Updates on the Clinical and Research Use of Magnetic Resonance Imaging in Neurodegenerative Disorders

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Dementia is the persistent state of serious cognitive, functional and emotional deterioration from a previously higher level of functioning leading to impaired abilities of self-care and independent living. Dementia most commonly results from insidiously progressive neurodegenerative disorders such as Alzheimer's disease (AD), dementia with Lewy bodies (DLB) and fronto-temporal dementia (FTD). These disorders invariably cause irreversible brain parenchymal changes, which can be frequently detected on structural imaging.

In recent decades the pre-dementia stages of neurodegeneration have attracted significant attention and led to the recognition of a state called mild cognitive impairment (MCI). MCI[1] also known as prodromal AD[2, 3] is an increasingly important focus of research and clinical attention in our efforts to identify and treat patients early.

Neuroimaging techniques have historically played an important role in the work-up of patients with dementia. The American Academy of Neurology (AAN) guidelines for the diagnostic evaluation of dementia require physicians to obtain one structural imaging study in patients with objective cognitive decline [4, 5]. It has been shown that 5% of cognitively impaired patients have non-degenerative and potentially treatable conditions such as slow-growing brain neoplasm, subdural hematoma, or normal-pressure hydrocephalus [5]. Structural imaging can additionally identify ischemic changes that prompt further work-up, treatment of vascular risk factors and behavioral modifications (i.e., dietary and exercise changes). The superior spatial resolution of structural MRI and the availability of sequences that can visualize various other pathologic findings render MRI preferable to computerized tomography (CT).

Recently the role of structural and functional neuroimaging in the initial assessment of patients with or at risk for cognitive decline has expanded. We now recognize the presymptomatic and prodromal AD stages in the settings of characteristic cognitive performance accompanied by a positive AD biomarker such as for instance hippocampal atrophy, positive amyloid positron emission tomography (PET) or cerebrospinal fluid Aβ and tau levels suggestive of AD.

The role of structural neuroimaging in AD

AD is the most common neurodegenerative disorder and the sixth most common cause of death in the US [6]. Although the disease becomes symptomatic after the age of 65 years in general, the evidence that amyloid pathology and early neurodegeneration start in mid-life is overwhelming [7-12]. This has led to the development of a hypothetical model for biomarker changes over time which details the accumulation of disease related

biomarker abnormalities as the disease transitions through the presymptomatic, than the early symptomatic and finally the late symptomatic stages [7, 13].

Of all the different neuroimaging modalities magnetic resonance imaging (MRI) and tau positron emission tomography (PET) correlate best with cognitive decline.

A) Hippocampal atrophy

Atrophy of the mesial temporal lobe structures, namely the entorhinal cortex and the hippocampus, are considered the structural imaging hallmark of AD [14-16]**.** These changes can be even appreciated in the presymptomatic and prodromal AD stages [9, 14, 17, 18]. With disease progression into the dementia stages global brain atrophy becomes more pronounced. The most affected regions are the temporal and parietal lobes. Ventricular enlargement becomes prominent [19-21]. These changes are oftentimes not subtle and are easily appreciated on CT or MRI.

State-of-the art research methodologies have been heavily used to study the spread of hippocampal atrophy from the subiculum and CA1 subfield to the CA2-3 region *in vivo* [9, 14, 18, 22-24]– a pattern that was previously only captured in post mortem studies [25]. Such technological advances might one day be used clinically in presymptomatic diagnosis and risk assessment.

B) Cortical atrophy and ventricular enlargement

Cortical atrophy and subsequent white matter tract degeneration are the culprits behind global brain atrophy and ventricular enlargement. These can be easily identified on MR and CT imaging. Contemporary cortical thickness approaches [20, 26, 27] allow us to visualize *in vivo* the progressive spread of cortical atrophy in subjects with MCI or AD dementia [19, 20] and ascertain the cortical subregions that most sensitively predict AD type dementia in the elderly [28, 29]. The cortical areas that are affected early include the entorhinal, parahippocampal, inferior and lateral temporal cortices. Next atrophy spreads to the parietal and finally the frontal association cortices [20]. Similar to hippocampal atrophy, cortical atrophy shows robust correlations with cognitive impairment [20, 30, 31]. Considering the highly specialized functionality of various associative cortical regions, the observed atrophy pattern can critically inform the diagnostic process.

D) White matter changes in AD

White matter changes are commonly seen in patients with neurodegenerative disorders [32, 33] and are associated with faster cognitive decline [34, 35]. Diffusion-weighted imaging (DWI) can be used to reveal microstructural changes in the myelin sheath. The observed greater diffusivity and reduced fractional anisotropy correlates with worsening cognition in MCI and AD [36]. These white matter changes are non-uniform. The uncinate fasciculus – the white matter tract connecting the hippocampus and amygdala with the anterior temporal lobe, and the superior longitudinal fasciculus – the white matter tract connecting the anterior (frontal) with the posterior (temporal, parietal and occipital) association cortices, seem to be most affected [37]. Smaller effect was demonstrated for the genu and the splenium of the corpus callosum, as well as the frontal and temporal white matter [37]. Decreased fractional anisotropy has been reported in preclinical Presenilin 1 mutation carriers in the fornix and orbitofrontal white matter suggesting that brain parenchymal changes begin years and possibly decades prior to dementia onset [38].

Confluent white matter changes can further exacerbate cognitive decline in those with AD and can give rise to pure vascular dementia in those without other neurodegenerative pathology.

E) Amyloid Angiopathy

Gradient echo or susceptibility-weighted MR sequences may reveal multiple small hemorrhages characteristically located at the cortical gray/white matter junction being most prominent in the occipital lobe area. These are the result of microhemorrhages from amyloid angiopathy. Amyloid angiopathy can also result in large life threatening lobar hemorrhages; hence, caution when prescribing anticoagulants in patients with suspected AD should be exercised.

E) AD variants

There are several atypical AD syndromes that are often misdiagnosed.

Patients with *frontal variant of AD* present with significant behavioral and/or personality changes out of proportion of the observed short-term memory impairment. Spouses and caregivers commonly complain of impatience, irritability, impulsivity, disinhibition and tactlessness. On formal testing they invariably show significant executive disturbances[39]. These patients might not show an aberrant structural atrophy pattern or might show greater frontal involvement.

Posterior cortical atrophy is an AD subtype that manifests with visuospatial dysfunction which can include any of the following - partial or full Balint syndrome (simultanagnosia, ocular apraxia and ocular ataxia), partial or full Gerstmann syndrome (acalculia, agraphia, right/left disorientation, finger agnosia), apperceptive visual agnosia and environmental disorientation. Patients often develop constructional, dressing and ideomotor apraxia early on while memory and insight are preserved until later in the disease course. Structural imaging reveals atrophy of the occipital lobes that is out of proportion to the remainder of the brain.

Finally, AD patients may also present with early progressive language involvement with pronounced anomic deficits and impaired repetition but preserved grammar and syntax. This form of AD is referred to as *logopenic aphasia*. The atrophy in this AD variant is asymmetric and involves the left greater then right temporoparietal areas.

The role of structural neuroimaging in the Frontotemporal Dementia Spectrum

As the name suggests the frontotemporal dementias (FTDs) are neurodegenerative dementias affecting the frontal and/or temporal lobes out of proportion to the rest of the brain. This diagnostic group consists of several distinct dementia syndromes – the classic behavioral variant FTD (bvFTD) which could also be associated with motor neuron disease (MND) – bvFTD-MND, and two language variants – nonfluent primary progressive aphasia (PPA) and semantic dementia (SD). bvFTD patients usually show striking frontal and/or temporal asymmetrical atrophy (right greater then left in most cases) at the time of diagnosis. Nonfluent PPA patients present with early dysfluent, effortful and agrammatic speech, anomia and phonemic paraphasic errors in the context

of preserved language comprehension and show left perisylvian atrophy centered on the inferior frontal gyrus, while SD patients manifest with loss of conceptual and word meaning (i.e., semantic knowledge) and left greater then right anterior temporal lobe involvement [40, 41].

DWI imaging is also abnormal in FTD. Reduced fractional anisotropy has been reported in the frontal and temporal white matter, and the anterior cingulate [42]. Presymptomatic changes are being increasingly recognized, for example Progranulin (PGRN) mutation carriers show reduced fractional anisotropy in the uncinate fasciculus and the occipitofrontal areas and possibly decades prior to dementia onset [43].

The role of structural neuroimaging in Dementia with Lewy Bodies

In addition to cognitive and functional decline meeting criteria for dementia patients with DLB manifest parkinsonian features such as rigidity, action or postural tremor, bradykinesia, parkinsonian gait and/or poor balance. They tend to have fluctuations in alertness and cognitive acuity and oftentimes also psychosis and REM behavior disorder. Patients with DLB often have mild to moderate nonspecific generalized brain atrophy on CT or MRI. Hippocampal involvement may or may not be present. Large studies have helped determine the spatial pattern of involvement consisting of diffuse temporal, parietal and frontal cortical atrophy [44-46], as well as atrophy of the dorsal midbrain, hypothalamus and substantia innominata [47]. DTI signal changes in DLB are somewhat similar to those in AD. Fractional anisotropy decline was found in the inferior longitudinal fasciculus in both disorders [48].

The role of structural neuroimaging in other Parkinsonian Dementias and Creutzfeld-Jacob Disease

Corticobasal degeneration patients clinically manifest asymmetric parkinsonism, cortical sensory loss and limb apraxia, and show contralateral greater then ipsilateral frontoparietal atrophy with clear involvement of the motor and sensory cortices.

The structural manifestations of progressive supranuclear palsy consist of atrophy of the midbrain tegmentum, enlargement of the third ventricle and T1 hyperintensity of the midbrain and inferior olives [49, 50].

MRI (as opposed to CT) could be very useful in establishing the diagnosis of Creutzfeld-Jacob disease (CJD). Patients with CJD often show increased T2, FLAIR and DWI signal of the basal ganglia and cortical ribbon in areas corresponding to the symptomatology. Such findings are essentially pathognomonic for CJD [51-55].

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The presentation will include a brief review of the characteristic changes in the disorders discuss develop probate case studies and interactive learning session with the audience.

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