Diagnostic Impact of Cerebrospinal Fluid Biomarkers in Atypical Dementias in Canada

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ABSTRACT: *Background:* In Canada, standard dementia workup consists of clinical, neurological, and cognitive evaluation, as well as structural brain imaging. For atypical dementia presentations, additional FDG-PET brain imaging is recommended. Cerebrospinal fluid (CSF) biomarkers have recently been proposed as the gold standard for in vivo detection of Alzheimer's disease (AD) pathophysiology (NIA-AA research framework, 2018). As clinical implementation of CSF assessment is still limited in Canada, the present study assessed its impact on diagnostic accuracy in atypical neurodegenerative disorders in the clinical practice. *Methods:* This retrospective clinical chart review included patients with cognitive complaints who underwent lumbar puncture (LP) in addition to the standard diagnostic workup. CSF analysis determined the presence of biological AD based on reduced amyloid-β_{42}-to-total-tau index (ATI) and increased phosphorylated-tau (p-tau) levels. CSF-based diagnoses were compared to standard workup and FDG-PET-based diagnoses. *Results:* A total of 28 patients with atypical dementia presentations were included in the present study after evaluation for cognitive complaints at a specialized dementia clinic between November 2017 and July 2019. CSF analysis changed or better specified the initial clinical diagnosis in 43.0% of cases (alternative diagnosis revealed in 25% and excluded in 18%). In patients with additional FDG-PET imaging ($n = 23$), FDG-PET and CSF-based diagnosis did not correspond in 35% of patients, even though FDG-PET appeared to increase diagnostic accuracy compared to the initial clinical diagnosis. *Conclusion:* CSF biomarkers improved diagnostic accuracy in atypical cognitively-impaired patients beyond standard workup and FDG-PET imaging. These results support CSF analysis implementation for atypical dementias in Canada, in addition to the standard diagnostic workup.

RÉSUMÉ : **Impact diagnostique des biomarqueurs du liquide cérébrospinal chez des patients canadiens atteints de démence atypique.** *Contexte* : Au Canada, l'ensemble des procédures standards de diagnostic de la démence consistent, outre des examens de la structure du cerveau, en une série d'évaluations cliniques, neurologiques et cognitives. Dans le cas de patients présentant des symptômes de démence atypiques, des examens additionnels de tomographie par émission de positrons au moyen du fluorodésoxyglucose (TEP-FDG) sont recommandés. À ce sujet, on a récemment suggéré d'utiliser les biomarqueurs du liquide cérébrospinal (LCS) comme référence standard dans la détection *in vivo* de la pathophysiologie de la maladie d'Alzheimer (cadre de recherche du *National Institute on Aging and Alzheimer's Association*, 2018). Compte tenu que la mise en œuvre d'évaluations cliniques utilisant les biomarqueurs du LCS demeure encore limitée au Canada, la présente étude a cherché à évaluer, dans le cadre d'une pratique clinique, leur précision diagnostique quand il est question de troubles neurodégénératifs atypiques. *Méthodes* : Cet examen rétrospectif de dossiers cliniques a inclus des patients souffrant de troubles cognitifs qui avaient subi une ponction lombaire (PL) et a qui l'on avait appliqué l'ensemble des procédures standards de diagnostic. Des analyses du LCS ont confirmé des cas « biologiques » de maladie d'Alzheimer sur la base d'un niveau réduit de protéines amyloïde β42 par rapport aux protéines tau totales et de niveaux accrus de phosphorylation des protéines tau (*p-tau*). Les diagnostics effectués à partir des biomarqueurs du LCS ont ensuite été comparés à l'ensemble des procédures standards de diagnostic et aux diagnostics effectués au moyen de la TEP-FDG. *Résultats* : Au total, 28 patients souffrant de démence atypique ont été inclus dans notre étude après qu'on a évalué leurs troubles dans une clinique spécialisée de la démence entre novembre 2017 et juillet 2019. Les analyses effectuées à l'aide des biomarqueurs du LCS ont modifié ou mieux précisé les diagnostics cliniques initiaux dans 43,0 % des cas (des diagnostics alternatifs ont emergé et ont été écarté respectivement dans 25% et 18% des cas). Chez les patients à qui l'on a fait passer un examen additionnel de TEP-FDG ($n = 23$), les diagnostics par imagerie et au moyen des biomarqueurs du LCS n'ont pas correspondu chez 35 % des patients, et ce, même si les examens additionnels de TEP-FDG ont semblé accroître l'exactitude diagnostique en comparaison avec le diagnostic clinique initial. *Conclusion* : Les biomarqueurs du LCS ont permis d'améliorer la précision diagnostique dans le cas de patients atteints de démence atypique bien au-delà des procédures standards de diagnostic et des diagnostics effectués au moyen de la TEP-FDG. En plus des procédures standards de diagnostic, de tels résultats justifient donc la mise en œuvre d'évaluations cliniques utilisant les biomarqueurs du LCS pour des patients canadiens atteints de démence atypique.

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As the aging population expands and the number of patients with dementia increases, correct discrimination between Alzheimer's disease (AD) and other neurodegenerative disorders is of vital importance in order to provide appropriate patient care and reduce rising healthcare costs.[1] However, despite the recent development of sophisticated diagnostic approaches based on in vivo biomarkers of AD pathophysiology, the assessment of atypical clinical presentations in cognitively-impaired patients poses a major challenge upon clinicians and complicates the evaluation of novel, potentially disease-modifying drugs.[2] As biomarker analyses mostly remain confined to research settings in Canada, it is pivotal to assess their impact in the clinical practice in order to optimize the differential diagnosis process, especially in atypical dementia patients.

Patients presenting with atypical dementia profiles, including non-amnestic variants of AD, usually show a wide variety of clinical and cognitive presentations, often resulting in an unclear initial clinical diagnosis.[3,4] On the other side, there is autoptic evidence of an imperfect match between clinical impression and neuropathological changes, even in the classic amnestic forms of AD.[5,6] Nonetheless, the recent development of brain imaging techniques and cerebrospinal fluid (CSF) biomarkers enabled the possibility to capture AD physiopathology (accumulated amyloid-β ($A\beta_{42}$) plaques and neurofibrillary tau tangles in the brain) in vivo, thereby dramatically changing the actual definition of AD from a clinical-pathological construct to a neurobiological process.[7] Abnormal physiopathological mechanisms underlying AD have been shown to arise long before the onset of clinical symptoms.[8] In line with this knowledge, AD-related neurobiological changes were incorporated in the most recent diagnostic criteria published by the National Institute on Aging (NIA) and the Alzheimer's Association (AA), which supports the use of CSF biomarker analysis, especially for atypical AD cases.[9]

The contribution of CSF analysis in detecting abnormal levels of amyloid-β, phosphorylated-tau, and total tau in CSF was further emphasized by the 2018 NIA-AA research framework, which describes AD as a unique pathological process contributing to cognitive decline.[7] In this research framework, AD can now be identified in vivo based on the amyloid-β (A), tau (T), and neurodegeneration (N) status of the patient. Moreover, in vivo detection of AD can now take place based on the neurobiological (A and T-positive status) abnormalities alone, even in the absence of clinical symptoms. Supporting evidence has been published validating the central role of CSF biomarkers in accurately detecting AD pathophysiology in both typical[10-13] and atypical[14] AD cases. Therefore, CSF biomarkers are currently considered the gold standard for in vivo detection of AD.

Despite the promise that is held by the use of CSF biomarkers, in Canada, and more specifically in Quebec, dementia workup is still based on the recommendations from the 2012 Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia.[15] These recommendations state that CSF biomarkers do not have clinical utility for typical AD patients given the current lack of a disease-modifying therapy for AD. Nevertheless, clinical CSF implementation in Canada is considered to potentially improve diagnostic certainty for atypical AD presentations[15,16], reduce wait times[17], and contribute to appropriate prescription of pharmacological treatment after early-stage dementia evaluation, such as acetylcholinesterase inhibitors.[15,18] Moreover, implementation of CSF biomarker assessment in Canada could potentially improve clinical trial effectiveness by biologically confirming the disease pathophysiology of enrolled patients and thereby facilitate the development of future AD treatments.

In line with the best clinical practice guidelines for dementia assessment in Canada, an initial dementia diagnosis is derived from the standard clinical workup (clinical and neurological examination), cognitive evaluation, and structural brain imaging (MRI or computerized tomography, CT).[15,19] Furthermore, supplementary FDG-PET brain imaging is recommended in patients whose underlying pathological condition remains unclear after the initial clinical workup.[15] Additional implementation of CSF biomarker assessment is still limited to research settings in Canada, although clinical implementation promises a substantial contribution to the differential diagnosis. This raises the need to evaluate to what extent CSF biomarker assessment of atypical dementia patients impacts the differential diagnosis in the clinical practice in Canada.

Consequentially, with this retrospective clinical chart review we aimed to elaborate on the rate of change of the initial clinical diagnosis after CSF biomarker assessment. Additionally, we aimed to provide knowledge regarding the relative level of diagnostic accuracy of FDG-PET brain imaging compared to the initial clinical diagnosis, when considering CSF status (positive or negative) as the gold standard to rule in or rule out AD. The results of this study are highly relevant for the potential implementation of CSF biomarker assessment for atypical dementias in the clinical practice in Quebec, and more generally, in Canada.

METHODS

Patient Sample

In the present study, we reviewed the clinical charts of patients referred to a behavioral neurologist (PV) running a specialized dementia clinic at Jean-Talon Hospital (Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'Île-de-Montréal) in Montreal, Canada, in collaboration with the McGill University Research Centre for Studies in Aging. Between November 2017 and July 2019, pursuit of the diagnostic workup was carried out on a total of 39 patients presenting atypical cognitive profiles at the initial evaluation for cognitive complaints by PV. Although many more patients were seen by PV for cognitive decline throughout this period, the 39 patients reported in our study were the patients for whom additional diagnostic investigation was judged to be essential and was pursued due to atypical presentations. Additional investigations were not carried out when etiologies were clearly non-neurodegenerative (e.g. vascular, alcohol, traumatic, medical, etc.), and when age or the stage of cognitive decline was too advanced. For the present study, 9 out of the 39 patients could not be included as they refused to undergo clinical lumbar puncture (LP) to assess CSF biomarkers and 1 patient was excluded due to anticoagulant use, as this is a contraindication for LPs.[18] Additionally, 1 patient presented inconsistent CSF biomarker results, meaning that 1 AD biomarker was consistent with AD pathology, whereas the other biomarker was not. Due to the lack of relevant evidence-based literature on interpreting inconsistent CSF profiles, no valid CSF-based diagnosis could be drawn for this patient, who was

therefore excluded from this study. As a result, 28 patients were included in the present study. The study was approved by the local research and ethics committee (CÉR).

Research Design

This is a retrospective clinical chart review. In the present study, final diagnoses, derived from CSF biomarker results, were compared to the initial clinical diagnosis and FDG-PET diagnosis in two separate models. Additionally, diagnostic accuracy of the initial clinical diagnosis versus FDG-PET diagnosis was compared in the third model, while considering the CSF-based final diagnosis as the gold standard.

Procedure

Medical records of patients were consulted to retrieve demographic data (age, sex, and education) and the results of patients' diagnostic workup. The consultation letter of the clinical workup provided the initial clinical diagnosis, and FDG-PET diagnoses were derived from nuclearists' reports for all patients who underwent FDG-PET brain imaging. Additionally, CSF biomarker analysis provided biological evidence for AD consistency, resulting in a final CSF-based diagnosis drawn by the neurologist in the context of the previous diagnostic findings.

All diagnostic assessments were carried out according to standard diagnostic criteria for AD[9], behavioral-variant frontotemporal dementia (bvFTD)[20], primary progressive aphasia (PPA)[21,22], vascular dementia (VaD)[23], major neurocognitive disorder (NCD)[24], and mild cognitive impairment (MCI).[25]

Outcome Measures

Initial Clinical Diagnosis

The first outcome variable was the initial clinical diagnosis, consisting of the categories "AD", "MCI" (core clinical criteria), "multiple possible diagnoses", and "other dementia". The initial clinical diagnosis was derived from clinical and neurological examination, cognitive screening, and structural brain imaging (MRI or CT). The cognitive screening always included the Mini-Mental State Examination (MMSE)[26], which is generally considered as an indicator of global cognitive functioning. More specifically, scores equal to or higher than 26 out of 30 are considered normal, whereas scores of 20–25 indicate mild cognitive impairment, and lower scores indicate impaired cognition ranging from (very) severe to moderate.[27] Additionally, a neuropsychological assessment was carried out in most cases (79% of patients). Overall, the following cognitive domains were tested: verbal and visual episodic memory (California Verbal Learning Test, CVLT-II[28], and geriatric version[29] and Memory Test for Older Adults, MTOA[30]), executive functions (Wechsler Adult Intelligence Scale-IV, WAIS-IV, digit span backward[31], Trail Making Test, TMT, part B[32,33], and phonemic verbal fluency[34]), attention and processing speed (TMT part A[32,33] and WAIS-IV digit span forward[31]), language (Boston Naming Test, BNT[35] and category verbal fluency[34]), visuospatial capacities (Rey–Osterrieth Complex Figure copy, ROCF[36,37]), and semantic functioning (Pyramids and Palm Trees Test, PPTT[38]).

FDG-PET Diagnosis

Nuclearists at the Centre Hospitalier de l'Université de Montréal received a referral from the neurologist (PV) with a clinical hypothesis and subsequently provided a written diagnostic impression based on the patient's metabolic patterns displayed on the FDG-PET brain scan.

CSF Biomarker Diagnosis

LP CSF collection was performed by a neurologist (PV) trained to perform LPs. The procedure was always carried out in the morning to minimize time-dependent variability of CSF biomarker levels.[39] After CSF collection, frozen samples were shipped to Athena Diagnostics (Marlborough, MA) in polypropylene tubes of 2 ml (0.5 ml minimum) for CSF analysis, which was carried out with the use of Enzyme-Linked Immunosorbent Assay (ELISA) kits. Specific combinations of $A\beta_{42}$, t-tau, and p-tau provided an indication of consistency (AD+) versus non-consistency (AD−) with AD. The $A\beta_{42}$-to-t-tau index (ATI) expressed the combination of $A\beta_{42}$ and t-tau results and was calculated as $A\beta_{42}/(240+1.18*t\text{-tau})$. In line with previous literature, Athena Diagnostics considers ATI values below 1.0 and p-tau values over 68 pg/ml typical of AD.[40–42] However, they added a "borderline" range for ATI values between 0.8 and 1.2 and for p-tau values between 54 and 68 pg/ml. Borderline results (AD±) were always interpreted with caution after extensive consideration of clinical history and examination and available brain imaging. Out of the three biomarkers, $A\beta_{42}$ appears to have the highest diagnostic accuracy (sensitivity 97% and specificity 83%) and is reported to be the strongest predictor for progression to AD.[43–45] Therefore, in patients with borderline CSF results, $A\beta_{42}$ was considered as the biomarker that was most indicative for AD versus non-AD diagnosis.

Change in Diagnosis

The correspondence between two diagnoses (e.g. initial clinical diagnosis vs. final CSF-based diagnosis) was defined as "change in diagnosis", with a dichotomous outcome indicating either "change" or "no change". "No change" represented equivalent diagnoses (A vs. A) and "change" was either defined by non-corresponding diagnoses (A vs. B) or by a precision of the clinical diagnosis, indicating that the CSF-based diagnosis ruled out one of multiple possible initial diagnostic hypotheses (A or B vs. B).

Data Analysis

Data were analyzed using the Statistical Package of the Social Sciences (SPSS, version 24.0; SPSS Inc., Chicago, IL) and a significance level of $p < .05$ was applied for all statistical analyses. For the descriptive data, means, medians, and percentages were calculated, and z-scores of available results of neuropsychological tests were averaged per final diagnosis.

Next, the percentage of patients for whom the clinical diagnosis changed after obtaining CSF results was calculated. A Fisher's exact test assessed the rate of diagnostic change per initial clinical diagnosis ("AD", "MCI", "multiple possible diagnoses", and "other dementia").

Furthermore, the percentage of FDG-PET diagnoses corresponding to AD+ versus AD−CSF status was calculated. Another Fisher's exact test assessed whether FDG-PET showed a
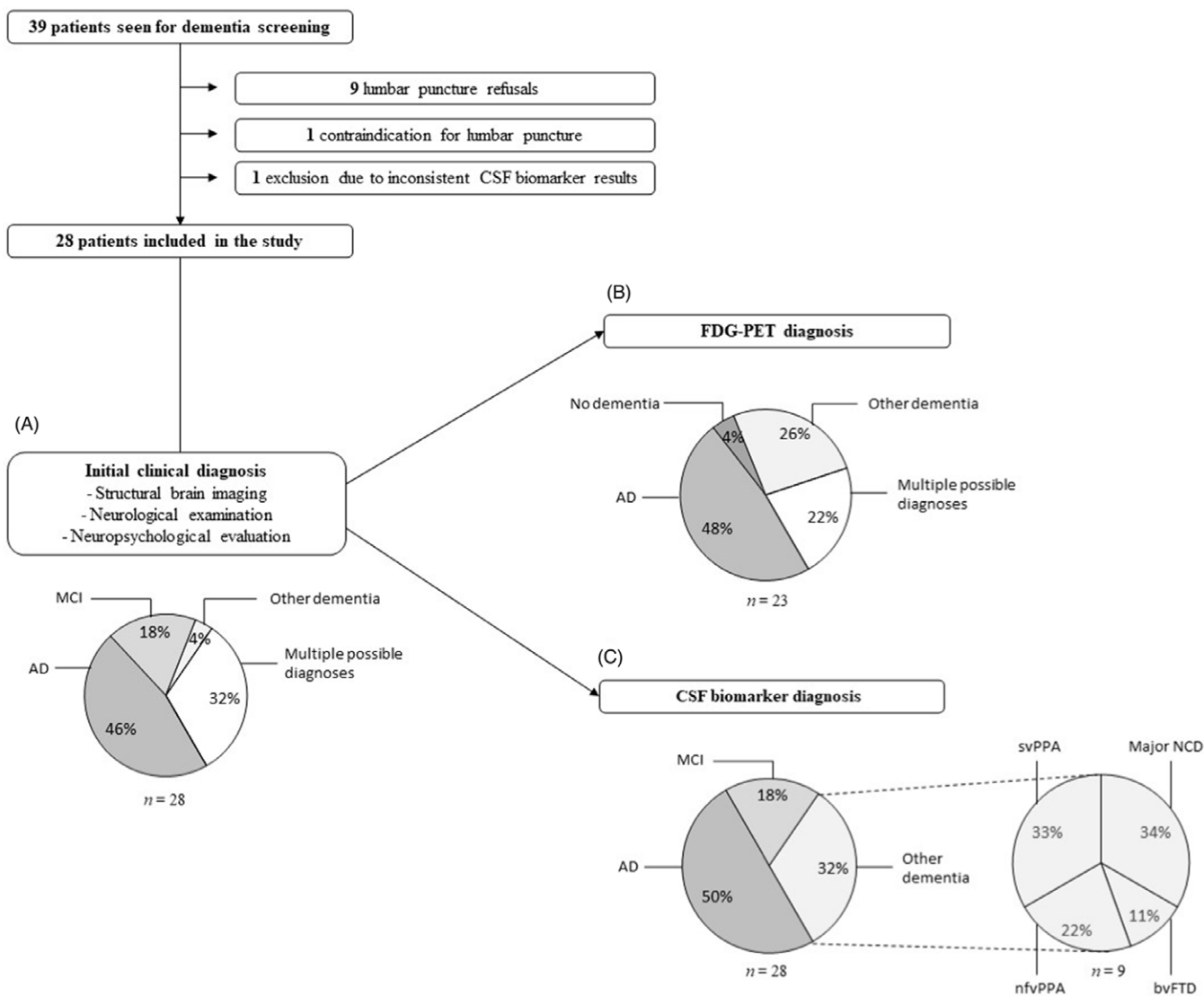
Figure 1: *Flowchart of the patient sample.*
Displayed are the initial clinical diagnoses (A), FDG-PET diagnoses (B), and final CSF-based diagnoses, including additional specification of "other dementia" diagnoses (C).
AD=Alzheimer's disease; byFTD=behavioral-variant frontotemporal dementia; CSF = cerebrospinal fluid; FDG-PET = [^{18}F] fluorodeoxyglucose positron emission tomography; MCI = mild cognitive impairment (before CSF analysis: MCI-core clinical criteria; after CSF analysis: MCI unlikely due to AD); NCD = neurocognitive disorder; nfvPPA/svPPA = non-fluent-variant/semantic-variant primary progressive aphasia.

difference in diagnostic accuracy for identifying AD+ versus AD−CSF results.

Subsequently, the last Fisher's exact test compared the correspondence of the final CSF-based diagnosis with (1) the initial clinical diagnosis versus (2) the FDG-PET diagnosis. This analysis assessed whether either initial clinical diagnosis or FDG-PET findings possibly provide superior diagnostic accuracy in atypical dementia patients when considering CSF biomarkers as the gold standard for identifying AD.

RESULTS

Patient Characteristics

Figure 1 illustrates a flowchart of the study and Table 1 displays the demographic characteristics of the patient sample. Experimental patients included in this study had a mean age of 66.25 years (±1.46), consisted of 18 females (64%) and had a mean education level of 12.70 years (±0.65). Global cognitive functioning, represented by the MMSE, displayed a median of 26.00 (IQR = 24–28), indicating that patients generally functioned on a level consistent with early stages of cognitive impairment. Final CSF-based diagnoses in this sample consisted of 14 AD patients (50%), 5 MCI patients (unlikely due to AD: 3 dysexecutive, 1 vascular, and 1 multi-domain MCI) (18%), 3 patients with unspecified major NCD (with suspected non-Alzheimer's pathophysiology) (11%), 1 patient with bvFTD (3%), 3 semantic-variant PPA patients (11%) and 2 non-fluent-variant PPA patients (7%). In line with the study of Boelaarts, de Jonghe and Scheltens (2020)[46], the diagnostic status of 1 patient who received an initial clinical MCI diagnosis was changed to a final CSF-based AD diagnosis based on an AD+ biomarker profile. Neuropsychological profiles of patients are reported in Table 2.

Table 1: Patient characteristics (_n_ = 28)

Age, mean (SD)	66.25 (1.46)
Sex, n (%) female	18 (64)
Education in years[a], mean (SD)	12.70 (0.65)
MMSE[b] median (25%–75%), years/range	26.00 (24.00– 8.00), 11–30
CSF biomarker results, n (%)	
AD-positive	14 (50)
AD-negative	8 (29)
Borderline	6 (21)

[a]Two missing cases; [b]one missing case.
AD clinical presentations: amnestic-, frontal- and posterior variants, and logopenic-variant primary progressive aphasia.
AD = Alzheimer's disease; CSF = cerebrospinal fluid; MMSE = Mini-Mental State Examination.

CSF Biomarker Assessment

Within the 28 patients included in the study, CSF biomarker results were AD+ in 14 patients (50%), AD− in 8 patients (29%), and provided borderline results in 6 patients (21%). Although Athena Diagnostics Lab does not provide a threshold for $A\beta_{42}$ values above which AD is excluded, for 5 out of the 6 patients with borderline CSF biomarker results, the neurologist considered $A\beta_{42}$ levels to deviate too far above plausible AD-consistency values to be in line with underlying AD physiopathology in the context of the patients' diagnostic workup.[44] Their $A\beta_{42}$ levels ranged between 618.35 pg/ml and 1141.80 pg/ml, whereas AD-consistency has been found to correspond to $A\beta_{42}$ levels generally below 450–550 pg/ml.[47–49] In the remaining patient with borderline CSF results, biomarker values were not helpful for the diagnostic interpretation, as $A\beta_{42}$ and ATI were closer to the cutoff values for AD-consistency in this case (481.85 pg/ml and 1.08, respectively) and p-tau was non-consistent with AD (34.55 pg/ml). The final diagnosis of this patient was derived from follow-up assessment in a research setting, which suggested possible progressive supranuclear palsy. Therefore, all six patients with borderline CSF results were considered as AD-negative in the present study.

No symptoms were reported by the patients following the LP procedure, apart from one report of headache immediately after the LP, which was successfully treated with appropriate medication.

Change of Initial Clinical Diagnosis

In 12 cases (43% of patients), CSF biomarker results caused a change in the initial clinical diagnosis. Table 3 provides a detailed description of these cases. Among them, 7 cases (25% of total patients) changed into another diagnosis, whereas diagnostic precisions occurred in 5 cases (18% of total patients). Overall, diagnostic changes occurred in 23% of patients initially suspected of AD, 20% of patients initially suspected of MCI, 89% of patients initially suspected of multiple possible diagnoses, and 0 patients initially suspected of another type of dementia, reflecting a statistically significant difference in proportions of diagnostic change across various initial diagnoses (p = .005, Fisher's exact test), as shown in Figure 2. Regarding the direction of

diagnostic changes, AD was ruled out for three initial AD diagnoses, AD was ruled in for one initial MCI diagnosis, and AD was ruled in 3 times and ruled out 5 times for multiple possible initial diagnoses. Stratification for age and sex resulted in comparable proportions of diagnostic accuracy of the initial clinical diagnosis for younger (<65) and older (≥65) patients (13 [62%] vs. 15 [53%], p = .718, Fisher's exact test), and for males and females (10 [50%] vs. 18 [61%], p = .698, Fisher's exact test).

Change of FDG-PET Diagnosis

In total, 23 patients included in the present study obtained an FDG-PET brain scan alongside standard clinical workup. In 8 cases (35% of FDG-PET patients), FDG-PET diagnoses were non-correspondent with CSF biomarker results (Table 3). FDG-PET diagnoses incorrectly suggested AD pathology in 5 patients (50% of AD− CSF results), whereas FDG-PET failed to detect AD in 3 patients (23% of AD+ CSF results). The diagnostic accuracy by which FDG-PET correctly identified or excluded AD did not differ between CSF-confirmed AD+ and AD− patients (p = .184, Fisher's exact test). Stratification for age revealed a trend towards significance for differences in diagnostic accuracy between younger (<65) and older (≥65) patients (12 [83%] vs. 11 [45%], p = .089, Fisher's exact test), suggesting that older patients received relatively more inaccurate FDG-PET diagnoses. For sex, comparable FDG-PET accuracy was found for males and females (7 [43%] vs. 16 [75%], p = .182, Fisher's exact test).

Initial Clinical Diagnosis Versus FDG-PET Diagnosis

For the 23 patients who received an FDG-PET brain scan, diagnostic accuracy of the initial clinical diagnosis versus FDG-PET diagnosis was assessed. Again, diagnostic accuracy was based on accordance with the final CSF-based diagnosis in terms of correct AD identification or exclusion. Of the 23 patients, 12 initial diagnoses (52%) were incorrect, whereas 8 FDG-PET diagnoses (35%) were incorrect, reflecting a statistically significant difference between the proportions of diagnostic accuracy (p = .027, Fisher's exact test), as shown in Figure 3. Variation in diagnostic accuracy of the initial clinical diagnosis versus FDG-PET diagnosis could not be attributed to age (<65 vs. ≥65) nor sex (males vs. females) differences (12 [58%] vs. 11 [27%]. p = .266, and 7 [29%] vs. 16 [50%], p = .364, respectively, Fisher's exact tests).

DISCUSSION

The results of the present study emphasize the diagnostic contribution of CSF biomarker analysis in atypical dementia patients in addition to the standard clinical workup and FDG-PET brain imaging, especially for cases with initial clinical incertitude. Additionally, the present study confirms that FDG-PET brain imaging yields more accurate diagnoses than clinical assessment alone in atypical dementia cases when considering CSF findings as the gold standard.

CSF workup led to an alternative diagnosis in 25% of patients. This result is in line with previous reports which found changes between 7% and 27% post-CSF results.[50-52] Moreover, additional

Table 2: Overview of cognitive functioning across the final (post-CSF) diagnoses

Cognitive domain	Z-scores, mean (SD)						
	AD (n = 7)	lvPPA-AD (n = 7)	MCI (n = 5)	Major NCD[a] (n = 3)	bvFTD[b] (n = 1)	nfvPPA (n = 2)	svPPA (n = 3)
Episodic memory							
CVLT-II/geriatric (verbal)							
Encoding: IR trial 5	−1.37 (0.98)[c]	−2.50 (1.13)[d]	−0.27 (0.92)[e]	−1.65 (1.20)[f]	−3.30	−2.50[f]	−2.37 (1.37)
Retrieval: free long DR	−2.80 (0.35)[c]	−2.40 (2.55)[d]	−0.83 (0.87)[e]	−2.70 (2.12)[f]	−3.00	−1.80[f]	−2.60 (1.25)
Consolidation: cued long DR	−2.13 (0.47)[c]	−2.95 (1.91)[d]	−0.93 (1.35)[e]	−2.95 (0.92)[f]	−3.60	−2.30[f]	−2.97 (1.35)
MTOA (visual)	−2.40 (0.71)[d]	−2.00 (1.06)[d]	−1.47 (1.39)[e]	−2.68 (2.10)[f]	−4.10	−0.70[f]	−2.40 (0.46)
Executive functions							
Phonemic verbal fluency	−0.66 (1.27)[c]	−1.51 (0.78)[g]	−1.39 (1.35)	−2.37 (0.61)	−2.10	−2.90[f]	−2.13 (0.68)
Digit span backwards WAIS-IV	−1.36 (0.57)[c]	−0.68 (0.91)[g]	−0.77 (1.14)	−1.76 (0.81)	−1.20	−1.00[f]	−1.10 (0.85)
Trail Making Test part B	−1.15 (0.78)[d]	−3.73 (4.46)[g]	−2.98 (3.34)	−4.02 (1.05)	−3.00	−3.00[f]	−3.10 (0.26)
Attention/processing speed							
Digit span forward WAIS-IV	−1.78 (0.69)[c]	−0.68 (0.62)[g]	−0.83 (0.44)[f]	−1.03 (0.58)	−1.10	−2.30[f]	−5.10 (6.89)
Trail Making Test part A	0.19 (0.35)[c]	−0.65 (1.41)[g]	−1.02 (1.49)	−2.15 (0.07)[f]	−2.00	−3.00[f]	−2.67 (0.73)
Language							
Category verbal fluency	−1.85 (2.09)[c]	−1.46 (1.06)[g]	0.77 (1.27)[f]	−1.87 (0.15)[f]	−1.40	−2.70[f]	−2.13 (1.59)
Boston Naming Test	−2.32 (2.43)[e]	−6.27 (3.35)[d]	0.76 (1.67)	2.60 (0.75)	−1.20	−2.70[f]	−5.25 (4.03)
Visuospatial							
ROCF copy	−0.02 (0.14)[b]	−1.13 (2.83)[a]	0.81 (0.68)[c]	−3.00 (3.96)[f]	−0.90	−1.50[f]	0.67 (0.23)
Semantic							
Pyramids and Palm Trees Test	−0.84[h]	−0.40 (0.77)[c]	−0.15 (0.58)[c]	0.40 (0.14)[f]	−0.80	−0.40[f]	−2.1 (1.13)

a = major NCD accounts for two non-specific dementia cases (with suspected non-Alzheimer's pathophysiology) and one case with an hypoxemic insult, b = verbal cognitive functioning possibly influenced by language barrier; c = 4 missing cases; d = 5 missing cases; e = 2 missing cases; f = 1 missing case; g = 3 missing cases; h = 6 missing cases. CSF biomarker results were AD-positive for all AD and lvPPA-AD patients, and AD-negative for all other patients. No standard deviation is described for bvFTD and nfvPPA as test results are only available for n = 1.

AD = Alzheimer's disease; CVLT = California Verbal Learning Test; DR = delayed recall; IR = immediate recall; lvPPA/nfvPPA/svPPA = logopenic-variant-/non-fluent-variant-/semantic-variant primary progressive aphasia; MCI = mild cognitive impairment unlikely due to AD (3x dysexecutive, 1x vascular, 1x multi-domain); MTOA = Memory Test for Older Adults; NCD = neurocognitive disorder; ROCF = Rey–Osterrieth Complex Figure; WAIS = Wechsler Adult Intelligence Scale.

diagnostic accuracy (18%) was gained when the initial clinical diagnosis raised doubts between AD and non-AD hypotheses. Supporting evidence recently confirmed the diagnostic contribution of CSF analysis in the clinical practice for cases that raised initial diagnostic doubts.[46] The relatively high rate of diagnostic changes or precisions in the present study (overall 43%) could be explained by the fact that similar studies in the literature did not focus specifically on atypical dementia and did not always attribute final diagnoses exclusively to CSF results.[50–52] Furthermore, our relatively smaller sample size, the impact of CSF analysis variability between research facilities, and differences in diagnostic approaches across countries need to be considered as they complicate comparative interpretations.[53,54] Regardless, CSF biomarkers seem to provide a substantial additional value to the standard clinical workup in all studies, including the present one. It is also reasonable to point out that CSF biomarkers could be even more informative in patients like ours at the early stage of disease, when it might be more difficult to determine the diagnosis.

The results of the present study also suggest that FDG-PET imaging provides a less important contribution than expected compared to CSF-based diagnostic accuracy in atypical cases, particularly in older patients. This effect of age on FDG-PET accuracy could possibly be explained by the increased likelihood of brain comorbidities at an older age, which complicates the interpretation of the cerebral pattern of metabolism.[55] An interesting observation in our study is the relative inconsistency of the hypometabolism of the posterior cingulate gyrus with AD. This brain region is part of the default mode network and its early disruption is usually considered to be a hallmark of AD physiopathology.[56] This specific metabolic finding, however, turned out to be inaccurate in four out of the five patients based on the CSF results. This finding highlights the need for validation studies of FDG-PET imaging in biologically confirmed atypical cases of AD. It is important to consider that neurodegeneration markers such as abnormal FDG-PET signal are characteristic of multiple neurodegenerative processes and cannot identify AD as a unique pathological disease process. These issues could be exacerbated

Table 3: Overview of patients with changed initial and/or FDG-PET diagnoses after incorporation of CSF biomarker results

Incorrect diagnosis	Initial clinical diagnosis	FDG-PET diagnosis	Post-CSF diagnosis	CSF biomarkers (pg/ml)				
				$A\beta_{42}$	t-tau	p-tau	ATI	AD status[a]
Initial	lvPPA-variant AD	svPPA (right side variant)	svPPA (right side variant)	673.10	372.90	65.85	0.99	AD±
	Dysexecutive MCI	lvPPA-variant AD	Early-onset AD	286.30	538.70	74.25	0.33	AD+
	AD/bvFTD	lvPPA-variant AD	AD	166.70	1391.70	153.10	0.09	AD+
	AD/svPPA	svPPA/possible FTD	svPPA	1141.80	480.60	61.30	1.41	AD±
	AD/svPPA	Possible vascular component/possible early detection bvFTD	MCI multi-domain (unlikely due to AD)	600.90	179.60	29.60	1.33	AD−
Initial and FDG-PET	Amnestic AD	Frontal AD	bvFTD	836.10	257.70	46.35	1.54	AD−
	Non-specific frontal ↓	svPPA	Frontal AD	371.25	689.00	97.60	0.35	AD+
	AD/subcortico-frontal ↓	Possible bvFTD	nfvPPA	707.15	285.50	52.80	1.23	AD−
	AD/svPPA	Possible AD	Possible svPPA	728.25	306.25	56.80	1.21	AD±
	AD/mixed	Possible AD	Non-specific major NCD	618.35	281.95	57.3	1.08	AD±
	AD/VaD	FTLD/Parkinson	Frontal AD	439.90	438.40	68.40	0.58	AD+
	AD/VaD	AD/bilateral cerebellar ↓ (Hypoxemic insult [b])	Major NCD (hypoxemic insult)	711.00	216.00	45.90	1.44	AD−
FDG-PET	lvPPA-variant AD	FTD/svPPA/lvPPA	lvPPA-variant AD	331.00	1526.30	185.20	0.16	AD+

[a]CSF biomarker analysis resulted in positive (AD+), negative (AD−), or borderline (AD±) consistency with AD. [b]Follow-up FDG-PET imaging suggested a hypoxemic insult, however, the first FDG-PET scan used for the analysis in this paper was considered non-consistent with CSF biomarkers. "Change of diagnosis" implies that the diagnosis was replaced by an alternative diagnosis or that one or multiple diagnoses were ruled out and therefore, the diagnosis became more precise.

$A\beta_{42}$ = amyloid-β_{1-42}; AD = Alzheimer's disease; ATI = $A\beta_{42}$-to-t-tau index; bvFTD = behavioral-variant frontotemporal dementia; CSF = cerebrospinal fluid; FDG-PET = [18F] fluorodeoxyglucose positron emission tomography; FTLD = frontotemporal lobar degeneration; lvPPA/nfvPPA/svPPA = logopenic-variant-/non-fluent-variant-/semantic-variant primary progressive aphasia; MCI = mild cognitive impairment; NCD = neurocognitive disorder; p-tau = tau phosphorylated at threonine; t-tau = total tau; VaD = vascular dementia; ↓ = impairment.
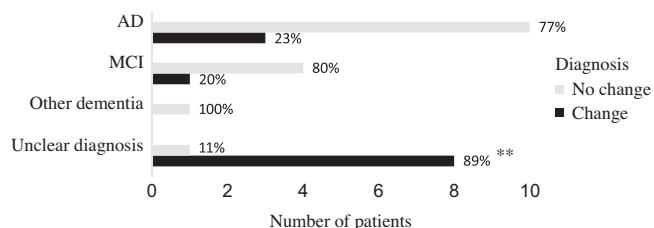

Figure 2: *% Change of the initial clinical diagnosis after CSF biomarker analysis.*
Displayed are the initial clinical diagnoses of the 28 patients included in this study. After incorporation of CSF biomarker results, diagnostic changes occurred in 43% of patients. These changes comprise an alternative diagnosis (A à B) or a precision of the diagnosis, in which case one of the multiple diagnoses was ruled out (A vs. B à B). The rate of diagnostic change differed significantly between diagnostic groups (**p = .005, Fisher's exact test), with patients with multiple possible initial diagnoses yielding relatively most diagnostic changes.
AD = Alzheimer's disease; MCI = mild cognitive impairment (core clinical criteria).

Figure 3: *Diagnostic accuracy of FDG-PET versus initial clinical diagnosis.*
Correspondence with CSF-based diagnosis was compared between initial clinical and FDG-PET diagnoses for 23 patients who underwent FDG-PET brain imaging. The proportion of diagnostic change differed significantly between the two diagnostic approaches (*p = .027, Fisher's exact test), with initial clinical diagnoses resulting in relatively more diagnostic changes after CSF implementation.
FDG-PET = [18F] fluorodeoxyglucose positron emission tomography.

in the diagnostic workup of patients with atypical clinical presentations who may have atypical patterns of FDG-PET abnormalities. However, even though our results suggest that FDG-PET imaging appears less sensitive and specific for AD than expected in atypical dementia c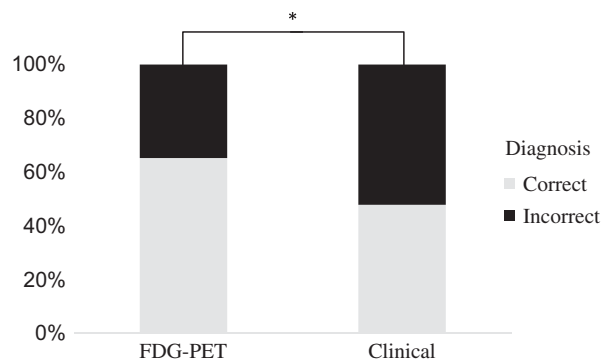ases, it remains a valuable tool in addition to regular clinical assessment, possibly raising diagnostic accuracy to a higher level compared to the clinical workup alone.

The main strength of the present study is its emphasis on clinical implementation of a still relatively uncommon diagnostic approach to dementia assessment in Canada based on CSF biomarkers. We present the first study to demonstrate the clinical utility of CSF analysis in atypical dementia patients in Quebec, thereby opening the debate on optimization of standardized clinical guidelines for its application in Canada. Future research is still warranted to standardize CSF biomarker analysis approaches and facilitate its implementation in the clinical practice.

Although CSF biomarker assessment is not intended as a replacement of the standard clinical workup or imaging modalities, it is important to consider that expenses for CSF analysis are substantially lower than for PET imaging.[17,18,57] Moreover, only 51 PET scanners are currently available in Canada and due to large geographical distances, these are not easily accessible for all demented patients.[17,58] Contrastingly, CSF collection can be performed in many facilities across the country.[17] Another important advantage of CSF analysis is its ability to concurrently measure both amyloid and tau pathologies, in contrast to PET imaging which requires a separate scan for each pathology.[59] A limitation of the present study is that the impact of comorbid disorders and possible mixed neurodegenerative pathologies have not been taken into account, as CSF biomarkers merely provided evidence for AD physiopathology. Previous research suggested that comorbidities may account for inaccurate clinical diagnoses and biomarker classifications and may influence the accuracy of CSF biomarker cutoff levels.[60] Thus, the impact of comorbidities may be reflected in patients showing inconsistent or borderline CSF biomarker results.

Additionally, it needs to be pointed out that the present study took place in the routine clinical practice of a single neurologist (PV) running a specialized dementia clinic and not in a standardized clinical trial setting. Consequentially, only a relatively small sample size could be included with little representation of each of the various dementia syndromes. Also, data was not consistently available for all subjects. Nevertheless, this study reflects the clinical heterogeneity of atypical dementia presentations and provides valuable knowledge on the implementation of CSF analysis and its integration with other diagnostic approaches in the clinical practice in Canada. Future multicenter trials are needed to determine whether CSF measures of AD pathology are associated with changes in the clinical management of patients with cognitive impairment, as similarly reported in a recent study of amyloid PET.[61]

Concluding, this study provides a stepping-stone to bring validated biomarkers to the clinical practice in Canada and emphasizes the promise that is held by the biological definition of AD to aid clinicians in improving diagnostic accuracy in atypical dementia patients.

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