Tau PET and tauopathies

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PET tracers for pathological deposits of tau protein aggregates in the brain are currently undergoing rapid development. They are targeting pathological deposits of tau aggregates, which are present in several neurodegenerative disorders, the so-called tauopathies. The most frequent of these is Alzheimer's disease, which is characterised by a combination of neurofibrillary tangles (primarily tau) and plaques (primarily beta-amyloid). However, pathological deposits of tau (without beta-amyloid plaques) also are present in rarer diseases, including progressive supranuclear palsy (PSP), cortico-basal degeneration (CBD), some types of fronto-temporal dementia (FTD), and secondarily also in post-traumatic encephalopathy [2, 12]. Most publications on PET tau imaging relate to Alzheimer's disease only, while a paper by Chiotis et al. in this issue also included a few cases of non-AD tauopathies.

The paper should be considered within the background of the main clinical research needs and expectations for tau imaging. The most obvious ones are related to the potential of tau PET as an imaging biomarker in clinical trials of therapeutic compounds to delay the onset or progression of dementia in AD. Alternatively, increased levels of tau in CSF are also being used as a biomarker of pathological tau deposition in such trials. CSF sampling includes the option to also assess abnormal tau phosphorylation as well as other potential biomarkers, such as inflammatory cytokines [5]. Longitudinal

studies will need to assess the merits of imaging the regional brain distribution of tau PET deposits compared to the analysis of their molecular diversity in CSF. Most importantly, a tau biomarker should measure disease progression at a prodromal stage where symptoms are absent or mild and do not show much change within typical trial durations. Tau PET could also help with accurate staging of prodromal AD, analogous to the pathological staging proposed and validated by Braak and Braak [10]. From a diagnostic perspective, tau PET would be expected to separate tauopathies from diseases associated with other pathological protein deposits such as Lewy bodies, TDP43, FUS, and prion protein [11], and to discriminate between different tauopathies by their regional distribution patterns [8].

What does the paper by Chiotis et al. demonstrate? A main result is an excellent discrimination between healthy controls and AD patients. However, patients were relatively young with a maximum age of 74 years (whereas most AD patients are older) and the sample of controls was quite small and even younger, including only four elderly controls with a maximum age of 65. Thus, the study could not address the issue of discriminating between primary age-related tauopathy (PART), which also increases substantially with old age, and preclinical or prodromal AD. PART is characterised by mesial temporal tau deposits in the absence of beta-amyloid plaques and is usually regarded as a relatively benign age-related condition that is different from AD [6]. This issue has been addressed in a recent study using another tau tracer, 18F-AV145, which demonstrated that elderly normal controls do show increased hippocampal tau signal, but with less intensity and extent than what is typically seen in subjects with amyloid-positive scans [9].

Chiotis et al. also show positive regional correlations of tau with amyloid PET, as to be expected in AD as both pathological proteins accumulate. A predominantly negative

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correlation with FDG PET confirms previous studies that had shown a similar correlation between FDG PET with phosphorylated tau in CSF [1].

In addition, some information is also provided in relation to the clinical research needs listed above. The study demonstrates very good test-retest reproducibility, which is important because it would allow the sensitive detection of relatively small changes during disease progression. Intraclass correlation coefficients (ICC) are excellent (0.9 or better) for most brain regions. Another potential imaging biomarker to assess disease progression is FDG PET, for which a comparable ICC of 0.92 has been reported [4]. However, that was a composite score as opposed to being derived from regional values, which tend to be less reproducible. Also, high reproducibility of FDG PET depends critically on maintaining cognitive resting state conditions during tracer accumulation, which is not easy to ensure in busy nuclear medicine laboratories. Thus, if the actual signal change during disease progression was similar or better to what is seen with FDG (although in the opposite direction), tau PET may actually provide superior performance as a progression biomarker. Compared to amyloid PET, which also has excellent test-retest reproducibility [7] but appears to reach a kind of plateau already very early during disease progression with little further change and poor correlation with clinical disease severity, tau PET clearly looks more promising.

The present study uses a new benzimidazole derivative from a series of tau tracers developed by a highly active research group at Tokoku University. It is therefore not entirely clear whether the results could be generalized to other tracers. Overall, results are similar to what has been reported for 18F-AV1451 (aka T807) [9]. Recently, the Tohoku group has released yet another tracer from the same series, THK5351, claiming improved kinetics but otherwise comparable properties [3]. Thus, it is plausible that the current results would also hold for at least these two other compounds which have been licensed by major commercial companies.

There are still many open questions with regard to early diagnosis of non-AD tauopathies using such tracers, and the two cases reported in the present paper are encouraging but not sufficient to resolve them. Both patients had severe clinical symptoms, providing confidence in the clinical diagnosis but precluding judgement of the sensitivity of tau PET. Doubts about sensitivity for early diagnosis are based on the fact that tau deposits are initially intracellular with relatively low

density, being released into the extracellular space where they might possibly be easier to reach only once neurons have been dying and their fate is no longer reversible. Also, different isoforms and tertiary formations may play a role, as well as the differential binding and kinetic properties of the various tracers. Thus, much more research will be needed to establish tau PET for early and differential diagnoses of tauopathies.

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