Ital J Neurol Sci (1999) 20:S250-S253

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The role of MRI in dementia

Abstract Neuroimaging techniques aimed at studying structural changes of the brain may provide useful information for the diagnosis and the clinical management of patients with dementia. Magnetic resonance imaging (MRI) may show abnormalities amenable to surgical treatment in a significant percentage of patients with cognitive impairment. MRI may also assist the differential diagnosis in dementia associated with metabolic or inflammatory diseases.

MRI has the potential to detect focal signal abnormalities which may assist the clinical differentiation between Alzheimer's disease (AD) and vascular dementia (VaD). Severe temporal atrophy, hyperintensities involving the hippocampal or insular cortex, and gyral hypointense bands are more frequently noted in AD. Basal ganglionic/thalamic hyperintense foci, thromboembolic infarctions, confluent white matter and irregular periventricular hyperintensities are more common in VaD.

The high sensitivity of MRI in detecting T2 hyperintense lesions and the low specificity of white matter lesions have resulted in a poor correlation between MRI findings and both neuropathological and clinical manifestations. In particular, MRI has disclosed a series of white matter focal changes in the elderly population, which are not necessarily associated with cognitive dysfunction.

The recent advent of a new MRI method sensitive to the microstructural changes of white matter, the so-called diffusion tensor imaging, may be helpful in correlating clinical manifestations with white matter abnormalities.

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Introduction

Dementia, a severe and frequent neurologic disorder in the elderly population, has important socio-economic implications. Several pathologic mechanisms can cause cognitive impairment, therefore the primary objective of clinicians is to identify possible underlying disorders in order to better define prognosis, treatment and patient management.

In 1994, The Quality Standards Subcommittee of the American Acadamy of Neurology [1] published "practice parameters" for the diagnostic evaluation of persons suspected to have dementia. These guidelines established neurologic examination as the standard and certain laboratory tests as essential components of the diagnostic procedure. However, neuroimaging studies were suggested only as "options", i.e. "management strategies for which there is unclear clinical certainty". A few years later, in 1997, the usefulness of these practice parameters for the evaluation of dementia was examined by reviewing 119 consecutive cases. The main result of this study was that diagnostic accuracy was improved by neuroimaging studies, although with a predictable increase in costs. Neuroimaging studies frequently changed clinical diagnosis (19%-28%) and management (15%).

One of the primary objectives of the diagnostic procedures entails the exclusion of treatable or reversible causes of dementia. Structural brain imaging using magnetic resonance imaging (MRI) or computed tomography (CT) to search for treatable lesions is a key component of this evaluation.

A large number of papers report that brain abnormalities amenable to surgical treatment, such as normal-pressure

hydrocephalus, subdural hematoma and tumors, may be found in a variable percentage (up to 20%) of patients with symptoms of dementia. Each of these pathological conditions has typical imaging findings. Therefore, CT or conventional MRI often allows a definitive diagnosis.

Imaging has a less crucial role in the diagnosis of other forms of dementia, such as those associated with inflammatory, toxic or metabolic encephalopathies. Diagnosis is supported in these forms of dementia by laboratory tests, patient history, and physical and neurologic examinations. MRI or CT, however, can assist the differential diagnosis since some of these forms of dementia are associated with typical imaging findings. On MRI, lesions of the corpus callosum and extensive symmetrical lesions of the corona radiata and centrum semiovale are typically observed in Marchiafava-Bignami syndrome [2]. Bilateral increased signal intensity in the basal ganglia and periventricular accentuated flat and striped hyperintense structures are suggestive of Creutzfeldt-Jacob disease [3, 4].

Structural brain imaging has a well-defined but more complex role in differentiating degenerative from vascular forms of dementia and in evaluating the severity of some structural changes, such as cortical atrophy or leukoaraiosis, associated with dementia. Its role in distinguishing between changes associated with aging and those with dementia and in correlating structural brain abnormalities with clinical deterioration remains less definite.

Alzheimer's disease

Alzheimer's disease (AD) is the commonest cause of dementia. Currently, the term AD refers both to patients 65 years old and older, previously classified as having the senile dementia of Alzheimer type as well as to those who develop symptoms earlier, said to have AD.

Neuroimaging and gross pathology show diffuse cerebral atrophy, attributed histologically to neuronal loss. The decrease in global cerebral volume, calculated by a novel method of registration and subtraction of serial MRI scans, was found to significantly correlate with rate of change in mini-mental state examination scores, implying clinical relevance to this marker of progression [5].

Individual neuronal groups show selective susceptibility for degeneration. Specifically, the hippocampal formation is consistently and heavily involved in the pathology of AD: subsequently focal, symmetric or asymmetric enlargement of the temporal horn is frequently seen in AD (Fig. 1). The in vivo quantitative assessment of the hippocampal formation by volumetric MRI assessment may be a valuable tool in the evaluation of patients with AD. Recently, the hippocampi and temporal horns were measured in 24 cognitively normal subjects aged 70-89 years and in 24 patients with AD. Each subject underwent an MRI protocol twice,

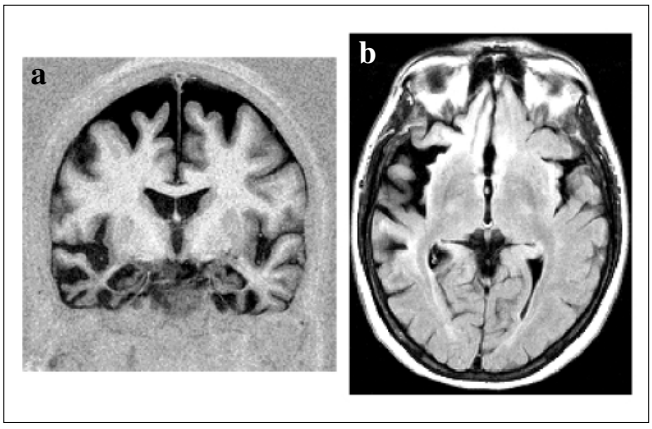

Fig. 1a,b *Patient with Alzheimer's dementia and severe, asymmetric atrophy of the temporal lobes*. **a** Coronal T1-IR image. **b** Axial T2 FLAIR image

separated by 12 months or more. A statistically significant yearly decline in hippocampal volume and an increase in temporal horn volume were identified in elderly control subjects. These rates were approximately 2.5 times greater in patients with AD than in individually age- and gender-matched control subjects [6]. Similarly, other volumetric MRI studies showed that the volume of the hippocampi was significantly smaller in AD patients than in controls, with a significant correlation between the hippocampal volumes and both the severity of the dementia and the patient's age [7, 8]. However, it is not completely clear if the temporal atrophy, as so sophisticatedly calculated in vivo by volumetric MRI assessment, is a specific marker of AD, or simply reflects the selective vulnerability of neuronal structures. An MRI study on patients with AD or vascular dementia (VaD) and on controls found that hippocampal volume is smaller in patients with dementia than in controls, but no significant volumetric differences were found between VaD and AD patients [9].

Some AD patients show hyperintense sylvian or hippocampal-uncal cortex on long repetition time (TR) images. This increased signal possibly has a pathologic correlate in the increased water content due to neuronal loss, gliosis, neurofibrillary tangles, and other histological changes typical of AD. Subtle gyral hypointense bands on T2-weighted images have also been described, possibly due to the accumulation of iron or other paramagnetic substances [10].

MRI and CT also show white matter lesions in AD patients more commonly than in normal elderly controls, but a demented patient with prominent sub-cortical lesions and periventricular hyperintensity (as well as basal ganglionic and cortical infarcts) is more likely to have VaD than AD [11, 12]. Hyperintensity on long-TR MR images has been found in AD patients to be of intermediate severity between the findings in normal elderly controls and in patients with VaD. However, no correlation between the severity of white matter lesions and severity of dementia exists [12].

Vascular dementia

MRI is important for the diagnosis of VaD. The presence of extensive periventricular hyperintensity, subcortical lesions, cortical infarcts and basal ganglia lacunar infarcts (Fig. 2) is necessary for the diagnosis of VaD. However, identifying the presence of these lesions, by neuroimaging alone, does not permit the diagnosis of dementia. In a patient with dementia, the above-mentioned MRI findings favor a clinical diagnosis of VaD or mixed dementia over AD. The absence or mild extent of these changes goes against a diagnosis of VaD.

White matter changes in the brain are termed leukoaraiosis [13]. It is believed that leukoaraiosis is due to arteriolosclerosis of long penetrating arteries that supply white matter. The myelin rarefaction typical of leukoaraiosis has been interpreted as the result of ischemia not severe enough to cause pannecrosis, but able to induce incomplete infarction [14]. Leukoaraiosis is a non-specific finding. It may be observed in aged patients with risk factors for cerebrovascular disease, especially hypertension, independently if they are demented or not. In a large population of 3301 elderly people aged 65 years or older who underwent MRI and denied a history of stroke or transient ischemic attack, only 4.4% of subjects were free of any abnormal signal in the white matter. Most subjects, however, showed only mild periventricular alterations [15].

Dementia may also occur as a consequence of a single large cortical infarct [16-19]. A single explanation for post-stroke dementia is not adequate: rather, multiple factors may independently contribute to the cognitive decline. Among these factors, the location of the infarct, such as in the dominant hemisphere [19] and in the frontal and temporal regions [16], may play a major role.

Multiple lacunar infarcts can be observed as the only finding in VaD, but are more often associated with white matter hyperintensity and cortical infarcts. The pathogenesis of lacunar infarcts is still incompletely established. There is presently no evidence for a close correlation between the severity of multiple lacunar infarcts and cognitive impairment in VaD. In patients with VaD and a lacunar state, important causes of dementia may be not only the presence of lacunae but also incomplete softening of the white matter [20]. Several investigators have suggested an association between extensive frontal lesions in the white matter and cognitive deterioration in patients with multiple lacunar infarcts [20, 21].

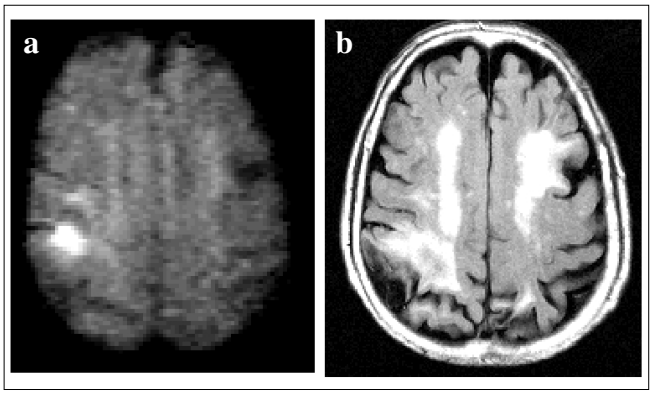

Fig. 2a,b *Patient with vascular dementia*. **a** Axial diffusion-weighted image (DWI). **b** Axial T2 FLAIR image. The T2 FLAIR image shows diffuse white matter hyperintensity (leukoaraiosis) and a right parietal infarct. DWI reveals a small area of acute ischemia within the T2 hyperintensity, which is markedly hyperintense and located in the right parietal lobe

Many points remain to be elucidated regarding the relationships between white matter changes observed with MRI and the cognitive impairment in elderly people. The high sensitivity of MRI in detecting T2 hyperintense lesions and the low specificity of white matter lesions have resulted in a poor correlation between MRI findings and both neuropathological and clinical manifestations. In particular, the advent of MRI has disclosed a series of white matter focal changes in the elderly population, which are not necessarily associated with cognitive dysfunction. Advancing age and hypertension show a strict correlation with these white matter changes. However, it is not clear yet why some hypertensive patients with leukoaraiosis develop dementia whereas others do not.

Recently a new MRI method has been introduced called "diffusion tensor imaging" (DTI) which is sensitive to microstructural changes of the white matter (e.g. demyelination, axonal loss, gliosis). This technique may provide further insight into the mechanisms that cause white matter changes and may help in correlating clinical manifestations with white matter abnormalities.

The application of gradients highly sensitive to the microscopic movements of water provides the possibility of creating maps of the diffusivity of water molecules. In the white matter, water diffusion is more restricted across the myelin sheaths than along the major axis of the axons. DTI is based on the measurement of diffusion in different directions in space and provides the directionally averaged diffusivity of water and the degree of diffusion anisotropy. In this way, DTI can provide more precise information about the severity of white matter rarefaction.

In patients with leukoaraiosis, the mean diffusivity is increased, whereas the (fractional) anisotropy is locally reduced [22]. Axonal loss, gliosis and increased extracellular space in areas of leukoaraiosis can explain this DTI pattern. In particular, the loss of directionally ordered axonal tracts and the coexistent gliosis account for reduced anisotropy. The extent and location of reduced anisotropy could explain clinical symptoms, in particular the loss of specific cognitive functions.

Sommario *Le tecniche di neuroimmagini per lo studio dei cambiamenti strutturali dell'encefalo possono fornire infor-*

mazioni utili alla diagnosi ed alla gestione dei pazienti con demenza. La risonanza magnetica (RM) è in grado di evidenziare anomalie trattabili chirurgicamente in una percentuale non trascurabile dei pazienti con deficit cognitivo e può essere utile nella diagnosi differenziale della demenza associata a malattie metaboliche od infiammatorie.

La RM è in grado di evidenziare lesioni che permettono la diagnosi differenziale tra malattia di Alzheimer (AD) e demenza vascolare (VaD). Una grave atrofia dei lobi temporali, aree di iperintensità nella corteccia ippocampale od insulare, bande ipointense spiraliformi si notano frequentemente nella AD. Lesioni iperintense dei gangli della base e del talamo, infarti tromboembolici, aree irregolari e confluenti di iperintensità periventricolari e della sostanza bianca sono più tipiche della VaD.

L'alta sensibilità della RM nel riconoscimento di lesioni iperintense in T2 e la scarsa specificità delle lesioni della sostanza bianca determinano una limitata correlazione tra i dati di RM e le manifestazioni sia neuropatologiche che cliniche delle sindromi dementigene. In particolare, l'avvento della RM ha reso visibile nella popolazione anziana una serie di anomalie focalizzate della sostanza bianca che non sono necessariamente associate a disturbi cognitivi.

Una nuova tecnica di RM più sensibile alle anomalie miscroscopiche della sostanza bianca, la cosiddetta diffusion tensor imaging, *potrebbe risultare utile nel chiarire la relazione tra le manifestazioni cliniche e le anomalie della sostanza bianca.*

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