learning and recall of serial list information. There were also mild but significant declines in object naming and mental flexibility. Performance on other tests of language and executive function declined minimally, while visuospatial functioning remained strong. MRI of the brain showed continued progression of cortical and hippocampal atrophy (Figure 2). FDG-PET showed interval progression of the hypometabolism involving the frontal and temporal lobes, far greater on the left, and also hypometabolism involving the left medial parietal lobe and cingulate cortex (Figure 3). PiB-PET showed no significant cortical uptake of the radiotracer, and the ratio was 1.1 (Figure 4). He was diagnosed with mild dementia. Based on his symptomatology, neuropsychological test results, and MRI demonstrating hippocampal atrophy, a clinical diagnosis of probable AD was made as the clinician was blinded to PiB-PET scan results.

At the age of 75 years, he was experiencing progressive difficulties with his short-term memory with marked difficulties recalling conversations or events minutes after they had occurred. He complained of more prominent word-finding difficulties in conversation and dysnomia for names of people had progressed. There were no problems with reading, writing, or comprehension. He had difficulty with complex decision-making and became dependent for most instrumental activities of daily living, such as managing the finances, driving, and house-work. His family reported mild apathy and an increased craving for sweets. There were otherwise no reported changes in behavior or personality and no disinhibition. In the preceding year, he developed a left foot drop for which he required an ankle-foot orthosis. He was also noted to be moving slower. He demonstrated limited insight into his cognitive and motor difficulties. On his examination, his STMS score was 15 out of 38. His examination revealed difficulties with verbal learning, delayed recall, calculation, and abstract reasoning. He had mild hypomimia, but no dysarthria. Strength in the cranial and cervical segments was normal. He had weakness at the iliopsoas bilaterally, worse on

the left than on the right. He also demonstrated significant weakness of the following muscles of his left lower limb: anterior tibialis, toe extensors, extensor hallucis longus, peronei, posterior tibialis, toe flexors, and gastrocnemius. There was mild gegenhalten of his upper limbs and mild spasticity of his lower limbs bilaterally. He had a mild tremor with action of his left upper limb. Fasciculations were present diffusely in his upper and lower limbs, including bilateral triceps, biceps, brachioradiales, quadriceps, and gastrocnemii. Fasciculations of the left latissimus dorsi were noted as well. Aside from the left foot drop, gait evaluation was normal. He had difficulty standing from a seated position without the use of his arms. There was no postural instability. He was diffusely hyperreflexic, except hyporeflexic at the Achilles tendon bilaterally, with flexor plantar responses. Neuropsychological assessment showed a considerable decline in tests of memory, language, and executive functioning (Figure 1). MRI of the brain demonstrated progression of atrophy (Figure 2). FDG-PET showed mild progression of hypometabolism involving the frontal and temporal lobes, again with the left side affected far more so than the right (Figure 3). PiB-PET was performed again, and the ratio was unchanged (1.1). Electromyogram was performed due to the suspicion of motor neuron disease and showed fibrillation potentials, fasciculations and large polyphasic motor unit potentials with reduced recruitment in the thoracic paraspinals, left deltoid, left triceps brachii, left first dorsal interosseous, left tibialis anterior, left medial gastrocnemius, left vastus medialis and left gluteus medius muscles. The clinical diagnosis was changed to atypical frontotemporal lobar degeneration plus amyotrophic lateral sclerosis.

Genetic Findings

DNA was available for analysis in our subject and the hexanucleotide expansion in *C9ORF72* was detected. No mutation was present in *MAPT* or *PGRN*. ApoE genotype was 3/4.

DISCUSSION

The phenotype associated with the *C9ORF72* mutation is typically behavioral variant FTD with or without parkinsonism and/or ALS (Boeve et al., 2012). Our subject's clinical features were atypical for this mutation, with the onset of memory decline and mild dysnomia without associated change in behavior, personality, or comportment early in his course. He initially presented with a picture consistent with amnestic MCI that evolved into an AD-type dementia which was followed by the insidious development of motor neuron dysfunction about six to seven years after the onset of cognitive difficulties. Mild parkinsonism evolved several years after disease onset. The changes in behavior were seen later in his clinical course and consisted of apathy and increased craving of sweets. The progression of his cognitive decline was gradual until the onset of motor neuron dysfunction, at which point he had a dramatic decline in both his performance on neuropsychological tests and in function. Even granting that our neuropsychological battery may not have used the most sensitive tests for executive functions, our patient scored well above expectation on executive tasks, suggesting that deficits in this domain were very mild at worst initially.

When both ALS and FTD are present in an individual with c9FTD/ALS, the features tend to emerge within the first two years (Boeve et al., 2012). Parkinsonism, as well, tends to become evident within the first two years of the onset of clinical symptoms (Boeve et al., 2012). Our subject had a much longer duration between the onset of ALS and parkinsonism from his initial symptom onset. ALS developed over the course of one to two years, during which time his cognitive symptoms also dramatically declined. Although it has been shown that survival in c9FTD/ALS is shorter in those with features of FTD and ALS versus FTD

alone (Boeve et al., 2012), rates of cognitive decline in these two groups have not been previously studied.

The neuroimaging findings in our case are somewhat atypical for what has been previously described in c9FTD/ALS. The majority of studies have reported symmetric atrophy and hypometabolism involving the bilateral frontal and/or temporal cortex in c9FTD/ALS cases (Boeve et al., 2012; Hsiung et al., 2012; Mahoney et al., 2012; Whitwell et al., 2012). One study noted more variability in left–right sided asymmetries and reported cases with both symmetric and asymmetric atrophy and/or hypoperfusion in cases with progressive aphasia or FTD (Snowden et al., 2012). Similar to our case, the asymmetric cases were most often associated with left predominant atrophy or hypoperfusion. Based on the FDG-PET findings, one would have presumed that clinical features consistent with corticobasal syndrome and/or a more obvious progressive aphasia syndrome would have developed, but this did not occur. This case is consistent with other rare cases with atypical FDG-PET findings (Boeve et al., 2012), and exemplifies that asymmetric neuroimaging findings should not exclude consideration of the *C9ORF72* expansion as a cause of an atypical dementing illness.

Clinicopathologic studies have demonstrated that the underlying substrate of amnestic MCI that progresses to dementia is most often AD (Jicha et al., 2006). The proband's initial MRI showed a moderate degree of mesial temporal atrophy which was slightly asymmetric, left more than right, and progressed over time. This was consistent with the prominent anterograde amnestic presentation and course initially. On the other hand, FDG-PET scans performed early in the course of his disease showed asymmetric hypometabolism, left more than right, involving the medial frontal regions and the lateral temporal lobes to a lesser degree, which also progressed. This pattern of hypometabolism was suggestive of an alternative diagnosis in the FTLD spectrum of disorders rather than AD (Foster et al., 2007). It was not until he developed ALS and he was screened for the *C9ORF72* expansion that the diagnosis of an FTLD-spectrum disorder could be made confidently as he did not meet clinical criteria for behavioral variant frontotemporal dementia or any of the progressive aphasia variants (Neary et al., 1998; Rascovsky et al., 2011; Gorno-Tempini et al, 2012). His ApoE genotype was 3/4, but his PiB PET did not show increased amyloid uptake, making coexisting AD pathology an unlikely explanation for his clinical features. Early amnestic features have been present with FTLD associated with a mutation in *PGRN* in those who carry at least one ApoE4 allele (Rademakers et al., 2007). In a study that compared sporadic FTD with cognitively normal control subjects, ApoE 3/4 genotype appeared to be overrepresented in cases of behavioral variant FTD and PPA (Seripa et al., 2011). ApoE4 carrier status has been associated with disease-specific patterns of grey matter atrophy, and in FTD more pronounced grey matter atrophy in the bilateral medial, dorsolateral, orbital frontal, cingulate cortices, and anterior insula with right predominance has been seen (Agosta et al., 2009). A similar pattern of atrophy was seen in our patient, but with left hemisphere predominance. Based on these studies, the ApoE genotype may play an important role in modifying the phenotype of FTLD including those associated with the *C9ORF72* expansion, and this may be mediated by loss of grey matter volume. Understanding the role of ApoE in FTLD requires further investigation.

Clinicopathologic studies of *C9ORF72* have found an AD phenotype in a minority of cases (Boeve et al., 2012; Hsiung et al., 2012; Mahoney et al., 2012). As these studies screened for the *C9ORF72* mutation in patients with a clinical diagnosis of one of the FTD syndromes, the true frequency of an AD-phenotype is likely underestimated. A recent report found the *C9ORF72* repeat expansion to account for a very small percentage of cases diagnosed with probable AD who also had a family history of late onset-AD (Majounie et al., 2012). Another study that included all patients with a diagnosis of AD, but did not limit their

selection of cases to those with a positive family history, did not identify the *C9ORF72* expansion in their large cohort of patients (Rollinson et al., 2012). In a pathologic study of twenty cases of c9FTD/ALS, there was pathological heterogeneity in the distribution and type of TDP-43 pathology (Murray et al., 2011). In addition, some cases of c9FTD/ALS had evidence of moderate to severe hippocampal sclerosis, all of whom had a clinical diagnosis of AD (Murray et al., 2011). Larger studies are needed to study this possible relationship.

Although the accuracy of the diagnosis of AD made in these studies may be questioned as clinical details are minimally provided, our case report provides the detailed clinical course of a patient who met criteria for amnestic MCI and then probable AD who later developed ALS at which point screening for a mutation in *C9ORF72* demonstrated the pathologic expansion. The clinicians caring for this subject were troubled by the discrepancy between the FDG-PET findings and the clinical phenotype that evolved early in his course. Yet this case also emphasizes the importance of regular follow-up of patients with cognitive impairment evaluated early in their course, particularly when imaging findings “don’t fit,” as clinical syndromes may evolve in an atypical manner which may prompt consideration of alternate diagnoses.

A broad spectrum of intrafamilial and interfamilial phenotypic variability has been associated with the mutation in *C9ORF72* (Boeve et al., 2012; Hsiung et al., 2012; Simon-Sanchez et al., 2012; Snowden et al., 2012). This case demonstrates that an amnestic dementia indistinguishable from AD dementia should be included in the spectrum of phenotypic expression of the *C9ORF72* expansion. An AD-like anterograde amnestic syndrome has been associated with mutations in other FTD associated genes, such as the genes encoding progranulin and microtubule associated protein tau (Kelley et al., 2010; Lindquist et al., 2008; Rademakers et al., 2003). *C9ORF72* expansion should be added to the list of mutations that may present with an AD-like phenotype. This case demonstrates the importance of considering mutations in the FTD-associated genes in cases when a familial disorder is suggested and neuroimaging studies reveal findings which are atypical of AD despite the classic AD phenotype. Future studies are needed to learn what factors determine the clinical presentation in c9FTD/ALS and to what degree the *C9ORF72* expansion length, ApoE genotype, TDP-43 subtype, and hippocampal neuronal loss and gliosis contribute to the clinical heterogeneity.

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ABBREVIATIONS

AD	Alzheimer’s disease
ALS	amyotrophic lateral sclerosis
ApoE	Apolipoprotein E
c9FTD/ALS	frontotemporal dementia and/or amyotrophic lateral sclerosis linked to chromosome 9
C9ORF72	gene encoding the mutation in chromosome 9 open reading frame 72

FDG	18F-fluorodeoxyglucose
FLAIR	fluid attenuated inversion recovery
FTD	frontotemporal degeneration
FTD/ALS	frontotemporal dementia and/or amyotrophic lateral sclerosis
gDNA	genomic DNA
GGGGCC	the hexanucleotide expansion of guanine-guanine-guanine-guanine-cytosine-cytosine
MOANS	Mayo's Older Americans Normative Studies
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
PET	positron emission tomography
PiB	11C-Pittsburgh compound B
STMS	Short Test of Mental Status
TDP-43	TAR DNA binding protein of molecular weight 43 kDa

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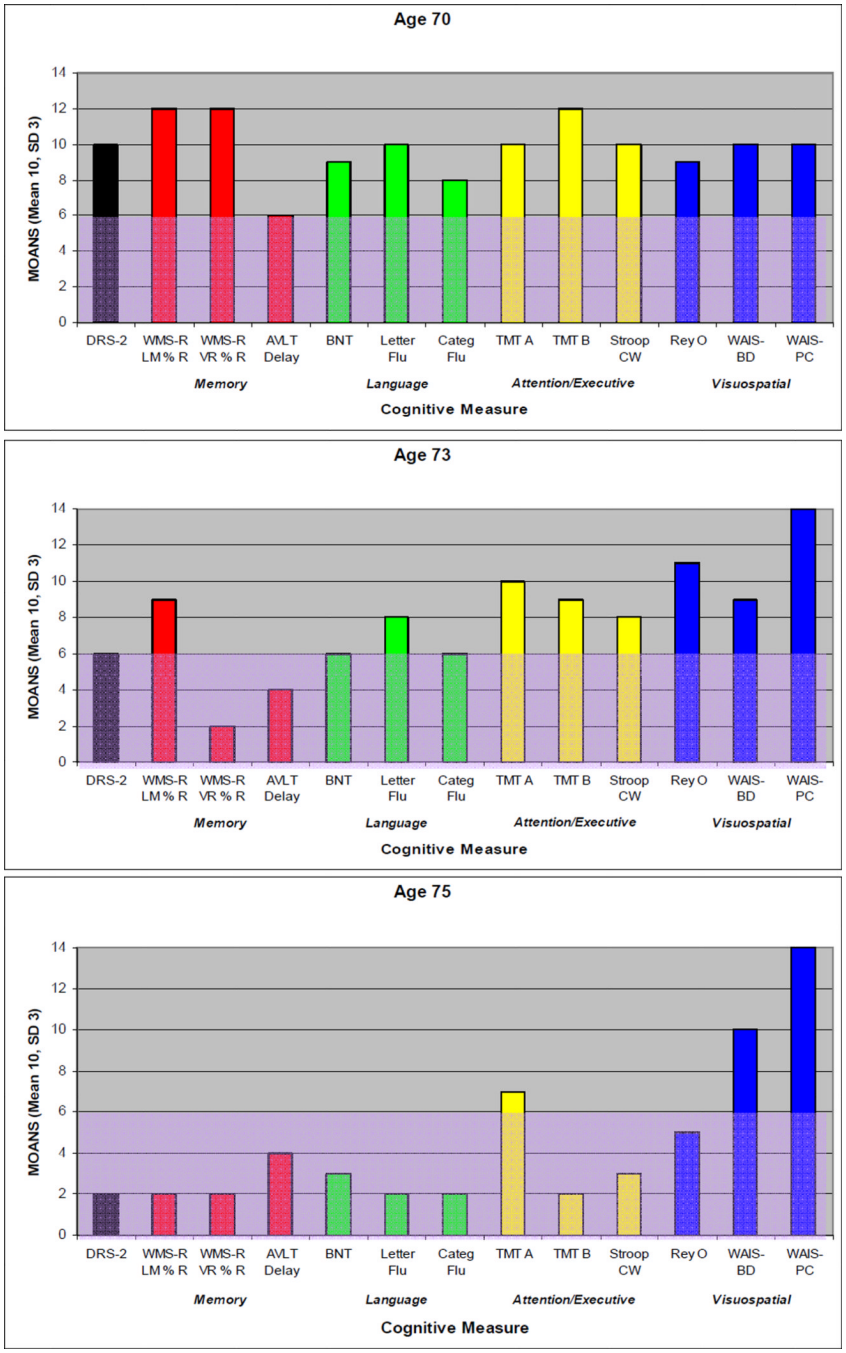

Figure 1. Neuropsychological Profile of Impairment

The subject's performance on serial neuropsychological tests are grouped according to cognitive domain and displayed graphically. Mayo Older American Normative Studies (MOANS) age-adjusted scaled scores are shown in which 10 represents the mean and the standard deviation is 3. Shaded areas represent scores in the abnormal range. Note the isolated weakness in word list memory task early in the course. Performance on all memory tests declined over time, followed by decline in language and executive functioning. Although percent retention of paragraph length information (WMS-R LM % R) at age 73 years appears to be preserved this is somewhat misleading as his immediate retention was significantly impaired. See text for details.

Abbreviations: DRS-2 = Dementia Rating Scale-2; WMS-R LM % R = Wechsler Memory Scale-Revised Logical Memory Percent Retention; WMS-R VR % R = Wechsler Memory Scale-Revised Visual Reproductions Percent Retention; AVLT LT % R = Auditory Verbal Learning Test Long Term Percent Retention; BNT = Boston Naming Test; Letter Flu = Letter Fluency; Categ Flu = Category Fluency; TMT A = Trail Making Test Part A; TMT B = Trail Making Test Part B; Stroop CW = Stroop Color-Word; ReyO = Rey-Osterrieth Complex Figure Test; WAIS-BD = Wechsler Adult Intelligence Scale Block Design; WAIS-PC = Wechsler Adult Intelligence Scale Picture Completion.

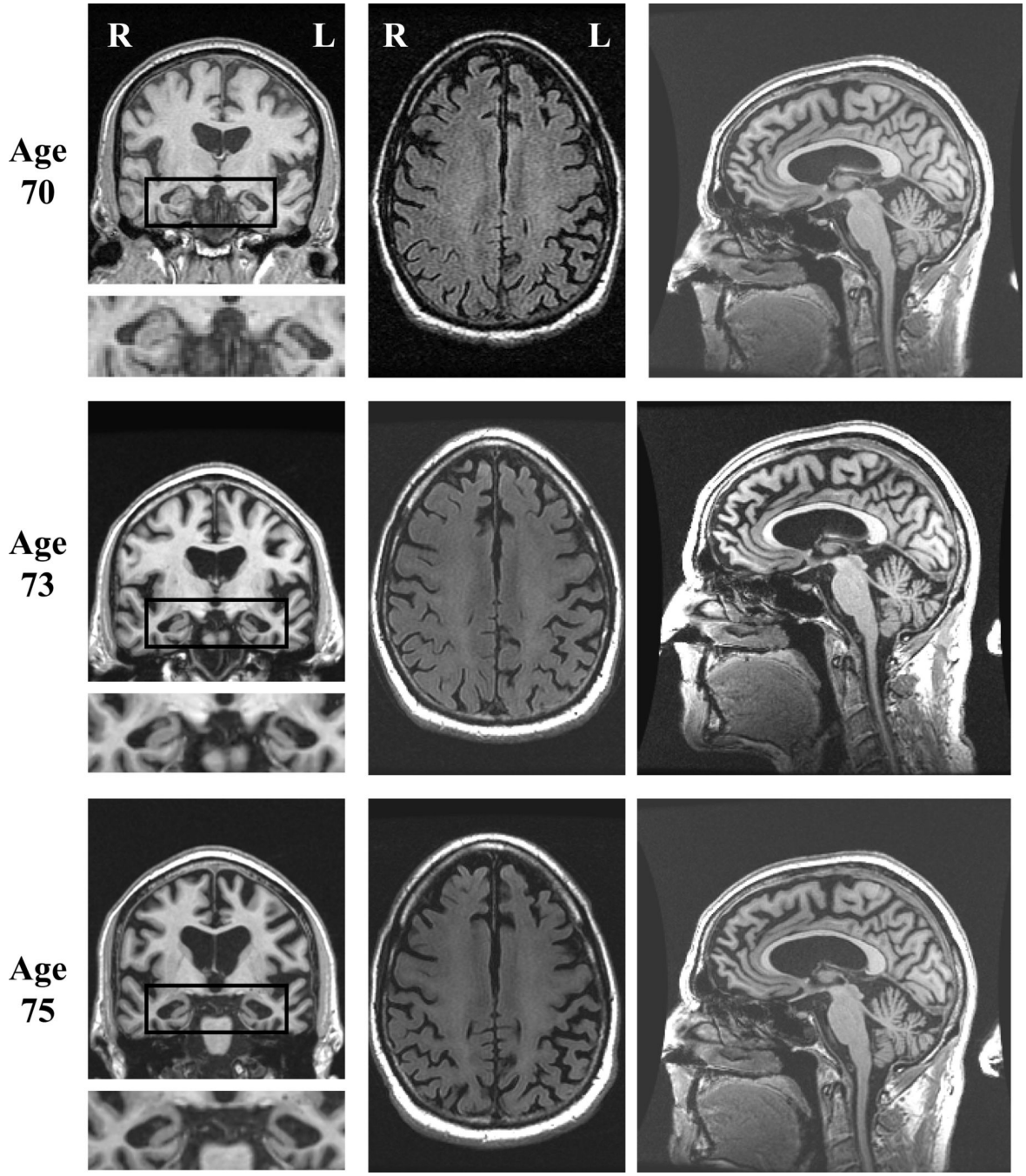

Figure 2. Brain MRI

MRI scans at ages 70, 73 and 75 demonstrating the topography of atrophy. Left column of images involves T1-weighted coronal slices (with mesial temporal lobe structures enlarged and placed below each coronal image), middle column of images involves FLAIR axial slices, and right column of images involves T1-weighted midsagittal slices. Note the left more so than right hippocampal atrophy and medial frontal atrophy that progressed over time. Atrophy in the posterior cerebrum and cerebellum is minimal to absent.

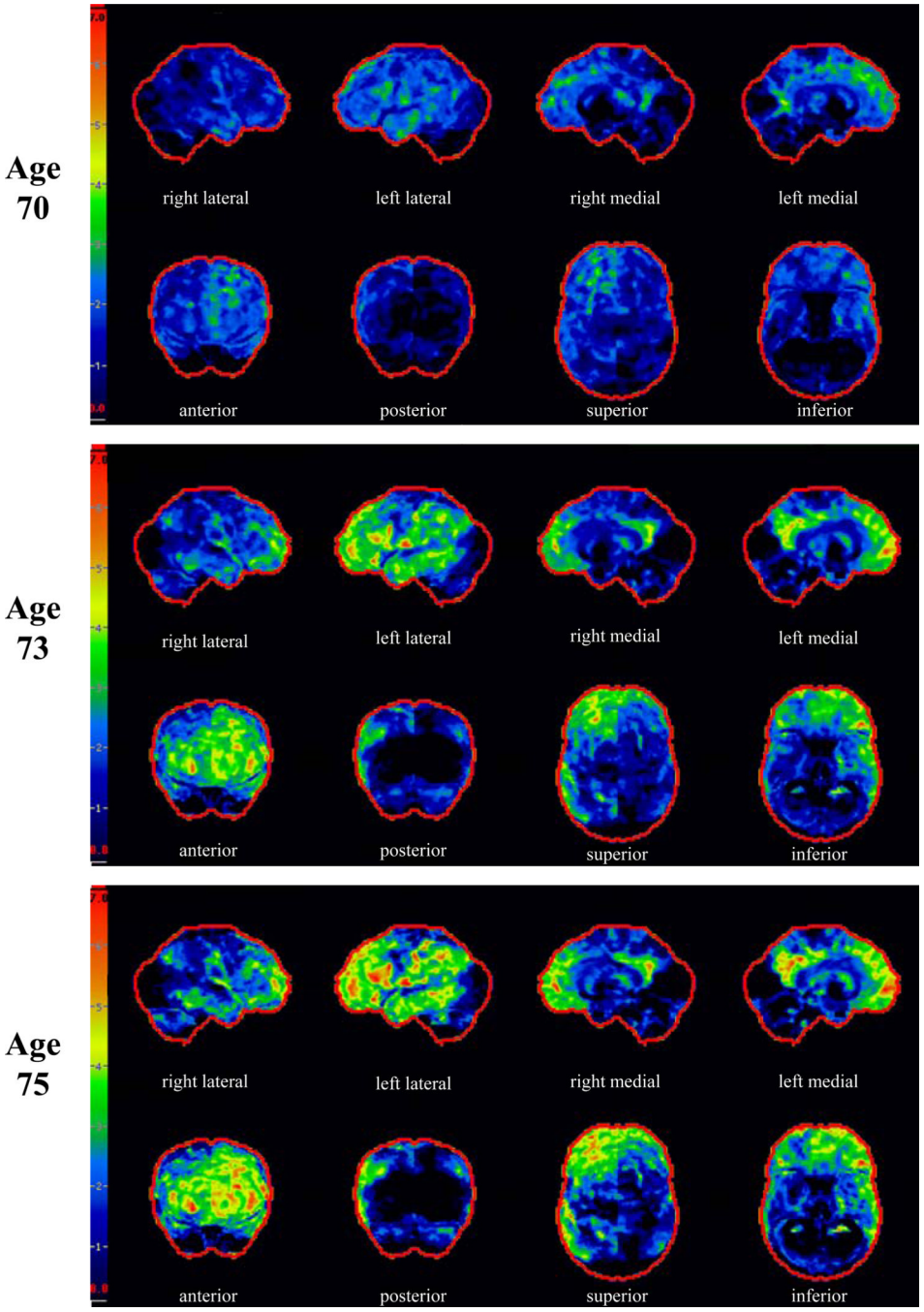

Figure 3. FDG-PET Scan

FDG-PET scans at ages 70, 73 and 75. The images from left to right represent Z-score projection maps. Top rows: right lateral, left lateral, right medial, and left medial. Bottom rows: Anterior, posterior, superior, and inferior where the right side of the brain corresponds to the left side of each image. Note that the initial FDG-PET scan shows mild hypometabolism primarily involving the medial and dorsolateral frontal and lateral temporal lobes, left more so than right. Over time, the scans show progression of fronto-temporal hypometabolism, worse on the left, with involvement of the posterior cingulate cortex. The cerebellum is slightly affected at ages 73 and 75 as well.

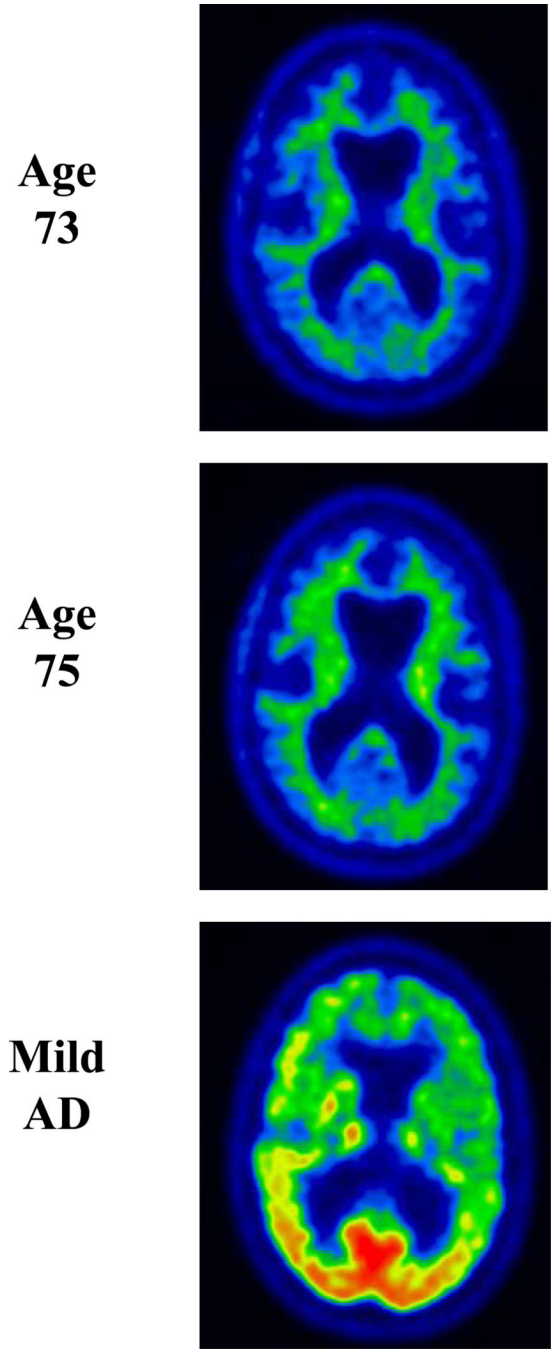

Figure 4. PiB-PET Scan

PiB-PET scan at age 73. Note the absence of significant PiB uptake in the cortex (ratio 1.1) in the proband compared to the AD case example.