Dementia in the Ageing Patient
Content

- Diagnosis
- Diagnostic testing
- Vitamins, diet, nutrition
- Screening
- Prevention
Diagnosis
Diagnosis of AD based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR) and the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders (NINCDS–ADRDA) working group.

These accepted criteria are fulfilled in a two step diagnostic process:

- initial identification of a dementia syndrome
- application of criteria based on the clinical features of the AD phenotype

DSM-IV-TR criteria require the presence of both a memory disorder and impairment in at least one additional cognitive domain, both of which interfere with social function or activities of daily living (ADL).

ADL impairment has come to define the threshold for the diagnosis of dementia beyond the identification of a cognitive abnormality.
Since publication of NINCDS–ADRDA criteria (1984) elucidation of the biological basis of AD has advanced greatly.

The clinical phenotype of AD is no longer described in exclusionary terms, but can be characterised more definitively on a phenotypic basis.

Distinctive markers of the disease are now recognised including:

- structural brain changes visible on MRI with early and extensive involvement of the medial temporal lobe (MTL)
- molecular neuroimaging changes seen with PET with hypometabolism or hypoperfusion in temporoparietal areas
- changes in cerebrospinal fluid biomarkers
Diagnostic Criteria for AD

Probable AD: A plus one or more supportive features B, C, D, or E

Core diagnostic criteria

A. Presence of an early and significant episodic memory impairment that includes the following features:

1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months

2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled

3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

Diagnostic Criteria for AD

Supportive features

**B. Presence of medial temporal lobe atrophy**

Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)

**C. Abnormal cerebrospinal fluid biomarker**

Low amyloid β1–42 concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three

Other well validated markers to be discovered in the future

Supportive Features

D. Specific pattern on functional neuroimaging with PET

- Reduced glucose metabolism in bilateral temporal parietal regions
- Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP

E. Proven AD autosomal dominant mutation within the immediate family

The new criteria suggest a four-step approach to diagnosing dementia due to AD:

Step 1 determines that dementia is present.

Step 2 determines that the dementia is due to AD.

Step 3 provides an increased level of certainty to the diagnosis.

Step 4 evaluates the biomarker probability of AD aetiology.

Diagnostic Testing
The Cognitive Continuum

- Amyloid-β accumulation (CSF/PET)
- Synaptic dysfunction (FDG-PET/IMRI)
- Tau-mediated neuronal injury (CSF)
- Brain structure (volumetric MRI)
- Cognition
- Clinical function

Normal → Preclinical → MCI → Dementia

Clinical Disease Stage
Ideal Biomarker for AD

• Should detect a fundamental feature of neuropathology and be validated in neuropathologically confirmed cases

• Should have a diagnostic sensitivity of more than 80% for detecting AD and a specificity of more than 80% for distinguishing other dementias

• Should be reliable, reproducible, noninvasive, simple to perform, and inexpensive

• It would be especially useful if the biomarker could capture
  – the beneficial effect of disease-modifying therapy
  – predict conversion from MCI to AD
  – correspond closely to available clinical detection methods and thus provide an opportunity for early intervention or prevention.

- structural brain changes visible on MRI with early and extensive involvement of the medial temporal lobe (MTL)

- molecular neuroimaging changes seen with PET with hypometabolism or hypoperfusion in temporoparietal areas

- changes in cerebrospinal fluid biomarkers

- **Blood test is the holy grail**
Recent Strategies

• Proteomics
Evaluation of a Previously Suggested Plasma Biomarker Panel to Identify Alzheimer’s Disease

Plasma proteins predict conversion to dementia from prodromal disease

Sixteen proteins correlated with disease severity, and cognitive decline. Strongest associations were in the MCI group with a panel of ten proteins predicting progression to AD (accuracy 87%, sensitivity 85%, and specificity 88%).

Hye et al. Alzheimers and Dementia 2014
Vitamins, diet, nutrition
Mediterranean diet

Most common version presented by Dr Walter Willett of Harvard University School of Public Health (mid-1990s)

- plant-based foods in abundance
- fresh fruit as the typical daily dessert
- olive oil as the principal source of fat
- dairy products (principally cheese and yogurt)
- fish and poultry consumed in low to moderate amounts
- zero to four eggs consumed weekly
- red meat consumed in low amounts
- wine consumed in low to moderate amounts

- Total fat in this diet is 25–35% of daily calorie allowance, with saturated fat at 8% or less of daily calorie allowance

Mediterranean diet and conversion of MCI to AD

*Figure 3.* Survival curves based on Cox analysis comparing cumulative Alzheimer disease (AD) incidence in subjects with mild cognitive impairment (MCI) at the first evaluation by Mediterranean diet (MeDi) adherence tertile ($P$ for trend = .02). The figure is derived from a model that is adjusted for cohort, age, sex, ethnicity, education, $APOE$ genotype, caloric intake, body mass index, and time between the first dietary assessment and the first cognitive assessment. Duration of follow-up is truncated at 10 years. Results
### Studies on diet and neurochemical effects

<table>
<thead>
<tr>
<th>Sl No</th>
<th>Brain food</th>
<th>Active principle</th>
<th>Effect/function</th>
<th>References</th>
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<td>Blueberries</td>
<td>flavonoids</td>
<td>Cognition, memory, and coordination</td>
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<td>2</td>
<td>Fish</td>
<td>Omega-3 fatty acids (DHA and EPA)</td>
<td>Reduces amyloid pathology by 70% (mice)</td>
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<td>3</td>
<td>Turmeric</td>
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<td>Antioxidant, anti-inflammatory, anti-amyloid</td>
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<td>4</td>
<td>Green tea</td>
<td>EGCG (an polyphenol)</td>
<td>Antioxidant, anti-inflammatory</td>
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<td>Antioxidant, anti-inflammatory</td>
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<td>Antioxidant</td>
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<td>Antioxidant</td>
<td>[27]</td>
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<tr>
<td>10</td>
<td>Fruits and vegetables</td>
<td>vitamin A (retinol)</td>
<td>Antioxidant</td>
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</table>
Micronutrients

- Selenium (↓ in AD, interventions?)
- Vitamins C and E (↓ in AD, no effect)
- Transition metals (?)
- Vitamin D (↓ in AD, no effect)
- B-complex vitamins (AD?, variable effect)
- Omega-3 fatty acids (AD?, variable effect)
Single nutritional approaches are unlikely to be the correct approach
Nutritional Interventions

- Cerefolin
- Axona
- Souvenaid
Souvenaid® Composition

Fortasyn™ Connect

- UMP
- Omega-3 fatty acids
- Choline
- Phospholipids
- B vitamins
- Antioxidants

Designed to:

Support the formation of synapses

DHA 1200 mg
EPA 300 mg
UMP 625 mg
Choline 400 mg
Folic acid 400 µg
B6 1 mg
B12 3 µg
Vit C 80 mg
Vit E 40 mg
Se 60 µg
Phospholipids 106mg
Exploratory Outcome: Sustainable NTB Memory Domain Improvement

Significant increase from week 24 to week 48 in both groups.
Active - Active: p=0.038
Control - Active: p=0.029

ITR, MMRM, data are mean ± SE

Manuscript in preparation, Developing Topics P4-349
Screening
Figure 1: **Timeline of disease progression**

- **Onset of neuropathology**
- **Reliably predictive biomarkers**
- **Onset of cognitive decline**
- **Onset of disability**
- **Subjective impairment/help seeking**

- **T1** Earliest possible diagnosis in the event that we develop reliably predictive biomarkers
- **T2** Earliest possible diagnosis using currently available technology
- **T3** ‘Timely’ diagnosis, responding to patient and carer concerns rather than proactively screening for the disease
- **T4** Current ‘late-stage’ diagnosis
“The Giants of Geriatric Medicine”

- Instability
- Immobility
- Intellectual decline
- Incontinence

Prevention
Blackfriars Consensus on promoting brain health

• Given the evidence that there may be a vascular component to many dementias, interventions to address vascular risk factors (tobacco, poor diet, physical inactivity and alcohol; and intermediate disease precursors such as raised blood pressure, raised blood cholesterol, obesity and diabetes which arise from behavioural and other factors) should also help reduce the risk, progression, and severity of dementia. Protective factors also play a part and these include education and intellectual and social engagement.
CAIDE Dementia Risk Score. Probability of late-life dementia according to risk score categories in middle age

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<tr>
<td>&gt; 30 kg/m²</td>
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<tr>
<td>&gt; 6.5 mmol/l</td>
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<tr>
<td>Physical Activity</td>
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<td>Yes</td>
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<td>no</td>
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<table>
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<th>Total Score</th>
<th>Dementia Risk</th>
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<td>10-11</td>
<td>7.4%</td>
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<tr>
<td>12-15</td>
<td>16.4%</td>
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JNHA 2008;12:89-94S
Thank You
...and the body finds it hard to replace lost synapses in AD because of nutritional deficiencies!

- Reduced plasma levels Folate, B12, Vit C, E
- Reduced CSF levels DHA / EPA
- Reduced mobilisation & synthesis DHA
- Homocysteine

**Increased turnover and destruction means increased need for synthesis**

- Reduced synthesis of Uridine monophosphate
- Age related reduced uptake of Choline by brain

[Diagram of biochemical pathways involving phosphatidylcholine, phosphocholine, CDP-choline, and synthesis of new neuronal membrane.]
CerefolinNAC

- Methylcobalamin 2 mg (B12), L-methylfolate 5.6 mg and N-acetylcysteine 600 mg

- Common adverse reactions: mild transient diarrhoea, polycythemia vera, itching, transitory exanthema and the feeling of swelling of the entire body, (associated with methylcobalamin). Nausea, vomiting, headache, other gastrointestinal symptoms and rash (± mild fever) have been associated with CerefolinNAC

- One possible advantage of CerefolinNAC over other B vitamin supplements is that it contains formulations of folic acid and vitamin B12, thought to be ‘active’, suggesting they are ready for use by the body without the need for conversion

- VITACOG showed reduction in atrophy only in the highest quartile of homocysteine

- No direct evidence of efficacy
Axona

- Phase II double-blind, randomized, multicentre, placebo-controlled trial of 152 patients with probable mild-moderate AD

- Those taking Axona had significant improvement in the ADAS-cog at day 45 ($p = 0.024$), which was maintained through day 90, although the difference was no longer significant at that point ($p = 0.0767$)

- The difference in ADAS-cog was significant at both day 45 ($p < 0.0005$) and day 90 ($p = 0.015$) in a subset of APOE ε4-negative patients
Axona

- Adverse event discontinuation rates were 23% in the treatment group and 6% in the placebo group.

- Most common adverse events: diarrhoea, flatulence and dyspepsia.

- No significant interactions seen with commonly prescribed AD drugs, including donepezil and/or memantine.

- The product contains caseinate, whey and lecithin, but is lactose free.