CASE 1

A Young Missionary with Problems Quoting the Bible

Pedro Rosa-Neto, Monica Shin, Tharick A. Pascoal, Andrea L. Benedet, Mira Chamoun, Jean-Paul Soucy, Kely Quispialayasocualaya, and Serge Gauthier

1.1 Main Complaint

A 55-year-old priest who retired due to significant cognitive decline.

1.2 Clinical History

The patient came to the consultation accompanied by his wife who provided most of the history. She described her husband as a priest with persuasive and eloquent oratory, which was highly appreciated by their religious community. However, during the last 3 years, there was a clear impoverishment of the patient's ability to preach. During the services, he also started losing the thread of his narratives and getting confused on quoting the bible. His ability of multitasking in the church was impaired. A year later, he clearly acquired difficulties in retaining information regarding conversations as well as a hard time in organizing his day and accomplishing all the commitments of his agenda. Soon after, he started to forget contents of conversations and lost the ability to deal with calculations, and consequently, his financial affairs. He became unable to write. His wife also remarked the patient's inability to focus attention on his tasks. He also had a little insight regarding his present limitations.

Apart from a general reduction in motivation and social isolation, from the neuropsychiatric perspective, there was no history of disinhibition, reduced impulse control, substance-related disorders, stereotypical or ritualistic symptoms, hallucinations, or delusions. He was previously evaluated by a neurologist who diagnosed him with Alzheimer's disease (AD) based on clinical history, MRI, positron emission tomography (PET) using [^{18}F]fluorodeoxyglucose (FDG; Figure 1.1), and results of biomarkers from the cerebrospinal fluid (CSF). He was on 10 mg of donepezil every morning.

1.3 General History

This patient completed grade 12 and worked as a pastor and missionary until 53 years old. He was married once and had two daughters. He and his immediate family lived in many places with precarious urban infrastructure and sanitation including the sub-Saharan Africa. He was exposed to many tropical diseases, many of them not diagnosed. His previous medical history was negative for cardiovascular diseases, high blood pressure, hyperlipidemia, stroke, or diabetes. There was no history of current sleep disorders and cardiovascular, respiratory, urinary, sensory, or motor complaints.

1.4 Family History

His family history was negative for early-onset familial AD (EOFAD) but positive for late-onset familial AD (LOFAD; grandmother) and amyotrophic lateral sclerosis (ALS; father).

1.5 Examination

The physical examination was unremarkable. During the mental status exam, he was cooperative, attentive, and responsive and partially oriented in time and space. The immediate recall was normal. He was not able to correctly tell the months in reverse order. He made few mistakes on the serial 7. The design copy and clock drawing were abnormal. Reading and repetition were normal. He was capable of writing a simple sentence, but his writing skills were impaired. The single word and the sentence comprehension were normal. The content of language was impoverished. Verbal and semantic fluency was reduced. Anterograde memory evoked by a delayed recall showed deficits that were not corrected by cueing. The capacity for abstraction was abnormal. Montreal Cognitive Assessment (MoCA) was 12/30 (visuospatial: –4, serial 7: –3, fluency: –1, abstraction: –2, delay recall: –5, orientation: –3) and the Mini-Mental State Examination (MMSE) was 17/30 (orientation: –3, serial 7: –5, delay recall: –3, design copy: –1). The patient was not capable of executing motor sequences. No significant perseveration, omission, or commissions were observed. The rest of the neurological examination was normal.

1.6 Diagnostic Workup

This patient had normal hematology, biochemistry, and autoimmune profile. He had an EEG without features of Creutzfeldt–Jakob disease. An MRI ruled out brain infarcts or white matter hyperintensities (Fazekas = 0) with a mild progression of hippocampal atrophy (Scheltens = 2–3). MRI diffusion imaging was normal. The FDG PET scan showed reduction on the FDG uptake in the precuneus, temporoparietal cortex, sparing the posterior cingulate. The CSF analysis showed Aβ1–42 of 397 pg/mL, a total tau (t-tau) of 488 pg/mL, a hyperphosphorylated tau (p-tau) of 61 pg/mL, and an ATI index of 0.52. The patient engaged in a research protocol and also had a positive amyloid PET and tau PET showing high uptake in the temporal lobe (mesial, basal, and neocortical), precuneous, inferior parietal cortex, orbitofrontal cortex, and amygdala (Braak stage 5; see Figure 1.1). He had a genetic assessment that was negative for MAP, C09orf72, progranuline, PS1, PS2, and APP mutations. He was an APOE 2/3 carrier.

1.7 Diagnosis

The diagnostic in this case is sporadic young-onset AD with evidence of the AD pathophysiological processes.

1.8 Discussion

The objective of this case report is to highlight the use of appropriated criteria for AD biomarkers in clinical practice. In the present case, our patient had the clinical history of a dementing disease characterized by an insidious onset, a clear-cut history of worsening of cognition and cognitive presentation encompassing language, memory, and executive deficits in the absence of cardinal features or other neurodegenerative conditions. The term "young-onset dementia" designates symptom onset before 65 years of age. The cutoff of 65 years is arbitrary and reflects aspects related to retirement age rather than any biological criteria.

As the prevalence of non-AD pathologies is higher in young-onset dementia, the knowledge of AD pathophysiology might affect the clinical management, in terms of therapeutics with cholinesterase inhibitors. Biomarkers are useful for providing to the caregiver and family members information regarding disease prognosis. In case of a positive family history, the presence of AD pathophysiology could guide genetic investigation.

The same logic is applicable to atypical dementia cases, which are clinically characterized by the predominance of behavioral, visuospatial, or language symptoms instead of the typical amnestic presentation of AD. As in young-onset cases, there is a higher

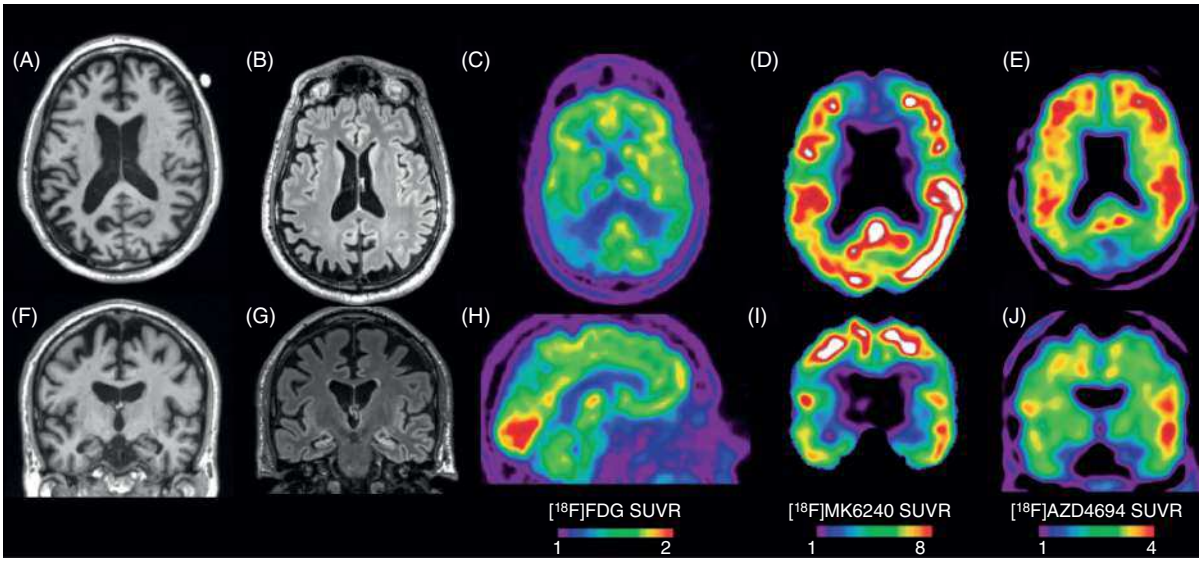

Figure 1.1 Structural MRI shows parietal (A) and hippocampal atrophy (F; Scheltens = 2–3) with no white matter hyperintensities in the FLAIR imaging (B, G; Fazekas = 0). FDG PET shows bilateral hypometabolism in the precuneous (H) and temporoparietal cortex (C; L ≫ R). Tau PET (D, I) shows deposition in limbic, temporal, and frontal cortices, sparing primary motor cortex (Braak stage 5). Amyloid PET (E, J) showed high load in the precuneous, posterior cingulate, inferior parietal, and frontal cortices.

Table 1.1 Biomarkers available in clinical practice

		Amyloid load	Tau load	Neuronal injury	Vascular pathology	Dopamine depletion
Fluid	CSF	Aβ1–42	p-tau181	t-tau	Plasma CSF albumin ratio	
	Blood	Not clinically useful (NCU)	NCU	NCU		
Imaging	MRI	NCU	NCU		FLAIR T2*	
	PET	[^{18}F]Amyvid [^{18}F]NeuraCeq [^{18}F]Vizamyl	None	[^{18}F]FDG		
	SPECT			99mTc hexamethylpropyleneamine oxime [HMPAO] 99mTc-ethylene cysteine [ECD]		DAT scans

Table 1.2 Summary of appropriated use criteria of biomarkers in clinical practice

	MRI	CSF	FDG	Amyloid imaging
Late-onset dementia	Yes	No	No	No
Typical MCI or prodromal AD	Yes	No	No	No
Young-onset dementia	Yes	Yes	Yes	Yes
Atypical features	Yes	Yes	Yes	Yes

prevalence of other pathological substrates rather than AD among patients with atypical dementias.

Although the knowledge of disease processes underlying atypical cases has modest but significant clinical applications, this scenario might change dramatically with the introduction of preventive pharmacological therapies since the identification of the specific neuropathological processes is a sine qua non condition for disease-modifying therapies. Despite significant progresses of biomarker research, there is a limited number of clinically useful biomarkers, which are summarized in Table 1.1. The most acceptable indications for biomarkers in dementia are summarized in Table 1.2.

Biomarkers indicative of cerebrovascular disease or the presence of AD pathophysiology are the most accepted in clinical practice. Regarding their origin, biomarkers can be classified into fluid biomarkers (i.e., blood, saliva, or CSF) or imaging biomarkers (MRI and PET). Biomarkers can be also classified according to their respective pathophysiological processes, for example, biomarkers of amyloid pathology, tau pathology, and neurodegeneration (Table 1.1).

Although guidelines for dementia management suggest that at primary level, a computer tomography would be sufficient for ruling out structural abnormalities in patients with cognitive decline, MRI has better sensitivity to detect tumors, vascular abnormalities, or brain atrophy commonly observed in dementia populations. Structural MRI allow for assessing the ventriculomegaly in patients with clinical symptoms of normal pressure hydrocephalus. T2 fluid-attenuated inverse recovery (FLAIR) allows for assessing white matter hyperintensities associated with microvascular changes as well as the pulvinar sign in Creutzfeldt–Jakob disease. Frequently, the white matter hyperintensities are reported as Fazekas scores or similar metrics. T2* gradient echo images permit the identification of hemosiderin deposits associated with microbleeds. MRI-restricted diffusion sequences are capable of detecting abnormalities associated with Creutzfeldt–Jakob disease. Assessment of structural abnormalities has been frequently utilized in dementia. In fact, reduction of hippocampal volume assessed with MRI has been considered as an important biomarker of neuronal damage in AD for a long time and can be quantified by visual inspection of appropriated acquisitions. The Scheltens score for medial temporal atrophy as well as similar scales has been frequently used to this end.

Fluid biomarkers have the advantage of simultaneously quantifying many pathophysiological aspects associated with dementias. They are easily obtained, and the cost is lower than imaging biomarkers. The major drawback concerns high variability across methods and laboratories. Only Aβ1–42, p-tau, and t-tau have clinical relevance for quantifying brain amyloidosis, tau phosphorylated at threonine 181, and total tau protein, respectively. Possibly, neurofilament light chain will become a clinically useful biomarker in the CSF and plasma.

The Aβ peptide, composed of 42 amino acids (Aβ1–42), is the result of the cleavage of transmembrane amyloid precursor protein by the sequential proteolytic action of beta and gamma secretases. The resultant Aβ1–42 is highly hydrophobic and lipophilic and therefore continuously aggregates as Aβ plaques in the extracellular brain compartment. As such, its concentration in the CSF declines as a function of plaque formation in the brain. Changes in CSF concentrations of Aβ are considered as one of the earliest pathophysiological events in AD, occurring more than 10 years before the dementia onset.

The microtubule-associated protein, tau, is abundantly present within neurons and glia compartment, where they play a role in cytoskeleton stabilization. In AD, neurofibrillary tangles occur as a result of hyperphosphorylation of tau proteins. Current research supports the concept that tau and phosphorylated tau are also released into the extracellular space, resulting in increased CSF tau concentrations in AD. It has been postulated that early forms of hyperphosphorylated tau and Aβ aggregates (oligomers) are the most neurotoxic forms of amyloid and tau; however, the mechanisms by which amyloid and tau leads to neurodegeneration remains elusive.

PET constitutes a powerful technique to identify and quantify metabolic abnormalities and deposits of amyloid and tau aggregates in the brain of patients with AD. Fluorodeoxyglucose ([^{18}F]FDG) is the most diffused PET imaging technique to investigate dementias particularly to differentiate AD from frontotemporal dementias. FDG is currently conceptualized as a marker of neuronal injury. The FDG signature in AD is characterized by hypometabolism in the hippocampus, posterior cingulate, precuneous, inferior parietal, lateral temporal, and mid-prefrontal cortices.

PET amyloid imaging agents such as [^{18}F]-Amyvid, [^{18}F]NeuraCeq, and [^{18}F]Vizamyl have been approved in various countries for clinical use; however, the price and the availability of PET cameras constitute a limitation for their uses. Although the recent introduction of tau imaging agents brings new perspectives to the research in disease pathophysiology and therapeutics, tau imaging agents are not yet indicated for clinical practice. It is possible that these agents could be used to differentiate patients with neurofibrillary tangle predominant dementia from frontotemporal dementia. Presently, "The Imaging Dementia – Evidence for Amyloid Scanning (IDEAS)" study will provide definitive answers regarding the clinical utility of amyloid imaging agents in clinical practice.

Single photon emission computed tomography (SPECT) remains an imaging modality more accessible than PET to investigate patients with atypical dementia. 99mTc hexamethylpropyleneamine oxime (HMPAO) and 99mTc-ethylene cysteine (ECD) have been clinically utilized; however, their contributions on the differential diagnosis of dementia remain debatable. The SPECT DaTscans (Ioflupane I 123 injections, also known as phenyltropane) is a radiopharmaceutical agent that shows depletion of dopaminergic projections to the basal ganglia. Although DaTscan is FDA approved to investigate cases of atypical Parkinson's disease, only few studies systematically assessed its value in the postmortem diagnosis of Lewy body dementia.

In the case presented here, the use of biomarkers provided sufficient evidence corroborating the diagnosis of AD. This information supported the indication of cholinesterase inhibitor and provided to the family relevant information necessary to take decisions regarding the care of this patient at home. The presence of AD pathophysiology also played a role on the decision to investigate genetic factors in this patient.

Specifically, in this case, there was a convergence between the CSF and imaging biomarkers toward the presence of AD pathophysiology. However, borderline or conflicting biomarker results are frequently observed in clinical practice. The choice between fluid and imaging biomarkers depends on the availability of the methodology (PET imaging agents) or clinical circumstances such as the use of anticoagulation (contraindication for lumbar puncture) or pacemaker (contraindication for MRI). A clinical equivalence between imaging and CSF amyloid biomarkers has been shown. In fact, information regarding fluid and

imaging biomarkers were described in this case report because the patient was a participant in a research protocol.

It is important to emphasize that a positive biomarker in the context of patients with atypical dementia should be carefully interpreted considering that frequent comorbidity between pathophysiological processes have been extensively described in various cohorts. Although biomarkers of amyloid and tau pathologies certainly advanced our understanding regarding pathophysiology of dementia, their clinical uses remain limited. These biomarkers will play a crucial role in the context of future interventions targeting specific disease process such as tau and amyloid.

1.9 Take-Home Messages

1. Biomarkers have a modest but significant impact on the management of patients with young-onset or atypical dementia.
2. There is a limited number of biomarkers that are considered useful in clinical practice.
3. Biomarkers play an important role on clinical trials for AD by excluding individuals without AD pathophysiology.

Further Reading

Atri A. Imaging of neurodegenerative cognitive and behavioral disorders: practical considerations for dementia clinical practice, 1 ed: Elsevier B.V., 2016.

Dubois B, Feldnam HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol.* 2014;13:614–629.

Gauthier S, Patterson C, Chertkow H, et al. 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia. *Can J Neurol Sci.* 2012;39:S1–S8.

Jack Jr CR, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7:257–262.

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer & Dementia disease. *Alzheimers Dement.* 2011;7:263–269.

Niemantsverdriet E, Valckx S, Bjerke M, Engelborghs S. Alzheimer's disease CSF biomarkers: clinical indications and rational use. *Acta Neurol Belg* 2017;117:591–602.

Risacher S, Saykin A. Neuroimaging biomarkers of neurodegenerative diseases and dementia. *Semin Neurol.* 2013;33:386–416.