Publication Highlights

Clinical application of CSF biomarkers for Alzheimer's disease: From rationale to ratios

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Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring (DADM)

27 April 2022
https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/dad2.12314

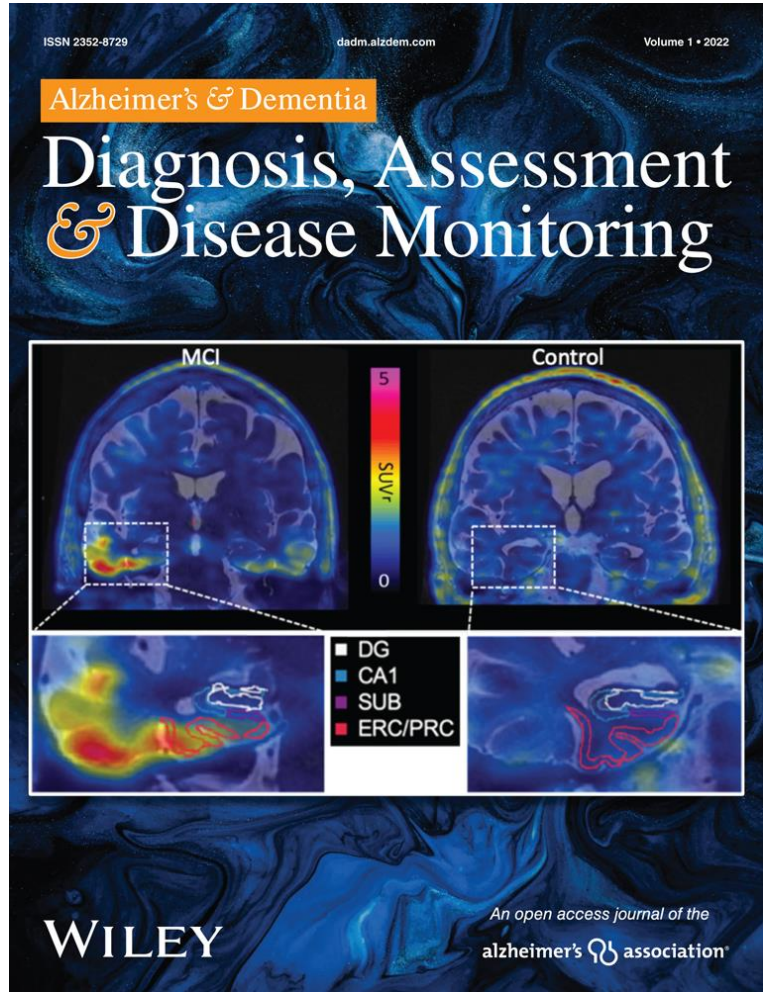
Publication Highlights

Overview and study objective

- Despite recommendations to incorporate fluid biomarkers into the diagnostic pathway of patients suspected of suffering from Alzheimer's disease (AD), they are underutilized outside of specialist centers.
- Using illustrative case narratives, this review and perspective considers how cerebrospinal fluid (CSF) biomarker tests may be used in different presentations of cognitive impairment to facilitate timely and differential diagnosis, improve diagnostic accuracy, provide prognostic information, and guide personalized management in diverse scenarios.

Study design

- Literature search of PubMed in February 2021 with search terms related to diagnosis of Alzheimer's disease and mild cognitive impairment with biomarkers
- Illustrative case studies were provided by the authors after anonymization



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Literature Review

- The core CSF biomarkers for AD are 42-amino acid β-amyloid peptide (Aβ42), phosphorylated tau (pTau) and total tau (tTau, i.e. both phosphorylated and non-phosphorylated forms of tau protein)
- Recent criteria from the IWG and NIA-AA research framework include recommendations for using clinical findings and abnormal biomarkers (Aβ and tau)
- Biomarker testing is recommended for those with clinical symptoms
- CSF biomarkers are in good agreement with amyloid PET
- Biomarker ratios perform better than individuals markers
- Aβ42/Aβ40, pTau/Aβ42 and tTau/Aβ42 ratios perform similarly
- Fluid biomarker abnormalities may precede detection limits of imaging tests
- CSF biomarkers are promising for clinical trial enrichment and to dentify patients for novel therapies targeting the specific disease pathology (i.e. Aβ)
- Clear guidelines and uniform reporting are still required for implementation of biomarkers into clinical practice
- Blood based biomarkers may provide a non-invasive solution to be used alongside cognitive tests for improving referral to specialists or advise additional testing

				Individual CSF biomarkers				CSF biomarker ratios		
Reference	Study objective	Platform	Measure	p-tau	t-tau	Aβ1-42	Aβ1-40	p-tau/Aβ42	t-tau/Aβ42	Aβ1-42/Aβ1-40
Schindler et al. 2018[23]	To measure relationship between CSF biomarkers and amyloid PET	Elecsys	PPA	82%	68%	90%	60%	92%	92%	96%
			NPA	76%	83%	73%	58%	89%	85%	82%
			OPA	78%	79%	77%	59%	89%	87%	86%
			AUC	0.84	0.81	0.85	0.60	0.96	0.95	0.93
Doecke et al. 2020[14]	To measure concordance between CSF biomarkers and pathological AD via PET imaging	Elecsys	PPA	81%	86%	81%		90%	83%	90%
			NPA	77%	66%	81%		91%	97%	90%
			OPA	79%	75%	81%		91%	91%	90%
			AUC	0.84	0.81	0.86		0.94	0.94	0.94
Willemse et al. 2020 (abstract)[24]	To measure CSF biomarkers compared to amyloid PET imaging	Elecsys	PPA			91%		96%		96%
			NPA			75%		89%		80%
			OPA							
			AUC							
	To measure CSF biomarkers compared to amyloid PET imaging	Lumipulse	PPA			91%		97%		99%
			NPA			73%		91%		83%
			OPA							
			AUC							
Keshaven et al. 2020[21]	To measure concordance between CSF biomarkers and PET imaging	Lumipulse	PPA	100%	54%	100%		100%	92%	100%
			NPA	66%	82%	74%		94%	90%	94%
			OPA							
			AUC	0.879	0.665	0.891		0.966	0.955	0.966
Alcolea et al. 2019[20]	To determine cut-offs between PET and CSF biomarkers	Lumipulse	PPA	80%	75%	95%		93%	81%	88%
			NPA	83%	83%	51%		80%	83%	77%
			OPA	81%	78%	79%		88%	82%	84%
			AUC	0.84	0.80	0.76	0.59	0.88	0.87	0.86
Kaplow et al. 2020[15]	To determine concordance of CSF biomarker ratios with amyloid PET (test cohort A/B)	Lumipulse	PPA		74.1%	98.8%			97.5%	
			NPA		89.8%	75.5%			89.8%	
			OPA		80.0%	90.0%			94.6%	
			AUC		0.87	0.92			0.95	
Moon et al. 2021[22]	To evaluate concordance of CSF biomarkers and PET imaging	Lumipulse	PPA	79.5%	59.0%	79.5%		84.6%	84.6%	84.6%
			NPA	78.6%	89.3%	88.1%		92.9%	88.1%	91.7%
			OPA							
			AUC	0.839	0.791	0.857		0.840	0.842	0.856

Table from Bouwman FH, et al. Alzheimer's Dement. 2022; 14:e12314

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CASE 1:

THE MAN WITH A LARGE HEAD

Background

- 61-year-old male
- Works as an abattoir
- Illiterate
- Spouse reported forgetfulness and agitated behavior, talks to strangers, and dysfunctional at work

Initial assessment

- Head circumference >97th percentile
- Cognitive test unreliable due to limited education
- Enlarged ventricles, no hippocampal atrophy
- Additional tests for hydrocephalus, depression, and AD ordered

Biomarker Results & Discussion

Biomarkers and Other Tests

- PET scan showed no β-amyloid uptake and AD was excluded
- PET was used instead of CSF biomarkers due to the enlarged ventricles

How tests helped guide patient management

- After AD exclusion, psychiatric evaluation revealed psychotrauma related to childhood abuse lending to a post-traumatic stress disorder (PTSD) diagnosis
- Patient treated with antidepressants and psychotherapy
- Biomarkers tests can rule out AD, providing clear direction for subsequent treatment
- Many non-AD related causes of dementia may be reversible with proper management

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CASE 2:

PROFESSIONAL BURNOUT

Background

- 61-year-old male
- Police Officer for 12 years
- No family history of dementia, though father has some undiagnosed memory problems
- Suffering memory impairment after professional burnout linked to overwork and shortage of staff

Initial assessment

- Cognitive testing did not show significant decline
- MRI report was within the normal range, except very discrete white matter abnormalities
- Neuropsychological evaluation found him distractible, verbalizing, showing anxiety and lacking confidence
- Diagnosed with cognitive impairment due to anxiety. Spouse requested a second opinion leading to biomarkers testing

Biomarker Results & Discussion

Biomarkers and other tests

- Further MRI examination showed a posterior atrophy pattern with milder medial temporal involvement
- CSF biomarkers showed abnormal Aβ42 and tTau
- Based on clinical symptoms and abnormalities in Aβ42, pTau/Aβ42 and tTau/Aβ42, diagnosis was changed to mild cognitive impairment (MCI) due to AD

How tests helped guide patient management

- The patient's prognosis changed after new diagnosis
- Biomarkers informed decision to consider drug therapy for symptom management
- Possibility of participation in a clinical trail was discussed

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CASE 3:

WORRYING SIGNS OF DEPRESSION

Background

- 63-year-old female
- Retired secondary school teacher
- 3 years after retirement started missing appointments and had trouble following or discussing books.
- Suffering memory impairment and depression 6 months before seeking medical attention

Initial assessment

- Cognitive testing showed memory deficits
- MRI showed only minor medial temporal atrophy consistent with age.
- No vascular damage was seen on MRI
- CSF testing ordered due to inconclusive results of initial tests

Biomarker Results & Discussion

Biomarkers and other tests

- CSF biomarkers showed abnormal Aβ42, tTau, and pTau/Aβ42 levels consistent with an AD diagnosis
- 1 year later, her situation deteriorated
- Further cognitive assessment and MRI based detection of progressive hippocampal atrophy led to a diagnosis of dementia with AD

How tests helped guide patient management

- CSF biomarkers identified AD pathology a year before conclusive cognitive and MRI based examination
- Cognitive impairment and mood changes are common in early symptoms of AD and CSF biomarkers can identify AD pathology in prodromal AD.

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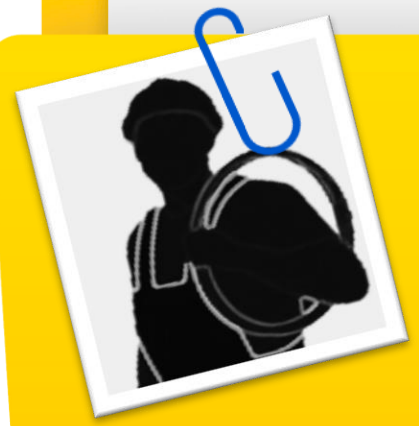
CASE 4:

3 NEW PAIRS OF GLASSES IN 2 YEARS



Background

- 58-year-old male
- Recently dismissed electrical engineer
- Progressing impairments in spatial orientation
- Needed 3 new glasses in 2 years
- Problems planning, reading and driving
- He and his spouse had trouble describing cognitive complaints

Initial assessment

- Cognitive testing showed memory and language were intact but had slight dyspraxia and severe spatial and visio-perceptive problems
- A clinical diagnosis of posterior cortical atrophy (PCA) was made
- PCA is commonly caused by underlying AD but other dementias can also cause it

Biomarker Results & Discussion

Biomarkers and other tests

- Amyloid PET imaging showed amyloid accumulation and he was diagnosed with PCA due to AD
- For research purposes, CSF biomarkers were also used and showed abnormalities consistent with AD
- There was good agreement between the CSF and imaging biomarkers, especially when evaluating CSF biomarkers ratios

How tests helped guide patient management

- Biomarker tests are useful in atypical presentations of AD
- The physician could counsel the patient and his caregiver on what to expect in terms of increasing cognitive dysfunction over the coming years

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CASE 5:

AN INCREASED RISK FOR DEMENTIA

Background

- 72-year-old male
- Retired office manager
- Presented with subjective memory complaint
- Father diagnosed with AD at age 75 years
- Enrolled in clinical registry 10 years prior, with no memory complaint
- ApoE ε4 positive (3/4)

Initial assessment

- Neuropsychological testing at age 62, 64, and 66 was normal. At 72, testing revealed cognitive decline compared to previous tests
- Impaired in delayed recall but performed high average or superior on other evaluations
- Presentation indicated a diagnosis of MCI

Biomarker Results & Discussion

Biomarkers and other tests

- CSF biomarkers and PET imaging were performed as part of the registry study
- CSF biomarkers from the Neurotoolkit showed abnormal Aβ42/Aβ40 and pTau/Aβ42 ratio levels. However, pTau, neurofilament light and neurogranin were all negative
- Amyloid PET was positive and increased from age 62
- Tau PET was positive at 70 years

How tests helped guide patient management

- MCI was first apparent at age 72 years, while CSF biomarkers were positive for amyloid 10 years prior
- Case illustrates potential of CSF biomarkers to assess risk of AD based on early detection of pathological change before clinical symptoms appear

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Main conclusions

- Cerebrospinal fluid (CSF) Alzheimer's disease (AD) biomarkers testing may be underused outside specialist centers
- CSF biomarkers improve diagnostic accuracy, guiding personalized management of AD
- CSF ratios Aβ42/Aβ40 and pTau/Aβ42 performed better than single markers in this case series and published literature
- CSF ratios may produce fewer false-negative and false-positive results than individual markers
- CSF biomarkers should be included in diagnostic work-up of AD and mild cognitive impairment due to AD

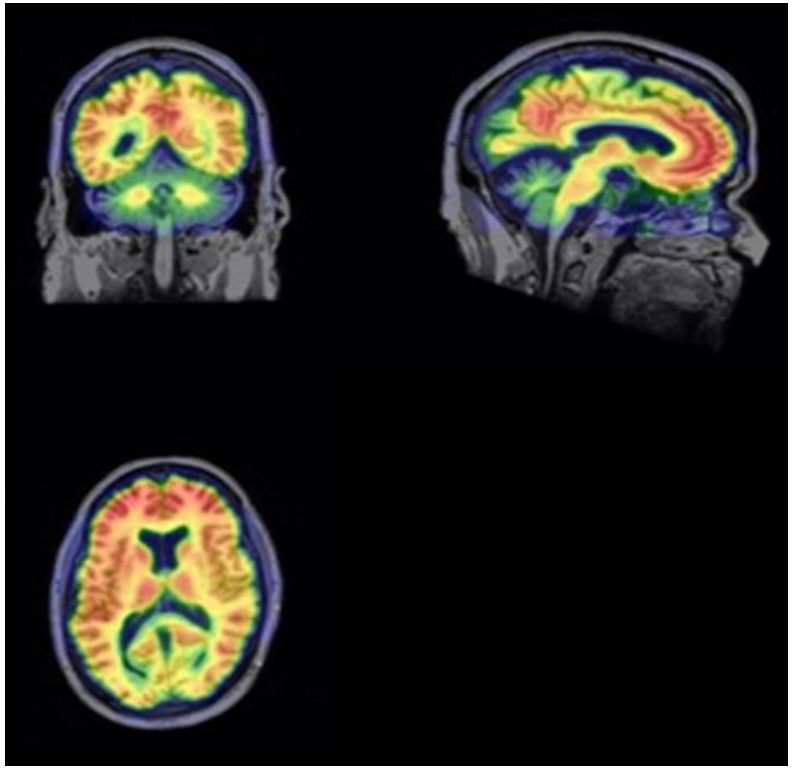

Figure from Bouwman FH, et al. Alzheimer's Dement. 2022; 14:e12314

Key summary

- The authors recommend that CSF biomarkers should be part of the standard of care for working up of MCI and dementia patients
- These case narratives show how CSF biomarkers may be useful in different stages of AD diagnosis and with different clinical presentations

Doing now what patients need next