Primary degenerative dementia syndromes are an increasingly relevant problem worldwide because of the progressive aging of the population. Their diagnosis is often a challenge for clinicians and, even in the best cases, only a possible or probable diagnosis can be reached. Molecular neuroimaging techniques can be very useful in dementia patients, especially for obtaining a diagnosis in the early stage of disease. The most diffuse and widely available nuclear medicine method for neurological studies is 18F-fluoro-deoxy-glucose (18F-FDG)-PET, which allows the quantification of glucose gray matter metabolism and helps visualize typical, adequately specific, patterns for many kinds of degenerative dementia, not only for the well-known and well-studied Alzheimer’s disease. This paper aims to describe the clinical and 18F-FDG-PET profiles of the principal non-Alzheimer type of degenerative dementias.

Introduction

Dementia is one of the major causes of disability and, because of the progressively aging population worldwide, is becoming an increasingly relevant problem, both for individuals and for society [1,2]. The main risk factor for developing dementia is age: 650 million people across the world are older than 65 years, and by 2050 there will be an estimated 1.2 billion with 35.7 million older than 80 years. European epidemiological studies have shown that the prevalence rate for any kind of dementia is 6.4% in individuals over 65 years, and it increases up to 30% among people older than 90 years [1]. In Italy the estimated incidence is 150,000/200,000 with a prevalence of one million and a mean survival from diagnosis of about 8 years [1].

Dementia can be defined as an acquired organic disorder that induces dysfunction in cognitive capabilities previously gained [3]. Dementia can also be considered a syndromic picture characterized by the impairment of at least two cognitive areas that causes a significant reduction in the patient’s everyday living capacities, interfering with social and occupational functioning [4–7]. Commonly, one of the two cognitive areas involved is memory, but it is not essential. For Conditio sine qua non dementia diagnosis, consciousness must be intact – in particular, the cognitive disorder must not arise in a ‘delirium’ context (also known as acute confusional state). Dementia is not a single nosological entity and many types of dementia exist. From a clinical point of view they may be classified as follows: (a) reversible dementia, if resulting from another disease (generally infective, metabolic, or psychiatric conditions, tumoral lesions, normal pressure hydrocephalus); (b) vascular dementia; and (c) neurodegenerative primary dementia [4–6].

The two most common types of dementia are vascular and Alzheimer’s dementia (AD), the former being the most frequent form of dementia in the neurodegenerative group [7,8]. Vascular dementia and AD, either alone or in combination, account for the majority of cases, whereas reversible dementia is diagnosed in less than 15% of patients [7].

Besides AD, the neurodegenerative group includes the following: dementia with Lewy bodies (DLB), Parkinson disease dementia (PDD), frontotemporal dementia (FTD), progressive supranuclear palsy (PSP),...
corticobasal degeneration (CBD), Huntington’s disease, and Creutzfeldt–Jakob disease [4–7].

Recently, neurodegenerative dementias have been classified on a molecular basis and have been divided into three groups depending on the principal neuropathological process that produces dementia [3,7]: (a) synucleinopathies (DLB, PDD), which are characterized by the progressive intracellular accumulation of abnormal α-synuclein, a soluble nervous tissue protein, coded on chromosome 4, usually involved in vesicular transport and fusion with membrane cells; (b) taupathies (AD, FTD, PSP, and CBD), characterized by progressive accumulation of phosphorylated tau protein, coded on chromosome 17, usually involved in microtubule stabilization and vesicular transport; and (c) amyloidopathy (AD).

Even if recent work suggests that synucleinopathies and taupathies are not always well separated and some overlap exists, this neuropathological classification has the advantage of elucidating the molecular pathway and the different protein targets toward which therapeutic efforts should be focused [7,9,10].

The diagnosis of dementia is still essentially clinical and it is currently made in terms of probability as the certainty of diagnosis can be reached only on post-mortem tissue examination [2]. Patients who present with symptoms of dementia are a great challenge for the clinician because a clear clinical pattern, typical for a specific type of dementia, may not always be recognized [7,11]. The overlapping of clinical symptoms is frequent, especially in advanced stage of dementia, when differences disappear and features are not well defined [4,5].

Even if the principal diagnostic orientation is clinical, neuroimaging techniques are acquiring a pivotal role, not only to address the diagnosis but also to monitor disease progression [5,8,11]. The improvements from a technical point of view, for both morphological and functional imaging, with the possibility of studying the molecular pathways involved in dementia conditions, have facilitated a more accurate diagnosis in many cases, especially in advanced stage when the clinical features are indistinct [5,8]. The careful assessment of the anatomical and functional features of each type of dementia decisively contributes to the diagnosis.

Although many improvements have been made in the therapeutic field, owing to the deeper knowledge about neuropathological alterations, a pharmacological therapy able to modify the natural course of dementia has not been developed yet [12]. Most of the effort has been directed toward Alzheimer’s dementia: a suitable therapy, especially with acetylcholinesterase inhibitors, may stabilize the disease and delay the unavoidable cognitive deterioration [12]. The objective is to start therapy as soon as possible in order to break the neuropathological process that leads to neurodegenerative alteration [12]. Reaching the correct diagnosis is important in order to avoid medicines that benefit a certain type of dementia but not all forms of the illness; it is worth noting that antipsychotics can cause severe and dangerous reaction in DLB because of an increase in neuroleptic sensitivity typical of this disease [4,7]. An accurate diagnosis is necessary from a psychological point of view as well, not only for the patient but also for the family and the caregivers.

After the identification of dementia through an accurate anamnestic phase, involving both the patient and the relatives, and through the application of cognitive tests to explore the various cognitive functions, it is essential to differentiate reversible dementia from a primary neurodegenerative form [4,5]. Therefore, after a blood examination to exclude metabolic alterations, such as anemia, hypothyroidism, hyperglycemia, hyponatremia, hypercalcemia, and B12 vitamin and folate deficiencies, the patient must be submitted to morphological neuroimaging to assess the presence of masses, normal pressure hydrocephalus, or subdural hematoma [1,5,8]. If a reversible dementia is excluded, the different forms of primary neurodegenerative dementia must be considered and, if possible, a differential diagnosis should be obtained [1,8]. At this point, together with the clinical pattern, functional neuroimaging, the results of which integrate the morphological ones, takes on an important role [4].

Functional neuroimaging

The neuroimaging techniques commonly used to evaluate neurodegenerative dementias are MRI and nuclear medicine imaging, especially PET. MRI is not a topic of discussion in the present paper; however, it is worth noting that nowadays it is not a simple anatomical technique that is useful for excluding the presence of a gross structural lesion, but, owing to recent advancements (including diffusion-weighted and diffusion tensor imaging, spectroscopy, and perfusion imaging) it is considered a functional technique facilitating the measurement of the integrity of tissue and biological metabolites (especially N-acetylaspartate and myo-inositol) and the evaluation of cerebral perfusion [11]. Moreover, functional MRI can assess brain activity during cognitive, motor, and sensory tasks or at rest, measuring blood flow and blood oxygen level [11].

Nuclear medicine techniques are considered functional examinations ‘in vivo’ par excellence. Depending on the chosen radiopharmaceutical, various aspects of the brain function can be studied, such as perfusion, metabolism, or specific neurochemical processes [13]. Both single photon emission computed tomography (SPECT) and PET are first choice techniques to measure ‘in vivo’ many neurochemical processes because of their high sensitivity that allows the assessment of a small
concentration of molecular components of the neurotransmission system [13]. Thus, they are able to detect small molecular and cellular changes not yet revealed in the anatomical structure [13]. The choice between SPECT and PET essentially depends on the radiopharmaceuticals available to study a specific brain function and on the availability of instrumentations. The advantage of PET lies in the possibility to mark biological molecules without modifying their properties; moreover, compared with SPECT, it has higher spatial resolution. However, SPECT is less expensive and has greater diffusion [13].

PET with $^{18}$F-fluoro-deoxy-glucose ($^{18}$F-FDG) is the most utilized nuclear medicine technique in clinical practice for evaluating dementia patients. In fact, nowadays, $^{18}$F-FDG-PET is a globally available technique, given that it is a daily routine examination in oncological studies. It is easily accessible for neurological studies at reduced costs.

$^{18}$F-FDG is a glucose analog that allows the evaluation of the glucose brain metabolism that is an index of brain perfusion, brain activity, and synaptic density [14]. As metabolism and flow reduction are coupled in dementia patients, perfusion studies and glucose metabolism studies are equivalent [4,14].

The principal clinical applications of $^{18}$F-FDG-PET in dementia patients are as follows: (a) differential diagnosis between dementia and benign forgetfulness due to aging; (b) differential diagnosis among the various forms of primary neurodegenerative dementias; (c) evaluation of pharmacological treatment effects [4,15].

The utility of $^{18}$F-FDG-PET in primary neurodegenerative dementias resides in the possibility of finding specific glucose metabolic patterns that could aid in the diagnosis. We now report on the clinical features and typical $^{18}$F-FDG patterns for the principal forms of primary neurodegenerative non-Alzheimer dementia.

**Dementia with Lewy body**

DLB is the second most common form of dementia after Alzheimer’s dementia (AD) and PDD, accounting for 15–20% of dementia cases examined post mortem [5,14,16–18]. From a clinical point of view DLB shows a progressive cognitive decline that interferes with normal social and occupational functions in association with some ‘core features’ that make the diagnosis probable (two core features associated) or possible (one core feature associated): fluctuating cognition and attention, recurrent visual hallucinations, and parkinsonian signs [3,16,17]. Other supportive symptoms could be present, such as repeated falls, syncope, transient loss of consciousness (as a consequence of dysautonomic alterations), rapid eye movement sleep behavior disorders, depression, and neuroleptic sensitivity [16,17]. Dementia symptoms can be very similar to Alzheimer’s, even if, especially in early phase, the memory function is less compromised than AD. The differential diagnosis between AD and DLB, sometimes difficult, is very important as DLB patients show high sensitivity to neuroleptic drugs, commonly used for psychiatric symptoms of dementia. Neuroleptic drugs in DLB patients can cause exacerbation of motor symptoms and mental instability leading to a two-fold to three-fold increase in mortality [16,19]. Another important difference between AD and DLB is the better response of the latter to cholinesterase inhibitors because of the greater cholinergic deficit [16].

The typical $^{18}$F-FDG-PET pattern for DLB consists of a diffuse cortical brain hypometabolism mainly involving the occipital lobe, especially primary visual and association areas [14]. Generally, the parietal, frontal, and anterior cingulate cortices are less compromised, but if parietal hypometabolism is present differential diagnosis with AD can be difficult [14,18]. In most cases, occipital hypometabolism facilitated DLB diagnosis with a sensitivity of 90% and a specificity of 80% [14–16]. Another $^{18}$F-FDG finding that can aid in DLB diagnosis is the relative sparing of the mesial temporal cortex that is usually involved precociously in AD [18]. Moreover, in DLB, subcortical structures and the somatosensitive primary cortex are usually not involved [14].

Radionuclide imaging of the dopaminergic system can help when a diagnosis cannot be reached with $^{18}$F-FDG-PET because of an unclear hypometabolic pattern: generally, DLB patients show decreasing uptake of dopaminergic tracers on the striatum, whereas AD shows a normal pattern (e.g. DOPA-PET and Datscan-SPET) [4,13,14]. Also neureceptor imaging of the adrenergic system at the level of the heart can separate DLB from AD. Cardiac SPET with $^{123}$I-MIBG (meta-iodobenzylguanidine), a noradrenaline analog that is a biomarker that enables visualization of catecholaminergic terminals in vivo, shows a positive picture in DLB patients (decrease cardiac uptake) because of the sympathetic degeneration of dysautonomic dysfunction, whereas it is normal in AD [3,20].

**Parkinson disease dementia**

From a neuropathological point of view, PDD is a synucleinopathy like DLB, with the same stigma: Lewy body accumulation [4]. A unique pathology spectrum, named Lewy body disease spectrum, has been proposed, at the extremities of which PDD and DLB are located. Whereas in DLB dementia and motor symptoms appear simultaneously, in PDD dementia symptoms are the final evolution of the disease that starts with pre-eminent motor extrapyramidal disorders [4]. The ‘1-year rule’ has been introduced to clinically differentiate these two entities: if cognitive dysfunctions occur within 12 months from motor symptoms, the probable diagnosis is DLB; if dementia occurs after 12 months the probable diagnosis is PDD.
PDD is a typical subcortical dementia with loss of retrieval memory and frontal execution functional defect such as alteration in working memory, problem solving, and bradifrenia [3].

The 18F-FDG-PET picture of PDD is very similar to that of DLB because of their similar neuropathologic characteristics. Also in PDD occipital hypometabolism is found with a possible involvement of the parietal, frontal, and lateral temporal cortices. In comparison with DLB, in PDD the lateral temporal cortex is usually less compromised.

Frontotemporal dementia
FTD is a common cause of dementia that manifests before the age of 65 years; however, 25% of FTD cases occur after 65 years of age [8,21]. It is a tau pathology characterized by phosphorylated tau protein accumulation and mainly involves frontal and temporal lobes. It has a high familial incidence, about 30–40%; however, tau protein mutation is found in only 10% of cases [18,21]. FTD is a new name that has replaced the old definition of Pick’s disease whose typical feature is the round intraneuronal inclusions (or Pick bodies) that give a swollen aspect to the cortical neurons. More recently it has become clear that cases of clinical Pick’s disease with frontal and temporal lobes symptoms may not show the typical histological picture of Pick bodies; the term ‘Pick’s complex’, along FTD, is preferred to indicate this kind of dementia [21]. FTD includes a heterogeneous group of different nosological entities that, in advanced stage, are indiscernible from AD but, in the early stage, are mainly characterized by behavioral symptoms, personality changes, and language disturbances rather than memory loss [6,21]. All these entities are marked out from selective and often asymmetric atrophy in the anterior portion of the frontal and temporal lobe and have in common some histological markers such as neuronal loss, gliosis, and superficial linear spongiosis [6]. As already mentioned, ballooned neurons or Pick cells occur with variable frequency in all varieties [21]. The principal forms of FTD have been described.

Frontotemporal dementia-behavioral variant
It is mainly characterized by behavioral and neuropsychological disorders, often apathy and disinterest, which could lead to an initial diagnosis of depression. If disinhibition symptoms are present, obsessive–compulsive or manic psychosis might be suggested. Usually, relatives complain of personality changes in the patient: often childish manners, inappropriate sexual remarks, excessive spending, inappropriate comments, insistence on certain foods, excessive food intake with neglect of personal hygiene, and disinterest toward the family. At the initial stage only a deficit in executive functions is visible, such as inability to plan or carry out complex tasks [21].

Primary progressive nonfluent aphasia
It involves perisylvian areas of the left hemisphere and is purely a progressive language deficit that presents with anomia (or word finding difficulty), with preserved memory and nonverbal cognition. The preservation of comprehension is typical. In advanced stages of the disease the patient usually becomes mute but all the other cognitive functions may be normal. Mutism is considered the end-stage condition for all forms of FTD even if the initial stage is characterized by behavioral disturbances.

Semantic dementia
It is a fluent form of primary progressive aphasia that involves the left temporal lobe, especially on the anterior pole. These patients lose the ability to grasp the meaning of words but preserve the ability to speak fluently and converse.

Other forms of FTD have been classified depending on the possible association with motor neuron disease (FTD motor neuron disease), with typical symptoms and pathological finding of CBD or PSP, and with parkinsonism [21].

The typical 18F-FDG pattern of FTD is an important glucose metabolism deficit of the frontal and temporal cortex with a milder hypometabolism of parietal regions that becomes more evident in advanced stage [14]. The prevalent frontal hypometabolism usually allows distinction of FTD from AD; however, especially in advanced stages, overlapping due to frontal involvement in AD can occur. Later stages of FTD and advanced AD might have very similar 18F-FDG patterns.

18F-FDG-PET may be useful for obtaining a differential diagnosis among the different variants of FTD.

From a functional neurodiagnostic point of view it is helpful to distinguish FTD in the behavioral and lingual variant. Glucose hypometabolism of the frontotemporal dementia-behavioral variant mainly concern the frontal lobe in the associative cortex, especially the orbitofrontal, frontopolar, medial frontal, dorsolateral, lateral inferior frontal regions, and anterior cingulated cortices. In advanced stages also the temporal cortex and subcortical regions are involved [8,14,18]. In the case of the lingual variant, temporal hypometabolism, generally left greater than right, is usually found. If the hypometabolism involves the anterior portion of the temporal lobe, a diagnosis of semantic dementia is suggested, whereas if the hypometabolism is mainly found in the fronto-temporal regions, especially in the inferior and middle frontal cortex, a primary progressive nonfluent aphasia could be suspected [14,11].

Progressive supranuclear palsy
It is a tau pathology and the most common form of parkinsonism, after Parkinson disease, usually occurring after the age of 40 years [6]. In the beginning, motor symptoms are
prevalent because of the extrapyramidal degeneration. In particular, postural instability with falls, upward gaze paralysis (or slowed vertical saccadic movements), retrocollis (cervical dystonia with neck hyperextension), and bilateral parkinsonism resistant to L-DOPA treatment are frequently present (linee guida musicco). Cognitive impairment occurs later and

---

**Fig. 1**

A 63-year-old man with important cognitive deficit, parkinsonian symptoms, and visual hallucinations. The pictures show glucose hypometabolism in the right occipital cortex with hypometabolism of the omolateral hippocampal and parahippocampal regions. Faint hypometabolism is also seen in the right posterior–parietal and temporoparietal cortices. This 18F-fluoro-deoxy-glucose pattern is suspected for dementia with Lewy bodies. (a) Transaxial sections of the brain oriented in the orbital–meatal plane. (b) Transaxial, sagittal and coronal views showing the area of hypometabolism.
An 80-year-old woman with cognitive and memory disorders. The clinician needed a differential diagnosis between AD and frontotemporal dementia (FTD). The pictures show moderate hypometabolism in the left temporal cortex, especially laterally, and in the posterior–parietal–ipsilateral region. The glucose metabolism in the frontal regions appears quite normal and hence the 18F-fluoro-deoxy-glucose (18F-FDG)-PET orients the diagnosis toward AD rather than toward FTD. (a) From top to bottom: transaxial, sagittal, and coronal sections of the brain oriented in the orbital–meatal plane. (b) Transaxial views of the brain in the temporal lobe.
is usually progressive and characterized by frontal dysfunction: apathy, alteration in abstract thought, reduced verbal fluency, imitative behavior, and disinhibition [3,4,6].

\[18\]F-FDG-PET usually shows diffuse hypometabolism more evident in the anterior portion of the frontal lobe and in the basal ganglia [22]. Useful for the diagnosis of

Fig. 3

A 58-year-old woman with recent and rapid loss of memory and psychiatric disturbances. The picture shows a diffuse, very important reduction in glucose uptake especially involving the frontal, postero-parietal, and temporal cortex bilaterally with hypometabolism of the right striatum, right thalamus, and left cerebellar hemisphere. In this case it is difficult to obtain a clear differential diagnosis because of the whole involvement of many cerebral regions. The picture shows, from top to bottom, transaxial, sagittal, and coronal sections of the brain oriented in the orbital–meatal plane.
PSP is neuroreceptor imaging with radiotracers for the dopaminergic system, which shows marked symmetrical uptake reduction in the putamen and caudate [4].

Corticobasal degeneration
Similar to PSP, CBD is a tau pathology included in Parkinsonism entities. Extrapyramidal and asymmetric motor symptoms are typical of the initial phase and they are insidious, progressive, and not responsive to L-DOPA treatment [6]. Usually there is the dystonia of one limb (generally an arm) with the ‘alien limb phenomenon’, postural and gait instability with falls, and supranuclear eye movement abnormalities, in particular an increased latency of horizontal saccadic movements with normal speed. CBD patients also show alteration of speech with dysphonia, echolalia, and they often become anarthric and aphonic [6]. Cognitive dysfunction with alteration of executive function related to the frontal lobe and neuropsychiatric disorders (depression, apathy, anxiety, irritability, disinhibition) is seen in advanced stage as well.

18F-FDG-PET pattern in CBD is mainly characterized by asymmetric hypometabolism of the subcortical structures and the omolateral frontoparietal cortex [5,8,15]. The hypometabolism is contralateral to the motor extrapyramidal symptom side [4]. Similar to PSP, for CBD diagnosis too neuroreceptor imaging with radiotracers for the dopaminergic system is helpful, but, unlike PSP, CBD shows an important asymmetric uptake reduction in the striatum [4] (Figs 1–3).

Conclusion
Similar to the increasing evidence in many fields of medicine, for dementia diagnosis too integration between clinical aspects and neuroimaging findings is needed. Cooperation among different specialists is vital for a correct overview of the patients and to reach the correct diagnosis as soon as possible. Despite the improvements in neuroimaging techniques, especially in the functional ones, their application alone cannot successfully achieve a diagnosis. Radionuclide imaging, in association with clinical data and morphological examination, can be very helpful in orienting the surgeon toward the probable disease. This is especially true in the initial phase when the overlapping among different dementia patterns is less frequent. In addition, the early diagnosis of a dementia syndrome facilitates an early start to the most adequate treatment, with less collateral effect and with the intent to break the neuropathological process that leads to neuronal degeneration.

Acknowledgements
Conflicts of interest
There are no conflicts of interest.

References
20 Rascol O1, Schelosky L. 11C-metaidoobenzylguanidine scintigraphy in Parkinson’s disease and related disorders. Mov Disorder 2009;24:2732–2741.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.