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The utility of neuroimaging in the management of dementia

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ABSTRACT

Dementia is a syndrome of progressive dysfunction of two or more cognitive domains associated with impairment of activities of daily living. An understanding of the pathophysiology of dementia and its early diagnosis is important in the pursuit of possible disease modifying therapy for dementia. Neuroimaging has greatly transformed this field of research as its function has changed from a mere tool for diagnosing treatable causes of dementia to an instrument for pre-symptomatic diagnosis of dementia. This review focuses on the diagnostic utility of neuroimaging in the management of progressive dementias. Structural imaging techniques like computerized tomography scan and magnetic resonance imaging highlights the anatomical, structural and volumetric details of the brain; while functional imaging techniques such as positron emission tomography, arterial spin labeling, single photon emission computerized tomography and blood oxygen level-dependent functional magnetic resonance imaging focuses on chemistry, circulatory status and physiology of the different brain structures and regions.

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INTRODUCTION

Dementia is a syndrome of progressive decline in cognitive functions like memory, reasoning, abstraction, language, executive function, orientation and perceptive abilities. It is usually associated with personality and behavioral changes, and progression to impairment of activities of daily living (ADL). Deficit in cognition without interference in activities of daily living is termed mild cognitive impairment (MCI). About 15-20% of MCI will progress to dementia[1], and 30% will return to normal cognition.[2]

An understanding of the pathophysiology of dementia and its early diagnosis is important in the pursuit of possible disease modifying therapy. Neuroimaging in dementia has been transformed from a mere tool for diagnosing treatable aetiologies to an instrument for pre-symptomatic diagnosis of dementia. It is useful in general monitoring of the disease progression and the effects of therapy.[3]

DEFINITION OF CONCEPTS

Brain connectivity and neural substrate of cognition

Brain connectivity describes the different structures and regions of the brain in humans that are interlinked by a network of complex and often poorly understood fibre bundles.[4] These incompletely linked networks are specifically organized into unique functional units that are modified by factors such as evolution, experience-dependence refinement and disease-associated changes. Our current understanding of the relationship between these connections and cognition in health and diseases is still provisional and uncertain, but more information is expected from efforts in theoretical and empirical research[5], a field where neuroimaging is contributing significantly.

Cognitive modalities have anatomical substrate in the nervous system sites and networks with diverse levels of control. Attention requires awareness and alertness organized within the reticular activating system in the brain stem and their connections projecting to the thalamus and cerebral cortex. Cortical control of attention originates from the frontal and parietal lobes. Defects in the parietal control results in the syndrome of inattention.[6]

The different processes in memory are localized to different anatomical and functional network areas including: regions of the medial temporal lobe (MTL) such as hippocampus, parahippocampus, and entorhinal cortex; deep gray matter like thalamus and limbic system; the ascending cholinergic projection pathway, and posterior cortical areas like posterior cingulate gyrus and temporo-parietal association cortex. Frontal lobe in memory serves to filter and organize the encoded information.[6]

A simplified approach to the cortical substrate of speech would suggest comprehension localized to the superior temporal gyrus; production in the inferior frontal gyrus, and repetition to the arcuate fasciculus. The emotional aspect of cognition lies within the limbic system that involves the fronto-temporal network and their subcortical structures such as amygdala. The localization of executive function is poorly understood, but it involves the frontal cortex and its subcortical connections. In support of this view is the fact that injury to the right anterior temporal and inferior frontal area results in disinhibition. Perception is a complex task with several processes localized to different structures. Spatial orientation is localized to the parietal lobe; motion and color to the visual cortex, and auditory perception is localized to the auditory cortex.[6]

Progressive Dementia

Alzheimer's disease (AD) is the commonest type of progressive dementia accounting for 50-70% of all dementias. Its incidence increases as the population ages.[7] Other progressive dementias include: dementia with Lewy bodies (DLB), Frontotemporal lobar degeneration (FTLD), vascular dementia (VaD), Creutzfeldt-Jakob disease (CJD) and Parkinson's disease dementia (PDD). In AD there is accumulation of amyloid plaque and neurofibrillary tangles in over 95% of cases.[8] The characteristic neuropathologic feature of FTLD is atrophy of the frontal and anterior temporal lobes mirroring the underlying gliosis and neuronal loss. This is usually associated with accumulation of tau protein or ubiquitin. The formation of Lewy bodies is characteristic of DLB and PDD[6], while CJD involves reactive gliosis of cortical and subcortical gray matter following abnormal deposition of cellular prion proteins.[9]

Neuroimaging techniques commonly applied in dementia

The available neuroimaging techniques can be grouped into structural imaging and functional imaging modalities. Structural imaging techniques like computerized tomography (CT) scan and magnetic resonance imaging (MRI) highlights the anatomical, structural and volumetric details of the brain; while functional imaging focuses on chemistry, circulatory status and physiology of the different brain structures and regions. Important functional methods include positron emission tomography (PET), arterial spin labeling (ASL), single photon emission computerized tomography (SPECT) studies and blood oxygen level-dependent functional magnetic resonance imaging (BOLD-fMRI), which have enhanced our understanding of the aetiology of dementia and improved the diagnostic accuracy. BOLD-fMRI measure T_2 signal differences that reflects the ratio of oxyhaemoglobin to deoxyhaemoglobin, an indication of neural activity and connectivity in the different parts of the brain at rest or during the performance of memory task. PET of 2-[^{18}F]-fluro-2-deoxy-D-glucose (^{18}FDG) correlates with the metabolic activity in the brain, while ASL assess brain perfusion using the hypothesis that links brain metabolism with perfusion using arterial water as an endogenous tracer for perfusion.[10]

Diffusion tensor imaging (DTI) is a technique that investigates the microstructure of the white matter tract using the diffusion property of water. Using fractional anisotropy (FA), which is indicative of the unrestricted movement of water molecule parallel to the fibre bundle length but restricted axially, improved integrity of white matter is correlated with a higher FA value.[11]

IMAGING MODELS IN DEMENTIA

CT and MRI

Earliest structural changes in the form of atrophy in AD occur in the entorhinal cortex before progressing to involve the neocortex. As a biomarker for AD it is best visualized with MRI coronary sections on T1 sequences. The assessment of gray matter volume has evolved from visual assessment to manual hippocampal volumetry and finally to a computer based-automated measure of parenchymal volume.[10] A study of patients with AD and MCI, using MRI to investigate the structural and functional abnormalities in these groups and comparing it with clinically obtained neuropsychological data, showed that the entorhinal volume is differs among the different groups and significant hippocampal atrophy was mainly seen in AD patients compared to MCI and controls.[12] Their findings also support an earlier report[13] that the entorhinal cortex is the most objective structural region for discriminating between MCI and normal subjects.

The use of CT in AD has largely been overtaken by MRI because it offers a better resolution, and can discriminate between gray and white matter. It can also highlight subtle white matter changes.[3] CT is mainly useful in observing atrophic changes in the Medial temporal lobe (MTL) in advanced AD. In a prospective study[14], of 200 patients with AD and 199 controls who had annual SPECT and CT scans to evaluate the diagnostic potential of functional and structural imaging in the diagnosis of dementia. Clinical diagnosis was based on the National institute of Neurological and Communicative Disorders and Stroke-Alzheimer's disease and Related disorders Association (NINCDS-ADRDA) and Diagnostic and Structural Manual of Mental Disorders, 3rd Edition (DSM-111-R). Findings from this study was significant because 143 (95%) had their diagnosis confirmed at autopsy, of which 80 had AD and 24 non-AD dementia. MTL atrophy seen on CT was able to predict the pathology of dementia; CT alone had a sensitivity of 85%, specificity of 78% and a diagnostic accuracy of 80%, and when combined with SPECT it was observed to be better than Apo E4 in discriminating among the cause of the dementia.

Using MRI measures, an Italian study[15] estimated the relative dimension of the temporal horn of the lateral ventricle and correlated it with the stage of AD as follows: 6.5mm for mild AD and 7.2mm for advanced AD. These measures have a sensitivity of 82% for advance AD and 74% for mild AD, while the specificity is 95% in both cases.

DTI

The white matter changes in normal aging as shown by a decreased FA value has been in the frontal lobe, temporo-parietal lobe, and the corpus callosum has been reported by several investigators.[16-18] The first report comparing the

brain's white matter connectivity in healthy-young adults and aging patients to that in MCI and AD was undertaken by Smith and colleagues.[19] Using the tract-based spatial statistics (TBSS) to study the effect of aging, MCI, and AD on white matter integrity and the relationship between this anatomical connectivity and cognitive function, they showed that in addition to the decreased FA in the frontal, temporal and parietal lobes there were changes in the body and genu of the corpus callosum. Furthermore they observed that in AD compared to normal aging, decreased FA was primarily documented in the left anterior temporal lobe, a finding that would suggest AD is not just a progression of normal aging. The changes in FA value correlated with neuropsychological measures. The advantage of this study over previous ones is that T2 weighted FLAIR was initially used to exclude patients with significant white matter changes suggesting VaD, which may be confounding. Secondly, TBSS used in this study provides a more accurate and consistent outcome among subjects at different times of assessment compared to voxel-based morphometry (VBM) used in previous studies. VBM has the inherent drawback in registration and smoothing.[20] Though these findings were very significant, one wonders if a system better than the 1.5T scanner used would not have generated additionally information. The small number of subjects in the healthy and MCI group is a limitation in this study, as well as the large difference in the age range between the young and elderly healthy subjects.

BOLD fMRI

fMRI studies had reported interesting findings in different stages in the cognitive continuum including changes in the default memory network[21] involvement of parietal lobe in memory retrieval[22]; parietal lobe involvement in metamemory processes[23] and an increased activation of memory networks in people with risk factors for AD.[24,25] The complex reciprocal relationship between the temporal activation and parietal deactivation in the memory process was first clearly elucidated using activation analytical technique in a fMRI study involving 52 subjects with normal aging, MCI and AD. They focused on revealing the MR signal changes specific to memory task. This study like other fMRI studies observed MR signal changes in the brain outside the primary medial temporal lobe.[26,27] The strength of their study was in the use of independent component analysis (ICA) a data driven technique, which is better than the traditional fMRI method in that it allows for the observation of additional units of the memory network. Secondly, this is the first study to observed the complex reciprocal relationship between deactivation of the parietal region and temporal activation during memory-specific task. Other interesting findings from this study was the observation that subjects with good cognitive reserve paradoxically display increased activation in the hippocampus and its functionally connected neocortex, while there was a deactivation in the default parietal network. Subjects with more cognitive impairment shows significantly decreased hippocampal activation and decreased deactivation in the default regions in the parietal lobe, findings similar to what is observed in the mild AD group. They concluded that there are changes in memory networks in pre-symptomatic phase of AD.

ASL

A ASL cerebral blood flow (CBF) MRI study[28], involving 18 patients with probable AD and compared to that from age-matched control, showed a significant reduction in CBF in temporal, parietal, frontal and posterior cingulate cortices in the AD patients when compared to the controls. This pattern of regional hypoperfusion is similar to that obtained using ASL MRI, ^{18}FDG-PET or ^{99}Tc-HMPAOSPECT. A recent study[29], scanned 19 healthy subjects and compared their results with those of 13 AD subjects using continuous-ASL and T1-weighted spoiled gradient recalled echo. Unlike previous studies, which enrolled patients from memory clinics with the inherent referral bias, this study was a well-characterized prospective cohort study. Despite the drawback of using a small sample size with a reduced power, they were able to observe that ASL has a higher sensitivity in separating mild AD from normal cognition when compared to data from T1-weighted volumetric structural MRI.

FDG-PET

Several studies have utilized FDG-PET imaging in the diagnosis of AD and its differentiation from other progressive dementias. A study[30] scanned 12 pathologically verified AD patients with memory loss, which was clinically difficulty to characterize.

The study attempted to verify the sensitivity, specificity and diagnostic accuracy of the metabolic pattern of bilateral temporo-parietal hypometabolism on FDG-PET in the diagnosis of AD, and differentiating it from other degenerative aetiology of dementias. Sensitivity, specificity and diagnostic accuracy of 93%, 63% and 100% was obtained respectively. This would suggest the usefulness of this tool in the diagnosis of dementia, but its discriminative ability is poor when compared to sensitivity and specificity of the clinical diagnosis for probable AD, which were 63% and 100%, respectively; and the sensitivity and specificity of the clinical diagnosis for possible and probable AD were 75% and 100%, respectively. The validity of these findings would depend on its replication in a larger proportion of patients with AD.

Landau et al[31], compared glucose metabolism in FDG-PET and clinical measurement among larger population of elderly patients with MCI and AD to ascertain the power of each measure to predict cognitive decline. The clinical measures involved the use of functional activities questionnaire and AD assessment scale-cognitive subscale (ADAS-Cog). The study showed that FDG-PET has a better predictive value to detect cognitive impairment in MCI and AD than ADAS-Cog. They also reported that FDG-PET predict further decline in cognitive function, a result that is useful in monitoring cognitive outcome in this group of patients after therapeutic intervention. The strength of this study lies in the fact that it involved a larger sample size of patients enrolled in the Alzheimer's disease neuroimaging initiative (ADNI), which is a multisite study with divergent background. Being a longitudinal study, they were able to observe changes in the cognitive functions over time. Other longitudinal studies have also confirmed that FDG-PET is better than clinical examination in the diagnosis of AD.[11, 32] The pattern of hypometabolism was observed to be temporo-parietal lobes in early AD, but the frontal lobes are involved in advanced cases. Normal FDG-PET results seen in patients with MCI suggest that it is of a pathophysiology that does not involve neurodegeneration.[33]

Other applications of PET imaging

Using special radio-ligands (C-PMP and C-MP4A) the acetylcholineterase activity has been observed to decrease in the temporal lobe of patients with AD compared with healthy controls.[34] Similarly a decreased level of acetylcholinesterase was also seen in patients with MCI who eventually convert to AD, thus indicating that it can be used as a marker for AD screening.[35] Using A-beta amyloid-specific ligands such as the Pittsburgh compound B (^{11}C-PiB), patients with AD can be differentiated from other neurodegenerative dementias as AD patients demonstrate an increase uptake compare to patients with PD and FTLD.[36,37]

SPECT

SPECT is comparatively cheap but has a high specificity and sensitivity particularly in early detection of changes in CBF in the different dementias. It remains the most widely available technique for the investigation of cerebral function.[38] Studies had reported that SPECT study of cerebral perfusion is very accuracy for the diagnosis of AD.[39,40] A recent study[41] attempted to correlate cerebral perfusion as seen on SPECT, cerebrospinal fluid (CSF) Tau protein and cognitive function in patients with dementia and controls. They evaluated 117 patients with AD, 67 patients with other neurological condition of which 26 had non-AD dementia and 23 age-matched controls. Cognitive functions and functional status was evaluated using Mini-mental state examination, Cambridge cognitive examination and functional rating scale for symptomatic dementia. The advantage of this study over others is the improvement of the diagnostic specificity by correlating ^{99m}TC-HMPAO SPECT scanning with the Tau protein level in CSF. Like previous studies, significant bilateral parietal and temporal hypoperfusion was observed in the AD patients when compared to controls, but in addition they observed a correlation between the cognitive results on neuropsychological test and the SPECT findings. They also reported that SPECT is a better specific diagnostic investigation in AD than CSF Tau protein. The major limitation of this study is that most of the patients had been diagnosed with AD hence it did little to contribute to the body of information on early diagnosis of AD.

Proton magnetic resonance spectroscopy (^{1}H-RMS)

As an imaging technique ^{1}H-MRS provides a noninvasive monitoring of brain chemistry by

quantifying the levels of brain metabolites such as N-acetyl-aspartate (NAA), creatine (Cr) and glutamate using the difference in chemical shift. Chemicals such as NAA are markers of neural integrity. The ratio of NAA to Cr, is reported to be reduced in the hippocampal gray matter in patients with AD compared to healthy controls.[42]

NEUROIMAGING IN THE DIFFERENTIAL DIAGNOSIS OF DEMENTIA

MRI AND CT

MRI is useful for the detection of pathological changes related to VaD such as strategic infarcts, leukoaraiosis, and microhaemorhages.[43] Susceptibility-weighted and T_2-gradient recall echo MRI is very useful in visualizing microhaemorrhages in cases of AD coexisting with VaD.[44] In DLB structural changes in the form of atrophy are commonly seen in the striatum and midbrain with relative sparing of the hippocampal gyrus.[45]

The structural change in FTLD varies according to the subtype and this is better visualized on MRI compared to CT scan.[46, 47]

^{1}H-RMS

The reduction of NAA to Cr ratio in the different part of the brain can be used in determination of a patients' type of dementia. The reduction in VaD is primarily in the frontal and parietal cortex, but in FTLD there is a greater decrease in the frontal region and the posterior cingulate cortex.[48,49] In DLB the ratio is usually normal in the posterior cingulate gyrus.[50]

DTI

This is particularly very useful in differentiating AD from VaD due to subcortical infarct when there are only mild white matter changes on T_2-weighted images as it can highlight changes in the white matter integrity. In VaD the attenuation measured as apparent diffusion coefficient (ADC) is commonly observed to be higher in regions of the superior longitudinal fasciculus, genu of corpus callosum and the inferior fronto-occipital fasciculus; while in AD it is higher in the temporal lobe and hippocampus.[51] There is elevated diffusivity despite normal amygdala gray matter in DTI of patients with DLB, which is the reverse of what is observed in AD.[52]

ASL

In FTLD it shows hypoperfusion in bilateral frontal and insular cortex, this was associated with compensatory hyperperfusion of the precuneus and posterior cingulate.[53]

CONCLUSION

As the incidence of dementia rises with increasing population of elderly people owing to the improvement in life expectancy, it is imperative that better modalities of making early definitive diagnosis; monitor disease progression and evaluating the effect of therapies on disease course is developed. Among other recent advances in dementia research, neuroimaging has been one of the most useful tools in meeting these emerging needs.

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