Fragile X Syndrome
In the Academic World

Authors:
Elyse Schoenwald, CPNP, MSN
Christina Aguirre-Kolb, LEP, ABSNP

Miller Children’s Hospital Long Beach
Memorial Care Health System

• Clinics offered:
  ➢ International Adoption Program
  ➢ High Risk Infant Follow-up Program
  ➢ Craniofacial Program
  ➢ Genetic Program
  ➢ Sleep Program
  ➢ Behavioral and Neurodevelopmental Program
  ➢ Fragile X Program

Agenda

Medical → Elyse
Educational → Christina
Take Away

Medical Objectives

➤ What is Fragile X Syndrome
➤ Genetic Testing
➤ Medical Problems & Physical Findings
➤ Developmental Characteristics
➤ Behavioral Characteristics
➤ Family History & Psychosocial Dynamics
➤ Treatment and Interventions
**Why?**

Knowledge and Perceptions About Fragile X Syndrome: Implications for Diagnosis, Intervention, and Research

Brenda Finucane, Barbara Haus-Gilter, and Elliott W. Simon

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**2013 Data**

To your knowledge, have you ever worked with a client diagnosed with fragile X syndrome?

- Yes: 48.7%
- No: 51.3%

How would you rate your overall knowledge about fragile X syndrome?

- Not at all knowledgeable: 44.2%
- Somewhat knowledgeable: 54%
- Very knowledgeable: 1.8%

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**Fragile X Syndrome**

- Leading known cause of inherited intellectual disabilities
- 30% individuals with FXS are diagnosed with an Autism Spectrum Disorder

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**Fragile X Mutations & Associated Disorders**

- Fragile X Syndrome (FXS)
- Fragile X associated Primary Ovarian Insufficiency (FXPOI)
- Menopause prior to 40 years of age
- Fragile X associated Tremor and Ataxia Syndrome (FXTAS)

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**FXTAS**

- Affects (mainly) males over 50 years of age
- Now reported in female premutation carriers
- Progressive neurological disorder with intention tremor, cerebellar ataxia and Parkinsonism
- Peripheral Neuropathy
- Lower limb muscle weakness
- Progressive cognitive decline
- Behavioral problems
What Causes FXS

- X Linked Chromosomal Disorder
- Abnormality of the fragile X mental retardation 1 (FMR1) gene
- FMR1 responsible for production of fragile X mental retardation protein (FMRP)
- FMRP responsible for brain development
- Individuals with FXS are deficient in FMRP
- Increased Cytosine-Guanine-Guanine (CGG) repeats accounts for the “fragile” site of the DNA

Inheritance

X – Linked Chromosomaly Disorder

<table>
<thead>
<tr>
<th></th>
<th>Mom (XX)</th>
<th>Dad (XY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td>Female</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>

Genetic Testing

AAP Genetic Testing Recommendations

“Chromosome microarray is designated as a first-line test and replaces the standard karyotype and fluorescent in situ hybridization subtelomere tests for the child with intellectual disability of unknown etiology. Fragile X testing remains an important first-line test.”
Interpreting Lab Reports

- Normal = 5 – 40 (or 44) repeats
- "Grey Zone" or Intermediate Alleles definition variability
  - 41-54 repeats = Newer research studies
  - 45-54 repeats = American College of Medical Genetics laboratory practice committee
- Premutation or "carrier" = 55 – 200 repeats
- Fragile X Syndrome or Full Mutation > 200 repeats
  - hypermethylation of FRM1 and decreased FMRP production

How should “Grey Zone” be defined?

- Likelihood of Expansion in later generation?
  - Reports of expansion over 2 generations to full mutation but typically takes 3 generations
- Associated phenotypes?
  - High rates of “grey zone” expansion in study of boys in SPED (UK)
  - “FXTAS-like” symptoms
  - Anxiety disorders
- Underlying molecular abnormalities?
  - 1.5 increased FMR1 mRNA starting at 39 repeats
  - Higher rates of mRNA correlate with neuropathology and peripheral neuropathy

Prevalence

- 2-8% of children with Autism have FXS
- Fragile X Syndrome:
  - 1 in 3600-4000 in males
  - 1 in every 4000-6000 females
- Premutation:
  - 1 in 151 in female
  - 1 in 468 in male
- Grey Zone (41-54):
  - 1 in 13 females
  - 1 in 21 males
- Grey Zone (45-54):
  - 1 in 35 females
  - 1 in 42 males

Table 2. Average age at diagnosis and intervention

<table>
<thead>
<tr>
<th>In Months...</th>
<th>Mean (std) age: Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>What was age at FXS diagnosis?</td>
<td>38.1 (30.5); 30 (0 - 168)</td>
</tr>
<tr>
<td>What age started in intervention?</td>
<td>22.6 (13.3); 20 (0 - 72)</td>
</tr>
<tr>
<td>Time lag between early intervention and diagnosis</td>
<td>15.0 (27.9); 9 (48 before - 138 after)</td>
</tr>
</tbody>
</table>
Medical Problems & Physical Findings

- Loose Connective tissue
- Pronated ankles
- Hyperextensive joints
- Pes Planus
- Heart murmurs
- Hypotonia
- Large Cupped Ears
- Single palmar crease

Medical Problems & Physical Findings continued...

- Taller
- 20-25% significantly shorter than general population
- Soft velvety skin
- Club foot
- Hallucal crease
  - (Single crease between 1st and 2nd toe)
- Pectus Excavatum
- Macroorchidism
- Attractive appearance
- Prader Willi Subtype

Visual impairments
- Narrow high arched palate
- Scoliosis
- Motor tics
- Larger head circumference and pronounced forehead

<table>
<thead>
<tr>
<th>Medical Problems</th>
<th>Prevalence (%)</th>
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</thead>
<tbody>
<tr>
<td>Visual impairments</td>
<td>45%</td>
</tr>
<tr>
<td>Narrow high arched palate</td>
<td>35%</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>25%</td>
</tr>
<tr>
<td>Motor tics</td>
<td>15%</td>
</tr>
<tr>
<td>Larger head circumference and pronounced forehead</td>
<td>5%</td>
</tr>
</tbody>
</table>

TABLE 1: Prevalence of Medical Problems by Comparison Group

<table>
<thead>
<tr>
<th>Medical Problem</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>Male (%)</th>
<th>Female (%)</th>
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</thead>
<tbody>
<tr>
<td>Visual impairments</td>
<td>30%</td>
<td>20%</td>
<td>35%</td>
<td>25%</td>
</tr>
<tr>
<td>Narrow high arched palate</td>
<td>40%</td>
<td>30%</td>
<td>45%</td>
<td>35%</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>50%</td>
<td>40%</td>
<td>55%</td>
<td>45%</td>
</tr>
<tr>
<td>Motor tics</td>
<td>60%</td>
<td>50%</td>
<td>65%</td>
<td>55%</td>
</tr>
<tr>
<td>Larger head circumference and pronounced forehead</td>
<td>70%</td>
<td>60%</td>
<td>75%</td>
<td>65%</td>
</tr>
</tbody>
</table>
Developmental Characteristics

- Cognitive Delays
- Speech Delays
- Gross and Fine Motor Delays
  - Loose connective tissue can impact this.
- Social/Emotional delays
- Delayed adaptive behavior

Early Development

### Table 3. Age when achieving developmental milestones

<table>
<thead>
<tr>
<th>Age in months when child:</th>
<th>Mean (std)</th>
<th>Proportion achieved (by typical milestone age*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Began to walk</td>
<td>17.5 (5.0)</td>
<td>67.7% (by 18 months)</td>
</tr>
<tr>
<td>Spoke first words</td>
<td>25.5 (14.0)</td>
<td>37.7% (by 18 months)</td>
</tr>
<tr>
<td>Was toilet trained</td>
<td>56.7 (25.6)</td>
<td>40.1% (by 60 months)</td>
</tr>
</tbody>
</table>

* CDC: Important milestones; checklist by age

Behavioral Characteristics
Behavioral Characteristics

- ANXIETY/Hyperarousal
- Intellectual Disabilities
- Autism and Autistic-like features
- ADHD symptoms
  - Hyperactivity/Impulsivity improves in adulthood but inattention can remain.
- Mood Dysregulation
- Depression
- Speech and Language characteristics:
  - Echolalia
  - Scripting

Behavioral Characteristics Continued...

- Hand flapping
- Hand biting – Calluses
- Stiffening, “Power Salute”
- Tantrums
- Gaze aversion
- Difficulty relating to others
- Hypervigilance

Hyperarousal?

- Tendency for the nervous system to become overwhelmed and over-activated by processing demands.
- Processing demands include:
  - Sensory environment
  - Social interaction
  - Internal processing loads for cognition
  - Language
  - Executive function

Relationship between Hyperarousal and behavior?

- Nervous system balanced state
- Nervous system becomes overstimulated
- Nervous System Takes Over
  - Shift to heightened responding and reactivity
  - Low level, automatic fear, fight or flight responses
- Much of the behavior is no longer under a person’s self-regulatory control
Family History
- Early onset menopause before the age of 40
- Difficulty getting pregnant
- Autoimmune Disorders
  - Fibromyalgia
  - Systemic Lupus
  - Arthritis
- Migraines
- Anxiety
- Schizophrenia
- Depression/mood disorders
- Parkinson’s/tremors
- Developmental Delays/Intellectual Impairments
- Autism

Family Dynamics;
Carrier Mothers
- Social Emotional
  - Anxiety
  - Depression
  - Guilt
  - “Pleasers”
  - Denial
- Intellectual Abilities
  - Accessing services
  - Understanding of child’s abilities
- Health Issues
  - FXTAS
  - Tremors
  - Movement Disorders
  - FXPOI
  - Pregnancy Issues
  - Menopause

Family History & Psychosocial Dynamics
- Fragile X Neurobiology
  - Sympathetic hyperarousal
  - GABA inhibitory system underactive
  - Amygdala hyper-connectivity
- Avoidance
  - Social anxiety
  - Selective mutism
  - Aggression
  - ASD

What do we know about hyperarousal in FXS?
Randi Hagerman, MD 2007
Family Dynamics Continued
- Unaffected Fathers
  - Coping Styles
    - Task oriented
    - Shut down
- Siblings
  - Affected vs unaffected
  - When/How to talk about Fragile X?
- Extended Family
  - Blame
  - Denial
  - How/When to tell?

Psychosocial Impact
- Divorce
  - Significantly higher rates
- Financial Impact
  - Percentage of families reporting excessive financial expense:

Medical Referrals
- Fragile X Clinic
- Genetic Testing & Genetic Counseling
- Neurology – Seizure Disorders
- Ophthalmologist – Strabismus
- Orthopedic – Pes Planus, orthotics
- Dental – Malocclusion
- ENT - Recurrent Otitis Media, Sinusitis
- Cardiac – Mitral Valve Prolapse
- GI – GERD, Constipation
- Endocrine – Metabolic disorders
Developmental Referrals

- Psychological Evaluations
- FX-specific cognitive phenotype
- Speech and Language Therapy
  - Delayed vs deviant
- Occupational Therapy
  - Sensory processing
  - Hyperarousal
  - Fine motor deficits
- Physical Therapy
  - Gross motor deficits

School District Referrals

- 3+ years
- School Interventions are not comprehensive
  - Must impact learning (Reading, Writing, or Math)
- Best practice:
  - Type your clinic notes
  - Write a letter expressing concerns
  - Request collaboration and feedback
Johnny Appleseed was seen in clinic today with his mother, Mrs. Appleseed. Johnny was recently diagnosed with Fragile X Syndrome with associated Global Developmental Delays and Autism Spectrum Disorder. I have attached a copy of my clinic notes summarizing today’s visit.

Our medical team is requesting collaboration with Johnny’s primary school. Please consider a psychoeducational evaluation to determine if Johnny is eligible for Special Education Services. Please send a copy of any evaluation reports, or IEP documents to our office Attn: Doctor/Nurse Practitioner, for me to review. I look forward to collaborating with Johnny’s school staff. If you have any questions or concerns, I encourage you to contact our office to discuss further.

Best regards,
Doctor/Nurse Practitioner
**What symptom are you treating?**

Antecedent → Behavior → Consequence

Antecedent + Biochemical factors → Behavior → Consequence

**What is causing the observed behavior?**

![Diagram showing Anxiety, Impulsivity, BEHAVIOR, Developmental Delays, Sensory (Hyperarousal), Mood Dysregulation]

**Medications**

- **Atypical antipsychotics**
  - Risperidone
  - Ability – Used more often in FX
- **Psychostimulants**
  - Methylphenidates (demonstrate better efficacy in FXS population)
  - Mixed Amphetamine Salts
- **Alpha 2 Agonists**
  - Clonidine
  - Guanfacine

**Medications Continued...**

- **SSRI**
  - Zoloft – Majority do well on Zoloft
    - Has been used in patients as young as 13 months
    - Language and cognitive benefits
  - Prozac ~ 25% respond better to Prozac than Zoloft
- **Off label medications**
  - Minocycline
    - Speech
    - Social anxiety
    - Hyperactivity
    - Anxiety
Targeted Treatments

- mGluR antagonists
  - "knock out" Mouse Model
- Ganaxalone
- NNZ-2566
  - modified version of a biologically active part of insulin-like Growth Factor (IGF-1)
  - IGF-1 is a protein in the human body that helps cells grow and respond to stress or damage
- Animal Model - improved behavior and cognition
- Metadoxine Extended Release (MDX)
  - Mouse Model - significant improvement in behavior and cognition (improved memory, learning, and social interaction)

Evidence for the mGluR Theory of Fragile X

In FMR1 knock-out mice, mGlu5 pharmacological inhibition:

Corrected
- Excessive protein synthesis in the hippocampus
- Elevated mGlu5-LTD in the hippocampus
- AMPA receptor internalization
- Learning and memory deficits
- Hypersensitivity to sensory stimuli
- Elevated locomotor activity and other behavioral phenotypes
- Increased susceptibility to audiogenic seizures
- Dendritic spine phenotype in the visual cortex
- Abnormal intracellular signaling in the cerebral cortex

Partially corrected
- Macrocystin upon chronic treatment

Educational Objectives

- Cognitive phenotype associated with Fragile X for assessment purposes
- Ideas to write solid IEPs and complete thorough assessments of students with Fragile X
- Approaches to providing support and behavioral remedies
  - Learn creative teaching strategies

Before Moving on....

Any Questions?
Evaluation of Abilities

- Simultaneous learning rather than sequential
- Look at what is naturally being learned
- Full Neuropsychological with Academic Assessment reveals:
  - Achievement Scores are typically higher than Developmentally Delayed control subjects.
  - Yet Overall Cognitive Scores are typically more scattered and lower than control subjects (DD)
  - Cornish et al. 2005

Evaluation of abilities continued

- Results of Direct Assessment
- WJ-IV : Relative Proficiency Index
- K-ABC

- Transformed z-scores of children with FX, there is more meaningful variation in intellectual ability.
  - Hessl et al. 2009

<table>
<thead>
<tr>
<th>Table 13.3</th>
<th>Neuropsychological Deficits Associated with Fragile X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Domain</td>
<td>Specific Abilities</td>
</tr>
<tr>
<td>Cognition</td>
<td>Intellectual Disability: cognitve disability occurs in mild to moderate</td>
</tr>
<tr>
<td>Auxiliary-motor</td>
<td>Executive Language: language development is more affected than receptive language development</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>Language comprehension ability is more affected than receptive language comprehension</td>
</tr>
<tr>
<td>Motor Function</td>
<td>Fine motor problems are frequent</td>
</tr>
<tr>
<td>Learning and Memory</td>
<td>Memory for meaningful information is intact, but memory for abstract information impaired</td>
</tr>
<tr>
<td>Attention/Concentration</td>
<td>Attention deficit, auditory attention and concentration impaired</td>
</tr>
<tr>
<td>Visual perception/Construction</td>
<td>Visual perceptual processing issues</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Impaired executive function</td>
</tr>
<tr>
<td>Processing speed</td>
<td>Impaired processing speed dependent on cognitive impairment and specific presentation</td>
</tr>
<tr>
<td>Achievement/Academic skills</td>
<td>Difficulties in academics</td>
</tr>
<tr>
<td>Behavioral/Emotional Symptoms</td>
<td>High frequency of anxiety symptoms and ADHD</td>
</tr>
<tr>
<td>Table: Riccio, Sullivan, Cohen, 2010</td>
<td></td>
</tr>
</tbody>
</table>
Cognitive Profile - Strengths

- Long Term Memory
  - esp. when associated with high interest (verbal knowledge on SB-V)
- Verbal-Visual Associations for Learning
- Social awareness – facial perception (NEPSY-II)
- Visual Discrimination

Areas of Need

- Cognitive Shifting, Sustained and Selective Attention (tests inadvertently assess anxiety)
- Short term visual memory, Working Memory
- Phonemic Awareness/Auditory Processing
- Speech- linguistic processing
  - Syntactic & Pragmatics: Delayed or Deviant?
- Visual Spatial cognition
- Social-Emotional: Anxiety

Writing the Individualized Education Plan

Fragile X in the Academic Environment

- Triple A
  - Alliance
    - Work with the family
  - Attitude
    - The tone of the classroom, teacher, the paraprofessionals
  - Approach
    - Initiation of relationships, interactions
Meeting

- How is the meeting being run?
- Are there side conversations?
- How does the meeting feel?
- How are questions directed?

Writing the Goals

- Consider how the child is assessed
  - Environment
  - Tasks
- For new goals, consider reviewing in 6 months
- Are they congruent with medical and outside professionals?

Other Considerations

- Consider inclusion in the general education environment with minimal aide support during periods of time that are engaging

<table>
<thead>
<tr>
<th>Domain</th>
<th>Necessary Supports</th>
</tr>
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<tbody>
<tr>
<td>Social</td>
<td>• Skills group</td>
</tr>
<tr>
<td></td>
<td>• Socialization</td>
</tr>
<tr>
<td></td>
<td>• Family setting</td>
</tr>
<tr>
<td></td>
<td>• Opportunities for social contexts</td>
</tr>
<tr>
<td>Behavioral</td>
<td>• Augment-able in class</td>
</tr>
<tr>
<td></td>
<td>• Augment-able in home</td>
</tr>
<tr>
<td></td>
<td>• Augment-able in community</td>
</tr>
<tr>
<td></td>
<td>• Opportunities for community activities</td>
</tr>
<tr>
<td></td>
<td>• Organizational activities</td>
</tr>
<tr>
<td></td>
<td>• Organizational supports</td>
</tr>
<tr>
<td>Academics</td>
<td>• Specialized instructor</td>
</tr>
<tr>
<td></td>
<td>• High-need content</td>
</tr>
<tr>
<td></td>
<td>• High-need curriculum</td>
</tr>
<tr>
<td></td>
<td>• High-need placement</td>
</tr>
<tr>
<td></td>
<td>• Enhance in social presentation</td>
</tr>
<tr>
<td></td>
<td>• Opportunities for core in pre-existing</td>
</tr>
<tr>
<td></td>
<td>• Opportunities for core in mainstream</td>
</tr>
<tr>
<td></td>
<td>• Opportunities for core in general education</td>
</tr>
<tr>
<td>Social/Emotional</td>
<td>• Skills with social</td>
</tr>
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<td></td>
<td>• Skills with emotional</td>
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<td></td>
<td>• Skills with emotional</td>
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<tr>
<td></td>
<td>• Emotional supports</td>
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</tr>
<tr>
<td></td>
<td>• Emotional supports</td>
</tr>
</tbody>
</table>

Providing Support and Remediating Behaviors
Understanding the Child in the Classroom

- “Most important variable to determine positive outcomes of student continues to be the quality of teacher and structure of the environment” Symons 2001
- Predictability, Structure and Calm
  - Side conversation about schedule with others to prepare
  - Inform general education students about Fragile X
- High interest material assists with sustained attention
- Aide support is facilitated and not hand over hand as anxiety gets increased

Learning Strategies

- High Interest Sustains attention because it is familiar (words, sounds, visuals etc.)
- More Visual Less Verbiage
  - Keep in mind this is not necessarily true of the environment. Look over your environment, ask for a third party to review it. Are there any areas that are possibly sensory stimulating?
- Repetition

Learning Considerations

- Allow child to place into context rather than create context (Closure technique)
- Utilize their need for completion to teach
  - Math instruction completion based
    - Simultaneous (dot math, patterns, matching)
    - Writing instruction also completion based
- Backward Chaining
  - The adult fades back, doing less and less while the child does more and more, always ending with the child performing the final step.
- Modeling/Pre-teaching
- Whole word reading less phonemic reading

Example of Logo Reading System

Developed and Copy written by Dr. Braden. Uses incidental learning to develop foundational reading skills.
Teaching Strategies

- Close proximity to instruction though not central focus (again, anxiety)
- Use of Technology for PECs, if-then, routine teaching
- Behavior Plans:
  - Attention and Learning Behaviors
  - Discriminate between fulfilling sensory need and communication
  - Calming Strategies Everyday as part of class
- Relaxed eye gaze from instructors (consider the approach)

Transition

- Adults with Fragile X can live and work successfully independent
- Struggles: Anxiety

Case Study – Common Issues

Transitions
Task oriented adults
Work demands

Take Away
**Pearls**  
**Working with Students & Families with FX Associated Disorders**

- **“Align, Attitude, Approach” Method**
  - Christina Aguirre-Kolb, Educational Psychologist
- Incorporate **known interests** into your exam/discussions
- Relaxed gaze
- Preview several times
- **Indirect prompting** - side conversations
- More visual, less verbiage

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**Resources**

- Stramski Children’s Developmental Center
  - Email Elyse: eschoenwald@memorialcare.org
  - Email Christina: caguirrekolb@memorialcare.org
  - [www.stramskicenter.com](http://www.stramskicenter.com)
- National Fragile X Foundation
  - [www.fragilex.org](http://www.fragilex.org)
- Center For Disease Control and Prevention

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**Remember:**  
Anxiety
References


• Broden, Marcia (2012). Fragile X presentation for Special Education. Stramski Children's Developmental Center


References Continued...


References Continued...


Hall, D. A. (2014). In the Gray Zone in the Fragile X Gene: What are the Key Unanswered Clinical and Biological Questions? Tremor and Other Hyperkinetic Movements. 4. 2014. doi:10.7916/D8NG4NP3


References Continued...

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- Dr. Marcia Braden for energy, laughter and knowledge
- Our Fantastic, Beautiful and Wonderful Patients and Families