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Letter to the Editor: New Observation

Positive Predictive Value of Cerebrospinal Fluid Biomarker Testing for a Clinical Diagnosis of Alzheimer's Disease

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Alzheimer's disease (AD) is a neurodegenerative illness that is defined neuropathologically by the presence of amyloid plaques and neurofibrillary tangles. The central importance of these neuropathologic findings is highlighted in recently revised 2024 criteria for the diagnosis and staging of AD, which propose that detection of AD-related neuropathologic change (ADNPC) by biomarkers is equivalent to making a diagnosis of AD biologically.[1] While there remains ongoing debate regarding this approach to diagnosis in cognitively normal individuals[2], there is general consensus that testing for biomarkers indicative of ADNPC in patients with suggestive cognitive symptoms can facilitate accurate AD diagnosis. One such biomarker test is the cerebrospinal fluid (CSF) p-tau181/Abeta-42 ratio, which we began offering at London Health Sciences Centre/St. Joseph's Health Care London (LHSC/SJHC) in November 2023 using Health Canada-approved Roche Elecsys immunoassays. An Elecsys p-tau181/Abeta-42 ratio cut-off of >0.023, as suggested by the manufacturer, has been reported to have a specificity of 89% – 98% for ADNPC when compared to the reference standard of amyloid PET.[3,4]

Importantly, such tests with high but imperfect specificity may have lower than anticipated positive predictive value (PPV) when introduced into clinical practice, where testing may be ordered in lower-probability scenarios.[5] This is of particular relevance when substantial diagnostic weight is placed on an abnormal test result, as has increasingly been emphasized for the diagnosis of AD. While detection of ADNPC by CSF biomarkers may be sufficient to diagnose AD biologically, investigations into the performance of this test when used to evaluate clinical symptoms potentially referable to AD are of practical importance. This is especially true in older patients (i.e. those ≥ 80 years of age), among whom ADNPC is relatively common but may not necessarily be the explanation for their clinical presentation.[6] While previously reported Canadian experience with sending samples out-of-country for CSF AD biomarker testing has been valuable in illustrating its potential utility[7], dedicated evaluations examining PPV following local test implementation are lacking. For this reason, we opted to examine the PPV of a positive CSF p-tau181/Abeta-42 ratio for a clinical diagnosis of AD, one year after test implementation at our tertiary care center.

We identified all patients at LHSC/SJHC who underwent Elecsys CSF AD biomarker testing (Abeta42, p-tau181, and t-tau) between November 1, 2023 (test inception) and October 31, 2024. Testing was performed using the Roche Cobas e801 immunoassay analyzer. Ordering of this testing at our center is restricted to neurologists and geriatricians. Patients with a positive p-tau181/Abeta-42 ratio (defined as a ratio of >0.023) were included in this PPV analysis. While both individual results for each analyte as well as the calculated p-tau181/Abeta-42 ratio were reported out for each patient, this study focused on the p-tau181/Abeta-42 ratio given its incorporation into the 2024 criteria.[1] Patients with a clinical presentation compatible with AD and no more likely alternative diagnosis were deemed to have a clinical diagnosis of AD and classified as having a true-positive result, while all other patients were deemed not to have a clinical diagnosis of AD and classified as having a false-positive result. Classifications were based on retrospective review by A.B. of the specialist clinical impression documented in the patient's electronic medical record. In cases where there was documented concern for a competing diagnostic consideration, discussion with the specialist was pursued to clarify whether AD was considered to be the most likely diagnosis. Because CSF AD biomarker testing at our center is a clinical service-based test that is reported directly into the patient's electronic medical record, specialists were not blinded to CSF AD biomarker test results. The PPV of the p-tau181/Abeta-42 ratio was calculated as the proportion of those with positive results who were classified as true-positive. This study was approved by the Western University Health Science Research Ethics Board.

Of 34 patients at LHSC/SJHC who underwent CSF AD biomarker testing over the one-year period examined, 25 (74%) had a positive p-tau181/Abeta-42 ratio and were included in study analysis (see Figure 1). The median age was 67 years (range 50–80 years) and 15/25 (60%) were male. The median Montreal Cognitive Assessment (MoCA) score was 20 (range: 2–27). Two of 25 (8%) with a positive p-tau181/Abeta-42 ratio had a normal Abeta-42

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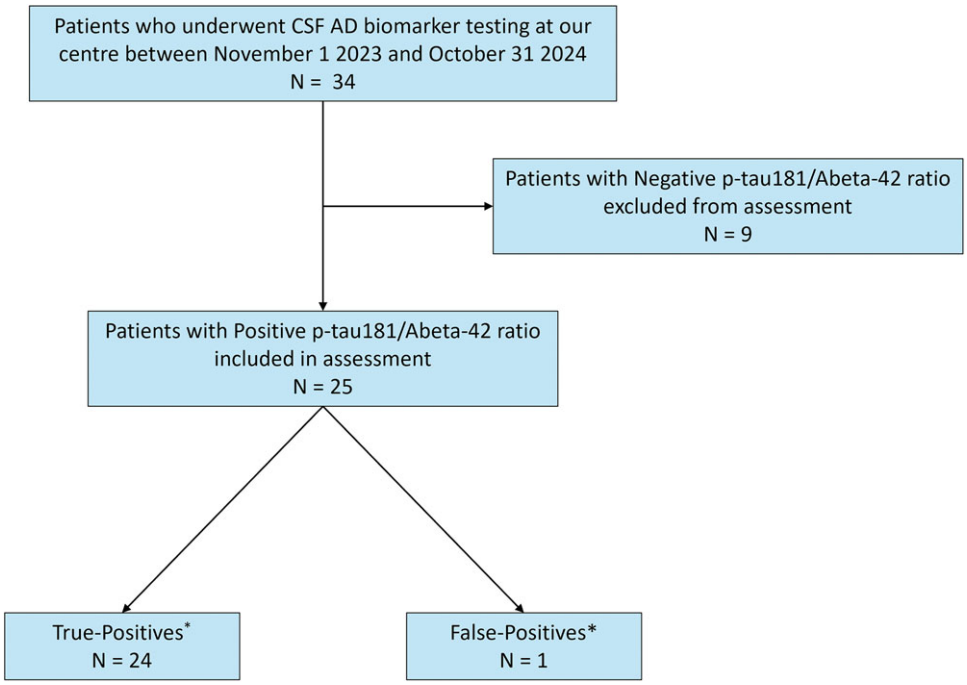

Figure 1. Flow diagram of positive p-tau181/Abeta-42 ratio results that were included in assessment.
AD = Alzheimer's disease; CSF = cerebrospinal fluid. *See text for further discussion surrounding true-positive and false-positive classifications.

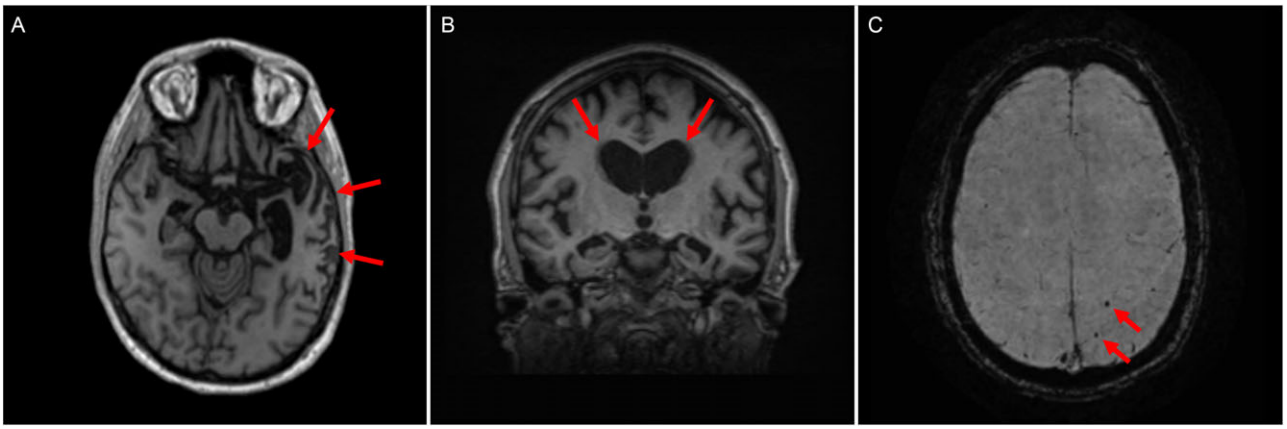

Figure 2. Neuroimaging of patients with positive p-tau181/Abeta-42 ratio and competing diagnostic considerations. In Panel A, axial T1-weighted image shows strikingly asymmetric left temporal lobe atrophy (arrows) in a patient with a positive p-tau181/Abeta-42 ratio, raising the diagnostic possibility of semantic variant primary progressive aphasia (typically associated with TDP-43 pathology rather than ADNPC). In Panel B, coronal T1-weighted image MRI shows ventriculomegaly (arrows) in a patient with a positive p-tau181/Abeta-42 ratio, raising the diagnostic possibility of obstructive hydrocephalus secondary to craniopharyngioma (not shown) that required endoscopic third ventriculostomy. However, both patients presented primarily with progressive amnestic complaints and were noted to have bilateral hippocampal atrophy on MRI; the second patient was also noted to have stable ventricular size post-third ventriculostomy when compared to previous imaging (not shown). In both patients, AD (typical amnestic phenotype) was therefore deemed to be the most likely clinical diagnosis, and both were classified as true-positives. In Panel C, axial susceptibility weighted image shows multiple cerebral microhemorrhages suggestive of cerebral amyloid angiopathy in a patient with a positive p-tau181/Abeta-42 ratio but a more likely alternative diagnosis of anti-LGI1 encephalitis, who was classified as a false-positive.
ADNPC = AD-related neuropathologic change; AD = Alzheimer's disease; TDP-43 = TAR DNA-binding protein 43.

concentration. All 25 (100%) were seen by a geriatrician or neurologist specializing in cognitive impairment. Twenty-four were classified as true-positives, resulting in a calculated PPV of 96% (95% CI [80, 100%] by binomial "exact" method). Of these 24, 21 (88%) had a typical amnestic AD phenotype while 3 (12%) had less typical AD phenotypes that are known variants (corticobasal syndrome, 2; logopenic variant primary progressive aphasia, 1).[2] In two patients, a competing diagnostic consideration was present (semantic variant primary progressive aphasia typically associated with TAR DNA-binding protein 43 [TDP-43] pathology rather than ADNPC, 1; obstructive hydrocephalus secondary to craniopharyngioma, 1). In the first patient, semantic variant primary progressive aphasia typically associated with TDP-43 pathology was raised as a diagnostic possibility because of strikingly asymmetric temporal lobe atrophy on MRI (see Figure 2A).[8] In the second patient, obstructive hydrocephalus was raised as a diagnostic possibility because of a prior diagnosis of obstructive hydrocephalus secondary to craniopharyngioma that required endoscopic third ventriculostomy (see Figure 2B). However, both patients presented primarily with progressive amnestic complaints and were noted to have bilateral hippocampal atrophy on MRI; furthermore, in the first case, it was noted that

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ADNPC has been reported in a minority of patients with semantic variant primary progressive aphasia[9], while in the second case, it was noted that the patient had stable ventricular size post-third ventriculostomy. In both patients, AD (typical amnestic phenotype) was therefore deemed to be the most likely etiology for their clinical symptoms, and both were classified as true-positives. One patient who was classified as a true-positive had an elevated p-tau181/Abeta-42 ratio of 0.051 (normal $\leq$ 0.023) but a normal Abeta-42 concentration; this patient had an Abeta-42 concentration just above the cut-off (1058.0 pg/mL, normal >1030.0 pg/mL) but a markedly elevated p-tau181 concentration (53.6 pg/mL, normal $\leq$ 27.0 pg/mL), and had a typical amnestic AD phenotype.

Of 25 patients with a positive p-tau181/Abeta-42 ratio, 1 (4%) was classified as a false-positive. This patient was an 80-year-old man with progressive cognitive difficulties, behavioral changes and multiple cerebral microhemorrhages suggestive of cerebral amyloid angiopathy (see Figure 2C); however, subacute onset of symptoms and spells ultimately recognized as faciobrachial dystonic seizures indicated a more likely diagnosis than AD for his clinical presentation (i.e. anti-LGI1 encephalitis, confirmed on serum and CSF antibody testing).[10] He had a modestly elevated CSF p-tau181/Abeta-42 ratio of 0.029 (normal $\leq$ 0.023) that was driven by an increased p-tau181 concentration (38.3 pg/mL, normal $\leq$ 27.0 pg/mL), while Abeta-42 concentration was normal (1304.0 pg/mL, normal > 1030.0 pg/mL). Resolution of clinical symptoms following immunotherapy indicated anti-LGI1 encephalitis rather than AD as the primary cause of symptoms and supported his false-positive classification.

Our study finds high PPV of a positive p-tau181/Abeta-42 ratio for a clinical diagnosis of AD at our institution. This supports the use of this testing to confirm a diagnosis of AD in a patient with suggestive clinical symptoms, although there are several important caveats. Firstly, in patients with a positive p-tau181/Abeta-42 ratio and competing diagnostic considerations, thorough review of the clinical history and other ancillary test data is essential to confirm whether ADNPC is the most likely explanation for their symptoms. It bears emphasizing that a positive p-tau181/Abeta-42 ratio may be detected in patients with ADNPC but an alternative cause for their clinical symptoms, including co-morbid neurodegenerative pathology (e.g. synucleinopathy) or even other treatable non-neurodegenerative diseases (e.g. autoimmune encephalitis). Recognition of this possibility is of particular importance when evaluating older patients, among whom ADNPC is relatively common.[6] Conceptually distinguishing between a biological and clinical diagnosis of AD is essential when interpreting CSF biomarker results in routine practice, in order to avoid misattribution of clinical symptoms to ADNPC in patients with alternative etiologies for their presentation. Of note, the single patient in our study who was classified as a false-positive had a modestly elevated p-tau181/Abeta-42 ratio that was driven by an increased p-tau181 concentration, while Abeta-42 concentration was normal. This infrequently encountered CSF profile (elevated p-tau181 with normal Abeta-42) is not typical of ADNPC, and its clinical significance is less certain[11]; our false-positive case thus highlights the value of scrutinizing individual analyte values in patients with a positive p-tau181/Abeta-42 ratio but concern for an alternative cause of clinical symptoms. It also emphasizes the importance of interpreting CSF AD biomarker results in the context of other clinical and ancillary test data (e.g. history, physical examination, neuroimaging) rather than in isolation, to avoid premature diagnostic closure resulting from faulty information synthesis in patients with a positive p-tau181/Abeta-42 ratio but red flags suggesting an alternative clinical diagnosis.[12] Early identification of such red flags should dissuade clinicians from ordering CSF AD biomarker testing at the outset, which would mitigate risk of AD clinical misdiagnosis that may arise from the "pre-pre-analytical error" of inappropriate test ordering.[13]

Our study has limitations. It is a single-center study of newly-introduced CSF AD biomarker testing performed at LHSC/SJHC, so sample size was relatively small despite identifying all patients at our institution who underwent this testing over a one-year period. This smaller sample size limits more precise estimation of PPV in our practice setting as reflected by the wider 95% confidence interval (CI) of our calculated PPV (96%, 95% CI [80, 100%]); while it is reassuring that all values within this CI indicate a reasonably high PPV, further studies in similar practice settings are needed to confirm the generalizability of our findings. Importantly, test ordering at our institution is restricted to neurologists and geriatricians; such ordering restrictions may skew toward a tested population undergoing specialist assessment that has a high prevalence of AD, and could explain the high proportion of those with a positive CSF p-tau181/Abeta-42 ratio (74%) as well as the high test PPV (96%). Because PPV is dependent on the prevalence of the disease in the tested population, it is plausible that the PPV of CSF AD biomarker testing would be lower in other practice settings where it may be ordered by a broader range of clinicians in lower-probability scenarios. Clinicians were not blinded to CSF AD biomarker test results that were reported out on a clinical service basis, but assessment of all patients by a geriatrician or neurologist specializing in cognitive impairment, as well as specialist discussion in cases with competing diagnostic considerations, aimed to mitigate potential bias. Comparison of test performance across biomarkers (e.g. CSF biomarker testing, plasma biomarker testing and amyloid PET, the latter two of which are not clinically available at our center at this time) was outside the scope of this evaluation, which focused on the PPV of CSF biomarker testing for a clinical diagnosis of AD. While CSF AD biomarker testing may be helpful in ruling out ADNPC in clinical practice, examination of patients with a negative p-tau181/Abeta-42 ratio to determine other test diagnostic measures, such as negative predictive value, was also outside the scope of this evaluation, given the tenuousness of making a clinical diagnosis of AD in the absence of supportive biomarkers.[1,2] Despite these limitations, our findings are of value to those ordering and interpreting CSF AD biomarker testing in clinical practice.

Disease-modifying therapies for AD are currently under review by Health Canada[14], and if they are implemented, then utilization of CSF biomarkers to identify patients who may benefit from such therapies will likely increase. Clinicians should keep in mind that while this testing can be immensely helpful in confirming ADNPC, thorough evaluation of patients with abnormal biomarker results, along with thoughtful consideration of competing diagnostic possibilities, remains essential to ensure accurate clinical diagnosis.

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