Primary Prevention of Dementia

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Objectives

• Brief overview on dementia prevalence and types
• Discuss risk factors and primary prevention of Alzheimer’s disease
  ▪ Genetic factors
  ▪ Vascular factors
  ▪ Lifestyle factors
  ▪ Medications
• Review recommendations from the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia
Dementia

• Clinical (DSM-IV) diagnostic criteria:
  • Memory impairment AND one or more:
    ▪ Aphasia: language problems
    ▪ Apraxia: motor problems
    ▪ Agnosia: sensory problems
    ▪ Disturbance in executive functioning
  • Deficits impair social/occupational function and represent a decline from baseline
  • Not delirium
Epidemiology

- > 24 million people worldwide with dementia
- Set to double every 20 years to 81 million in 2040
- In Canada, over 60,000 new cases of dementia each year

Types of Dementia

- Vascular: 9%
- Alzheimer disease: 47%
- Lewy body: 3%
- Frontotemporal: 5%

Feldman et al. (ACCORD study) Neuroepidemiology 2003;22:265-74
Case

52 year old female, at annual health exam. Post-menopausal, on HCTZ for BP for past 2 years. Non-smoker, rare alcohol intake, office worker, sedentary lifestyle. Her mother, age 80 has just been diagnosed with Alzheimer’s Disease. She is concerned about her own risk and wonders what she can do.
• Strongest risk factor for dementia, especially AD.

• Prevalence of AD:  
  - 65-74 years: 1%
  - 75-84 years: 6.9%
  - 85 years and older: 26%

• Meta-analysis of 23 studies, AD increased exponentially with age up until 90 years with no signs of leveling off.

  Jorm, AF et al. Neurology 1998;51:728

Genetic Factors

- Early onset AD (<60 years) significant genetic component
- All 3 known causative gene mutations lead to early onset form:
  - amyloid precursor protein gene
  - presenilin 1 gene
  - presenilin 2 gene
- Late onset AD, only ApoE gene confirmed as genetic risk factor
  - 3 common allele forms: epsilon 2, 3 and 4
  - Epsilon 4 linked to development of AD and possibly vascular dementia: single e4 OR 11.6, e4/e4 OR 11.6
Canadian consensus recommendations:
• Predictive genetic testing may be offered to at-risk individuals with an apparent autosomal dominant inheritance when a family-specific mutation has been identified. [B,2]
• Genetic screening for the ApoE genotype in asymptomatic individuals is NOT recommended. [E,2]
Vascular Factors - Hypertension

- SYST-EUR study
  - >3000 patients over 60 with hypertension
  - BP protocol medication vs. placebo
  - Outcome: dementia (MMSE, diagnostic testing)
  - Incidence of dementia 7.7 cases per 1000 (placebo) compared to 3.8 (treatment), RR 0.47 (0.28-0.78)

- Meta-analysis of 4 RCT trials: RR dementia after htn treatment = 0.80 (0.63-1.02)

Vascular Factors
Hyperlipidemia

• Longitudinal studies established that midlife elevation of total cholesterol associated with increased risk of AD.

• RCT: Pravastatin vs. placebo in 5,894 people aged 70-82 years
  ▪ No difference in cognitive function after 3.2 years

• RCT: Simvastatin vs. placebo in 20,536 people aged 40-80 years
  ▪ No difference in incidence of dementia
    Heart Protection Study Collaborative Group. Lancet, 2002;360:7-
Canadian consensus recommendations:

- Good evidence to treat sys htn ( >160 mmHg) in older individuals (age > 60 years), reduce risk of stroke and dementia. Goal <140mmHg. [A,1]

- Insufficient evidence to recommend for or against reducing risk of dementia:
  - ASA and statin post-MI, antithrombotic therapy for nonvalvular a fib, correction carotid artery stenosis > 60% - all these shown to ↓stroke risk [C,1]
  - DM 2, hyperlipiedmia, hypermocysteinemia [C,2]
Lifestyle Factors

• Review in 2010 analyzed the results of impact of lifestyle on cognition or dementia:
  - Physical activity
  - Social, cognitive and leisure activity
  - Nutrition

Polidori MC et al. Alzheimer’s Disease 2010
• Several longitudinal and short-term RCT evidence that physical activity improves cognitive function in older subjects.

• Limitation to studies:
  - Cross-sectional design, frequent lack of adjustment of potential confounding variables.
  - Self addressed nature of cognitive performance and performed physical activity
Lifestyle - Physical Activity

- Honolulu-Asia Aging Study
- Prospective cohort
- 2,257 men, 71-93 years
- Men who walked the least (<0.25 miles/day) had 1.8 fold excess risk of dementia compared to those who walked > 2 miles/day, RH 1.77 (1.04-3.01)

Abbott RD et al. JAMA. 2004;292(12):1447-
Lifestyle - Physical Activity

- Nurses Health Study
- Prospective cohort
- 18,766 women
- Energy expenditure by questionnaire
- 20% lower risk of cognitive impairment in those with the highest level of activity.
- Even walking 1.5 miles/week associated with better cognitive performance

Weuve J et al. JAMA 2004;292(12):1454-1461
• Canadian Study of Health & Aging
• 6,434 participants, 5 year f/u, 283 developed dementia (194 AD)
• Self reported frequency & intensity rated:
  ▪ High ≥ 3x/week & > vigorous than walking
  ▪ Moderate ≥ 3x/week & equal to walking
  ▪ Low ≤ 3x/week or < vigorous than walking
• High activity: AD OR = 0.50 (0.28-0.90)
• Trend for increase protection with increase physical activity

Laurin et al, Arch Neurol 2001; 58:498-504
Lifestyle - Cognitive Activity

• Concept of cognitive reserve: innate intelligence or aspects of life experience like educational or occupational attainments may supply reserve in form of set of skills or repertoires that allow some people to cope with progressing AD pathology better than others

• Intellectually challenging activity of various types has been associated with a reduced risk of dementia in longitudinal studies. Currently no published RCT.
Lifestyle - Cognitive Activity

- Washington Heights Study
  - Prospective cohort, 1,772 healthy participants
  - Reduced risk of all cause dementia (RR 0.62) among participants who engaged in higher level of leisure activity (self-reported >6 of 13 activities vs. < 6 activities in previous month)
    Scarmeas et al. Neurology 2001;57:2235-42

- RCT: 2,832 healthy participants, improved cognition with different cognitive training interventions
  Willis SL et al. JAMA 2006; 296:2805-14
Lifestyle - Diet

• With the exception of one study, association between high dietary antioxidant intake and decreased risk for AD consistently reported.
• Intervention trials of antioxidant supplementation have demonstrated no major benefit against cognitive impairment.
## Lifestyle - Diet

### Prospective cohort trials with healthy subjects:

<table>
<thead>
<tr>
<th>#</th>
<th>Outcome</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>8085</td>
<td>Dementia</td>
<td>Fruit and vegetable intake vs. fish and omega-3 fat</td>
<td>Decreased risk for dementia with high fruit, vegetable, fish and omega-3 intake</td>
</tr>
<tr>
<td>980</td>
<td>AD</td>
<td>Daily intake of calories, carbs, fats and proteins</td>
<td>Increased risk for AD with increased caloric and fat intake</td>
</tr>
<tr>
<td>1718</td>
<td>Cognition</td>
<td>High vs low fruit and vegetable intake</td>
<td>Slower cognitive decline with high vegetable intake</td>
</tr>
<tr>
<td>2258</td>
<td>AD</td>
<td>Adherence to Mediterranean diet vs. no adherence</td>
<td>Decreased risk for AD with increased adherence to Mediterranean diet</td>
</tr>
<tr>
<td>1041</td>
<td>AD</td>
<td>Nutritional folate, B12, B6 vitamins</td>
<td>No association</td>
</tr>
</tbody>
</table>
Lifestyle Factors

Canadian consensus recommendations:
• Insufficient evidence to recommend for or against reducing risk of dementia: (although physicians may advise patients about and advocate for)
  ▪ Reduction risk of serious head injuries [C,2]
  ▪ Wearing protecting clothing during administration of pesticides, fumigants, fertilizers, defoliants [C,2]
  ▪ Higher levels physical or mental activity [C,2]
  ▪ Appropriate levels of education and strategies to retain students in appropriate learning environments [C,2]
  ▪ Increased consumption of fish, reduced
Medications: Anti-Inflammatory Drugs

- Meta-analysis of 9 case control, cohort studies, pooled RR of AD among NSAID users of 0.72; RR among short terms users 0.95 (0.70-1.29), intermediate users 0.83 (0.65-1.06) and long-term users 0.27 (0.13-0.58)
  
  Etminan M et al. BMJ 2003;327:128

- RCT: Naproxen vs. Celebrex vs. Placebo
  - 2,528 people > 70 years with FamHx AD
  - Study stopped after 3 years: no evidence anti-inflammatories prevent AD
  - After 2 years f/u, AD risk actually increased in both treatment groups (HR = 4.1, 3.6)
Medications: Estrogen/Progestin

• Women’s Health Initiative Memory Study
  - 4,352 healthy post-menopausal women (65-79 years) randomized to estrogen + progestin or placebo
  - Outcome “probable dementia
  - 40 cases in estrogen + progestin group
  - 21 cases in placebo group
  - Estrogen+progestin increased risk for probable dementia (HR 2.05)

  Shumaker SA, et al. JAMA, 2003;289(20)
Medications: Estrogen Only

- Women’s Health Initiative Memory Study
- 2,947 healthy post-menopausal women randomized to estrogen only or placebo
- Outcome “probably dementia”
- 28 cases in estrogen group
- 19 cases in placebo group
- Increased risk of development of probable dementia (HR 1.49)
- Pooled data increased risk (HR 1.76; CI 1.19-2.6)

Shumaker SA, et al. JAMA 2004; 291(24)
Medications

Canadian consensus recommendations:

- Insufficient evidence for or against for purpose of reducing dementia:
  - NSAIDs [C,2]
  - Vitamin E, C supplementation [C,2]
    - High dose vitamin E (≥ 400 IU/d) associated with excess mortality and NOT recommended [E,1]
- Good evidence to avoid estrogen +/- progesterone for purpose of reducing dementia [E,1]
52 year old female:
- Ensure good BP control - most evidence
- No proven therapies to prevent dementia
- Other CV RF: cholesterol
- No role for genetic testing
- No role for HRT, evidence to avoid
- Encourage healthy lifestyle