CLINICAL PROFILES OF CHILDREN WITH FXS+ASD

Audra Sterling, Ph.D., University of Wisconsin-Madison
Lizbeth H. Finestack, Ph.D., CCC-SLP, University of Minnesota

ACKNOWLEDGMENTS AND CONFLICTS OF INTEREST

- Families and children who have volunteered their time
- Our colleagues and labs at the University of Wisconsin-Madison, University of Minnesota, University of Kansas, and UC-Davis MIND Institute
- Support from the following grant awards from the National Institutes of Health: R03DC011616, R01 HD074346, R01HD024356, T32HD007489, and P30HD003352.
- The authors have no conflicts of interest relating to this presentation

AGENDA FOR TODAY

- Describe FXS and genetic implications
- Gender Differences
- FXS group characteristics
- FXS+ASD
  + Diagnostic considerations
  + Language characteristics for FXS-Only and FXS +ASD

http://www.fragilex.org/
WHAT IS FRAGILE X SYNDROME (FXS)?

FXS

• Leading inherited cause of intellectual disability
• Males 1 in 2,500; females 1 in 6,000
• Mutation of FMR1 gene on X chromosome

GENETIC IMPACT

- Typical
  - 5-44 CGG Repeats
- Premutation Carrier
  - 55-200 CGG Repeats
- Full Mutation
  - >200 CGG Repeats

Related to expansion of the trinucleotide (CGG) repeats on the fragile X mental retardation 1 (FMR1) gene

FXS: FAMILY-WIDE IMPACT

Related to expansion of the trinucleotide (CGG) repeats on the fragile X mental retardation 1 (FMR1) gene

FXS: FAMILY-WIDE IMPACT

Related to expansion of the trinucleotide (CGG) repeats on the fragile X mental retardation 1 (FMR1) gene
GENETIC IMPLICATIONS (McConkie-Rosell et al., 2005)

**FEMALE CARRIERS**

- Premutation:
  + 50% risk of passing to affected X to son or daughter
  + Gene could pass in premutation form or expand to full mutation

- Full Mutation:
  + 50% risk with each pregnancy to pass the full mutation to son or daughter
  + Rare cases of passing decreased numbers of the repeat

**MALE CARRIERS**

- Premutation:
  + All daughters will be premutation carriers
  + No sons will inherit the mutation

- Full Mutation:
  + Some rare reports of fathers with full mutation passing full mutation to daughters
  + No sons will inherit the mutation

FXS TESTING GUIDELINES

American College of Medical Genetics’ Policy Statement on FXS

- Individuals with intellectual disability, developmental delay, or autism
- Individuals with a family history of FXS or undiagnosed ID who are seeking reproductive counseling
- Prenatal testing of individuals who are known premutation carriers
- Women with reproductive or fertility problems especially if there is a family history of POF, FXS, or undiagnosed ID
- Individuals with late onset tremor or cerebellar ataxia especially if there is a family history of movement disorders, FXS, or undiagnosed ID

PRENATAL SCREENING FOR FXS (Yaron et al., 2012)

- Detection rate almost 100%; false-positive rate < 0.5%
- Original Southern blotting tests expensive; newer molecular tests much less expensive
- Counseling is complicated by potential health consequences for maternal and fetal carriers

FXS TESTING IN YOUNG CHILDREN

- Few readily identifiable physical characteristics at birth
- Often not detected until delays in development are significant enough to prompt genetic testing
- May go undiagnosed or misdiagnosed
FRAGILE X RELATED DISORDERS

**Associated Conditions**
- Language impairment
- Cognitive delay
- Autism spectrum disorder (30-70%)
- Middle ear infection
- Gross and fine motor delay
- Seizures (20%)
- Hyperactivity and ADHD (80% males; 30% females)
- Anxiety
- Premature ovarian failure**
- Fragile X-associated tremor/ataxia syndrome (FXTAS)**

GENDER DIFFERENCES
- Females with FXS are typically less impaired than males
- Most males with FXS have moderate to severe intellectual disability; 1/3 of females with full mutation have mild to moderate delays
- Females may exhibit more anxiety and depression
- Females may be identified as having a learning disability

COGNITIVE DEVELOPMENT
- Males typically have IQs in the moderate to severe range of intellectual disability
- Delays/impairments related to language learning:
  - Sequential processing
  - Working memory
  - Auditory and visual-spatial

VIDEO EXAMPLE

COGNITIVE DEVELOPMENT
- Males typically have IQs in the moderate to severe range of intellectual disability
- Delays/impairments related to language learning:
  - Sequential processing
  - Working memory
  - Auditory and visual-spatial
COGNITIVE DEVELOPMENT

- Significant problems with attention
  - Sustained attention
  - Inhibitory control

- High rate of FXS and ADHD co-morbidity
  - 80% of males
  - 30% of females

DEFINING ASD

DSM-V criteria:

1. Deficits in Social Communication/Interaction
2. Restricted/repetitive behaviors and interests

Autism Spectrum Disorders

DEFICITS IN SOCIAL COMMUNICATION/INTERACTION

- 1) Problems reciprocating social or emotional interaction, including difficulty establishing or maintaining back-and-forth conversations and interactions, inability to initiate an interaction, and problems with shared attention or sharing of emotions and interests with others.

- 2) Severe problems maintaining relationships — ranges from lack of interest in other people to difficulties in pretend play and engaging in age-appropriate social activities, and problems adjusting to different social expectations.

- 3) Nonverbal communication problems such as abnormal eye contact, posture, facial expressions, tone of voice and gestures, as well as an inability to understand these.

RESTRICTED AND REPETITIVE BEHAVIORS

1. Stereotyped or repetitive speech, motor movements or use of objects
2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change
3. Highly restricted interests that are abnormal in intensity or focus
4. Hyper or hypo reactivity to sensory input or unusual interest in sensory aspects of the environment
**How is ASD Diagnosed?**

- **GOLD Standard:**
  - Autism Diagnostic Observation Schedule 2nd edition (ADOS-2)
    - Observe social, communication and play in structured and semi-structured settings
  - Autism Diagnostic Interview-Revised (ADI-R)
    - Provides severity score for communication, reciprocal social interaction, & restricted and repetitive behaviors
    - Used with verbal & nonverbal children
    - For children over 3 years of age

**ADOS-2**
- **Purpose:** Assess and diagnose ASD across ages, developmental levels, and language skills
- **Ages / Grade:** Toddlers to adults
- **Administration Time:** 30 to 60 minutes
- **Format:** Standardized behavioral observation and coding
- **Score:** Cutoff scores for ASD and a severity score

**ADI-R**
- **Purpose:** Useful for diagnosing ASD, planning treatment, and distinguishing ASD from other developmental disorders
- **Ages / Grade:** Children and adults with a mental age above 2.0 years
- **Administration Time:** 1 1/2 to 2 1/2 hours, including scoring
- **Format:** Standardized interview and response coding
RATES OF ASD IN FXS

- Generally reported about 50%
- Clinical Rates:
  + Parents reported 46% of boys and 16% of females had received an ASD co-diagnosis
- Research Rates:
  + Studies using ADOS report 50-74% of males meet for ASD
  + Studies using ADOS and ADI-R together have found rates varying from 27-81% meet for ASD
  + Studies using the CARS report rates from 24-30%

HOW DO DIAGNOSTIC SYMPTOMS VARY?

FXS & ASD

- 50-90% reported to have symptoms concurrent with ASD regardless of diagnosis (Bailey et al., 1998; Feinstein & Reiss, 1998)
  + Lack of responsiveness
  + Poor eye contact
  + Perseverative speech
  + Self-aggression (e.g., hand biting)
  + Abnormal body use (e.g., rocking, spinning, hand flapping)
IS IT ASD?

✗ Not "true ASD"
  ➢ Abbeduto and colleagues argue ASD in FXS is not the same underlying psychological and neurobiological impairments (Abbeduto et al., 2014)

✗ Meaningful clinical group
  ➢ Behaviors and symptoms more closely aligned with idiopathic ASD than FXS-Only (Budimirovic & Kaufmann, 2011; Hernandez et al., 2009)

EARLY LANGUAGE DEVELOPMENT IN FXS

✗ First indicators
  ➢ Weak gesture use
  ➢ Limited communication reciprocity
  ➢ Poor play skills
  ➢ Late emergence of first words
EARLY LANGUAGE DEVELOPMENT

× In a study 55 mothers of 18- to 36-month old children with FXS with and without ASD, 42 reported that their children were nonverbal or producing very few words (Brady et al., 2006)
  + 29 were nonverbal (average age 26 months)
  + 13 emerging verbal (average age 28 months)
  + 13 verbal (average age 34 months)

PRELINGUISTIC COMMUNICATION

× Joint attention
  + Based on CSBS scores with boys under the age of 8, relative strengths in:
    × Social affective signaling
    × Gaze shifts
    × Vocalizations and gestures used in conjunction
  + Weakness in:
    × Repair strategies
    × Positive affect

PRELINGUISTIC COMMUNICATION

× Gestures:
  + Weakness in:
    × Conventional gestures (e.g., pushing away)
    × Distal gestures (e.g., pointing at a distance)
    × Complex action schemes

LATER GESTURE DEVELOPMENT (LORANG & STERLING, IN PREP)
**EARLY LEXICAL DEVELOPMENT IN FXS**

- Delayed first spoken word
  - 28 months

- Delayed expressive language
  - One study reported development at approximately 1/3 rate of typical development

- Expressive more delayed than receptive

**ORAL-MOTOR CHARACTERISTICS (HAGERMAN, 1996)**

- Children with FXS have a number of oral-motor problems including:
  - High, narrow arched palate
  - Generalized hypotonia
  - Oral tactile defensiveness and drooling
  - Cleft palate reported in 5% of children with FXS

**PHONOLOGICAL DEVELOPMENT**

- Overall delayed development

- Early-, middle-, and later-developing consonants acquired in same sequence as typical development

**LATER DEVELOPMENT**

- Speech and language abilities continue to be significantly delayed.

- Speech and language abilities traditionally examined by comparing children and adolescents with FXS to:
  - Children and adolescents with Down syndrome
  - Younger children with typical language and cognitive development
VOCABULARY

- Some children with ASD have an atypical profile of better production than comprehension
- School-age boys with ASD and FXS+ASD
  - Compared PPVT and EVT: Co-normed Vocabulary assessments
  - 36% of boys with ASD had lower PPVT scores compared to EVT scores
  - 14% of boys with FXS+ASD had lower PPVT scores compared to EVT

GRAMMATICAL DEVELOPMENT

- Delayed morphosyntax compared to nonverbal mental age matches
- Children use shorter, less complex utterances
  - Less complexity in noun and verb phrases (Price et al., 2008)

GRAMMATICAL DEVELOPMENT

- Impact of ASD
  - Boys with FXS-only use questions and negations more than boys with FXS+ASD (Price et al., 2008)

- Impact of context
  - Grammatical use in conversation appears to be weaker than in narrative context

GRAMMATICAL COMPLEXITY (PRICE ET. AL, 2008)

Younger Boys

*Controlling for Leiter-R mental age and maternal education
**Grammatical Complexity** [Finestack & Abbeduto, 2011]

<table>
<thead>
<tr>
<th>FXS</th>
<th>DS</th>
<th>TD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.66</td>
<td>0.68</td>
<td>0.70</td>
</tr>
<tr>
<td>0.72</td>
<td>0.74</td>
<td>0.76</td>
</tr>
<tr>
<td>0.78</td>
<td>0.80</td>
<td>0.82</td>
</tr>
<tr>
<td>0.84</td>
<td>0.86</td>
<td>0.88</td>
</tr>
</tbody>
</table>

**Grammatical Development** [Sterling et al., 2009]

- Tense and agreement markers
  - Third person singular -s (e.g., paints, digs) and past tense (e.g., painted, dug)
  - 26 boys with FXS between the ages of 8-16
  - Grouped by severity of autistic behaviors (CARS scores)
  - Test of Early Grammatical Impairment (TEGI: Rice & Wexler, 2001)

**Narrative Language**

- Macrostructure Level [Keller-Bell & Abbeduto, 2007]
  - Density and diversity of Evaluation Devices
    - Character names
    - Character dialogues
    - Use of repetition
    - Onomatopoeia, sound effects
    - Fantasy or exaggeration
  - No different than younger TD children, but less than DS
**Narrative Language**

**How Does the Story Start?**

13-year-old boy

1. At first he's getting dressed for dinner.
2. The dog is on the chair.
3. Petting his dog.
4. And say goodbye to his dog and the turtle.
5. And his frog with him to dinner.
6. (Get) They get there.
7. He go to the restaurant.
8. They order.
9. They go.
10. And then they get the menus and stuff like that.
11. They walk in the restaurant.

16-year-old girl

1. As George gets ready for dinner, he tells his pet frog that he must stay home because it’s such a fancy restaurant.
2. He says goodbye to his dog and his turtle.
3. But meanwhile his frog jumps into his pocket.
4. He says see you later as the frog waves bye quietly.
5. George looks at the sign and tries to read what it says.
6. But he can’t understand it because he doesn’t know how to read it.

**Language Growth - Vocabulary**

- EVT - raw score
- PPVT - raw score

**Language Growth - Grammar**

- CASL - raw score
- TROG - blocks passed

Boys and girls with FXS 10-16 years at Year 1
(Finestack & Abbeduto, in progress)
Perseverative/repetitive language argued to be a defining characteristic of FXS regardless of ASD co-diagnosis (Sudhalter et al., 1990)

- Phoneme
- Word
- Phrase & Utterance
- Topic
- Conversational device repetitions (e.g., “that’s a wrap,” “right on”)

Other difficulties in pragmatics:
- Atypical turn-taking
- Poor topic maintenance
- Tangential language
- Difficulty repairing communication breakdowns

**Impact of Gender**
- Compared to unaffected females, girls with FXS have:
  - Difficulty initiating and sustaining conversation
  - Longer to initiate interactions
  - Parents report more social problems related to language

PRAGMATICS

**Impact of ASD**
- Boys with FXS-Autism
  - Greater use of tangential language compared to boys with FXS-only
  - More topic changes
  - Perseveration: same rates regardless of autism co-diagnosis

SPEECH INTELLIGIBILITY

- FXS associated with speech intelligibility problems
  - Rapid rate of speech
  - Decreased range and precision of tongue movements
  - Dysfluencies in speech
  - Associated with increases in anxiety

THANK YOU!

- Questions and comments?