








CSF biomarkers for dementia

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ABSTRACT

Although cerebrospinal fluid (CSF) biomarker testing is incorporated into some current guidelines for the diagnosis of dementia (such as England's National Institute for Health and Care Excellence (NICE)), it is not widely accessible for most patients for whom biomarkers could potentially change management. Here we share our experience of running a clinical cognitive CSF service and discuss recent developments in laboratory testing including the use of the CSF amyloid- β 42/40 ratio and automated assay platforms. We highlight the importance of collaborative working between clinicians and laboratory staff, of preanalytical sample handling, and discuss the various factors influencing interpretation of the results in appropriate clinical contexts. We advocate for broadening access to CSF biomarkers by sharing clinical expertise, protocols and interpretation with colleagues working in psychiatry and elderly care, especially when access to CSF may be part of a pathway to disease-modifying treatments for Alzheimer's disease and other forms of dementia.

INTRODUCTION

While cerebrospinal fluid (CSF) has been used in the investigation of dementia for many years, the context of its use has changed recently from excluding 'treatable conditions' (eg, neuroinflammation) to detecting the core pathologies underlying specific forms of dementia using biomarkers. There is a particular emphasis on Alzheimer's disease (AD), where CSF can be used to demonstrate its three main pathologies— β -amyloid deposition, hyperphosphorylated tau (p-tau) accumulation and neurodegeneration—all of which can also be evaluated using imaging techniques like amyloid and tau positron emission tomography (PET) or MRI for assessing brain volumes/atrophy (figure 1).

AD dementia is classically associated with a CSF profile of a reduced amyloid- β 1–42/1–40 ratio (A β 42/40), increased p-tau and increased total tau (t-tau) compared with cognitively normal individuals.¹ However, in clinical practice, it is more important to be able to distinguish those with AD dementia from other types of slowly progressive dementia, particularly as the phenotypical manifestations of the dementias often overlap. A recently updated meta-analysis² shows that low A β 42, increased p-tau181 and increased t-tau can differentiate clinically defined AD dementia from many conditions that may present to the memory clinic, including frontotemporal, vascular and Lewy body dementias (table 1). Combinations of these classical biomarkers can also discriminate neuropathologically confirmed AD from frontotemporal lobar degeneration, with areas under the receiver operating characteristic curve of 0.94–0.98.^{3,4}

Some limitations of lumbar punctures (LPs) are that they are more invasive than amyloid PET; they require caution in people with coagulopathies; and they carry a risk of low CSF pressure headache (about 1 in 10 using atraumatic needles).⁵ However, CSF testing allows for a single sample to be assayed for several proteins of interest and is cheaper than amyloid PET. The 2018 NICE guideline NG97 for dementia⁶ recommends testing if the diagnosis of dementia is uncertain, and knowing the dementia subtype would both be useful and change management. The Alzheimer's Association has published some appropriate use criteria for CSF AD biomarker testing⁷ (table 2); conditions considered appropriate for CSF testing include both typical and atypical presentations of AD dementia, mild cognitive impairment and some presentations of subjective cognitive decline at high risk of AD.



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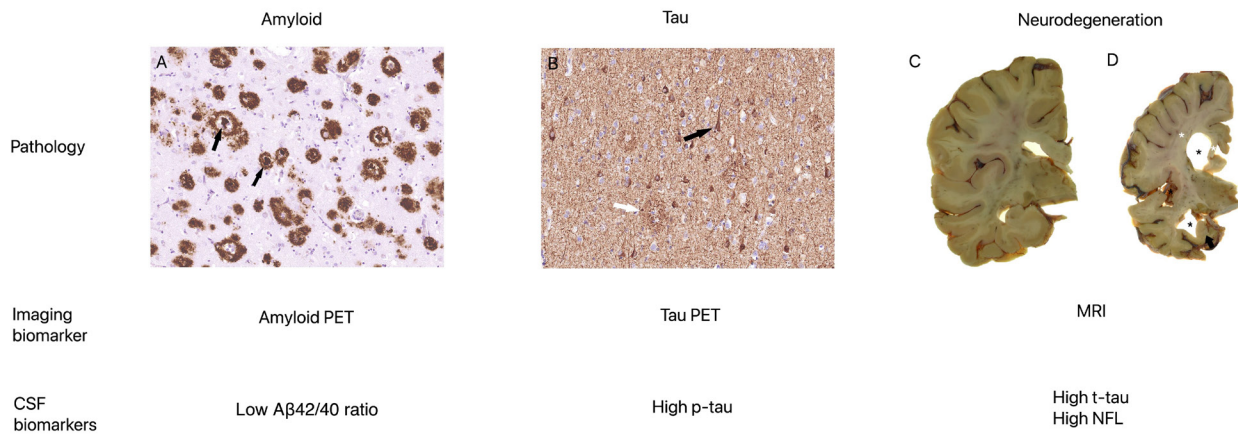


Figure 1 Biomarker correlates of pathologies of amyloid, tau and neurodegeneration in AD. (A) Immunostaining for amyloid-β (clone 6F3D, DAKI, M0872) shows frequent parenchymal deposits in the neocortex, including many plaques with central amyloid cores (black arrows). (B) Immunostaining for hyperphosphorylated tau (clone AT8, Thermo MN1020) shows a dense meshwork of neuropil threads in the neocortex with neuritic plaques (white arrow) and frequent neurofibrillary tangles (black arrow). (C) Coronal section at the level of the lateral geniculate nucleus from a patient with no known neurological disease shows mild dilation of the frontal and temporal horns of the lateral ventricle but no other macroscopically visible pathology. (D) Coronal section from a patient with AD shows prominent dilatation of the frontal and temporal horns of the lateral ventricle and enlarged insular space (black asterisks). Cortical ribbon shows widespread thinning and blurred outlines between the cortical grey and white matter. The white matter volume is significantly reduced and the corpus callosum is thin (white asterisks). The hippocampus is severely atrophic (black arrow). AD, Alzheimer’s disease; CSF, cerebrospinal fluid; NFL, neurofilament light chain; PET, positron emission tomography.

Another context for CSF testing is to evaluate rapidly progressive dementia, where prion disease is a consideration. Non-specific biomarkers of neuronal damage, such as 14-3-3, neurone-specific enolase and S100B proteins, are elevated in CSF from people with sporadic Creutzfeldt-Jakob disease (CJD).⁸ The combination of a very high CSF t-tau (>1400 ng/mL on INNOTEST assays) and a high t-tau to p-tau ratio (>25) has >99% specificity for sporadic CJD in relation to both AD and other dementias,⁹ and high CSF t-tau is also seen in variant CJD.¹⁰ However, the use of real-time quaking-induced conversion (RT-QuIC) for prion protein has superseded these

methods; RT-QuIC takes several hours to days to perform¹¹ but has significantly greater specificity and slightly better sensitivity for sporadic CJD than these other proteins.^{11 12} In a recent multicentre validation of the revised diagnostic criteria for sporadic CJD, CSF RT-QuIC on its own had 91.6% sensitivity and 100% specificity for neuropathologically confirmed cases, outperforming MRI signs of cortical ribboning (67.9% sensitivity and 86.5% specificity) and basal ganglial hyperintensity (58.7% sensitivity and 91.9% specificity).¹³

CSF biomarkers are also useful in considering whether there is evidence for neurodegeneration

Table 1 Heatmap showing the ability of CSF Alzheimer’s biomarkers to discriminate AD dementia from other types of dementia

CSF biomarker	Effect size/fold change compared with AD (95% CI)		
	Aβ42	p-tau181	t-tau
Frontotemporal dementia	1.66 (1.57 to 1.75)	0.52 (0.48 to 0.56)	0.52 (0.49 to 0.56)
Progressive supranuclear palsy	1.48 (1.35 to 1.62)	0.43 (0.38 to 0.48)	0.37 (0.33 to 0.41)
Parkinson’s disease	1.68 (1.22 to 1.55)	0.46 (0.42 to 0.50)	0.35 (0.32 to 0.39)
Dementia with Lewy bodies	1.16 (1.10 to 1.22)	0.56 (0.52 to 0.60)	0.49 (0.46 to 0.53)
Parkinson’s disease dementia	1.37 (1.22 to 1.55)	0.53 (0.46 to 0.60)	0.43 (0.39 to 0.47)
Multiple system atrophy	1.55 (1.45 to 1.65)	0.41 (0.37 to 0.46)	0.39 (0.33 to 0.46)
Normal pressure hydrocephalus	1.37 (1.20 to 1.57)	0.35 (0.29 to 0.42)	0.35 (0.27 to 0.46)
Vascular dementia	1.31 (1.23 to 1.39)	0.55 (0.49 to 0.61)	0.40 (0.53 to 0.67)

Data are adapted from the Alzbiomarker database V.3.0 (July 2021).²

Orange indicates a higher level of the biomarker in the non-AD dementia compared with AD dementia. Cyan indicates a lower level of the biomarker in the non-AD dementia. All fold changes are significant at the p<0.0001 level.

AD, Alzheimer’s disease; CSF, cerebrospinal fluid.

Table 2 Clinical indications for appropriate use of lumbar puncture and cerebrospinal fluid testing in the diagnosis of AD, as detailed by the Alzheimer's Association's appropriate use criteria

Clinical indication	Alzheimer's Association's appropriate use criteria	
Meeting core clinical criteria for probable AD dementia with typical age of onset	Appropriate	
Symptoms suggesting possible AD dementia*		
Dementia with onset age below 65 years*		
Mild cognitive impairment with onset age below 65 years		
Persistent, progressing or unexplained mild cognitive impairment		
Subjective cognitive decline but considered to be at high risk of AD (persistent decline in memory rather than other cognitive domains; onset in the last 5 years, age at onset >60 years, worries associated with subjective cognitive decline, feeling of worse performance than others of the same age group, confirmation of cognitive decline by an informant; carriage of <i>APOE ε4</i>)		
Dominant symptom of change in behaviour, where AD diagnosis is being considered*		
Determining disease severity in patients who have already received a diagnosis of AD		Inappropriate
Subjective cognitive decline not considered to be at high risk of AD		
Symptoms of rapid eye movement sleep behaviour disorder		
Carriers of autosomal dominant AD mutations, with or without symptoms		
In lieu of genotyping for suspected carriers of autosomal dominant AD mutations		
Carriers of <i>APOE ε4</i> with no cognitive impairment		
Cognitively unimpaired on objective testing and no subjective cognitive decline but considered as high risk due to family history of AD		
Cognitively unimpaired on objective testing, no subjective cognitive decline, no expressed concern about developing AD and no condition suggesting high risk		

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*Indications that would be considered appropriate according to the current NICE guideline.⁶

AD, Alzheimer's disease; APOE, apolipoprotein E gene; NICE, National Institute for Health and Care Excellence.

of any form. In a wide range of processes involving either acute or chronic neuronal damage, neurofilament light chain (NfL) concentrations are elevated in CSF. Pronounced CSF NfL elevation occurs in prion disease.¹⁴ Compared with AD dementia (where there is an average 1.9-fold change relative to cognitively normal controls), there are greater elevations in CSF NfL in certain non-AD dementias such as some types of frontotemporal dementia (fold change 3.9 relative to healthy controls) and HIV-associated cognitive impairment (fold change 21.4).¹⁵ However, it is important to note that CIs are wide, and a normal CSF NfL concentration does not exclude the presence of neurodegeneration.

CSF SAMPLING

We have had a dedicated cognitive CSF clinic at London's National Hospital for Neurology and Neurosurgery (NHNN) since 2013. Diagnostic LPs are undertaken in a day care setting with an option for research sample donation. **Box 1** summarises the standard operating procedure for this clinic, which is broadly in line with the recommendations of a consensus guideline for LP in patients with neurological diseases.¹⁶ Key recommendations to minimise post-LP complications include adequate counselling of patients to allay fears beforehand, using atraumatic needles, limiting the number of attempts to four or fewer, and using passive (drip) CSF collection. Bed rest

has not been shown to improve outcomes, so we offer an opportunity for seated rest. Although the consensus recommendation is to use ≤ 25 G atraumatic needles in the lateral decubitus position, a multicentre feasibility study did not show a significant benefit of using smaller gauge needles,⁵ and so we use 22 G needles and allow for collection in the seated position. This improves the speed of collection especially when larger volumes (eg, 20 mL) are routinely taken, where the patient has additionally consented to research sample collection, and where measurement of CSF opening pressure is not of clinical concern.

Since 2018, an advanced nurse practitioner (FO'S) has been performing the LPs at the NHNN cognitive CSF clinic following the development of a local clinical guideline on nurse-performed LP (available on request) and appropriate competency-based training. The advanced nurse practitioner now runs the clinic independently, with back-up support from a rota of trainee doctors if technical difficulties are encountered, and research staff where research samples are also taken.

PREANALYTICAL HANDLING

We exclusively collect CSF in standardised polypropylene tubes, as polystyrene (the material in standard universal containers) results in artefactual lowering of the measured A β peptide concentrations by up to 30% and of t-tau by up to 15%.¹⁷ We also avoid collecting

Box 1 Standard operating procedure for cognitive CSF clinic at NHNN, including clinical and research sampling of CSF and blood

Referral information

- ▶ Demographic and contact details.
- ▶ Need for coordination with other tests.
- ▶ Not likely to require radiological guidance for LP.
- ▶ Specify whether CSF opening pressure is needed (not routinely done).
- ▶ Arrangements for antiplatelet and anticoagulant medication cessation if relevant.
- ▶ Full blood count and coagulation profile not required unless the patient has known history of thrombocytopenia or coagulopathy.

Preclinic telephone call (if not already addressed in clinic from which patient was referred/if patient requests additional call)

- ▶ Address concerns/questions.
- ▶ Ask if willing to receive research information.
- ▶ Arrange to send LP information leaflet by post/email, along with research information leaflet if relevant.
- ▶ Participant not instructed to fast but to drink copious fluids on the day if not contraindicated.
- ▶ Confirm not on antiplatelets or anticoagulants for the proposed appointment date or has a plan for cessation and recommencement (following the Association of British Neurologists 2018 guideline).³⁸

Clinic day

History and investigation review

- ▶ Review of recent neuroimaging (within the last 6 months) to confirm no contraindications (tonsillar descent/large mass lesion) OR confirm no history of features of raised intracranial pressure and no papilloedema on funduscopy.
- ▶ Confirm no allergies (latex, plasters and lignocaine).

Consent

- ▶ Formal written consent on hospital's general procedure consent form 1, or if patient is deemed to lack capacity to consent, document consultee discussion on consent form 4.
- ▶ Indication: diagnostic.
- ▶ Risks: common—headache (10%) and back pain (25%); rare—failure of procedure, bleeding, infection and nerve damage; very rare—hearing loss, double vision, need for a blood patch to treat prolonged post LP headache (<1 in 500).
- ▶ Separate consent for research sample donation (CSF and blood).

LP

- ▶ Second member of staff acts as an assistant/chaperone.
- ▶ CSF collected between 08:00 and 12:00.
- ▶ Patient in either lateral decubitus position or seated with lumbar forward flexion (when CSF opening pressure is not required).

Box 1 Continued

- ▶ Intervertebral space between L2/L3 and L5/S1 located by palpation.
- ▶ Skin preparation as per local clinical guidelines (with chlorhexidine 2%/ethanol 70%, allowed to dry fully before proceeding).
- ▶ Technique: aseptic (sterile gloves, standard personal protective equipment including plastic apron).
- ▶ Local anaesthesia: lignocaine 2%, maximum 3 mg/kg.
- ▶ Spinal needle: atraumatic 22 G, no more than four passes.
- ▶ Method of collection: drip without suction.
- ▶ If manometer is used, contents are emptied into routine CSF analysis container and manometer is removed before collection for AD CSF biomarkers.
- ▶ Primary containers for clinical CSF collection: polypropylene screw top yellow cap 25 mL (Sarstedt 63.9922.254).
- ▶ Volume collected for clinical sample, each into different tubes: routine tests (cell counts, protein, glucose, microscopy culture and sensitivities) 1 mL; AD CSF biomarkers 2 mL, virology (if needed) 1 mL, cytology (if needed) 5 mL.
- ▶ Primary containers for research CSF collection: polypropylene screw top clear cap 10 mL (Sarstedt 62.610.018).
- ▶ Volume collected for research sample (if relevant): maximum 15 mL.
- ▶ Needle bevel reinserted before withdrawal.
- ▶ Dry adhesive dressing applied to site.
- ▶ Patient assisted to supine position.

Paired venous blood sample

- ▶ Taken immediately after LP, tourniquet used.
- ▶ Venepuncture location: upper limb peripheral vein.
- ▶ Needle: 21 G or 23 G butterfly needle with BD Vacutainer adaptor.
- ▶ Blood collection tubes (clinical), BD Vacutainer: 1×SST serum (gold top) 4 mL, 1×fluoride oxalate (grey top) 2 mL.
- ▶ Blood collection tubes (research), BD Vacutainer: up to 1×lithium heparin plasma 6 mL, up to 4×SST serum 5 mL, up to 4×K2 EDTA plasma 6 mL.
- ▶ Dry adhesive plaster applied to site.

After-care

- ▶ Patient transfers to reclining chair, is offered a beverage and rests for 1 hour before going home; advised to avoid bending/straining for the rest of the day; plaster removed on the following day. Offer patient-initiated telephone follow-up post-LP: document any symptoms and arrange further follow-up if needed (eg, to monitor post-LP headache and arrange blood patch if persistent); organise radiologically guided LP if procedure failed.

AD, Alzheimer's disease; CSF, cerebrospinal fluid; K2 EDTA, dipotassium ethylenediaminetetraacetic acid; LP, lumbar puncture; NHNN, National Hospital for Neurology and Neurosurgery.

Continued

AD biomarker samples through manometers, as they may reduce measured A β peptide concentrations by up to 5%.¹⁸

CSF AD biomarker testing in the UK is currently carried out at a single UK Accreditation Service-accredited laboratory (the Neuroimmunology and CSF Laboratory (NICL) at the Queen Square Institute of Neurology). We recommend that all external samples that may incur a transport delay of >2 hours after LP are first processed in the referring hospital's laboratory. This involves centrifugation of CSF for 5 min at room temperature at 1750 g (3000 rpm) and aliquoting into 2 mL polypropylene aliquot tubes, ensuring a minimum volume of 0.5 mL per tube. The aliquots must then be frozen directly at minus 80°C on the same day of the LP and transported on dry ice to the NICL. Information about the tests offered, sample requirements, costs and turnaround times can be found in the NICL's user handbook.¹⁹

CSF AD BIOMARKER ASSAYS

Until recently, we used Conformité Européenne (CE-marked) INNOTEST ELISAs for A β 1–42, t-tau and tau phosphorylated at serine 181 (p-tau181). However, we switched to the automated Lumipulse platform (Fujirebio) in July 2020 to allow for testing of A β 1–42, A β 1–40, t-tau and p-tau181 using CE-marked assays, the main advantages including

- ▶ Improved diagnostic accuracy: the CSF A β 42/40 ratio improves the classification of clinical AD versus non-AD dementias and improves detection of cerebral fibrillar amyloid deposition (as defined by amyloid PET) compared with CSF A β 42 alone.²⁰ This is probably because use of CSF A β 40 concentration corrects for interindividual variability in the overall rate of A β peptide production.
- ▶ Reduced susceptibility of results to variations in pre-analytical handling: normalising to A β 40 concentrations at least partly mitigates against the artificial lowering of A β 42 through adsorption to sample tube surfaces,¹⁷ across multiple freeze–thaw cycles²¹ and through repeated tube transfers.²²
- ▶ Fewer possible pipetting errors when performing manual ELISAs.
- ▶ Increased throughput and reduced turnaround time (results may be obtained in 10 or fewer days, as opposed to 25 days).
- ▶ Potential for harmonisation of cut-points or interpretation with other centres using the same automated platform calibrated against certified reference material.

It is not straightforward to determine cut points for clinical use. Some of the challenges include accurate definitions of case–control status (noting that some healthy people will have preclinical disease) and balancing sensitivity (favouring minimising false negatives) with specificity (minimising false positives). The trade-off between sensitivity and specificity is

somewhat arbitrary and depends on the diagnostic aim, so it is important for the clinician to bear in mind. We undertook a validation of CSF A β 42/40 ratio testing on the Lumipulse platform in relation to both the INNOTEST platform and to amyloid PET data, resulting in a cut-point of 0.065 for this ratio, which gives 95% sensitivity and 89% specificity for identifying symptomatic individuals previously defined as having AD-like CSF on INNOTEST, and 85% sensitivity but up to 96% specificity for identifying asymptomatic amyloid PET-positive individuals using 18F florbetapir PET scans.²³ The t-tau and p-tau assay cut-points we use are from the manufacturer but also validated in local samples.

CEREBROSPINAL FLUID NEUROFILAMENT LIGHT CHAIN

Since 2019, the NICL has offered CSF NfL testing using the CE-marked UmanDiagnostics NF-light ELISA, which allows measurement of CSF NfL over a wide range of values encountered in normal physiology and pathological states (100–10 000 pg/mL in CSF, although the assay's dilution linearity allows higher values to be quantified reliably if needed). Figure 2 shows the values obtained by measuring CSF NfL at the NHNN lab in the first 300 CSF samples since the assay was adopted; as NfL increases with age, the normal ranges we use are age-specific (by decade), taken from a group of >350 normal controls in an international multicentre study.²⁴

INTERPRETING BIOMARKER RESULTS

The National Institute on Aging—Alzheimer's Association (NIA-AA) research framework for AD biomarkers

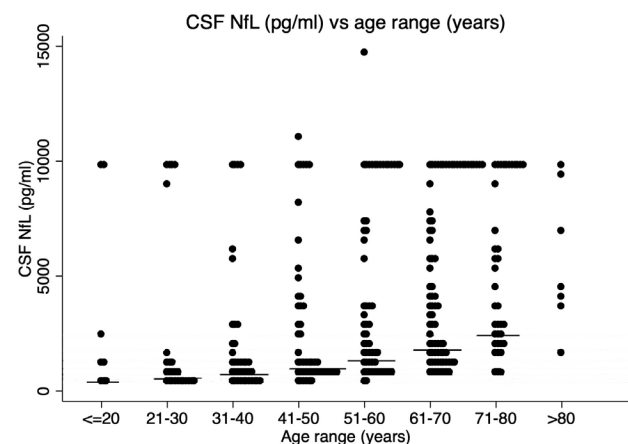


Figure 2 Results from the first 300 samples measured for CSF NfL at the Neuroimmunology and CSF laboratory of the Queen Square Institute of Neurology. Where available, age-adjusted norms (black horizontal lines) are shown from an independent cohort of 359 healthy controls from Yilmaz *et al*.²⁴ Note: usually, the upper limit of quantification is 10 000 pg/mL; however, where CSF NfL has been quantified as >10 000 pg/mL, the sample has been retested after further dilution. CSF, cerebrospinal fluid; NfL, neurofilament light chain.

conceptualises a spectrum of amyloid, tau and neurodegeneration (A/T/N) biomarkers on which everyone may be defined independently of clinical status; for example, an individual with A+T–N– would be classified as having ‘Alzheimer’s pathological change’, even if they were asymptomatic. However, in routine clinical practice, and as advocated by the latest International Working Group consensus on *clinical* diagnosis of AD,²⁵ we believe it is essential to interpret AD CSF biomarkers in the clinical context. Biomarkers should be used to lend support for, or against, a clinical formulation of the patient’s presentation and not on their own to make a diagnosis of dementia or any subtype. This is because currently available biomarkers do not reliably predict clinical progression in an individual, and there are problems of interpreting values near to

binary cut-points, and issues of classifying people with evidence of AD along with other pathologies.

In our own practice, after having first requested the test only in the appropriate clinical context (see the Introduction section and [table 2](#)), we use a staged approach as shown in [figure 3](#). Here, a low CSF Aβ42/40 ratio is required, but not sufficient, for making a diagnosis of clinical AD. This is because a proportion of people with normal cognition will have amyloid deposition as defined by CSF (about 18% at age 50 years, 25% at age 60 years, 33% at age 70 years and 43% at age 80 years).²⁶ We therefore interpret a normal Aβ42/40 ratio to mean that AD is unlikely to be the cause for an individual’s cognitive concerns at any age, but because AD pathology may be coincidental rather than causal at older ages, the positive predictive

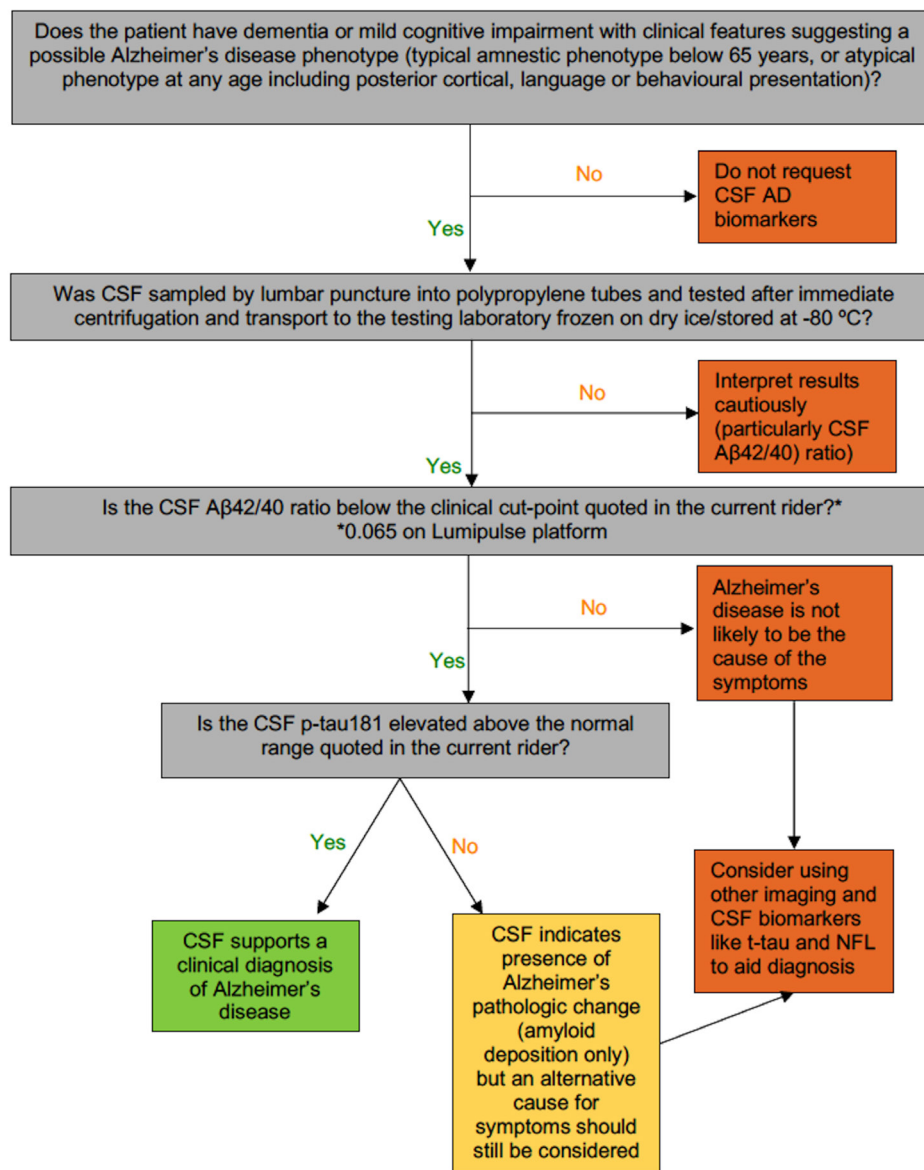


Figure 3 Flow diagram for interpretation of CSF AD biomarkers requested in the context of a possible AD phenotype. AD, Alzheimer’s disease; CSF, cerebrospinal fluid; NfL, neurofilament light chain.

value of a low A β 42/40 ratio for AD reduces with increasing age. We currently do not routinely request t-tau, as in the AD context it gives similar information to p-tau. However, in situations where prion disease is a consideration, a very high t-tau (eg, above the upper limit of quantification of the assay) with an elevated t-tau to p-tau ratio would support a diagnosis of prion disease that could then later be confirmed with other more specific biomarkers like CSF RTQuIC for prion protein or characteristic diffusion-weighted MRI changes.

Box 2 discusses some illustrative case studies in which CSF contributed to the clinical diagnosis, with accompanying figure 4.

The setting of cut-points for interpreting CSF biomarkers, and harmonising reporting to patients and clinicians, is a topic of active work. Currently the NICL participates in the Alzheimer's Association's external quality control programme²⁷ for CSF A β 42, A β 40, t-tau, p-tau181 and NfL. This allows for monitoring of performance relative to other laboratories performing these tests globally, and for assessing drift of results over time. Certified reference materials and methods^{28–30} are available for CSF A β 42 and are being developed for A β 40, t-tau, p-tau181 and NfL.

A recent survey of 40 laboratories across 15 countries³¹ indicated that cut-points are more similar across centres (but still not exactly the same) when automated assays are used, and this may in part relate to differences in preanalytical conditions but also to differences in the populations served. This study proposed a harmonisation of reporting of CSF AD biomarkers according to the eight different combinations that may be derived when the axes of amyloid, t-tau and p-tau are interpreted using centre-specific binary cut-points. Other methods of reporting used mostly in Europe include the Paris-North, Lille and Montpellier score,³² derived simply as the number of these three biomarkers that is abnormal, and the Erlangen score, which incorporates the concept of border zones to account for the possible influence of assay imprecision on the interpretation.^{33 34}

FUTURE

Most patients assessed in 'memory clinics' or dementia services in the UK are under the care of psychiatrists or geriatricians. A recent report by Alzheimer's Research UK and the Royal College of Psychiatrists³⁵ detailed the many barriers that need to be overcome for these services to be ready to deliver disease-modifying treatments. Such treatments have become particularly topical, given the US Food and Drug Administration's recent accelerated approval of one anti-A β antibody for therapeutic use in mild cognitive impairment AD or mild AD dementia and the pending applications for approval of other similar agents in the USA and Europe. Deployment of molecular biomarkers such as CSF testing at scale in these services currently is limited by

Box 2 Case studies

Patient 1

- ▶ A 61-year-old woman presented with a 4-year history of cognitive decline starting with reduced motivation, followed by word finding difficulty and mispronunciation. There were no ritualistic/obsessive behaviours and memory was not a significant complaint. She had a history of depression and anxiety but denied feeling low or anxious currently. She took mirtazapine, propranolol and folic acid. Her mother had been diagnosed with AD in her 50s and had died a few years later. She retired before symptom onset, and drove a car on familiar routes with no concerns from family. She was an ex-smoker and drank minimal alcohol.
- ▶ On examination, she turned frequently to her son for reassurance. She was not orientated to time (day, date, month or year) or location (town or country). She could register three items but could not recall after a delay. Her reading was slow with frequent pauses and some mispronunciations. Spontaneous speech was fluent but with word-finding pauses.
- ▶ On neuropsychological testing, single-word and phrase repetition was satisfactory; naming was impaired. Single-word comprehension was intact, but sentence comprehension was impaired. Visuo-perceptual processing was impaired, but simple visual detection was intact. Speed was very slow and there was executive dysfunction.
- ▶ MR scan of the brain (figure 4A) did not show significant atrophy or vascular burden, but a fluorodeoxyglucose (FDG) PET scan (figure 4B) showed hypometabolism in the temporoparietal region with involvement of the precuneus bilaterally, more pronounced on the left side, and also minimal FDG hypometabolism in the left frontal lobe.
- ▶ CSF showed white cell count of 1/ μ L (0–5), red cells 1/ μ L, protein 0.24 g/L (0.13–0.45), albumin quotient 3.02 (<7.2), glucose 3.3 mM (2.2–4.2), plasma glucose 5.2 mM (3.9–5.8), oligoclonal bands negative in CSF and serum.
- ▶ CSF dementia biomarkers were A β 42/40 ratio 0.036 (\geq 0.065), p-tau181 216 pg/mL (\leq 57), t-tau 1041 pg/mL (146–595) and NfL 2892 pg/mL (<1781); this profile was considered typical of AD.
- ▶ She was given a diagnosis of AD dementia (logopenic variant) and advised that she would need to stop driving and inform the Driver and Vehicle Licensing Agency of her diagnosis. She was offered treatment with a cholinesterase inhibitor, referred for speech and language therapy and, in view of her family history, offered genetic testing for rare monogenetic causes of AD.

Patient 2

Continued

Box 2 Continued

- ▶ A 68-year-old woman presented with a 2-year history of deteriorating driving ability, vision problems, emotional blunting, reduced social interaction, increased eating, word-finding problems and frequent falls. Her mood had become low since failing a road driving test that identified problems with attention, information processing and vehicle placement. Her medical history included hypercholesterolaemia and urinary urgency and she took a statin, omeprazole, calcium-vitamin D supplements and mirabegron. She lived alone and was independent in daily activities, as well as being a carer for her mother who had been diagnosed with dementia at age 84. Her father had late-onset ataxia and had died at age 81. She had two siblings and two daughters who were all well. She was an ex-smoker of 40 pack years and drank 1 bottle of wine per week.
- ▶ On examination, she was intermittently tearful and had frequent pauses in spontaneous speech. She scored 27/30 on the Mini-Mental State Examination, losing two marks for orientation and one for recall. Bedside cognitive testing showed impaired letter fluency (9 'C' words in 1 min) but intact naming, repetition and comprehension. There was patchy difficulty with memory and arithmetic. She gave concrete explanations for proverbs and had mild difficulty with the Stroop test. Physical examination showed square wave jerks in primary gaze, and 'round the houses' vertical eye movements. There was left arm bradykinesia with no rigidity, ataxia or tremor, and reflexes were symmetrical with down-going plantars.
- ▶ On neuropsychological testing, expressive language was slightly lacking in grammar but she could use sentences. She made occasional semantic and phonemic errors, but single-word and phrase repetitions were intact. Single-word comprehension was good for concrete but poor for abstract nouns and also for grammar. Tests of executive function showed significantly impaired response inhibition (Stroop), impaired letter and category fluency, and inflated cognitive estimates, with mildly slowed processing speed. Visuospatial functions were acceptable, but visuospatial processing (Adult Memory and Information Processing Battery figure copy <5th centile) was impaired.
- ▶ MR scan of brain showed mild generalised parenchymal volume loss without lobar preference or asymmetry. The choroidal fissures were prominent but hippocampal volumes appeared preserved (Figure 4C–E). A mild burden of white matter microangiopathy was noted without evidence of recent infarct (figure 4F).

Continued

Box 2 Continued

- ▶ CSF showed white cell count of 1/μL (0–5), red cells 2/μL, protein 0.48 g/L (0.13–0.45), albumin quotient 7.35 (<7.2), glucose 3.2 mM (2.2–4.2), plasma glucose 5.0 mM (3.9–5.8), oligoclonal bands negative in CSF and serum.
- ▶ CSF dementia biomarkers were Aβ42/40 ratio 0.054 (≥ 0.065), p-tau181 46 pg/mL (≤ 57) and NfL 4318 pg/mL (<1781). Despite the low Aβ42/40 ratio, the normal p-tau181 did not support AD as the cause of symptoms.
- ▶ She was diagnosed with progressive supranuclear palsy–frontotemporal dementia and given speech therapy input with an 8-week course in communication partner training, as well as signposted to Rare Dementia Support and the PSP Association. Normal ranges for CSF biomarkers are shown in brackets. Aβ42/40, amyloid-β 1–42/1–40 ratio; AD, Alzheimer's disease; CSF, cerebrospinal fluid.

physical infrastructure, availability of clinical expertise and clinical commissioning. Through better multidisciplinary working, neurologists and allied professionals in neurology services will have a role in supporting our colleagues in these areas of significant unmet need, by

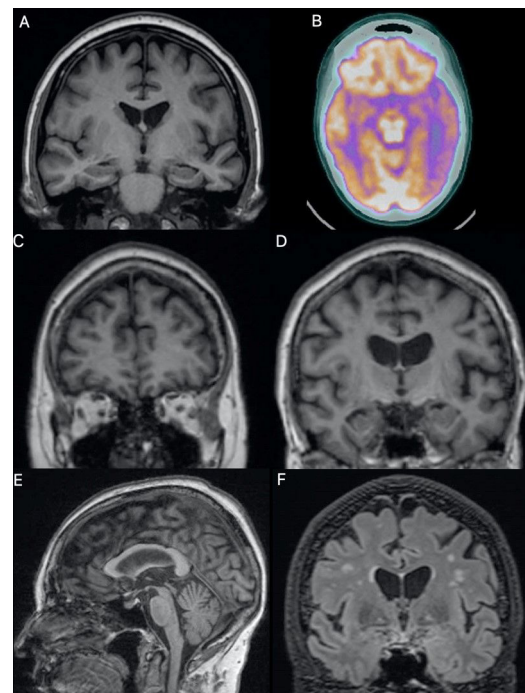


Figure 4 MRI brain scans from the two patient case studies. (A) Patient 1, MR T1 coronal multiplanar reconstruction at mid-hippocampal level. (B) Patient 1, FDG PET axial fused. (C) Patient 2, MR T1 coronal multiplanar reconstruction at orbitofrontal level. (D) Patient 2, MR T1 coronal multiplanar reconstruction at mid-hippocampal level. (E) Patient 2, MR T1 sagittal multiplanar reconstruction at midbrain level. (F) Patient 2, MR fluid-attenuated inversion recovery coronal.

sharing our clinical experience and our pathways to accessing these investigations.

Blood measurement of NfL on the Simoa platform is set to enter the clinical testing schedule in the UK soon via the NICL, and this will be followed by technical validation and application of plasma phospho-tau. While blood biomarkers may in due course have sufficient sensitivity and specificity to be used alone, currently the most likely scenario is for these to be used to prescreen individuals before proceeding to CSF examination or amyloid PET.

As clinical trials move into earlier stages including the preclinical and mild cognitive impairment stages

Key points

- ▶ Current guidelines/appropriate use criteria for cerebrospinal fluid (CSF) testing in dementia indicate it should be carried out where knowing the molecular diagnosis will change management.
- ▶ The typical CSF profile of Alzheimer's disease is a low amyloid- β 1–42/1–40 ratio, elevated p-tau181 and t-tau.
- ▶ An elevated CSF neurofilament light chain concentration may occur in a wide variety of conditions involving either acute or chronic neuronal damage.
- ▶ Services incorporating CSF neurodegeneration biomarker testing should incorporate the relevant clinical expertise in procedures, logistical requirements for sample transport and processing, robust processes for interpreting and feeding back of results to requesting clinicians and patients, and improved access to testing for patients cared for in neurology, psychiatry and elderly care services.

Recommended reading

1. Olsson B, Lautner R, Andreasson U, *et al.* CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *The Lancet Neurology* 2016;15(7):673–84.
2. Duits FH, Martinez-Lage P, Paquet C, *et al.* Performance and complications of lumbar puncture in memory clinics: Results of the multicenter lumbar puncture feasibility study. *Alzheimers Dement* 2016;12(2):154–63.
3. NICE. Dementia: assessment, management and support for people living with dementia and their carers. NICE Guideline 97. London, 2018 (available at <https://www.nice.org.uk/guidance/ng97>)
4. Shaw LM, Arias J, Blennow K, *et al.* Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease. *Alzheimers Dement* 2018;14(11):1505–21.

of disease, it would be ideal to be able to predict individualised risks for conversion to dementia. In research cohorts outside the UK, algorithms have been derived incorporating CSF biomarkers³⁶ or plasma biomarkers³⁷ with demographic factors, cognitive testing and imaging findings to predict conversion of mild cognitive impairment to AD dementia. Further work is needed to validate this type of approach in the UK National Health Service.

Efforts are ongoing to discover and validate molecular biomarkers for other dementias and related disorders, such as specific tau strains in non-AD tauopathies, such as progressive supranuclear palsy, α -synuclein in dementia with Lewy bodies, and TAR DNA-binding protein 43 in frontotemporal dementias. In time, it may become possible to index the relative contributions of different coexisting molecular pathologies to a patient's symptoms or likelihood of progression to dementia, and provide evidence for targeted therapies in a more personalised way.

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Competing interests RWP is codirector of the NFL consortium (an industry-funded research consortium) and has given educational lectures sponsored by GE Healthcare. JDR has served on a medical advisory board and had a consultancy agreement with Alector, Arkuda Therapeutics, Wave Life Sciences and Prevail Therapeutics, and had a consultancy agreement also with UCB, AC Immune, Astex Pharmaceuticals, Biogen, Takeda and Eisai. CJM has been an advisor to IONIS, Biogen, Lilly and Roche, is on the international steering committee for aducanumab, and has lectured for Biogen. NCF's research group has received payment for consultancy or for conducting studies from Biogen, Eli Lilly Research Laboratories, Ionis and Roche. NCF received no personal compensation for the aforementioned activities. NCF also serves on a Data Safety Monitoring Board for Biogen. JMS has received research funding from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly), has consulted for Roche Pharmaceuticals, Biogen, Merck, and Eli Lilly, given educational lectures sponsored by GE Healthcare, Eli Lilly, and Biogen, and serves on a data safety monitoring committee for Axon Neuroscience SE. HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, Annexon, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nerygen, Pinteon Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; and has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen and Roche. HZ is a cofounder of Brain Biomarker Solutions in Gothenburg AB, which is a part of the GU Ventures Incubator Programme.

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