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Alzheimer's Disease: A Current Review

SUMMARY

Alzheimer's disease is characterized by a progressive decline in cognitive function from a previously established level, and is the most common cause of all the dementias. While the exact etiology remains to be determined, there are several theories about possible genetic, immunological, biochemical and viral causes. Clinical diagnosis is by exclusion of other established causes of dementia and requires a careful history, physical examination and, often, psychological testing. Definitive diagnosis is made at post-mortem, although some cases show none of the histological hallmarks such as neurofibrillary tangles or senile plaques. There is no effective preventive or therapeutic treatment. Symptomatic management includes pharmacotherapy, socialization, support for the patient and his family and, ultimately, institutionalization. Patients are best managed by an interdisciplinary team using community resources. (Can Fam Physician 1984; 30:595-599).

SOMMAIRE

La maladie d'Alzheimer est caractérisée par une détérioration progressive des fonctions cognitives à partir d'un niveau antérieurement établi, et elle est la cause la plus fréquente de toutes les démences. Bien que son étiologie exacte reste à déterminer, il existe plusieurs théories concernant la possibilité de causes génétiques, immunologiques, biochimiques et virales. Le diagnostic clinique s'établit par l'exclusion d'autres causes établies de démence et requiert une histoire et un examen physique minutieux et, souvent, une évaluation psychologique. Le diagnostic définitif s'établit à l'autopsie, bien que certains cas ne révèlent aucune des caractéristiques histologiques, tels les enchevêtrements neurofibrillaires ou les plaques de sénilité. Il n'existe pas de traitement préventif ou thérapeutique efficace. Le traitement symptomatique inclut la pharmacothérapie, la socialisation, un support pour le patient et sa famille et, ultimement, l'institutionnalisation. Le meilleur traitement pour ces patients est l'équipe interdisciplinaire utilisant les ressources communautaires.

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DEMENTIA IS A form of organic mental disorder, and is quite common in the geriatic population. Estimates of dementia in the over 65-year-old population range from 5% to 20%[2] with perhaps half this percentage suffering from mild forms. Prevalence rates for severe forms increase to about 20% of the population by age 80.[1, 2] It has been estimated that 50-70% of those affected with dementia in these populations suffer from Alzheimer's disease.[3, 4, 5] It has been estimated that 100,000 to 300,000 people in Canada are presently affected by Alzheimer's disease, and that as many as 10,000 people die of it each year.[6] These figures can only be estimates because Alzheimer's disease is never the immediate cause of death. Nonetheless, if the estimates are accurate, Alzheimer's disease is the fourth leading cause of death in the country.

Historical Background

Historically, dementia was thought to be caused by evil spirits,[7] although the word comes from the Latin "demtatus" meaning "out of one's mind". In 1845, dementia was classified into acute, chronic and senile varieties. The acute forms were thought to be caused by fever or hemorrhage, the chronic ones by masturbation and drunkenness, and the senile form by old age.[8] In 1907, Alzheimer, who had previously reported senile plaques in the brains of patients suffering from senile dementia, reported the occurrence of these changes and a second change which he labelled "neurofibril-

lary tangles'' in presenile dementia.[7] Thus, presenile dementia became known as Alzheimer's disease. The psychiatric nosology still maintains a difference between the presenile and senile forms of Alzheimer's type dementia.[9] However, because the clinical and pathological findings are basically the same regardless of age of onset, the medical literature no longer maintains any distinction.[10]

The disease strikes both sexes, and geographic location and race do not seem to have any relationship to incidence; however, there are few good epidemiological studies.[2] With the exception of prize fighting[11, 12] and isolated instances of Alzheimer's disease following acute head trauma,[13, 14] the disease does not appear to be related to occupation, common exposure or previous medical or psychiatric history.

Pathophysiology

From the turn of the century until the mid 1960s, Alzheimer's disease was thought to be caused by cerebral arteriosclerosis.[7] It remained for investigators to show that most patients who died of clinically diagnosed Alzheimer's disease had pathological findings similar to those originally described by Alzheimer and no excess of arteriosclerosis compared to controls without dementia.[15-19]

Normal aging is associated with a loss in overall wet brain weight and alterations of the synapses in the brain. In Alzheimer's disease this generalized atrophy is more marked, especially in the frontal and temporal areas. The hippocampus, a brain area associated with memory and learning, is also markedly affected.[20-22]

The classical microscopic changes are neurofibrillary tangles (masses of neurofibers arranged as paired helical filaments), senile plaques derived from degenerating neurites and granulovacuolar degeneration. However, these are not unique to Alzheimer's disease. All are found to a lesser extent in the normal aging brain.[23] They are also found in other types of dementias, most notably in dementia associated with Down's syndrome.[24]

The association between the pathological changes of Alzheimer's disease and Down's syndrome have led some investigators to speculate that Alzheimer's is a late onset form of Down's syndrome.[2] It has been speculated that because Down's syndrome is caused by information contained on chromosome 21, the cause of Alzheimer's may also be related to this chromosome.[7] One group of investigators found the prevalence of Down's syndrome to be five times greater than expected in the families of patients with early-onset Alzheimer's disease.[25] It has therefore been suggested that physicians consider offering amniocentesis to expectant mothers from families with early-onset or familial Alzheimer's disease, to detect the possibility of the fetus having Down's syndrome.[26]

A defect in the immune system of Alzheimer's patients has also been implicated in the etiology. The autoimmune theory rests on the possible immunological origin of amyloid in senile plaques and the increased levels of brain reactive antibodies in Alzheimer's disease. This process may be stimulated by virus induced neuronal alteration. There have also been reports of impaired T-cell function in patients with Alzheimer's disease, compared to age-matched controls.[20, 21, 27] Some investigators have studied the relationship between HLA antigens and Alzheimer's disease. It appears that there are more B7 and CW3 antigens in patients with Alzheimer's disease.[28, 29] The clinical significance of this finding is unclear; however, these same antigens are not found in increased numbers in patients suffering from Down's syndrome.[2]

Aluminum toxicity has been suggested as a possible cause of Alzheimer's disease. Early studies suggested that high aluminum levels in the nuclei of neurons containing paired helical filaments were one of the neuropathological hallmarks of Alzheimer's disease.[30-32] However, while aluminum is neurotoxic to rabbit brain, the neurofibrillary tangles produced are morphologically distinct from those found in Alzheimer's disease.[33] There are conflicting results about aluminum levels in cerebral tissue.[34, 35] In addition, serum aluminum levels have been normal in patients with Alzheimer's disease, making environmental exposure an unlikely etiology.[32]

Perhaps the leading, though still unproven, theory implicates slow viruses. Various viral encephalitides cause psychiatric and neurological sequelae many years after the acute infectious attack. Examples include subacute sclerosing panencephalitis following measles and postencephalitic Parkinson's disease culminating in dementia.[36] Experiments have shown that virus-like agents from the brains of patients with Alzheimer's disease and Creutzfeldt-Jakob disease can be transmitted to experimental animals.[37-39] Nonetheless, definitive proof is difficult to obtain because incubation periods can be as long as 30 years.

It has been suggested that Alzheimer's disease is transmitted as an autosomal dominant disease with incomplete penetrance or with age-dependent penetrance. Polygenic factors have also been suggested.[2] In one study of 125 autopsy-proven cases, 40% were found to be familial.[25] There appears to be an increased risk among first order relatives, especially when the disease occurred early in life and when a parent of the victim also suffered from Alzheimer's disease.[20, 21, 25]

The most significant recent advances have been in studies of neurotransmitters and the enzymes involved in their metabolism. The major finding has been that choline acetyl transferase, the enzyme that synthetizes acetylcholine, is decreased in patients with Alzheimer's disease. The decrease is most marked in the cerebral cortex, hippocampus and amygdala—areas which correlate to the clinical pathology.[40, 41] Attempts to augment the cholinergic nerve endings by using acetylcholinesterase inhibitors such as physostigmine or by supplementing the diet with choline and lecithin have been unrewarding so far.[42, 43] Other peptide neurotransmitters such as somatostatin and vasopressin have also been shown to be decreased in the brains of patients with Alzheimer's disease and may be an important factor in the pathophysiology.[40]

Diagnostic Considerations

The family physician is often the first to see patients who have symptoms of dementia. These patients present with deterioration of memory, thinking and conduct. They are usually accompanied by a family member, who often initiates the consultation and provides important historical background.[44] It is important to remember that there are many other causes of dementia, some of which can be reversed or arrested (see Table 1).

The history, physical examination and investigations must therefore be directed towards ruling out treatable causes of dementia.

Early changes involve the loss of short-term memory, which causes patients to forget actions and events which have just occurred.[44, 45] Patients may also repeat questions, even after responses have been given, and forget names, addresses and other pieces of common but essential information. Impaired judgment may be manifested by subtle changes. For example, the patient may make unnecessary purchases, unreasonable decisions or errors. Patients with Alzheimer's disease often suffer more distress in the evening or at night; they display increased symptoms of severe agitation, aggression and paranoid behavior. Patients may present with vague symptoms, including the inability to think as quickly and efficiently as they used to, difficulty in coping with new decisions or new situations, suspiciousness and increased outbursts of temper. Eventually a spouse, relative or employer becomes aware of the gradual deterioration and arranges a consultation with the family physician.

The initial assessment requires a thorough, general physical examination, including a neurologic examination. It is imperative that a mental status examination be performed to assess alertness, attention, orientation, memory, comprehension, calculation and language. When more detailed neuropsychological testing is available, it extends the mental status examination with more objective and comprehensive methods. These methods may be useful in differentiating dementia from other neurologic and psychiatric conditions.[46]

Three stages of clinical progression and corresponding behavioral changes have been described.[7] In the first stage, known as the 'forgetfulness' phase, only a subjective cognitive deficit exists. Onset is insidious and the patient and family are often unaware that any change has occurred. The patient may sense a lack of energy manifested by slower reactions to situations and may tend to blame others, rather than himself, for problems he encounters.[47] This may be accompanied by increased anxiety.

Stage two or the 'confusional' phase is characterized by a definite impairment of cognitive functioning. The patient may require help for specialized tasks such as writing checks, shopping and travelling on public transit. Remote memory generally remains intact during this stage. Vocabulary is largely unaffected, but the patient may find it difficult to recall appropriate words. At this point, the patient and/or his family are likely to seek medical attention. In stage three, the 'dementia' phase, memory and the ability to learn are obviously disabled. A distinct memory loss is evident, as is global disorientation. Constant care will be required if the process continues. Death results from complications of being bedridden (e.g., from pneumonia or other infections).

Differential Diagnosis

While history, physical, laboratory and mental status examinations are usually sufficient to exclude other causes of dementia, nothing short of brain biopsy can confirm the diagnosis of Alzheimer's disease. Many of the early signs are easily confused with depression, drug or alcohol induced dementia or other reversible organic brain syndromes. These must be ruled out (see Table 1).

One major pitfall is the difficulty of distinguishing depressive pseudodementia from Alzheimer's disease.[47] Depressed patients often show a transient cognitive dysfunction with a clear onset and marked disturbance of affect. The patient is nearly always aware of deficits, is quite distressed, and cooperates poorly on psychological testing. Also, patients with depressive pseudodementia show the usual vegetative signs of depression: sleep disturbances, lack of energy and lack of pleasure. The onset of Alzheimer's disease is more gradual, and the patient exhibits little insight and may be unaware of deficits. Also, the patient shows good cooperation and effort on testing (see Table 2).

Patients with focal brain disorders, such as strokes, tumors, abcesses, and hematomas, may present with symp-

TABLE 1
Causes of Dementia

Central Nervous System

Degeneration
Alzheimer's disease
Pick's disease
Huntington's chorea
Parkinson's disease
Progressive supernuclear palsy

Metabolic and Endocrine
Hypothyroidism
Hypopituitarism
Hypoparathyroidism
Hyperparathyroidism
Addison's Disease
Cushing's Syndrome
Hyperinsulinism
Chronic electrolyte disturbance
Wilson's disease
Paget's disease
Porphyria
Hepatic, renal or pulmonary disease
Hypoxia of any etiology

Toxic
Numerous medications
Alcohol
Heavy metals

Other
Normal pressure hydrocephalus
Trauma
Sarcoid
Seizure disorders
Multiple sclerosis

Vascular
Multiinfarct Dementia
Carotid artery insufficiency
Cranial arteritis
Subarachnoid hemorrhage
Cerebral embolism
A.V. Malformation

Nutritional
Avitaminosis
- B_{12}
- folic acid
- niacin
- thiamine

Hypervitaminosis
- vitamin A
- vitamin D

Infections
Meningitis
Encephalitis
Neurosyphilis

Space/Occupying Lesions
Any type of neoplasm
Aneurysm
Abscess
Chronic subdural hematoma

toms of dementia. Dementia must be ruled out with appropriate investigations. Also, reversible acute organic brain syndromes must be recognized early so permanent sequelae can be prevented. Laboratory investigations should include complete blood cell count, sedimentation rate, serology, liver function studies, thyroid function tests, serum B_{12} and folic acid and drug screen where appropriate. An EEG, brain scanning, skull X-rays and CT scanning may also be necessary to rule out suspected focal disorders.

Management

Once the diagnosis has been made, counselling is the most important initial step. The patient, if he is lucid enough, and his family should be made aware of the diagnosis and its significance must be discussed. Literature from Health and Welfare Canada[6] and/or the Alzheimer Society[48] can supplement the discussion. The physician should be prepared for further counselling sessions once this information is assimilated and periodically when the disease is mentioned in the public press.

Particular attention must be paid to the needs of the family as well as to those of the patient. A team approach with visiting nurses and social services agencies is advisable. The physician must realize that caring for a patient with Alzheimer's disease is a 24 hour a day job that ultimately becomes a burden to the family. As the disease evolves, changing responsibilities may become very stressful for the family, and they may require further counselling. Legal issues may have to be dealt with if and when the patient becomes legally incompetent. Considering the complexity of some of the potential legal ramifications, legal counsel should be sought as early in the disease as possible.[6, 49, 50]

For patients with severe agitation, aggressive or paranoid behavior, tranquillizers given at the evening meal or at bedtime may enable the caregiver to manage the patient better, to get a full night's sleep and perhaps even to keep the patient at home, rather than placing him in an institution. A low dose of haloperidol or thiothixene may be started once or twice a day. The dose should be titrated according to the patient's response and the appearance of side effects such as sedation, extrapyramidal effects or an increase in psychotic behavior. Depression may accompany Alzheimer's disease and can sometimes be ameliorated with tricyclic antidepressants. However, these are often reactive depressions and do not respond to antidepressants. They may be better treated with supportive psychotherapy and attempts at increasing socialization and decreasing isolation.[51]

Day care for the elderly is a relatively new phenomenon in North America, and may assist the patient and family to cope with the problems of Alzheimer's disease.[51] Daily activities are based on therapeutic recreations such as cooking, washing dishes, watering plants, and participating in physical and relaxation exercises. Also included are educational and support groups which may help families to cope better with the illness by allowing them to ventilate feelings in a group setting.

Finally, the patient and family must be constantly reassured and listened to. Like victims of any incurable disease, they are targets for unproven or miracle cures. A good rapport between

TABLE 2
Dementia vs. Depressive Pseudodementia

	Dementia	Depression
Onset	• Insidious onset • Intellectual impairment precedes depression	• More sudden onset often after a major psychological trauma • Depression predates cognitive deficit
Clinical course	• Progressively steady decline	• Uneven • May not progress • May remit
Presentation	• Patient may deny problems exist • Relatives may force consultation • Patient not distressed	• Patient usually aware of cognitive deterioration and complains of it • Patient quite distressed
Appearance behavior and affect	• Inappropriately dressed and groomed • Indifferent manner • Emotional lability	• Appears worried and sad • Concerned • May ridicule himself • May be agitated • Affect flattened, disturbed
Response to history taking	• Cooperative but may be evasive • Appears to try but does not have the ability to answer or remember • May become angry or sarcastic	• Uncooperative • Doesn't have answers
Short-term memory	• Often impaired	• Sometimes impaired
Longterm memory	• Unimpaired early in disease	• Often impaired
General intellectual performance	• Usually global impairment	• Often confined to memory only • No consistency
Amobarbital interview	• Cognitive deficits accentuated	• Performance improved

the physician, the patient and his family is essential.

Conclusion

Many questions remain about the etiology of Alzheimer's disease, if indeed it really is a disease as opposed to a manifestation of the normal aging process. If the latter is the case, a discovery about how to prevent Alzheimer's disease will benefit the entire population. In the meantime, Alzheimer's disease is perhaps the top priority for health care planners. If no advances are made, the acute shortage of institutional beds will present us with a crisis. Canada's geriatric population may have tripled by the year 2015, meaning that perhaps one million patients with Alzheimer's disease will be searching for care. ◉

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