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Aging with the FMR1 Gene: A Life Course Perspective

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AGING WITH THE *FMR1* GENE : A Life Course Perspective

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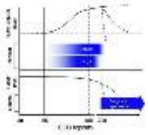

Fragile X is a single gene disorder that can result in 1 of 3 different clinical pictures depending on the extent of the DNA expansion. The 3 Fragile X- associated Disorders have different clinical pictures. The associated disorders can be simultaneously expressed in different generations in the same family or can remain silent over several generations before reemerging. Physical Therapists have a role in establishing a differential diagnosis and developing effective intervention plans.

FRAGILE X (FXS)

Gene Pathology: >200 CGG repeats of the *FMR1* gene, freq. is 1:3600 males, FXS is the result of FMRP protein deficiency

Full FXS transmitted by mother to ♂ or ♀ (usually milder form). All offspring from a FXS male will be typical.

Impairments in Childhood to Young Adult ± 25 years

- *Physical Impairments*
  - Low muscle tone, Soft skin
  - Hyperextensible joints
  - Excessive ankle pronation
  - Pectus excavatum
  - Mitral valve prolapse (10%) 2nd to abnormal elastin structure
  - High arch palate, Large ears
- *Behavioral Impairments*
  - Delayed development (motor and speech)
  - Hyper/hypoactive sensory responses
  - Hyperactivity
  - Dislikes change
  - Increased Anxiety

Impairments of the Adult over 25 years

- Significant decline of intellectual development in men
- Regression of communication skills - Increasing dyspraxia
- Increasing social isolation with less peer interaction
- Additional late diagnosis of autism in 30% to 60% in men
- Behavioral problems may improve between adolescence and adulthood

AGING with FRAGILE X (FXS)

There is currently no evidence that FXS progresses to FXTAS in the adult with >200 CGG repeats. There are indicators that there is a higher rate of medical problems of aging with FXS:

- PD is 20% higher than normal for men with FXS
- Increasing neurological problems develop
- Risk for seizures increases with age
- +50% of men develop heart disease or mitral valve prolapse
- 63.9% of men with FXS are overweight and have additional gastrointestinal issues.

FRX PRIMARY OVARIAN INSUFFICIENCY-FXPOI

Gene Pathology: 50-200 CGG repeats of the *FMR1* gene, frequency is 1:151, FXPOI is the result of mRNA toxicity

Transmitted from female carrier to 50%♀ offspring who are then carriers, and to 50% of ♂ offspring who have FXS

Impairments in Childhood and Adolescence

- Social anxiety or social ineptness
- Extreme shyness
- Depression
- ADHD or Learning Differences
- Above plus limited endurance consider FXPOI Dx

Impairments of the Adult over 30 years

- Premature menopause (±5 years earlier than typical) and elevated FSH levels
- Increased occurrence of twinning pregnancies
- Early onset and progression of osteopenia to osteoporosis
- Increased risk of Hypertension with higher number of CGG repeats
- Increased risk of thyroid dysfunction, (2.7-3.3 fold)
- Fibromyalgia and/or undifferentiated muscle pain
- Anxiety or depression disorder

Problems Encountered in Physical Therapy

- Differentiate FXTAS symptoms from normal aging pathology
- Monitor at ±50 years for symptoms of FXTAS
- Monitor for estrogen deficiency
- Monitor and treat cardiovascular symptoms
- Teach osteoporosis prevention and management
- Treat neurological and musculoskeletal symptoms to maximize function
- Support implementing a regular preventative exercise routine

FRX TREMOR/ ATAXIA SYNDROME (FXTAS)

Gene Pathology: 50-200 CGG repeats of the *FMR1* gene, frequency 1:468, FXTAS is the result of mRNA toxicity

Transmitted from ♂ parent to all daughters but not to sons, all daughters will be carriers

Impairments in Childhood to Adult ± 50 years

- May be completely asymptomatic until age ±50years
- Poor judgment and mood instability in adults
- Subtle declining executive function in adults
- Experiencing non-clinically significant psychiatric issues such as anxiety, depression, irritability, agitation

Impairments of the Aging Adult after FXTAS onset

Onset of initial motor signs in adults is related to size of the CGG expansion. Expected sequence after the onset of symptoms is:

- Ataxia within 2 years
- Significant increase in falls within 6 years
- Dependence on walking assistive devices within 15 years
- Death within 21 years; life expectancy ranges from 5-25 years
- Significant increase risk of hypertension
- Additional comorbidities: LE neuropathy, tremor, bowel and bladder incontinence, impotence, dysautonomia, dysphagia
- Higher rate of suicide

OLDER Adult Onset of FXTAS

- Definitive diagnosis of FXTAS requires the combination of intention tremor or gait ataxia ***and*** MCP T2-weighted sign on MRI
- Differential diagnosis of FXTAS from any other movement disorder
- Assess safety awareness function including driving risk related to declining executive function
- Advocate for genetic testing of the family cohort to determine carrier status.

REFERENCES