NEUROIMAGING IN NEURODEGENERATIVE DEMENTIAS*

SLIKANJE ŽIVČEVJA PRI NEVRODEGENERATIVNIH DEMENCAH

Lojze M. Šmid, Mara Bresjanac

Laboratory for Neural Plasticity and Regeneration, Institute of Pathophysiology, Faculty of Medicine, Zaloška 4, SI-1000 Ljubljana, Slovenia

Abstract *This brief review presents the role of neuroimaging, both structural and functional, in dementia diagnosis and monitoring with emphasis on recent developments in positron emission tomography imaging of dementia-related pathology. Neurodegenerative dementias (with Alzheimer disease as the most prominent representative) affect a large proportion of elderly population worldwide. Structural neuroimaging, either computerized tomography or magnetic resonance imagining, is routinely used to exclude non-neurodegenerative and potentially treatable dementia causes. Global or localized brain atrophy is the most frequent morphological findings in the majority of neurodegenerative dementia types, regardless of the cause. Functional neuroimaging detects changes in brain activity before first detectable structural changes can be observed. Traditional applications of positron emission tomography in dementia (brain perfusion and metabolism quantification) have recently been joined by experimental imaging of brain amyloid deposition using several new imaging probes. In vivo imaging of dementia-related pathology shows potential for early disease detection, progression monitoring and in research of treatment strategies.*

Key words *magnetic resonance imaging; positron emission tomography; Alzheimer disease; prion diseases; amyloid*

Izvleček *Alzheimerjeva bolezen in druge nevrodegenerativne demence prizadanejo številne starostnike. Prispevek podaja kratek pregled vloge strukturnih in funkcionalnih slikovnih metod pri diagnostiki in spremljanju demenc. Posebna pozornost je namenjena nedavnemu napredku rabe pozitronske izsevne tomografije za zaživljenjsko prepoznavo specifičnih, z demenco povezanih sprememb v možganih bolnikov. Strukturne slikovne metode (magnetno resonančna tomografija in računalniška tomografija) sodijo med rutinske preiskovalne metode, katerih namen je izključiti strukturne in potencialno reverzibilne vzroke demence; najpogostejša strukturna najdba pri bolnikih z demenco je splošna ali lokalizirana možganska atrofija. Funkcionalne slikovne metode prikažejo spremembe v delovanju možganov preden se pojavjo zaznavne morfološke spremembe. Njihovi ustaljeni uporabi za prikaz in kvantifikacijo delovanja možganov (z merjenjem področne prekrvitve ali rabe glukoze) so pred kratkim dodali novo področje – prepoznavo amiloidnih patoloških odlag v možganih. Raba molekularnih označevalcev amiloida v povezavi s pozitronsko izsevno tomografijo utegne pomembno prispevati k zgodnjemu odkrivanju demence, spremljanju patološkega dogajanja v možganih in raziskovanju novih pristopov k zdravljenju.*

Ključne besede *magnetno resonančna tomografija; pozitronska izsevna tomografija; Alzheimerjeva bolezen; prionske bolezni; amiloid*

Correspondence / Dopisovanje:

Lojze M. Šmid, MD, Laboratory for Neural Plasticity and Regeneration, Institute of Pathophysiology, Faculty of Medicine, Zaloška 4, SI-1000 Ljubljana, Slovenia

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Introduction

Aging of the population is causing a steady rise in the dementia prevalence. The availability of new neuroimaging approaches, developed in the last decades, provides neuroscientists and clinicians with a set of valuable noninvasive tools for research, early diagnosis and monitoring of the course of these disorders. Improved *in vivo* diagnostic tools, which would better differentiate between the causes and types of dementia, could enable a more reliable and earlier diagnosis, opening the door to development of treatment strategies, which may be effective early in the clinical course. New neuroimaging approaches are particularly promising in this context, since they convey information necessary for the understanding of the mechanisms behind clinical disease presentation and represent objective and quantitative methods for determination of disease onset and progression.
A number of imaging modalities are currently being used in neurodegenerative disease patients. This review briefly describes major neurodegenerative dementias and gives an overview of structural and functional neuroimaging approaches in these disorders. It then focuses on recent developments in dementia-related pathology detection using amyloid specific molecular imaging probes.

Definition and classification of dementia

Dementia is an acquired, persistent and progressive pathologic decline of intellectual ability, beyond those normal for individuals age, and manifests itself with deficits in memory, personality, language, visiospatial skills and other cognitive abilities (e. g. abstraction, mathematics, judgment).[1] It may occur at any age but primarily affects the elderly (about 5 % of those aged 65 to 74 and 40 % of those > 85). Current demographic trends are causing a steady increase in dementia prevalence along with its heavy emotional and financial burdens.[2] The availability of specific treatment strategies, which are most effective when started early,[3] and identification of predisposing conditions (such as mild cognitive impairment) raise the importance of reliable and early dementia diagnosis. Diagnosis of dementia is clinical and determination of the cause is based on its characteristic features.[4–6] Clear clinical distinctions between dementias however appear late and are often impossible to discern at an early stage of the disease. Laboratory tests and structural imaging are currently employed to identify potentially treatable dementia causes and identify other secondary causes, or to support the diagnosis of primary dementia. Definitive diagnosis is established by postmortem neuropathologic examination, which is often not done, precluding verification of most clinical diagnoses.
Dementias can be classified in several ways, depending on the criteria employed. The predominant distribution of pathological changes in the brain and the resulting clinical picture differentiates cortical dementias (with prominent disturbances of memory, language and calculation) form subcortical dementias which are associated with basal ganglionic diseases (e.g. progressive supranuclear palsy, Parkinson and Huntington disease). Cognitive decline associated with these disorders presents as slowed thought process, lack of initiative and depression of mood with sparing of vocabulary and praxis.[7] Dementias can also be classified as irreversible or potentially reversible. The latter group accounts for approximately one tenth of dementia cases and includes patients with possibly treatable structural brain lesions, secondary dementias due to systemic disorders and patients with pseudodementia caused by psychiatric disorders.[8] The pathogenesis of the vast majority of irreversible dementias is either neurodegenerative or vascular. The presentation of vascular multi-infarct dementia can be one of stepwise cognitive decline caused by episodes of stroke accompanied by focal deficits on neurological examination and demonstration of ischemic lesions by structural neuroimaging. Recent evidence suggests frequent coexistence or even interaction of vascular and neurodegenerative processes in demented patients. Presence of cerebrovascular disease should thus not be used for exclusion of underlying neurodegenerative pathology.[9] Neurodegenerative diseases are progressive neurologic disorders caused by gradual neuronal loss; dementia can be the only presentation of neurodegenerative process or can be accompanied by other neurologic abnormalities.
There are four clinical dementia syndromes that account for 90 % of all cases after excluding reversible causes of cognitive decline: Alzheimer disease, vascular dementia, dementia with Lewy bodies and frontotemporal dementia. All except vascular dementia are primary neurodegenerative disorders, as are most of the remaining 10 % of dementia syndromes. This short review deals mostly with neuroimaging approaches to the four types of neurodegenerative dementia, namely Alzheimer disease, dementia with Lewy bodies, frontotemporal lobar degeneration and prion disorders. All included neurodegenerative diseases are characterized by disordered metabolism of different proteins, pathologic protein aggregation with intra and extracellular deposition.[10]
Alzheimer disease is the most common neurodegenerative disorder and accounts for approximately two thirds of cases of dementia. It is estimated that 1.5 % of population of 60 to 69 years suffers from this disorder and the prevalence doubles every 5 years until about age 90.[11] Insidious onset of forgetfulness, gradual restriction of vocabulary, dyscalculia, loss of visiospatial orientation and apraxia are all part of typical clinical presentation of the Alzheimer disease. Neurofibrillary tangles, which result form intraneuronal deposition of hyperphosphorylated tau protein and beta amyloid senile plaques are the two hallmark pathohistologic findings in this disorder. The pathological changes can first be detected in transentorhinal cortex and gradually spread to the limbic and then to the neocortical brain regions with relative sparing of the primary somatosensory and motor cortices and the cerebellum.[12]

Dementia with Lewy bodies differs from Alzheimer disease in its clinical presentation by fluctuating cognitive decline, presence of visual hallucinations and extrapyramidal signs. The characteristic neuropathological finding in this disorder are Lewy bodies (alpha synuclein deposits); both senile plaques and fibrillary tau inclusions can also be present to a variable extent.[5]

Frontotemporal lobar degeneration accounts for a substantial proportion of neurodegenerative dementia cases occurring in the population before the age of 65 years. The three main syndromes associated with this disorder are frontotemporal dementia, progressive nonfluent aphasia and semantic dementia. Two types of histopathologic changes are associated with this disease: neuronal loss and microvacuolation or astrocytic gliosis and formation of Pick bodies by aggregation of hyperphosphorylated tau protein. The clinical presentation however, depends on the distribution of pathology rather than on its type.[6]

Prion diseases, or transmissible spongiform encephalopathies, are a group of neurodegenerative disorders associated with formation and accumulation of conformationally altered prion protein. The most common form is sporadic Creutzfeldt-Jakob disease (CJD), presenting as rapidly progressive dementia. Inherited prion disorders are autosomal dominantly inherited conditions of variable clinical presentation (Fatal familial insomnia, Gerstmann-Sträussler-Scheinker disease, GSS). Prions can also be transmitted, either iatrogenically (e.g., through dural grafts,[13] human cadaveric growth hormone[14] or even blood transfusion[15]) or by ingestion of affected animal (or human) tissue (variant CJD[16] and Kuru).[17]

Overview of imaging modalities

Neuroimaging modalities can be divided into two groups, based on the objective of their use. Structural imaging uses physical properties of the brain to obtain accurate data about its anatomy and composition, while functional neuroimaging conveys data related to physiology and activity in different regions of the brain.

Structural neuroimaging

Computed tomography generates a three-dimensional image of the brain based on the different blocking of X-rays by different types of tissue. Its routine use in patients with dementia[18] is becoming less frequent, since *magnetic resonance* (MR) *imaging* provides more detailed images because of its superior soft tissue contrast.[19]

MR scanner uses a combination of a powerful magnetic field (which aligns the magnetization of hydrogen atoms) and specific combinations of pulses of radio waves (which alter the alignment of this magnetization) to elicit emissions of weak radio signals from the scanned tissue. These emitted signals are used for construction of three-dimensional images of the brain. Different radio wave pulse sequences are used in MR imaging in order to acquire images with different tissue contrast. T2-weighted images are used in imaging of white matter, cerebrovascular, basal ganglia and thalamic pathology,[19] while high resolution T1-weighted images are used for analysis of global and localized brain atrophy.[20]

Diffusion weighted imaging (DWI) is a specific MR imaging modality, which is sensitive to the random mobility of water molecules in the tissue (called diffusivity).[21] Microstructural alterations in the brain that cannot be detected using conventional MR can alter the pattern of water diffusivity and thus become apparent upon DWI.

Functional neuroimaging

Functional neuroimaging modalities use a range of different approaches to collect and display information related to brain activity. The potential clinical applications of these modalities stem from numerous studies which found that alterations in brain function occur prior to morphologic changes detectable by CT or MR.[19] Functional neuroimaging studies in neurodegenerative dementias are based on functional MR, SPECT and PET modalities.

Functional MR detects difference in ferromagnetic properties of oxygenated and deoxygenated hemoglobin; regional brain activity is thus measured as a function of local changes in deoxygenated hemoglobin concentration in response to defined stimuli or tasks.[22] This technique is the least invasive of all functional neuroimaging modalities. It also has the highest spatial and temporal resolution. Higher temporal resolution enables advanced task designs such as event related designs, which enable more detailed study of cognitive processes that could be impaired in neurodegenerative dementias.

Cerebral single photon emission computed tomography (SPECT) is a widely available technique based on local brain uptake of technetium 99m-labeled lipid-soluble compounds hexamethylpropylene amine oxime (HMPAO),ethyl cysteinate dimer (ECD) or iodine-labeled 123I-isopropyl-iodoamphetamine (123I-IMP).[23] Radioactivity measured by a rotating gamma camera is used as an indicator of local neural tissue perfusion. Semiquantitative, relative values of brain perfusion can thus be obtained, which can be normalized to the activity measured in cerebellum, as this region is among those least affected by the disease.[24]

Positron emission tomography (PET) is a nuclear medicine imaging technique, which measures the body or organ distribution of imaging tracers labeled with short-lived positron-emitting radioisotopes. The emitted positron, which is an antimatter particle, is combined with electron and the mass of these two particles is then converted into energy in the process called annihilation; two high-energy photons are emitted from the site of annihilation and this electron pair is detected by PET scanner camera. The detection of pairs of photons traveling in exactly opposite directions makes PET more sensitive than SPECT (with a spatial resolution of approx. 5 mm), which allows quantification of the concentration of the radiotracer

and *in vivo* assessment of the molecular processes that the tracer is involved in.[25] PET can be used for regional cerebral perfusion imaging, glucose metabolism analysis and assessment of neurotransmitter systems *in vivo;* its application is defined by the pharmacological properties of the tracer.
Oxygen-15 labeled water ($H_2{}^{15}O$) and 15-O2 ($^{15}O_2$) are two PET tracers used for *brain perfusion imaging;* regional cerebral perfusion is directly proportional to cortical activity and the short half-life of isotope 15-O (2 minutes) makes it suitable for repetitive administrations in activation studies.[26] The most commonly performed PET studies of the brain in patients with dementia that are aimed at *cerebral metabolism assessment* are those using 2-deoxy-2-[F18]fluoro-D-glucose (FDG). FDG concentration is proportional to cell glucose metabolism, since it competes with glucose for the uptake into the cells and undergoes phosphorylation as the first step in glycolytic pathway, but is not metabolized further and remains trapped in cells.[27] A promising new strategy has recently been employed in PET dementia imaging. Several amyloid-specific PET tracers were developed with the intention of *in vivo* quantification of dementia-associated pathology.[28]

Imaging findings in neurodegenerative dementias

Numerous neuroimaging approaches have been used in patients with dementia. Structural neuroimaging can detect differences in localized brain atrophy distribution, functional neuroimaging modalities provide an early insight into altered functioning of the brain whereas novel imaging probes provide promise of in-vivo detection of protein deposits.

Computed tomography and structural magnetic resonance imaging

Noncontrast CT or MR scan is currently recommended as part of routine diagnostic procedures in patients presenting with dementia[4] in order to exclude potentially treatable structural causes, such as subdural hematomas, intracranial tumors and normal pressure hydrocephalus.[18] The most frequent finding of structural neuroimaging in neurogenerative dementias is generalized brain atrophy, a non-specific condition that is also common in the non-demented individuals of the same age.[29]
Localized medial temporal lobe atrophy, in particular of the hippocampus, parahippocampal gyrus and amygdala, is the main structural feature detected and analyzed in Alzheimer disease.[20] Early CT-based methods demonstrated significant reduction in hippocampal volumes[30] and linear width of the temporal lobe[31] in these patients. Several approaches to quantification of medial lobe atrophy were later proposed, based on linear measurements, complex volumetry of the hippocampus or visual rating scales. A simple linear measurement that can be used on both, CT and MR images and yields high specificity and sensitivity for Alzheimer disease detection (93 % and 75 %, respectively) is the width of the temporal horn of the lateral ventricle.[32] Scheltens et al. described a visual rating scale for medial temporal lobe atrophy which encompasses subjective assessment of choroidal fissure, temporal horn and hippocampus;[33] this method was compared to objective volumetry and was found to be more practical and equally effective.[34]
Dementia with Lewy bodies is associated with atrophy of the putamen[35] and less pronounced atrophy of the medial temporal lobe[36] when compared to Alzheimer disease using MR imaging. Voxel based morphometry study of both disorders showed significant atrophy of basal forebrain associated with dementia with Lewy bodies.[37] Interestingly, severe atrophy of hippocampus was described in dementia associated with Parkinson disease, a finding that positions this disorder closer to Alzheimer disease then to (pathohistologically similar) dementia with Lewy bodies.[38]
Structural neuroimaging studies in patients with frontotemporal lobar degeneration show atrophy in the areas of anterior temporal and frontal cortex[39] and volumetric MR imaging analysis was able to distinguish Alzheimer disease patients from patients with frontotemporal degeneration based on a topographical pattern of atrophy involving the frontal lobes and anterior temporal regions.[40] Asymmetric atrophy is associated with both, semantic dementia (involving left inferolateral and anterior temporal regions) as well as progressive nonfluent aphasia, where left frontal and perislyvian structures are predominantly affected.[41]
Generalized brain atrophy can only be seen in a minority of CT scans performed on patients with sporadic CJD.[42] Inherited prion disorders can be associated with progressive generalized cortical[43] or cerebellar atrophy;[44] similar findings are described in some variant CJD patients.[45] The main MR characteristics of sporadic CJD are bilateral hyperintensive signal in the area of caudate and putamen[46, 47] and signal intensity increase in the cerebral cortex, termed cortical ribbon hyperintensity.[46] Pulvinar sign is diagnostic for variant CJD and has a sensitivity of 78 % and specificity of 100 % for diagnosis of variant CJD[48] and is defined as bilateral symmetrical pulvinar high signal relative to the signal intensity of other deep gray matter.[49] Additionally, high MR signal can also be seen in the regions of both, pulvinar and dorsomedial thalamic nuclei in variant CJD.[48]

Diffusion weighted MR imaging

DWI detected increased diffusivity in the temporal lobes of Alzheimer disease patients,[50] which could be explained by a reduction of axonal density in the region as a consequence of neuronal loss. Another study demonstrated statistically significant difference in mean diffusivity in the hippocampus was demonstrated between groups affected by Alzheimer disease, minimal cognitive impairment and healthy population.[51]
Abnormalities seen in prion disorders using DWI appear early in the course of the disease and may be the only positive findings in prion disorders.[46] DWI

appears to be the most sensitive imaging modality for sporadic CJD and it can also be used to monitor disease progression.[44] A possible microstructural explanation for the change in diffusivity of water, detected on DWI is the presence of spongiform degeneration with swelling of cells and restriction of the extracellular space in the brain tissue in prion disorders.[44] Particularly suitable image acquisition technique in these patients is echoplanar DWI, which has lower resolution than conventional MR image, but can be acquired within seconds.[52] Such rapid technique may be the most valuable (and the only diagnostic) modality in patients with movement or attention disorders.

Functional MR imaging

Functional MR studies in groups of individuals at risk for development of Alzheimer disease have shown either increased[53] or decreased[54, 55] brain activation in temporal lobe regions when compared to control groups. Increased activation by at-risk group could be explained by compensatory recruitment of additional brain tissue to accommodate the task given to experimental subjects. Substantial neuronal loss (in symptomatic individuals) presumably results in the loss of the compensatory response and thus causes the decrease in activation.[53] There were no published functional MR studies of patients with dementia with Lewy bodies or frontotemporal lobar degeneration known to the authors at the time of this review.

Cerebral SPECT

Cerebral SPECT has been widely used in dementia studies for brain perfusion imaging. Relative hypoperfusion of the hippocampus[56] and parietotemporal association cortex[57] was described in Alzheimer disease patients, which generally correlated with the severity of cognitive impairment. The sensitivity and specificity of brain SPECT for the diagnosis of AD are reported to be as high as 86 % and 96 %, respectively.[58] Dementia with Lewy bodies is associated with occipital hypoperfusion which is not found in Alzheimer disease.[59] This disease is also associated with characteristic distribution of dopaminergic presynaptic SPECT ligand with high specificity.[60] SPECT can also detect hypoperfusion in ventromedial frontal region of patients with frontotemporal dementia before atrophy becomes evident.[61] All prion disorders are associated with regional decreases in blood flow which can be seen prior to structural changes.[44]

Positron emission tomography

PET perfusion studies of Alzheimer disease patients show a pattern of hypoperfusion similar to the one described by SPECT findings. Parietotemporal regional hypoperfusion correlates well with cognitive performance[62] and posterior cingulate cortex is described to be affected early in the disease.[63] Unsurprisingly, these same areas also show the most marked hypometabolism in FDG PET studies with relative sparing of the basal ganglia, thalamus, cerebellum and primary sensory and motor cortex.[64]

The differential diagnostic value of FDG PET in neurodegenerative dementias was evaluated in a number of studies.[65–69] The largest of those[68] was multicentric study of 248 patients, mostly presenting with dementia (mean Mini-Mental State Examination score was 24). The sensitivity of FDG PET for diagnosis of histopathologically confirmed Alzheimer disease was 94 % and the specificity 73 %. The metabolic changes in nondemented individuals with mild cognitive impairment can also be detected[68, 70] with overall accuracy of FDG-PET only slightly lower in this group of patients (from 75 % to 100 %).[64] The method can also be used as a prognostic tool; it can predict the likelihood of progression of the dementia with high sensitivity (95 %) and specificity (75 %).[68] Dementia with Lewy bodies can be distinguished form Alzheimer disease with 86 % sensitivity and 91 % specificity based on FDG PET scan where less sparing of occipital (visual association) cortex metabolism can be detected.[71] A characteristic pattern of hypometabolism distribution can also be seen in patients with frontotemporal lobar degeneration. A recent study of 22 patients with frontotemporal dementia showed a significant symmetrical hypometabolism of the frontal lobes (sparing the motor cortex), the caudate nuclei, insula and thalamus bilaterally.[72] On the other hand, there is no pattern in hypometabolism in patients with sporadic CJD, where widespread cortical glucose hypometabolism is the most frequent observation.[73–75]

PET imaging of pathologic protein deposits in the brain

A more specific approach to dementia PET imaging has recently been taken by development of several amyloid-targeting imaging probes with the aim of direct *in vivo* imaging of dementia-related pathologic protein deposits (amyloid) in the brain.[76] These probes show potential role for early disease detection and monitoring of anti-amyloid therapeutic approaches. All are small hydrophobic molecules and some are structurally related to traditional histology amyloid dyes Congo Red and Thioflavin T. Four of these compounds have so far been used in human *in vivo* neuroimaging: FDDNP, PIB, SB13 and BF-227.

The first successfully used amyloid imaging probe was FDDNP (2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile[77]), followed by PIB (Pittsburgh Compound-B[78]), a compound structurally related to Thioflavin T. PIB has been used in the studies of Alzheimer disease, where marked retention of the tracer was reported in the frontal and parietal cortex when compared to non-demented control subjects.[78] Parkinson disease patients[79] and most of the patients with frontotemporal lobar degeneration[80, 81] did not differ from control groups in PIB-PET studies. C11-SB13 (4-N-methylamino-4'-hydroxystilbene) is a Congo Red derivative in which a charged part of the molecule was removed to enhance blood-brain barrier permeability; it has shown properties similar to PIB in Alzheimer disease patients imaging.[82] The most recent tracer reported to distinguish Alzheimer disease patients from healthy individuals by

retention of the tracer in the posterior association area of the brain was BF-227, 2-(2-[2-Dimethylaminothiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy)benzoxazole.[83]
FDDNP is a small, fluorescent, hydrophobic molecular imaging probe with high *in vitro* affinity for beta amyloid fibrils, as shown by fluorescent and radioactive assays. Its fluorescence is enhanced by hydrophobicity of its microenvironment when bound to amyloid fibrils.[84] It can be used in fluorescence microscopy[85] and its excitation spectrum, which lies within the visible light wavelenghts (440–490 nm), minimizes tissue autofluorescence.[86] FDDNP fluorescently labels several types of pathologic amyloid and amyloid-like protein deposits in the histological brain sections of neurodegenerative disorders: senile plaques, vascular beta amyloid and neurofibrillary tangles, which are all associated with Alzheimer disease,[84,87] prion protein amyloid deposits in variant and sporadic CJD as well as GSS[88] and Lewy bodies in dementia with Lewy bodies and Parkinson disease.[87]
In vivo FDDNP-PET scanning of Alzheimer disease patients has evolved from early »proof of principle« studies,[77] to recently published longitudinal study of FDDNP use in Alzheimer disease and minimal cognitive impairment. FDDNP-PET was shown to differentiate between groups of Alzheimer disease patients, individuals with mild cognitive impairment and cognitively non-impaired subjects better that FDG-PET or structural MR imaging. Furthermore, global FDDNP binding increase was shown to be related to disease progression during the two year follow-up.[89] In vitro study of FDDNP labeling properties in histological brain sections in CJD, vCJD and GSS[88] has led to the use of FDDNP-PET as the first successful prion amyloid *in vivo* detection method.[90,91]

Discussion

Structural neuroimaging has evolved beyond its main role as a method for exclusion of potentially reversible conditions underlying dementia. The major advantage of structural neuroimaging and also the main reason for its frequent use as a research tool is its wide accessibility. It should be noted that variant CJD is the only neurodegenerative condition reviewed here, that lists MR imaging finding among its diagnostic criteria.[49] Apart from prion disorders and obvious structural causes discussed previously, there are several limitations in the use of structural neuroimaging techniques for the diagnosis of the dementia cause. First, the approaches to quantification of localized brain atrophy can be complex and time consuming and therefore hardly suitable for routine clinical use. Automated voxel-based morphometry is suitable for group-level studies and cannot yet be reliably applied to individual patients. Most importantly, structural changes occur late in the course of the disease and represent gross and predominantly irreversible changes in the brain.
Functional imaging detects dementia-associated changes in the brain prior to the occurrence of detectable atrophy. Currently, MRI data is limited to Alzheimer disease patients, where compensatory hyperactivation has been demonstrated to occur early in the disease. Both, SPECT and PET have been used to demonstrate similar regional perfusion and metabolic deficits in neurodegenerative dementias.
The importance of early diagnosis of dementia was shown in studies of long-term effects of cholinesterase inhibitors in Alzheimer disease patients. Treatment postponed the need for institutionalization of the patients,[92] whereas a delayed start of therapy correlated with faster cognitive decline later in the disease.[3] PET detection of dementia-related pathology shows huge promise. FDDNP and other amyloid PET probes may play a role in diagnosis of neurodegenerative dementias by helping to identify the group of the patients that would benefit most by the timely therapy. Furthermore, amyloid PET imaging could also help to reduce the risks and cost of dementia-related therapeutic trials. The number of research subjects enrolled could be lowered by reliable identification of brain amyloid presence in asymptomatic or mildly symptomatic individuals, and by providing a sensitive and objective method to measure anti-amyloid therapy efficacy. A study demonstrating the use of PET amyloid imaging in the monitoring of effects of anti-amyloid therapy was recently performed in a transgenic mice study using PIB.[93]

Conclusions

Different imaging modalities serve a range of roles in the neuroimaging of dementia. Wide accessibility of CT and MR imaging is a prerequisite for their routine use in everyday diagnostic procedures and exclusion of obvious treatable conditions causing cognitive decline. These modalities can also be used in analysis of disease-specific localized brain atrophy. Changes in brain physiology occur earlier than atrophy and functional neuroimaging techniques detect those changes with high specificity and provide useful prognostic information. Recent advances in PET imaging of dementia-related pathology *in vivo* are opening new possibilities as a specific and sensitive method for detection of neurodegenerative disorders. It could allow early recognition of dementia patients, and provide a specific method for monitoring of disease progression. Additionally, amyloid imaging may provide an objective method for evaluation of anti-amyloid therapy strategies.

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