Current CT and MRI possibilities to diagnose and differentiate dementia

Ewa Kurys-Denis[1], Ewa Papuć[2], Witold Krupski[1], Zbigniew Stelmasiak[2]

[1.] 2nd Department of Radiology, Medical University of Lublin
[2.] Department of Neurology, Medical University of Lublin

Abstract

All of the major neurodegenerative disorders have relatively specific imaging findings that can be identified. New MRI imaging techniques carry the hope of revolutionizing the diagnosis of neurodegenerative disease so as to obtain a complete molecular, structural, and metabolic characterization, which could be used to improve diagnosis and to stage each patient and follow disease progression and response to treatment. In this review we provide an overview of the various structural computed tomography (CT) and magnetic resonance imaging (MRI) methods used to image neurodegenerative disease and discuss their usefulness in specific neurodegenerative disorders.

Keywords: dementia, computed tomography, magnetic resonance imaging, differential diagnosis of dementia

Streszczenie

Wszystkie główne choroby neurodegeneracyjne posiadają swoje charakterystyczne cechy w obrazowaniu ośrodkowego układu nerwowego. Nowe techniki obrazowania rezonansu magnetycznego (RM) dają nadzieję na zrewolucjonizowanie dzisiejszej diagnostyki chorób neurodegeneracyjnych poprzez otrzymanie dokładnych obrazów molekularnych, anatomicznych i metabolizmu na poziomie komórkowym. Mogłoby to polepszyć diagnostykę, ocenę zaawansowania i progresji choroby oraz analizę odpowiedzi na leczenie. W naszej pracy omawiamy zastosowanie metod strukturalnych (anatomicznych) tomografii komputerowej i rezonansu magnetycznego w obrazowaniu chorób neurodegeneracyjnych oraz dyskutujemy na temat ich przydatności w różnicowaniu typów demencji.

Słowa kluczowe: demencja, tomografia komputerowa, magnetyczny rezonans jądrowy

Introduction

Dementia is a common illness with an incidence that is rising in the aging population. It is a chronic and progressive process which leads to impairment of multiple intellectual functions because of diffuse involvement of the brain or through involvement of multiple cortical and subcortical areas. Progressively, memory, language, visuospatial skills, behavior, executive abilities, or the capacity for managing information can be affected to a different extent and in different proportions. There are a number of neurodegenerative diseases that cause dementia, including Alzheimer's disease, dementia with Lewy bodies, and frontotemporal dementia, which is subdivided into the behavioral variant, the semantic variant, and nonfluent variant. Numerous other neurodegenerative illnesses have an associated dementia, including corticobasal degeneration, Creutzfeldt–Jakob disease, Huntington's disease, progressive supranuclear palsy, multiple system atrophy, Parkinson's disease dementia, and amyotrophic lateral sclerosis. Vascular dementia and AIDS dementia are secondary dementias. Even though, diagnostic neurological criteria of dementias depend on a constellation of clinical symptoms, they may be misleading and the definite diagnosis still remains a pathologic one. On the other hand, treatments of dementias become more available and target specific molecular pathologies nowadays, such as β-amyloid in patients with Alzheimer's disease (AD), tau in various taupathies, such as corticobasal syndrome and progressive supranuclear palsy, and TDP-43 in TDP-43 proteinopathies, such as the semantic variant of frontotemporal dementia (FTD) [1,2]. That is a reason why doctors need to differentiate between different dementias early on in a course of a disease and that is where neuroimaging becomes essential and important.

The role of imaging in dementia has traditionally been directed at ruling out treatable and reversible etiologies and not to use imaging to better understand the pathophysiology of the different dementias. The most recent recommendation of the American Academy of Neurology also includes the use of structural imaging in this routine way, i.e., computed tomography (CT) or magnetic resonance imaging (MRI), to assist in the diagnosis of dementia and to specifically rule out reversible, treatable causes [3]. For exclusion of mass lesions a CT scan may be sufficient, but for the demonstration of tissue abnormalities that may indicate a specific degenerative disease of the brain, MRI is necessary. However, as neurodegenerative diseases are associated with the development of pathologic changes long before the develop-

ment of structural impairment, functional and biochemical neuroimaging has a potential role in the diagnosis of early - even presymptomatic - stage of dementing disorders. The aim of this review is to provide an overview of the various CT and MRI methods used to image neurodegenerative disease and to discuss their usefulness in specific neurodegenerative disorders.

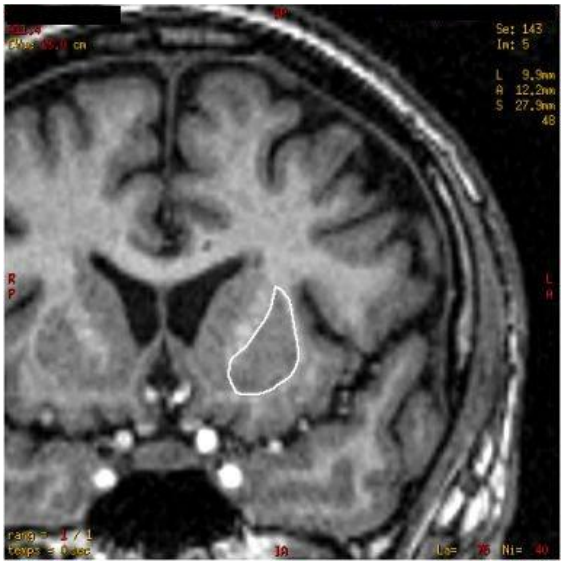
CT and MRI as structural imaging and volumetric methods (T1-weighed images)

Neuroimaging may be divided into structural techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) and functional techniques such as single photon emission computed tomography (SPECT), positron emission tomography and functional MRI. In neurodegenerative disease structural scans prove themselves useful in assessing volumetric changes in the brain (Fig.1 a-c). Those changes involve decreases in gyral and increases in sulcal size and are probably secondary to decreases in synaptic density, neuronal loss, and cell shrinkage [1,4]. Every neurodegenerative disease has a predilection for specific brain systems or networks, with each associated with tissue loss in particular brain regions.

Classical CT examination is most often used in acute settings and/or in clinical settings where MRI is not available or contra-indicated with the aim of ruling out alternative or underlying pathologies. Although CT scanning is still widely used because of its better accessibility over MRI, MRI is currently the modality of choice for assessing abnormalities in neurodegenerative syndromes. In Alzheimer's disease (AD), for instance, the medial temporal lobes, especially the hippocampus and entorhinal cortex (ERC), are among the earliest sites of pathologic involvement and it has been shown that volume loss of the hippocampus is strongly associated with actual neurofibrillary pathology [5,6]. There are studies that have shown decreased hippocampal and ERC volumes in patients with AD compared with age-matched controls [7]. Other severely affected areas include the lateral parietal and posterior superior temporal regions and medial posterior portion of the cingulate gyrus [8], but because AD is a diffuse disease, atrophy can be also observed in the frontal, temporal, and occipital lobes [9]. CT can already visualize structures touched by atrophy in AD. It visualizes enlargement of the temporal horns and widening of the hippocampal fissures as indirect changes due to atrophy of the hippocampal complex. CT of the temporal lobes, however, is hampered by bone hardening artefact and limited view angle. MRI being free of the bone hardening artefacts and giving the possibility of imaging in a plane perpendicular to the long axis of the hippocampus, thus reducing volume averaging, provides better visualization of the medial temporal lobes, including the hippocampus. Numerous researchers tried to find

Fig 1 a-c. Volumetric segmentation of the putamen on T1-weigthed MRI images

a)



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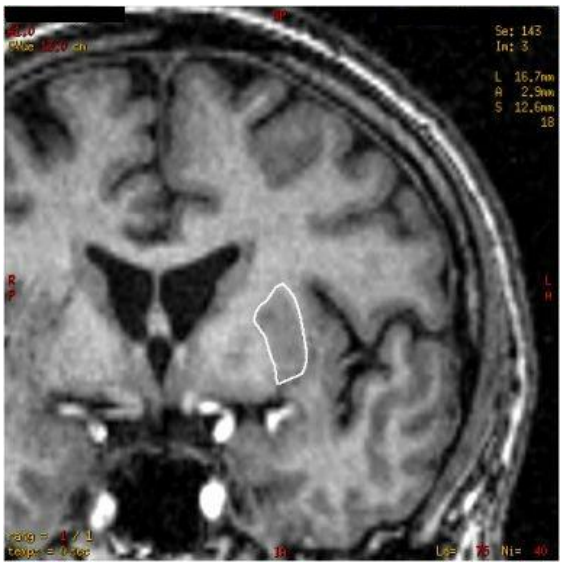

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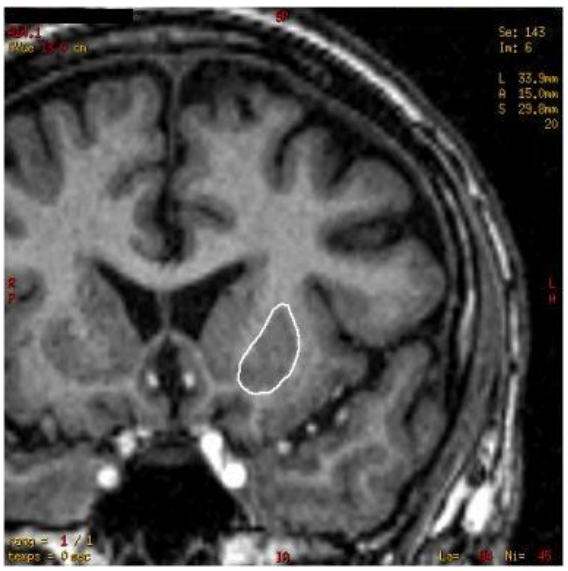


the best structural marker for the diagnosis of AD using CT and/or MRI examination. De Leon et al. found the sensitivity of widening of the hippocampal fissure in AD patients to be 75–95%, increasing with the age of the subject studied [10]. Specificity of this marker, however, dropped markedly after the age of 60 years. Jobst et al. measured the average thickness of the medial temporal lobe (hippocampal formation and gyrus) on axial CT slices and found that a level of 11.5 mm was a cutoff value for hippocampal atrophy (49 of 51 AD patients) [11]. This measurement turned out to be non-specific, however, for AD, as 6 of 10 patients with other types of "dementia" (vascular dementia, PSP, major depression) also had atrophy of the medial temporal lobe according to this criterion.

MRI provides a better accuracy in detecting hippocampal atrophy. High-resolution MRI coronal T1-weighted images reveal more details of the hippocampus than the CT images. Furthermore, with advanced postprocessing techniques of MRI images, either by hand tracing or by region growing, it is possible to obtain volumetric measurements of the hippocampus. Kesslak et al. studied eight AD patients and seven age-matched controls using coronal inversion recovery T1-weighted MRI [12]. They found that volumetric measurements values of the hippocampus and parahippocampal gyrus were significantly lower in AD patients than in controls. Based on these values they were able to discriminate between the two groups completely. Moreover, they found good correlations between the observed atrophy and the severity of dementia measured by the Mini-Mental State examination. Killany et al. [13] and Pantel et al. [14] published similar results and hypothesized that hippocampal and parahippocampal atrophy occur early in AD since they found similar values in possible and in probable AD cases.

CT and especially volumetric MRI have been also used to study patients with other neurodegenerative diseases. In mild cognitive impairment (MCI), where there is a high risk of progression to AD, with a conversion rate to dementia reaching about 12–15% per year, MRI studies have shown that hippocampal volumes and cortical volumes in the parietal and lateral temporal regions are able to predict the likelihood of progression [1,15]. In MCI patients higher atrophy rates in ERC were observed [16] compared to controls. However, although regional volume loss occurs in both MCI and AD, the utility of using structural imaging for diagnosis remains unsure because in most volumetric studies of MCI and even AD, at least some overlap exists between patients and controls.

Another disease in which structural imaging can be useful in advanced cases is frontotemporal dementia (FTD). It is a disorder that encompasses a heterogeneous group of patients sharing focal degeneration within the anterior frontal, temporal, and insular regions. There are behavioural and semantic variants of this disease. MRI has revealed unique patterns of brain atrophy with frontal lobe volumes reduced in patients with the behavioural variant of FTD (bvFTD), compared with those of both AD patients and age-matched controls. The target sites in FTD are the ventromedial frontal cortex, the posterior orbital frontal regions, the insula, and the anterior cingulate cortex, which are relatively spared in AD. Furthermore, atrophy in the frontal lobes in FTD is often seen in the lateral frontal lobe. The atrophy of the target regions in bvFTD explain unique behavioral symptoms seen in that disorder. Patients with the semantic variant of FTD (svFTD) have relative preservation of frontal lobe volumes but marked loss of volumes in the temporal lobes, in particular the neocortex in the temporal pole, as well as atrophy in the amygdala, which is a critical structure for emotional processing [17,18].

Dementias in Parkinsonian syndromes cause damage in different networks within the brain They are mostly associated with regional, subcortical grey matter volume loss. Volumetric MRI in this disease may be useful in diagnosing and follow-up of early grey matter loss or in finding a cerebral origin of some less common syndromes. Bonneville et al. and Bloch et al. investigated whether camptocormia in PD has a central origin [19,20]. Seventeen PD patients with camptocormia were prospectively enrolled and were compared to 10 matched PD patients without camptocormia and 12 normal controls. The normalized volumes of the brain, striatal nuclei, and the cross-sectional areas of the midbrain and pons were measured on three-dimensional magnetic resonance imaging. Data were correlated with the severity of the symptoms. The authors found that the normalized axial surface of the midbrain was statistically smaller in PD patients with camptocormia than in normal controls ($p=0.01$). The normalized volumetric data were not statistically different in PD patients with camptocormia. There was a significant negative correlation between the severity of camptocormia and the normalized brain volume ($p<0.009$; $R = -0.649$) and sagittal pons area ($p<0.01$; $R = -0.642$). Based on MRI volumetric images, the authors suggest that PD with camptocormia may represent a selective form of PD in which a specific neuronal dysfunction possibly occurs within the brainstem.

Other neurodegenerative diseases in which structural neuroimaging can be useful include progressive supranuclear palsy (PSP), corticobasal syndrome, dementia with Lewy bodies (DLB) and spinocerebellar atrophies. Characteristic of progressive supranuclear palsy – although not diagnostic of this condition - are third ventricle dilatation and midbrain atrophy with shortening of the anteroposterior length of the midbrain. In corticobasal syndrome, on the contrary, frontally predominant atrophy is more typical [21]. Dementia with Lewy bodies (DLB)

is associated with diffuse atrophy, and no established pattern is characteristic on structural MR images. Some forms of spinocerebellar atrophy are associated with cognitive impairment and display both cerebellar and cerebral atrophy along with caudate and putamen atrophy in some variants [22].

High-field structural MRI

MRI scanners with high-field of 3T and 4T provide good structural data but the resolution remains still limited because of the relatively high signal-to-noise ratio. The hippocampus and its subfields cannot be well visualized using most clinical or research scanners, which are currently 1.5 or 3T. The introduction of 7T MRI, currently only used in research, holds promise for better visualization smaller details of the macrostructures of subcortical structures and cells, including the hippocampus and basal ganglia. The higher field strength will likely also improve spectral acquisition and functional MRI (fMRI).

A recent study [23] using 7T MRI shows possibilities of visualization of an early target of AD pathology that is the CA1 apical neuropil. In their work Kerchner et al found a selective thinning of the CA1 apical neuropil layer relative to the CA1 cell body layer in subjects with mild AD, with the thickness of the CA1–stratum lacunosum–moleculare (SRLM) being a better indicator than overall hippocampal volume for distinguishing subjects with AD from normal controls [23]. These neuropil areas of the hippocampus are claimed to be the sites for tau pathology in AD. With the development of clinical signs of AD, the varicose, tau-filled CA1 dendrites in the stratum lacunosum-moleculare disappear, which possibly corresponds to the thinning of the CA1–SRLM observed in vivo in the studies Scheff et al and Mizutani et al [24, 25]. High-field MRI gives therefore hope for diagnosing structural microchanges in the brain directly linked to molecular pathology in AD.

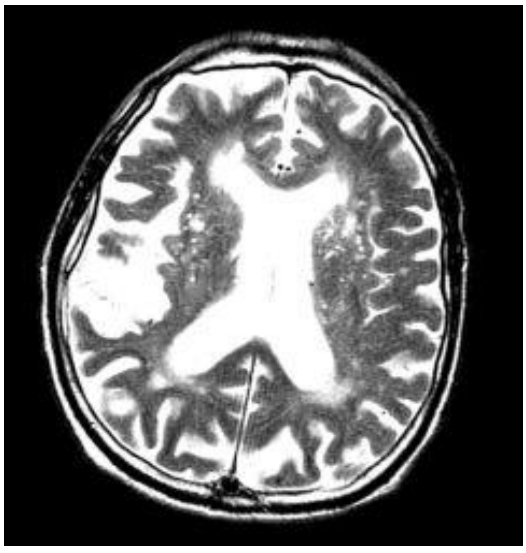
Vascular dementia in MRI

Vascular dementia is a common cause of late-life cognitive decline. Senile dementia which was earlier commonly referred to as "cerebral arteriosclerosis" or "hardening of the arteries", is a heterogeneous disorder. Vascular risk factors, transient ischemic attacks, silent and clinically evident strokes, and ischemic white matter changes on brain imaging studies are all factors associated with the development of dementia. There is no clear interaction between vascular risk factors for dementia, the presence of ischemic infarctions in the brain and the degree of impairment in cognitive functions. Some complicated interactions between vascular disease factors and dementia may include the angiotensin II system. Stimulation of this system leads to increased amyloid production in the endothelium of brain microvessels, which is involved in the pathogenesis of AD [26]. This mechanism could explain why hypertension is a risk factor for dementia. Another factor that is an active field of research involves the MEOX2, or GAX, gene, a regulator of vascular differentiation whose expression is low in brains of patients with AD. This gene also regulates angiogenesis, reduces apoptosis, and increases production of a protein involved in the clearance of amyloid [27].

Microvascular pathologies are best visualized on T2–weighted and fluid-attenuated inversion recovery (FLAIR) MRI images (Fig.2 a, b). Hyperintensity, or increased (bright) signal in this sequences is associated with cerebral edema and gliosis. Small vessel disease causes incomplete or complete infarcts in the white matter (WM) or in subcortical gray matter nuclei that on

Fig 2. Microvascular pathologies seen as hyperdensities of the white matter signal on T2 (a) and FLAIR (b) images in a patient with dementia. Notice the irregular atrophy in the right parietal lobe and generalized cortico-subcortical atrophy

a)



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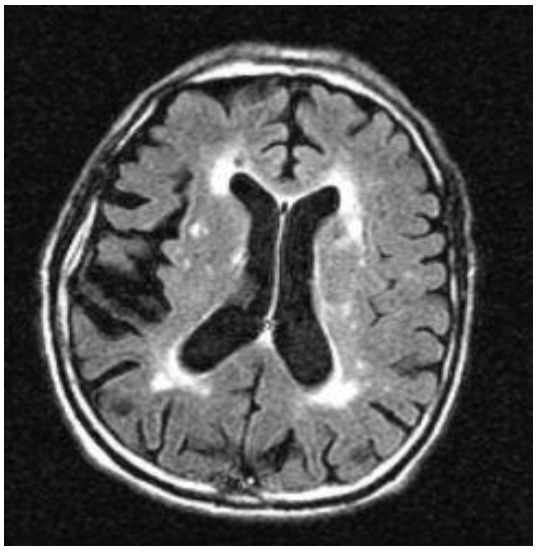


FLAIR images appear as hyperintensities, whereas complete infarcts present as lacunes (diameter, 2–15 mm), which are hypointense to the brain and isointense to the cerebrospinal fluid. T2/FLAIR imaging, especially T2*-gradient echo images, are also sensitive to microhemorrhages, which appear as hypointense lesions due to the inhomogeneities in the local field caused by the cerebral iron deposition and can be seen in up to 65% of patients diagnosed with vascular dementia [28] Common neurodegenerative disorders, such as AD and FTD, are usually not associated with major changes on T2/FLAIR scans.

Diffusion-weighted imaging (DWI)

Diffusion-weighted imaging (DWI) is based on the analysis of the random motion of water molecules in the brain. Mobile (diffusible) protons experience a signal void that is related to the velocity of the spins and the direction of the applied magnetic gradient. For quantification of apparent diffusion coefficients (ADC), different gradient strengths (b-factors) have to be employed. In the brain, diffusion is anatomically restricted along the direction of the myelin fibres. Changes in the diffusion pattern reflect microarchitectonical desintegrities of the brain tissues. Diffusion option in MRI examination is necessary during any assessment of acute stroke victims, as it shows all acute injury extremely well. In most neurodegenerative diseases, DWI images appear to be normal; however, in Creutzfeldt–Jakob disease (CJD), decreased diffusion in the cerebral cortex (called cortical ribboning) with an associated decrease in basal ganglia is a highly sensitive (91%) and specific (95%) diagnostic marker of CJD [29]. Diffusion-weighted MRI can eventually be advocated in patients with multiinfarct dementia to differentiate recent, acute changes from chronic brain ischemia.

Diffusion-tensor imaging (DTI)

Diffusion tensor imaging (DTI) is a new MRI technique that enables the exact assessment of white matter tracts (tractography), revealing injury that may not be apparent with other imaging techniques. DTI, unlike DWI, evaluates the diffusion of water in each of the three main directions (right/left, front/back, up/down) and so allows quantification of the degree of anisotropy and local fiber direction on a voxel-by-voxel basis. Axons and myelin sheaths act as barriers and consequently diffusion of water is anisotropic (directionally dependent) in WM fiber tracts, being significantly greater along the axis of those fibers, thereby providing a tensor measurement [30]. Fractional anisotropy (FA) is a measure of the degree of anisotropy of a diffusion process and ranges from zero, when diffusion is isotropic (i.e., unrestricted in all directions), to one, when diffusion occurs only along one axis and is fully restricted in the other directions.

DTI technique may be useful in differentiating different dementias and assessing white matter changes. Zhang et al compared AD and FTD and found that patients with FTD had reduced FA in frontal and temporal regions,including the anterior corpus callosum, bilateral anterior, and descending cingulum (Cg) tracts, and in the uncinate (UNC) fasciculus compared to controls, while patients with AD had reduced FA in the parietal, temporal, and frontal regions, including the left anterior and posterior Cg tracts, bilateral descending Cg tracts, and left UNC fasciculus [27].

MRI spectroscopy

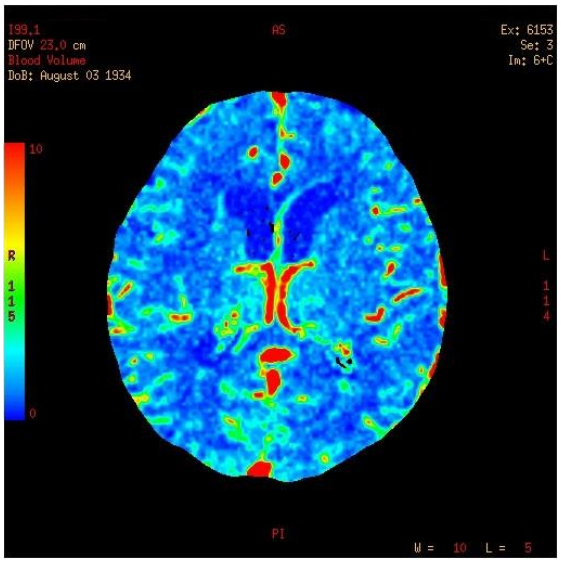
In vivo MR spectroscopy (MRS) is a unique method which can detect some of the biochemical compounds in the brain without interfering with their metabolism. Proton MRS (^{1}H MRS) yields information about the energy metabolism (creatine, lactate), membrane turnover (choline, myo-inositol), and N–acetyl–aspartate (NAA), a putative marker of neuronal integrity. The advantage of MR–spectroscopic imaging over single volume approaches is the assessment of the regional distribution of metabolite concentration. Many studies have reported on NAA content in patients with dementia. NAA is consistently reported as being lower in the parietal gray matter and hippocampus of patients with AD than in cognitively normal elderly subjects [31]. In vascular dementia, the greatest deficits occur in the frontal and parietal cortex [32].

Perfusion CT / MRI

Perfusion imaging (CT or MRI) delivers the information about regional differences of cerebral perfusion, which may be helpful in the assessment of severity of dementia and eliciting different types of dementia. The main values measured include cerebral blood volume (CBV), blood flow (CBF), and mean transit time (MTT), the distribution of which can be presented visually as perfusion maps (Fig.3 a, b). Perfusion imaging may be performed to demonstrate areas of reduced CBV and CBF in vascular dementia where CBF reductions are usually multifocal and subcortical. Zimny et al evaluated the usefulness of perfusion CT (pCT) in differentiating Alzheimer's disease (AD) from vascular dementia (VaD) and mixed dementia (MixD). They calculated regional perfusion parameters (rCBF, rCBV, and rMTT) from 31 ROIs in the grey and white matter of the frontal and temporal lobes, basal ganglia, and internal capsules bilaterally in 41 patients with different types of dementia. On the basis of these studies they concluded that perfusion CT may be a valuable method of distinguishing between AD and VaD but it seems to be of little significance in differentiating MixD from VaD and of no usefulness in distinguishing between AD and MixD [33].

Fig 3. a) CBV map of a 72-year-old male with the diagnosis of mild AD, CT perfusion at the level of the basal ganglia. Marked diffuse cortex hypoperfusion, especially in the frontal lobes and right parietal lobe. Enlargement of frontal horns of lateral ventricles. b) Normal CBV map of a 18-year-old female at the same level.

a)



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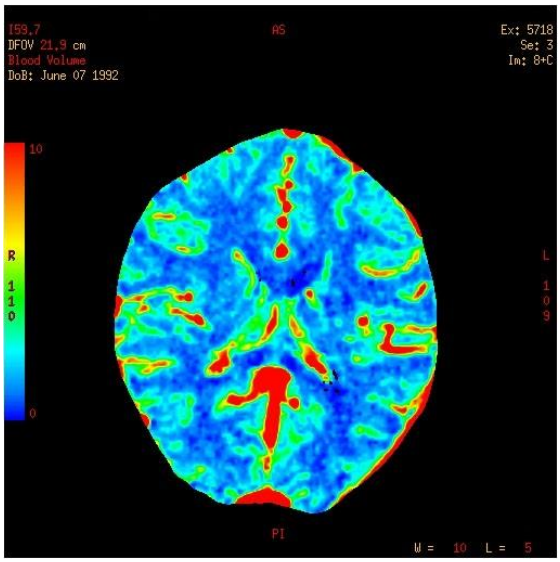

Perfusion CT is still more available as an imaging option, whereas MRI perfusion excludes the risk of X-ray radiation. When compared to single photon emission tomography (SPECT) the MRI imaging has also superior spatial resolution.

Conclusions

Brain imaging with both structural and functional neuroimaging techniques has the potential to provide clinicians with more precise information in specific dementias. As our understanding of neurodegenerative disease progresses and treatments become available, the need for more accurate diagnosis is emerging making the future of brain imaging involve combinations of imaging techniques to identify the presence of a molecular abnormality, to assess its impact on the brain structure and function, and to predict and follow the effects of treatment. Because of its multimodal capability, MR has become the most versatile method for differential diagnosis in dementia. The primary role of structural and volumetric MR and CT in the exclusion of other underlying disorders and primary differentiating also plays an important role in every day diagnosis.

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Correspondence address

Dr Kurys-Denis Ewa,
Department of Radiology, Medical University of Lublin,
Staszica 16, 20-081 Lublin, Poland,
tel/fax. +48(81)5321084,
e-mail: ekurys@mp.pl