

Dementia: Reversible & Treatable?

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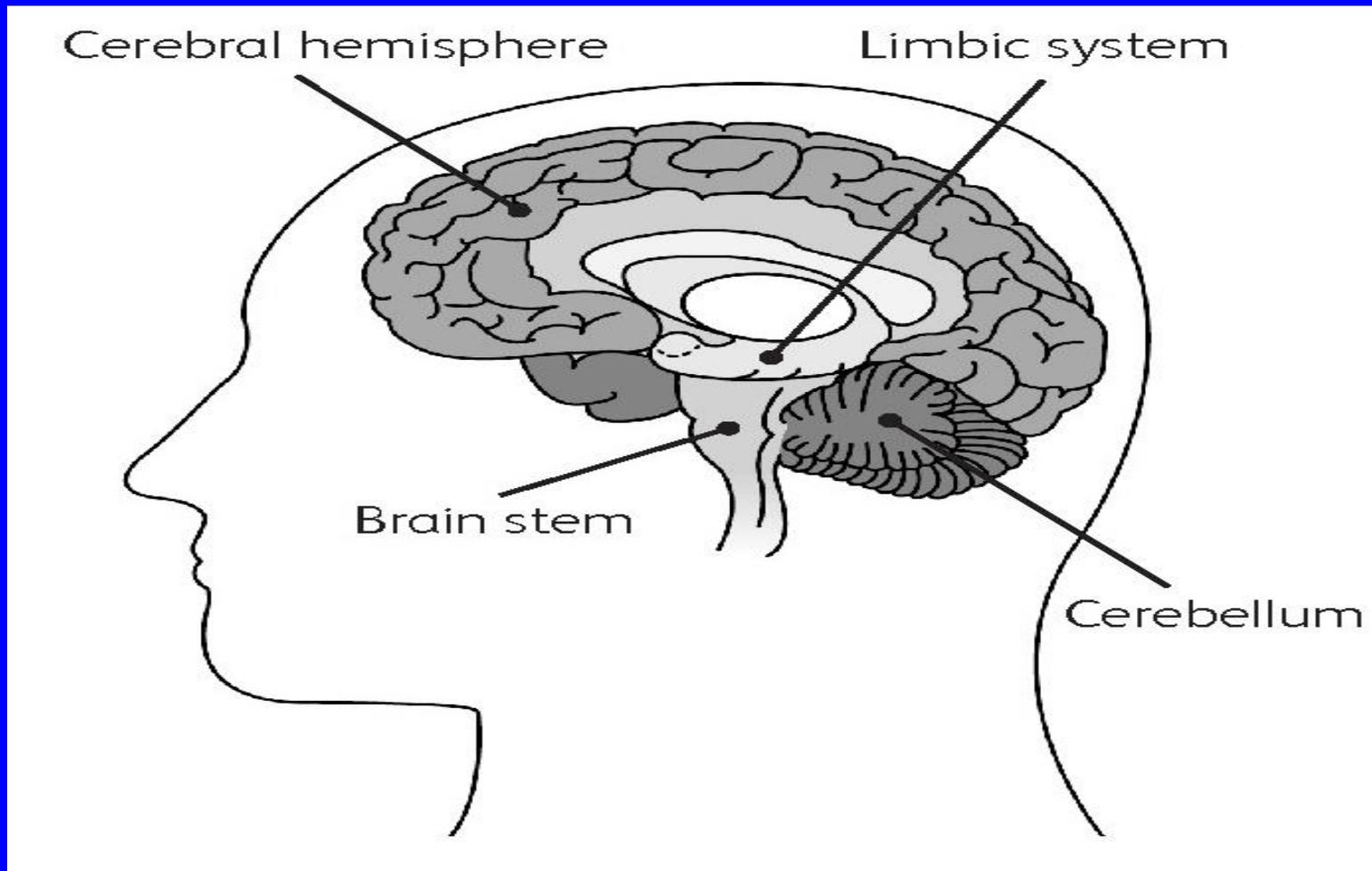
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The Brain

A brief reminder of
structures and functions

The brain



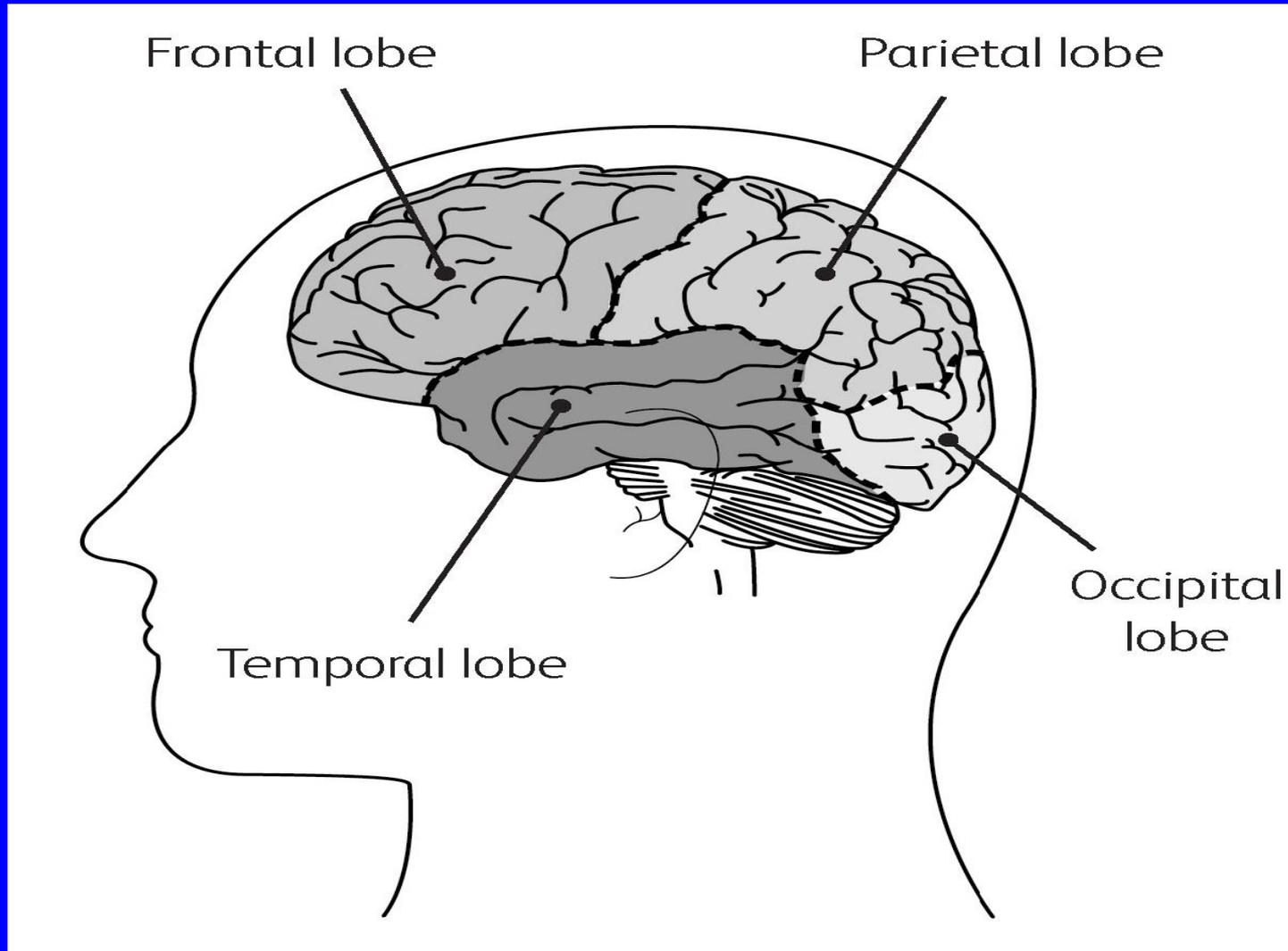
The brain

- The brain can be divided into different parts: the brain stem and cerebellum, the limbic system, and the cerebral hemispheres
- **The brain stem** is at the base of the brain. It controls basic bodily functions such as heartbeat and breathing
- The nearby **cerebellum** controls balance and posture

The brain

- **limbic system** is deep inside the brain. It links the brain stem and the cerebral hemispheres. The limbic system includes structures with key roles in memory (the hippocampus) and emotions (the amygdala).
- **Cerebrum** makes up $\frac{3}{4}$ of the brain and responsible for consciousness, memory, reasoning, language and social skills.
- A deep groove that runs from the front to the back of the cerebrum divides it into left and right halves: the two cerebral hemispheres.

The Lobes of the Brain



The lobes of the brain

- The cortex of each cerebral hemisphere is divided into lobes. There are four lobes in each hemisphere.
- **Occipital lobes** at the back of the brain deal with visual information.
- **The parietal lobes** are in the upper-rear part of the brain. They mainly handle information from our senses about space, perception and size

The lobes of the brain

- **The temporal lobes** are on either side of the brain, near the temples. They deal with memory (including recognition of faces and objects) and language.
- **The frontal lobes** are large and complex. They have a wide range of functions. They deal with solving problems, setting goals and making decisions, as well as with starting, carrying out and finishing tasks.
- This management role is called 'executive function'

Dementia

Of old and new songs

Prevalence & Burden

- One study (1995) prevalence rates of dementia and Alzheimer's disease in Ibadan were 2.29% and 1.41%, respectively.
- In 2006, another study reported 10.1% in same Ibadan
- In 2006, a study in Jos reported 6.1%
- In Africa, average Prevalence of 2.4%

Dementia as it was then known?

- 2011

- National Institute on Aging and the Alzheimer's Association (NIA/AA) published new diagnostic guidelines for Alzheimer's disease.
- The original guidelines had not been updated for 27 years.
- The aim of the new guidelines was to improve current diagnosis, and establish research priorities for the future.

Dementia as it was then known?

- 2013
- American Psychiatric Association (APA) published the DSM-5.
- Dementia has been renamed '**major neurocognitive disorder**', which also recognises earlier stages of cognitive decline as '**mild neurocognitive disorder**'.
- The aims of this reclassification include reducing stigma associated with dementia and bringing the diagnostic guidelines into line with current practise

NIA/AA, DSM-5 & ICD-11

- Many similarities btw NIA/AA & DSM-5
- BUT, NIA/AA primary focus on future research directions, while the DSM-5 focuses exclusively on clinical diagnosis
- NIA/AA guidelines for Alzheimer's disease only, while the DSM-5 includes diagnostic criteria for various causes of cognitive impairment, & forms of dementia
- ICD-11 due for release in 2017 and may adopt the DSM-5 views and concept

Name Dementia still alive!!!

- The introduction of 'NCD' does not mean that 'dementia' will no longer be used.
- DSM-5 includes 'or dementia' in parentheses when referring to major NCD, in recognition of dementia's history and familiarity.
- The new diagnostic criteria will also not have an immediate impact on diagnosis in clinical practice, which relies on many other factors in addition to the diagnostic guidelines.

So what are NCDs

- NCDs are characterised by cognitive impairment as the most prominent and defining feature of the condition.
- The term '**cognitive**' broadly refers to thinking and related processes, and the term '**neurocognitive**' was applied to these disorders to emphasise that brain disease and disrupted brain function lead to symptoms, and that, in most cases, such disruption can be reliably measured.

Cognitive domains affected

1) *Complex attention*

- includes sustained attention, divided attention, selective attention and information processing speed

2) *Executive function,*

- includes planning, decision making, working memory, responding to feedback, inhibition and mental flexibility

3) *Learning and memory*

- includes free recall, cued recall, recognition memory, semantic and autobiographical long term memory, and implicit learning

Cognitive domains affected

4) *Language*

- includes object naming, word finding, fluency, grammar and syntax, and receptive language

5) *Perceptual-motor function*

- includes visual perception, visuo-constructional reasoning and perceptual-motor coordination

6) *Social cognition,*

- includes recognition of emotions, theory of mind and insight

Mild NCD

- Diagnosis requires evidence of **modest** cognitive decline from a previous level of performance in one or more cognitive domains.
- These decline must be **INSUFFICIENT** to interfere with independence in daily activities, although greater effort and compensatory strategies may be required to maintain the level of independence.
- cognitive deficits must not be due to another mental disorder (such as depression).

Major NCD

- Diagnosis requires evidence of **significant** cognitive decline from a previous level of performance in one or more of the cognitive domains outlined above.
- Additionally, decline must be **SUFFICIENT** to interfere with independence in activities of daily living.
- The cognitive decline must not be attributable to another mental disorder.
- The criterion of maintenance or loss of independent functioning represents the key distinction between mild and major NCD.

Subtypes of NCD

- Diagnosing mild or major NCD should be followed by an examination of potential causes so that a subtype can be assigned.
- In many people with NCDs, there is evidence of a causative disorder, such as Huntington's disease or HIV infection.
- In others, the cognitive symptoms emerge first and progression provides evidence of a causative disorder such as Alzheimer's disease or Lewy body disease.

Reversible dementias?

How Reversible are 'Reversible
Dementias'?

Differential Diagnosis

- Consideration of the differential diagnosis of dementia is a complex process, and accurate diagnosis is challenging.
- Primary degenerative dementias result from irreversible aetiologies, such as beta-amyloid deposition, inclusion of Lewy bodies, tau-pathies or other dysfunctional proteins
- Whereas, Reversible dementias are secondary to other treatable conditions

Differential Diagnosis

- When patients present with cognitive symptoms, especially in the younger age groups, the first thought of the attending neurologist should be to try to identify an underlying treatable cause
- Reversible dementias comprise different groups of variable aetiologies, such as structural brain lesions or metabolic, infectious, toxic, autoimmune, paraneoplastic and psychiatric disorders

Approach to reversibility

- The incidence of degenerative dementia rises with older age and its symptoms progressively become more evident and typical; in such cases, the differential diagnosis is limited and the chance of uncovering a treatable disorder is minimal.
- However, in patients with younger onset dementia, the process is different. The possibility of revealing a reversible cause is higher and the differential diagnosis and work-up are broadened.

"Traditional" causes of Reversible Dementia

Structural Brain Lesions

- **Normal Pressure Hydrocephalus (NPH)** presents with the classical triad of gait disturbance, memory complaints and urinary incontinence. CSF drainage recommended.
- **Subdural haematomas and brain tumours** are also likely to see a resolution of their cognitive symptoms after surgical treatment.

"Traditional" causes of Reversible Dementia

Alcoholic Dementia

- Deterioration in cognition, behavioural changes and personality changes are well known to result from chronic alcohol abuse.
- Still not clear whether there is a direct toxic effect or a secondary cognitive decline due to other factors related to alcohol consumption.
- Abstinence may improve cognition, but true reversibility is uncertain.

"Traditional" causes of Reversible Dementia

Nutritional Disorders

- **Vit B12 deficiency** may cause subacute combined degeneration, psychiatric symptoms, multiple-sclerosis-like syndrome, delirium and dementia or cognitive impairment.
- Even after B12 supplementation in patients with low serum cobalamin, most studies still show lack of evidence of resolution of dementia- **epiphenomenon rather than a cause of cognitive deterioration?**

"Traditional" causes of Reversible Dementia

Nutritional Disorders

- Wernicke's encephalopathy and Korsakoff's syndrome are potentially treatable after alcohol withdrawal and nutritional supplementation.
- Wernicke's encephalopathy is characterised by the triad of ophthalmo-paresis, ataxia and confusion, and is a consequence of thiamine deficiency.

"Traditional" causes of Reversible Dementia

Endocrine Disorders

- **Hypo and hyperthyroidism**, can potentially cause depression and memory dysfunction.
- With the stabilisation of thyroid function, mood and memory may return to normal.
- **Idiopathic hypoparathyroidism** is a rare disorder that causes cerebral calcification or Fahr's disease. As the disease progresses, dementia appears, together with other neurological complications such as epilepsy, Parkinsonism and raised intracranial pressure. Treatment is mainly symptomatic and dementia symptoms partially resolve.

"Traditional" causes of Reversible Dementia

Metabolic Disorders

- Electrolyte disturbances and hepatic, renal or pulmonary insufficiency may present as transient cognitive impairment that can mimic dementia.
- Cognition may be restored after treatment of the underlying disorder.
- Wilson's disease is an autosomal recessive disorder of copper metabolism. Manifestations include psychiatric and movement abnormalities resulting from copper accumulation and toxicity.
- Treatment is through chelation with trientine and zinc supplementation. Cognitive symptoms are also present and improve with therapy.

"Traditional" causes of Reversible Dementia

Toxic Conditions

- Exposure to toxic agents may occur in some professions and cause neurocognitive impairment.
- For example, **lead exposure** causes lead encephalopathy in industrial workers. Heavy metals such as **mercury, bismuth, aluminium, manganese and arsenic** have also been implicated in dementia symptoms. **Carbon monoxide intoxication** can present with confusion and altered memory.
- Most of these symptoms are often not reversible; however, sequestration of the offending agent may prevent further clinical decline.

"Traditional" causes of Reversible Dementia

Psychiatric Disorders

- **Depression** in older people was initially thought to cause dementia-like symptoms. However, depression may actually be the first symptom of a dementia illness.
- Older people who were treated for depression showed improvement in cognition without absolute reversibility of dementia, indicating a possible overlap between the two conditions in older patients.
- The question still is: does pseudo-dementia really exist or are we dealing with pseudo pseudo-dementia?

"New" causes of Reversible dementia

Epileptic Disorders

- **Transient epileptic amnesia** is a syndrome characterised by recurrent, brief attacks of memory loss in middle-aged or older people, usually after sleep, associated with symptoms of temporal lobe epilepsy (automatisms, electroencephalogram findings, etc.).
- It is a benign syndrome that is responsive to antiepileptic medication, but complete resolution of cognitive symptoms is unusual.

"New" causes of Reversible dementia

Autoimmune Encephalopathies (AEs)

- AEs (or **autoimmune dementias**) is a newly proposed term for dementias underlying an autoimmune process. They constitute a heterogeneous group of disorders that may present with cognitive decline
- With the discovery of antibodies such as anti-Yo, anti-Hu and anti-Ri, which are related to paraneoplastic disorders, the spectrum of potentially treatable dementias has been broadened

"New" causes of Reversible dementia

Autoimmune Encephalopathies (AEs)

- A favourable prognosis is achieved with resection of the underlying tumour and/or immunosuppression
- **Hashimoto's encephalopathy** is another potentially treatable disorder that presents as rapidly progressive dementia accompanied by myoclonus, epileptic seizures and altered level of consciousness.
- Steroid initiation is the treatment of choice, with immediate improvement (steroid-responsive encephalopathy).

"New" causes of Reversible dementia

Inflammatory Vasculopathies

- Other inflammatory or autoimmune diseases may present with CNS involvement. SLE, Sjögren's syndrome, Behçet's disease, antiphospholipid syndrome and sarcoidosis can affect CNS vasculature.
- Isolated CNS angiitis is another condition that may initially present with cognitive symptoms.
- The diagnosis of these disorders is usually difficult and requires a high degree of suspicion.

"New" causes of Reversible dementia

Infections

- Infections of the CNS such as cryptococcal meningitis, Lyme disease, Whipple's disease, syphilis and HIV could induce dementia symptoms.
- Early mgt of these infections may result in reversibility of the cognitive impairment.
- However, permanent damage & irreversibility of the cognitive symptoms is not an unusual scenario in untreated or undetected cases.

"New" causes of Reversible dementia

Infections

- **HIV dementia** is irreversible, but HIV-related neurocognitive impairment may be reversed by highly active antiretroviral therapy.
- Treatment response is strongly related to the neurocognitive status of the patient prior to initiation of treatment
- Cognitive symptoms are a late complication of **neurosyphilis**. Diagnosis is easy and based on the evaluation of serology for *Treponema pallidum*.

"New" causes of Reversible dementia

Medications

- Many drugs that can provoke cognitive impairment, especially in older people who are susceptible to polypharmacy and drug-drug interactions.
- Benzodiazepines, antipsychotics, antiepileptics and tricyclic antidepressants are implicated in worsening memory and executive functioning.
- Newer and older antiepileptic drugs, such as topiramate and sodium valproate, have been implicated in worsening cognition.
- Cognitive symptoms may be reversed after withdrawal of the responsible drug

So, what do we know about reversible dementias?

- Reversible dementias comprise a group of diseases with different aetiologies.
- With a detailed history, a thorough clinical examination and sometimes extensive laboratory investigations, a treatable cause of dementia is often difficult to be reached but can alter the patient's progress.
- Traditional treatable dementias, such as those arising from NPH, brain tumours, B12 deficiency, endocrine disorders and depression, are partially reversible

So, what do we know about reversible dementias?

- Reversibility depends on the time of diagnosis and concomitant medical problems. In vitamin B12 deficiency, for example, if supplementation can be started early, stabilisation of memory complaints and improvement may be seen - however, many people with dementia present with low serum B12 concentrations
- For autoimmune dementias, with an accurate diagnosis and early treatment, the chance of reversibility is higher.

Are the "Irreversible" Dementias Treatable?

Arresting the degeneration and
treating the symptoms

Major NCDs

Pharmacologic - FDA approved

- 2 major types - Acetylcholinesterase Inhibitors & NMDA Receptor antagonists
- ACE-I - Donezepil (Aricept), Rivastigmine (Exelon) and Galantamine (Reminyl, Razadyne, Acumor, Gatalin); Tacrine (no longer prescribed due to possible liver damage)
- NMDA-RA - Memantine (Ebixa)
- Between 40-70% of patients taking these drugs report benefit

Major NCDs

Pharmacologic - FDA approved

- ACE-I prevent ACE from breaking down Acetylcholine in the brain. The increased concentration of acetylcholine (which normally helps to send message between certain nerve cells) leads to increase communication between cells.
- Memantine regulates activity of glutamate, which is involved in information processing, storage and retrieval
- While Galantamine & Rivastigmine are usually prescribed for Mild to moderate problems , Memantine is for Moderate to severe and Donezepil for all stages

Major NCDs

Behavioural and Psychological symptoms

- Before considering medications, any person with dementia who developed these symptoms should be assessed to try to establish any possible underlying factors that may trigger them
- Simple non-drug treatments like Reminiscence therapy and Social Interaction may prevent need for drugs
- Example of treatment include Massage, CBT, music and dance therapies
- With drugs, immediate results should not be expected

Major NCDs

Behavioural and Psychological symptoms

- **Antipsychotic medications** can help reduce the intensity of psychotic symptoms like hallucination and delusion
- Risperidone is the only antipsychotic medication licenced for use (Although haloperidol can be used)
- Helpful for people with alzheimers, vascular dementia or mixed dementia
- Using antipsychotics for Lewy body dementia must be with caution as they often have high risk of adverse effect

Major NCDs

Behavioural and Psychological symptoms

- **Antidepressants and anti-convulsants:** Specifically Setraline and Citalopram may help reduce agitation and antidepressants may also treat apathy
- There is evidence that Carbamazepine can be effective for treatment of aggression
- **Antidementia** drug like ACE-I & Memantine has also been shown to be effective for behavioural and psychological symptoms in alzheimers
- In Lewy body dementia, care must be taken and other methods must be tried first
- For vascular dementia, ACE-I should not be used

Major NCDs

Behavioural and Psychological symptoms

- **Sleep medications:** It is better to use one of the newer generation tranquilisers like Zopiclone or Zolpidem.
- Trazodone, a sedative antidepressant may also be used instead

Mild NCD

- Several definitions and descriptions have existed for the state between normal cognitive aging and dementia
- "Questionable Dementia", "Possible Incipient Dementia", "isolated short term memory loss", "amnestic dementia", "mild neurocognitive dementia", "mild cognitive impairment (MCI)" or of lately Mild NCD
- Persons with MCI are at high risk of progression to Alzheimers or other types of dementia

Mild NCD

- MCI have annual conversion rate of 10-15% to AD (compared with normal population with 1-2% rate)
- Follow up studies show that 80% of MCI convert to AD in about 6 years
- MCI has increasingly been focussed upon either to look for biomarkers of progression to AD or to find effective treatment that can provide neuro-protection from future progression to full AD

Mild NCD

- Neurology, functional imaging and volumetric imaging studies in probable AD patients and MCI suggest that cognitive deficit may be related to medial temporal lobe dysfunction
- Due to the high conversion rate, many pharmacological treatments have been tested to prevent or postpone this conversion

Mild NCDs

- Drugs under investigation
 - Insufficient evidence for ACE-Is
 - No convincing evidence to recommend the use of NSAIDs, Estrogen Replacement Therapy, Ginkgo Biloba, Vitamin E, Statins etc
 - Limited evidence of effectiveness of physostigmine for the symptomatic treatment of Alzheimer's disease

Mild NCDs-Dietary advice

Homocysteine and B vitamins

- Homocysteine is a neurotoxin, capable of directly damaging the medial temporal lobe, which is the area of the brain that rapidly degenerates in AD
- The lower your level throughout life the smaller your chances of developing serious memory decline..
- Homocysteine is easily lowered with inexpensive B vitamins

Mild NCDs-Dietary advice

Omega-3 fats

- Omega-3 fats are most prevalent in carnivorous, cold water fish such as salmon, tuna, herring and mackerel. According to a study (Morris et al, 2003), eating fish once a week reduces your risk of developing Alzheimer's by 60 per cent

Mild NCDs-Dietary advice

Antioxidants

- Inflammatory reactions invariably mean increased production of oxidants, and hence an increased need for antioxidants such as vitamin A, beta-carotene, and vitamins C and E, all of which have been shown to be low in those with Alzheimer's.
- Other antioxidants, including cysteine, glutathione, lipoic acid, and co-enzyme Q10 and melatonin may also prove important.
- In simple terms this means eating a lot more fresh fruit, vegetables, and oily fish

Mild NCDs-Dietary advice

Stress, cortisol and memory loss

- Under prolonged stress, the body produces the adrenal hormone cortisol.
- Although cortisol is a powerful anti-inflammatory hormone, raised cortisol can damage the brain, So postulated that brain cell loss in ageing and Alzheimer's may be, in part, due to high levels of cortisol
- Recommends that corticosteroid drugs should not be used in Alzheimer's patients for other medical problems like asthma or arthritis.

Mild NCDs

- Non- Pharmacological interventions may be promising for a number of reasons
 - Older adults may prefer non- pharmacological strategies to maintain cognitive function and community independence
 - non-pharmacological interventions have less risk of side effects
- Recommendations - Cognitive intervention, Physical activity, Psycho-social intervention showing benefit

Mild NCDs-Cognitive Intervention

- Cognitive training intervention can be grossly categorised into (1) Remediation or (2) compensation approaches
- **Cognitive Remediation** - attempts to improve cognitive functions through focussed training and practises
- **Cognitive compensation** focus on training individuals to maintain independence, safety or engagement in daily activities through the use of external aids or adapted methods

Mild NCDs-Cognitive Intervention

- From a review of 24 studies, 15 showed that cognitive intervention was of adequate benefit.
- Findings showed that Remediation may be more likely to improve selected cognitive abilities than compensation
- Review of 9 studies focusing on impact of cognitive change on activities of daily living also showed improvement

Mild NCDs-physical exercise and psychotherapeutic intervention

- Latest review (2015, not yet published) of 8 studies showed the benefit of Aerobic exercise for improved cognitive function
- However review of the studies on psychotherapeutic intervention reported no significant change in cognitive function

Short and long of it?

The earlier the better

- It is better to focus on detecting the symptoms and signs of cognitive decline at an early stage (Mild NCD) while it is still "reversible" and "treatable".
- Early intervention may help in preventing the conversion into the Major NCD
- Even the Major NCD stage is not a death sentence, with new discoveries we can help improve their cognition and help their daily living

Thank you

Questions?