Dementia- Early Diagnosis and Management

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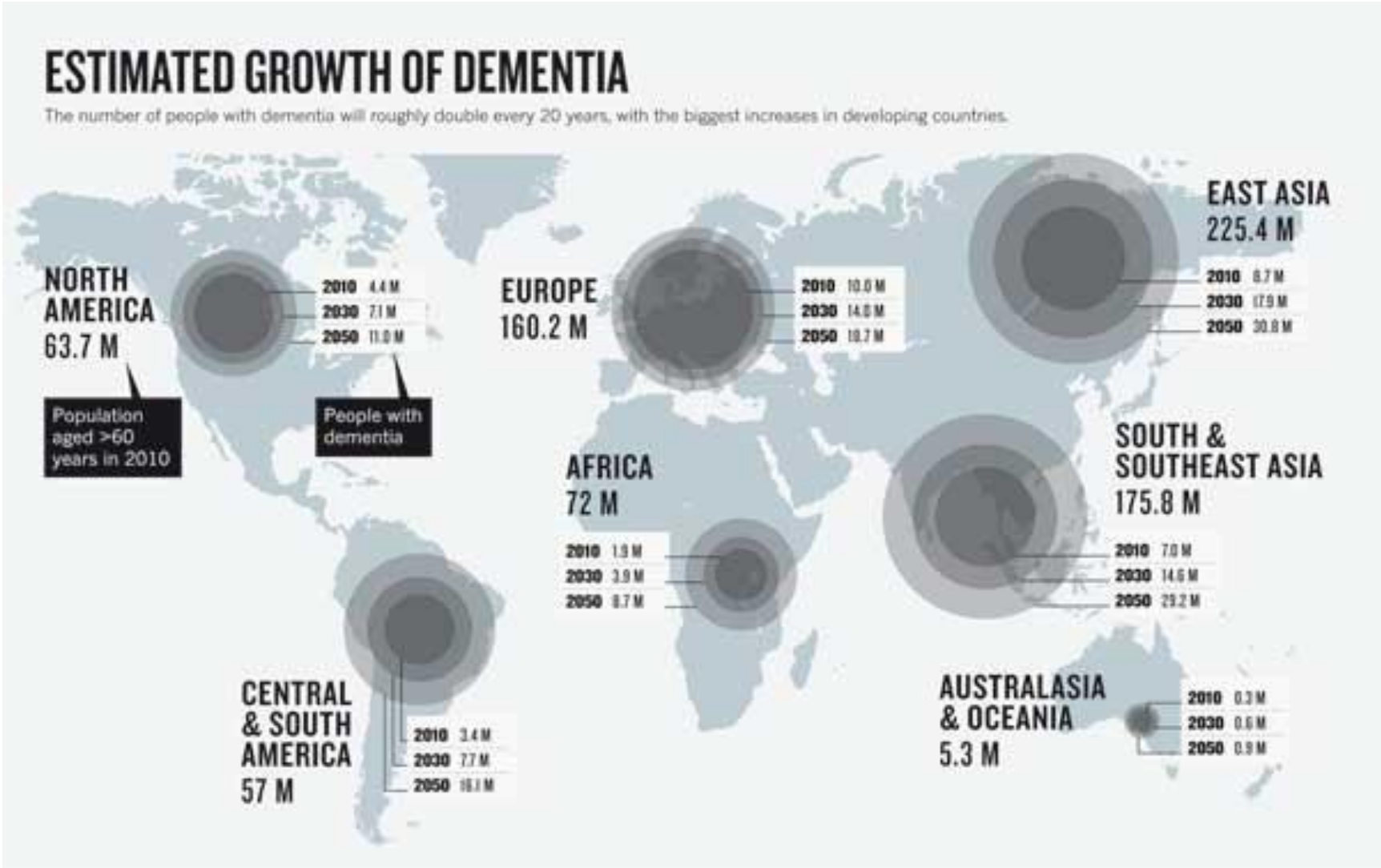

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Prevalence Estimates

WISE Study

	10/66 Dementia*		
	Cases	Unadj.	**Adj.**
	n	%	%
Overall	399	16.5	10
Age group			
60-74	45	3.2	3.4
75-84	134	21.2	21.9
85+	220	57.1	56.2
Gender			
Female	275	19.9	11.6
Male	124	11.9	8
Ethnicity			
Chinese	166	17.8	10.4
Malay	138	19	10.2
Indian	95	13.1	7.8

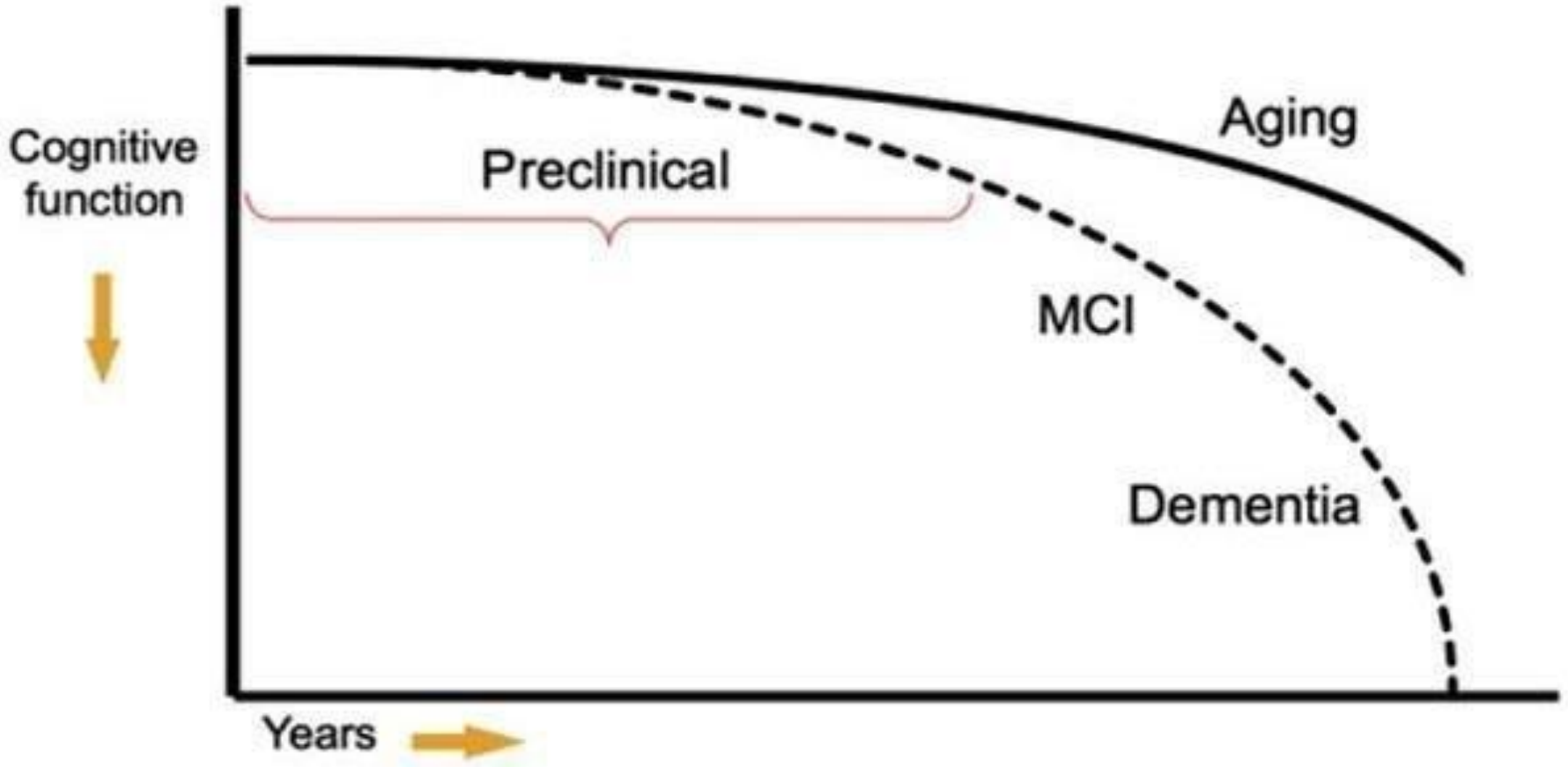
* Education adjusted

Memory & Normal Ageing

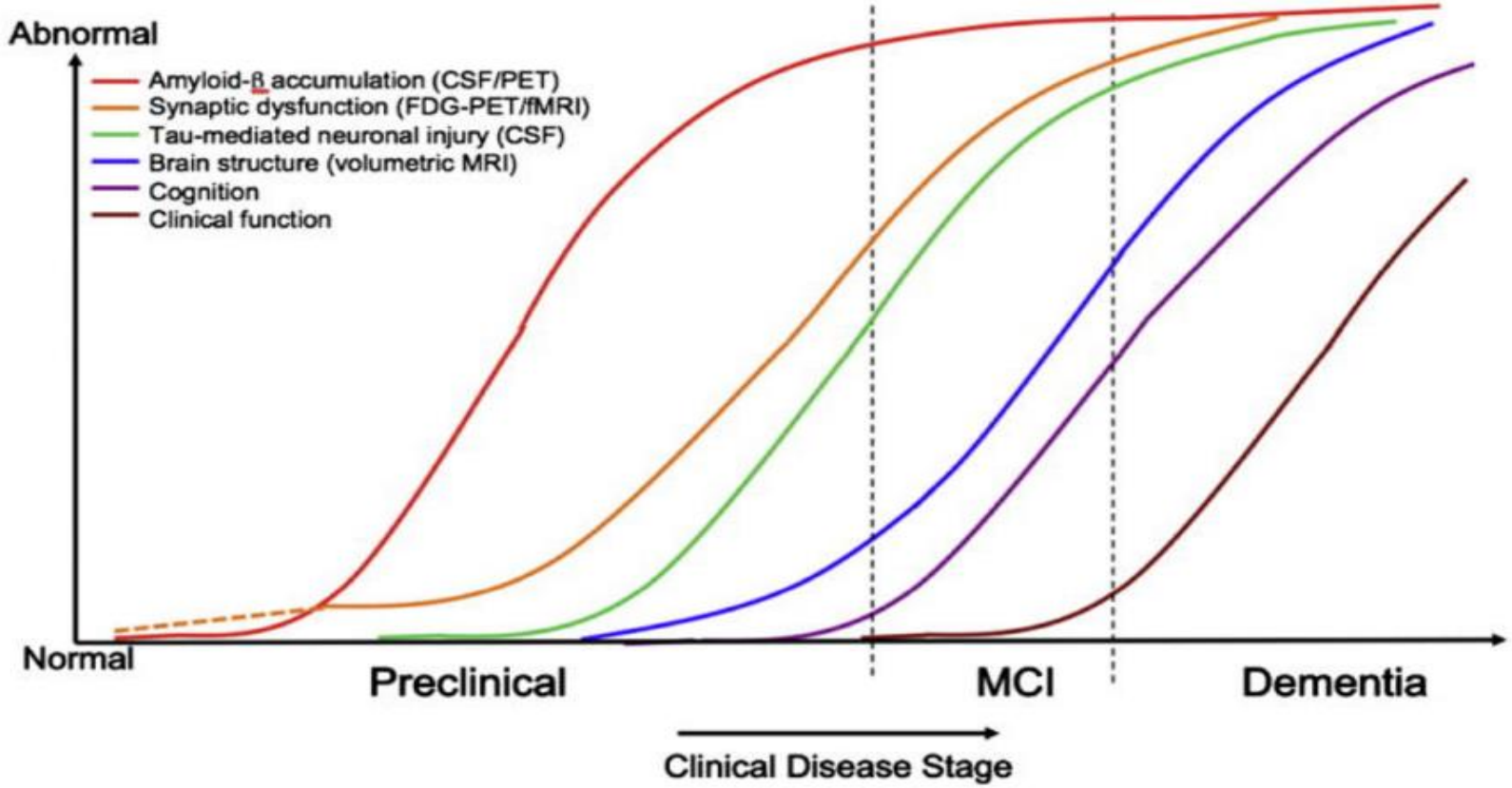
- Mild changes in rate of information processing.
- Non progressive changes in memory.
- Learning/acquisition declines uniformly with age.
- Delay in recall.
- Memory retention is normal.

- All the above are mild, non progressive and does not interfere with function.

Cognitive Decline and Ageing



Pre-Clinical AD



Jack CR, Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010;9:119–28.

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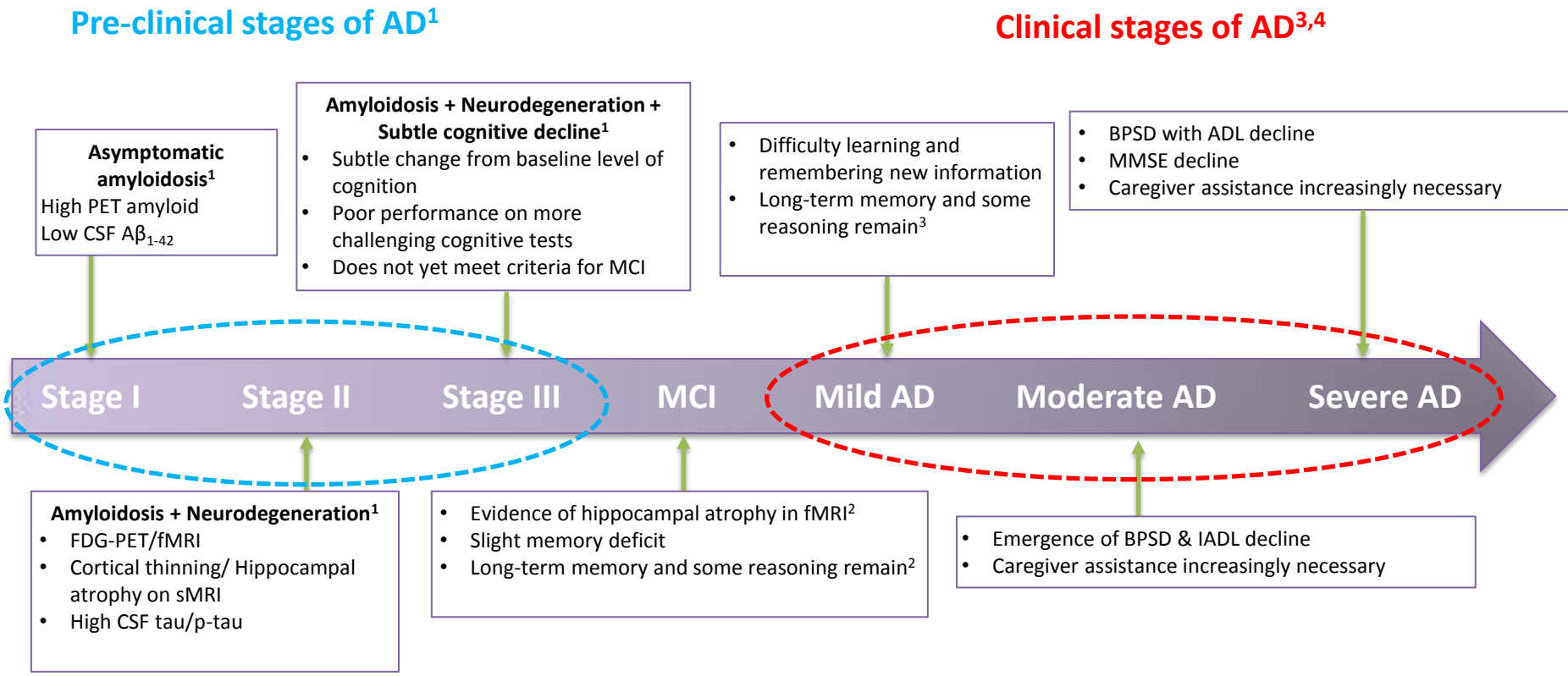
Pre-clinical and Clinical Stages of AD



AD, Alzheimer's disease; FDG-PET, Fluro deoxy glucose positron emission tomography; fMRI; functional magnetic resonance imaging; MCI, mild cognitive impairment

1. Sperling RA, *et al. Alzheimer's & Dementia*. 2011:1-13, doi:10.1016/j.jalz.2011.03.003
2. Langa KM and Levine DA. *JAMA.* 2014;312(23):2551-61
3. https://www.nia.nih.gov/alzheimers/topics/symptoms . Accessed June 5, 2015
4. Alzheimer's Disease Education & Referral (ADEAR) Center https://www.nia.nih.gov/sites/default/files/alzheimers_disease_fact_sheet_0.pdf Accessed on June 5, 2015

Subjective Memory Complaints

- Common among the elderly. Present among 20-50% of community dwelling elderly.
- Previously thought to be asc with depression, level of education, apo ε4 status, vascular load, education level.
- Subjective complaints of remembering names, recalling where something was kept, in the presence of normal scores like MMSE.
- SCI lasts for 15yrs before progressing to MCI. Therefore, there is a 6.67% conversion rate per yr to MCI.

Mild Cognitive Impairment

- Transition period between normal ageing and the diagnosis of mild AD.
- Some degree of cognitive impairment, with very slight functional impairment, causing minor inconveniences but not severe enough to qualify for diagnosis of dementia.
- MCI is a risk factor for dementia, with 12% risk of progression per year. At 6y follow up, 80% would have converted to mild dementia. (1)
- Difficult cut off between normal ageing and MCI/ MCI and mild dementia.

- 1.) Peterson RS. Mild cognitive impairment: clinical characterisation and outcome. Arch Neurol 1999; 56: 303-8.

Diagnostic Criteria for MCI

- Subjective memory complaint, corroborated by an informant.
- Objective memory impairment (1.5 SD below expected for age).
- Essentially preserved general cognitive function- visuospatial, language, executive function.
- Largely intact functional activities- IADL & ADL.
- Not demented. Not occurring during delirium.

Ultimately the judgement is the physician's.

RC Petersen. Mild Cognitive impairment as a diagnostic entity. J of Int Med 2004; 256: 183-194.

Delirium

- An acute medical emergency.
- Clinical features- acute onset (hours-days), reduced attention/ concentration, arousal, perceptual abnormalities, psychomotor changes, all the symptoms fluctuate.
- Management strategies- early identification, look for cause(s), treat cause(s), medication review, supportive care, prevent complications-falls, incontinence, functional decline, residual cognitive deficits, high mortality and increased risk of institutionalisation.

Predisposing Factors

Environmental	New environment, changes in routines, caregiver changes, immobility incl restraint use.
Neurodegenerative diseases	Stroke, dementia, Parkinson's disease
Sensory impairment	Visual and hearing impairment
Drugs	Psychoactive drugs- antipsychotic, benzodiazepines, antidepressant. Drugs with anticholinergic properties- piriton, hydroxyzine, annarex. Others- opioids, high dose madopar, steroids.
Pain	Poorly controlled pain.
Medical causes	Multiple co-morbidities, organ dysfunction, cancers.
Age	Older age >75
Cognition	Background dementia, depression

Precipitating Factors

- Drugs- anticholinergics, psychoactive meds, antihistamines, alcohol, drug withdrawal.
- Infections.
- Perioperative- anaesthetic drugs, hypovolaemia, pain, BP fluctuations, Hb drop, hypoxia.
- Nutrition and hydration.
- Metabolic derangement- Na, Ca, PO_4, Mg, $\uparrow PCO_2$, glucose, $\downarrow PO_2$, dehydration, malnutrition.
- Endocrine-T_4, PTH, pituitary, adrenals.
- CNS- infections, seizures, head injury.
- Organ dysfunction- CCF, hepatic failure, pulmonary diseases, renal failure, haematological.
- Sleep deprivation

Diagnostic Criteria of Dementia

DSM V criteria (2013):

Evidence from history and clinical assessment of at least one of the following:

- Learning and memory
- Language
- Complex attention
- Executive function
- Perceptual-motor function
- Social cognition

The deficits interfere with everyday activities, needs assistance for IADL. Cognitive deficits do not occur during the course of delirium. Cognitive deficits are not better explained by another mental disorder and has an insidious onset and is progressive.

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DSM IV (AD)

- Amnesia, plus **two** of the following:
- Agnosia
- Aphasia
- Apraxia
- Executive dysfunction

The above must be severe enough to interfere with social and vocational functioning. Slowly and progressively declining. Not occurring in the presence of delirium, substance intoxication or due to psychiatric disorder.

Always good to screen for depression!

Taking a History for Dementia

- **Amnesia**- short term memory loss. Eventually long term memory loss too. Repetitive, misplaces items, delusional ideation of thefts.
- **Apraxia**- inability to do previously learned motor tasks, in the absence of neurological deficits- like dressing, grooming, feeding, using common utensils, remote control.
- **Aphasia**- expressive/ receptive/ semantic- answer questions wrongly, uses wrong words or phrases, doesnot seem to understand conversations/ questions.
- **Agnosia**- inability to recognise people, places, objects. Unable to use common gadgets at home- like can opener, washing machine, taking a long time and fail to learn how to use a new gadget like handphone.

Taking a History for Dementia (2)

- **Executive dysfunction**- complex multi-step tasks which involve planning, sequencing and mental flexibility- cooking, banking, driving, housework. Cooking tastes odd, cooks the same dish over and over, burned food, chaotic kitchen, reckless withdrawal of money from bank accounts, frequently getting lost while driving in familiar territory, more accidents while driving etc.
- **Social cognition**- unacceptable behaviour in public, recognise emotion, appropriate dressing/ grooming/ topics of conversation. Social/sexual disinhibition.
- **Complex attention**- difficulties in environment with multiple stimuli, multi-tasking, normal tasks take longer with repeated checking.

Physical Examination

- Look for localising neurological signs- UMN signs, visual/ auditory deficits, extrapyramidal signs, movement disorders, gait disorders, eye movements.
- Basic office cognitive assessment- AMT, MMSE, MOCA, clock drawing. No one test is superior to the others. Useful to monitor progress. Abnormal test is not diagnostic and may miss early / subtle cognitive changes.

Dementia Workup

- Basic blood investigations- FBC, UE, glucose, TFT, LFT, folate, B12, Ca^{2+}, PO_4^{3-}, syphilis. Consider HIV if indicated.
- Imaging- either CT or MRI brain.
- Other tests (if indicated)- sleep studies, EEG, LP- CSF for autoimmune panel, HIV, infection, genetic tests. SPECT, Amyloid PET, FDG-PET.
- CSF fluid for amyloid and tau for a more definitive diagnosis of AD. Currently a research tool, not recommended as a general tool.

Disclosing the Diagnosis

- May be distressing. Currently no available cure. So why bother?
- There are clinically and cost effective treatment options available.
- Education and caregiver support to prevent burnout.
- Early conversations on Advanced care Plans (ACP) and Preferred Plans of Care PPC) and End of Life Care when the patient still has mental capacity.
- Referrals to community services.
- Delay nursing home placement.
- Opportunity to enroll in research.

Management of AD

- Assess the ABC- ADL, BPSD and cognition. Reassess cognition every 6/12.
- Identify caregiver and other informal support.
- Caregiver education and support- community services, support group, legal/financial support, respite care, future care needs.
- Assess and manage co-morbidities.
- Develop a mutually agreeable care plan- AChEI, CVS risk factors, referrals to community services.
- Watch out for elder abuse esp poorly managed BPSD.
- Notify LTA when driving is no longer safe for other road users.

Biomarkers and AD

- AD is associated with low CSF $A\beta_{42}$ levels and positive amyloid deposit on amyloid PET scan. All patients with AD have positive scans for amyloid PET.
- CSF tau correlates with neuronal injury. Total Tau is not specific for AD, phosphorylated tau is specific for AD. Total Tau is high with ischaemic and traumatic brain injury.
- FDG-PET measures brain metabolism and is indicative of synaptic activity. Decreased FDG-PET uptake is indicative of AD.
- Structural MRI provides volume and severity of atrophy. Location of brain atrophy may help with diagnosis.

Biomarkers

- 20-40% of normal older adults demonstrate evidence of Aβ deposit.
- Pre-dementia stage- MCI, if correlated with positive CSF biomarkers may enhance diagnostic specificity.

<u>Imaging and CSF Biomarkers:</u>

- **Brain A plaque deposit**

1. CSF $A\beta_{1\text{-}42}$
2. PET $A\beta$ imaging

- **Neurodegeneration**

1. CSF tau
2. Fluorodeoxyglucose-PET (FDG PET)
3. Structural MRI

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Case 1

- 65 year old lady was brought in by her daughter for assessment of ?dementia.
- History of increasing difficulties with answering questions correctly. Occasionally misplaces her keys and searches for her IC. IADL and ADL are all independent. Physical examination was unremarkable. AMT 2/10, MMSE <10 because of expressive aphasia.
- Dementia work up was unremarkable. MRI brain showed cerebral atrophy, with predominance over left frontotemporal areas.

Case 1

Diagnosis:

- Alzheimer Disease
- Vascular Dementia
- Fronto-Temporal Dementia- language deficit (primary Progressive Aphasia)

Primary Progressive Aphasia

- Early onset- 55-65. Male > Female.
- Insidious onset and gradual progression of word finding, object naming or word comprehension.
- ADL limitations are due to language deficits.
- Absence of apathy, disinhibition, STML, visuospatial / visual recognition deficits in the initial 2yrs.
- Other domains may be affected after 2yrs, with language being the most impaired.
- Neurodegenerative disease with absence of stroke or space occupying lesions on imaging.

PPA

- Can be either fluent or non-fluent.
- Speech is often halting because of word finding difficulties. Fluent aphasia shows patient circumventing word finding difficulties with use of generic/loosely fitting words, substitution of words by fillers, substitution of incorrect words with similar sounds.
- Speech is empty with preserved melody and fluency but no information.
- Function and memory are largely preserved initially.

- M Mesulam. Primary Progressive aphasia. Ann neurol 2001.; 49: 425-432.

Case 2

- 70 year old man brought in by family complaining of strange behaviour, worsening over 4+yrs.
- “Getting very lazy”, behave like a “different person”, overly friendly towards strangers, happy, embarrassing behaviour in public areas like restaurants, buys 15 packs of fish balls daily. No severe memory complaints, still IADL and ADL independent.
- Physical findings unremarkable. Dementia workup unremarkable. MRI showed cerebral atrophy, predominance over frontotemporal lobes.

Case 2

Diagnosis:

- Alzheimer Disease
- Frontotemporal dementia (behaviour variant)
- Mixed dementia (AD + VaD)

Case 2

- Gradually, goes out less. At home, paint on the walls words saying his family torture him, threw A4 papers with “they are trying to kill / poison me, please call police” out of the house windows. Police were called several times.
- Significant dysphagia after a year of follow up. Requiring tube feeding.
- Developed widespread muscle wasting with proximal and distal weakness. Eventually diagnosed with motor neurone disease by neurologist.

Behaviour Variant Fronto Temporal Dementia

- Younger onset. 45-65. Familial link Chr 9p13.2-21.3.
- Predominance of the behavioural symptoms and early emergence are typical of BvFTD.
- Overlaps with motor neurone disease. 10% of FTD develop clinical and pathological evidence of MND. There is also overlap of extrapyramidal disorders like PSP and CBD with FTD with similar tau pathology.
- Change in personality, interpersonal conduct, emotional recognition, apathy, executive dysfunction, repetitive / stereotypic behaviour, change in eating behaviour.

BvFTD

- Lack of social cognition- empathy, emotional coldness, difficulties understanding other people's views, understanding sarcasms, understanding situations which require moral judgement.
- Psychotic symptoms- delusion and hallucinations are uncommon, except for FTD+MND.
- Challenges in making a diagnosis- behavioural changes often go unnoticed, until it upsets the caregivers. Cognitive tests are often normal.
- No specific Rx available. Symptomatic and supportive Rx. SSRI are commonly used to treat behaviouarl symptoms- eating disorders, impulsiveness and disinhibition-mixed results. Memantine also mixed results. Atypical antipsychotics for agitation and aggression works.

Case 3

- 72 year old man who works at a local coffee shop was brought in by her daughter with complaints of strange behaviour.
- She said her father was noted to be seeing strangers in his house, tidying up the house, sweeping, cleaning and putting away his valuables. On several occasions, he actually took orders for drinks for these visitors and to his dismay, after he brought back their drinks, they have all “left”.
- He was still independent and going to work, with no complaints from the customers/ owner.
- There were occasions when he would get up in the middle of the night to buy coffee for his “visitors” and got lost coming back.

Case 3

- Past medical history is only significant for asteototic eczema which he needed 4 hospitalisations in the prior 6/12 for flare ups. His daughter noticed that few days prior to skin flares, he would become more confused and the behaviour worsened.
- During his stay in hospital, he was given piriton / hydroxyzine by dermatologist and risperidone / quetiapine by psy for psychosis. Every admission, his mental state deteriorated and on occasions NG tube was inserted for low GCS.

Case 3

- Physical examination and dementia work up were all unremarkable. Gait was slow, wide based.
- Multiple CT brain scans were all unremarkable.

Case 3

Diagnosis:

- Alzheimer Disease
- Delirium
- Vascular dementia
- Mixed AD and VaD
- Lewy Body dementia

Lewy Body Dementia

Dementia- progressive decline in cognition of sufficient magnitude to interfere with IADL / ADL, is an essential to the diagnosis.

- Fluctuations- like delirium. Spontaneous alterations in arousal, attention and cognition. Changes in behaviour, blank stares, drowsiness, incoherent speech.
- Visual hallucination- 80% of DLB have recurrent complex and well formed visual hallucinations, sometimes accompanied by passage hallucination, sense of presence and visual illusions.

DLB

- Parkinsonism- 85% of DLB. Not due to drugs/ stroke. Presence of 1 of the following- bradykinesia, rigidity, tremor.
- REM sleep disorders.

Supportive features:

- Severe sensitivity to antipsychotics- instability, falls, syncope, episodes of unresponsiveness, autonomic dysfunction, hypersomnia, psychosis, anxiety, depression.

DLB

- Patients with DLB are especially susceptible to develop delirium with anticholinergic / antipsychotics.
- Evidence supporting rivastigmine and donepezil use in improving cognition, function and ADLs. Clonazepam may be an option for management of REM sleep disorders.
- Symptomatic management of BPSD symptoms and caregiver support.

- Ian G Mc Keith et al. Diagnosis and management of dementia with Lewy Bodies. Fourth consensus report. Neurology 89, July 4,2017.

Role of Primary Care

- First point of contact for patients / relatives who are worried about dementia.
- Exclude potentially reversible causes- depression, thyroid diseases, vitamin B_{12} deficiency.
- New or cognitive decline which progresses rapidly should not be labelled as common dementias. Exclude delirium, find cause(s) and manage appropriately.
- Refer to a specialist centre for further work up, confirm diagnosis and initiate treatment for atypical cases.
- Complementary role with the specialist centre in care provision, caregiver support, referral to community services.
- Screening for dementia? Case find is probably more sensible.
- Caution with anticholinergic drugs.

Thank you

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