Clinical Utility of Amyloid PET Imaging in the Differential Diagnosis of Atypical Dementias and Its Impact on Caregivers

Mémoire

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Sous la direction de :

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RÉSUMÉ

La maladie d'Alzheimer (MA) se caractérise pathologiquement par l'accumulation de plaques amyloïde dans le cerveau. La tomographie par émission de positrons (TEP) permet d'imager les plaques amyloïde in vivo. Le but de ce projet est d’évaluer le rôle de la TEP amyloïde dans le processus diagnostique de la MA dans des cas de démences atypiques. Le deuxième but de ce projet est de déterminer l'impact de la révélation d’un diagnostic plus certain chez les proches aidants. 28 patients sans diagnostic malgré une investigation exhaustive ont été sélectionnées et imagées avec le traceur amyloïde $^{18}$F-NAV4694 (âge 59,3 ans, é-t. 5,8; MMSE 21.4, é-t 6.0). Les neurologues référents documentaient par la suite tout changement de niveau de certitude, de diagnostic, de traitement et/ou de prise en charge. Les proches aidants consentants ont été rencontrés subséquemment, et un questionnaire avec une échelle de Likert a été utilisé afin de documenter l’impact de l’imagerie leur perception de la maladie. Notre cohorte a été également divisée entre amyloïde positifs (14/28) et négatifs (14/28). Un changement de diagnostic a lieu dans 9/28 cas (32,1% :17.8% ont changé de MA à non-MA, 14,3% de non-MA à MA). Il y avait une augmentation significative (p<0,05) de 44% dans la certitude du neurologue suite à cet examen. Un changement de prise en charge a été obtenu dans 20/28 (71,4%) des cas. Bien que non significatifs statistiquement, un impact favorable sur les proches-aidants a été noté. Cette étude suggère que l’imagerie amyloïde a un rôle bénéfique dans les cas de démences atypiques n’ayant pu être éclucidés avec les techniques d’investigations actuellement recommandées. De plus, le processus a été perçu positivement par les proches aidants, notamment en encourageant du temps de qualité avec leurs personnes chères. Ceci illustre un rôle prometteur des biomarqueurs, qui sont de plus en plus explorés.
ABSTRACT

Recent studies have supported a role for amyloid PET imaging in distinguishing Alzheimer’s disease (AD) pathology from other pathological protein accumulations leading to dementia. We investigated the clinical utility of amyloid PET in the differential diagnosis of atypical dementia cases and its impact on caregivers. Using the amyloid tracer $^{18}$F-NAV4694, we prospectively scanned 28 patients (mean age 59.3 y, s.d. 5.8; mean MMSE 21.4, s.d. 6.0) with an atypical dementia syndrome. Following a comprehensive diagnostic workup (i.e., history taking, neurological examination, blood tests, neuropsychological evaluation, MRI and FDG-PET), no certain diagnosis could be arrived at. Amyloid PET was then conducted and classified as positive or negative. Attending physicians were asked to evaluate whether this result led to a change in diagnosis or altered management. They also reported their degree of confidence in the diagnosis. Caregivers were met after disclosure of amyloid PET results and completed a questionnaire/interview to assess the impact of the scan. Our cohort was evenly divided between positive (14/28) and negative (14/28) $^{18}$F-NAV4694 cases. Amyloid PET resulted in a diagnostic change in 9/28 cases (32.1%; 17.8% changed from AD to non-AD, 14.3% from non-AD to AD). There was a 44% increase in diagnostic confidence. Altered management occurred in 71.4% (20/28) of cases. Knowledge of amyloid status improved caregivers’ outcomes in all domains (anxiety, depression, disease perception, future anticipation, and quality of life). This study suggests a useful additive role for amyloid PET in atypical cases with an unclear diagnosis beyond the extensive workup of a tertiary memory clinic. Amyloid PET increased diagnostic confidence and led to clinically significant alterations in management. The information gained from that test was well received by caregivers and encouraged spending quality time with their loved ones. This study underscores the promising role of biomarkers in the study of dementias.
TABLE DES MATIÈRES

RÉSUMÉ.......................................................................................................................... III
ABSTRACT ......................................................................................................................... IV
TABLE DES MATIÈRES .................................................................................................. V
DÉDICACE ....................................................................................................................... VII
REMERCIEMENTS ........................................................................................................ VIII
AVANT-PROPOS .......................................................................................................... IX
INTRODUCTION ........................................................................................................... 1
  Background Theory ...................................................................................................... 1
  Objectives .................................................................................................................... 3
METHODS ...................................................................................................................... 5
  Patients and diagnostic procedures ........................................................................ 5
  Amyloid PET imaging and interpretation .................................................................. 6
  Assessment of the impact of amyloid PET on the diagnostic process ....................... 7
  Assessment of the impact on caregivers’ life .............................................................. 7
  Statistical analysis ..................................................................................................... 8
RESULTS ...................................................................................................................... 9
  Subjects ...................................................................................................................... 9
  Illustrative case example .......................................................................................... 9
  Amyloid status .......................................................................................................... 10
  Change in diagnosis and diagnostic confidence following amyloid PET .................... 10
  Effect on treatment and patient management ......................................................... 11
  Impact on caregivers ................................................................................................. 12
DISCUSSION .................................................................................................................. 14
  Impact on caregivers ................................................................................................. 15
  Limits ........................................................................................................................... 16
CONCLUSION ............................................................................................................... 18
REFERENCES ............................................................................................................... 20
ANNEXES ..................................................................................................................... 24
TABLES .......................................................................................................................... 24
  Table 1. Patient characteristics ............................................................................... 24
  Table 2. Diagnostic change following amyloid PET scan ........................................... 25
  Table 3. Effect of amyloid scan on treatment and patient management ..................... 26
  Table 4. Most polarized answers on the caregiver questionnaire. ............................... 27
FIGURES ..................................................................................................................... 28
  Figure 1 ...................................................................................................................... 28
Figure 2. Assessment of the impact of amyloid imaging on the diagnostic process and main caregiver

Figure 3. Positive amyloid-PET study using NAV4694

Figure 4. Global Aβ burden with NAV4694 in our 28 participants

Figure 5. Change in diagnostic confidence following amyloid scan

Figure 6. Impact of amyloid imaging on caregivers

LIST OF ABBREVIATIONS

SUPPLEMENTARY MATERIAL

Caregiver Questionnaire

* Les parties en gras sont les sections qui proviennent de manière quasi-intégrale de l’article que nous avons publié dans le « Journal of Alzheimer’s Disease » (voir section Avant-Propos)
À mes parents, ma sœur, mes grands-parents, mes oncles et ma tante.
Pour m’avoir toujours poussé à me dépasser.
REMERCIEMENTS

J’aimerais tout d’abord remercier Dr. Robert Laforce, pour tout l’enseignement qu’il m’a offert et pour m’avoir transmis sa passion pour les sciences neurologiques.

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AVANT-PROPOS

Ce mémoire de maîtrise est fait sur un projet effectué à la Clinique Interdisciplinaire de Mémoire, du Centre Hospitalier Universitaire (CHU) de Québec. Le projet a ultimement été soumis au « Journal of Alzheimer’s Disease » et a été officiellement publié le 18 avril 2016 (PUBMED ID : 27104896).

Une large partie de ce mémoire est basé sur l’article. Plus précisément, les sections MÉTHODS, RESULTS, DISCUSSION sont identiques à celle du mémoire. L’introduction et la conclusion sont différentes, et ont été faites afin de fournir une vision encore plus globale que celle publiée ; publiée dans un journal que lisent déjà des experts du domaine. Afin d’avoir un texte continu, tout le mémoire a été rédigé en anglais, langue originale de l’article.

Les auteurs de l’article sont les suivants : Dr. Robert Laforce (neurologue), Dre Marie-Pierre Fortin (Gériatre), Dr Jean-Mathieu Beauregard (radiologiste nucléiste), Dr. Stéphane Poulin (psychiatre), Dr. François-Alexandre Buteau (radiologiste nucléiste), Dr. Jean Guimond (radiologiste nucléiste), Dr Louis Verret (neurologue), Dre Michèle Houde (gérontopsychiatre), Dr. Rémi W Bouchard (neurologue), Dr Jean-Paul Soucy (radiologiste nucléiste), David Bergeron (étudiant MD-Ph.D) et moi-même. Ces personnes ont tous été nécessaires à la réalisation du projet ; soit en référant des patients, en interprétant des images radiologiques, ou en donnant des conseils qui ont bénéficié à la bonne réalisation du projet.

Dans cet article, j’ai été premier auteur et j’ai entrepris, sous les corrections et la supervision du Dr Laforce, la rédaction de l’article. Les co-auteurs ont tous approuvé l’article avant sa publication et ont permis d’apporter des commentaires qui ont augmenté la qualité du rapport. Évidemment, chaque auteur a accepté à ce qu’une partie majeure de l’article soit inséré dans ce mémoire.

En espérant le tout à votre convenance, je vous invite à vous plonger dans le monde fascinant des démences atypiques par la lecture de ce mémoire.

Réda Bensaïdane
INTRODUCTION

Background Theory

Dementias are a group of neurodegenerative diseases characterized by a significant dysfunction of cognitive function associated with impairment in functionality (McKhann, 2011). Since age is the most important risk factor for dementia (van der Flier, 2005), it is important to acknowledge the increasing prevalence of the disease in today’s ageing society (Lobo, 2000; Fratiglioni, 2000). In fact, over 750 000 Canadians are living with a dementing disorder, and this number is expected to double to 1.4 million by 2031 (Alzheimer Society of Canada, 2012). On a more global scale, over 40 million individuals are living with dementia and this has humongous economic impacts, as over 1% of the global gross domestic product (GDP) is dedicated to health-related costs of such conditions (Prince, 2013). While Alzheimer’s disease (AD) is the most common cause of dementia, accounting for about 40-60% (World Health Organization, 2012), other causes include frontotemporal lobar degeneration (FTLD), vascular dementia, Lewy Body dementia, and Parkinson disease with dementia (Caselli, 2003).

AD was first described by German psychiatrist, Alois Alzheimer, who examined the brain of a cognitively impaired patient that fascinated him (Cipriani, 2011). He showed the histological features that are today associated with AD: amyloid beta senile plaques and neurofibrillary tangles (NFTs). The former is an accumulation of a constitutively generated peptide, named amyloid beta, formed from the cleavage of amyloid precursor protein. The extra and intracellular accumulation of this peptide has been shown to be toxic to neurons. However, several studies have showed, through its complex uptake and breakdown pathways, that amyloid beta is not just a toxic protein but that it may have a physiological role that is yet to be fully understood (Pearson, 2006). NFTs are intracellular microtubule-associated aggregations of hyperphosphorilated tau protein. In addition to being toxic to synaptic function (Spires-Jones, 2014), they are highly correlated in their spatial distribution with the cortical atrophy observed in AD (Braak, 1991) and are correlated in an inversely proportional manner to cognitive performance (Nelson, 2012). Whether these two pathological entities are related or independent is still a matter of debate, and their review exceeds the objectives of this introduction. However, let us underscore an important study, conducted by Jack and colleagues, which had major impacts on the field and that allows us to see the big picture (Jack, 2010; Jack, 2013). Indeed, they suggested a model in which there is a temporal ordering of
AD biomarkers: first appear amyloid plaques, several years before symptom onset; then appear tau protein abnormalities causing neuronal injury. It is not until after brain structure begins to significantly alter, as objectified with magnetic resonance imaging (MRI), that early AD symptoms begin.

Until recently, AD was considered to be a homogenous entity that required distinctive memory impairment, as it was indicated in the 1984 criteria (McKhann, 1984). It is now clear that AD includes several distinct cognitive profiles, ranging from the typical late-onset amnestic AD to more focal syndromes (Galton, 2000; Alladi, 2007; Lam, 2013; Warren, 2012; Bergeron, 2015). Briefly, these include language variants of AD, a condition with different variants called primary progressive aphasia (PPA) (Mesulam, 1982; Gorno-Tempini, 2011), behavioural-executive variant (Taylor, 2008; Ossenkoppele, 2015), and visuospatial variant, also known as posterior cortical atrophy (Crutch, 2012). For this, new criteria have been developed, which not only take in account nonamnestic presentations, but can also incorporate biomarkers (McKhann, 2011). Despite such definitions, AD diagnosis remains challenging especially in younger patients with atypical symptoms or comorbid conditions (Vandenberghe R, 2013). Indeed, trained physicians can diagnose “probable AD” with a sensitivity and specificity of only 71% when compared to pathology, and up to 39% of patients diagnosed with non-AD dementia show postmortem AD-histopathological features (Beach, 2010). In addition, misdiagnosis rates are higher in complex, atypical patients with an uncertain diagnosis, approaching 30% (Grundman, 2013; Wolk, 2012).

In Canada, dementia diagnosis follows the recommendations of 4th Canadian Consensus Conferences on the Diagnosis and Treatment of Dementia (CCCDTD4) (Gauthier, 2012). In these, structural imaging, using MRI, is reserved for young patients (< 60 years) or for those with unexplained symptomatology despite a thorough history, physical examination and basic laboratory tests. Nuclear imaging, using fluorodeoxyglucose (FDG) positron emission tomography (PET), is reserved for patients who have undergone structural brain imaging and who have been evaluated by a dementia specialist but whose diagnosis remains unclear. FDG-PET can show distinctive patterns of hypometabolism, all depending on the different underlying pathologies (Schöll, 2014). It can significantly aid in the differential diagnosis of complex/atypical dementing disorders with accuracies varying between 79 and 93% (Jagust, 2007; Laforce, 2011; Soucy, 2013).

Because of its high sensitivity and specificity for the detection of neuritic plaque densities associated with AD (Klunk, 2004; Clark, 2012; Curtis, 2015; Sabri, 2015), amyloid PET imaging
(or amyloid PET) has recently been shown by several studies to be useful in the differential diagnosis of atypical dementias (Wolk, 2012; Ossenkoppele, 2013; Bensaïdane, 2014; Sanchez-Juan, 2014; Zannas, 2014; Mitsis, 2014). When compared to FDG-PET in discriminating AD (n=62) from FTLD (n=45), it was shown to have higher sensitivity and inter-rater agreement in the diagnosis of FTLD (90%, k=0.96, vs. 78% and k=0.72, p<0.05) (Rabinovici, 2011). In another effort where amyloid accuracy was assessed against pathologically confirmed cases (n=37), negative predictive value was 100%, along with excellent sensitivity and specificity, being 90% and 100% respectively (Rabinovici, 2014). Furthermore, in a major study in which authors recruited 229 patients from 19 clinical sites (Grundman, 2013), amyloid PET was found to change diagnosis in 54.6% of cases, increase diagnostic confidence by 21.6%, and to significantly alter care management. Intended acetylcholinesterase inhibitors (AChEI) or memantine treatment increased by 17.7% with positive scans and decreased by 23.3% with negative scans. Similar findings were reported by another group (Zwan, 2015), which studied 211 early-onset dementia patients (aged ≤70 years) with an MMSE ≥18, and in whom diagnostic confidence was <90% after routine diagnostic work-up. After disclosure of PET results, change in diagnosis occurred in 19% of cases, diagnostic confidence increased from 69% to 88%, and here again PET led to a significant change in patient management. Altogether, this has major implications for a cohort of individuals who are often younger than 65 years old and still active in the workforce. In those patients, an accurate diagnosis can help direct therapy, determine a better care plan, and enable patients to participate in legal and financial planning that will directly affect them.

**Objectives**

Beyond converging evidence for the clinical utility of amyloid imaging in complex cases, two particular issues remain poorly studied. First, definitions of what constitutes a “complex atypical/unclear dementia case” vary among authors. For some, this would be a case where age, symptoms and/or standard diagnostic evaluation do not fit a recognizable pattern while for others it would be a case where diagnosis is confounded by comorbid psychiatric issues and/or polypharmacy. Moreover, the sequence of investigations which leads to amyloid imaging can be very different from one center to another, some having access to hippocampal volumetry and FDG-PET, while others must rely on more limited techniques. Second, to our knowledge, none of these studies have addressed the impact of a more definitive pre-mortem diagnosis on caregivers. Caregivers constitute an essential part of the care of patients with early-onset atypical dementias, yet no authors have explored their emotional reaction to the results from an amyloid imaging study.
Clinicians find it to be beneficial because it helps them arrive at a more definite diagnosis, but how is this viewed from the caregiver perspective? Would they do it again? Does it impact quality of life, and how so?

The main goal of this study was therefore to investigate the clinical utility of amyloid PET imaging in the differential diagnosis of early-onset atypical cases. It is different from previous work in two distinct ways. First, we followed appropriate use criteria for amyloid imaging (Johnson, 2013) which recommend using it only in cases where three prerequisites are met: (1) there is an objectively confirmed cognitive impairment, (2) AD is a possible diagnosis but it remains unconfirmed after a comprehensive assessment, and (3) evidence of increased levels of amyloid in the brain is expected to increase diagnostic certainty and alter management. We defined “comprehensive assessment” as the combination of history taking, neurological examination, basic blood tests, detailed neuropsychological examination, magnetic resonance imaging (MRI) – dementia protocol (see below) – and FDG-PET. The important nuance here is that we recruited highly atypical cases, assuming from previous literature and clinical experience that the sequence of testing described above should have a sensitivity and specificity well above 90% (Jagust, 2007; Laforce, 2010; Rabinovici, 2011). Yet, none of the patients included in this study had a clear diagnosis, and therefore were considered to be highly complex/atypical cases. The second way in which our study differed from previous work is that we specifically addressed impact on caregiver by exposing them to the results of the amyloid PET and measuring a number of key variables using a 21-item Likert scale questionnaire along with a 1-hour interview. Based on recent literature we hypothesized that amyloid imaging would provide important added clinical information in atypical cases with an unclear diagnosis beyond the detailed workup of a tertiary memory clinic, and that the overall process would have a positive impact on caregivers’ life.
METHODS

Patients and diagnostic procedures

Patients were recruited from La Clinique Interdisciplinaire de Mémoire du CHU de Québec (www.cliniquedememoire.ca), one of the oldest tertiary memory clinics in Canada, which relies on the expertise of six dementia specialists (3 behavioral neurologists [RWB, LV, RL], 1 geriatrician [MPF], 1 geriatric psychiatrist [MH], and 1 neuropsychiatrist [SP]). This clinic is visited by an average of 1,000 patients per year, referred from Eastern Quebec, generally for further evaluation after an inconclusive initial assessment.

Compliance with guidelines on human experimentation was enforced at all phases of the study and protocol approval by our local Institutional Review Board was obtained. Each patient and caregiver provided written consent.

Prospective recruitment took place between January 1st 2013 and September 1st 2015. During that period, a total of 3,542 patients were seen at our clinic. All patients were assessed according to the “Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia” (Gauthier, 2012). Following history taking, detailed neurological examination, basic blood tests (complete blood count, ions, TSH, B12, Ca/Mg/Ph, Rapid Plasma Reagin for screening of syphilis), comprehensive neuropsychological evaluation (Trail Making Test A and B, Stroop Color-Word Test, Consonant Trigrams, IVA Continuous Performance Test, Wechsler Adult Intelligence Scale-III, Controlled Oral Word Association Test, Boston Naming Test, Clock Drawing test, Rey Complex Figure [copy], Hooper Visual Organizational Test, Wisconsin Card-Sorting Test, Wechsler Memory Scale-III, California Verbal Learning Test, ABC 15 items, Beck Depression Inventory), and MRI (dementia protocol – includes axial and coronal T2/FLAIR, axial SWI and diffusion, and 3-D T1 sequences with detailed atrophy measures using Scheltens scale and grading of white matter changes using Fazekas scale interpreted by a neuroradiologist with expertise in dementia [MB]), only a limited number of cases remained unclear (n=270). In such a situation, our investigative sequence is to request an FDG-PET scan, which is covered by the Quebec public health insurances. Cerebrospinal fluid (CSF) analyses were not covered at the time of the study and therefore were only very rarely used. Among the 270 FDG-PET scans that were requested during that period (and interpreted by nuclear medicine specialists with expertise in dementia [FAB, JMB, JPS, JG]), 30 cases corresponded to our inclusion and exclusion criteria, which are: inclusion
criteria: 1) ≤ 65 years old, 2) an atypical/unclear case with no specific diagnosis despite history taking, neurological examination, neuropsychological assessment, MRI, and FDG-PET; exclusion criteria: 1) typical dementia syndrome (see Figure 1), and 2) absence of FDG-PET. Of note, one patient was cancelled twice because of unavailability of the tracer and decided to withdraw. Another patient was deemed typical after blinded review of the FDG-PET by one of the co-authors (JPS). Consequently, a total of 28 patients underwent an amyloid scan.

Amyloid PET imaging and interpretation

Patients underwent amyloid imaging using $^{18}$F-NAV4694 (NAV4694; Navidea Biopharmaceuticals, Dublin, OH, USA). Authorization was obtained from Health Canada to use this non-approved tracer in a research protocol. This fluorine-based ligand was shown to be equivalent to the reference standard carbon-11 ($^{11}$C)-labeled Pittsburgh Compound B (PiB), but with a 110 minutes half-life (Jereus, 2010; Cselényi, 2012; Rowe, 2013), it has the added advantage of much more flexible scanning scheduling. NAV4694 was radiolabeled at the PET Unit, McConnell Brain Imaging Centre (McGill University, Montreal [QC], Canada). Briefly, it was produced by radiofluorination of the corresponding N-Boc–protected nitro precursor, followed by acidic deprotection with hydrochloric acid. Average radiochemical yield is 16% after a synthesis time of 65 min, with radiochemical purity greater than 98% and an average specific activity of 555 ± 230 GBq/μmol.

PET scans were acquired in 3-D mode on a Siemens Biograph 6 PET/CT scanner (Siemens Medical Solutions, Erlangen, Germany) at our PET unit, CHU de Québec, Québec City (QC), Canada. After the intravenous injection of 200 to 370 MBq of NAV4694, an uptake period of 40 minutes was observed. A low-dose, non-contrast CT of the head was acquired for attenuation correction and anatomical correlation, followed by a 30 minutes dynamic PET acquisition. Three 10-minute frames were reconstructed using 3-D ordered subset expectation maximization with a point-spread function (Siemens HD-PET) with a 256 x 256 matrix. Analysis was performed with automated Brass software (Hermes Medical Solutions, Stockholm, Sweden), which co-register the PET images to an atlas and segment the brain in standard regions of interest (ROIs) to generate standardized uptake
value ratios (SUVRs) referenced to the cerebellar cortex, a region relatively unaffected by dense Aβ plaques in sporadic AD, for NAV4694. Global Aβ burden was expressed as the average SUVR of the mean of the following cortical ROIs: frontal (consisting of dorsolateral prefrontal, ventrolateral prefrontal, and orbitofrontal regions), superior parietal, lateral temporal, lateral occipital, and anterior/posterior cingulate and precuneus. As in previous studies using NAV4694 (Jereus, 2010; Cselenyi, 2012; Rowe, 2013), SUVR cutoff was set at 1.50. In addition to quantitative interpretation using SUVRs, images were qualitatively interpreted by two highly trained nuclear medicine physicians (JPS, JMB). These clinicians were blinded to clinical information and performed their readings independently. In the end, each amyloid PET scan was judged as either positive or negative based on qualitative and quantitative reads.

Assessment of the impact of amyloid PET on the diagnostic process

Amyloid PET was presented to both the patient and the caregiver as an additional test that was part of a research protocol and that could help clarify the diagnosis. Following each amyloid PET, the principal investigator (RL) of the study met with the patient and family to disclose amyloid status (either positive or negative) and further inquire about any side effects or discomfort associated with the process. The amyloid PET image was shown to each case. Amyloid status was then disclosed to the patient’s treating dementia expert who scheduled another appointment to discuss the most recent diagnostic opinion. Each physician filled a questionnaire detailing pre-scan and post-scan diagnoses with their corresponding confidence levels. Confidence level was assessed on a scale of 5 where 1 = very weak, 2 = weak, 3 = average, 4 = high, and 5 = very high. Treatment changes and altered management following scan were also documented in this questionnaire. Physicians were asked to explain in what way the amyloid scan had contributed to the overall assessment process.

Assessment of the impact on caregivers’ life

All participating caregivers were very close to the patients and aware of each step of the diagnostic process. They were present at each appointment with their treating physician, and for this reason had access to the same information as the patient prior to the amyloid scan. Amyloid PET was presented as an additional test that could help clarify the diagnosis (the sequence of events that led to disclosure of amyloid status is detailed in the section above).

Consenting caregivers were met at least 30 days after disclosure of amyloid status by their treating dementia expert. A 21-item Likert scale questionnaire along with a 1-hour interview designed to assess the impact of the amyloid scan results was then administered (see Supplementary Material –
Caregiver Questionnaire). More specifically, the purpose of this interview was to go over each question individually, and, by taking in account the caregivers’ psychosocial contexts, try to understand the reasons that motivated his or her answers. This was done in order to try and correct for the different interpretations that may have the caregivers of the different statements.

The questionnaire and interview covered the following domains: anxiety, depression, disease perception, future anticipation, and quality of life. In fact, 4 questions assessed “Anxiety” (e.g. I am more afraid of developing a neurodegenerative disease since the diagnosis has become more certain), 4 assessed “Depression” (e.g. I sleep better since my loved one’s condition is known), 6 assessed “Disease perception” (e.g. The family atmosphere is better since the precise diagnosis of my loved one has become clearer), 4 assessed “Future anticipation” (e.g. Better assessment has allowed us to better plan for the future) and 3 assessed general “Quality of life” (e.g. I appreciate more every moment with my loved one since clarification of the diagnosis). In some cases, more than one caregiver was interviewed (e.g. both parents, or spouse and daughter). Figure 2 recapitulates the sequence of events that occurred following amyloid PET scan.

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Insert Figure 2 here
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**Statistical analysis**

Independent sample t-tests were used to assess group differences. Paired-sample t-tests were used to assess change in diagnostic certainty before and after amyloid PET scan. Pearson $\chi^2$ tests were used to assess differences in patient management plan.
RESULTS

Subjects

Patient characteristics are shown in Table 1. Treating physicians’ hypotheses (AD vs. non-AD) of the 28 participants with complex/ataypical dementias are listed in Table 1. There were a total of 16 AD diagnoses; 8 amnestic AD, 3 behavioral/dysexecutive AD, 3 language variant AD/logopenic variant of primary progressive aphasia, 1 visual variant AD/posterior cortical atrophy and 1 corticobasal syndrome. A total of 12 cases were judged non-AD; 3 behavioral variant frontotemporal dementia, 2 corticobasal degeneration, 1 non-fluent/agrammatic variant primary progressive aphasia, and 6 of other causes (psychiatric condition, intellectual deficiency, etc.). Diagnostic confidence of attending physicians in their hypotheses before amyloid scanning (scale 1-5) is also listed in Table 1.

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Insert Table 1 here
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Illustrative case example

A 65-year-old woman was referred to our Memory Clinic for complaints of progressive memory difficulties. No changes in behavior were noted. Memory problems were combined with increasing functional difficulties. Neurological examination documented the absence of eye movement irregularities as well as of extrapyramidal signs. Initial blood tests were non-contributory. Neuropsychological evaluation showed spared verbal episodic memory but impaired visual memory along with visuospatial deficits. There were impairments in lexical verbal fluency as well. MRI did not show any specific pattern of focal atrophy or significant vascular burden. Given the atypical nature of her deficits, her young age and the functional impact of her symptoms, FDG-PET was ordered. This test showed diffuse fronto-parieto-temporal hypometabolism with a frontal predominance and sparing of the posterior portions of the cingulate gyri, suggestive of frontotemporal lobar degeneration (FTLD). The treating behavioral neurologist (LV) explained to the family that there was a discrepancy between the clinical presentation and the results of the investigation, and suggested further imaging. Amyloid imaging revealed high deposition of amyloid
plaques with an average SUVR of 2.15 (figure 3) with a positive read from two different nuclear medicine specialists blinded to clinical data. A diagnosis of Alzheimer’s disease was announced with greater confidence. The full one-hour interview with the primary caregiver revealed that family members were glad to be finally clear on diagnosis, as they had been seeking answers for over a year at that time.

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Insert Figure 3 here
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**Amyloid status**

Based on qualitative (visual interpretation) and quantitative (SUVR > 1.5 means positive) blinded reads by 2 independent expert nuclear medicine specialists, half of our patients (n=14) had a positive amyloid scan (see Figure 4). No significant differences were found between amyloid-positive and amyloid-negative groups in terms of age, gender, education, disease duration and MMSE scores. The average SUVRs were 2.12 (± 0.19 ; 1.80 – 2.51) and 0.97 (± 0.85; 0.84 – 1.19) in the amyloid-positive and amyloid-negative groups, respectively. Therefore, no overlap was found, and the difference between the highest SUVR value of the negative group and the lowest SUVR value of the positive group was quite large. The concordance rate between our two nuclear medicine specialists was 100%. Of interest, 3 patients (2 amyloid-positive and 1 amyloid-negative) also had lumbar punctures with analysis of Aβ1-42, total tau and p-tau, and their CSF levels were consistent with amyloid PET scan results.

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**Change in diagnosis and diagnostic confidence following amyloid PET**

Table 2 indicates the changes in diagnosis following the amyloid scan. Overall, diagnostic changes occurred in 9 (32.1%) cases and were found slightly more often in the direction from AD to non-AD (17.8%) then the opposite (14.3%). Diagnostic change occurred in 28.6% and 35.7% in amyloid positive and amyloid negative groups respectively. There were no statistical differences between
these 2 groups in terms of diagnostic change.

Amyloid imaging generated a significant increase (p<0.05) of 44% in diagnostic confidence from pre- to post-amyloid scanning (see Figure 5). This did not significantly differ between the amyloid-positive and amyloid-negative groups (p=0.169).

Effect on treatment and patient management

A total of 11/28 patients saw their medication changed (initiation of an AChEI, change in dosage or molecule, or discontinuation of the treatment) following amyloid PET (see Table 3). All amyloid-positive patients who saw their diagnosis changed also had a change in medication (initiation or modification, but no discontinuation). Amongst the patients who were amyloid-negative and saw their diagnosis changed from AD to non-AD, 3 did not have medication change because they were not previously on an AChEI. The other two patients were previously on such medication, which was discontinued.

Changes in patient management (or care plan) are also shown in Table 3. This excludes medication changes and includes, but is not limited to, registration to a vaccine trial, lumbar puncture for CSF analysis, referral to a speech therapist and/or referral to a psychologist. The amyloid-negative group showed the most care plan changes (57% vs. 21%; p=0.120 by chi-square test). When there was a negative amyloid scan and no diagnostic change, the care plan changed most often (67%). This proportion approached significance when compared to the amyloid-positive group without change in diagnosis (67% vs. 20%; p=0.07 by 2-sided chi-square test).
Impact on caregivers

A total of 23 caregivers were met. All participating caregivers completed the 21-item Likert scale questionnaire as well as the 1-hour interview. Figure 6 illustrates the impact of amyloid imaging on various variables. There were no statistically significant differences between the amyloid-positive and amyloid-negative groups.

An in-depth and purely qualitative exploration of the most polarized answers from the questionnaire revealed interesting characteristics (see Table 4). Most importantly, and not surprisingly, different questions were understood differently by caregivers depending on their standpoint and life situation (for example, in one instance the caregiver was the 82-year-old father of the patient).

The 1-hour interview with caregivers provided a different perspective on things. Caregivers expressed in their own words the impact of amyloid PET results on their overall appreciation of life. First and foremost, caregivers reported a better understanding of their loved one’s condition. They consistently described their state of mind prior to amyloid imaging, all of them reporting many periods of confusion and frustration towards unexplainable behavioral and cognitive changes seen in their loved ones. They expressed frustration towards the difficulty physicians showed in providing appropriate answers to their questions. Amyloid imaging was correctly perceived as the final test that was meant to indicate if Alzheimer’s disease was the causal pathology. Generally, after amyloid imaging, caregivers felt more confident as to the next steps ahead. For example, in question #10 of the questionnaire “I appreciate every instant with my beloved one even more since we know the precise diagnosis”, some caregivers described how they stopped working in order to spend more time with their loved one now that the diagnosis was clear and that the reserved
prognosis of the disease was clarified. Examples of future plans were given as well (buying plane tickets for vacations and making sure that wills and testaments were completed). For such reasons, despite remaining saddened by the incurable nature of neurodegenerative diseases, they all saw themselves as having a better acceptance of the disease.
DISCUSSION

This study investigated the clinical utility of amyloid PET imaging in the differential diagnosis of early-onset atypical cases of dementia. It demarcated itself from previous work in two ways. First, by defining ‘uncertainty after a comprehensive assessment’ (see AUC criteria (Johnson, 2013)) as an “uncertain diagnosis after history taking, neurological examination, blood tests, comprehensive neuropsychological examination, MRI – dementia protocol and FDG-PET”, therefore recruiting the most challenging atypical cases. Second, it addressed impact on caregivers using a 21-item Likert scale questionnaire and a 1-hour interview specifically designed for this study. Amyloid PET was associated with a diagnostic change in 9/28 cases (32.1%). There was a 44% increase in diagnostic confidence. Altered management occurred in 71.4% (20/28) of cases. Knowledge of amyloid status improved caregivers’ outcomes in all domains (anxiety, depression, disease perception, future anticipation, and quality of life). Altogether, our results suggested a useful and additive role for amyloid PET in atypical cases with an unclear diagnosis beyond the detailed workup of a tertiary memory clinic. Amyloid PET increased diagnostic confidence and generated clinically significant alterations in management. The overall process was positive for caregivers notably by making it easier to spend quality time with their loved ones.

Usefulness of amyloid imaging in cases where diagnostic confidence is low has been reported in several studies (Grundman, 2010; Ossenkoppele, 2013; Zannas, 2013; Wolk, 2013), and our results are consistent with those findings. Indeed, a total of 32.1% of the subjects had a diagnosis change following amyloid PET scan. Despite this, amyloid imaging did not replace clinical judgment. In some instances, ACheI treatment was maintained in the presence of a negative amyloid scan because of a lack of negative impact on the patient. Most often, however, acetylcholinesterase treatment was initiated in patients thought to have AD pathology and stopped in FTLD cases. This is relevant because FTLD patients were shown to have worsening of their symptoms following acetylcholinesterase treatment (Mendez, 2007; Boxer, 2013; Arciniegas, 2013).

Clinically significant alterations in management have been defined in various ways by authors. The most obvious problem regarding this claim is what is significant exactly? In all cases, the pre-test diagnosis was an incurable dementia and neurodegenerative disease, as was the post-test diagnosis. Does a change in cholinesterase inhibitor use really indicate a significant alteration in therapy?
Nonetheless, it is important to try and quantify this concept. The definition of altered management used in our study excluded medication changes and included registration to a vaccine trial, lumbar puncture for CSF analysis, referral to a speech therapist and/or referral to a psychologist, as well as other similar interventions. Although it failed to reach statistical significance, we found a change in careplan (or management) in up to 11/28 (39.2%) of our cohort.

Interestingly, the group that had the most careplan/management changes (excluding medication change according to the definition used in the current study) was the group with a negative amyloid PET and no change in diagnosis. In that group, 2 patients were referred to speech-therapy, 1 for psychotherapy, 1 was encouraged to focus on a number of compensatory strategies, and 2 had lumbar puncture for further investigations. This opposes our amyloid positive group without diagnosis change where out of all patients in this group, the only management change included 2 patients referred for vaccine protocol trials. The most likely explanation for this could be that non-AD entities appear to have more components where clinicians can intervene. For example, non-AD cases can benefit from speech therapy, when appropriate. Our pseudo-dementia case could benefit from psychotherapy but no amyloid positive AD got such referral because of lack of expected benefit from psychotherapy. Another explanation could be that once clinicians eliminate the possibility of prescribing acetylcholinesterase inhibitors; they take an extra step in attempting to help their patients. This could explain why 2 patients had lumbar puncture for more advanced analyses.

There was a 100% inter-rater agreement in the readings of amyloid scans in this study. The experts’ interpretations also matched with quantitative (SUVR) results 100% of the time. This has also been reported previously in the literature. For instance, a major multicenter study identified an overall agreement of 93% between 3 independent readers (Barthel, 2011). The higher agreement in our study may reflect the quality of the ligand, as NAV4694 has less white matter binding than other fluorine-based compounds commonly used (Rowe, 2013). Consequently, images are easier to interpret. SUVRs in our study followed a bimodal distribution with no borderline cases approaching recommended threshold. This certainly made the cases easier for the nuclear medicine physicians to interpret.

**Impact on caregivers**

Caregivers constitute an essential part of the care of patients with early-onset atypical dementias, yet no authors have explored their emotional reaction to the results of an amyloid scan in the
context of a tertiary memory clinic investigation. Clinicians believe it is beneficial because it helps them establish a diagnosis but we wished to explore how this is viewed from the caregiver’s perspective. In a study where participants were asked whether they wanted or not to know if they had AD pathology, older adults with subjective memory complaints had two kinds of reactions: there were those who did not want to know, who stated it would create anxiety, whereas those who wanted to know reported several potential benefits (Elson, 2006). Amongst those were developing plans for the future, considering early treatment, facilitating psychological adjustments, enabling family members to understand behaviours, and the desire to be kept informed. Another study suggests that disclosure of AD status could help patients deal with anxiety (Mormont, 2014). Overall, these results suggest a benefit in the disclosure of a correct diagnosis. However, no study had investigated the impact of a more confident AD diagnosis on caregivers, particularly when their loved ones present with an atypical syndrome. Since no disease-modifying treatments are available yet for AD, we believe that it is of the uttermost importance to assess the impact of a correct diagnosis on caregivers. Hence, the second objective of this study was to see the impact on caregivers of disclosure of diagnosis following amyloid imaging.

Overall, we found a clear qualitative improvement in the variables assessed namely anxiety, depression, disease perception, anticipation of the future, and quality of life following disclosure of the amyloid scan findings. However, none of these trends reached statistical significance. This could be biased by the fact that, at the end of the day, one can be informed with greater confidence about a diagnosis but the fact remains that a young individual is faced with a progressive and irreversible neurodegenerative disease. This can never be a source of joy. Following amyloid PET, caregivers appreciated more each moment with their loved ones and were better able to make plans for the future, as shown in Table 4. Most reported they did not regret going through all of the investigations. Furthermore, there were no differences between amyloid-positive and amyloid-negative groups with respect to caregiver impact. Nevertheless, those with a negative scan often had a more nebulous understanding of the disease and of its natural history.

**Limits**

This study has limitations. First, it was conducted on a small sample of 28 patients without pathological confirmation. However, this sample was carefully selected by experienced experts in the field of behavioral neurology. It is also unique in that contrary to previous reports, it addressed the value of amyloid imaging in the most atypicals among atypicals. Second, the questionnaire used
to assess impact on caregivers was not validated and only reflected the general feelings of the caregivers. A difficulty that was encountered with our questionnaire is variable interpretations of the same statement. Caregivers sometimes showed problems relating to how they actually felt at the moment when the diagnosis was announced. In other words, caregivers tended sometimes to answer the questions relating to how they lived through their loved one’s disease in general, instead of concentrating on what happened at the point in time where they obtained a more accurate diagnosis. A possible way to prevent this type of confusion would have been to perform the questionnaire before the amyloid PET, and to re-perform it after the amyloid PET. Third, those with a negative scan often had a more nebulous understanding of the disease and of its natural history. Fourth, this study was conducted in young dementia patients in whom the prevalence of “age-related” amyloid pathology is less likely to be present compared to older patients in whom (mixed) amyloid pathologies are more frequently found. Finally, all were recruited from a tertiary memory clinic, which may not reflect the impact of amyloid PET in a general, often older aged population. However, it supports the usefulness of appropriate use criteria for amyloid PET imaging, which describe a potential added value in patients with early-onset dementia with unclear clinical presentations (Johnson, 2013; Dubois, 2015; Laforce, 2016)
CONCLUSION

Our findings support an additive value to amyloid PET imaging in the context of a comprehensive tertiary memory clinic work-up in patients suspected of early-onset atypical dementia. This has an impact on clinical diagnosis, it increases overall diagnostic confidence and alters patient management plan. In these patients, an accurate diagnosis can help direct therapy (i.e. avoid unnecessary or undesired ACheI or memantine prescriptions), determine a better care plan (which considers patient safety and minimizes the risk of preventable complications), and enable patients to participate in legal and financial planning. The information gained from this technique is well received by caregivers and encouraged spending quality time with their loved ones.

Since our main inclusion criteria was that our patients did not have a clear diagnosis despite a thorough investigation, our results provide additional evidence for the recommendations put forward in the appropriate use criteria for amyloid PET in clinical practice (Johnson, 2013; Laforce, 2016). As previously mentioned in the introduction, these criteria are: (1) there is an objectively confirmed cognitive impairment, (2) AD is a possible diagnosis but it remains unconfirmed after a comprehensive assessment, and (3) evidence of increased levels of amyloid in the brain is expected to increase diagnostic certainty and alter management. Such evidence-based criteria are important because amyloid imaging can be harmful if not used properly. A recent cross-sectional study which measured amyloidosis and neurodegeneration in 985 cognitively normal participants aged 50-89 years old, it was demonstrated that amyloid inevitably accumulates with age. Yet, many people retain normal cognitive function despite this substantial amyloid burden (Jack, 2014). Despite some evidence suggesting that participants who are APOE e4 positive (an allele known to be a risk factor for AD) and have high amyloid beta burden on amyloid PET show the highest cognitive decline on MMSE, these are merely risk factors for developing the disease (Mormino, 2014). Thus, inappropriate amyloid imaging can lead to disclosure of results that can create distress and be harmful.

Our study can be continued as part of doctoral studies and could investigate the overall use of biomarkers in atypical dementias. Recent advances in neurosciences have led to a better understanding of neurodegenerative diseases’ pathophysiological processes, and have resulted in the incorporation of biomarker evidence as part of some disorders’ criteria (see updated McKhann criteria for AD for example). However, the combined use of these biomarkers in a large (>100)
cohort of atypical dementias has never been studied. Such biomarkers not only include amyloid imaging, but also CSF analyses, and tau imaging, whose clinical role is still ambiguous. Subgroups analyses can then be performed to compare each biomarker and better define their roles and limitations within a complete clinical setting that assesses every variable, from the diagnosis to the management of patients.

Furthermore, much is expected from the recently launched Imaging Dementia – Evidence for Amyloid Scanning (IDEAS) Study, a $100M open-label longitudinal cohort effort on approximately 18,500 US Medicare beneficiaries. In this venture, diagnostically uncertain cases of mild cognitive impairment and atypical dementia will be referred by physicians of all specialities, including those in primary care, to be scanned to determine whether knowledge of amyloid status leads to significant changes in patient management and if this translates into improved medical outcomes.

In addition to enhancing the diagnostic process of atypical dementing syndromes and allowing earlier treatment, we can expect amyloid imaging to be a major contributor to future advancements and discoveries in the field of Alzheimer disease and the natural evolution of dementias. For example, amyloid imaging has served as a secondary outcome measure in Alzheimer disease clinical trials with disease-modifying agents such as the anti-amyloid monoclonal antibodies bapineuzemab and solanezumab. Recently, a study has shown brain amyloid reduction and slowing of cognitive decline after one year of treatment with aducanumab, a human IgG1 monoclonal antibody against a conformational epitope found on Aβ (Keller, 2015). Hence, confirming the amyloid-positive status of patients in clinical trials (e.g., the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4) Study) will be of the uttermost importance for validation of therapies.
REFERENCES


Amyloid versus FDG PET in the differential diagnosis of AD and FTLD. Neurology 77, 2034-2042


### Table 1. Patient characteristics.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Age (mean ± SD; range)</strong></td>
<td>59.3 ± 5.8; 48 – 68</td>
</tr>
<tr>
<td><strong>Gender (% female)</strong></td>
<td>13 (46.4%)</td>
</tr>
<tr>
<td><strong>Education (mean ± SD; range)</strong></td>
<td>13.3 ± 3.4; 8 – 23</td>
</tr>
<tr>
<td><strong>Disease duration (mean ± SD; range)</strong></td>
<td>3.0 ± 1.5; 1 – 6</td>
</tr>
<tr>
<td><strong>MMSE (mean ± SD; range)</strong></td>
<td>21.4 ± 6.0; 9 – 29</td>
</tr>
<tr>
<td><strong>CDR (mean ± SD)</strong></td>
<td>1.1 ± 0.6</td>
</tr>
<tr>
<td><strong>CDR-SB (mean ± SD)</strong></td>
<td>5.9 ± 4.2</td>
</tr>
<tr>
<td><strong>Pre-amyloid diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>AD*</td>
<td>16 (57.1%)</td>
</tr>
<tr>
<td>Non-AD‡</td>
<td>12 (42.9%)</td>
</tr>
<tr>
<td><strong>Confidence level in pre-amyloid diagnosis§ (mean ± SD)</strong></td>
<td>3 ± 0.90</td>
</tr>
</tbody>
</table>

**Abbreviations:** AD: Alzheimer’s disease; CDR: Clinical dementia rating; CDR-SB: Clinical dementia rating – Sum of boxes; MMSE: Mini-Mental State Examination; SD: Standard deviation.

*AD means: 8 amnestic AD, 3 behavioral/dysexecutive AD, 3 language variant AD (or logopenic variant of primary progressive aphasia), 1 visual variant AD (or posterior cortical atrophy) and 1 corticobasal syndrome.

‡Non-AD means: 3 behavioral variant frontotemporal dementia, 2 corticobasal degeneration, 1 non-fluent/agrammatic variant primary progressive aphasia, and 6 of other causes (psychiatric condition, intellectual deficiency, etc.).

§Confidence level was assessed on a scale of 1-5.
Table 2. Diagnostic change following amyloid PET scan.

<table>
<thead>
<tr>
<th></th>
<th>No change</th>
<th>Diagnostic change from AD to non-AD</th>
<th>Diagnostic change from non-AD to AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=28)</td>
<td>19 (67.9%)</td>
<td>5 (17.8%)</td>
<td>4 (14.3%)</td>
</tr>
<tr>
<td>Amyloid-positive patients (n=14)</td>
<td>10 (71.4%)</td>
<td>0 (0%)</td>
<td>4 (28.6%)</td>
</tr>
<tr>
<td>Amyloid-negative patients (n=14)</td>
<td>9 (64.3%)</td>
<td>5 (35.7%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Table 3. Effect of amyloid scan on treatment and patient management.

<table>
<thead>
<tr>
<th>Change in medication</th>
<th>Amyloid + (n=14)</th>
<th>Amyloid – (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change in diagnosis (n=4)</td>
<td>No change in diagnosis (n=10)</td>
</tr>
<tr>
<td>No change in medication</td>
<td>0</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Change in medication</td>
<td>Initiation</td>
<td>2 (50%)</td>
</tr>
<tr>
<td></td>
<td>Modification</td>
<td>2 (50%)</td>
</tr>
<tr>
<td></td>
<td>Discontinuation</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Care plan change</td>
<td>1 (25%)</td>
<td>2 (20%)</td>
</tr>
</tbody>
</table>
Table 4. Most polarized answers on the caregiver questionnaire.

<table>
<thead>
<tr>
<th>Question</th>
<th>Global result (mean ± SD; range)</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>I appreciate every instant with my beloved one even more since we know the precise diagnosis.</td>
<td>*4.13 ± 0.92; 2 – 5</td>
<td>11/23 strongly agreed, 7/23 agreed and only 1/23 disagreed.</td>
</tr>
<tr>
<td>In hindsight, I would have preferred if we didn't go through all of the investigations to determine the diagnosis of my beloved person.</td>
<td>1.26 ± 0.54 ; 1 – 3</td>
<td>18/23 strongly disagreed, 1 caregiver neither agreed nor disagreed, and no caregiver was in agreement with this statement.</td>
</tr>
<tr>
<td>It scares me to develop a neurodegenerative disease even more now that we know the diagnosis of my beloved one.</td>
<td>1.78 ± 0.90; 1 – 4</td>
<td>Only 1/23 agreed with this statement. When asked about it, he said that if something happens to him, his wife would not be there for him and he would not be there for her. 4/23 neither agreed nor disagreed with this statement.</td>
</tr>
<tr>
<td>If I had an uncurable neurodegenerative disease, I'd rather not go through all of the investigations (including amyloid imaging) to know what my diagnosis is.</td>
<td>1.70 ± 0.82; 1 – 4</td>
<td>Only 1/23 agreed with this statement. His reason was that it is uncurable so there is no use. This caregiver was the father of the patient, and he was 82 years old.</td>
</tr>
</tbody>
</table>

Scores on the Likert scale were as follows:
1 = strongly disagree; 2 = disagree; 3 = neither agree nor disagree; 4 = agree; 5 = strongly agree.
FIGURES
Figure 1. Proposed investigative sequence in complex/atypical dementia cases.

History taking, neurological examination, blood tests, neuropsychological evaluation and MRI

Unclear diagnosis?

FDG-PET*

Unclear diagnosis and 65 years old

Amyloid imaging

*Brain FDG-PET is covered by the provincial public health insurances in Quebec (QC), Canada. Cerebrospinal fluid analyses were not covered at the time of the study.
Abbreviations: FDG-PET: $^{18}$F-fluorodeoxyglucose positron emission tomography; MRI: magnetic resonance imaging.
Figure 2. Assessment of the impact of amyloid imaging on the diagnostic process and main caregiver.

*In 46.4% of the cases included in this study, the Principal Investigator (RL) was also the treating physician.

‡Caregiver evaluations were conducted by a graduate student blinded to the clinical context and were two-fold: 1) Structured one-hour interview, and 2) 21-item Likert scale questionnaire. Both were designed to assess the impact of the amyloid scan.
Figure 3. Positive amyloid-PET study using NAV4694. This test shows significant deposition of fibrillary amyloid plaques in the cingulate cortex (A) as well as diffusely throughout the brain (B).
Figure 4. Global Aβ burden with NAV4694 in our 28 participants.

Horizontal line denotes 1.50 threshold between high and low radiotracer binding.

Abbreviation: SUVR: Standard Uptake Value Ratio.
Scores on the diagnostic confidence scale were as follow: 1= very weak, 2=weak, 3=average, 4=high, 5=very high.

*Change is significant by paired-sample t test (p<0.05)
Scores are taken from a 21-item Likert-scale questionnaire. A score approaching 5 suggests a strong impact on “Anxiety” or “Depression” and therefore less symptoms. On the contrary, a score closer to 1 suggests minimal impact and therefore more anxiety or depressive symptomatology. For the variable “Disease perception”, a score closer to 5 suggests a better understanding of the nature of the disease and its natural history. For the variable “Future anticipation”, a score closer to 5 suggests a positive attitude towards future issues. A score approaching 5 on “Quality of life” highlights better quality time (in general and with the loved one). Finally, the global score is an average of the scores on all variables.
LIST OF ABBREVIATIONS

AChEi: acetylcholinesterase inhibitor
AD: Alzheimer's disease
CSF: cerebrospinal fluid
FDG: fluorodeoxyglucose
FTLD: frontotemporal lobar degeneration
GDP: Gross domestic product
MRI: magnetic resonance imaging
NFG: neurofibrillary tangles
PET: positron-emission tomography
PiB: Pittsburgh compound B
ROI: region of interest
SUVR: standard uptake value ratio

SUPPLEMENTARY MATERIAL

Caregiver Questionnaire

Patient Name: ______________________________
Date: ______________________________________
Caregiver Name: _____________________________ Age: ______________

Relation (circle): Parent Husband/Wife Sibling Friend
Stepbrother/Stepsister Cousin Uncle/aunt Son/Daughter

The purpose of the following questions is to assess your perceptions concerning your beloved person's disease since the disclosure of amyloid imaging results. After answering the questionnaire, each question will be discussed with the interviewer in order for us to have the most accurate representation of your situation.

A. Please answer the following questions by checking the appropriate box. Note that when we ask "since you know the diagnosis", we are referring to the very last meeting with your treating dementia expert following the amyloid PET scan, and not since the beginning of the disease.

1 – Strongly disagree 2 – Tend to disagree 3 – Neither agree nor disagree
<table>
<thead>
<tr>
<th>#</th>
<th>Question</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I am more anxious since we know the diagnosis of my beloved one. (A)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>I sleep better since I know that my loved one’s condition is known. (D)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>The family atmosphere is better since we know the diagnosis of my beloved one (S).</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>A new technique like amyloid PET shows me that there is hope in scientific progress. (P)</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>I spend more quality time with my beloved one since we know the diagnosis. (H)</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>Since we know the diagnosis of my beloved one, I sometimes have palpitations and/or tremors. (A)</td>
<td></td>
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<tr>
<td>7</td>
<td>The revelation of the diagnosis had made me more depressed. (D)</td>
<td></td>
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<td></td>
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<tr>
<td>8</td>
<td>I am reassured to know the exact diagnosis of my beloved one. (S)</td>
<td></td>
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<tr>
<td>9</td>
<td>The revelation of the diagnosis has allowed me to make future plans (financial decision, travel, etc.) (P)</td>
<td></td>
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<tr>
<td>10</td>
<td>I appreciate every instant with my beloved one even more since we know the precise diagnosis. (H)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>11</td>
<td>It scares me to develop a neurodegenerative disease even more now that we know the diagnosis of my beloved one. (A)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>12</td>
<td>Since we know the diagnosis, I often feel guilty when I think of my dear person’s disease. (D)</td>
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<tr>
<td>13</td>
<td>In hindsight, I would have preferred if we didn’t go through all of the investigations to determine the diagnosis of my beloved person. (S)</td>
<td></td>
<td></td>
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<td></td>
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<td>14</td>
<td>I feel like the future scares me less since we know the precise diagnosis. (P)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>15</td>
<td>My life (social activities, work, hobbies) is better since we know the precise diagnosis. (H)</td>
<td></td>
<td></td>
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<tr>
<td>16</td>
<td>Since the revelation of the diagnosis, I feel like I can lose control even more. (A)</td>
<td></td>
<td></td>
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<tr>
<td>17</td>
<td>I lost interest in many activities since I know the precise diagnosis of my beloved one. (D)</td>
<td></td>
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</tr>
<tr>
<td>18</td>
<td>If I had an untreatable neurodegenerative disease, I’d rather not go through all of the investigations (including amyloid imaging) to know what my diagnosis is. (S)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>19</td>
<td>I understand the course of the disease of my beloved one better now that we know</td>
<td></td>
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</table>

4 – Tend to agree  5 – Strongly agree
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<tbody>
<tr>
<td>20</td>
<td>I find that my beloved one's disease is even harder for me to accept since we know the exact diagnosis. (S)</td>
</tr>
<tr>
<td>21</td>
<td>My perception of my beloved one's disease has not changed since we know the precise diagnosis. (S)</td>
</tr>
</tbody>
</table>

Note for interviewer: (A) = anxiety, (D) = depression, (P) = future anticipation, (S) = disease perception, and (H) = quality of life.
B. The purpose of the following questions is to determine what you think of your beloved one's condition SINCE the disclosure of the amyloid imaging results.

1 – Strongly disagree  2 – Tend to disagree  3 – Neither agree nor disagree  4 – Tend to agree  5 – Strongly agree

<table>
<thead>
<tr>
<th>#</th>
<th>Question</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>My beloved one seems saddened since the revelation of the diagnosis.</td>
<td></td>
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<tr>
<td>2</td>
<td>My beloved one seems to understand his or her disease better since the revelation of the diagnosis.</td>
<td></td>
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<tr>
<td>3</td>
<td>I noticed an overall improvement in my beloved one's condition since we know the diagnosis.</td>
<td></td>
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<td>4</td>
<td>In general, I think that my beloved one seems to have been affected negatively by the announcement of his or her diagnosis.</td>
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</tbody>
</table>
C. Please answer the following questions by checking YES, NO, or DO NOT KNOW.

<table>
<thead>
<tr>
<th>#</th>
<th>Question</th>
<th>YES</th>
<th>NO</th>
<th>DO NOT KNOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Did your beloved one attend support groups (ex. Alzheimer's association) BEFORE the diagnosis was known?</td>
<td></td>
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<tr>
<td>2</td>
<td>Did your beloved one attend support groups (ex. Alzheimer's association) AFTER the diagnosis was known?</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
| 3  | *If you answered YES to question #1 or #2, please answer this question. Otherwise, go directly to question #4.*

  Going to support groups makes a difference in your beloved one's perception of his or her disease.

| 4  | Are there any changes in your beloved one's habits and lifestyle since the diagnosis is precisely known? |     |    |             |

If you answered YES to question #4, please circle how did his/her habits change?

Nutrition  Physical exercise  Cognitive exercise  Other

Specify: _______________________________________________________________________

| 5  | Are there changes in your own habits and lifestyle since the diagnosis is precisely known? |     |    |             |

If you answered YES to question #4, please circle how did his or her habits change?

Nutrition  Physical exercise  Cognitive exercise  Other

Specify:: _______________________________________________________________________