

YOUNG ONSET DEMENTIA: DIFFERENT DISORDERS? DIFFERENT EXPERIENCES?

Siobhan Hutchinson MRCPI, Neurologist
Cognitive Clinic, St. James's Hospital

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YOD - overview

- Different Disorders?
 - Prevalence
 - Spectrum of diagnoses depend on clinical setting
 - Diagnostic journey
 - Approach for clinicians
 - Experience for patients
- Different Experiences?
 - Care-gap
 - Personal assault
 - Whole-family illness
 - Positive approach
- What is needed?

YOD - Prevalence

- How many people under 65 develop dementia?

PAPER

The prevalence and causes of dementia in people under the age of 65 years

R J Harvey, M Skelton-Robinson, M N Rossor

J Neurol Neurosurg Psychiatry 2003;**74**:1206–1209

Objectives: To determine the prevalence of dementia in people under the age of 65 in a large catchment area, and use these figures to estimate the number of younger people affected by dementia in the UK.

Design: Epidemiological catchment area prevalence survey.

Setting: The London boroughs of Kensington and Chelsea, Westminster, and Hillingdon with a total population of 567 500 people.

Participants: All residents of the catchment area with dementia, where the illness began before the age of 65 years. Participants were notified to the study by medical and care professionals. The diagnosis and age of onset was established from all available health and social care records. In total, 227 people were identified, of whom 185 fulfilled the inclusion criteria of having a dementia which started before their 65th birthday.

Main outcome measures: Diagnosis of dementia and differential diagnosis of the cause of the dementia.

Results: The prevalence of dementia in those aged 30–64 was 54.0 per 100 000 (95% CI 45.1 to 64.1 per 100 000). For those aged 45–64 years, the prevalence was 98.1 per 100 000 (95% CI 81.1 to 118.0 per 100 000). From the age of 35 onwards, the prevalence of dementia approximately doubled with each 5 year increase in age. Extrapolating these figures nationally suggests that there are 18 319 (15 296–21 758) people with dementia under the age of 65 in the UK.

Conclusions: The study confirms previous “guesstimates” of the number of younger people affected by dementia in UK. The prevalence figures generated are robust, and are supported by other smaller and targeted prevalence surveys. The prevalence figures provided by this study will allow health planners to accurately estimate need and plan services.

See end of article for authors' affiliations

Correspondence to:
Dr Harvey, Community
Mental Health, The
Geelong Hospital, Ryrie
Street, Geelong, Victoria,
Australia;
rj.harvey@virgin.net

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YOD – Prevalence variability

Table 1 Age and gender specific prevalence rates in the study population

Population		All causes of dementia										Significance†
		All			Male			Female				
Age range	Male (n)	Female (n)	n	Rate*	95% CI	n	Rate	95% CI	n	Rate	95% CI	
30–34	23898	23375	6	12.7	(4.7 to 26.7)‡	3	12.6	(2.6 to 36.7)	3	12.8	(2.7 to 37.5)	NS
35–39	18526	19106	3	8.0	(1.6 to 23.3)	1	5.4	(0.1 to 30.1)	2	10.5	(1.3 to 37.8)	NS
40–44	18982	19643	6	15.5	(5.7 to 33.8)	1	5.3	(0.1 to 29.4)	5	25.5	(8.3 to 59.4)	NS
45–49	16549	16799	11	33.0	(16.5 to 59.0)	6	36.3	(13.3 to 78.9)	5	29.8	(9.7 to 69.5)	NS
50–54	15185	15237	19	62.5	(37.6 to 97.5)	10	65.9	(31.6 to 121)	9	59.1	(27 to 112)	NS
55–59	13983	13626	42	152.1	(110 to 206)	28	200.2	(133 to 289)	14	102.7	(56.2 to 172)	NS
60–64	12716	13141	43	166.3	(120 to 224)	26	204.5	(134 to 300)	17	129.4	(75.4 to 207)	NS
30–64	119839	120927	130	54.0	(45.1 to 64.1)	75	62.6	(49.2 to 78.4)	55	45.5	(34.3 to 59.2)	NS
45–64	58433	58803	115	98.1	(81.1 to 118)	70	119.8	(93.4 to 151.0)	45	76.5	(55.8 to 102)	NS
Over 65§			55			33			22			

*Rate per 100 000 people at risk.

†Significance of difference between genders by inference from 95% CI.

‡95% confidence interval for the prevalence rate.

§Subjects who had a dementia starting before the age of 65 years, but were over 65 but still living on the study census day.

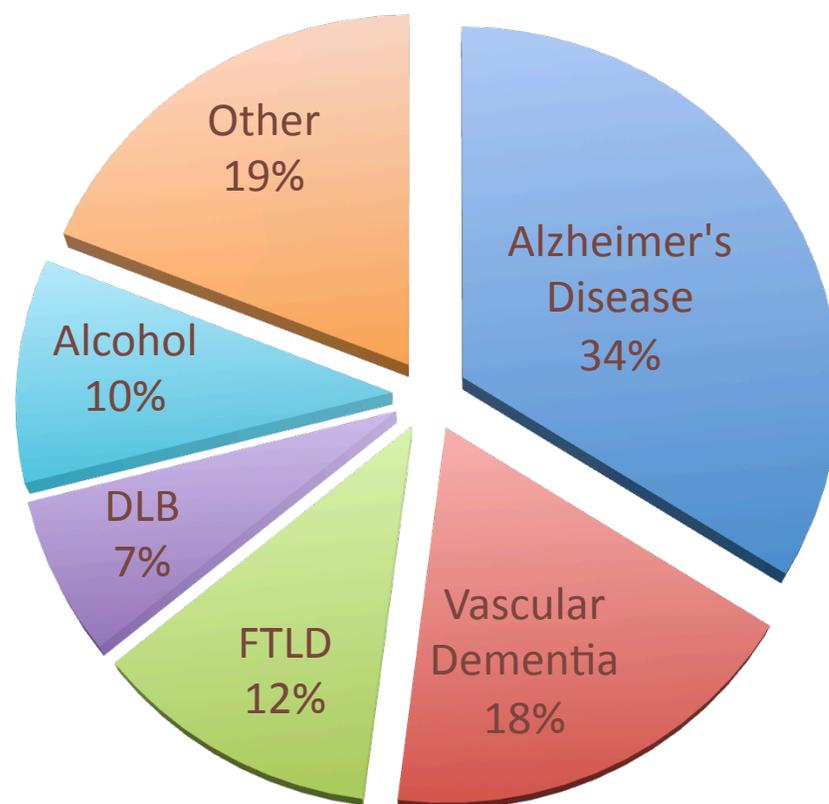
YOD – Prevalence variability

Table 2 Age specific prevalence rates for the most common causes of young onset dementia

Age range	Alzheimer's disease			Vascular dementia			Frontotemporal dementia			Alcohol related dementia		
	n	Rate*	95% CI	n	Rate*	95% CI	n	Rate*	95% CI	n	Rate	95% CI
40-44	1	2.6	(0.7 to 14.4)									
45-49	2	6.0	(0.7 to 21.7)				4	12.0	(3.3 to 30.7)	2	6.0	(0.7 to 21.7)
50-54	5	16.4	(5.3 to 38.4)	2	6.6	(0.8 to 24.4)	1	3.3	(0.8 to 18.3)	6	19.7	(7.2 to 42.9)
55-59	14	50.7	(27.7 to 85.1)	9	32.6	(14.9 to 67.9)	7	25.4	(10.2 to 52.2)	5	18.1	(5.9 to 42.3)
60-64	20	77.3	(47.2 to 119)	10	38.7	(18.5 to 71.1)	6	23.2	(8.5 to 50.5)	3	11.6	(2.4 to 33.9)
30-64	42	17.4	(12.6 to 23.6)	21	8.7	(5.4 to 13.3)	18	7.5	(4.4 to 11.8)	16	6.6	(3.8 to 10.8)
45-64	41	35.0	(25.1 to 47.4)	21	17.9	(11.1 to 27.4)	18	15.4	(9.1 to 24.3)	16	13.6	(7.8 to 22.2)

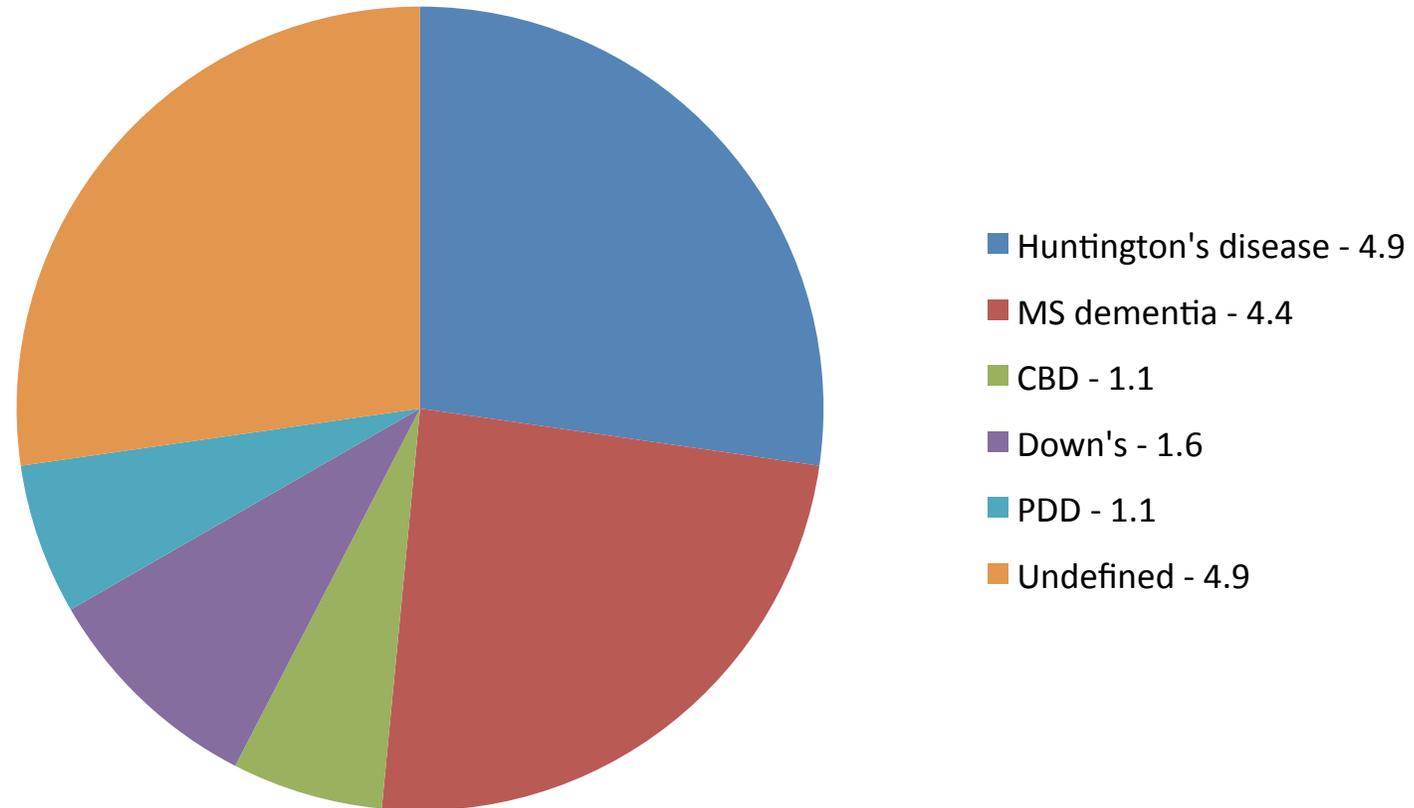
*Rate per 100 000 people at risk.

YOD – Prevalence of different diagnoses



Harvey et al, 2003 Prevalence 45-64 98/100,000

YOD – Prevalence of “Other”



YOD – different cohorts in different clinics

- Case mix – definition of YOD, referral patterns, type of clinical setting

ORIGINAL CONTRIBUTION

Young-Onset Dementia

Demographic and Etiologic Characteristics of 235 Patients

Brendan J. Kelley, MD; Bradley F. Boeve, MD; Keith A. Josephs, MST, MD

Background: Onset of dementia before age 45 years presents a difficult clinical circumstance, having a broad differential diagnosis and numerous psychosocial implications for the patient and their family. Few data exist regarding the demographics characterizing this population or the etiologic diagnoses among those affected.

Objectives: To characterize the demographic characteristics and the etiologic causes of dementia with age at onset younger than 45 years.

Design: Observational, retrospective, single-cohort study.

Setting: Multispecialty group academic medical center.

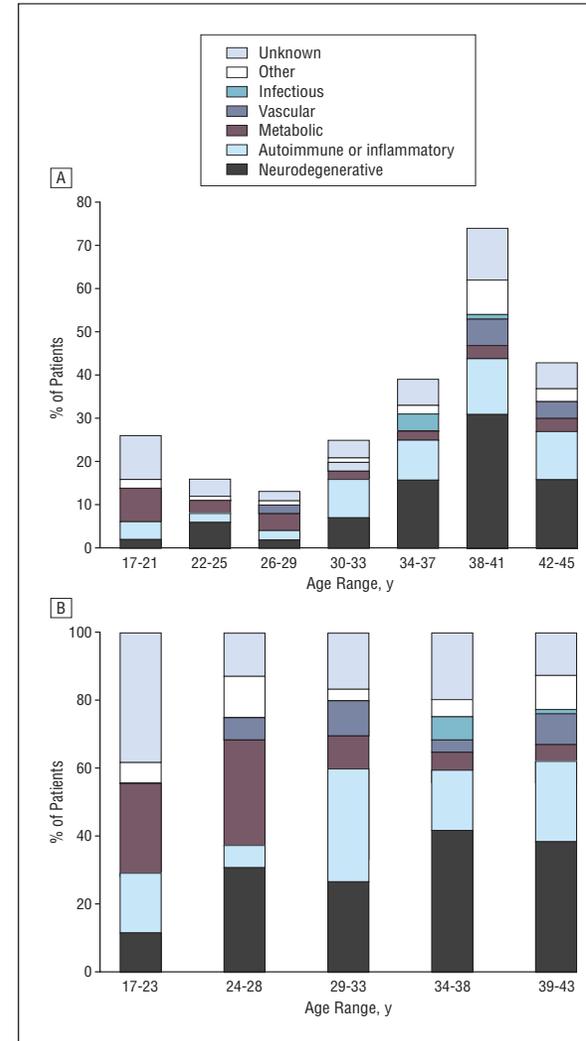
Patients: We searched the Mayo Clinic Rochester electronic Medical Record Linkage System to identify individuals who were seen for evaluation of progressive cognitive decline between the ages of 17 and 45 years from January 1996 through December 2006. This search identified 235 individuals who met the established inclusion and exclusion criteria.

Main Outcome Measures: All available clinical, laboratory, magnetic resonance imaging, and pathological data were reviewed.

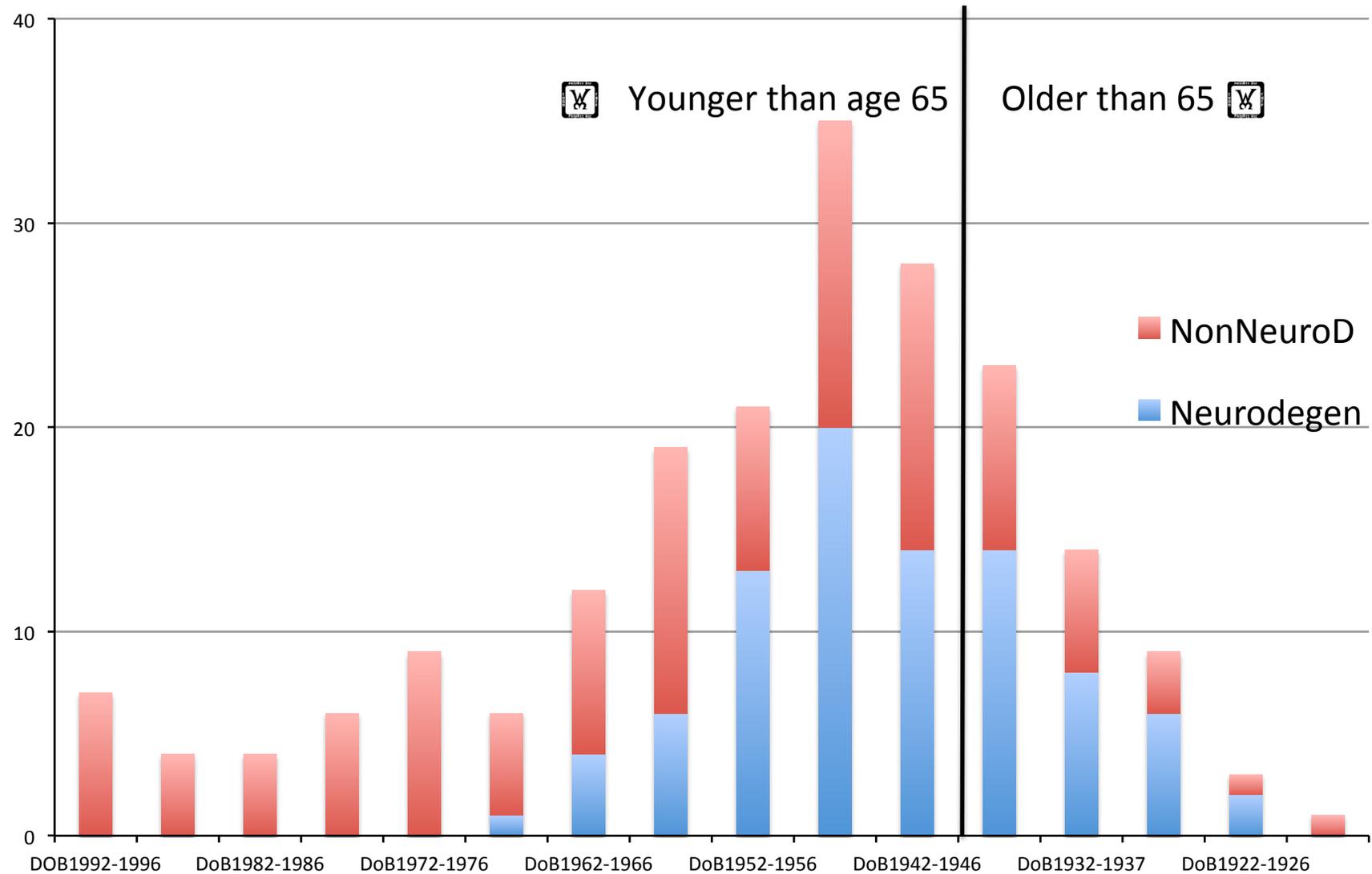
Results: Causes varied, with neurodegenerative etiologies accounting for 31.1% of the cohort; Alzheimer disease was uncommon. Autoimmune or inflammatory causes accounted for 21.3%. At last follow-up, 44 patients (18.7%) had an unknown etiology, despite exhaustive evaluation. Cause varied with age, with inborn errors of metabolism being more common before age 30 years and with neurodegenerative etiologies being more common after age 35 years.

Conclusions: Young-onset dementia (age at onset, <45 years) includes a broad variety of etiologies, with few patients having a potentially treatable disorder. The etiologic spectrum and the relative percentages of patients within etiologic groups differed in important ways from existing reports of early-onset dementia (ie, age at onset, <65 years).

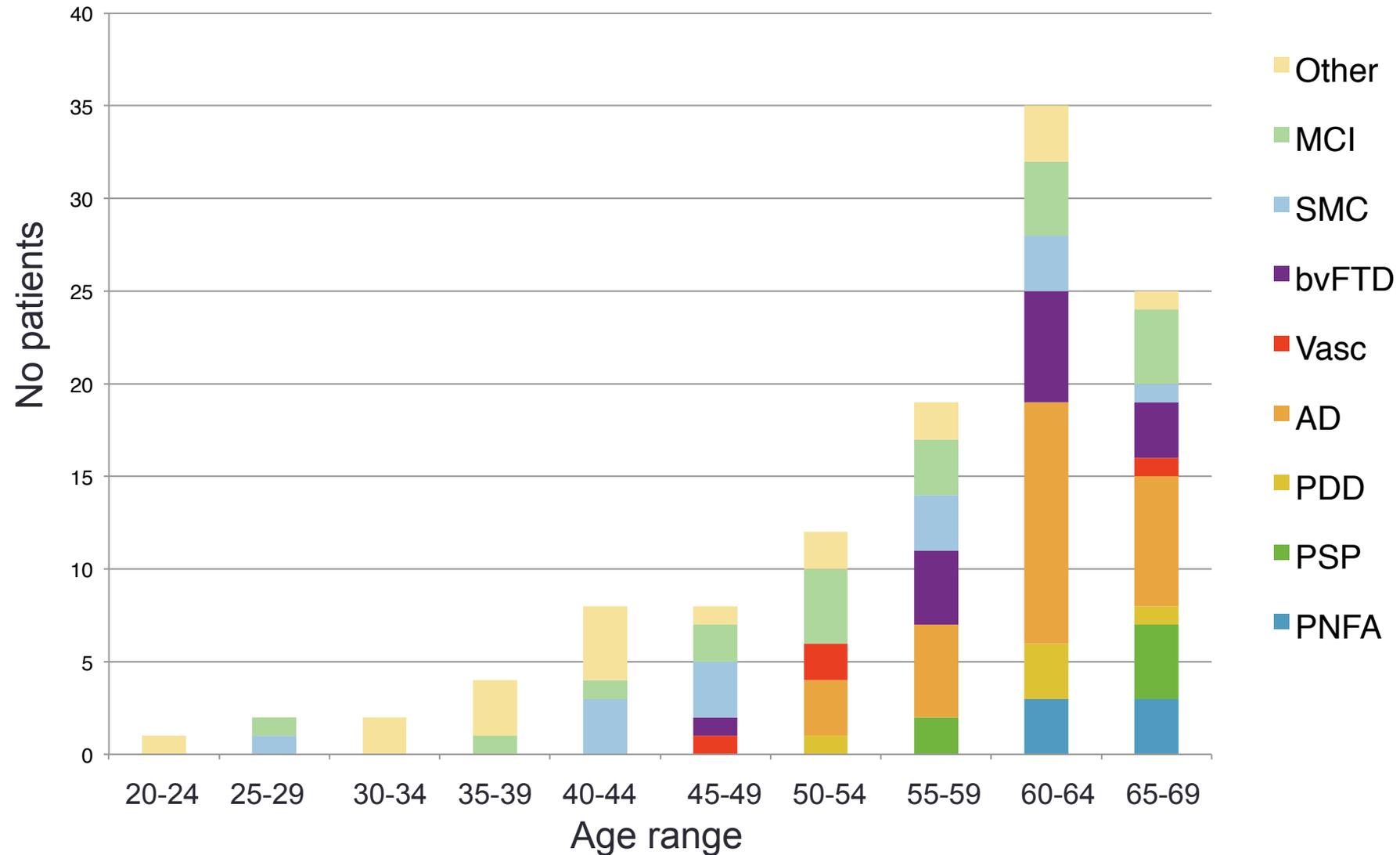
Arch Neurol. 2008;65(11):1502-1508



YOD – our experience



YOD – our experience



YOD – diagnostic journey

- Delayed diagnosis and misdiagnosis
- Recognition?
 - Poor disease awareness among public and professionals
 - Different presenting symptoms than older pwd
 - Memory less likely the presenting complaint
 - Non-specific functional decline
 - Behaviour, mood and language
 - Movement, falls, clumsiness, visual complaints
- Referral?
 - No defined referral pathway for under 65's
 - No 'ownership' by professionals of ypwd under 65
- Rare disorders?
 - Long list of diagnostic possibilities
 - What investigations?

YOD – diagnostic possibilities

- Neurodegenerative
 - **AD, FTD, DLB, PDD, PSP, CBD, MSA, Huntington's, CTE**
- Vascular
 - **Vascular dementia, CADASIL, CAA**
- Inflammatory
 - **MS, Neurosarcoid, Bechet's, Lupus, Limbic encephalitis**
- Infectious
 - **HIV, TSE, Neurosyphilis, PML, Whipples**
- Toxic/Metabolic/Systemic/Nutritional
 - **Alcohol, Heavy metal, Wilson's, Metabolic and Endocrine encephalopathies, B12/Thiamine/Niacin def**
- Late-onset childhood neurodegeneration
 - **Mitochondrial, Lysosomal storage disorders, Leukodystrophies**

YOD – diagnostic approach

The diagnosis of young-onset dementia

Martin N Rossor, Nick C Fox, Catherine J Mummery, Jonathan M Schott, Jason D Warren

A diagnosis of dementia is devastating at any age but diagnosis in younger patients presents a particular challenge. The differential diagnosis is broad as late presentation of metabolic disease is common and the burden of inherited dementia is higher in these patients than in patients with late-onset dementia. The presentation of the common degenerative diseases of late life, such as Alzheimer's disease, can be different when presenting in the fifth or sixth decade. Moreover, many of the young-onset dementias are treatable. The identification of causative genes for many of the inherited degenerative dementias has led to an understanding of the molecular pathology, which is also applicable to later-onset sporadic disease. This understanding offers the potential for future treatments to be tailored to a specific diagnosis of both young-onset and late-onset dementia.

Lancet Neurol 2010; 9: 793–806

See [In Context](#) page 763

Dementia Research Centre,
Department of
Neurodegeneration, UCL
Institute of Neurology,
Queen Square, London, UK
(Prof M N Rossor FRCP,
Prof N C Fox FRCP,
C J Mummery FRCP,
J M Schott MRCP,
J D Warren FRACP)

Cogn Behav Neurol. 2009 March ; 22(1): 22–27.

Rapidly Progressive Young-Onset Dementia

Brendan J. Kelley, MD, Bradley F. Boeve, MD, and Keith A. Josephs, MD MST
Department of Neurology, Mayo Clinic, Rochester, Minnesota; and Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program of the Mayo Foundation

Abstract

Objective—To characterize a cohort of individuals who have experienced rapidly progressive dementia with onset prior to age 45.

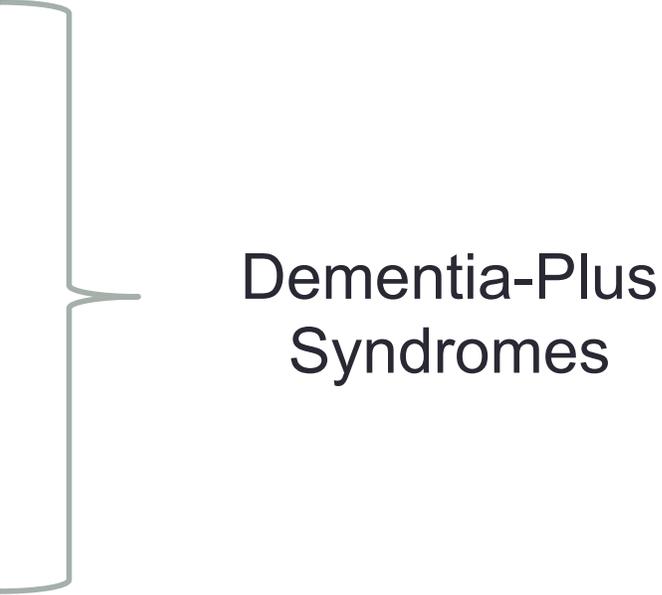
Background—Very little data regarding the clinical features or clinical spectrum of rapidly progressive young-onset dementia (RP-YOD) is available, primarily consisting of case reports or small series.

Methods—A search of the Mayo Clinic medical record was employed to identify patients who had onset prior to age 45 of rapidly progressive dementia. All available medical records, laboratory data, neuroimaging studies, and pathological data were reviewed.

Results—Twenty-two patients met the pre-defined inclusion and exclusion criteria. Behavioral and affective disorders, cerebellar dysfunction and visual and/or oculomotor dysfunction were common early clinical features within the cohort, as were clinical features often associated with Creutzfeldt-Jakob disease (CJD). Diagnostic testing identified an etiology in most patients.

Conclusions—Presentations of RP-YOD result from a variety of etiologies and significant overlap in clinical features is observed. Clinical features often associated with CJD appear to be common within the entire cohort of RP-YOD patients. Diagnostic studies aided in establishing a diagnosis in most patients, however five had uncertain diagnoses despite exhaustive evaluation.

YOD – diagnostic approach

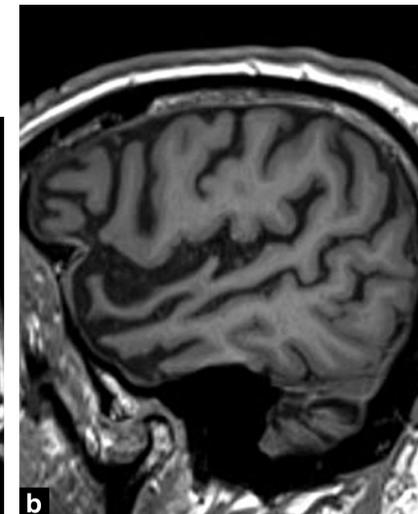
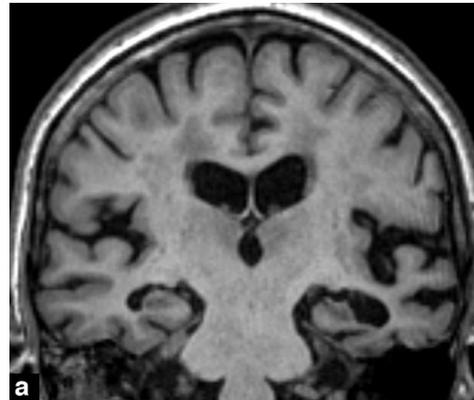
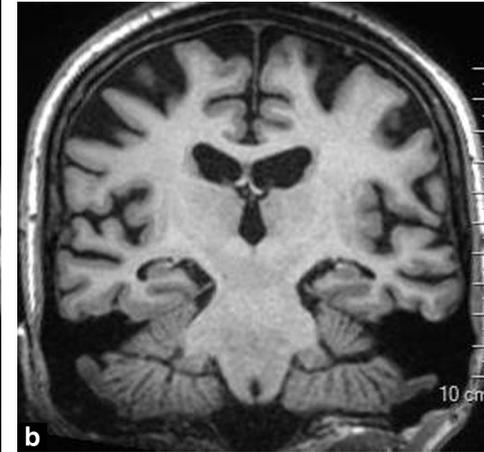
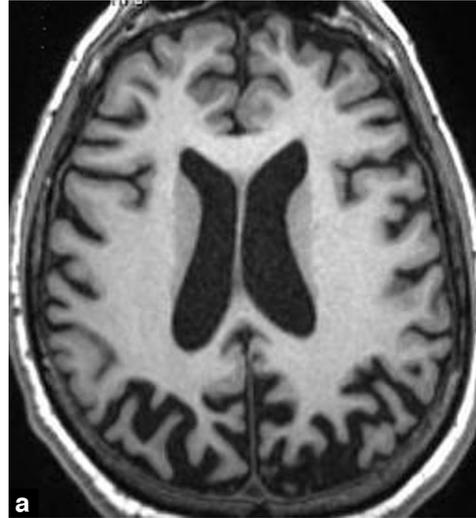
- Initial features and temporal course – collateral history
 - Cognitive- behavioral profile
 - Other neurological networks involved?
 - Parkinsonism
 - Cortico-spinal tract
 - Neuropathy or myopathy
 - Ataxia
 - Visual or Gaze Palsy
 - Movement disorder
 - Seizures and myoclonus
 - Dysautonomia
 - Deafness
 - Other systemic features?
 - Haematological, liver, renal, respiratory, skin, bone, cataracts, hyponatraemia
- 
- Dementia-Plus Syndromes

YOD - investigations

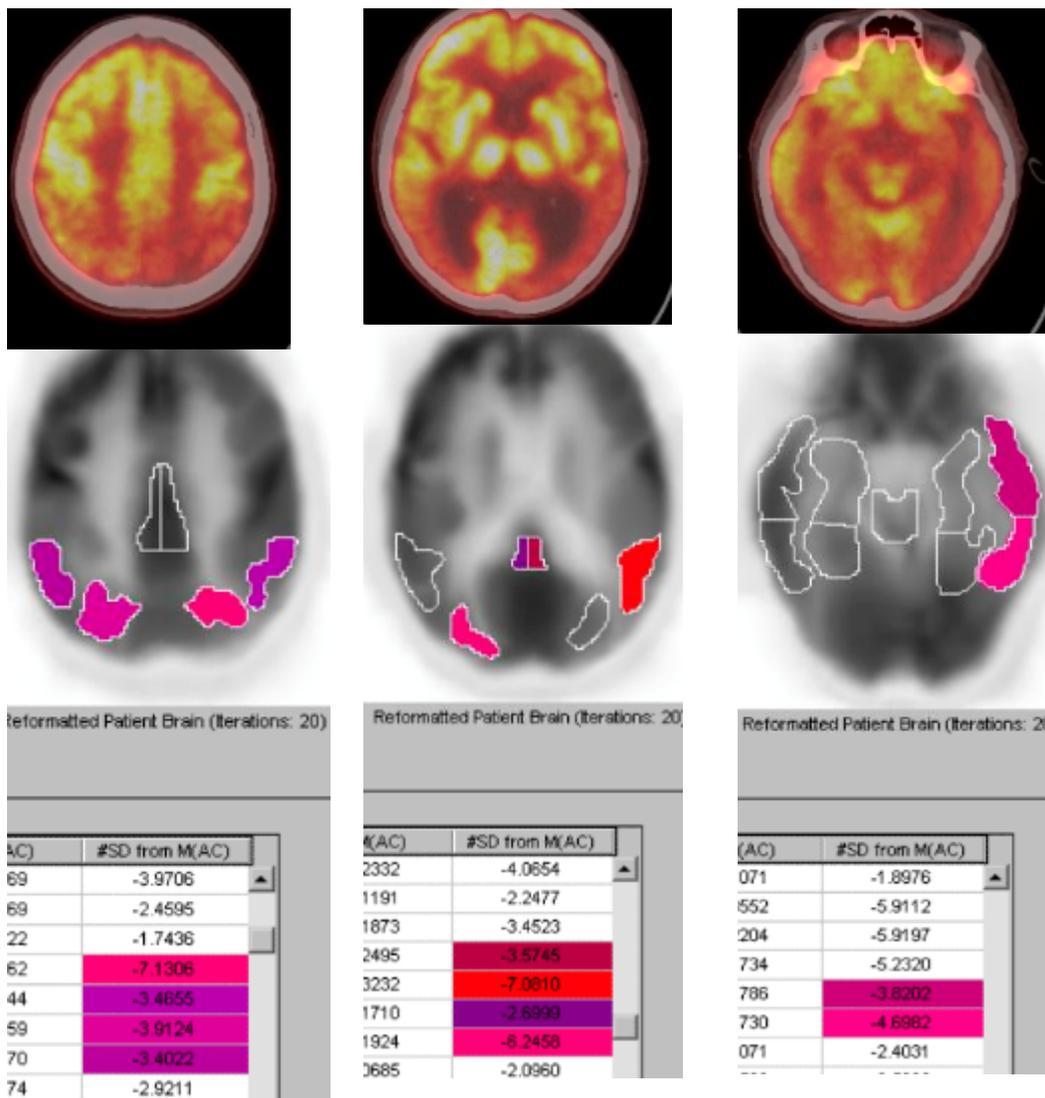
- Blood analysis
 - Systemic disease screen; B12/folate; HIV; Syphilis
 - Limbic encephalitis (Oxford Neuroimmunology Grp):
 - Cell surface anti-VGKC (LGI1 and CASPR2); GAD; NMDA, AMPA, GABA_B, Glycine receptors
 - Paraneoplastic: Ma1, Ma2, CV2
- Brain imaging
 - Structural : MRI
 - Functional : FDG PET
- CSF analysis
 - Unusual clinical features, rapid progression, unusual MRI, immunosuppressed, less than 55 year
 - Biomarkers
- Other tests if indicated
 - EEG, EMG/NCS, Autonomic function, Genetic analysis

YOD – imaging biomarkers

- Structural MRI
 - T1/T2 FLAIR/T2 gradient echo/DWI
 - Exclusion
 - Pattern of atrophy
 - Rate of atrophy



YOD – imaging biomarkers



- Functional imaging
 - PET 18-F- FDG
 - DAT dopamine transporter scan
 - (Amyloid PET; FMRI (resting or activation))

YOD – CSF biomarkers

CSF Biomarkers and Incipient Alzheimer Disease in Patients With Mild Cognitive Impairment

Niklas Mattsson, MD

Henrik Zetterberg, MD, PhD

Oskar Hansson, MD, PhD

Niels Andreasen, MD, PhD

Lucilla Parnetti, MD, PhD

Michael Jonsson, MD

Sanna-Kaisa Herukka, PhD

Wiesje M. van der Flier, PhD

Marinus A. Blankenstein, PhD

Michael Ewers, PhD

Kenneth Rich, MD

Elmar Kaiser, MD

Marcel Verbeek, PhD

Magda Tsolaki, MD, PhD

Ezra Mulugeta, PhD

Erik Rosén, PhD

Dag Aarsland, MD, PhD

Pieter Jelle Visser, MD, PhD

Johannes Schröder, MD, PhD

Jan Marcusson, MD, PhD

Mony de Leon, MD, PhD

Harald Hampel, MD, PhD

Philip Scheltens, MD, PhD

Tuula Pirttilä, MD, PhD

Anders Wallin, MD, PhD

Maria Eriksdotter Jönhagen, MD

Lennart Minthon, MD, PhD

Bengt Winblad, MD, PhD

Kaj Blennow, MD, PhD

Context Small single-center studies have shown that cerebrospinal fluid (CSF) biomarkers may be useful to identify incipient Alzheimer disease (AD) in patients with mild cognitive impairment (MCI), but large-scale multicenter studies have not been conducted.

Objective To determine the diagnostic accuracy of CSF β -amyloid₁₋₄₂ (A β 42), total tau protein (T-tau), and tau phosphorylated at position threonine 181 (P-tau) for predicting incipient AD in patients with MCI.

Design, Setting, and Participants The study had 2 parts: a cross-sectional study involving patients with AD and controls to identify cut points, followed by a prospective cohort study involving patients with MCI, conducted 1990-2007. A total of 750 individuals with MCI, 529 with AD, and 304 controls were recruited by 12 centers in Europe and the United States. Individuals with MCI were followed up for at least 2 years or until symptoms had progressed to clinical dementia.

Main Outcome Measures Sensitivity, specificity, positive and negative likelihood ratios (LRs) of CSF A β 42, T-tau, and P-tau for identifying incipient AD.

Results During follow-up, 271 participants with MCI were diagnosed with AD and 59 with other dementias. The A β 42 assay in particular had considerable intersite variability. Patients who developed AD had lower median A β 42 (356; range, 96-1075 ng/L) and higher P-tau (81; range, 15-183 ng/L) and T-tau (582; range, 83-2174 ng/L) levels than MCI patients who did not develop AD during follow-up (579; range, 121-1420 ng/L for A β 42; 53; range, 15-163 ng/L for P-tau; and 294; range, 31-2483 ng/L for T-tau, $P < .001$). The area under the receiver operating characteristic curve was 0.78 (95% confidence interval [CI], 0.75-0.82) for A β 42, 0.76 (95% CI, 0.72-0.80) for P-tau, and 0.79 (95% CI, 0.76-0.83) for T-tau. Cut-offs with sensitivity set to 85% were defined in the AD and control groups and tested in the MCI group, where the combination of A β 42/P-tau ratio and T-tau identified incipient AD with a sensitivity of 83% (95% CI, 78%-88%), specificity 72% (95% CI, 68%-76%), positive LR, 3.0 (95% CI, 2.5-3.4), and negative LR, 0.24 (95% CI, 0.21-0.28). The positive predictive value was 62% and the negative predictive value was 88%.

Conclusions This multicenter study found that CSF A β 42, T-tau, and P-tau identify incipient AD with good accuracy, but less accurately than reported from single-center studies. Intersite assay variability highlights a need for standardization of analytical techniques and clinical procedures.

JAMA. 2009;302(4):385-393

www.jama.com

tangles consisting of the protein tau and extracellular deposits of synaptotoxic β -amyloid (A β) peptides in fibril struc-
mens will be developed raise a need for methods enabling early diagnosis.^{4,5} Treatments would need to be initiated

YOD – diagnostic experience

- Delayed referral – multiple physician visits
- Assessment – many steps – prolonged
 - YPWD come alone – collateral hx missing
 - Periodic clinical assessments needed
 - Step-wise or repeated investigations
- Disclosure of diagnosis
 - Piece-meal with each visit
 - Doctor to ypwd/family without support
 - ‘Teach-back’ – poor communication/comprehension initially
- Post-diagnosis support
 - None in community
 - Hospital social-worker reaches out – poor response
 - Continued care in Cognitive Clinic

YOD – what then?

- “Every step is a fight”
- “Nothing out there for me”
- ‘Care-gap’
 - (Cahill, O’Shea, Pierce 2012)



Early-Onset Dementia

The Needs of Younger People
with Dementia in Ireland

Trutz Haase

August 2005



CREATING EXCELLENCE IN DEMENTIA CARE

A Research Review for Ireland's
National Dementia Strategy

Suzanne Cahill, Eamon O’Shea & Maria Pierce

YOD – ‘Care-gap’ wider

- Service provision is age-defined, fragmented, ad-hoc
- Problems with access to:
 - Medical and psychiatric services
 - Community health and social care
 - Residential care
 - Peer support or counseling for ypwd
 - Carer support
- Rely on health professionals ‘bending rules’
- Rely on voluntary organisations providing care

YOD – personal assault

- Sense of identity
- Employment (income, status)
- Dependants
 - Young or teenage children
- Relationship with partner
 - Increased conflict; Reduced intimate contact
- Relationship with friends
 - Retreat – poor awareness and sense of helplessness?
 - Unlike any other chronic disability – in cognitive impairment old relationships loose context. New friendship with carers.
- Awareness much greater in ypwd (van Vliet, 2013)
 - Apathy, depression and higher awareness in YO AD (NeedYD, 2012)

“shot down in the prime
of life”

“totally unprepared”

“I’ve lost myself....lost
everything”

YOD – “whole family illness”

- Greater burden on nuclear family
 - Partner and dependent children provide most of care
 - Family become isolated as extended family and friends re-treat
- Partner struggles
 - Financial – Care of ypwd – Care of children
 - Difficulty with behavioural symptoms
 - Grief at loss of spouse and mid-life projects and uncertain future
 - High levels of burden, stress and depression (Van Vliet, 2010)
- Children as carers (NeedYD, 2013)
 - Difficulty coping, difficulty understanding change in parent, not included in discussions with professionals, concern for future
- Greater proportion of ypwd live at home for longer (NeedYD, 2013)
 - Struggle to find support – flexible person-specific care required
 - More likely to precarious balance with un-supervised ypwd
 - Formal care when crisis - disease advances or behavioural symptoms or failure with ADLs or safety risk high-lighted

YOD – positive approach

- Diagnosis
 - Provides explanation
 - Focus on living well and management of symptoms
 - Plan for future
- Cognitive adaptation and rehabilitation
 - Not just memory – language/visuospatial/motor deficits
 - Energy and focus into rehabilitation
 - Driven and sourced by ypwd
- Normalise the life-cycle
 - Workplace engagement program: side by side (Roberston et al Dementia 2013)
 - Improve peer group contact

YOD – what's needed: close the gap

- Awareness of the disorder and experience
 - Professional and Public
 - Experience of ypwd and family
- Access to well demarcated care pathway
 - Health and social care 'ownership'
 - Integration of existing services
 - Resourced specific services for ypwd
 - Recognition of importance of community care for ypwd
- Professional advocate for ypwd
 - Case-manager/ Key-worker
 - Dementia Advisor of ASI
 - Needs assessment

YOD - summary

- Different Disorders?
 - Wider spectrum of disorders – clinically challenging
 - Same disorders with different presentations
- Different Experience?
 - Poor health and social provision: Wider Care-Gap
 - Specific and significant psycho-social effects on ypwd and their family
- Appeal
 - Inclusion in National Dementia Strategy
 - Recognition of and Provision for the specific needs of ypwd