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Case report

Accuracy of Quantitative Positron Emission Tomography Assessment for Differentiating Cerebral Age-related from Pathological Amyloid Deposition: A Preliminary Report from a Case-series Study

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Abstract

Previous observational studies using old qualitative methods have not clarified the role of amyloid positron emission tomography (PET) in the assessment of dementia. Given the moderately positive predictive value, the presence of amyloid deposition does not necessarily imply the diagnosis of dementia. Conversely, the absence of amyloid PET deposition has been shown to be useful in excluding the neurodegenerative pathology, irrespective of the aging process. We describe the clinical application of new innovative software recently developed to increase the sensitivity of this technique and to discriminate pathological deposition of cerebral amyloid from the age-related changes, reporting preliminary findings from a case-series study. In three different clinical profiles, we underline the need of integrating neuropsychological assessment and findings with this new PET scan and software that provide quantitative information of the cerebral amyloid and may increase the probability of rapid and accurate assessment of Alzheimer's disease. Although this amyloid quantification is promising, these preliminary results should be confirmed in future prospective studies with adequate sample size.

Keywords: Alzheimer disease, amyloid positron emission tomography, flutemetamol positron emission tomography, molecular imaging

Introduction

The incidence of Alzheimer's disease (AD) is estimated to be 1 on 9 older persons in the next future,[1] and this huge number of people with dementia has been considered at the G8 meeting as one of the most important health global priorities. The ambition is having an effective cure for them by 2025[2] and reduce not only years of disability but also costs for patients with dementia.[3]

This urgent necessity of developing a successful treatment for dementia is related to the cogent opportunity to realize an early diagnosis of this disease.[2] In the past, neuropsychological assessment and standard neuroimaging were integrated with the clinical history of the subjects, for defining a probable diagnosis of AD.

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Currently, innovative methods that could indirectly evaluate amyloid and tau cerebral deposition *in vivo*, such as amyloid positron emission tomography (PET), could be utilized for anticipating the diagnosis before clinical appearance of the cognitive deficit.[2]

However, many epidemiological studies have demonstrated that amyloid PET should be interpreted with caution when amyloid deposition is present,[4,5] due to its moderate positive predictive value. Conversely, the same technique has been shown to have a high negative predictive value, and thus, the absence of deposition should exclude neurodegenerative pathology, irrespectively of the aging process.

However, recent dedicated software uses a semiquantitative and not just a qualitative evaluation of the amyloid cerebral deposition. Based on these methods and similarly to other diseases, such as osteoporosis or sarcopenia, it is possible to calculate the "z-score of the amyloid deposition" to differentiate a clear disease from age-related changes.

Thus, the aim of this study is to provide preliminary evidence of the diagnostic values of the amyloid PET using innovative software that could give a clear evidence of the pathological deposition of cerebral amyloid in comparison to the age-related changes according to the cognitive performance, describing in details three case reports.

Materials and Methods

Patients were evaluated at the Cognitive and Motoric Ambulatory evaluating motoric and cognitive function of the University Hospital of Parma, Italy. PET scans were performed at the Nuclear Medicine Department of University Hospital of Parma (Parma, Italy). Patients were first evaluated by trained geriatrician with a standard clinical evaluation[6] and then referred to a neuropsychologist with long-term experience in the clinical and experimental neuropsychology of degenerative diseases.[7] The diagnosis of diagnosis in the absence of symptoms, diagnosis of cognitive impairment due to AD (prodromal stage) and diagnosis of dementia due to AD, independent of etiology, was established using a standard evaluation protocol based on the new IWG criteria.[8] In details, we classified subjects as "Asyntomatic at risk," "Prodromal AD" and "AD dementia" according to the classification proposed by IWG criteria.[9] The neuropsychological battery, where appropriate, included tests assessing abstract reasoning, memory, attention, language, praxis, and visuoperceptive functions. All tests included in the neuropsychology battery had normal ranges and cutoffs available for the Italian population.[10-12]

Depressive symptoms were assessed by the 15-item Geriatric Depression Scale (GDS-15) which is a widely used screening instrument for depressive symptoms in the elderly. The GDS-15 detects changes in depressive symptoms after a major negative life event.[13] Physical performance was assessed by the Summary Performance Physical Battery (SPPB).[14] Hand Grip strength was measured by manual dynamometer.[15] Weight and height were assessed for having body mass index (BMI). All patients underwent a brain magnetic resonance imaging (MRI) or computed tomography (CT) scan in the previous 3 months. Chronic drug treatment was recorded. Missing data were integrated by checking in the original clinical sheet. All patients gave written informed consent to record these data. The data were treated in agreement with Italian law for the privacy guaranty following good clinical practice rules.

Positron emission tomography/computed tomography imaging

Amyloid PET scans were performed using a whole-body hybrid system Discovery IQ (GE Healthcare) operating in three-dimensional (3D) detection mode. Head holder was used to restrict patient movement, and head movement was checked on a regular basis.

18F-flutemetamol positron emission tomography

All cerebral emission scans began 90 min after a mean injection of 2 MBq/kg weight (150–250 MBq) of 18F-flutemetamol. For each subject, 10 min frames were acquired to ensure movement-free image acquisition. All PET sinograms were reconstructed with a 3D iterative algorithm, with corrections for randomness, scatter, photon attenuation and decay, which produced images with an isotropic voxel of 2 mm × 2 mm × 2 mm and a spatial resolution of approximately 5 mm full width at a half maximum at the field of view center.

PET images were assessed visually by two trained, independent readers blinded each other with a previously described technique.[16,17]

Quantitative assessment of 18F-flutemetamol PET images was performed by a dedicated software (Cortex ID, GE Healthcare software) creating a Z-score for each of the cerebral areas exanimate.

CortexID supports data acquired on PET and hybrid PET scanners. It is a fully automated, postprocessing software solution capable of quantifying beta amyloid brain scans (http://www3.gehealthcare.com/en/products/categories/advanced_visualization/applications/cortexid).

Results

We described three suggestive case reports for showing the accuracy of quantitative PET assessment for differentiating cerebral age-related from pathological amyloid deposition.

First Case (Prodromal Alzheimer's disease)

An 83-year-old woman with memory complaints was evaluated in our Ambulatory twice. Her medical history was characterized by hypertension, hypothyroidism with hormonal supplementation and osteoporosis. At the first visit, the initial cognitive assessment showed a normal Mini-Mental State Examination (MMSE 25/30 adjusted for age and education). The GDS was normal (GDS: 0/15), and she was not disable at the activity of daily living. BMI was 30. Cerebral CT scan showed light chronic vascular disease. The neurological examination was free of neurological signs.

After 6 months, she returned to the Ambulatory for checking her cognitive performance. She repeated the comprehensive geriatric assessment. At MMSE she showed slight reduction 24/30 (but with impairment of the executive function). The SPPB was 7/12 with normal-low 4-m walking speed at usual space. Grip strength was 22 kg in the right hand and 17 kg at the left hand. BMI was 29.

We required a formal second level neuropsychological evaluation showing a slightly normal cognitive performance with the necessity of follow-up after 8 months.

Given that her daughter referred change of the normal activities at home, such as for cooking, we prescribed the amyloid PET that showed significant deposition of amyloid in many cerebral areas [Figure 1]. The Z-score of the amyloid deposition was pathological in almost all cerebral areas exanimate. The diagnosis of probable AD was thus established.

Second case (age-related neurodegeneration without cognitive impairment)

An 85-year-old man with referred fatigue was evaluated. His medical history was characterized of only hypertension and benign prostatic hypertrophy. At the initial cognitive assessment, the MMSE adjusted for age and education showed normal values (30/30). The neurological examination was normal. His cerebral CT scan showed marked atrophy related to neurodegeneration.

After 6 months, we evaluated again the patient due to an increase of apathy and irritability. The MMSE showed unchanged cognitive performance, but given that daughter was really worried about the father's cognitive performance, we prescribed the amyloid PET. The amyloid PET was negative for brain amyloid deposition [Figure 2]. The diagnosis of age-related neurodegeneration without cognitive impairment was established (also defined: Suspected non-AD pathophysiology).[18]

Third case (depressed, normal cognitive function)

A 69-year-old woman with a history of hypertension, rheumatic polymyalgia, obesity, and atrial fibrillation in therapy with oral anticoagulant was evaluated for episodes of transient amnesia since 6 months before. At the initial cognitive assessment, she showed a normal Mini-Mental Examination State adjusted for age and

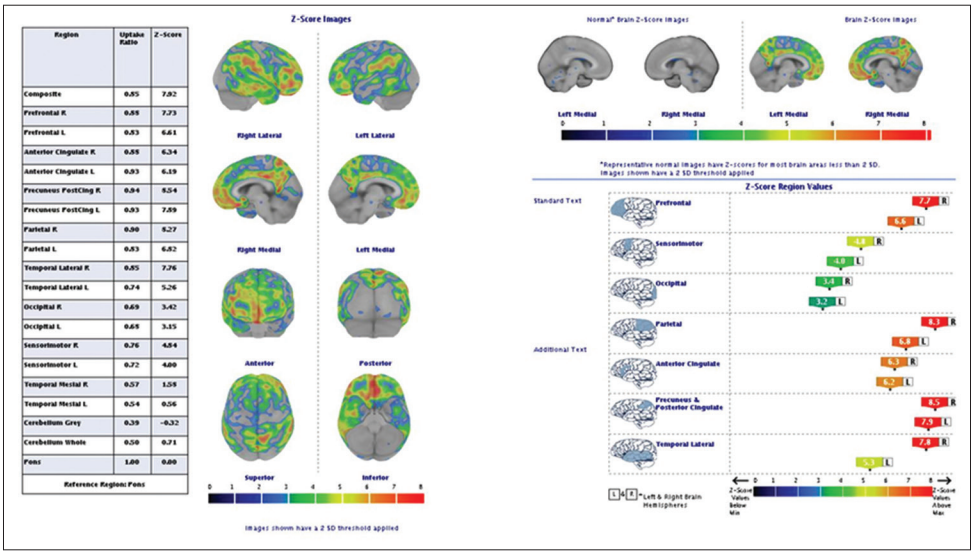

Figure 1: Amyloid positron emission tomography with pathological deposition of b-amyloid, but still normal cognitive profile

education (30/30). Trail making test A and B was normal (TMB-A: 37.59 s; TMB-B: 145 s). Her cerebral MRI was negative for vascular lesions and cortical atrophy, and also electroencephalogram was normal for age. At the neurological examination, we did not find minor or major neurological signs, while at the motoric evaluation, realized by SPPB score, we obtained a score of 7/12 with balance deficit and difficulty to maintain Tandem position for at least 10 s. Hand grip strength was 17 kg at the right hand and 11.4 at the left hand. A diagnosis of sarcopenia, according to her grip strength was established. The GDS was pathological (GDS: 12/15). The patient was really distressed about episodes of amnesia; therefore, we prescribed amyloid PET and not only cognitive assessment.

The amyloid PET showed a total absence-presence of amyloid plaques [Figure 3]. The conclusive diagnosis was therefore of major depression with episodes of transient amnesia.

Discussion

We briefly described three case reports showing the added value of cerebral amyloid deposition, quantitatively measured using PET imaging and dedicated software, in supporting the neuropsychological assessment by discriminating the pathological from the age-related cerebral deposition. The quantitative evaluation of amyloid by PET scans could really help in the diagnostic algorithms of dementia.

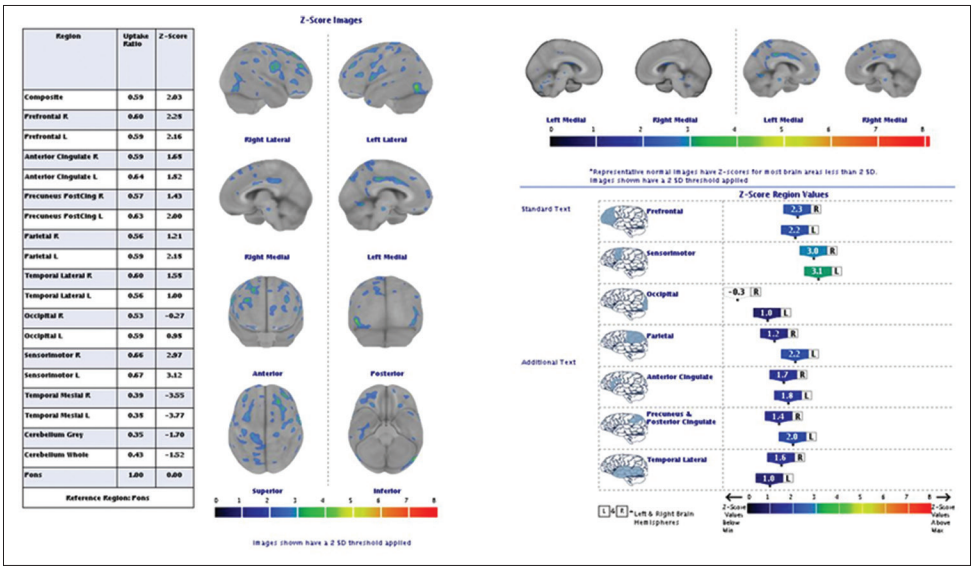

Figure 2: Amyloid positron emission tomography of suspected non-Alzheimer's disease pathophysiology

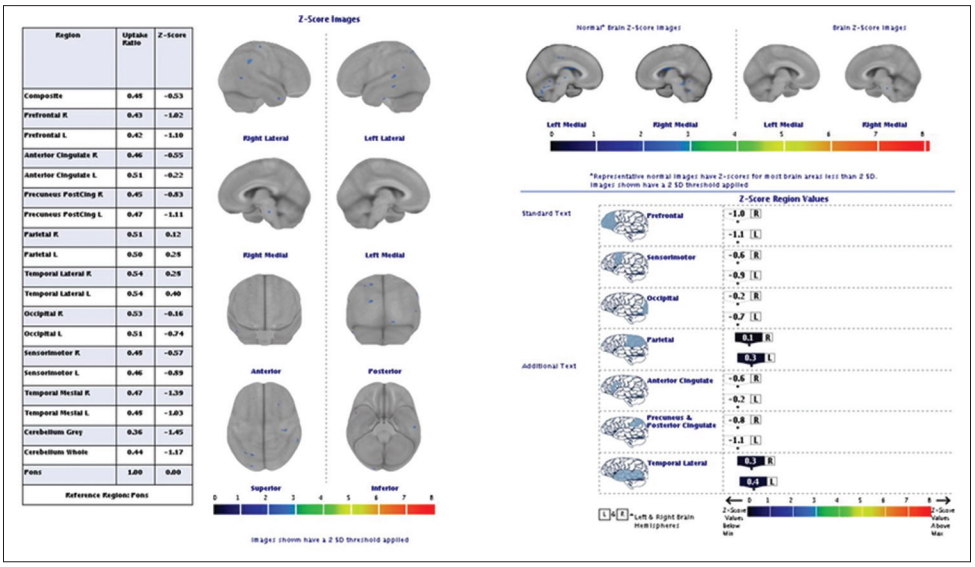

Figure 3: Amyloid positron emission tomography with absence of b-amyloid deposition

Our report introduces the potential clinical importance of the quantification of the cerebral amyloid integrated with the cognitive performance to increase the specificity in the diagnosis of dementia in older persons.

In cases when of the cognitive evaluation realized by screening tests, such as MMSE and second level neuropsychological assessment, show borderline neuropsychological deficits that do not allow a definitive diagnosis of dementia, the amyloid PET by the quantification of cerebral pathological deposition, could increase the probability of performing a diagnosis [Figure 1, case report one].

Conversely, the standard neuropsychological assessment may show a normal cognitive performance, with minimal changes, with brain CT scan evidence of significant cerebral atrophy, expressive of neurodegeneration. In this case, the absence of cerebral deposition at PET imaging can guide to define the case as part of age-related changes of the brain volume without any present and future impact on a cognitive function which is extremely common especially in very old subjects [Figure 2, case report two].

Moreover, amyloid PET might also help in selected cases of major depression with the slight cognitive deficit. Cases of major depression with episodes of transient amnesia and normal amyloid PET might contribute to confirm a psychiatric disorder, especially when the clinical history is suggestive of depression but neuropsychological assessment showed some cognitive deficits [Figure 3, case report three].

Our case reports highlight the need of increasing the utilization of new objective techniques, for the quantification of cerebral amyloid *in vivo* and anticipating as soon as possible the diagnosis of dementia, especially in older persons. This new method could anticipate time for diagnosis and therefore, increase the chance of the effect of new modifying-disease drugs.

Since the burden of AD in older persons is predicted to increase worldwide,[9] it is imperative in both geriatric and neurological settings to develop accurate diagnostic techniques, particularly in older individuals where the coexistence of cerebral age-related changes, cerebrovascular lesions, depression and neurodegenerative diseases may increase complexity in the diagnostic process.

Our cases showed elements that reinforce the need of differentiating the age-related neurodegeneration, with no evidence of cognitive impairment related to β-amyloid deposition, from AD-dementia. This point was recently highlighted in an elegant study conducted in older persons showing that the only imaging evidence of amyloid, but not cerebral atrophy expression of aging neurodegeneration, influences the cognitive process.[18] These authors concluded that brain amyloidosis, a surrogate marker of AD pathology, is a risk factor for cognitive decline and progression from preclinical stages to symptomatic stages of the disease, with neurodegeneration acting as a confounding factor. Therefore, neurodegeneration alone does not confer a significantly different risk of cognitive decline in comparison with the group with neither brain amyloidosis nor neurodegeneration.[18]

In conclusion, earlier and more accurate diagnosis of AD, by using PET scan and software that could provide quantification of the cerebral amyloid may help to accurately identify patients with AD, contributing to improve patient's health status, despite the high costs of this technique. On the other hand utilization of PET, both tau and amyloid could permit to evaluate probably with more accuracy drugs or nutritional supplement to reduce amyloid deposition.[19,20] A recent study showed that at least one-third of patients evaluated in a tertiary memory clinic changed management after amyloid PET execution, and if these findings are confirmed, PET scans should be always included in the standardized diagnostic workup of suspected demented patients.[21]

Showed results should be confirmed in future studies with adequate sample size and prospective studies to confirm, even postmortem, diagnosis suggested by integrating neuroimaging and neuropsychological findings.

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Conflicts of interest

There are no conflicts of interest.

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