Alzheimer Disease and Down Syndrome: What is the Connection?

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Down Syndrome

- Down Syndrome (DS) is the most common genetic cause of mental retardation.
- It occurs in about 1 out of 800 live births
- It is caused by
  - Trisomy 21 - child has extra copy of chromosome 21 in every cell (94%)
  - Translocation - part of one chromosome becomes attached to part of another (usually involves chromosomes 14 and 21) (3-4%)
  - Trisomy 21 mosaicism - caused by an error in cell division and results in different cells having different numbers of chromosomes (2-3%)
Figure 6-2 Karyotype of a trisomy 21 cell. Trypsin-Giemsa (GTG) banding. (From Simpson JL, Elias S: Genetics in Obstetrics and Gynecology, 3rd ed. Philadelphia, WB Saunders Company, with permission.) from MD Consult retrieved 02/24/2010
Individuals with Down Syndrome are Living Longer

In early 20th century, mean survival was nine years; today it is approximately 60 years.

Why?

Congenital heart defects are now promptly corrected.

Improvements in public health, nutrition and medical care resulting in increased life expectancies in general population.
Causes of Mortality in DS

- **Early life**
  - Congenital heart disease (still)
  - Leukemia

- **Later in life**
  - Alzheimer Disease (AD)
  - Increased tendency toward premature aging
Because adults with DS are now living longer, they are subject to many of the same age-related diseases as the general population.

Additionally persons with DS are more susceptible to many age-related processes.
Accelerated Aging in Persons with Down Syndrome

- Age related skin changes and graying of hair
- Early Menopause
- Osteoporosis
- Osteoarthritis
- Hypothyroidism
- Increased hearing and vision problems (especially cataracts)
- Increased incidence of seizures
- Immunological changes (therefore ↑ infections)
But NO acceleration of atherosclerosis
- Less high blood pressure
- Less heart disease
- Less stroke

No increase in cancer (solid tumors)

No increase in diabetes—despite prevalence of obesity.
There has long been an association between dementia and Down syndrome—even before AD was formally recognized as a disease.

- For many years, this association was of academic interest only since few persons with DS lived long enough to actually manifest AD.
As longevity for adults with DS increased, it was thought that 100% of persons with DS, if they lived long enough, would develop Alzheimer disease.

*Kumar: Robbins and Cotran Pathologic Basis of Disease, Professional Edition*, 8th ed

From MD consult accessed 02/24/2010
Why?

- At autopsy, the brains of patients with AD and adults with DS have many similarities—namely the plaques and neurofibrillary tangles that are characteristic of AD.

http://www.ahaf.org/alzheimers/about/understanding/plaques-and-tangles.html
Neuropathologic changes consistent with those seen in Alzheimer Disease appear early (around 30-40 yrs.) in almost persons with DS

BUT

Actual symptoms of dementia often don’t appear until after age 50, if at all.
Although persons with DS have a greater risk of developing Alzheimer disease, NOT ALL DO
and “some people with DS survive dementia free into their middle and late 70’s”¹

Diagnosing Alzheimer Disease in any adult can be difficult

- Presenting signs and symptoms of Dementia can be difficult to distinguish from those of
  - Delirium
  - Depression
It can be even more difficult in adults with Down Syndrome

- Commonly used screening tests such as the Mini-mental status exam or the Mini-cog were created for individuals with an average IQ of about 100. Individuals with Down syndrome can often have IQ of 70 or below. Many of the tests also require
  - Good verbal skills
  - Compliance
  - Dexterity
  - Ability to pay attention
Folstein Mini-Mental Status Exam


CLOSE YOUR EYES

1. Write a complete sentence.

1. Copy design.
Even more so than in the general population, physicians have to rely on informant (caregiver) reports.

- Often caregivers are themselves aging and experiencing cognitive difficulties.
- Informants may not know the individuals well or
- They may know them too well.

\[\text{”Detecting change might be paradoxically more difficult for those who see the individual with Down syndrome daily than for those who see them weekly or monthly.”}\] \(^1\)

\(^1\)Nieuwenhuis-Mark, R. E. (2009) p.828
Memory problems are often **not** first (as they are in the general population with AD)

In persons with DS, “frontal lobe” or behavioral symptoms are generally seen first.

- Personality changes
- Indifference
- Uncooperativeness
- Apathy
- Irritability
- Aggressive behavior
- “Silliness”
These symptoms are, in turn, difficult to distinguish from depression.

- Depression is the most common mental health issue among individuals with DS and can complicate neuropsychological testing.
Risk of developing Alzheimer’s disease in individuals with Downs syndrome is NOT related to:

- Living arrangement
- Degree of mental retardation
- Gender
Risk of developing Alzheimer disease in individuals with Down syndrome MAY be related to:

- Genetic make-up: APOE allele
- Hormones: Estrogen
- Cholesterol
- Statin use
Genetic make-up

- Apoliprotein E gene on 19th chromosome: one allele inherited from each parent to make up gene
  - e2 – decreased risk for AD (also increases longevity in adults with DS)
  - e3 – most common
  - e4 – increased risk (two alleles greater risk than one)
Estrogen

- In all women, AD seems to be associated with decreasing levels of estrogen (controversial whether exogenous estrogen helps protect against, or hastens onset of AD).
  - Women with DS experience menopause at earlier ages than typically developing women.
  - This may contribute to the higher incidence of AD in the population with DS when compared with the population without.
There may be an association between high levels of cholesterol in midlife and the development of AD in all populations. 

- In one study of adults with DS, participants with cholesterol levels greater than 200 mg/dl had twice the likelihood of developing AD.
- In those receiving statin medications, that likelihood reversed to normal.

However, the reduction of AD with the use of statins may be related to an effect other than the cholesterol lowering effect.
General Recommendations for improving diagnosis of AD in adults with DS

(a) Introduce a clause into standard classification systems of dementia to include the Down syndrome population

(b) Educate carers, families and specialists on how to recognize change in individuals with Down syndrome

(c) Follow up patients over the long term (begin at age 35 at yearly intervals)

Nieuwenhuis-Mark, R. E. (2009)
General Recommendations cont’d

(d) Assess cognition, emotion, personality and daily living changes

(e) Recognize that those living in institutions may not be intellectually stimulated making change even harder to detect

(f) Recognize that memory problems may not be the first sign of dementia

Nieuwenhuis-Mark, R. E. (2009)
(g) Clinical judgment and (neuropsychological) testing are both important because clinicians tend to overestimate dementia in this population (Burt et al., 2005)

(h) Be aware that informants also age and that this can affect their judgment (Bush & Beail, 2004)
Neuropsychological Assessment Tools

Book: Neuropsychological Assessments of Dementia in Down Syndrome and Intellectual Disabilities, 2009 by Vee P. Prasher (Editor)
When diagnosing dementia, the diagnosis requires a change in status over a period of at least six months in both

- Cognitive functioning
- Behavioral functioning
Instruments Administered to Informants

- Family members, caregivers, professionals can comment on an individual’s past performance, abilities, and changes in everyday function.
- Use with caution but can be useful when repeated over time.
- Used when baseline measures may not be available.
- There is an issue of interrater reliability.

Some scales include:

- Dementia Questionnaire for People with ID (DMR)
- Dementia Scale for Down Syndrome (DSDS)
- Early Signs of Dementia Checklist (ESDC)
- Short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)
Instruments Administered to Persons with ID

- Difficult to administer neuropsychological tests to those with severe ID
- Sequential testing has been recommended to identify decline
- Researchers are investigating alternatives

- Down Syndrome Mental Status Exam (DSMSE)
- Test for Severe Impairment (TSI)
- Severe Impairment Battery (SIB)
- Cambridge Cognitive Exam (CAMCOG)
- Dyspraxia Scale
- Adaptive Behavior Dementia Questionnaire (ABDQ)
Dementia Questionnaire for People with ID (DMR)

- Original test published in Dutch by Evenhuis (1990)
- 50 items divided into two subcategories
  - Cognitive Scores:
    - short term memory, long-term memory, spatial and temporal orientation
  - Social Scores:
    - speech, practical skills, mood, activity and interest, behavior and disturbance
DMR

- Family member or staff scores his/her behavior over the previous 2 months
- Does not require previous training to use
- Takes about 15 – 20 minutes to complete
- Specifically designed for use with people with ID
- Drawback: less sensitive for persons in the severe and profound ranges of ID
DMR

Copyrighted (there is an abbreviated DMR). Two examples of questions.

• Understands what you want to make clear to him/her (by means of speaking, writing or gesticulation)

• Remembers where he/she put away something just a minute ago (no longer than a half hour ago)

- Rate by using: yes, sometimes, no
Can screening instruments detect dementia in adults with ID?

OPEN to debate because of:

- Premorbid level of intellectual functioning
- Decline in individuals with more severe ID can present with a different picture
- Changes in cognition but be accompanied by changes in behaviors and function
- Changes over time must also be greater than those related to normal aging in adults with ID
- Difficult to establish cut off scores
References


Additional Resources