Alzheimer's disease pathogenesis in Down syndrome

Elizabeth Head, Ph.D.
Department of Pharmacology & Nutritional Sciences
Sanders-Brown Center on Aging
University of Kentucky
Lexington, KY
Learning Objectives

- Cause of Down Syndrome
- Alzheimer’s Disease in Down Syndrome
- Sequence of pathological events
- Treatments/Prevention
- Longitudinal Aging study at UK – outcomes so far and future directions
Down Syndrome in the US

- Down Syndrome (DS) is the most common cause of intellectual disability and there are a total of >6,000 births/year in the USA (2010).
- 1 in 691 babies are born with DS in the US – up from 1990 (1 in 1087)
- Current prevalence rates?
DS Births are slowly increasing

Total births by year for 1909-2008. Although the US and Down syndrome curves are mostly parallel, there is a notable dip in the births of infants with Down syndrome in the 1970s owing to fewer births among women in their 30s and 40s. Both curves show an increase in births during the 1946-1964 baby boom, followed by a decline in the 1970s. This decline was primarily among older women, possibly related to the advent of the birth control pill in 1960, which enabled them to prevent additional pregnancies. Fewer births among older women translated to even fewer births of infants with Down syndrome. Presson et al., J Peds., 2013.
Down syndrome in the USA

- After age 35 years, mortality rates double every 6.4 years vs 9.6 years for non DS (Strauss & Eyman, 1996)

- Average life expectancy has improved from 25 years in 1983 to 60 years today
Mortality in Down syndrome

Mean, median, and 25th and 75th percentiles for age at death in persons with Down syndrome, 1900-2007. The mean and median age at death for persons with Down syndrome have increased significantly over the past 40 years. In 2007, the mean and median ages at death were 47.3 and 53 years, respectively, reflecting a 3.75-fold increase in average life expectancy since 1970 (Presson et al., J Peds., 2013).
ON SOME OF THE
MENTAL AFFECTIONS
OF
CHILDHOOD AND YOUTH
BEING
THE LETTSOMIAN LECTURES
DELIVERED BEFORE THE MEDICAL SOCIETY OF LONDON
IN 1887
TOGETHER WITH OTHER PAPERS
BY
J. LANGDON DOWN, M.D.LOND.
FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS OF LONDON, SENIOR PHYSICIAN TO, AND
LECTURE ON CLINICAL MEDICINE AT, THE LONDON HOSPITAL, FORMERLY LECTURE ON
MEDICINE, MATERIA MEDICA, AND COMPARATIVE ANATOMY AT THE LONDON HOSPITAL, AND PHYSICIAN TO THE EARLSDON ASYLUM

With a Foreword by
Ann Gath

1887
Down syndrome

J. Langdon Down - 1887

LeJeune and Gautier, 1959**
Causes of DS

- full triplication of chromosome 21 (95%)
- translocation - piece of chromosome 21 is triplicated (may be on another chromosome -3-4%)
- mosaicism - some but not all cells of the body contain 3 chromosomes (1-2%)
Features of Down syndrome

- Hypothyroidism
- Psychiatric conditions (autism)
- Higher tendency towards obesity
- Obstructive sleep apnea
- Seizures
- Cardiovascular abnormalities
- Visual impairments
- Leukemia (children)

- Low prevalence of coronary artery disease
- Absence of atherosclerosis
- Lower blood pressure (compared to other ID)
- Less likely to have insulin resistance syndrome
- Reduced solid tumor formation
Brain Structural Differences - Cerebellum

Down syndrome – 46 years

Non-Down syndrome – 46 years
Structural Differences – Frontal/Cerebellum

Down syndrome – 46 years
Non-Down syndrome – 46 years
Structural Differences - Hippocampus

Down syndrome – 46 years

Non-Down syndrome – 46 years
Chromosome 21

2001

127 known genes – 300-400 predicted

Smallest chromosome

1.5% of total DNA

APP – Alzheimer’s disease
Aging in Down syndrome – A case study of MJ
Case History

- 33 year old man with DS in the mild to moderate range of disability
  - Special Olympics swimming champion
  - Many interests/hobbies
  - Took bus alone to workshop
  - Conversant, socially appropriate
  - No pathological reflexes
  - Chemically corrected hypothyroidism

- At age 39 years was still stable
At age 44 years presented clinically with:

- More prompts required for ADL activities
- Tasks took longer to complete
- Workshop productivity declined
- Onset of aggressive behaviors
- Developed irrational fears
  - Water phobia
  - Fear of walking stairs, heights
- Lost motivation for previously pleasurable activities
- Articulation and language production declined
- Pathological reflexes present
Case History Continued

- New onset seizures
- Developed pneumonia
- Died after a course of 36 months at age 46
- Consent for postmortem brain examination
880 g - 36 month course, died at 46 years
Extensive Plaque Pathology in Frontal Cortex
Extensive Plaque and Tangle Pathology in the Hippocampus
Adults with DS are vulnerable to AD with an earlier age of onset.

Earliest report of premature aging by Fraser and Mitchell in 1876.
What is the age of onset of AD neuropathology in DS?

Virtually all adults with DS over the age of 40 years have sufficient neuropathology for AD (Struwe, 1929; Jarvis, 1948) – including plaques and tangles.

Is this primarily due to APP overexpression or are other genes involved?

Mann et al., 1993
What happens if we don’t have full trisomy 21?
Case Study - Partial Trisomy 21

- Female with general phenotype of DS
- Mild learning disability
- No sign of dementia
- MRI - 6 mos prior - normal
- Died of pneumonia
- 78 yrs old female
- No AD pathology
- S100β triplicated not APP nor SOD1

Case Study – Partial Trisomy 21

- male followed for 42 months with no signs of dementia
- 66 years old
- Trisomic for SOD-1 but not APP
Case Study-
Mosaic DS

Mosaicism for Trisomy 21 in a Patient With Young-Onset Dementia

A Case Report and Brief Literature Review

John M. Ringman, MD; P. Nagesh Rao, PhD; Po H. Lu, PsyD; Stephen Cederbaum, MD

**Objective:** To describe a case of young-onset Alzheimer disease (AD) due to mosaicism for trisomy 21.

**Design:** Case report of a single patient.

**Setting:** Tertiary referral dementia clinic.

**Patient:** A 55-year-old man with a mild degree of developmental delay but no previous diagnosis of Down syndrome and only minimal physical manifestations of Down syndrome presented with gradually progressive cognitive impairment consistent with probable AD.

**Results:** Fluorescent in situ hybridization analysis of interphase chromosomes revealed trisomy 21 in 10% of peripheral lymphocytes.

**Conclusions:** As mosaicism for trisomy 21 can present with no or minimal manifestations of Down syndrome, it may be underdiagnosed as a cause of early-onset AD. Occult mosaicism for trisomy 21 may explain in part the previously described association between family history of Down syndrome and risk of AD. Screening for mosaicism with fluorescent in situ hybridization is indicated in selected patients with mild developmental delay and those with AD of young onset.

_Arch Neurol. 2008;65(3):412-415_

---

**Figure.** The patient with mosaicism for trisomy 21 at ages 6 to 12 months (A), 21 years (B), and 55 years (C). Micrognathia is apparent but many specific features of Down syndrome are absent. D. Clinodactyly with a shortened middle phalanx of the fifth digit bilaterally is present.
Given that all individuals with DS over the age of 40 years have neuropathology consistent with a diagnosis of Alzheimer’s disease then….

Studying the brains of individuals with Down syndrome at various ages will allow us to characterize early events in AD pathogenesis

Focus on Aβ first…. 
Senile Plaques

Plaques accumulate consistently after 30 years (Mann & Esiri, 1989)
Even younger?

Aβ42 Plaques in Young Down Syndrome Frontal Cortex

Photos courtesy of Cindy Lemere, Harvard Medical School
Amyloid Imaging in Down syndrome

Table 1  Demographic and clinical data of participants with DS

<table>
<thead>
<tr>
<th></th>
<th>DS (N = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD), range (min-max)</td>
<td>46.3 (4.7), 40-56</td>
</tr>
<tr>
<td>Sex, M/F, n (% M)</td>
<td>21/18 (53.8)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian, white</td>
<td>37 (94.9)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td>DSQI-ID total score, mean (SD), range</td>
<td>6.2 (8.0), 0-41</td>
</tr>
</tbody>
</table>

Abbreviations: DS = Down syndrome; DSQI-ID = Dementia Screening Questionnaire for Individuals with Intellectual Disabilities; max = maximum; min = minimum.

Age dependence of brain [beta]-amyloid deposition in Down syndrome: An [18F]florbetaben PET study.
Jennings, Danna; Seibyl, John; Sabbagh, Marwan; Lai, Florence; Hopkins, William; Bullich, Santi; Gimenez, Monica; Reinerger, Cornelia; Putz, Barbara; Stephens, Andrew; MD, PhD; Catafau, Ana; MD, PhD; Marek, Ken
DOI: 10.1212/WNL.0000000000001212

Table 1  Demographic and clinical data of participants with DS
[18F]Florbetaben PET scans in Down syndrome. Figure 2. Axial slices from [18F]florbetaben PET scans in 2 subjects affected by Down syndrome (DS). These images are representative of an individual with DS without amyloid deposition (upper row: negative scan) and an individual with DS with amyloid deposition (bottom row: positive scan). SUVR = standardized uptake value ratio.
Composite standardized uptake and age and classification of positive PET scans by visual assessment. Figure 1. (A) Scatterplot of the composite standardized uptake value ratio (SUVR) vs age. SUVR = 0.030[middle dot]age + 0.045, R² = 0.39. (B) SUVR for Down syndrome (DS) by age subgroup. DS subgroups showed mean composite SUVR values with age, in the following distribution: DS 40-44 years (n = 14): 1.27 +/- 0.11; DS 45-49 years (n = 15): 1.43 +/- 0.16; and DS >=50 years (n = 10): 1.62 +/- 0.26 (*p < 0.05). (C) Percentage of positive PET scans by visual assessment for DS classified by age subgroups. The highest number of positive scans was found in the subjects with DS aged 50 years and older (9/10, 90%), followed by the subgroup aged 45 to 49 years (8/15, 53%), and the subgroup aged 40 to 44 years (1/14, 7%). (D) Scatterplot of the composite SUVR vs Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID) score. Subjects with a positive scan are shown as closed circles and those with a negative scan are open circles. For this analysis, n = 34 as DSQIID was not available for 5 subjects.
Aβ accumulates prior to neurofibrillary tangle formation

- Anti- Aβ 1-42 and anti-phosphorylated tau (PHF)
- Mann, 1993
Prevalence of SP and NFT in DS – what do we predict is the age of onset for dementia?

Mann et al., 1993
AD progression in DS

10 20 30 40 50 60 YEARS

% affected

Age (years)
The triple challenges associated with age-related comorbidities in Down syndrome

Visual impairment

Hearing impairment

Epilepsy

Thyroid disorders

Dementia

Journal of Intellectual Disability Research
Volume 58, Issue 4, pages 393-398, 19 MAR 2013 DOI: 10.1111/jir.12026
Welcome!

Adults with Down syndrome are living long, productive, and healthy lives but face several challenges as they grow older. Although many people remain healthy, they are a vulnerable group of people who may develop Alzheimer’s disease.

Alzheimer’s disease is the most common form of dementia in our aging population and the earlier one is diagnosed, the better the possibilities are for symptomatic treatment of this disease. Currently, however, there are no cures for Alzheimer’s disease.

Adults with Down syndrome are, unfortunately, at higher risk for developing Alzheimer’s disease because most have an extra copy of chromosome 21. On this chromosome is a gene that is strongly linked to the development of Alzheimer’s disease. The good news is, not everyone with Down syndrome will develop dementia.

The goal of our research is to follow people with Down syndrome as they get older. This will help us to understand why and who will develop dementia. Importantly, if we follow people who do not develop dementia we may be able to learn how to prevent this from occurring in others. The Down syndrome aging study is a new 5 year federally funded project taking place at the University of Kentucky that will allow us to follow adults with Down syndrome as they age to learn more about the challenges they might face.
DS Aging Study

- Recruiting people with DS ages 25 years and older, with and without dementia
- Will be followed for 5 years, annual visits
- Blood sample, health labs
- Neurologic examination
- Neuropsychological testing
- MR imaging
- Autopsy studies (separate cohort)
What are we learning?
White Matter Integrity (DTI)

Diffusion Tensor Imaging

- In vivo method to characterize structural white matter properties connecting distributed networks
- Measures the rate and direction of the diffusion of water molecules
- Fractional Anistropy (FA) reflects white matter integrity
- Higher FA = more integrity
Does white matter integrity reflect DS phenotype and/or dementia status?

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>All DS (n=20)</th>
<th>DS (n=10)</th>
<th>DSAD (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>51.38 (6.48)</td>
<td>50.61 (5.53)</td>
<td>52.16 (7.54)</td>
</tr>
<tr>
<td>Gender (men/women)</td>
<td>7/13</td>
<td>4/6</td>
<td>3/7</td>
</tr>
<tr>
<td>BPT (mean, SD)</td>
<td>63.65 (16.78)</td>
<td>73.40 (4.06)</td>
<td>53.90 (19.15)</td>
</tr>
<tr>
<td>SIB (mean, SD)</td>
<td>74/70 (22.04)</td>
<td>85.40 (11.18)</td>
<td>64.00 (25.45)</td>
</tr>
</tbody>
</table>

N=10 Age and Gender matched general population controls (to DS without dementia)

Powell et al., 2014, Neurobiology of Aging
**Brief Praxis Test (BPT)**

**Scoring:**
- **4 Points:** A correct response on request (1 repeat) without any prompts within 5-8 seconds.
- **3 Points:** A correct response following additional verbal cues and verbal hints.
- **2 Points:** A correct response following a display by the examiner of how the correct response should be executed.
- **1 Point:** A correct response following "physical prompting" using hand-over-hand, in which the examiner may place his/her hand over the person's hand, or doing something for the person.
- **0 Points:** Person is unable or unwilling to perform the response.

**Note:** Scores of 0, 1, 2, 3, or 4 are used for items 1-16 only. Scores of 0 or 4 only are used for items 17-20 with no prompting.

**WHILE STANDING**

<table>
<thead>
<tr>
<th>1. Clap your hands</th>
<th>5. Turn your head to the other side</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 4</td>
<td>□ 4</td>
</tr>
<tr>
<td>□ 3</td>
<td>□ 3</td>
</tr>
<tr>
<td>□ 2</td>
<td>□ 2</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 1</td>
</tr>
<tr>
<td>□ 0</td>
<td>□ 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Lift one arm over your head</th>
<th>6. Lift one leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 4</td>
<td>□ 4</td>
</tr>
<tr>
<td>□ 3</td>
<td>□ 3</td>
</tr>
<tr>
<td>□ 2</td>
<td>□ 2</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 1</td>
</tr>
<tr>
<td>□ 0</td>
<td>□ 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Lift the other arm over your head</th>
<th>7. Lift the other leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 4</td>
<td>□ 4</td>
</tr>
<tr>
<td>□ 3</td>
<td>□ 3</td>
</tr>
<tr>
<td>□ 2</td>
<td>□ 2</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 1</td>
</tr>
<tr>
<td>□ 0</td>
<td>□ 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Turn your head to the side</th>
<th>CONTINUED ON NEXT PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 4</td>
<td>□ 3</td>
</tr>
<tr>
<td>□ 3</td>
<td>□ 3</td>
</tr>
<tr>
<td>□ 2</td>
<td>□ 2</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 1</td>
</tr>
<tr>
<td>□ 0</td>
<td>□ 0</td>
</tr>
</tbody>
</table>

**WHILE SEATED**

<table>
<thead>
<tr>
<th>8. Place each of the coins in the Jar</th>
<th>14. Close the Jar</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 4</td>
<td>□ 4</td>
</tr>
<tr>
<td>□ 3</td>
<td>□ 3</td>
</tr>
<tr>
<td>□ 2</td>
<td>□ 2</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 1</td>
</tr>
<tr>
<td>□ 0</td>
<td>□ 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. Place each of the coins in the Jar with the other hand</th>
<th>15. Unlock the padlock</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 4</td>
<td>□ 4</td>
</tr>
<tr>
<td>□ 3</td>
<td>□ 3</td>
</tr>
<tr>
<td>□ 2</td>
<td>□ 2</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 1</td>
</tr>
<tr>
<td>□ 0</td>
<td>□ 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10. Salute</th>
<th>16. Lock the padlock</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 4</td>
<td>□ 4</td>
</tr>
<tr>
<td>□ 3</td>
<td>□ 3</td>
</tr>
<tr>
<td>□ 2</td>
<td>□ 2</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 1</td>
</tr>
<tr>
<td>□ 0</td>
<td>□ 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>11. Scratch your head</th>
<th>17. Point to your index finger</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 4</td>
<td>□ 4</td>
</tr>
<tr>
<td>□ 3</td>
<td>□ 3</td>
</tr>
<tr>
<td>□ 2</td>
<td>□ 2</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 1</td>
</tr>
<tr>
<td>□ 0</td>
<td>□ 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>12. Snap your fingers</th>
<th>18. Give me a nickel</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 4</td>
<td>□ 4</td>
</tr>
<tr>
<td>□ 3</td>
<td>□ 3</td>
</tr>
<tr>
<td>□ 2</td>
<td>□ 2</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 1</td>
</tr>
<tr>
<td>□ 0</td>
<td>□ 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>13. Open the Jar</th>
<th>19. Give me a quarter</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 4</td>
<td>□ 4</td>
</tr>
<tr>
<td>□ 3</td>
<td>□ 3</td>
</tr>
<tr>
<td>□ 2</td>
<td>□ 2</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 1</td>
</tr>
<tr>
<td>□ 0</td>
<td>□ 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>14. Give me a dime</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 4</td>
</tr>
<tr>
<td>□ 3</td>
</tr>
<tr>
<td>□ 2</td>
</tr>
<tr>
<td>□ 1</td>
</tr>
<tr>
<td>□ 0</td>
</tr>
</tbody>
</table>
White Matter Integrity and Cognition

**Blue** – lower FA in DS vs. nonDS; **Green** – AD+DS have lower FA than DS
**Red** – decreased FA correlates with decreased BPT scores in DS
Changes in white matter and cognition in DS

Higher BPT score = better performance, Higher FA = better WM integrity
Cerebrovascular contributions to dementia in Down syndrome?
Vascular Imaging

T2* and FLAIR

Susceptibility weighted imaging - SWI
Cerebrovascular pathology

MicroBleed Count vs. Controls

- Number of Bleeds
- Sample Group

Legend:
- Young Controls Average
- CS Average
- Middle Age Control Average
- USDAO Average
- Old Controls Average
- Aporotic AD Average
- Individual Sample (Bleed Count)
AD progression in DS

10  20  30  40  50  60 YEARS

?}

% affected

Age (years)

35-40  41-45  46-50  51-55  56-60  >60
Drugs approved for use to treat AD in DS

- 5 approved drugs for AD (tacrine, donepezil, galantamine, exelon, memantine)
- Donepezil - studies small and show modest or no effect with high adverse events (2009), recent 2011 study in 21 females with severe cognitive impairment suggests improvement
- Galantamine – no studies (2009)
- Exelon – one small study of rivastigmine patch n=10 (2012)
- Tacrine – no studies
Summary – aging in DS

- Individuals with DS are at high risk for AD with an earlier age of onset
- Due to APP overexpression and early onset beta-amyloid accumulation
- Age-dependent brain changes involve beta-amyloid, then tangles, and then dementia
- By studying tissue from individuals with varying ages we can learn what the earliest signs are of AD pathology
- We can identify appropriate ages for prevention or treatment clinical trials
People with Down syndrome may teach us about early changes that help us diagnose and prevent Alzheimer’s disease in the general population.
The most important people in our team!
Our Research Team