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EDITORIAL

Potential of PET/CT in assessing dementias with emphasis on cerebrovascular disorders

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Vascular dementia is a progressive cerebrovascular disorder caused by reduced blood flow to the brain, which may lead to significant loss of brain function [1]. This cerebrovascular disease has an estimated prevalence of 1–4% of adults over age 65, a percentage that approximately doubles every 10 years [2]. The progression of vascular dementia depends on numerous factors, including age-related risks such as hypertension, diabetes, and hyperlipidemia, which lead to the buildup of atherosclerotic plaques in the carotid arteries [3, 4]. Moreover, many cases of dementia have been reported to display both Alzheimer's disease (AD) and vascular dementia traits, and over 80% of AD cadavers show evidence of cerebrovascular disease [5]. A molecular imaging approach using positron emission tomography (PET) for the detection and diagnosis of atherosclerosis upstream of vascular dementia could have a substantial impact on treating an aging population suffering from cognitive impairment.

It is well-established that the brain has high metabolic demands, primarily to maintain neuronal membrane potential and ionic homeostasis. Although the brain constitutes just 2% of adult body mass, up to 20% of cardiac output is directed toward cerebral blood flow [6]. Moreover, prolonged disruption of either oxygen or glucose supply to the brain may result in irreversible neuronal cell damage in a matter of minutes [7]. Consequently, hypoxia secondary to vascular disease can lead to profound impact on cognitive function [8–11]. Prolonged cerebrovascular disease for years is considered a major cause of age-related cognitive decline [12–14]. Vascular dementia, a progressive cerebrovascular disease, is caused by reduced cerebral blood flow and possible emboli and eventually leads to significant loss of brain metabolism and function [15–17]. Individuals at the highest risk for vascular dementia are those with a recent history of stroke or transient ischemic attacks [18, 19]. While these episodes would lead to an acute decline in cognitive function, prolonged alterations in cerebral blood flow over years or decades will also result in profound loss of cognitive function [20]. Preliminary data from our lab has showed that subjects with cardiovascular risk factors demonstrate significantly lower FDG uptake values compared with age- and sex-matched healthy controls (Fig. 1). These findings suggest an association between cardiovascular risk factors and altered global brain metabolism.

The development of vascular dementia is far from uniform. In many cases, vascular dementia is stroke-related, following either a large stroke or a series of smaller strokes [21]. This form of vascular dementia leads to long periods of normalcy, interjected with short time points of sudden decline of cognitive function [22]. In contrast, vascular dementia may be related to subcortical white matter disease due to cerebral small vessel disease, resulting in gradual cognitive impairment over

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many years [23]. These two vascular dementia subtypes share a key commonality: association with atherosclerosis. Bos et al. demonstrated that atherosclerosis, particularly in the extracranial carotid arteries, is not only the strongest risk factor for stroke but also a key underlying player for the development of small vessel disease [22, 24]. In this study, the authors examined the relationship between dementia risk and the vascular calcification volume in various cerebral arteries. They further concluded that the presence of atherosclerosis adversely contributed to premature cognitive degeneration prior to its transition to full-blown dementia. Therefore, these findings suggest that the early detection of atherosclerosis may play a role in preventing irreversible cognitive loss in this population.

Patterns of cerebral ^{18}F-fluorodeoxyglucose (FDG) uptake in the brain have been characterized extensively in both healthy controls and in patients with dementia, and also global uptake of this tracer has been shown to represent an excellent marker for changes in cognitive function [25–28]. Several groups have published data that support this concept. Recently, Shivamurthy et al. demonstrated the usefulness of FDG-PET/CT by highlighting distinct differences in metabolic activity between healthy brains and those of patients with dementia [26, 27, 29–31]. As such, this imaging modality is essential in assessing the consequences of atherosclerotic disease on cognition and mental performance of the affected population. Future studies should be designed to investigate the presence of a direct correlation between cardiovascular disease risk factors and cognitive function.

Atherosclerotic plaques can be identified using structural imaging modalities, including ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) [32–34]. However, these structural imaging modalities rely large plaques, which present only in late stages of disease, at which point the damage is irrversible (Fig2) [35]. In contrast, fused PET/CT imaging has demonstrated potential early diagnosis of atherosclerosis. While FDG-PET/CT is a powerful tool to assess brain function and inflammation, it has become increasingly apparent that ^{18}F-sodium fluoride (NaF) is both a sensitive and specific tracer for the early diagnosis of atherosclerosis [36]. FDG-PET/CT has been used to detect vascular inflammatory processes with variable success [37, 38]. Blomberg et al. noted that cardiovascular disease risk factors are associated with thoracic aortic calcifications detected by NaF-PET/CT, but not with inflammation as detected by FDG-PET/CT [39]. Arani et al. demonstrated that

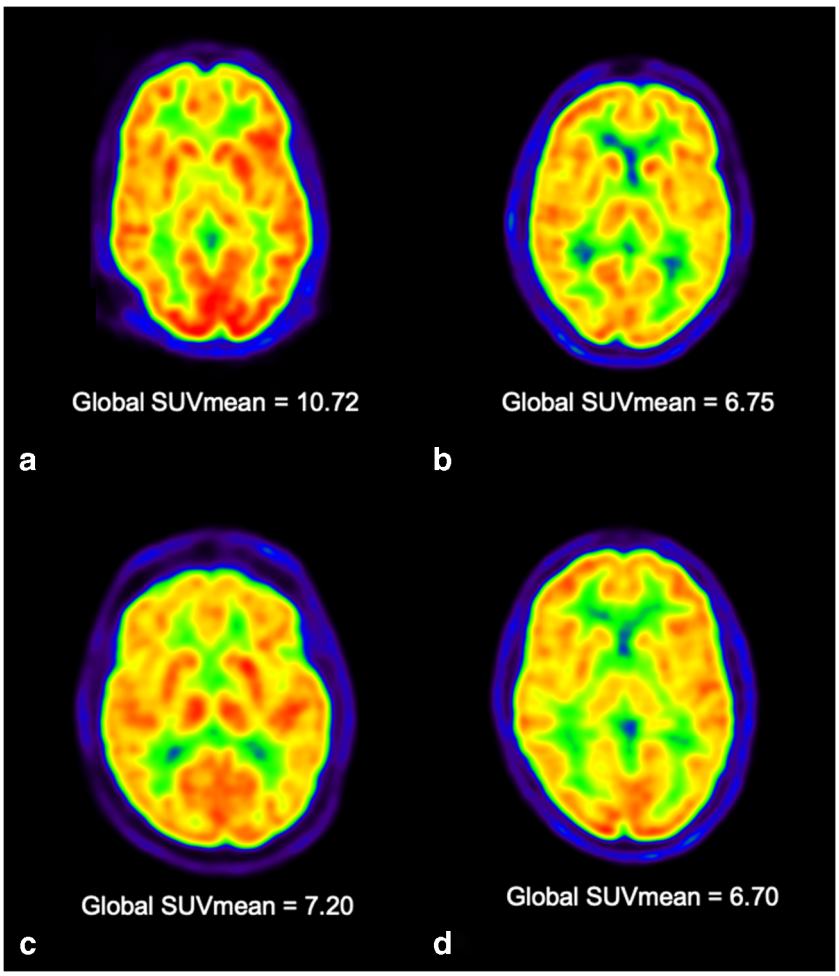

Fig. 1 ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET/CT) images and global SUVmean of the brain displayed according to the same quantitative scale in (**A**) young healthy control, (**B**) young subject with cardiovascular risk factors, (**C**) old healthy control, and (**D**) old subject with cardiovascular risk factors, demonstrating the decrease in global cerebral metabolism in at-risk subjects

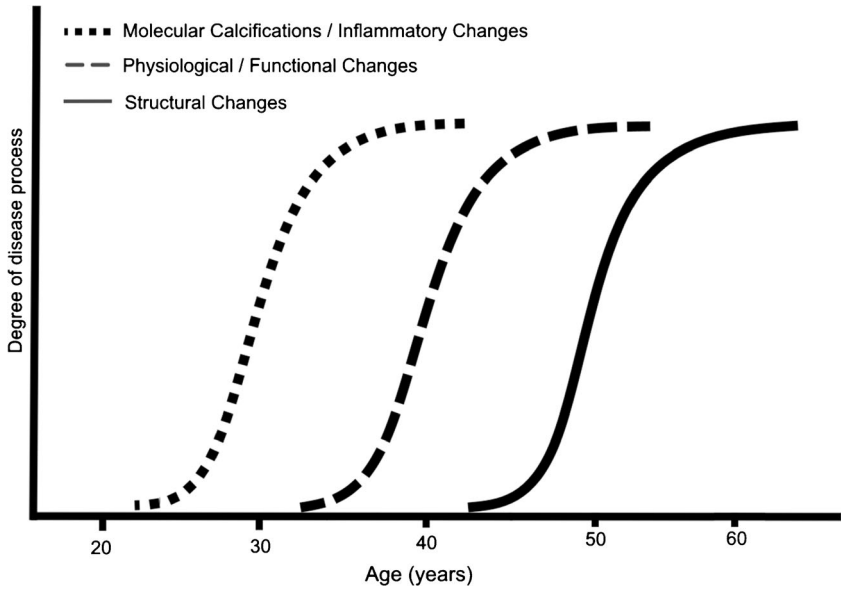

Fig. 2 The sequence of biological changes that occur during atherosclerotic vascular diseases. Atherosclerotic disease begins at the molecular and cellular level. This gradually leads to changes in blood flow and consequently functions in the brain and other organs. Finally, structural alterations occur many years following the disease process. Therefore, imaging techniques that portray early evidence for atherosclerosis, such as calcification and inflammation, may be used to diagnosis and treat the disease years before the luminal abnormalities

NaF, but not FDG, uptake within the abdominal aorta significantly correlated with age and Framingham Risk Score [40, 41]. Moreover, Castro et al. showed that atherosclerotic risk factors are significantly correlated with left common carotid artery NaF mean and maximum standardized uptake value, revealed by NaF-PET-CT [42–45]. Based on these data, NaF-PET imaging appears to be a powerful modality to detect microcalcifications as early evidence for presence of atherosclerotic plaques.

While NaF-PET/CT may be more sensitive and specific in identifying atherosclerotic microcalcifications, FDG can be used as an effective marker to monitor brain metabolic and functional activity in this setting. As such, FDG-PET allows accurate assessment of brain function regionally and globally in patients with atherosclerotic diseases and impaired cognition and mental performance. FDG has been employed for decades as a molecular biomarker to measure metabolic consequences of several diseases and disorders [46]. We believe NaF-PET may also prove to be the tool of choice for detecting early stages of atherosclerosis when therapeutic interventions may be most effective in reversing the process. Therefore, molecular imaging techniques such as FDG- and NaF-PET/CT in populations at risk for cognitive impairment may offer an exciting opportunity to detect atherosclerosis early in the disease course and treat successfully with effective therapeutic interventions.

Atherosclerotic plaques are known to lead to stroke and myocardial infarction in advanced stages of the disease [3]. Plaque formation is especially prevalent in the carotid arteries, which leads to impaired cognitive function due to luminal narrowing and micro-emboli [22]. Not surprisingly, strokes arising from atherosclerosis are considered a risk factor for the development of vascular dementia. Ivan et al. have shown that patients with past stroke history are nearly twice as likely to eventually develop vascular dementia compared to the normal populace [4]. In their analysis, the authors determined that the 10-year risk of developing dementia in patients who had sustained their first stroke, and they determined that the occurrence of a stroke significantly increased, even in groups without genetic, sex-based, or social predispositions to the disease. These data suggest that cerebral infarcts and the underlying atherosclerosis in cerebral diseases may have long-term effects on cognitive function in the affected subjects.

Derlin et al. identified a positive correlation between cardiovascular risk factors and NaF uptake in the common carotid arteries in neurologically asymptomatic individuals [47]. As the carotids are the primary source of blood flow to the brain, there may be a major role for NaF-PET/CT imaging in the assessment of patients with various underlying causes of cognitive impairment and dementia. Additionally, NaF-PET/CT may prove to be the tool of choice for detecting early stages of atherosclerosis when therapeutic interventions may prove to be effective in reversing the process.

Recent studies have demonstrated that intracranial vascular calcification is significantly correlated with cognitive impairment in both AD and vascular dementia [22, 24, 48]. Such findings precede the so-called vascular hypothesis of AD. It has therefore been hypothesized that the cognitive impairment later in life may be due to significant overlap between amyloid pathology and vascular-related brain damage [16]. Therefore, vascular dysfunction may lower the threshold of the presentation of dementia for patients with AD [21].

AD is a progressive neurodegenerative disorder, characterized by memory loss and cognitive decline [49]. The primary risk factor for AD is advanced age, but genetic factors, such as mutations affecting the amyloid precursor protein, are believed to precede early-onset cases of AD [50–54]. It was

estimated that 35.6 million people lived with dementia worldwide in 2010, with numbers expected to nearly double every 20 years, to 65.7 million by 2030 and 115.4 million by 2050, which demonstrates a need to enhance the ongoing research to determine the causes of and potential treatments for AD [55]. Currently, the clinical diagnosis of AD is confirmed through a battery of neurocognitive tests that focus on behavioral changes and mental state assessment [56]. Yet, the earlier stages of MCI and preclinical AD often show no detectable changes in cognition. A large segment of patients with MCI patients go on to develop full AD within a matter of years [57]. Thus, there remains an unmet need for the diagnosis and treatment of early dementia due to any cause.

PET imaging has significant potential for the early diagnosis of the causes of dementia. Published data in the literature indicate that ^{18}F-florbetapir and other amyloid-targeting agents can track the pathological changes associated with AD prior to behavioral manifestation [58, 59]. However, recent studies have challenged the efficacy of such approaches and have emphasized the superiority of FDG-PET for accurate diagnosis of AD (Fig. 3) [60, 61]. Newberg et al. demonstrated that though both tracers have high specificity and sensitivity, FDG is the superior modality for the assessment of cognitive performance [62]. The authors determined that, while the patterns of uptake of both FDG and florbetapir revealed evidence for AD, florbetapir does not sufficiently reflect the severity of the cognitive decline in comparison to FDG. Furthermore, multiple therapeutic trials which have used antibodies that specifically target amyloid plaques in the brain have proven to be ineffective [63, 64]. These failed attempts have demonstrated the alternate methods to monitor cognitive decline during the course of the disease [65]. Thus, FDG as a molecular probe for assessing brain glucose metabolism and NaF for detecting early atherosclerosis may prove to be of great importance in patients with dementia.

Cognitive impairment later in life may be due to significant association between neuronal degeneration and cerebrovascular disease [6]. Currently, drugs approved for treating AD have minimal and oftentimes unpredictable impact on the cause of the disease, and these treatments are associated with significant side effects, which lead to further deterioration of the affiliated population. Therefore, by establishing evidence for cerebrovascular disease in patients with dementia patients, clinicians may be improve and stabilize the cause of the disease. The medical community should be aware of the great potential of NaF-PET and FDG-PET in addressing this major healthcare issue affecting the aging population worldwide. We believe that future prospective and longitudinal studies should

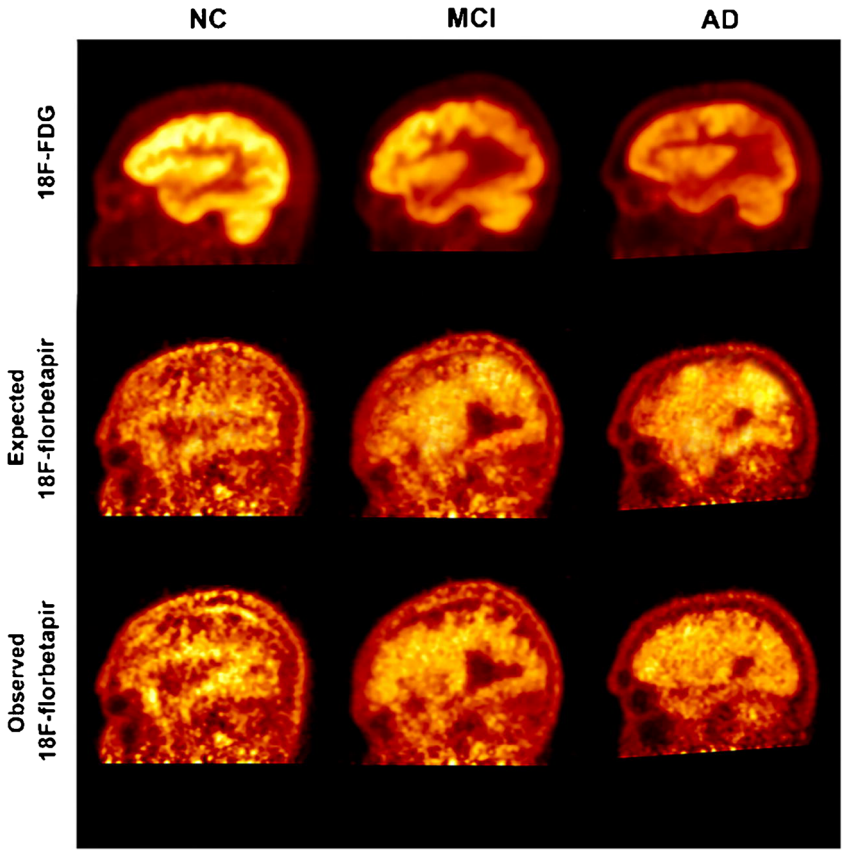

Fig. 3 ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET/CT) and ^{18}F-Florbetapir images of the brain in controls (NC), mild cognitive impairment subjects (MCI), and Alzheimer's disease (AD) patients, demonstrating the superiority of FDG-PET/CT (reproduced with permission from Alavi et al. [64])

be conducted to validate the role of these powerful imaging techniques in the diagnosis and management of patients with dementia.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Statement on published images Images presented are fully anonymized and were collected with the patient's consent in the Department of Radiology, Hospital of the University of Pennsylvania, PA.

Abbreviations AD, Alzheimer's Disease; MRI, magnetic resonance imaging; FDG, ^{18}F-fluorodeoxyglucose; NaF, ^{18}F-sodium fluoride; PET/CT, positron emission tomography/computed tomography

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