

---

# Inherited Disorders Causing Dementia



By Grace Yoon, MD; Richard Camicioli, MD, FRCPC  
and Dawna Gilchrist, MD, FRCPC, FCCMG

---

Currently, 12% of Canadians are over 65 years of age. By the year 2031, the percentage of Canadians over age 65 is expected to be as high as 25%.<sup>1</sup> Dementia affects 8% of people over 65 years, 30% of people over 85 years and 58% of people over 95 years.<sup>1</sup>

Dementia affects all spheres of a patient's life, as well as that of his/her family. For the patient, important issues revolve around autonomy, quality of life and end-of-life decisions. For family, major concerns include loss of a previously functional relationship with the patient, as well as the assumption of responsibility for the patient's care. It is estimated that up to 50% of caregivers suffer from "burnout", and families may be placed under financial strain. The health care costs associated with caring for patients with dementia are substantial — an estimated \$40,000 US per patient.<sup>2</sup>

Diagnosis of dementia in the early stages allows the patient to plan for the future while still competent, and the family is given time to prepare for the upcoming changes to their lives. Many conditions, both genetic and acquired, can lead to dementia. A solid clinical approach to the diagnosis of dementia is, therefore, an important tool to virtually all primary care and many specialist physicians.

## Case Presentation

A 42-year old woman was referred to a medical genetics clinic for assessment of possible hereditary dementia. She was healthy, with no signs of cognitive impairment. Her family history is as follows: Her mother was diagnosed with dementia at 62. A computed tomography (CT) scan of the head revealed generalized atrophy and no vascular changes. There was no other history of dementia on the maternal side of the family. Her father was diagnosed with dementia at the age of 76, having suffered three strokes, as well as a myocardial infarction. A CT scan of the head revealed multiple small infarcts with ischemic white matter changes. Her paternal uncle was diagnosed with dementia at 78. He had a history of stroke, cardiovascular disease and diabetes. Her paternal grandmother was diagnosed with dementia at 66, and also had hypertension and diabetes.

## Inherited *versus* Acquired Dementia

Dementia is defined as “acquired loss of cognitive and emotional function severe enough to cause dysfunction in daily living.”<sup>3</sup> There must be multiple cognitive deficits in addition to memory impairment, with a gradually progressive course in the setting of a normal level of consciousness. The DSM-IV diagnostic criteria consist of memory impairment plus one of aphasia, apraxia, agnosia or impairment of executive functioning.<sup>4</sup> The differential diagnosis of dementia is broad. (Table 1).

A positive family history of dementia with multiple affected members is usually the feature which brings a family to the attention of medical genetics. The assessment should start by obtaining a detailed family history and examining the pedigree for indications of a definite inheritance pattern. For example, single gene disorders may be inherited in an autosomal dominant, autosomal recessive, or sex-linked manner. Mitochondrial disorders are usually inherited from the maternal side of the family, and may be associated with additional clinical features. Most dementias are multifactorial in origin (*i.e.*, the result of complex interactions between multiple genetic and environmental factors).

Inherited dementia is most often characterized by a young age of onset (under 65) and may or may not be accompanied by specific signs or symptoms. For example, a characteristic movement disorder, chorea, is seen in Huntington disease. Other hereditary dementias may be accompanied by prominent behavioural change, as seen in frontotemporal dementia.<sup>5</sup> Pathological confirmation of the diagnosis is extremely valuable to provide maximum accuracy for genetic counselling as the differential is broad and many conditions are difficult to distinguish on a purely clinical basis.

## Alzheimer's Disease

Alzheimer's disease (AD) was first described in 1907 by Alois Alzheimer. It is now recognized as one of the most common causes of dementia, and represents approximately 64% of all dementia cases.<sup>6</sup> Both incidence and prevalence rise with the increasing age of the population. The prevalence is 1% by age 60. By age 70 it is 4% and by age 80 it is 18%. That figure increases to 45% by age 90.<sup>7</sup> The disease duration is eight to 12 years, with a range of one to 25 years.

A definite diagnosis of AD requires the clinical features of probable AD, as well as pathological confirmation of AD at autopsy, the gold standard for diagnosis.<sup>8</sup> Pathological features include gross cerebral cortical atrophy, senile plaques, neurofibrillary tangles, neuropil threads and loss of neuronal synapses.<sup>9</sup> The presence of Hirano bodies, which consist of polymers of F-actin in neuronal dendrites, or granulovacuolar degeneration (especially of the hippocampus), lend support to the diagnosis of AD.

---

Dr. Yoon is a resident in the medical genetics program at the University of Calgary, Alberta.

---

---

Dr. Camicioli is associate professor of medicine, University of Alberta, Edmonton.

---

---

Dr. Gilchrist is associate professor of medicine and medical genetics, University of Alberta, Edmonton.

---

# Inherited Disorders Causing Dementia

Amyloid angiopathy, which can be seen without other features of AD, is also frequently present, and affects the leptomeningeal and superficial cortical vessels.<sup>9</sup>

A diagnosis of probable AD is made on clinical grounds.<sup>10</sup> Dementia on clinical exam, documented by standardized mental status assessment, such as the Folstein Mini-Mental Status Examination (MMSE), is necessary. Confirmation by neuropsychological testing is recommended, but not absolutely required, for diagnosis. Progressive deficits in memory and at least one other cognitive domain must be present.

## Other Features of AD

- Confusion
- Language impairment
- Agitation
- Poor judgment
- Hallucinations.

## Rare Features of the Disease

- Seizures
- Hypertonia
- Myoclonus
- Mutism.

The clinical diagnosis of AD is estimated to be correct 75% to 90% of the time.<sup>9</sup> The accuracy is somewhat lower for older patients who often have mixed pathology (*i.e.*, vascular changes in addition to AD pathology). A possible diagnosis of AD is made when there are variations in presentation or clinical course.

The major acquired dementia that is often confused with Alzheimer's disease is vascular (formerly called multi-infarct) dementia. Patients with vascular dementia may present with symptoms of abrupt onset or stepwise progression, fluctuating cognitive decline, nocturnal confusion, relative preservation of personality, and emotional lability – features which are also consistent with a diagnosis of possible AD.<sup>11</sup> A complete physical examination may reveal the presence of focal neurological signs in the patient with vascular dementia, findings unusual for AD. Vascular risk factors, such as a history of stroke or transient ischemic attack (TIA), hypertension, hypercholesterolemia, atherosclerosis, atrial fibrillation, diabetes or smoking, would suggest a diagnosis of vascular dementia. In cases where there is a history of dementia consistent with both vascular causes and AD, pathological confirmation of the diagnosis may be the only means of distinguishing the two conditions.

It is also important, however, to recognize that co-existence of more than one condition leading to dementia in the same patient is common, particularly in the most elderly patients. It is estimated that only 2% to 3% of dementia is attributable to pure vascular dementia and that many cases have “mixed pathology” — small vascular infarcts associated with pathology con-

Table 1

## Differential Diagnosis of Dementia

Delirium/acute confusional state  
Recurrent seizures  
Structural  
Metabolic  
Toxic/drugs  
Psychiatric  
Infection  
Vascular  
Neurodegenerative disease  
Neoplastic  
Inflammatory

---

# Inherited Disorders Causing Dementia

sistent with AD on autopsy.<sup>12</sup> It can, therefore, be difficult to determine whether multiple cases of dementia in a family are due solely to AD, or whether there is overlap with vascular causes of dementia. These issues are confounded by recent evidence that cerebrovascular disease may represent a risk factor for AD.<sup>13</sup>

Two other neurodegenerative conditions which must be considered in the differential diagnosis of AD include Dementia with Lewy Bodies (DLB) and the Frontotemporal Dementias (FTDs). The cognitive disorder in DLB is difficult to reliably distinguish from that of AD, however, DLB is associated with extrapyramidal signs, such as rigidity, masked facies, shuffling gait, stooped posture, resting tremor, and postural instability.<sup>12</sup> In addition, DLB is characterized by visual hallucinations and fluctuating level of consciousness. Marked neuroleptic sensitivity, syncope and unprovoked falls are supportive features.<sup>14</sup> The pathological hallmark is the presence of eosinophilic intracellular inclusions (Lewy bodies) in cortical neurons, in addition to the substantia nigra, which is typically affected in Parkinson's Disease.<sup>12</sup> FTD is characterized by disordered social conduct and marked changes in character.<sup>12</sup> The cognitive dysfunction is insidious and progressive, and there is decline in the areas of interpersonal conduct, personal awareness, insight, mental flexibility, as well as emotional blunting. Hyperorality, perseverative and stereotyped behaviour may be present. Pathological changes include the presence of Pick bodies, progressive subcortical gliosis and anterior horn cell disease.<sup>12</sup>

## Early Onset Familial AD

Early onset familial AD (EOAD) accounts for less than 10% of all AD cases. The diagnostic criteria for EOAD consist of: age of AD onset less than 65 years (usually 45 to 55), and a positive family history usually with an autosomal dominant pattern of inheritance. First degree relatives (*i.e.*, offspring or siblings) of a patient with EOAD are at 50% risk of developing EOAD. EOAD may occur also as an isolated sporadic (*i.e.*, non-familial).

## Late Onset AD

The vast majority of AD cases present as late onset AD (LOAD), with an age of onset of symptoms greater than 65 years. Both sporadic and multifactorial family histories have been observed, and 20% to 30% of patients have at least one affected first degree relative.<sup>17</sup> The risk of an individual developing AD increases with the number of cases in the individual's family, but the exact magnitude of this increased risk is unknown.

A number of risk factors have been identified, which have been associated with increased incidence of AD. Advanced age is by far the most important. Previous head trauma, female sex, lower educational level and small head size have also been shown to predispose to the development of AD in some studies.<sup>17</sup> A positive family history of LOAD is also associated with an increased risk of developing AD. The increase in risk for first degree relatives of an affected individual is estimated at two to four times the baseline population risk.<sup>17</sup>

---

# Inherited Disorders Causing Dementia

The complex interaction between environmental and genetic factors, characteristic of multifactorial conditions, has given rise to the concept of “vulnerability” genes. Variations in these genes contribute to AD predisposition without obligatory association with the disease, and may require interaction with environmental factors in order for the disease phenotype to manifest. One such vulnerability gene which has received much attention is the ApoE gene. ApoE-*E4* is neither necessary, nor sufficient, for a diagnosis of AD and is not recommended for routine population screening.

## Clinical Approach to Inherited Dementia

The assessment of a patient who presents with dementia starts with a history of the patient’s onset of symptoms and clinical course, corroborated by a reliable informant other than the patient. A functional assessment, including evaluation of instrumental activities of daily living, is necessary. Evaluation of the past medical history must include assessment of vascular risk factors, seizures, TIAs, trauma, and malignancy, as well as a complete medication history and any history of drug and alcohol abuse in order to assess the importance of these factors in the differential diagnosis. A three-generation (or greater) family history is extremely important, and all cases of dementia should be confirmed with medical records and pathological reports, if available. In order to complete such a family history it is important to identify all individuals — affected and unaffected.

A complete mental status assessment that evaluates all cognitive domains is necessary. The use of a standardized cognitive test, such as the MMSE, is recommended.<sup>20</sup> A complete physical examination, with emphasis on the detection of focal neurological signs and gait impairment, is also necessary.

Baseline laboratory investigations include a complete blood count (CBC), thyroid-stimulating hormone (TSH), Ca, electrolytes, glucose, vitamin B12 and folate levels.<sup>20</sup> Other tests may be ordered if clinically warranted, such as a blood urea nitrogen (BUN) and creatinine level, liver function tests, venereal disease research laboratory (VDRL) and HIV serology.<sup>20</sup> Neuroimaging studies are formally recommended only in specific situations — if the age of dementia onset is less than 60 years, and if there is rapid or unexplained deterioration, trauma, new neurological findings, history of malignancy, bleeding diathesis, or gait anomalies.<sup>20</sup> This is a controversial area, however, as many centres do incorporate neuroimaging studies into their protocols for evaluation of dementia.

## Molecular Genetic Testing

There are a number of limitations to molecular genetic testing. First, the putative gene suspected must have been fully characterized and a useable test available. Some tests are generally available in government-funded molecular diagnostic labs; other tests are available at only a few laboratories; still others at research laboratories only. Even when a genetic test

---

# Inherited Disorders Causing Dementia

is freely available, technical difficulties may make the test less than 100% sensitive and/or specific. These technical issues include size of the gene, numbers of possible genes involved, numbers of possible mutations, true mutations *versus* polymorphisms, and “silent” areas of genes resistant to any genetic testing.

Should a genetic test be available and accurate, it cannot predict any individual’s clinical course as many dementias demonstrate great variability in age of onset, severity of symptoms, *etc.* even within the same family with the same mutation. There is no guarantee the detection of a mutation will enable a patient to alter his/her clinical course, as the genetic mutation cannot be repaired and the treatment of the specific dementia may be non-specific or non-existent, particularly in the pre-symptomatic stage.

Whether the patient is affected or pre-symptomatic, there are a number of psychosocial and ethical issues which must be carefully considered prior to ordering molecular genetic tests. A genetic diagnosis in one family member may reveal the genetic status of another, and family relationships may be altered, depending on existing family dynamics. Depression may affect those anticipating onset of the disease. Genetic testing may greatly affect an individual’s long-range plans for a career, marriage, children, *etc.* A positive genetic test may adversely affect a patient’s ability to obtain disability or life insurance, and may influence employment and immigration potential. For these reasons, it is strongly recommended that pre-symptomatic testing of children for adult-onset conditions not be carried out, as it violates the child’s right to make an informed decision regarding this aspect of his/her health care as an adult.<sup>21</sup> To fully inform patients of the pros and cons and limitations of molecular genetic testing, it is strongly recommended that patients receive complete genetic counseling prior to undergoing the test. This usually involves referral to a medical genetics center or clinic.<sup>22</sup>

## Treatment

Until recently, the mainstay of treatment for dementia patients was limited to caregiver and family support, as well as optimization of concomitant medical problems, and symptom control. Treatment of depression with antidepressants (selective serotonin reuptake inhibitors are the first-line choice) is well recognized.<sup>23</sup> Psychosis and agitation can be treated with antipsychotics and other agents.<sup>23</sup>

Recent advances in AD research has lead to the development of medications which have been found to improve cognitive and functional outcome in AD patients by maximizing the brain’s cholinergic activity. Available drugs include cholinesterase inhibitors. There has also been recent evidence suggesting the use of NSAIDs may confer protection from AD, independent of COX activity.<sup>24</sup> Other therapies, which are currently under investigation, include the use of statins, neurotrophic factors (such as nerve growth factor), immunization with Ab42, caspase inhibitors and selective b and g secretase inhibitors.<sup>25</sup>

# Inherited Disorders Causing Dementia

## Summary

Many disorders cause dementia, which presents a challenge to physicians involved in the diagnosis and care of these patients and their families. The understanding of the genetic basis of some of these conditions is particularly important for accurate diagnosis and genetic counselling for families at risk. For rare families that present with early onset autosomal dominant AD or FTD, referral to a genetics clinic may facilitate appropriately informed genetic testing. **Dx**

### References

1. The Canadian Study of Health and Aging Working Group: The Incidence of Dementia in Canada. *Neurology* 2000;55:66-73.
2. Petersen RC, Stevens JC, Ganguli M, et al: Practice Parameter: Early Detection of Dementia: Mild Cognitive Impairment (an evidence-based review) Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;56(9):1133-42.
3. Geldmacher DS, Whitehouse PJ: Evaluation of Dementia. *New England Journal of Medicine* 1996;335(5):330-36.
4. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association .1995
5. McKhann GM, Albert MS, Grossman M, et al: Clinical and Pathological Diagnosis of Frontotemporal Dementia: Report of the Work Group on Frontotemporal Dementia and Pick's disease. *Archives of Neurology* 2001;158(11):1803-09.
6. Gauthier S, Panisset M, Nalbantoglu J, Poirier J: Alzheimer's disease: Current knowledge, management and research. *Canadian Medical Association Journal* 1997;157(8):1047-52.
7. Hebert LE, Scherr PA, Beckett LA, et al: Age-specific incidence of Alzheimer's disease in a community population. *JAMA* 1995;273:1354-59.
8. McKhann G, Drachman DD, Folstein M, et al: Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-44.
9. Dickson DW: Neuropathology of Alzheimer's disease and other dementias. *Clinics in Geriatric Medicine* 2001;17(2): 209-28.
10. Patterson C, Gauthier S, Bergman H, et al: The recognition, assessment, and management of dementing disorders. *Canadian Journal of Neurological Sciences* 2001;28 (Suppl. 1):S3-S16.
11. Moroney JT, Bagiella E, Desmond DW, et al: Meta-analysis of the Hachinski Ischemic Score in pathologically verified dementias. *Neurology* 1997;49(4):61096-1105.
12. Knopman DS: An overview of common non-Alzheimer dementias. *Clinics in Geriatric Medicine* 2001;17(2):281-301.
13. Jagust W: Untangling Vascular Dementia. *Lancet* 2001;358:2097-98.
14. McKeith IG, Ballard CG, Perry RH, et al: Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies international workshop. *Neurology* 2000;54(5):1050-58.
15. Cummings JL, Vinters HV, Cole GM, et al: Alzheimer's disease: Etiologies, pathophysiology, cognitive reserve, and treatment opportunities. *Neurology* 1998;Jul;51(1 Suppl 1):S2-17.
16. Knopman DS, DeKosky ST, Cummings JL, et al: Practice parameter: Diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;May 8;56(9):1143-53.
17. The American Society of Human Genetics Board of Directors and The American College of Medical Genetics Board of Directors: ASHG/ACMG REPORT Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents. *American Journal of Human Genetics* 1995;57:1233-41
18. Bird TD: Risks and Benefits of DNA Testing for Neurogenetic Disorders. *Seminars in Neurology* 1999;19(3): 253-59.
19. Richards SS, Hendrie HC: Diagnosis, Management, and Treatment of Alzheimer Disease — A guide for the internist. *Archives of Internal Medicine* 1999;159:789-98.
20. Weggen S, Eriksen JL, Das P, et al: A subset of NSAIDs lower amyloidogenic Ab42 independently of cyclooxygenase activity. *Nature* 2001;414: 212-16.
21. Maimone D, Dominici R, Grimaldi LME: Pharmacogenomics of neurodegenerative diseases. *European Journal of Pharmacology* 2001;413:11-29.



### Suggested Readings

1. Rosenberg RN: The molecular and genetic basis of AD: The end of the beginning. The 2000 Wartenberg lecture. *Neurology* 2000;54(11): 2045-54.
2. Natte R, Maat-Schieman ML, Haan J, et al: Dementia in hereditary cerebral hemorrhage with amyloidosis — Dutch type is associated with cerebral amyloid angiopathy but is independent of plaques and neurofibrillary tangles. *Annals of Neurology* 2001;50: 765-72.
3. National Institute on Aging/Alzheimer's Association Working Group: Apolipoprotein E genotyping in Alzheimer's disease. *Lancet* 1996;347:1091-95.
4. St George-Hyslop PH: Genetic Factors in the Genesis of Alzheimer's Disease. *Annals New York Academy of Sciences* 2000;924:1-7.