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The number of individuals affected by dementia is increasingly growing worldwide. Based on the Global Burden of Disease study (GBS), more than 130 millions of people affected by dementia by the year 2050. About at least seventy per cent of these cases are AD or mixed dementia. A definitive AD diagnosis, according to the 1993 NINDS-NIA criteria is achievable only by postmortem examination. On the other hand, the clinical diagnosis of dementia is still challenging for the dementia specialists applying both the old and the new clinical criteria. It is clear that the diagnostic accuracy can be improved by the support of paraclinical investigations such as imaging (structural and functional) plus fluid biomarkers (biomarkers of pathological specific process,neuronal damage, and inflammation). This is important for clinical work especially in the differential diagnosis process but probably essential to anticipate the diagnosis after first symptom and in the preclinical stage, as required in the recent classification systems and in trials for new therapies. The advancement of imaging Alzheimer disease pathology has included several markers for PET β-amyloid imaging agents. The recognized growing importance of neocortical neurofibrillary tangles as marker of disease progression and pathology has determined the development of several tau imaging compounds such as [(18)F]T807, [18F]THK523, [18F]THK5117, [18F]THK5105 and [18F]THK5351, [18F]AV1451(T807) and [11C]PBB3. In particular F T807 binding has been described as associated with clinical impairment particularly in the inferior temporal gyrus, stronger than the association of betaamyloid marker in the cortex with the same clinical features.

In this direction several cell and animal studies suggest that tau propagation from cell to cell along specific anatomic pathways with a prion like mechanism may favour the aggregation and region-to-region spread of tau pathology within the central nervous system, determing the clinical phenotype. The pathological accumulation of the tau protein is important not only for other dementias both mainly environmental like chronic traumatic encephalopathy and others of more complex clinical and genetic classification such as frontotemporal dementias, progressive supranuclear palsy, and corticobasal degeneration. In AD, It has been clearly shown that the hyperphosphorylated tau tangles and not beta amyloid accumulation, correlates with neuronal dysfunction and death. Therefore also the clinical stage and severity of AD seem more closely correlate to tau load and spreading than with beta-amyloid accumulation.The pathogenesis and some data on the clinical progression seem to suggest that tau imaging, a surrogate in vivo of tau accumulation, may be instrumental in the classification and staging of dementias.

On the other hand recent neuropathological studies in subjects over 85 with samples collected in population-based studies show that for older subjects the relationship between clincal features and tau accumulation may be non linear. This is particularly important in subjects with dementia where the correlation is lost after diagnosis.

Therefore, the benefit of follow-up of patients with dementia and in some cases even the diagnosis may be less significant in subjects in advanced age.
The age structure of people with dementia is rapidly changing with 2/3 of subjects being 85 and older. The challenge is therefore to obtain a valid and early diagnosis taking into account the changing pattern of disease phenotype of subjects with dementia. Subjects with dementia, being mostly in late stages of life, are going to have more than one pathological condition (more likely several pathological conditions and furthermore to be frail and with a short expectation of life , in most of cases less than ten years). Diagnostic and therapeutic research, including imaging in the area fo dementia should carefully taking account this shift to determine improvement of clinical management and prognosis of patients. In this conceptual framework the challenge of early diagnosis should look carefully at change in tau accumulation with age.

For disease progression other markers may be important: imaging markers of inflammation may be at least as important as tau deposition. Both genetic (particularly GWAS) and epidemiological studies have shown a link between neuroinflammation and neurodegeneration in AD. Microglial activation and reactive astrocytes have been described in critical area for dementia. Inflammatory genes like IL6r and C9 genes in particulart have been associated with Aβ and tau burden. Recent work has shown that PET ligands for neuroinflammation may act as good markers of disease progression, allowing for the development of more complex and integrated model of AD natural history,

PET tau imaging probably enables the assessment of the longitudinal pattern of tau deposition. This is, however, not the only imaging marker important for the assessment of the the clinical evolution of disease. There are however significant problems that needs to be addressed before considering tau imaging key in diagnostic and especially in the follow-up of subject with dementia . These controversial issues will be discussed in the presentation.