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Title: Posterior Cingulate Involvement Does Not Argue Against LATE

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Running: PCC Involvement in LATE

To the Editor:

Accurate antemortem diagnosis of neurodegenerative dementia is vital for appropriate counseling and enrollment of patients in disease modifying clinical trials. While the advent of biomarker imaging such as amyloid and tau PET has drastically improved our antemortem ability to diagnose Alzheimer's disease (AD) pathology, the recognition of specific patterns of glucose metabolism on ^{18}F-FDG-PET is crucial for the diagnosis of degenerative conditions without disease specific neuroimaging biomarkers, such as dementia with Lewy bodies (DLB) or limbic-predominant age-related TDP-43 encephalopathy (LATE). Due to the significant clinical overlap between LATE and typical AD, FDG-PET serves as a valuable diagnostic tool for the workup of amnestic dementia. (*1*)

In this issue of The Journal of Nuclear Medicine,(*2*) the authors aim to highlight FDG-PET neuroimaging findings differentiating LATE from other neurodegenerative dementias with a case example. The authors report a patient with multidomain amnestic cognitive dysfunction with FDG-PET imaging showing moderately severe anterior temporal and parietotemporal hypometabolism with preservation of the posterior cingulate cortex (PCC) and occipital cortex. The authors argue that sparing of the PCC in their patient would be inconsistent with AD while the absence of occipital hypometabolism would argue against DLB, both of which may support LATE as an etiology for the patient's amnestic cognitive impairment. While sparing of the PCC compared to the precuneus/cuneus ("cingulate island sign") and involvement of the occipital lobe is indeed the classic pattern for DLB, we disagree that sparing of the PCC in this case is supportive of LATE and inconsistent with AD.(*3*)

Recent data suggest medial temporal, posterior cingulate, and frontal supraorbital hypometabolism are predictors of LATE whereas prominent inferior temporal involvement may

be predictive of AD.(*4*) Antemortem studies of amnestic dementia cases have demonstrated medial temporal and PCC hypometabolism to be more prominent in amyloid negative (*5*) and tau negative cases,(*6*) whereas tau positive (i.e. AD) cases showed more lateral and inferior temporal as well as parietal involvement. This pattern was corroborated by autopsy data showing cases of LATE with hippocampal sclerosis that had prominent medial temporal and PCC hypometabolism.(*6*) Based on these data, an elevated ratio of inferior-to-medial temporal lobe metabolism was proposed as an FDG-PET marker of LATE, as the authors correctly point out. This pattern was subsequently confirmed by an independent group of investigators in ADNI.(*7*)

The relevance of PCC involvement or sparing in predicting the underlying pathology is more nuanced. While not all studies have supported PCC hypometabolism as predictive of LATE (*4*), some autopsy confirmed LATE cases had marked, focal hypometabolism of the PCC ('inverse cingulate island sign').(*6*) We provide three case examples of amyloid and tau negative amnestic dementia cases with clear PCC involvement in Figure 1. Molecular pathology data have shown lower mitochondrial DNA copy numbers in the PCC that was explained by the presence of TDP-43 pathology, but not tau, further supporting the link between LATE and PCC hypometabolism. (*8*) PCC hypometabolism has also been tied to hippocampal atrophy in cognitively normal individuals and those with MCI whereas it was attributed local atrophy in AD dementia.(*9*) PCC hypometabolism likely reflects the presence of limbic, and more specifically medial temporal neurodegeneration, which would explain why the PCC is involved in LATE and typical AD but relatively spared in DLB and some hippocampal-sparing AD phenotypes. (*10*) As such, the preservation of PCC metabolism in the absence of medial temporal hypometabolism in the authors' case is entirely expected and should not be taken as evidence for LATE or against some forms of AD, especially in light of the inferior temporal and parietal hypometabolism.

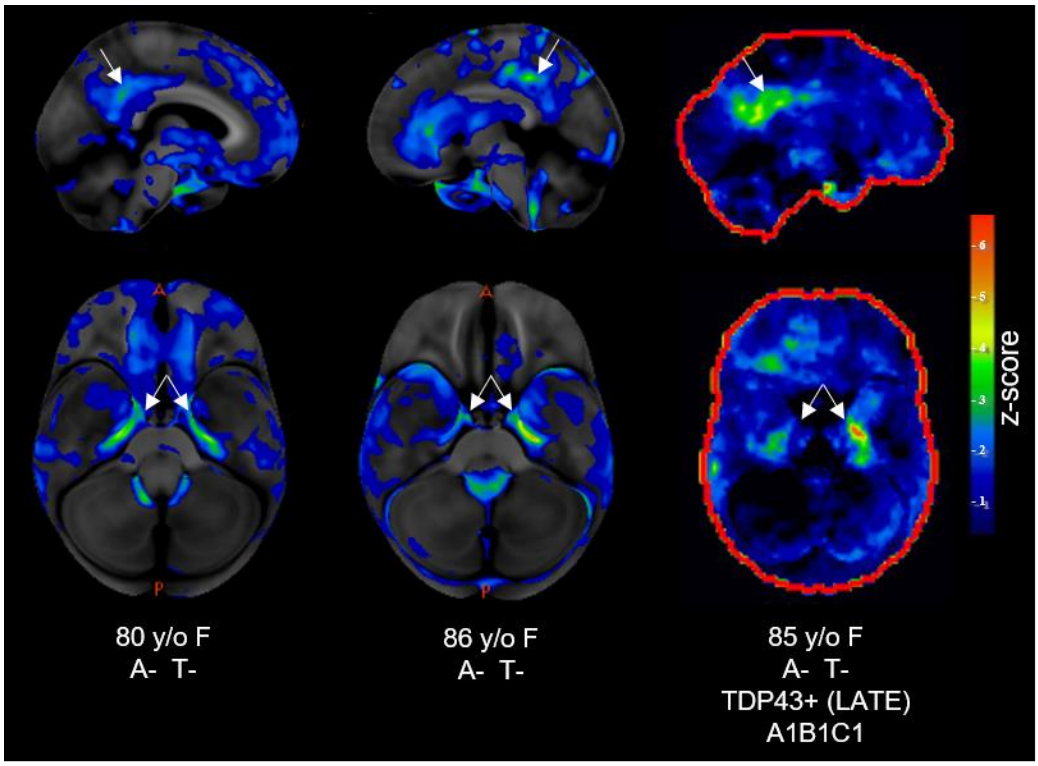

Figure 1: Amyloid and tau negative amnestic dementia cases with PCC involvement

Shown are 3D stereotactic surface projections Z-score image generated with CortexID (GE Healthcare) indicating hypometabolism in the cases compared to age and sex matched controls. All three cases were from our recent paper on FDG PET in tau-negative amnestic dementia.(*6*) All three cases had PCC hypometabolism (top row arrows) as well as prominent medial temporal hypometabolism (bottom row arrows). The third case (right column) has since come to autopsy and had low stage NIA-AA Alzheimer's disease (A1B1C1) and hippocampal sclerosis with TDP-43 (LATE).

While we await TDP-43 specific tracers for an antemortem diagnosis of LATE, FDG-PET, in conjunction with structural brain imaging remains our most useful neuroimaging tool in individuals presenting with amnestic cognitive impairment. Clinicians and radiologists should pay specific attention to the medial temporal lobe and PCC in older patients with amnestic dementia. Specifically, greater medial than inferior temporal lobe hypometabolism is highly suggestive of the presence of LATE. Finally, PCC metabolism may be affected by multiple processes, highlighting the importance of integrating the clinical phenotype with all available neuroimaging data to obtain the most accurate diagnosis.

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