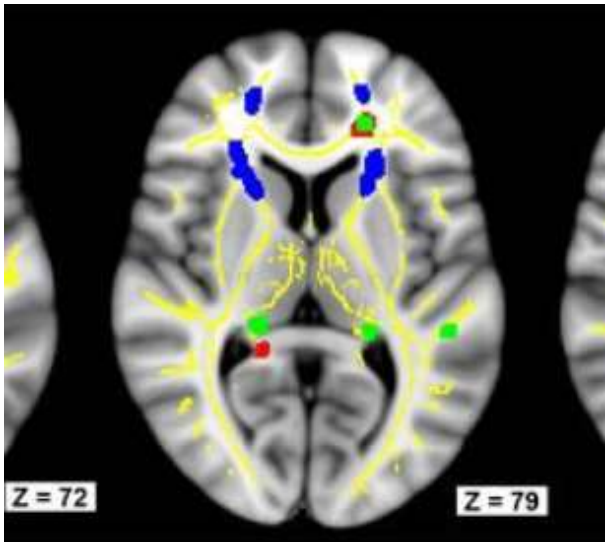
Neurobiology and Characteristics of Down Syndrome

Dr. Shaguna Mathur



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Disclosure

I do not have any disclosures.

- *This presentation is for educational purposes only and should not be used as a substitute for clinical judgement.*
- *The presenter assumes no responsibility or liability resulting from the use of information contained herein.*

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Clinical Presentation

- Named after Dr. John Down who first described the clinical features in 1866
- Chromosomal changes identified in 1959 by Dr. Jerome Lejeune

  - Decreased muscle tone
  - Excess skin at the nape of the neck
  - Brushfield spots (white spots in iris)
  - Upslanting eyes
  - Flattened nose and midface
  - Upward slanting eyes
  - Small ears
  - Small jaw
  - Large tongue
  - Wide, short hands with small fingers
  - Single crease in the palm of the hand
  - Increased space between big toe

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Epidemiology

- Incidence in 1/800 live births
- Over 350,000 people in the US have Down syndrome
- Over 6million people worldwide have Down syndrome
- Occurs equally in all ethnic, racial, religious and socioeconomic groups

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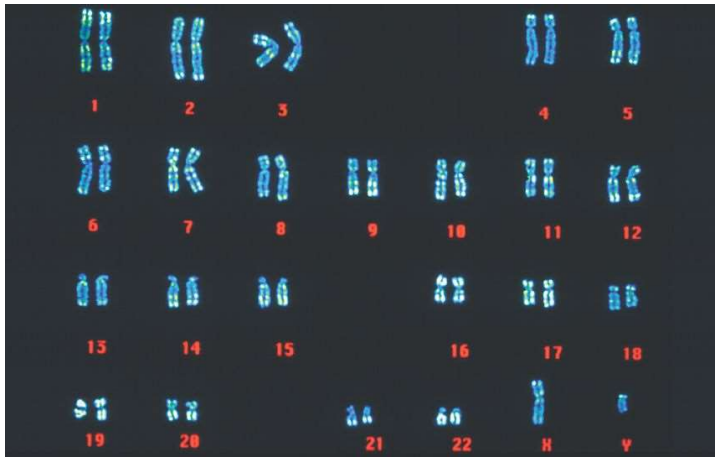
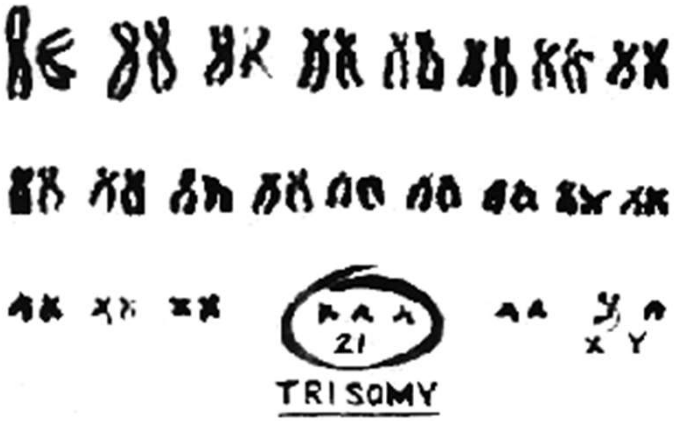
Etiology

- Often due to extra chromosome 21 (called non-dysjunction)
  - Normally, each egg and sperm cell has 23 chromosomes
  - The union of these creates 23 pairs, or 46 total chromosomes
  - Occasionally, an egg or sperm cell does not develop properly and contributes 24 chromosomes instead of 23





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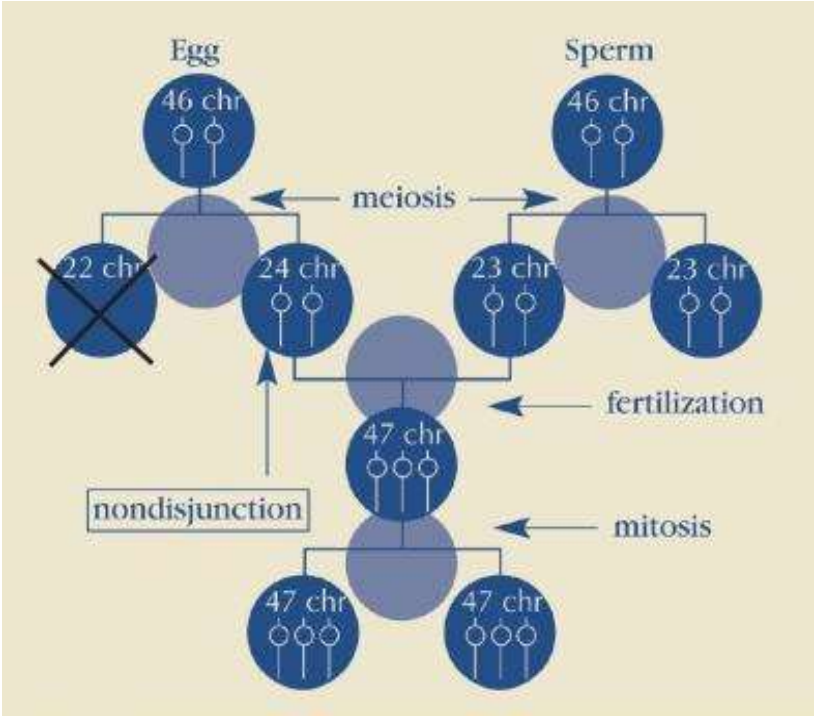
Genetics

- 90-95% complete trisomy 21 from non-dysjunction during meiosis
- 2-4% translocation
  - (usually 13-15 or 21-22)
  - Translocations are only type inheritable, potentially (1%)
- 2-4% mosaicism
  - Non-dysjunction occurs after fertilization resulting in two different cell lines



Non-dysjunction cell division-47 chromosomes

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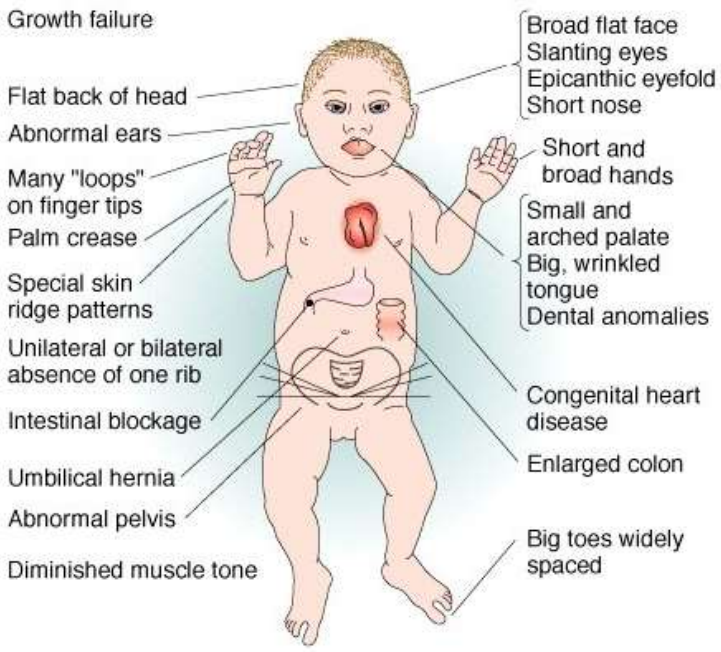
Conditions Associated with Down Syndrome

- Seizures
- Developmental concerns
- Autism (12%)
- ADHD (8%)
- Memory issues
- Low tone
- Hearing issues
- Hormonal disturbances
- Heart defects
- Vision concerns
- Sleep apnea
- Celiac disease
- Leukemia



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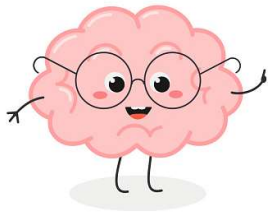
Neurological

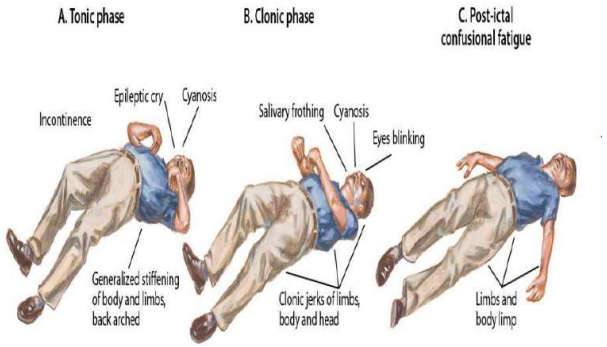


- Seizures
  - Incidence varies by age
    - High risk of infantile spasms in infancy
      - Prevalence 3% in Down syndrome population
      - Prevalence 0.4% in general population
    - 6% of school age children with Down syndrome experience seizures
    - 9% of young adults with Down syndrome experience seizures
    - 46% of adults >50yo with Down syndrome experience seizures

Glob Pediatr Health. 2019; 6: 2333794X18821939.
Published online 2019 Jan 9. doi: 10.1177/2333794X18821939

Tonic-Clonic

- The tonic phase (first phase) refers to stiffening
  - All the muscles stiffen
  - Patient loses consciousness
  - Air being forced past the vocal cords can cause a cry/groan
  - A person may bite their tongue or inside of their cheek
  - Often excess drooling is seen
- The clonic phase (second phase) refers to shaking
  - Limbs begin to jerk rapidly and rhythmically
  - The person may lose control of their bladder/bowel
  - The person may have respiratory compromise
- The post-ictal phase (recovery phase)
  - Consciousness, or a person's awareness, returns slowly



https://www.youtube.com/watch?v=FBEj9H42fa4

Epilepsy Toronto

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Infantile Spasms

- Infantile spasms are most common seizure type in Down syndrome
- Refers to a seizure with sudden stiffening of the body
  - Can be "flexor" where there is brief motion forward of the arms, legs and head
  - Can be "extensor" where there is brief motion backward of the arms, legs and head
  - Often mistaken for "morrow" reflex or "reflux"
- Usually very brief (1-2sec) but often cluster and cause alarm to infant
- Often occur in drowsy state (ex waking up)
- Can often cluster together in a row
- Peak incidence around 7months of age
- Associated with West syndrome

https://www.youtube.com/watch?v=VU6qNLOlU_A

UK Infantile Spasms Trust

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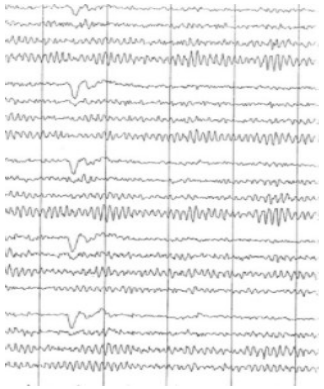
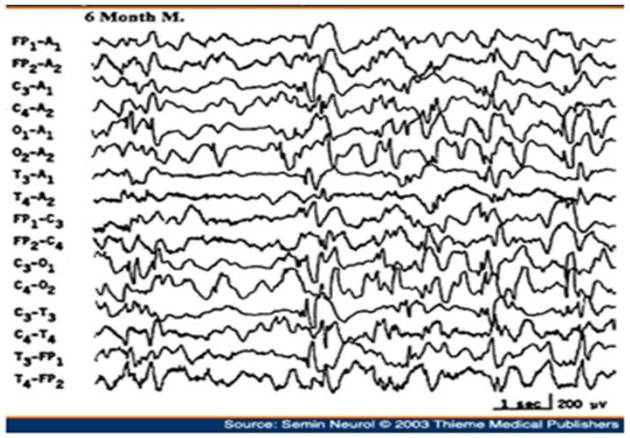
West Syndrome

- Triad of infantile spasms, developmental regression and abnormal EEG
- EEG classic disorganized pattern called "Hypsarrhythmia"
- Reason for increased risk of infantile spasms in Down syndrome unclear but Neuroscientists suspect it may be related to …
  - Underlying structural brain anomalies
  - Increased risk of hypoxia or stroke due to cardiac defects
  - Genetic overexpression



EEG: Normal



EEG: Hypsarrhythmia

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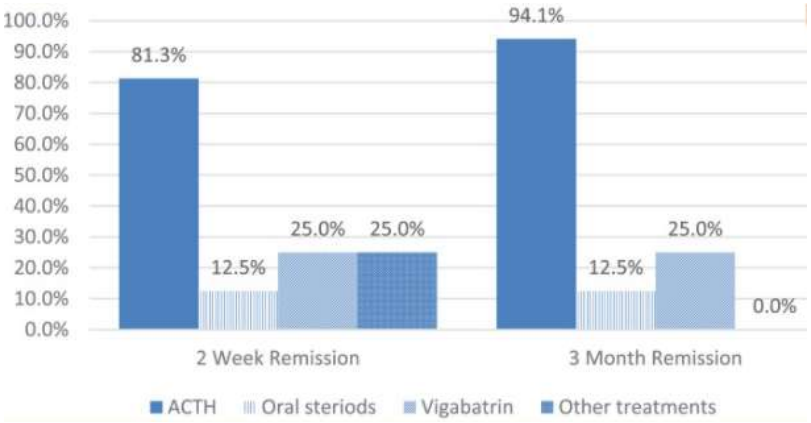
Treatment

- Treatment includes ACTH and Vigabatrin
- Roughly 12 of general population experiences control, with majority progressing to refractory epilepsy
- In Down syndrome there is noted favorable response to treatment if detected and treated early
- With ACTH 80%-90% experienced remission, however in some cases relapses were noted to occur up to 2years after cessation of medication
- After Vigabatrin discontinuation, and with a follow-up ranging from 2 to 4 years, none of the responders experienced spasm recurrence or other types of seizures



Treatment Outcomes of West Syndrome in Infants With Down Syndrome

Oranee Sanmaneechai MD[a,*], Yoshimi Sogawa MD[a,b,c], Wendy Silver MD[a,b], Karen Ballaban-Gil MD[a,b,c], Solomon L. Moshé MD[a,b,c,d,e,f], Shlomo Shinnar MD, PhD[a,b,c,f]

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Development

- Social and self-help skills usually are on track or early. They often remain as strengths
- Motor skills (sitting, walking, running) delayed due to low muscle tone, joints
- Language skills often start on time, but usually slow in second year and affect talking more than understanding

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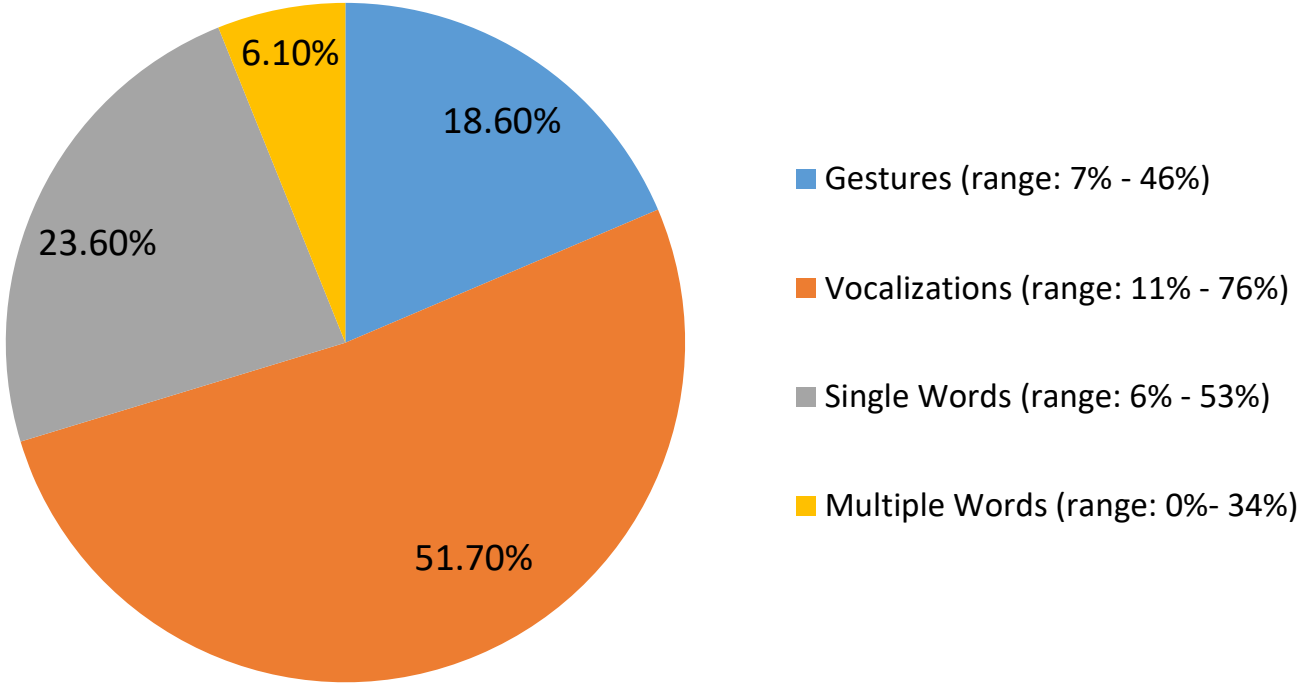
Early Communication Skills



The MIND Institute

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Autism and Down Syndrome

- Patients with Down Syndrome have an increased risk of developing Autism Spectrum Disorder
  - Suspect it is due to abnormal development of corpus callosum and limbic system
  - Role of gender unclear (2:1 ratio in boys vs girls)
    - Autism alone 4:1 ratio boys vs girls
- ~12% of patients with Down syndrome have a concurrent diagnosis of autism, however surveys indicate that it may be 30% in actuality
  - Reason for disparity is due to lack of consensus over diagnostic criteria
  - Children with Down syndrome + autism typically exhibit less impairments in social communication (A symptoms) and greater impairments in repetitive/compulsive behaviors (B symptoms)
  - Sometimes autism is overlooked in a child with Down syndrome due to level of cognitive impairment

(DiGuiseppi et al., 2010; Lowenthal et al., 2010; Moss et al., 2012)

Signs of Autism in Down Syndrome

- Repetitive motor behaviors (fingers in mouth, hand flapping)
- Fascination with and staring at lights, ceiling fans, or fingers
- Extreme food refusal
- Receptive language problems (poor understanding and use of gestures) possibly giving the appearance that the child does not hear
- Spoken language may be highly repetitive or absent

*If your child is exhibiting these symptoms, seek evaluation from Neurodevelopmental team trained in working with individuals with Down syndrome.
*Early diagnosis can guide therapies and teaching strategies to promote learning.

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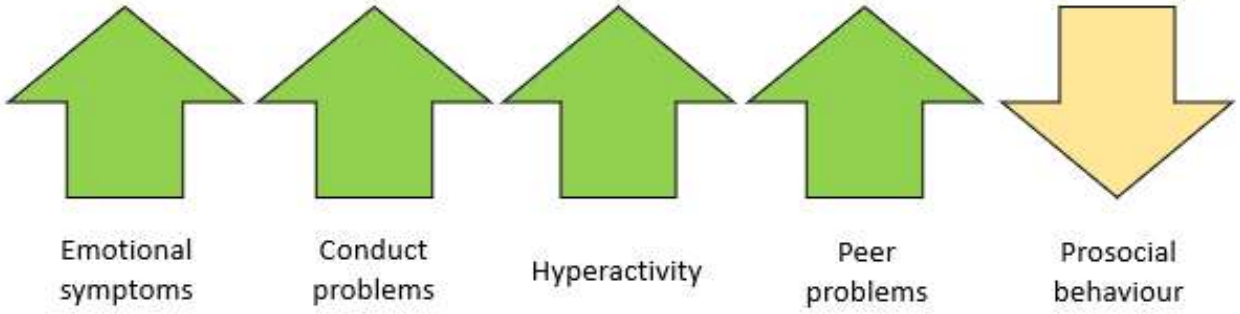
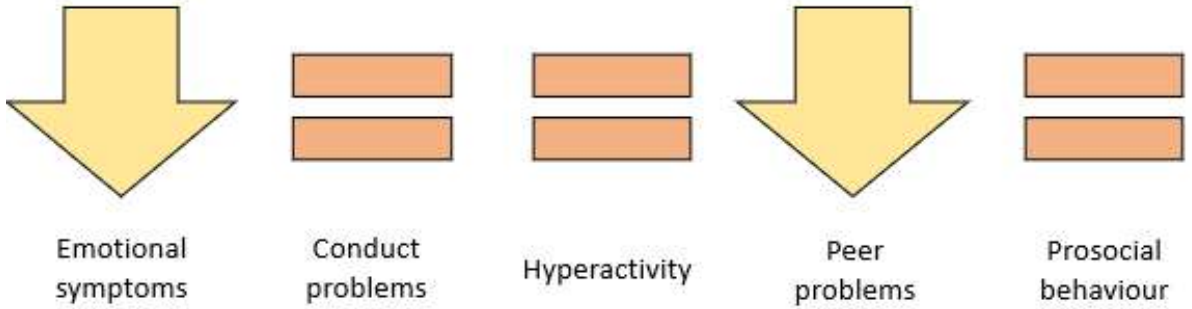
DS+ASD vs DS only



DS+ASD vs ASD only



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Employment

Social supports, cognitive skills, emotional and physical health predict adaptive function and employment

2015 survey

- 57% employed (3% full time)
- 20% volunteered
- 3% self-employed
- 30% unemployed

Kumin et al (2015) J of Applied Research in Intellectual Disability

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Mortality

- Life span
  - 25yrs of age in 1983
  - 50yrs of age in 1997

    Last population surveys (2015)
  - 44% live to > 60yrs of age
  - 14% live to >70yrs of age

- With increased life span comes its own challenges
  - More disorders of old age such as dementia and diabetes
  - Aging parents no longer able to continue care at home
  - Need residential options suitable for individuals with Down syndrome

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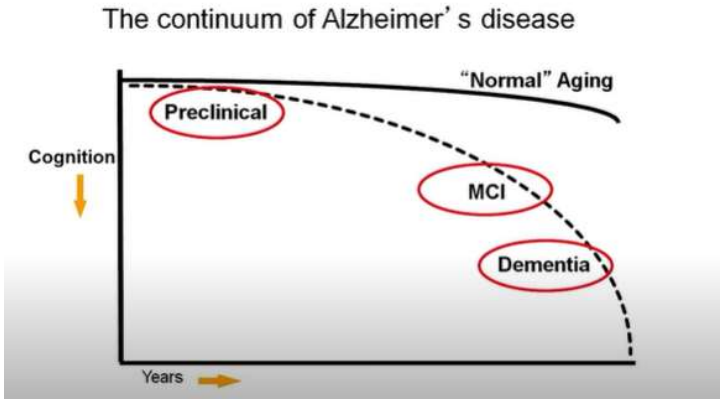
Memory

- Dementia is more common in individuals with Down syndrome
  - Overexpression of the amyloid precursor protein (APP) gene on chromosome 21
- Onset of dementia is about 10-20years earlier than general population
- Incidence of dementia in Down syndrome
  - 30yr of age: 15%
  - 50yr of age: 40%
  - 60yr of age: 55%
- Compared to general population, where 1/3 adults have dementia above 85yr of age
- Dementia takes years to manifest however preclinical changes present many years before



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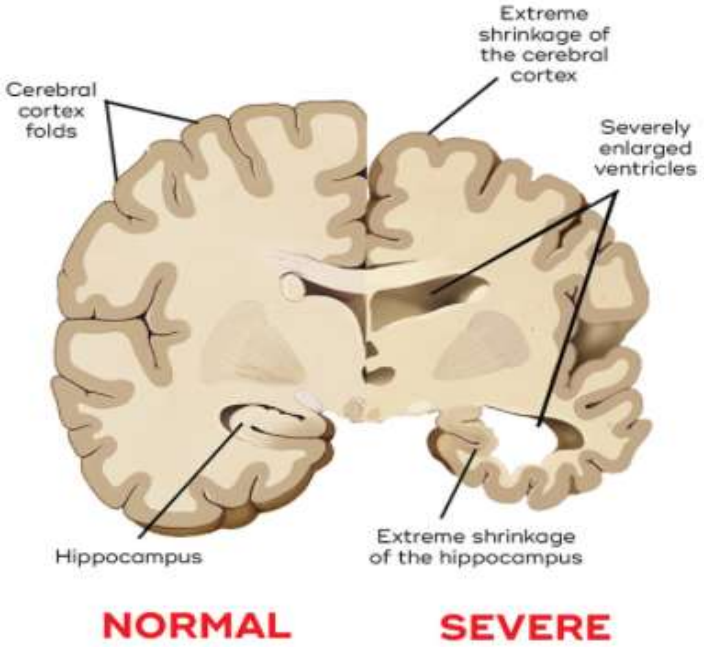
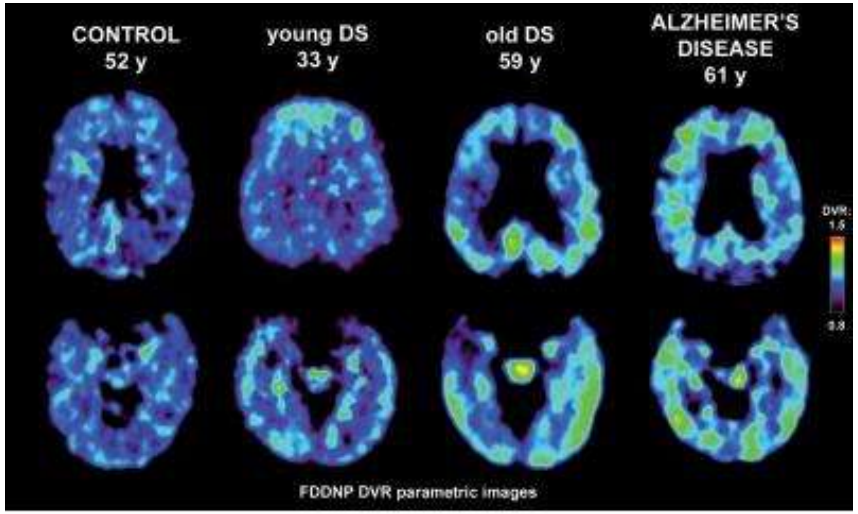
Preclinical Changes in Dementia





PET-FDDNP Brain Scans (IMAGE)
UNIVERSITY OF CALIFORNIA - LOS ANGELES HEALTH SCIENCES

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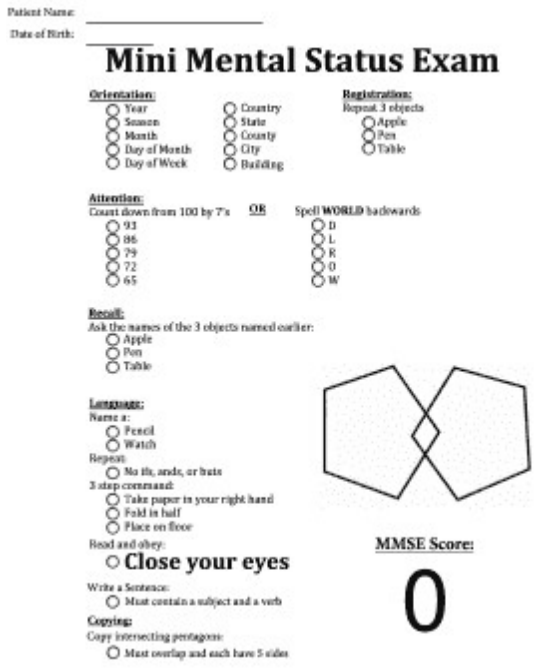
Clinical Signs of Dementia

Early signs include changes in personality/behavior along with cognitive decline

- Reduced interest in being sociable
- Decreased verbal skills
- Decreased enthusiasm for usual activities
- Sadness, fearfulness or anxiety
- Irritability, uncooperativeness or aggression
- Seizures that begin in adulthood
- Memory loss
- Persistent forgetfulness
- Loss of daily living skills


Patient Name: _____

Date of Birth: _____

Mini Mental Status Exam

Orientation:
- Year
- Season
- Month
- Day of Month
- Day of Week
- Country
- State
- County
- City
- Building

Registration:
Repeat 3 objects
- Apple
- Pen
- Table

Attention:
Count down from 100 by 7's **OR** Spell **WORLD** backwards
- 93
- 86
- 79
- 72
- 65
- D
- L
- R
- O
- W

Recall:
Ask the names of the 3 objects named earlier:
- Apple
- Pen
- Table

Language:
Name a:
- Pencil
- Watch

Repeat:
- No ifs, ands, or buts

3 step command:
- Take paper in your right hand
- Fold in half
- Place on floor

Read and obey:
- **Close your eyes**

Write a Sentence:
- Must contain a subject and a verb

Copying:
Copy intersecting pentagons:
- Must overlap and each have 5 sides

MMSE Score:

0

- Guidelines recommend routine screening and documenting baseline cognition
- Important to rule out other causes which could contribute to symptoms
- Medications for dementia (such as Aricept) may be recommend

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Sleep

- Sleep dysregulation
  - Melatonin for sleep initiation
  - Clonidine for sleep maintenance
- Sleep apnea
  - Adults with Down syndrome are predisposed to obstructive apnea/hypopnea syndrome (OSAHS)
    - Tend to have large tongue and small jaws
    - Large adenoids and tonsils can also lead to sleep apnea
  - Approximately 42% of individuals with Down syndrome have sleep apnea, 10x than the general population
  - Symptoms include behavioral disturbances (irritability), daytime sleepiness, heavy snoring
  - Treated with CPAP (continuous positive airway pressure), surgery
- Sleep should be screened as part of regular health surveillance

Audiology/ENT

- Hearing loss
  - Occurs in 30-75% children with Down syndrome by preschool
- Can be unilateral or bilateral
  - Some children may need hearing aid
- Can be conductive, sensorineural or mixed
- Ear infections (otitis media) is also common
- It is important to detect and intervene early
  - Hearing should be evaluated every 2 years*

*At Boys Town we check monitor hearing more closely

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Cardiovascular

- 40-60% born with congenital heart disease
  - Atrioventricular Septal Defect
  - Ventricular Septal Defect
  - Persistent Ductus Arteriosus
  - Tetralogy of Fallot
    - Ventricular septal defect
    - A narrowing of the passage from the right ventricle to the lungs
    - An over-enlarged right ventricle because of the backup of blood
    - An over-enlarged aorta, which carries blood from the left ventricle to the body
- Diagnosis is often made by echocardiogram
- Surgery is often recommended before 5-6 mo of age

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Ophthalmology

- Eyes: cataracts and glaucoma
  - 76% need glasses
  - 70% Cataracts
  - 57% Strabismus
  - 1% Glaucoma
- Vision should be checked annually

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Endocrine

- Hypothyroidism (low thyroid)
  - 1/140 congenital hypothyroidism
  - 30% by 25 years of age
  - Symptoms include weight gain, brittle nails, dry skin, sensitive to cold and lethargy
- Diabetes
  - Type 1 (insulin deficiency) – 3x risk in down syndrome
  - Type 2 (insulin resistance) – 4x risk in down syndrome

Thank you!

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