EDITORIAL

Hide-and-seek for radiotracers and neurodegenerative pathology

Karl Herholz[1]

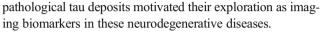## Hide-and-seek for radiotracers and neurodegenerative pathology

Semantic dementia is much less frequent than Alzheimer's disease and is one of the several dementia types not associated with deposition of amyloid beta in the brain. Thus, the question arises whether PET radiotracers binding to pathological markers other than amyloid might be useful for early diagnosis of the disease. However, the issue is complex, and the paper by Schaeverbeke et al. in this issue addresses one particular aspect of that story which should be seen in a larger context.

From a clinical perspective, progressive aphasia with impaired word comprehension and poor confrontation naming but relatively spared repetition and fluency is a key symptom of semantic dementia. Semantic dementia has therefore been grouped together with other types of primary progressive aphasia (PPA). It is now called the semantic variant of primary progressive aphasia (svPPA), which is distinct from non-fluent and logopenic variants of PPA (1). Corresponding to clinical symptoms, svPPA typically presents with cortical atrophy and glucose hypometabolism predominantly in the anterior temporal lobe of the dominant hemisphere.

From a pathological perspective, these clinical syndromes exhibit considerable heterogeneity (2). Semantic dementia has also been classified as a manifestation of frontotemporal lobar atrophies (FTLD), with the behavioural variant of frontotemporal dementia (FTD) and progressive non-fluent aphasia as other manifestations of FTLD (3). Most frequently tau protein and TAR DNA-binding protein 43 (TDP-43) are found as pathological protein deposits, while other pathological proteins may also be present. When suitable tau PET radiotracers became available; the possible presence of

pathological tau deposits motivated their exploration as imaging biomarkers in these neurodegenerative diseases.

This resulted in a discrepancy between PET findings and expectations based on pathological studies. As described by Schaeverbeke et al. and a corresponding study by Cho et al. (4), the most frequent pathological protein observed in post-mortem studies of svPPA is TDP-43, while tau deposits are relatively rare. In contrast, PET studies using the tau radiotracer 18F-flortaucipir (aka 18F-AV1451 and 18F-T807) demonstrated increased uptake in the majority of svPPA patients. Thus, there is some doubt about the molecular specificity of 18F-flortaucipir for pathological tau deposits, even though a close correspondence of stage-dependent regional tau distribution patterns between pathological studies and 18F-flortaucipr PET has been observed in Alzheimer's disease (5).

Off-target binding limiting the specificity of tau tracers had already been observed in previous studies. Most notably, another tau tracer, 18F-THK5351, has been shown to bind to monoamine oxidase B (MAO-B) and glial fibrillary acidic protein (GFAP) (6). While this limits the specificity for tau, it is also of interest as MAO-B and GFAP are expressed in astrocytes, which may play a role at the earliest stages of neurodegeneration (7). The study by Schaeverbeke et al. did not find signs of 18F-flortaucipir binding to MAO-B in post-mortem specimens, inevitably representing late stage disease. As astrocytic activation and associated MAO-B expression are more pronounced at early than at late stage, this does not completely exclude off-target in vivo binding to higher MAO-B expression at an earlier disease stage. Off-target binding of 18F-flortaucipir has previously been noted for iron and neuromelanin (8). Thus, accumulation in svPPA could possibly also be related increased uptake of iron due to blood-brain barrier (BBB) alterations in atrophic brain areas (9).

As discussed by Schaeverbeke et al., their study and other recent studies in PPA or FTLD patients do not allow firm conclusions as they only cover a limited set of possible off-target sites and do not directly compare in vivo and pathological findings in the same subjects. Thus, further research is necessary, which then should also cover second-generation tau PET tracers. Dynamic PET studies may allow

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✉ Karl Herholz
karl.herholz@manchester.ac.uk

[1] Division of Neuroscience and Experimental Psychology, University of Manchester, 27 Palatine Road, Manchester M20 3LJ, UK

differentiation between specific binding and BBB-related alterations of uptake (10). The limitations of current studies also underscore the urgent need for development of PET ligands binding specifically to TDP-43, as this pathological protein is involved in many neurodegenerative diseases including svPPA as well as other PPA and FTLD variants, limbic-predominant age-related TDP-43 encephalopathy (LATE), which mimics Alzheimer's disease (11), and amyotrophic lateral sclerosis.

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