Congenital Etiologies: (Part 2)

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Down Syndrome & Fragile X Syndrome

Terry Broda
NP-PHC, CDDN

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What is Down Syndrome?

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- A common genetic variation (3 genetic ways)
- So certain genes on chromosome 21 are "overexpressed" & this usually causes health problems, intellectual & developmental disabilities (I/DD)
- Exact causes currently unknown
- Most common cause of I/DD
- Not related to race, nationality, religion or socio-economic status

What is it?

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- Incidence: about one in 700-900 live births
- Likelihood of giving birth to a child w/ DS increases with maternal age

BUT:

- 80% of babies w/ DS are born to women <35yrs (because women <35yrs give birth to more babies overall!).
- Wide variation in I/DD, behavior & physical development. Each has his/her own unique personality, capabilities & talents!

How?

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3 genetic ways:

- 95% have Trisomy 21 (an extra chromosome 21 in all their cells),
- 3-4% have a translocation form of the extra chromosome (where the extra chromosome 21 is attached to one of a different chromosome pair)
- About 1-2% are mosaic (only some cells are trisomic, the rest are normal)

Physical Features

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- Upward slanting eyes w/ epicanthal folds
- Brushfield spots (eyes)
- Flat nasal bridge
- Simean crease (hands)
- Clinodactyly (hands)
- Short stature
- Small ears & mouth
- Protruding tongue w/ high arched palate

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DS: Health Watch Table

- http://www.surreyplace.on.ca/Primary-Care/Pages/Tools-for-primary-care-providers.aspx

Health Watch Table — Down Syndrome

Forster-Gibson and Berg 2011

CONSIDERATIONS	RECOMMENDATIONS
1. HEENT (HEAD, EYES, EARS, NOSE, THROAT)	
Children and Adults: Vision: ~15% have cataracts; – 20%-70% have significant refractive errors 5%-15% of adults have keratoconus Hearing: 50%-80% have a hearing deficit	☐ Neonatally: refer immediately to an ophthalmologist if the red reflex is absent or if strabismus, nystagmus or poor vision is identified ☐ Arrange ophthalmological assessment: first by 6 months for all; then every 1-2 years, with special attention to cataracts, keratoconus, and refractive errors ☐ During childhood: screen vision annually with history and exam; refer as needed ☐ Arrange auditory brainstem response (ABR) measurement by 3 months if newborn screening has not been done or if results were suspicious ☐ During childhood: screen hearing annually with history and exam; review risks for frequently occurring serious otitis media ☐ Undertake auditory testing: first at 9 – 12 months, then every 6 months up to 3 years, annually until adulthood, then every two years
2. DENTAL	
Children and Adults: tooth anomalies are common Increased risk of periodontal disease in adults	☐ Undertake initial dental exam at 2 years, then every 6 months thereafter. Encourage proper dental hygiene. Refer to an orthodontist if needed ☐ Undertake clinical exams every six months with referral, as appropriate
3. CARDIOVASCULAR	

Physical Health

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- Sensory Issues:
  - Hearing deficits (66-89%)
  - Higher risk AOM/OE
  - Visual problems (60%)
    (strabismus, keratoconus, cataracts)
- Skin conditions (50%): eczema, dry skin
- Early onset menopause (44.6yrs)
- Cancers:
  - Leukemias (10-30X more common in childhood)
  - Testicular (25% have undescended testes)

Physical Health

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- Obesity (50-60%)
- Dental concerns (60-100%):
  - gingivitis, bruxism, malocclusion
- Respiratory Issues:
  - Obstructive sleep apnea (OSA)
  - Higher risk of pneumonia & URTI
- Cardiac issues:
  (17% in previously undiagnosed adults, of which 25% needed semi-urgent care; Vis&al)
  - Congenital heart defects (30-50%)
  - Mitral valve prolapse
- Life expectancy: 45-55 yrs old but they can even live into their 90s now!

Physical Health

- Hypothyroidism (by age 50: 40%)
- Epilepsy (6-13%, but 50% have adult onset by 50yrs, & if DS + dementia, it can be as high as 80%!)
- Ortho:
  - Atlanto-axial instability
  - Degenerative disc disease of C-spine
  - Hip disease (28%)
- Gastrointestinal issues:
  - GI tract abnormalities at birth (8-12%) (duodenal stenosis or atresia, imperforate anus, Hirschsprung disease)
  - Celiac disease
  - Constipation, GERD, H. Pylori

Mental Health

- Depression (6-11%, & higher levels if they have dementia, too)
- OCD :obsessional slowness & "the groove"
- GAD (anxiety)
- ASD, ADHD
- Self-talk (81%!): typical or a sign of mental health issues: psychosis, depression or anxiety?
- Early-onset Alzheimer's dementia (>40yrs: 15-45%)

DS & Az

- DVD clip => 7:22-8:50
- New resource for screening: http://aadmd.org/ntg/screening

NTG-EDSD

v.1/2013.2

The **NTG-Early Detection Screen for Dementia**, adapted from the DSQIID*, can be used for the early detection screening of those adults with an intellectual disability who are suspected of or may be showing early signs of mild cognitive impairment or dementia. The NTG-EDSD is not an assessment or diagnostic instrument, but an administrative screen that can be used by staff and family caregivers to note functional decline and health problems and record information useful for further assessment, as well as to serve as part of the mandatory cognitive assessment review that is part of the Affordable Care Act's annual wellness visit for Medicare recipients. This instrument complies with Action 2.B of the US National Plan to Address Alzheimer's Disease.

It is recommended that this instrument be used on an annual or as indicated basis with adults with Down syndrome beginning with age 40, and with other at-risk persons with intellectual or developmental disabilities when suspected of experiencing cognitive change. The form can be completed by anyone who is familiar with the adult (that is, has known him or her for over six months), such as a family member, agency support worker, or a behavioral or health specialist using information derived by observation or from the adult's personal record.

The estimated time necessary to complete this form is between 15 and 60 minutes. Some information can be drawn from the individual's medical/health record. Consult the NTG-EDSD Manual for additional instructions (www.aadmd.org/ntg/ screening).

Depression?

Changes in:

- Behavior (irritability, listless, paranoia, decrease in skills (ADLs), more self-talk)
- Appetite
- Sleep patterns
- Activity level
- Interactions: passivity, withdrawal & mutism
- Changes in memory?

DM-ID, (2007), p.30-32.
NDSC website:
www.ndsccenter.org/?page_id=778

DS – Strategies vs. Challenging Behaviours

- **Functional Analysis: A-B-C data collection**
- "Stubbornness" or "running away" may be due to fear or avoidance: need to identify the underlying purpose of the behaviour!
- May also be d/t underlying medical problem: always rule out the physical!
- Scrapbook & adaptations to environment may be helpful to the person with dementia

Interventions

- Early intervention is best: OT, Speech Referrals
- Work together with the families
- Have families also work with the school
- Respite & community supports!

- See handouts on websites
- Also DSE website for educational software: http://www.down-syndrome.org/practice/350/

Web Sites (Cdn)

Health Watch Tables & "Canadian Consensus Guidelines" developed at Surrey Place in Ontario, Canada:

- http://www.surreyplace.on.ca/primary-care?id=137

- Canadian Down Syndrome Society: www.cdss.ca/
- Down Syndrome Research Foundation (Canada): www.dsrf.org
- Down Syndrome Association of Ontario: www.dsao.ca/
- Down Syndrome Association - National Capital Region: www.dsancr.com/

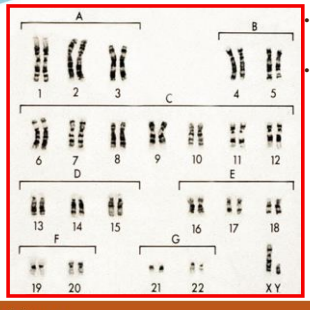
Web Sites (USA and UK)

- National Down Syndrome Congress: www.ndsccenter.org
- National Down Syndrome Society: www.ndss.org
- National Association for Down Syndrome: www.nads.org
- Down Syndrome Association-UK: www.dsa-uk.com

Additional Web Site

International Mosaic Down Syndrome Association: www.imdsa.org

Fragile X Syndrome (FXS)



- Section **q27.3** of chromosome X
- Incidence :
  - 1/1 500-4 000 males
  - 1/2 500-8 000 females
  - 1/256 females are carriers of the premutation (Rousseau et al., 1995)
  - 1/800 males are carriers
  - Present in all ethnic groups

Fragile X Syndrome

- Most common inherited cause of DD
- Females usually have milder symptoms (compensation by other X chromosome)
- Often initial dx of autism or PDD-NOS
  - *39% of males with fragile X had dx of autism or PDD in childhood*
  - *16-17% of adults with fragile X meet DSM criteria for autism*
  - *0-16% males with dx of autism test + for fragile X*

Fragile X Syndrome

- Fragile X syndrome is associated with an expanded repetition of the trinucleotide CGG which, in “normal persons”, is repeated between 6 and 50 times.

  1) normal = 6 - 50 CGG repeats
  2) premutation = 50-200 CGG repeats (FXTAS)
  3) full mutation = 200 + CGG repeats (Fragile X)

  - An FMR1 gene with a full mutation becomes inactive (methylated) & cannot produce the FMR1 protein (which plays a key role in brain development!).

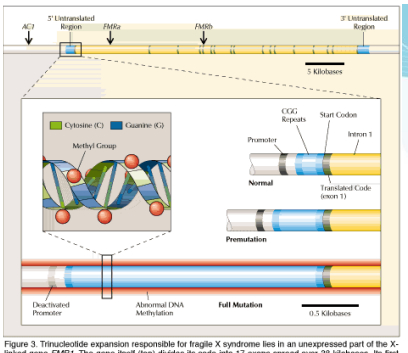


Figure 3. Trinucleotide expansion responsible for fragile X syndrome lies in an unexpressed part of the X-linked gene *FMR1*. The gene itself (top) divides its code into 17 exons spread over 38 kilobases. Its first and last exons include regions transcribed into messenger RNA that are not represented in the final translated protein. In turn, the 5′ untranslated region (in exon 1) includes a sequence of CGG repeats (bottom). Normally, the tract is polymorphic, ranging from 7 to 52 repetitions. The example shown is the most common, with 30. In a premutation, the number is 60 to 200; the example has 96. In a full mutation, the number is almost always several hundred; the example has 720. When the number exceeds 230, the entire region is hypermethylated (inset), receiving a methyl group at the C in each CG dinucleotide along both strands of the DNA double helix. The gene’s promoter is deactivated, and the gene becomes silent. Arrows in and near *FMR1* mark the locations of three polymorphisms.

- An FMR1 gene with a full mutation becomes inactive (methylated) & cannot produce the FMRP (a protein which plays a key role in brain development!).

*FXTAS: Fragile X-associated Tremor/Ataxia Syndrome

- Progressive neurological disorder:
  - tremor & ataxia (& eventually memory problems, moodiness & irritability)
- Onset 50-60yrs (granddads of Fragile X kids)
- ONLY 20-30% of male carriers >50 affected
- Often misdx’ed as atypical Parkinson’s, multiple system atrophy, etc
- May provide insight into FMR1 gene deactivation

FMR Premutation

In 20-40% of premutation females:

- Premature ovarian failure (POF) with cessation of menses <40 yrs.

Characteristic Features:

- Long face
- Prominent chin
- Prominent ears
- Larger head circumference
- Joint hypermobility/hyperextension
- Macro-orchidism

Characteristics:

Associated problems:

- Strabismus (30-56%)
- Recurrent serous otitis in childhood
- Dislocated hips, Scoliosis, hernias
- ADHD
- Mental retardation
- Autistic features (poor eye contact, hand-flapping, hand-biting)
- Tactile sensitivity
- Hyperextensible joints, flat feet
- Epilepsy (13% - 50%)
- Mitral valve prolapse (55%), cardiac murmurs, hypertension
- Hypotonia, poor muscle tone in childhood

Shyness, Social Anxiety & Hypersensitivity

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- Shy, timid personality
- Difficulties w/ peer interactions compared to interactions w/ adults.
- Excessive anxiety in new situations/environments.
- Hypersensitivity: Tendancy to “overreact” to “minor” frustrations .

Sensory Issues:

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- Hyper arousal (sound of fluorescent lights, sight of too many decorations on wall)
- Hypo arousal (sound of the teacher's voice, rather than the sound of the humming computer, fluorescent lights, and aquarium bubbler)
- Sensory motor integration problems (including motor planning issues and fine motor weaknesses)
- Tactile defensiveness (hypersensitivity to touch)
- Difficulty in many new, confusing, or loud situations (because of a combination of sensory integration problems, anxiety, and attention deficit disorders)

Tactile Defensiveness

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- Affects 60-90% FXS boys & some FXS girls
- Overreaction to touch & may avoid it
- Increased or decreased reactions to textures:
  - Clothing & tags
  - Need soft fabrics, no elastic cuffs or hems
  - May prefer deep pressure of heavy clothing for increased feedback
- May have difficulty identifying objects or feeling & receiving info by touch

Tactile Defensiveness

SOLUTION-S

- Firm, sure touches (handshakes & bearhugs) may be tolerated better than light touch (tickling, soft touch of face)
- May prefer to be at end of the line, separate from crowd
- Infants may/may not be comforted by cuddling
- May not enjoy finger painting or other tactile art activities

Tactile Defensiveness

SOLUTION-S

- Difficulties with hygiene:
  - Bathing, face & hair washing, shaving, nail cutting
- Dental visits may be difficult & anxiety provoking
- Difficulties with eating:
  - Difficulty nursing from breast or bottle
  - Strong food preferences related to textures of food
  - Mouth stuffing due to high “cathedral” palate, before realizing they may gag

Remember:

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- A specific problem in the environment that can be modified will often effect a much larger improvement in behavior than medication!
- Maximize environment FIRST to get a reasonable baseline!

Tactile Defensiveness: strategies for intervention

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- Sensory diet: individualized by an OT.
- Uses neurodevelopmental therapy working with muscle tone & sensory integration therapy (SI), involving all senses plus proprioreception (body position in space) & vestibular (sense of gravity & motion) input.
- To find best combination & timing of various sensory inputs & decreases sensory overload.

Tactile Defensiveness: strategies for intervention

SOLUTION-S

- Calming activities:
  - Rocking, swinging child
  - Applying deep pressure
  - Brushing child's skin with therapeutic brush
  - Break time: quieter area, playing computer game or listening to music or a story on headphones

Tactile Defensiveness: strategies for intervention

SOLUTION-S

- Environmental changes:
  - Increase natural light
  - Limit/avoid exposure to loud situations
  - Gradual desensitization to be able to tolerate more noise
  - Adapted seating to help maintain upright posture with enough feedback:
    - Donut-shaped cushions, foam wedges

FXS – ADHD

- ⬇ distractions: study cubicles, desk at front of classroom or in calm area (facing a wall), periods of quiet time, decreased flow of traffic in room, adequate natural lighting & heat, small group instruction, reduced noise
- Seating near an exit, & allow exit PRN
- ⬆ use of visual cues (photos) 4 transitions
- Provide non-verbal cues & feedback
- Simple phrases & concrete communication
- Structure/routine/predictability

FXS- General approach

- Do not force eye contact! (gaze aversion)
- Be careful invading personal space & touching the person! (tactile sensitivity)
- Consistency important! (staffing, schedules, environment)
- *Provide a book to carry with them containing info that may be difficult to remember

FXS – ADL stuff

- Sleep:
  - PJs & bedding
  - Dark room/shades
  - Soothing sounds, music
  - Bedtime routine
- Eating:
  - Try various nipples/positions
  - OT interventions for improved oral motor functioning

FXS – ADL stuff

- Dressing:
  - Remove tags, soft fabrics
  - Buttons, snaps easier or T-shirts
  - Shoes w/ velcro, curly laces
- Hygiene:
  - Desensitization to water on skin, calming strategies
  - Pictures of sequence of activities
  - Firm pressure with facecloth vs light strokes
- Dental
  - Egg timer
  - Desensitization: books, visits w/ mom, sibling

Fine & Gross Motor Skills

- Movement therapy to improve balance, muscle tone & proprioception:
  - dance, martial arts, sports, physical play
- Practice to improve use of:
  - pens/pencils for writing & drawing
  - utensils, scissors & tools
  - Keyboard (computer use)

Oral-Motor activities

- Activities to
  - increase tolerance to touch around face & mouth
  - improve chewing, swallowing & speaking
- Use of foods & toys:
  - Blow toys, whistles, straws
  - Crunchy or chewy food: fruit snacks, celery, bagels, gum
  - *may decrease chewing on clothing, straps or skin!

Fragile X Syndrome - more teaching approaches…..

- Using pictograms, photos, objects of special interest or hands-on approach
- Using clocks, license plates & cooking to help with number concepts
- Indirect explanation: teach task to neighbour
- Apply person's strengths: long-term memory, imitation skills, sense of humor
- Teach complete tasks: present whole process (not step-by-step) & use cover up method to follow sequence (Ø lose his place)

FXS – strategies vs. aggression

- **<u>Functional Analysis</u>: A-B-C data collection**
- Aggression may be preceded by giggling, non-compliance or avoidance
- Most common cause: anxiety!
- May be d/t sensory processing problems or hypersensitivity: sensory stimulation "adds up" during the day & sensory activities may be more challenging later in the day (⬆ demands are more difficult)
- *higher incidence in adolescents: hormones!

FXS - strategies vs. aggression

- Indications of anxiety:
  - Worry/anxiety over changes in routine or upcoming stressful events (fire drills, assemblies): "hyper vigilance"
  - Will stiffen up when angry or upset, becoming rigid & tense
  - May simply tighten up hands
  - Crying, whining tantrums may all be d/t overwhelming settings!

FXS – strategies vs. aggression

- "Catch them being good!" with reinforcement of + behavior
- Specific interventional approaches: ABA, Lovaas, token economy, "time-outs" (removal of attention)
- Psychotherapy & individual counselling (self-esteem, depression, anxiety, coping skills, frustration, anger management, social skills)
- Family Therapy

FXS - strategies vs. aggression

- Relaxation training, sensory stimulation/ sensory integration (OT), music
- Deep pressure massage
- Use of imagery
- Group Therapy & Social Skills training (role playing, especially with behavioral consequences)

FXS – strategies vs. aggression

Consider differentials:

1. Panic episodes: "fight or flight": flushing, turning pale, rapid breathing, sudden sweating
2. Mood disorders: Depression or Bipolar disorder (disturbed or absent sleep, excess or loss of appetite, changes in activity level, mood changes, increased irritability)
3. Seizure disorder (aggression appears aimless, or unassociated with any ongoing event, occurring with unusual movements, brief loss of consciousness, confusion or need to sleep afterwards)

*Fragile X Syndrome - issues around sexuality

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- Social Sexual skills
- Sex Ed. throughout & beyond puberty
- Sexual abuse prevention information
- Psychotherapy & counselling (self-esteem, depression, anxiety/frustration) (especially helpful for transition from parents' home to independent living)

Treatment

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- Referrals to: speech Tx, OT, behavioural Tx
- Medications for medical problems: epilepsy, MVP & HTN
- Medications for psychiatric problems: anxiety (anti-anxiety: SSRIs) & ADHD
- FXS clinic at Surrey Place in Toronto
- Current research trials: in TO, Europe & Canada.
- Future prospects: gene therapy

Health Watch Table — Fragile X Syndrome

Forster-Gibson and Berg 2011

CONSIDERATIONS	RECOMMENDATIONS
1. HEENT (HEAD, EYES, EARS, NOSE, THROAT)	
Children Vision: strabismus, refractive errors are common	☐ Undertake newborn vision and hearing screening and an auditory brainstem response (ABR)
Hearing: recurrent otitis media is common	☐ Refer for a comprehensive ophthalmologic examination by 4 years of age
Nose: sinusitis is common	☐ Visualize tympanic membranes at each visit
Adults: strabismus and refractive errors are common	☐ Undertake hearing and vision screening at each visit with particular attention to myopia and hearing loss
2. DENTAL	
Children and Adults: High arched palate and dental malocclusion are common	☐ Refer to a dentist for an annual exam
3. CARDIOVASCULAR	
Children: Mitral Valve Prolapse (MVP) is less common in children (~10%), but may develop during adolescence	☐ Auscultate for murmurs or clicks at each visit. If present, do an ECG and echocardiogram; refer to cardiologist, if indicated
Adults: MVP is common (~ 80%). Aortic root dilation usually is not progressive Hypertension is common and exacerbated by anxiety	☐ Undertake an annual clinical exam. Based on findings, obtain an ECG and echocardiogram. Refer to cardiologist, as appropriate ☐ Measure BP at each visit and at least annually ☐ Treat hypertension when present
4. RESPIRATORY	
Children & Adults: Obstructive sleep apnea (OSA) may be due to enlarged adenoids, hypotonia or connective tissue dysplasia	☐ Ascertain a sleep history and assess for evidence of OSA ☐ Obtain a sleep study as appropriate

Websites

Health Watch tables for several genetic syndromes & other tools from the Canadian Consensus Guidelines developed at Surrey Place in Ontario, Canada: http://www.surreyplace.on.ca/primary-care?id=137

FXS Websites

- The Fragile X Research Foundation of Canada

  Website: http://www.fragile-x.ca
- FRAXA Research Foundation (USA)

  Website: www.fraxa.org
- The National Fragile X Foundation (USA)

  Website: http://www.nfxf.org/html/what.htm or http://www.fragilex.org/html/home.shtml

Genetics Websites

- Geneclinics: http://geneclinics.org/ (see: Gene Reviews)
- Your Genes, Your Health: http://www.ygyh.org/
- Online Mendelian Inheritance in Man: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM

Genetics Websites

- Genetics Education Center, University of Kansas Medical Center: http://www.kumc.edu/gec/support/
- The Family Village: http://www.familyvillage.wisc.edu

Websites

Genetics Website

(In English, French, Spanish, German, Italian & Portuguese!):

- Orphanet: http://www.orpha.net/consor/cgi-bin/index.php

THANK YOU!


solution·s
29-2450 Lancaster
Ottawa, Ontario K1B 5N3
T 613 249-8593
F 613 249-0198
info@solution-s.ca
www.solution-s.ca