REVIEW

MRI of the ‘Alzheimer syndrome’
IRM du ‘syndrome d’Alzheimer’

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Abstract Interest in the identification of cognitive decline in its earliest manifestations and the heterogeneity of clinically diagnosed Alzheimer’s disease (AD) explain the growing number of neuroimaging studies of AD. Alzheimer-type lesions are associated with loss of neurons, and magnetic resonance imaging (MRI) can detect predominantly left atrophic changes in the entorhinal cortex, amygdala and anterior hippocampus several years before the onset of clinical symptoms. Cerebrovascular disease can mimic AD in the elderly whereas MR markers of subcortical vascular disease–leukoaraiosis, lacunar infarcts, microbleeds, ventricular enlargement, cortical and hippocampal atrophy–appear to be structural changes associated with vascular-related cognitive impairment. Furthermore, analysis of prodromal forms of late-onset dementia of Alzheimer’s type (DAT) differentiates amnesic single-domain mild cognitive impairment, which shows MR patterns similar to those observed in early-onset DAT, from other predementia patterns without atrophy at the earliest sites of AD pathology. Mesiotemporal atrophy on MRI predicts late-onset DAT, but the current rating scales or measurements of mesiotemporal atrophy do not differentiate anteromesial temporal atrophy that is highly suggestive of AD from predominantly hippocampal atrophy, suggestive of non-AD damage and, usually, vascular disease. The other, most common MRI predictors of late-onset DAT may be considered indirect markers of arterial senescence whereas brain atrophy is diffusely milder and MR markers of small-vessel disease more frequent in late-onset, compared with early-onset, DAT. Thus, MRI suggests an overestimation of AD pathology while underestimating ‘arteriosclerotic brain degeneration’ in the clinical picture of ‘Alzheimer syndrome’.

MOTS CLÉS
Maladie d’Alzheimer ; Déficit cognitif léger ; Vieillissement ; Démences tardives ; IRM ;

Résumé Si le diagnostic de la maladie d’Alzheimer (MA) reste encore basé sur le tableau clinique, la nécessité d’un diagnostic précoce avant la survenue de lésions irréversibles et l’hétérogénéité des démences de type Alzheimer (DTA) conduisent à un intérêt grandissant pour l’imagerie cérébrale. Les lésions de la MA sont associées à une perte neuronale débutant dans les régions entorhinales et l’IRM peut détecter, plusieurs années avant la survenue de déficits cognitifs, une atrophie de toute la région temporale antéro-interne à prédominance gauche. La pathologie cérébrovasculaire sous-corticale, principale cause vasculaire de déclin cognitif, peut contribuer au « syndrome d’Alzheimer » et l’IRM est particulièrement adaptée
Introduction

Aging is the major risk factor for dementia and, at present, there is no efficient treatment for this devastating illness. Thus, dementia has become a major public-health problem within the worldwide aging population, with major implications in terms of both human suffering and monetary cost.

Alzheimer’s disease (AD) is considered the most common cause of dementia. In clinical practice, it is synonymous with a progressive deterioration of memory and other cognitive functions that is severe enough to interfere with social and occupational activities. Current AD diagnostic criteria do not require neuroimaging evidence of structural Alzheimer-type brain alterations [24]. Exclusion criteria mainly consist of symptoms suggestive of stroke such as sudden-onset or focal neurological signs [24]. However, given only these most commonly used standard criteria means that AD is only diagnosed at the late stage of dementia, when severe neurodegeneration and thus, irreversible neuronal loss limit the reversibility of symptoms. Indeed, AD is highly insidious, and even fully developed Alzheimer’s pathology can be present with no signs of cognitive impairment [6].

It is increasingly recognized that subcortical vascular disease can clinically mimic AD in the elderly, and the current diagnostic criteria for AD are unable to exclude ‘silent’ subcortical vascular disease. As this condition is also being increasingly recognized as a major cause of cognitive impairment, it appears that clinically diagnosed AD is, in fact, a heterogeneous condition in the elderly. As postmortem studies of late dementia show that only 20-30% of cases are solely AD and suggest that a diagnosis of AD is merely a neuropathological description, the term ‘Alzheimer syndrome’ may be a more appropriate diagnosis in late-onset dementia.

Finally, AD diagnostic criteria were first published more than 20 years ago [24]. Since then, considerable advances in magnetic resonance imaging (MRI) and an increasing knowledge of AD now suggest that routine neuroimaging may play a central role in detecting incipient AD, and in assessing the contributions of AD and cerebrovascular dysfunction in late-onset dementia.

From neuropathological descriptions to ‘pure’ AD on MRI

Alzheimer-type lesions are associated with loss of neurons and synapses. Typically, there is a hierarchical and gradual expansion of the lesions over decades. Involvement of the transentorhinal and entorhinal cortices, and adjacent anterior hippocampi characterizes the early rhinal stages (Braak stages I-II), becoming worse as the disease progresses to the limbic (Braak stages III-IV) and neocortical stages (Braak stages V-VI) [8]. The earliest Braak stages (I-II) are clinically silent. Mild cognitive alterations with an isolated and progressively worsening amnestic syndrome may be seen at the limbic stages (III-IV) whereas fully developed AD (stages V-VI) is commonly thought to be a prerequisite for clinical evidence of dementia in pure AD. Yet, as previously stated, extensive AD, including Braak stages V-VI, can coexist with intact cognition in the elderly, while moderate or severe AD (Braak stages III-V) is found in up to 41% of the non-demented elderly [6]. However, severe destruction of primarily the entorhinal cortex and surrounding regions is already evident in the early limbic stages, and worsens as the disease progressively spreads to other regions of the brain. Thus, in AD, there is early and disproportionate atrophy of the entorhinal cortices, hippocampi, amygdala, temporal poles and adjacent fusiform gyri [8,17].

Three-dimensional (3D) T1-weighted sequences allow accurate in vivo demonstration of this particular pattern of atrophy and also suggest a predominance of left-sided atrophy—at least in the earliest stages. Indeed, normal, presymptomatic patients with autosomal-dominant early-onset familial AD present a predominantly left temporomodal atrophy on MRI several years before the onset of dementia [34]. In the elderly with only isolated mild memory impairment—the so-called ‘amnesic single-domain mild cognitive impairment’ (A MCI)—there is also a predominantly left-sided atrophy on MRI involving the amygdala, anterior hippocampus and entorhinal cortex [5]. All these structural changes are present several years before the diagnosis of dementia of the Alzheimer’s type [5,36,39]. In both A MCI and early-onset AD, there is a lack of significant cerebrovascular change [5,14].
MRI in vascular cognitive impairment

There is, as yet, no consensus regarding the pathological diagnosis of vascular cognitive impairment (VCI); both the clinical and neuroimaging criteria for VCI are still under debate. However, structural changes in the brain associated with small-vessel disease are increasingly being recognized as indirect markers of VCI. The concepts of multi-infarct dementia and of strategic infarcts responsible for persistent dementia are no longer widely accepted and, in post-stroke dementia, stroke is now recognized as the ‘tip of the iceberg’ rather than the direct cause of dementia. Indeed, large- and small-vessel diseases are associated with dementia in the elderly [12]. The most common cerebral small-vessel disease in the elderly is lipohyalinosis (arteriosclerosis), the logical consequence of age-related arterial stiffening and arteriosclerosis, arterial hypertension or other causes of atherosclerosis [29,33]. Arterial stiffness induces insufficient modulation of blood pressure variations and this so-called ‘windkessel dysfunction’ in turn induces mechanical damage to the small arteries in target organs, including the brain and kidneys [29,33]. Inefficient damping of arterial pulsations may damage capillary exchanges, which require an almost pulseless, smooth flow, and there is also growing evidence that subcortical cerebrovascular disease in the elderly may be an indirect marker of more widespread chronic low-grade cerebral hypoxia [33].

MRI is a more sensitive tool than computed tomography (CT) in the assessment of biomarkers of small-vessel disease such as leukoaraiosis, lacunar infarcts, microbleeds, ventricular enlargement and brain atrophy. FLAIR T2-weighted sequences best delineate periventricular high signal intensities; fast spin-echo T2-weighted sequences are more sensitive to infratentorial white-matter changes and deep lacuna; T2*-weighted sequences are required to detect microbleeds. Even 3D MRI sequences can help in the assessment of subcortical disease whereas diffusion-weighted sequences and MR angiography are routinely used in acute complications of cerebrovascular disease. Finally, the value of phase-contrast MRI sequences in the investigation of cerebral hydrodynamics is becoming more and more recognized [1,19,28]. But these sequences also offer a unique opportunity to functionally assess cerebral perfusion in clinical practice. The rigid, fixed-volume enclosure of the skull creates a common compliance environment that links craniospinal compliance and cerebral hemodynamics. These flow-quantification sequences also allow direct measurement of cerebral blood flow. Thus, more systematic use of flow-quantification MRI in the elderly may help to create a better understanding of ‘age-related’ clinical syndromes, including VCI [2,15,19,28].

Aging, arterial hypertension and other vascular risk factors are the main risk factors for structural MR markers of cerebral small-vessel disease in the elderly, consistent with an underlying large-artery dysfunction. MR markers of subcortical cerebrovascular disease in the elderly are also associated with increased risk for both small-vessel and large-vessel stroke subtypes, cardiovascular morbidity and death. In addition, chronic respiratory disease has been recently identified as yet another risk factor associated with these MR markers [32]. Hypoxia may act like arterial stiffness by encouraging deeper penetration of blood-pressure pulsations into the capillary network.

The presence of a structural MR marker of subcortical cerebrovascular disease or, more generally, of any clinical indicator of vascular disease or chronic respiratory disease in the elderly increases the risk of VCI. Executive dysfunction and slowing of processing speed are typical features of VCI, whereas episodic memory deficits, initially thought to be a clinical hallmark of AD, also appear to be related to subcortical cerebrovascular disease in the elderly [35]. In addition, VCI is associated with a higher risk of walking difficulties, depression and urinary incontinence and, more generally, an inability to carry on with day-to-day activities. However, as would be expected with only an indirect relationship between structural changes and cerebrovascular dysfunction, the degree of clinical disability is highly variable in the elderly patient with MRI evidence of cerebrovascular disease.

Subcortical leukoaraiosis (LA)

Leukoaraiosis, a radiological term describes, bilateral and symmetrical white matter changes in the elderly. The prevalence of subcortical LA is approximately 95% in the general population aged 60-90 years. However, confluent LA, subcortical LA larger than 10 mm, periventricular LA greater than 5 mm and infratentorial locations are infrequently seen in the healthy elderly.

Specific pathomechanisms

Subcortical lesions of leukoaraiosis are commonly considered to be ‘incomplete infarcts’ resulting from arteriolar stenosis and local reduction in arterial inflow. Neuroradiological studies have confirmed that lipohyalinosis (arteriosclerosis) is a common finding in areas of subcortical LA in the elderly. Yet, medullary arteries in leukoaraiotic areas demonstrate only an increased external arterial diameter and increased perivascular spaces, without a significant reduction in arterial lumen diameter [26]. There is no correlation between cerebral arterial flow rates and subcortical LA in the elderly [2]. However, endothelial dysfunction, an expected finding in patients with arterial stiffness [23], appears to correlate well with leukoaraiosis [20]. These recent observations support a pathomechanism of blood-brain barrier damage rather than an ischemic process related to subcortical LA [38].

MRI presentation

Subcortical LA is characterized by edema-like features: a slight low signal intensity on T1-weighted sequences; high signal intensity on both fast FLAIR T2- and fast spin-echo T2-weighted sequences; involvement of white matter rather than dense gray matter; and at least relative sparing of the subcortical U-fibers [18]. These white-matter changes do not show true vascular systematization, although confluent changes especially involve the posterior circulation territories that are particularly vulnerable to increased variations in blood pressure. 3D MRI can detect perivascular involvement along the perforating pathways [18]. Thus, subcortical LA may be considered a radiological expression of the cottonwool perivascular changes seen on funduscopic examination of patients with arteriosclerosis.
Cognition and subcortical leukoaraiosis

The degree of mechanical damage to cerebral arterioles due to windkessel dysfunction depends on an individual’s arteriolar vulnerability as well as a complex interaction of both genetic and environmental risk factors. Thus, the association between subcortical LA and cerebrovascular dysfunction is often slight and not always clinically relevant. Extensive leukoaraiosis can be observed without significant clinical symptoms in the elderly, and there is no correlation between the extent of subcortical LA and severity of clinical symptoms [27]. Also, there is no consistent correlation between the precise locations of these white-matter changes and clinical symptoms. However, as previously stated, the posterior regions are especially sensitive to windkessel dysfunction, and the presence of posterior subcortical leukoaraiosis is of greater clinical relevance [7,40].

Lacunar infarcts and enlarged perivascular spaces

‘Lacunar infarcts’ refer to small subcortical foci of necrosis (diameters range from 3-5 mm to 15-20 mm). Normally microscopic perivascular spaces, or Virchow-Robin spaces, surround the perforating arteries as they enter brain tissue, and are not in communication with the cerebrospinal fluid (CSF) in the subarachnoid spaces. Determining whether or not the perivascular spaces are dilated is based on their shape (evidence of focal enlargement), diameter (≥ 2 mm) or, simply, their visibility. Their detection is strongly influenced by the contrast and resolution characteristics of the MRI examination [16].

Specific pathomechanisms

Lacunar infarcts are thought to result from occlusion of a single small perforating artery. Approximately 15% of small subcortical infarcts are due to an embolism from the heart or large arteries. But, most often, on neuropathological examinations, lacunar infarcts, along with subcortical LA, share a perivascular location an underlying small-vessel disease without neuropathological evidence of significant arteriolar stenosis or occlusion [25]. Indeed, the windkessel dysfunction responsible for arteriolosclerosis may also cause disturbances in capillary exchanges and lead to chronic hypoxia. Perforating arteries that directly arise from the anterolateral part of the circle of Willis are especially vulnerable to windkessel dysfunction, and lacunar “infarcts” related to small-vessel disease are most often found in the basal ganglia.

Although the pathogenesis of enlarged perivascular spaces (EPVs) is still controversial, they may, along with subcortical LA, share a causal endothelial dysfunction and breakdown of the blood-brain barrier. Indeed, EPVs may be the first stage of cerebral small-vessel disease, and the visibility of perivascular spaces increases with aging, arteriolar hypertension and arteriolosclerosis. In addition, brain shrinkage may favor EPVs in cerebral white matter [16].

MRI presentation

At this late stage of tissue necrosis, the signal intensity of lacunar “infarcts” is similar to that of CSF, except for the peripheral parts of these lesions, which typically demonstrate high signal intensity on FLAIR T2-weighted sequences. Also, lacunar “infarcts” related to small-vessel disease are likely to be silent, multiple and present along with other MR markers of small-vessel disease such as LA and EPVs.

Dilated perivascular spaces in healthy subjects are frequently seen around the anterior commissure in the lower third of the corpus striatum of the basal ganglia or in infraputaminial locations. Other regions with potentially visible perivascular spaces include the supratentorial white matter, insular cortex and extreme capsule, hippocampus, thalamus, midbrain and cerebellum, and the optical tract. Perivascular spaces are, by definition, located along the perforating pathways. They most often appear as small areas with the same signal intensity as CSF on all pulse sequences. However, mild gliosis around EPVs can lead to peripheral high signal intensities on FLAIR T2-weighted sequences [18]. Numerous visible perivascular spaces define the état criblé (hole-riddled tissue) usually associated with multiple microinfarcts (less than 5 mm) on neuropathological examination.

Clinical presentation

Foci of necrosis related to small-vessel disease are most often neurologically ‘silent’—lacking clinically overt stroke-like symptoms. Their precise location within the deeper gray matter does not reliably predict the clinical presentation. However, these changes are more closely related to hypoxia than is subcortical LA, and show a stronger correlation with cognitive decline than does subcortical LA [35,37]. There is no direct relationship between visible perivascular spaces and cognitive function, although extensive enlargement of the perivascular spaces is increasingly associated with vascular cognitive impairment or vascular dementia in the elderly.

Other structural markers of subcortical cerebrovascular disease in the elderly

Greater pulsatile stress on the subependymal tissue and splenium of the corpus callosum may well explain the periventricular leukoaraiosis and frequent splenial high signal intensities seen in the elderly [18]. As there is no evidence of arteriolar disease or hypoxia within areas of subependymal leukoaraiosis, periventricular LA is still often considered a benign senescent change. But this somewhat ‘traumatic’ leukoaraiosis is more directly related to arterial stiffness than is subcortical LA, and thick periventricular LA has a stronger correlation with clinical dysfunction [27] and is a better predictor of dementia than is subcortical LA [30].

In recent years, gradient-echo T2*-weighted sequences have allowed the detection of ‘silent’ microbleeds in 3-6% of asymptomatic elderly subjects and more than 50% of patients with a known cerebral microangiopathy or history of stroke. Microbleeds correspond to hemosiderin deposits in the microvascular perivascular spaces due to microvessel-wall damage, and can be identified on these MR sequences as focal areas of signal loss with diameters less than 5-10 mm. Compared with signal loss due to a void in vascular flow, the low signal intensities that result from microbleeds are more prominent on these sequences than on T2-weighted sequences. Microbleeds must be differentiated from areas of...
symmetrical low signal intensities in the basal ganglia that are likely to represent calcifications or non-hemorrhagic iron deposits. Other parenchymal lesions with a hemorrhagic component are most often locally associated with other abnormalities.

The number of deep microbleeds has been correlated with the severity of leukoaraiosis and the presence of lacunar infarcts, but all these changes appear to be independent markers of an underlying small-vessel disease. Thus, central microbleeds are most often thought to be indirect markers of arteriolosclerosis whereas predominantly posterior peripheral locations suggest an underlying cerebral amyloid angiopathy.

Ventricular dilatation and sulcal enlargement are limited in the healthiest elderly, with a mean score of 2 on rating scales (ranging from 0 to 8) in the American Cardiovascular Health Study [22]. Windkessel dysfunction may lead to increased intraventricular pulse pressure and ventricular dilatation [2,15,19]. Thus, leukoaraiosis, and combinations of leukoaraiosis and infarcts, are more generally associated with greater ventricular (mean scores of 4 and 5, respectively) than sulcal enlargement (mean scores of 3 and 4, respectively). There is also a growing body of evidence of a poor clinical outcome in patients with prominent ventricular enlargement [9], but not in patients with MRI patterns of balanced ventricular and sulcal enlargements [22].

Atrophy of white matter than gray matter seems to underlie the predominantly anterior frontal and temporal brain shrinkage seen with aging, vascular risk factors or cerebral vascular disease. However, chronic low-grade brain hypoxia in the elderly with windkessel dysfunction may lead to global cortical thinning. The hippocampus is especially vulnerable to atrophy. Variable but potentially severe hippocampal atrophy has been reported with aging, vascular risk factors or small-vessel disease whereas marked neuron loss in hippocampal sclerosis is thought to result from cerebrovascular dysfunction.

The discrete pattern of cortical thinning may be difficult to assess visually, but MRI cortical measurements in elderly patients with small-vessel disease indicate an association between cortical atrophy and cognitive decline. Also, diffuse cortical atrophy and hippocampal atrophy may be more closely related to cognitive decline than other structural changes in subcortical vascular disease [13].

MRI in late-onset dementia of the Alzheimer’s type or the resurgence of “dementia arteriosclerotica”

Late-onset DAT is not exclusively predicted by amnestic single-domain MCI. In fact, few patients with MCI have memory loss as the sole feature, and multiple-domain cognitive deficits appear to be the most common prodromal state of late-onset DAT [11,31]. Contrary to the amnestic single-domain MCI subtype, mesiotemporal atrophy in the multiple-domain MCI subtype does not include the earliest sites of AD such as the entorhinal cortex, but only comprises non-specific bilateral and symmetrical hippocampal atrophy, in contrast to the extensive anteromesial temporal atrophy seen in AD and, more generally, the asymmetrical pattern seen in primary neurodegenerative diseases [5,21].

Even hippocampal atrophy is not invariably present in this MCI subtype [4]. Leukoaraiosis is frequently present in this subtype in contrast to the rarely seen LA in the amnestic single-domain MCI subtype. These data all suggest an underlying cerebrovascular disease, rather than AD, in this MCI subtype, which is also a strong predictor of vascular dementia [41].

Severe mesiotemporal atrophy predicts late-onset DAT [10] but, as currently assessed, it is not a specific hallmark of AD. Indeed, current evaluations of mesiotemporal atrophy, mainly focused on hippocampal or entorhinal atrophy, temporal-horn enlargement and widening of the choroidal/hippocampal fissure, do not take into account the heterogeneous pattern of mesiotemporal atrophy in the elderly, the potential dissociation between hippocampal atrophy and atrophy of the surrounding parahippocampal structures (Figs. 1,2). This last pattern suggests hippocampal sclerosis or shrinkage related to small-vessel disease rather than AD pathology. Moreover, MRI predictors of late-onset DAT are not limited to mesiotemporal atrophy; leukoaraiosis, ventricular enlargement and silent subcortical infarcts are also associated with a higher risk of progression to DAT [9,30,35,37].

Thus, MRI predictors of late-onset DAT, including hippocampal atrophy, can be considered to be partially independent markers of brain damage related to arterio/atherosclerosis [12,18]. The prominent role of windkessel dysfunction in late-onset DAT also contributes to understanding of the neuropathological and MRI patterns of late-onset DAT. Whereas early-onset DAT is characterized by a major AD pathological burden and widespread brain atrophy, late-onset DAT usually has a small AD pathological burden, and a diffuse and milder brain atrophy and additional cerebral small-vessel disease [14].

All of these observations point to a need to reconsider the concept of ‘senile’ dementia as defined more than a century ago. At that time, dementia in the elderly was attributed to ‘hardening of the arteries’, a prominent feature of aging: senile dementia was synonymous with ‘arteriosclerotic’ dementia. AD was only considered to be a cause of presenile dementia. Chronic cerebral hypoxia related to arterial senescence was thought to be the most common cause of senile dementia. Later, failure to detect severe cerebral hypoperfusion, marked arterial stenoses or occlusions in generalized arterio-atherosclerosis and late-life dementia contributed to a progressive abandoning of the concept.

However, recent evidence of hypoxia without significant arterial stenosis or occlusion suggests that these observations, in fact, did not refute the idea of arteriosclerotic dementia. Neuropathological evidence of Alzheimer-type lesions in late-onset dementia has also contributed to AD and senile dementia being considered a single process. But Alzheimer’s lesions in late-onset DAT are usually not sufficient to explain dementia. Today, there is also increasing evidence that cerebral hypoxia may favor the accumulation of amyloid-β peptide and, in good agreement with the amyloid-cascade hypothesis, the development of Alzheimer-type lesions [42]. Atherosclerotic disease is now more widely recognized as a risk factor for both arteriosclerosis and Alzheimer-type lesions [3,12,29]. Preexisting, mildly reduced
amyloid clearance with aging and reduced capillary density probably contributes to a significant imbalance between production and clearance of amyloid-β peptide in elderly patients with cerebrovascular disease [2]. In the most severe forms of cerebral hypoxia, however, a marked reduction in metabolic activity may reduce the production of toxic metabolites, the imbalance between amyloid clearance and production and, thus, the AD pathological burden. Thus, the frequent but moderate AD pathological burden in late-life dementia may only be an indirect marker of cerebrovascular dysfunction in the elderly, the associated ‘toxic’ consequence of a predominantly hypoxic disease such as ‘invisible’ windkessel dysfunction induced by ‘hardening of the arteries’.

**Conclusions**

Regional MRI assessment of brain atrophy provides sensitive biomarkers of Alzheimer’s lesions; the structural MRI hallmarks of vascular cognitive impairment include subcortical and periventricular leukoaraiosis, lacunar ‘infarcts’, microbleeds and ventricular dilatation, and secondary atrophic...
changes such as hippocampal atrophy. The pathomechanisms and clinical significance of these frequently seen MRI changes in the elderly are now better understood. These recent advances highlight the deleterious effects of arterial senescence in late-onset dementia and the importance of functional disturbances in cerebral perfusion. Further MR investigations of the intracranial dynamics will help to better define vascular cognitive impairment, and guide the development of targeted interventional programs designed to prevent cognitive decline and to treat late-life dementia.

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