IMAGING ALZHEIMER'S: NICE PATHWAY CHANGES FROM CG42 TO NG97

Salma Hussain & Collette Bennion

1. INTRODUCTION

The term dementia is characterised by a progressive decline in cognitive abilities impacting on personal, social and occupational functioning, often caused by degenerative changes and positively correlated to age[1]. The most prevalent form being Alzheimer's (AD)[2].

With projections estimating up to 5 million people within the UK are aged 85+, accounting for approximately 5% of the population[3]. Age appears to be the strongest risk factor in dementia, with the incidence of dementia increasing exponentially from ages 65>[4]. An official report into the prevalence rates of dementia estimate the number of people with dementia in the UK is to reach over 1 million by 2025 and over 2 million by 2051[5]. With costs rising from £14 billion in 2007 to £34 billion by 2026[6].

2. ALZHEIMER'S

CLINICAL FEATURES	ALZHEIMER'S
ONSET	Gradual
MEMORY IMPAIRMENT	Early, pronounced deficit
EXECUTIVE DYSFUNCTION	Late appearance
NEUROLOGIC FINDINGS	None or subtle in early stages
NEUROIMAGING	Later stages: hippocampal, temporal and parietal atrophy most common
CARDIOVASCULAR HISTORY	Less commonly observed

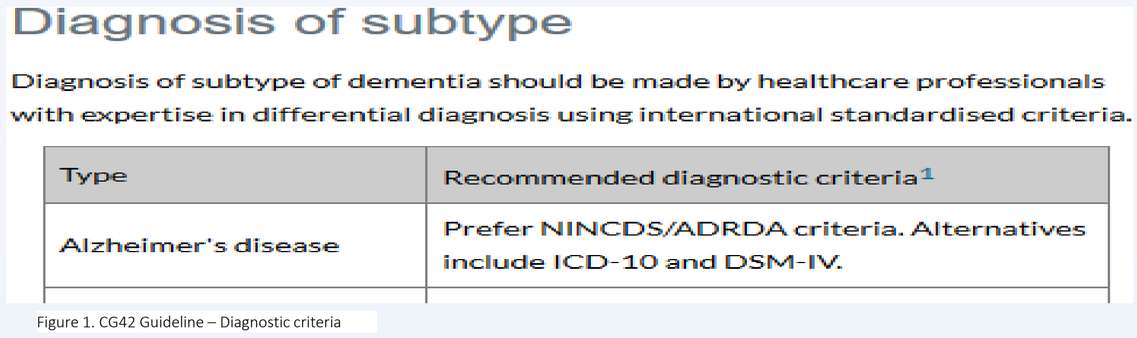
Table 1. Clinical features of Alzheimer's

3. ROLE OF IMAGING

Historically, the role of structural imaging in dementia has primarily been one of exclusion, with the aim of uncovering any conditions which may themselves account for cognitive symptoms e.g. tumours, hydrocephalus, or haemorrhages[7]. Although, in recent years, this role has changed from one of exclusion to one of supporting a diagnosis[8].

4. DIAGNOSTIC CRITERIA

Up until June 2018 the NICE guidelines CG42 recommended the use of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS/ADRDA) criteria for diagnosing AD[9]. CG42 recommended structural imaging in the form of MRI or CT to rule out underlying pathologies and to support a diagnosis, while favouring SPECT imaging to distinguish between dementia subtypes over FDG PET.



Diagnosis of subtype

Diagnosis of subtype of dementia should be made by healthcare professionals with expertise in differential diagnosis using international standardised criteria.

Type	Recommended diagnostic criteria[1]
Alzheimer's disease	Prefer NINCDS/ADRDA criteria. Alternatives include ICD-10 and DSM-IV.

Figure 1. CG42 Guideline – Diagnostic criteria

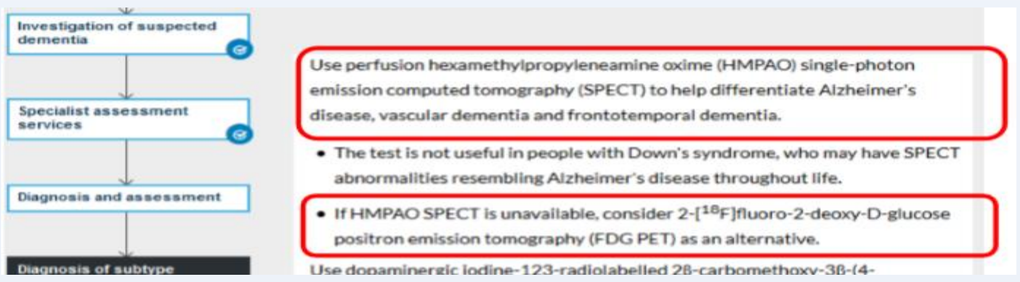


Figure 2. CG42 Guideline – Diagnosing dementia subtype

In 2011, the National Institute on Aging (NIA) and Alzheimer's Association (AA) updated the original criteria from 1984[10,11]. They proposed that AD develops long before symptoms present. The criteria has three categories for diagnosis; preclinical AD, MCI and dementia (Figure 3). In the preclinical stage. biomarkers have a greater role to play in early detection. Biomarkers are specific characteristics that can be objectively measured to predict the presence or risk developing a disease[12]. For dementia, these include atrophy, protein levels and patterns of perfusion. Specific regions and patterns can assist with determining dementia subtype.

5. NIA CRITERIA

Preclinical AD
- This stage is characterised by measurable changes in biomarkers that can be indicative of the earliest signs of disease, before symptoms become apparent (such as memory loss)

MCI due to AD
- This stage is marked by mild changes in cognitiion, to the extent that they are noticeable to individual affected and can be measured via imaging, but do not affect the ability to conduct everyday tasks

Dementia due to AD
- In this final stage, cognitive functions have deteriorated to a point where they have an impact on ability to function.

Figure 3. Breakdown of NIA's stages/ progression of dementia

6. NINCDS-ADRDA – NIA-AA COMPARISON

CRITERIA	NINCDS-ADRDA (1984)	NIA-AA (2011)
PROBABLE AD		
Dementia diagnosis	Impairments in 2 cognitive domains based on clinical exam and documented by cognitive testing	Impairments in 2 cognitive domains, and expands the definition on the non-memory forms of AD (language, executive function)
Onset and Progression	Progressive worsening of memory symptoms and other cognitive functions	Insidious onset and clear-cut history of worsening of cognition by report or observation
Age	Between ages 40-90	No age limitation
Biomarkers	Not available in 1984 criteria	Use of MRI, PET and CSF and other biomarkers to positively increase the certainty of AD in patients with probable AD. Recommended only for research purposes.
POSSIBLE AD		
Atypical presentations	Presence of variations in the presentation, onset or clinical course	Presence of atypical course, sudden onset or there is insufficient historical detail or documentation of progressive decline
NON-AD phenotype	Not addressed	At least 2 biomarker categories positive (Aβ CSF, tau CSF, PET, or MRI) to support the presence of underlying AD pathology

Table 2. Comparison of NINCDS-ADRDA AND NIA-AA diagnostic criteria

7. KEY CHANGES FROM CG42 TO NG97

NICE published the dementia guidelines NG97 in June 2018 replacing the pre-existing CG42. There were several changes made:

- The most notable being the replacement of the outdated NINCDS-ADRDA (1984|) diagnostic criteria with the NIA's (2011) criteria.
- NG97 Guideline 1.2.12 recommends the use of structural imaging to rule out reversible causes of symptoms as well as assisting with diagnosing dementia subtype in cases where subtype is unclear.
- Further tests and functional imaging are to be conducted only when it would help to diagnose a dementia subtype
- Guideline 1.2.15 (NG97) states that if Alzheimer's is suspected, the use of FDG-PET is recommended in order to arrive at a definitive diagnosis, with SPECT to be used if FDG is unavailable. As an alternative to the functional tests, cerebrospinal fluid (CSF) could also be examined for levels of tau and beta fluids.

REFERENCES

1. Gorelick, P.B., Scuteri, A., Black, S.E., Decarli, C., Greenberg, S.M., Iadecola, C., Launer, L.J., Laurent, S., Lopez, O.L., Nyenhuis, D., Petersen, R.C., Schneider, J.A., Tzourio, C., Arnett, D.K., Bennett, D.A., Chui, H.C., Higashida, R.T., Lindquist, R., Nilsson, P.M., Roman, G.C., Sellke, F.W. & Seshadri, S. (2011), "Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association", *Stroke; a journal of cerebral circulation,* vol. 42, no. 9, pp. 2672-2713.
2. Tanev, K., Sablosky, M., Vento, J. & O'Hanlon, D. (2012), "Structural and functional neuroimaging methods in the diagnosis of dementias: A retrospective chart and brain imaging review", *Neurocase (Psychology Press),* vol. 18, no. 3, pp. 224-234 11p.
3. Office for National Statistics (2012), "*Population Ageing in the United Kingdom, its Constituent Countries and the European Union*". Available at: http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/dcp171776_258607.pdf
4. Gavett, B.E., John, S.E., Gurnani, A.S., Bussell, C.A. & Saurman, J.L. (2016), "The Role of Alzheimer's and Cerebrovascular Pathology in Mediating the Effects of Age, Race, and Apolipoprotein E Genotype on Dementia Severity in Pathologically-Confirmed Alzheimer's Disease", *Journal of Alzheimer's Disease,* vol. 49, no. 2, pp. 531-545.
5. Prince, M., Knapp, M., Guerchet, M., McCrone, P., Prina, M., Comas-Herrera, A., Wittenberg, R., Adelaja, B., Hu, B., King, D. and Rehill, A. (2014) 'Dementia UK: update', *Alzheimer's Society, London*.
6. McCrone, P., Dhanasiri, S,. Patel, A., Knapp, M. & Lawton-Smith, S. (2008), "*Paying the Price. The Cost of Mental Health Care in England to 2006*", Kings Fund.
7. Falahati, F., Fereshtehnejad, S., Religa, D., Wahlund, L., Westman, E. & Eriksdotter, M. (2015), "The Use of MRI, CT and Lumbar Puncture in Dementia Diagnostics: Data from the SveDem Registry", *Dementia & Geriatric Cognitive Disorders,* vol. 39, no. 1, pp. 81-91.
8. Cirillo, M. & Caranci, F. (2012), "Structural neuroimaging in dementia", Journal of Alzheimers Disease, vol. 29, no. 1, pp. 16-19.
9. McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. & Stadlan, E.M. (1984), "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease", *Neurology,* vol. 34, no. 7, pp. 939-944.
10. Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., Iwatsubo, T., Jack,Clifford R.,,Jr, Kaye, J., Montine, T.J., Park, D.C., Reiman, E.M., Rowe, C.C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M.C., Thies, B., Morrison-Bogorad, M., Wagster, M.V. & Phelps, C.H. (2011), "Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease", *Alzheimer's & Dementia: The Journal Of The Alzheimer's Association,* vol. 7, no. 3, pp. 280-292.
11. Jack,Clifford R.,,Jr, Albert, M.S., Knopman, D.S., McKhann, G.M., Sperling, R.A., Carrillo, M.C., Thies, B. & Phelps, C.H. (2011), "Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease", *Alzheimer's & Dementia: The Journal Of The Alzheimer's Association,* vol. 7, no. 3, pp. 257-262.
12. Ahmed, R.M., Paterson, R.W., Warren, J.D., Zetterberg, H., O'Brien, ,J.T., Fox, N.C., Halliday, G.M. & Schott, J.M. (2014), "Biomarkers in dementia: clinical utility and new directions", *Journal of neurology, neurosurgery, and psychiatry,* vol. 85, no. 12, pp. 1426-1434.