Alzheimer’s disease pathogenesis in Down syndrome

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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 51 years, respectively, reflecting a 3.75-fold increase in average life expectancy since 1970 (Presson et al., J Peds., 2013).
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

Case History Continued

- 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
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 (Struve, 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 with Brief Literature Review

John W. Wagens, MD, and John T. O'Dell, MD, F.A.C.P., F.A.A.M., Naples, Florida

Objectives: To describe a case of mosaic Down's syndrome with a female mosaicism of trisomy 21.
Design: Case report of a single patient.
Setting: tertiary academic medical center.
Method: A 51-year-old woman presented with a 3-year history of progressive memory loss and mild ataxia. Neurologic examination findings included hyperactive deep tendon reflexes, a wide-based gait, and mild speech abnormalities. Cerebrospinal fluid analysis was normal. A computed tomography scan of the brain showed mild atrophy. A karyotype analysis revealed a mosaic karyotype of 46,XX,47,XX,+21/46,XX,47,XX,+21.

Results: There were no abnormalities detected in the karyotype analysis, and the patient's symptoms improved with supportive care.

Conclusions: A mosaic karyotype for trisomy 21 can present with a clinical picture resembling that of Down's syndrome. The management of mosaic Down's syndrome should focus on symptom control and support services.

Senile Plaques

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

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….
Even younger?

**AB42 Plaques in Young Down Syndrome Frontal Cortex**

Photos courtesy of Cindy Lemere, Harvard Medical School

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**Amyloid Imaging in Down syndrome**

<table>
<thead>
<tr>
<th>Table 1 Demographic and clinical data of participants with DS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DS (N = 8)</strong></td>
</tr>
<tr>
<td>Age, y, mean (SD), range [min-max]</td>
</tr>
<tr>
<td>49.3 (4.7), 40-60</td>
</tr>
<tr>
<td>Sex, M/F, n (%)</td>
</tr>
<tr>
<td>21/18 (53%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
</tr>
<tr>
<td>Caucasian, white</td>
</tr>
<tr>
<td>97 (94.6)</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>2 (2.1)</td>
</tr>
<tr>
<td>EQD2 total score, mean (SD), range [min-max]</td>
</tr>
<tr>
<td>0.2 (0.1), 0.2-0.4</td>
</tr>
</tbody>
</table>

**Abbreviations:** DS = Down syndrome; DISQID = Dementia Screening Questionnaire for Individuals with Intellectual Disabilities; SUVR = standardized uptake value ratio.

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**Amyloid Imaging in Down syndrome**

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.
Amyloid Imaging in Down syndrome

Aβ accumulates prior to neurofibrillary tangle formation

31 years  37 years  40 years

- 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

The triple challenges associated with age-related comorbidities in Down syndrome
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 Anisotropy (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
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

AD progression in DS

10 20 30 40 50 60 YEARS

?
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