Alzheimer’s disease: current knowledge, management and research

Serge Gauthier, MD; Michel Panisset, MD; Josephine Nalbantoglu, PhD; Judes Poirier, PhD

Abstract

ALZHEIMER’S DISEASE IS A COMMON NEUROLOGICAL CONDITION, appearing as early as age 40 but increasing dramatically in incidence over age 85. Different genetic factors are at play, modified by events over a lifetime. Clinical diagnosis is possible through careful history taking with a reliable informant and a minimum number of laboratory tests. A relatively predictable natural history can be observed, with progression through stages of cognitive loss, functional impairment and behavioural disinhibition or apathy. New medications such as donepezil offer hope for improving or stabilizing symptoms. Such treatment can be administered by primary care physicians with experience in the diagnosis and management of Alzheimer’s disease. Disease stabilization, or even prevention, may be possible in the future.

Résumé

LA MALADIE D’ALZHEIMER EST UNE AFFECTION NEUROLOGIQUE FRÉQUENTE, se manifestant dès 40 ans, mais augmentant dramatiquement en incidence au delà de 85 ans. Divers facteurs génétiques sont en jeu, modifiés par les événements de toute une vie. Le diagnostic clinique est possible grâce à une anamnèse bien structurée, avec une personne bien informée, et un minimum de tests de laboratoire. Une évolution naturelle relativement prévisible peut être observée, avec progression à travers des stades d’altération cognitive, pertes fonctionnelles et désinhibition comportemental ou apathie. De nouveaux médicaments tels que le donepezil offrent un espoir pour une amélioration symptomatique ou une stabilisation des symptômes. Un tel traitement peut être administré par les médecins de première ligne avec expérience dans le diagnostic et le traitement de la maladie d’Alzheimer. La stabilisation ou même la prévention de cette maladie sera peut-être possible dans l’avenir.

Causes

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder with characteristic clinical and pathological features. Terms such as “senility,” “retrou en enfance” and “hardening of the arteries” that had been used to describe this condition reflect the nature of AD: it usually occurs in old age, it is associated with a loss of functional autonomy, and it is often brought on by cerebrovascular changes superimposed on synaptic and neuronal loss. The precise cause in the last category is still unclear, and it may differ greatly between early-onset AD (occurring as early as age 40 and up to age 65) and late-onset AD (occurring after age 65). AD may thus be a syndrome, but as our review will emphasize, there are reliable diagnostic criteria to allow basic and clinical research.

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and localized inflammation associated with acute-phase reactants. Finally, there is a significant loss of white matter, as demonstrated by subcortical atrophy in late stages of AD, in part because of small-vessel atherosclerosis (leukoaraiosis) and cerebral amyloid angiopathy, and in part because of loss of long axonal processes.

The loss of neuronal cell bodies in the nucleus basalis of Meynert had suggested the possibility of a nucleus-specific illness (similar to the substantia nigra in Parkinson’s disease), but more recent evidence indicates a diffuse pathological process involving medium-sized cortical neurons, particularly those using acetylcholine as a transmitter in the hippocampus and those found in associative temporal and parietal regions. The reason for this relative vulnerability is unknown, but it may have to do with impaired plasticity or repair mechanisms, which are to a great extent driven by apolipoprotein E (apo E) genotype. Indeed, recent evidence indicates that apo E plays a central role in the brain response to injury by transporting cholesterol and phospholipids to neurons undergoing dendritic and synaptic remodelling. The coordinated expression of apo E and its main receptor, the apo E/apo B (LDL) receptor, appears to regulate the transport and cellular internalization of lipids such as cholesterol and phospholipids during the early phase of the reinnervation process in the brain. During synaptic remodelling, neurons progressively repress the intracellular synthesis of cholesterol in favour of cholesterol internalization through the cell surface apo E/LDL receptor pathway. A strong link was discovered between apo E-4 (a mutation in the apo E) and both sporadic and familial late-onset AD. This raises the possibility that a dysregulation of lipid transport and internalization by neurons could be central to AD pathophysiology, because the cholinergic system, unlike amino acid-based neurotransmitter systems, relies heavily on lipids to sustain its activity.

Genetic abnormalities other than apo E-4 clearly play a major role in early-onset AD, usually in a Mendelian dominantly inherited pattern. Chromosomes 1, 14 and 21 have been linked to AD, and the proteins called pre-senilins are being extensively studied. AD has so far been a uniquely human disease, but researchers are trying to recreate at least certain components of AD neuropathology in mice using transgenic models.

The overall emerging pattern of causes of AD is a convergence syndrome, particularly in the later-onset forms of the disease, in which a variety of mechanisms could converge over a lifetime toward the neuropathology of AD. Acquired and concurrent diseases such as stroke would play an important role in determining the presence and severity of the clinical symptoms of AD.

**Epidemiologic characteristics**

AD is the most common cause of dementia in adults worldwide. In 1991 the Canadian Study of Health and Aging (CSHA) documented prevalence rates of dementia (8.0% among people over age 65, 28.5% among those over 85 and 58% among those over 95) and found that AD was the cause in 64% of all cases of dementia, whereas vascular dementia was present in only 19% of all cases. A surprisingly large number (16.8%) of people over 65 had cognitive impairment but not dementia. The main risk factors for AD were found to be a family history of dementia (odds ratio [OR] 2.62) and a lower level of education (OR 4.00), whereas the main protective factor was a history of arthritis (OR 0.54). In addition, 98% of all the people with dementia in the study had one caregiver (spouse in 37% of cases, daughter in 29%) and underutilized available community support services. These results are similar to those from other epidemiologic research on AD in countries with populations of western European origin. In Japan, the relative predominance of vascular dementia over AD as a cause of dementia may be due to the rarity of apo E-4 in this population. Studies of prevalence and incidence rates and of risk factors between different countries may give us important clues about the multiple
clinical and physical examination. Knowledge of risk factors may allow a preventive approach in the future.

The second phase of the CSHA was completed early in 1997. By re-examining the original 1991 cohort, the study group set out to (a) estimate the incidence of dementia among Canadians aged 71 and older, (b) determine the risk factors for AD and for vascular dementia and (c) determine the natural history of mild cognitive impairment and of dementia. Other issues studied included “successful aging” (aging without functional decline), physical dependence, frailty, caregiving and utilization of health services. Results of this phase of the CSHA will be available early 1998.

Diagnosis

Clinical diagnosis of AD is possible by obtaining a good history from a reliable informant. First, the presence of dementia has to be confirmed, close attention being paid to the presence of delirium, depression and the misuse of psychotropic drugs. Then the differential diagnosis is determined, including common causes of dementia such as AD, vascular dementia, dementia with Lewy bodies and frontotemporal dementia. The operational definition of AD in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (Table 1) captures the main elements of the presentation of AD.

The typical presentation of AD is a slowly progressive loss of memory for recent events, complicated some months later by impairment of speech and perhaps of orientation to time and place. At this stage, patients are alert, tend to minimize their symptoms and are usually in good general health with unremarkable findings on neurological and physical examination. The Mini-Mental State Examination (MMSE) is commonly used to assess cognition in clinical practice. One has to be careful not to overinterpret MMSE scores, because low levels of education (below grade 4) and speech impairment will reduce its validity. Conversely, highly educated people may have high MMSE scores despite an obvious decline in their prior abilities. Nevertheless, the MMSE is useful for confirming the impression from history taking that there is cognitive loss, and the test can be repeated over time to assess deterioration and possibly response to treatment. The MMSE and a semistructured questionnaire encompassing the main symptomatic domains of AD (memory, orientation, judgement and problem solving, community affairs, hobbies, personal care, affect and behaviour) could be used at certain intervals, such as before treatment and every 3 months. In specialized clinical research settings, the distinction is made between “definite” AD (i.e., the disease has been confirmed by biopsy or autopsy), “probable” AD (i.e., all other causes of dementia have been ruled out, and the clinical presentation and progression of symptoms have been typical) and “possible” AD (i.e., patient has some atypical features such as early and prominent speech loss relative to memory loss, vascular features and abnormal laboratory test results).

Laboratory investigation is driven primarily by the history and objective examination (physical, neurological and neuropsychological). The Canadian Consensus Conference on the Assessment of Dementia (CCCAD) has recommended that laboratory tests be limited to the following in all cases of suspected AD: complete blood count, thyroid function tests, and measurement of serum electrolyte, calcium and glucose levels. Further tests would be patient specific. The CCCAD questioned the need for a head CT scan of all patients: the yield in terms of radiological findings that would change the diagnosis or treatment is very small among those presenting with symptoms typical of AD of at least 2 years’ duration. On the other hand, the CCCAD has recommended that a head CT scan be obtained of all patients with certain characteristics: age less than 60 years, use of anticoagulants or history of bleeding disorder, recent head trauma, history of cancer, unexplained neurological symptoms (e.g., new headaches or seizures), rapid (within 1–2 months) and unexplained decline in cognition or function, short (less than 2 years) duration of dementia, urinary incontinence and gait disorder early in the course, any new localizing sign (e.g., hemiparesis or Babinski reflex), and gait ataxia. Other groups have suggested similar laboratory criteria.

Table 1: Diagnostic criteria of Alzheimer’s disease

<table>
<thead>
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<th>Development of multiple cognitive deficits manifested by both:</th>
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<tr>
<td>• Memory impairment (impaired ability to learn new information or to recall previously learned information)</td>
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<tr>
<td>• One or more of aphasia, apraxia, agnosia or disturbance in executive functioning</td>
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Substantial impairment of social or occupational functioning and significant decline from prior level of functioning caused by these cognitive deficits

Gradual onset and continuing cognitive decline, not occurring exclusively during the course of delirium and not better accounted for by a primary psychiatric disorder such as major depression or schizophrenia

Development of cognitive deficits not due to:

- Other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., stroke, Parkinson’s disease, subdural hematoma, normal-pressure hydrocephalus or brain tumour)
- Systemic conditions that can cause dementia (e.g., hypothyroidism, vitamin B12, or folic acid deficiency, neurosyphilis, HIV infection)
- Condition induced by substance abuse (e.g., alcohol or sedatives)
in order to simplify the work-up of AD, which is primarily done through careful history taking.

**Clinical course**

In typical cases, AD progresses through relatively predictable stages, as described in the Global Deterioration Scale of Reisberg and associates (Table 2). There is thus a deterioration of memory for recent events, ability to name people and objects, and orientation to time and space (detectable using the MMSE). There is a loss of autonomy for instrumental and self-care activities of daily living. Mood changes may also be present in early as well as more advanced stages, at which point behavioural agitation may be the only manifestation of depression. Most patients have some degree of neuropsychiatric changes, including hallucinations, misidentifications (Capgras syndrome), delusions and paranoid ideation, aggression or apathy, wandering and sexual disinhibition. This stage is usually the most difficult for caregivers to deal with and often leads to institutionalization.

An atypical presentation of AD (usually requiring consultation with a neurologist, psychiatrist or geriatrician), would include depression not responding to treatment, psychosis or early behavioural disturbances, rapid (within weeks) onset of symptoms, and early-onset motor or gait disturbances, including asymmetrical grasp responses. These signs and symptoms suggest conditions other than AD (e.g., vascular dementia, frontotemporal dementia, CNS infection, hydrocephalus or brain tumour) or an atypical form of AD, which usually entails a more rapid progression.

**Treatment**

Physicians should start with as accurate a diagnosis as possible, ruling out or treating depression, delirium and systemic disorders such as hypothyroidism, correcting nutritional deficiencies and eliminating sedative drugs. A period of observation of 3–6 months may be required to confirm the progression of cognitive loss and assess its functional impact. At that point the diagnosis must be discussed with the patient and his or her designated legal guardian. The Alzheimer Society of Canada has published a document, “Communicating the diagnosis,” that may be of great help to clinicians, patients and families. Other steps in the management of early AD include advice on will-making and advance directives, and monitoring the patient’s driving ability and ability to use household appliances safely. All patients and their families should be made aware of the Alzheimer Society of Canada and its regional chapters, since this volunteer association can provide information relevant to the stage of disease, support services and referral to formal community-based support services.

Special issues may come up in early-stage management of AD, such as the need to refer patients for a second opinion on the diagnosis, genetic testing or participation in research. Clinicians can call member sites of the Consortium of Canadian Centres for Clinical Cognitive Research (C5R; Secretariat, tel 403 244-7314).

In later stages of AD the clinician will have to look for and treat neuropsychiatric symptoms, arrange support through local health services (day programs, respite care), and monitor the health and well-being of caregivers. Admission to an institution, which is required for most (but not all) patients, can be facilitated by planning ahead with caregivers and community resources. In the end stages of AD, caregivers and clinicians will have to make decisions respecting advance directives, if available.

At the time of publication, the only medication targeted at AD symptoms available in Canada was donepezil (Aricept); others are in late stages of clinical development. Some (tacrine, donepezil, ENA-713, metrifonate and galantamine) enhance cholinergic function by inhibiting acetylcholinesterase, whereas propentofylline acts as a selective adenosine reuptake inhibitor and phosphodiesterase inhibitor. Other drugs (xanomeline, milameline and SKB 202026) are selective muscarinic receptor agonists. All of these drugs are being tested in double-blind placebo-controlled randomized studies involving patients in early to intermediate stages (score of 3–5 on the Global Deterioration Scale [Table 2]) of “probable AD” (all other potential causes of dementia have been excluded). Studies using these agents generally last 3–12 months and exclude patients with neuropsychiatric symptoms that could interfere with testing of their cognition, or concomitant medical disorders such as insulin-dependent diabetes or seizures. Efficacy is being measured in all studies by multiple raters using a cognitive assessment instrument and a global assessment scale. Little information is available on the effect of these drugs on neuropsychiatric manifestations of AD. There is some evidence that the apo E genotype can predict response to some of these drugs.

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<td>4</td>
<td>Decreased ability remembering current events, travelling or handling complex finances</td>
</tr>
<tr>
<td>5</td>
<td>Disorientation to time and place; need for assistance in choosing clothes</td>
</tr>
<tr>
<td>6</td>
<td>Disorientation to people; need for supervision in dressing, eating, toileting</td>
</tr>
<tr>
<td>7</td>
<td>Severe speech loss; incontinence; motor rigidity</td>
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**Table 2: Global Deterioration Scale**

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How best to use these medications after regulatory approval in regular clinical practice, where many patients with AD have concomitant disorders and take other medications and where there is time and staff constraints? This issue will be addressed in a consensus conference, to be held Feb. 27–28, 1998, under the auspices of the C5R, with the use of drug product monographs and details of pivotal studies when published. In terms of which AD drug to use for individual patients, one will have to consider each drug’s safety and efficacy profile and its ease of use as the information becomes available. There will be little data about long-term use, because this information has to come from extensive phase IV studies in order to establish effectiveness and safety.

Donepezil is the first drug approved by the Health Protection Branch of Health Canada for the symptomatic treatment of early to intermediate stages of AD. We have used it in Table 3 to illustrate a strategy, modified from one described by Murali Doraiswamy, for the optimal use of AD-specific drugs by clinicians experienced in the diagnosis and management of AD. Other agents currently being reviewed by the Health Protection Branch include propentofylline and ENA 713. The product monographs should be consulted for detailed information about indications, contraindications, warnings, precautions, adverse reactions, dosage and administration.

Treatment will involve a number of visits over many months in order to ensure accurate diagnosis, efficacy and safety of use for individual patients. The prescription of AD-specific drugs must be considered as one component of a global biopsychosocial treatment that will span many years. Atypical cases in terms of diagnosis, response to treatment or complex psychosocial issues can be referred to specialized memory clinics, but the bulk of patients prescribed these new agents will be managed by primary care practitioners.

In addition, physicians will have to face the new clinical and ethical issue of when to stop AD drug therapy. This issue is similar to that in Parkinson’s disease, where physicians have to decide when to stop L-dopa therapy if patients are not responding to treatment or are in late stages of the disease.

The future

Over the last 20 years we have seen a remarkable increase in the knowledge about AD. This has happened to a great extent because of the positive interaction between all concerned, from patients and their families to clinicians, researchers and people working in government regulatory and funding agencies.

Clinicians will be facing many challenges, including disease stabilization in very early stages of AD and prevention in people at risk. Etiology-driven hypotheses may allow testing in well-defined populations with safe agents such as α-tocopherol and estrogen. Higher risk drugs, such as nonsteroidal anti-inflammatory drugs, will require careful consideration. A new generation of medications targeted specifically at amyloid deposition may become available for testing in humans at the turn of the century. Task forces are already working on the methodology for studies to determine the efficacy of such preventive treatments.

There is a strong possibility of substantially delaying the onset of symptoms in future generations, while managing efficiently and with compassion people currently affected by AD.

We thank Ms. Christina Kyriakou for her secretarial assistance in preparing the manuscript.

The authors’ work is supported by grants from the Medical Research Council of Canada, the Medical Research Council of Canada/Pharmaceutical Manufacturers Association of Canada Health Program, the Fonds de la recherche en santé du Québec, the National Health Research and Development Program and the Alzheimer Society of Canada.

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### Table 3: Strategy for drug treatment (e.g., with donepezil) of Alzheimer’s disease (AD)

1. Confirm diagnosis of dementia (e.g., progressive cognitive loss with impact on daily and social life) by (a) carefully interviewing patient and family or friends and (b) administering objective test such as the Mini-Mental State Examination (MMSE): Confirm diagnosis of AD by documenting typical pattern of symptoms and progression over time, with unremarkable findings on neurologic and physical examination; stage disease severity
2. Treat concomitant medical problems such as depression and eliminate nonessential drugs that could interfere with cognition
3. Discuss diagnosis and prognosis with patient and family; advise on will-making and advance directives while patient’s competency is not in doubt; refer to local branch of Alzheimer Society of Canada; assess caregiver’s health and coping skills
4. Explain potential effectiveness of AD-specific medications such as donepezil and the known side effects
5. Establish cognitive, functional, behavioural and emotional status before treatment, by interviewing patient and caregiver and by administering MMSE and other structured questionnaires
6. Start drug therapy (e.g., donepezil 5 mg once daily at bedtime [may need to be changed to morning if treatment interferes with sleep])
7. Assess efficacy and tolerance to treatment at week 6, 12 and 24 by interviewing patient and caregiver; maintain dosage if improvement in condition is detected, particularly with regard to functional abilities; consider increasing dose (e.g., to 10 mg once daily for donepezil) after week 12 if there is no clear evidence of response, unless there is a contraindication (e.g., low body weight) (refer to product monograph)
8. Treatment beyond 24 weeks is warranted as long as there is evidence that the condition is stabilized


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A Canadian face on aging

“Florida” was painted in 1965 by Canadian artist Jean-Paul Lemieux (1904-1990). The medium is oil on canvas. The painting was a gift to the Montreal Museum of Fine Arts from Louise and Clément Massicotte.