

Alzheimer's disease in family practice

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Abstract

21 September 2009 is hailed as World Alzheimer's Day, creating awareness for the most common type of all the dementias. Senile dementia of the Alzheimer's type (SDAT) has a four to five year survival rate if a patient is living in the community and a much shorter survival rate for institutionalised patients. The family practitioner is often consulted first by family members who seek advice for a family member with suspected dementia and possibly Alzheimer's disease. Although a multi-disciplinary team approach is mostly needed, the family practitioner will in most cases co-ordinate referrals and advise family members on practical nursing aspects and decisions about institutionalisation. This article gives a short overview on SDAT, a classification of drugs used in dementia and a treatment approach to Alzheimer-specific pharmacotherapy.

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Prevalence

It is estimated that 10–15% of individuals over the age of 65 years suffer from some form of dementia and this incidence rises to 20% in individuals over the age of 80 years. Of those affected at present, 55% suffer from SDAT and 15% from multi-infarct dementia. Some 22% suffer from mixed forms of dementia of which the most important is Lewy body dementia. The remainder suffer from various other less common, but potentially reversible, conditions. Ten to twenty percent of patients who undergo further investigations for dementia will be diagnosed with another disease.

SDAT is more common in women than in men, with a higher incidence in less fertile women – 40% of the women in one study had no children. The incidence is also higher in the better-educated part of the population and it is said to be much lower in the Third World Countries.

Progression of disease and prognosis

SDAT takes approximately five years to develop and is the fourth or fifth most common cause of death in the United States of America. Its relentless downhill course usually results in death five to fifteen years after onset. The average post-institutionalisation survival time does seem to be quite consistently around two years. Larsson et al included data on age of onset and found the likely survival time between onset and death slightly less than five years for men and slightly more than five years for women. This obviously depends on the time of diagnosis and the age of the patient leading to a longer survival rate in patients diagnosed at a younger age.

Aetiology and histopathology

The cause of dementia is still unclear. Macroscopically SDAT is associated with brain shrinkage, with microscopic loss of neurons in the hippocampus and basal forebrain. Loss of cholinergic neurons is thought to underly

the cognitive deficit and loss of short-term memory is characteristic of SDAT. Extra-cellular amyloid plaques, consisting of amorphous extra cellular deposits of β -amyloid protein and intra-neuronal neurofibrillary tangles are the most important microscopic features.

Diagnosis

Alzheimer's disease (AD) can, therefore, only be confirmed on cerebral histology during autopsy and this is frequently performed for medico-legal purposes, often due to family inheritance disputes. In the clinical setting, however, the diagnosis of Alzheimer's disease remains difficult and often requires a multi-disciplinary approach. No single test can detect or confirm Alzheimer's disease. The disease is diagnosed by symptoms, findings on neurologic examination, and results from diagnostic tests. These tests help exclude other conditions that might cause the signs and symptoms.

Clinical features of SDAT

The essential feature of SDAT is the presence of dementia of insidious onset and a gradually progressive course for which all other specific causes have been excluded by history, physical examination and other specific investigations. The dementia involves a multifaceted loss of intellectual abilities, such as memory, judgement, abstract thinking and other higher cortical functions, as well as changes in personality and behaviour.

Other features that must be carefully assessed are:

Orientation for time, place and person

Immediate recall and memory of recent and past events

It is important to ascertain whether normal daily functioning is impeded. Articles are often mislaid and faces may not be recognised. There are misunderstandings and statements need to be repeated. Initially, there is difficulty in learning new information (short-term memory), but later

on, long-term memory is also affected. Increasingly, these people live in the past.

Personality and interpersonal relationships

These involve either an alteration or an accentuation of pre-morbid traits, such as histrionic, impulsive or paranoid traits. The patient becomes increasingly apathetic and withdrawn, and there is narrowing of social involvement. Personality loses its sparkle and afflicted people may become self-centred, hypochondriacal, cantankerous and slovenly.

Cognitive functioning

This relates to the arithmetic, abstract reasoning and synthesising functions of the brain. Patients may no longer read, listen to the radio, watch television or occupy themselves constructively. They are no longer able to grasp the essence of a conversation. Thinking becomes more concrete and the patient cannot cope with novel tasks. Inappropriate spending of money may be the first signs of impaired judgement and lack of impulse control.

Speech and linguistic ability

Language may become more vague and stereotyped, imprecise and dysphasic. Jargon dysphasia is common.

Emotional changes

Sensitivity, interest and affection may disappear and the subtle interchange of feelings and understanding in a relationship may become distressingly absent. These people are described as being "cold". Mood is not usually depressed and an emotional shallowness is more common.

It is vitally important to interview close relatives, or people who care for these patients on a daily basis as well. They will be more aware of subtle changes and will have an objective judgement as far as behaviour and emotional changes are concerned.

The diagnosis of Alzheimer's is therefore at best "probable", meaning that other causes of the symptoms have been ruled out and the most likely cause is Alzheimer's disease.

A complete physical examination should be performed, along with a detailed history of symptoms and medical history, including medications, especially alcohol and the possibility of other drug abuse.

Special investigations and referrals

In an attempt to identify early markers for "probable" Alzheimer's disease it has recently been proposed to add certain biomarkers as part of the criteria. The proposed criteria suggest that patients should, in addition, have at least one or more abnormal biomarker over and above the supporting tests:

- Structural neuro-imaging on magnetic resonance imaging (MRI) in order to confirm hippocampal atrophy, OR
- A specific metabolic pattern on molecular neuro-imaging with positive emission tomography (PET) and cerebrospinal fluid (CSF) analysis of amyloid-beta or tau proteins, OR
- The presence of one of three autosomal dominant mutations related to AD on genetic testing.

These criteria, however, still need to be validated, but may assist in making an early diagnosis before patients are demented.

In order to exclude other underlying psychiatric disorders and to determine which thinking and memory functions may be affected and to what degree, the patient should be referred to a psychiatrist. Cognitive

functions for attention, learning, recall, language and visuo-spatial abilities are measured. Test results are usually compared to the tests of other patients of similar age and education.

Examination by neurologists will help to identify signs of Parkinson's disease, strokes, tumors and other medical conditions that may impair memory and thinking (i.e. head injuries), as well as physical function.

Blood tests should aim to exclude vitamin deficiencies, anaemia, medication levels, disorders of the thyroid, kidneys or liver, and other factors that can cause memory loss.

Brain imaging may include computed tomography (CT scan), (MRI) and in some countries PET or single-photon emission computerised tomography (SPECT).

Current therapeutic approach

SDAT sufferers have a longer life expectancy if they are not institutionalised and if they are cared for by spouses or family members in a known environment. It is therefore ideal to delay institutionalisation for as long as the spouse and/or family members can cope and within the borders of self-dignity of the patient and overall affordability.

Other goals for SDAT patients living in the community are the following:

- Maintain, encourage and support activities of daily living and cognitive functions such as ability to participate in conversations, reading and writing, TV entertainment, radio and music
- Improve the patient's and caregiver's quality of life
- Limit care costs, hospitalisation, doctors visits, etc
- Maintain an acceptable level of personal hygiene and living conditions

The family practitioner will often have to facilitate discussions with spouses and family members and make important decisions regarding institutionalisation.

Drug development for dementia is particularly challenging and some of these difficulties have been outlined in Box 1. Research should, however, focus on better trial design and more accurate/sensitive rating scales. A classification of all the drugs that have, or may have an effect on patients suffering from dementia, irrespective of the cause, is outlined in Box 2.

The majority of these drugs have not shown significant benefit in the clinical situation, like the pre- and post-synaptic cholinergic drugs, some of the antioxidants and perhaps tacrine, the latter because of its hepatotoxicity.

Box 1: Why is it difficult to develop drugs for dementia?

1. Clinical improvement is not well understood or defined
2. The clinical relevance of the small degree of difference one sees in clinical trials on cognitive, ADL (activities of daily living) and clinical impression scales has not been established
3. Rating scales used in evaluating patients are not quantified or sensitive enough
4. Time necessary to achieve significant changes is extremely long
5. All clinical evaluations relate to symptoms, not to disease-modifying parameters
6. Disease progression varies substantially in different patients, which influences evaluation of efficacy
7. Disease severity is not adequately evaluated clinically, so time from diagnosis to institutionalisation or death is not a valid metric

Box 2: Classification of dementia drugs**A. Cholinergic deficiency****1. Pre-synaptic agents:**

These drugs either increase the synthesis of acetylcholine (ACh) or promote the release of ACh.

- Acetylcholine-precursors: choline or lecithin
- Increased ACh synthesis/release: piracetam, 4-amino-pyridine
- Selective muscarinic 2 receptor antagonists: gallamine, scopolamine
- Anti-cholinesterases: tetrahydroaminoacridine (THA)

2. Synaptic agents:

These drugs limit the removal of ACh from the synapse – Choline Esterase Inhibitors or CHEIs e.g. physostigmine and metrifonate.

- First generation: tacrine
- Second generation:
 - donepezil
 - galantamine
 - rivastigmine
 - butyrylcholinesterases
- NGF gene delivery

3. Post-synaptic agents:

Cholinergic agents acting directly on the muscarinic receptors:

Pilocarpine
Oxotremorine

B. Antioxidants

1. Selegeline
2. Alpha-tocopherol

C. Anti-amyloids

1. Statins
2. Aβ-vaccination
3. Immunotherapy – bapineuzumab, and A β-peptide antibody
4. Secretase effectors:
 - i) LY450139 a non-selective γ-secretase inhibitor
 - ii) Memapsin 2, (β-secretase)
5. Selective amyloid lowering agents (SALA)
 - i) Tarenflurbil – α γ-secretase modulator
 - ii) NSAID's – regulate γ-secretase

D. Excitotoxicity

Glutamate toxicity to neurons

- i) Memantine – NMDA receptor antagonist

E. Herbal and other drugs

- i) Huperzine A
- ii) Ginkgo Biloba
- iii) Mediterranean diet

Of all these drugs only the following four are registered for clinical use in dementia in South Africa:

- Donepezil (Aricept®)
- Rivastigmine (Exelon®)
- Galantamine (Reminyl®)
- Memantine (Ebixa®)

The first three drugs are indicated for mild to moderate SDAT, and memantine for moderate to severe SDAT.

The following key points will assist the practitioner to select drugs when treating an Alzheimer's patient:

- Cognitive symptoms of dementia can be improved by donepezil, galantamine and memantine

- Rivastigmine and tacrine can improve cognitive function in people with dementia, but may have high rates of adverse effects
- CHEIs often cause gastrointestinal, muscular and other side-effects
- There is no evidence that stopping CHEI treatment necessitates weaning
- No double-blind, randomised comparative trials have compared donepezil, galantamine and rivastigmine, so we do not know which one of these is the most efficacious.
- Agitation and aggression in the short term are best treated with carbamazepine rather than adding another Alzheimer drug.

A practical approach to treatment will be the following:

1. A thorough clinical examination and special investigations to exclude other causes of dementia
2. Treat underlying conditions and other chronic diseases like hypertension, diabetes, etc
3. Severity scoring of the dementia
4. Start with either a second generation or an excitotoxicity drug (memantine)
5. Start on a low dose and evaluate side-effects/tolerability in the first month, and efficacy over the next two months
6. Increase the dose to the maximum recommended dose if not efficacious
7. Add either a CHEI or memantine to the regimen, depending on which one was started first

In conclusion

Remember to take care of the caretakers! Emotionally, dementia often affects them more than the patients. The website of Alzheimer's South Africa is a valuable source of information for patients and family members and can be visited at www.alzheimers.org.za.

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Alzheimer's South Africa

Visit www.alzheimers.org.za for:

1. News on vacancies in care centres country wide
2. Patient information for family to understand the disease and how to care for family members suffering from Alzheimer's disease
3. Links to memory tests: <http://www.nationalmemorytest.net.au/> or visit www.gomemory.co.za and <http://www.memoryrehab.co.uk/> for a memory workbook
4. Alzheimer's posters and information booklets
5. National call line: 0860 102 681

