

Medical Problems in Fragile X Syndrome - A Review from the FXCRC Database and Q&A with Clinicians*



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**The information presented today is part of a larger paper titled "Fragile X Syndrome: A Review of Associated Medical Problems", which will be published in the journal Pediatrics in November of 2014*

INTRODUCTION

- **Individuals with fragile X syndrome (FXS) may be seen for a variety of medical problems related to FXS including seizures, recurrent ear infections and gastrointestinal disturbances.**
- **Need to know how big an impact medical problems in FXS have, so that physicians will diagnose and treat these problems earlier, to improve the long-term outcome and quality of life of patients with FXS.**
- **Awareness may help prevent and/or decrease certain behavioral problems, and may also provide clues to the diagnosis of FXS leading to testing**



METHODS FOR REVIEW OF THE DATA

The medical problems under review were chosen both because they are considered hallmark or typical medical problems for FXS and also would be commonly seen in general pediatric practice

Review of previous data from published studies

- All papers that could be identified from PubMed searching of key words related to FXS and medical problems were included
- Comparisons were made by gender and to typically developing populations where possible to demonstrate differences between groups



METHODS FOR REVIEW OF THE DATA (CONTINUED)

The FXCRC Database (CDC-funded database through middle of 2011)

- **Nine fragile X specialty clinics from the FXCRC contributed data:**
 - **260 individuals (198 males and 62 females) with FXS**
 - **Age of subjects ranged from birth to 55 years (average of 11 years old)**
 - ***87.7% of parents reported their children as Caucasian and 6.5% as Hispanic.***
- ***Questionnaires on a wide variety of medical, behavioral, and other concerns.***
- ***All medical conditions were assessed by medical history and physical exam.***

This database is similar to the CDC-funded FORWARD Database which is currently collecting data from families of individuals with FXS since 2012



CARDIAC DISORDERS

Review of the data:

<i>Mitral Valve Prolapse</i>	FXS Males	FXS Females	FXS All	TYP
FXCRC	0.5%	1.7%	0.8%	n/a
Other Studies	n/a	n/a	55%	0.7%

Common questions:

What is mitral valve prolapse?

Why should I be concerned about this condition?

Does my child with fragile X syndrome need to see a cardiologist (or heart specialist)?



CARDIAC DISORDERS

Recommended treatment and follow-up:

- **No evidence currently supports the routine cardiac evaluation of children and young adults with fragile X syndrome.**
- **Mitral valve prolapse, long thought to be associated with fragile X syndrome, does not appear to occur more frequently in FXS**
- **Children with a normal cardiac exam who have no cardiac symptoms (i.e. fainting, dizziness, recurrent fatigue) should not need to be referred to a cardiologist.**



EAR, NOSE, AND THROAT DISORDERS

Review of the data:

Recurrent Otitis Media	FXS Males	FXS Females	FXS All	TYP
FXCRC	54.7%	45.8%	52.6%	n/a
Other Studies	45-63%	n/a	n/a	12.6%

Common questions:

- Why is this a problem in FXS?
- What are the symptoms associated with otitis media (ear infections)?
- Why is it a problem to have recurrent otitis media?



EAR, NOSE, AND THROAT DISORDERS

Recommended treatment and follow-up:

- Children who are non-verbal or have developmental delay may not be able to communicate problems
 - They may present with behavioral problems, sleep disturbances, irritability, change in appetite.
- Recurrent otitis media may lead to hearing loss and further problems with language and speech.
 - Parents should consider an evaluation by an Ear, Nose, and Throat (ENT) specialist for a hearing test and possible PE tube placement for drainage of fluid.



GASTROINTESTINAL (GI) DISORDERS

Review of the data:

Gastrointestinal Problems	FXS Males	FXS Females	FXS All	TYP
FXCRC	Loose stools: 12.0%	Loose stools: 7.0%	Loose stools: 10.8%	n/a
	Gastroesophageal Reflux: 10.5%	Gastroesophageal Reflux: 13.6%	Gastroesophageal Reflux: 11.2%	
Other Studies (general GI)	31.8%	27.8%	30.6%	1.8-8.2%

Common questions:

- **Why does my child have loose BMs?**
- **What is gastroesophageal reflux?**
- **Does something hurt - in irritable child?**



GASTROINTESTINAL (GI) DISORDERS

Recommended treatment and follow-up:

- **Implement a healthy diet with high fiber and limit juice to 4 oz or less per day.**
- **Consider if lactose intolerance could be part of the problem.**
- **Discuss possible sources of pain with PCP (including Gastroesophageal Reflux Disease or GERD).**



NEUROLOGICAL DISORDERS

Review of the data:

Seizures	FXS Males	FXS Females	FXS All	TYP	
FXCRC	12.1%	3.2%	10.0%	n/a	
Other Studies	13.3-18.2%	4.8-7%	12-16%	1.2%*	*Epilepsy or other seizure disorder
Motor tics					
FXCRC	5.4%	6.7%	5.7%	n/a	
Other Studies	19%	n/a	15.0%	4.2%†	† Motor and vocal tics

Common questions:

- How likely is a patient with FXS to have a seizure?
- What should be done if a patient is having spells that might be seizures?
- Should an abnormal EEG be treated if there are no clear clinical seizures?
- Do seizures cause autism or more brain damage in patients with fragile X syndrome?
- Are hand flapping and other repetitive movements types of seizures or tics?



NEUROLOGICAL DISORDERS

Recommended guidance, treatment, follow-up:

Risk:

- Males with FXS in the FXCRC study had about a 12% chance of having a seizure
 - This percent is lower than what was found in prior large studies because these were often conducted in clinics with neurology specialists and the FXCRC population is likely a less biased (toward seizures) population of individuals with FXS than would be seen by a neurology specialist

EEGs (or electro-encephalograms):

- Patients having spells that might be seizures should have an EEG, usually an ambulatory EEG during which the spells can actually be captured on the EEG
- There is no evidence that treating patients that have abnormal EEGs when they don't have clinical seizures is beneficial;
 - many patients, including those with FXS, have an abnormal EEG and never have a seizure

NEUROLOGICAL DISORDERS

Recommended guidance, treatment, follow-up (cont'd):

Anticonvulsants:

- If patients are found to have seizures, they should be treated with anticonvulsants least likely to worsen behavior or cognition, until 2 years seizure-free
 - Seizures in FXS are usually easily treated with one anticonvulsant
- patients with very difficult to control seizures are unusual and may have a secondary genetic influence increasing their seizure susceptibility
- the large majority of patients will grow out of their seizures before reaching adulthood

NEUROLOGICAL DISORDERS

Recommended guidance, treatment, follow-up (cont'd)

Autism in seizures:

- There is a growing body of evidence that seizures are more common in individuals with FXS AND autism
 - Seizures probably do not cause autism but there are likely common brain wiring problems and genetic influences that make a person more likely to have both seizures and autism
- only prolonged uncontrolled seizures in which the patient does not get enough oxygen are thought to cause brain damage

Tics vs stereotypies:

- Hand flapping and other repetitive motor movements are not usually tics or seizures, they are motor stereotypies
- true tics are uncommon in FXS and in studies noting a high percentage of tics, there is probably confusion between tics and stereotypies

OCULAR DISORDERS

Review of the data:

Strabismus	FXS Males	FXS Females	FXS All	TYP
FXCRC	17.5%	12.9%	16.4%	n/a
Other Studies	4.4-57%	n/a	n/a	2.6-4%

Common questions:

What are the implications of strabismus?

What other eye problems might children with FXS have?

What should parents do about eye and vision problems?



OCULAR DISORDERS

Recommended treatment and follow-up:

- **Strabismus can lead to amblyopia, which is secondary vision loss due to the failure of binocular fusion**
 - **this eventually leads to suppression of the visual image from the discordant eye.**
- **Children with FXS have a higher prevalence of refractive errors including hyperopia, myopia, and astigmatism.**
- **Children with FXS may be difficult to evaluate due to developmental delays, attention problems, anxiety, and sensory processing problems.**
 - **Regular evaluation by an ophthalmologist or optometrist who has patience and experience working with children with special needs is critical.**



SLEEP PROBLEMS

Review of the data: Sleep Problems	FXS Males	FXS Females	FXS All	TYP
FXCRC	26.0%	29.8%	26.9%	n/a
Other Studies	n/a	n/a	32-47%	10-25%
Obstructive Sleep Apnea				
FXCRC	7.2%	7.1%	7.2%	n/a
Other Studies	n/a	n/a	34%	1.2%*

*Moderate sleep-disordered breathing

Common questions:

How frequent are sleep problems in children with FXS?

What type of sleep problems can they have?

How common are obstructive sleep apneas?

What type of treatments are available?

Why is important to diagnose and treat the sleep disturbances?



SLEEP PROBLEMS

Recommended treatment and follow-up:

- Previous data show that up to half of children with FXS have some sleep problem, but our data suggest that the prevalence is lower.
- Sleep problems include: difficulty with falling asleep, walking up at night, sleep walking or sleep terrors, and obstructive sleep apneas.
 - Your doctor should inquire about potential sleep problems at every well child visit.
- Symptoms such as snoring and pauses in breathing (or apnea) during the night are suggestive of OSA (obstructive sleep apnea)
 - This is observed in up to one third of children with FSX.

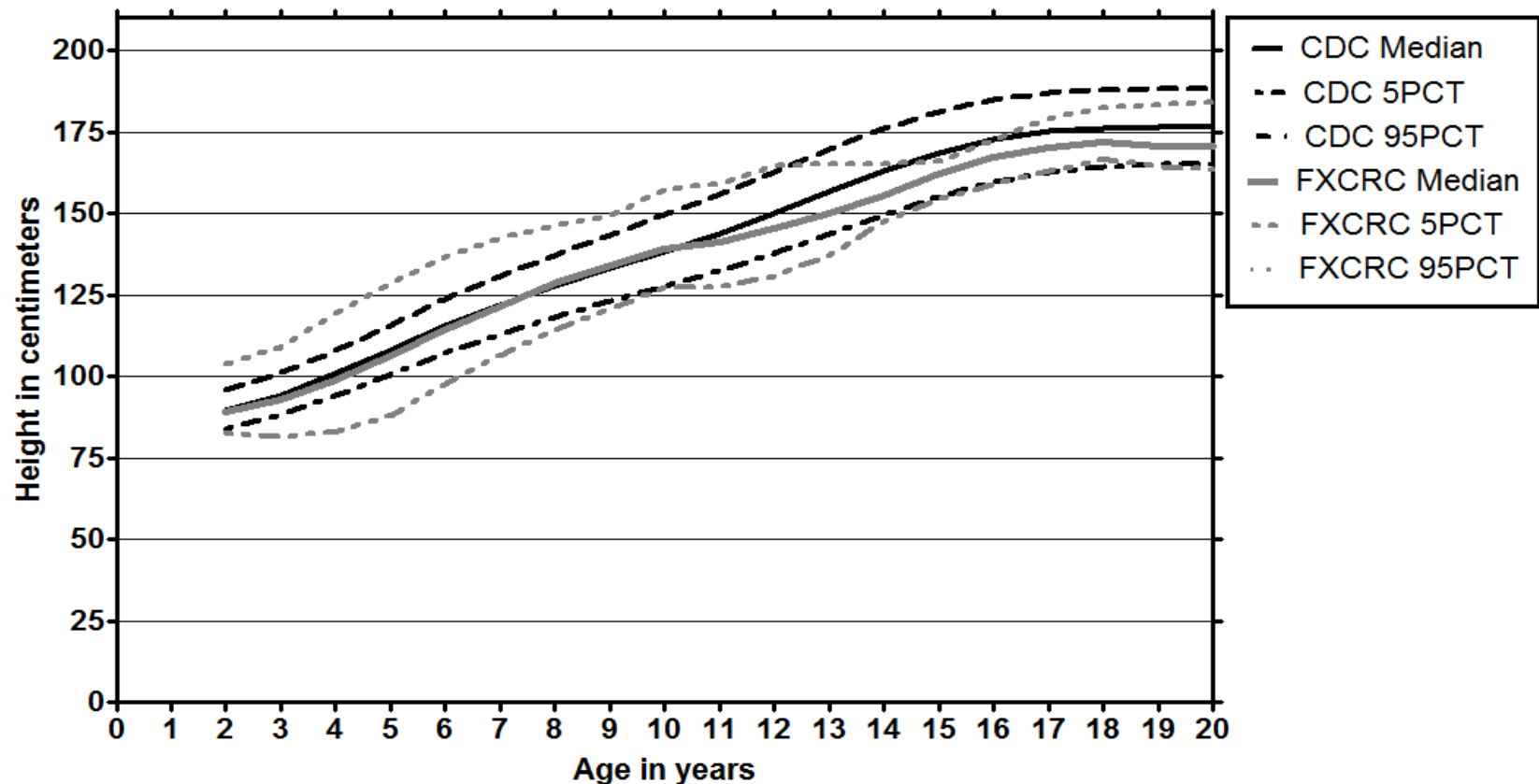
SLEEP PROBLEMS

Recommended treatment and follow-up (cont.):

- Sleep may also be affected by environmental, health and emotional factors which should be addressed and treated.
- Depending on the severity of the sleep problems, it may require behavioral or/and medical treatment or a referral to a sleep specialist.
- Children, especially those with ID, require adequate sleep for optimal development, learning, and functioning.
- Monitoring and managing OSA and other sleep problems are of particular importance in FXS, due to their relationship to poor daytime performance and behavior.

GROWTH

Figure 1: Height of males (CDC TYP and FXCRC FXS) in centimeters by age in years*

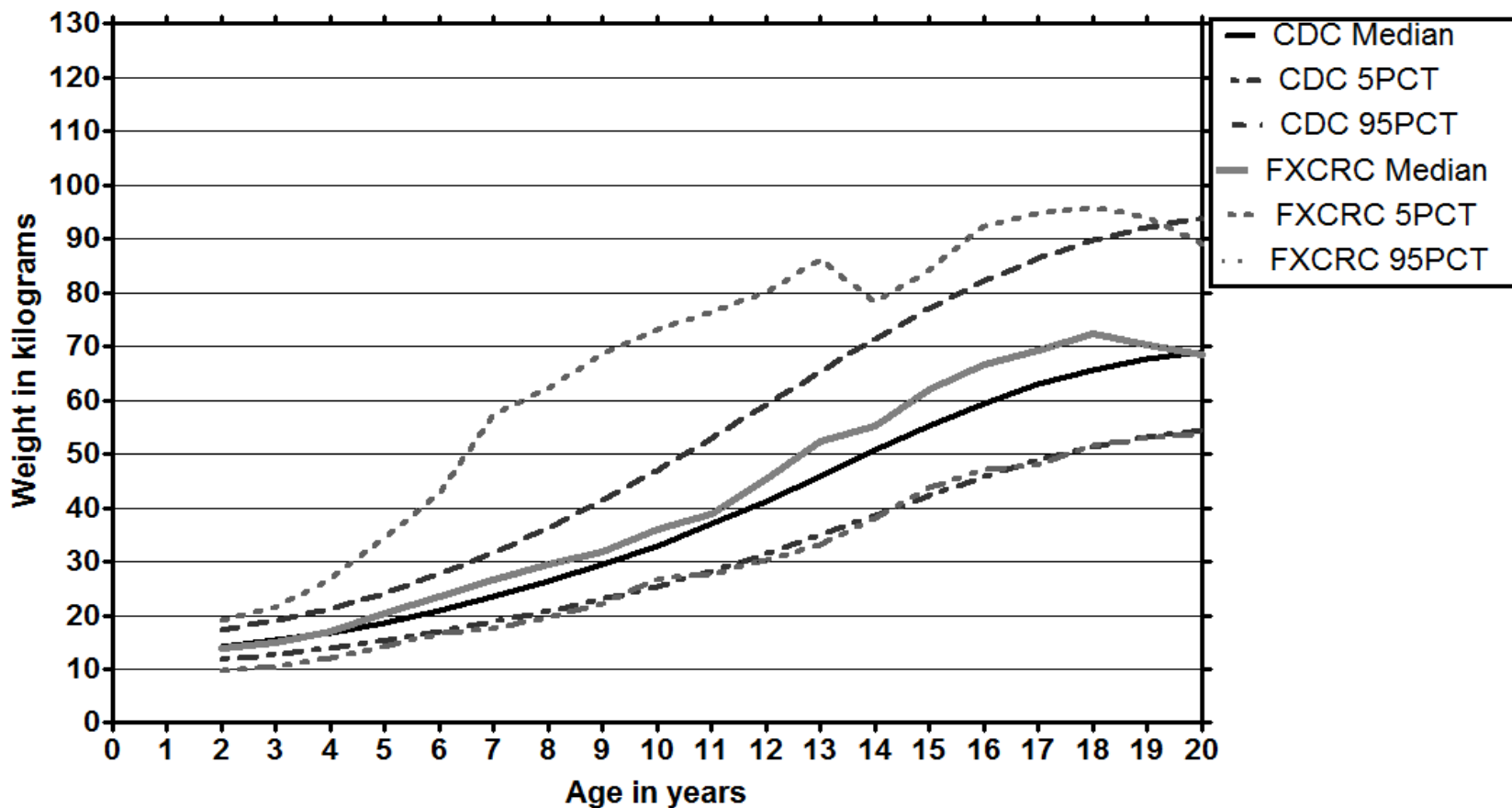


* Comparing FXCRC Database (FXS) to a typically developing (TYP) population from CDC growth charts: Centers for Disease Control and Prevention, National Center for Health Statistics. CDC growth charts: United States. 2000; <http://www.cdc.gov/growthcharts/>.



GROWTH CONT'D

Figure 2: Weight of males (CDC TYP and FXCRC FXS) in kilograms by age in years*



* Comparing FXCRC Database (FXS) to a typically developing (TYP) population from CDC growth charts: Centers for Disease Control and Prevention, National Center for Health Statistics. CDC growth charts: United States, 2000; <http://www.cdc.gov/growthcharts/>.



GROWTH CONT'D

Common questions:

Do individuals with fragile X have normal growth?

- **Males with fragile X have normal to slightly above average growth through childhood but tend to be slightly shorter after about age 10 yrs.**

Do individuals with fragile X have normal weight?

- **Based on these growth curves, males with fragile X weigh somewhat more than average through age 20.**

Do boys with fragile X have an average birth weight?

- **Yes, and they are born at the average gestational age**

Do they have average head circumferences?

- **Head circumferences tend to be somewhat above average after birth.**



GROWTH CONT'D

Common questions:

Are there data on the females?

- There was very limited information on females.
 - The limited information on females suggested that heights and weights were somewhat above average between eight and fourteen years.

Recommended treatment and follow-up:

- Based on this information we primarily recommend that weight be carefully monitored.
- We recommend good diets and exercise programs.



THE MEDICAL HOME FOR CHILDREN WITH FRAGILE X

What is a Medical home?

- An approach to provide comprehensive and coordinated primary care to optimize outcomes for children with special healthcare needs
- A pediatric team to deliver accessible, continuous, comprehensive, family-centered, coordinated, culturally effective care to children and their families

What is the goal of a medical home?

- To ensure the child's medical, developmental, and behavioral needs are being met

How does this paper help?

- Provide information to your child's pediatrician to increase their knowledge and support their ability to provide a more comprehensive medical home to your child with FXS

MANAGEMENT AND FOLLOW-UP OF MEDICAL PROBLEMS IN FXS

Medical Problem

Otitis Media

- Since children with FXS frequently have expressive language delays, it is important that all otitis media and/or any otologic issues be treated promptly and appropriately.
- Hearing testing may be considered if there is concern about a child's hearing.

Gastrointestinal Problems

- If a child with FXS who also has symptoms suggestive of GER, such as frequent vomiting, feeding difficulties and failure to thrive, particularly if they also have hypotonia and oromotor problems, should be referred for appropriate medical evaluation and management.
- If a child presents with unexplained irritability or poor growth, then diagnosis of FXS should be considered.
- Evaluation and treatment for loose BMs or constipation would be similar to that for a child without FXS.



MANAGEMENT AND FOLLOW-UP OF MEDICAL PROBLEMS IN FXS (CONT.)

Medical Problem

Seizures

- For concerns about episodes that might be seizures, an electroencephalogram (EEG) evaluation should be obtained along with neurology referral.
 - Ambulatory EEG can be used to distinguish behavioral spells from seizures.
- Special attention should be given to children with FXS and ASD, since they seem to be particularly at risk for epilepsy.
- Typically, patients would be treated after two documented seizures with anticonvulsants that are least likely to cause sedation or behavioral aggravation
 - A view to discontinuation of treatment after an individual with FXS is seizure-free for two years.



MANAGEMENT AND FOLLOW-UP OF MEDICAL PROBLEMS IN FXS (CONT.)

Medical Problem

Ocular Disorders

- As strabismus and other ocular disorders, such as refractive errors, are common in children with FXS, pediatricians should monitor these conditions and refer children during the first 3 years for evaluation by a pediatric ophthalmologist or optometrist.
 - This should be followed by yearly eye exams to continue to monitor for refractive errors.

Sleep Problems

- The primary care physician should inquire about potential sleep problems in children with FXS at every well child visit.
- Depending on the severity of the sleep problems, it may require behavioral or/and medical treatment or a referral to a sleep specialist.
- Sleep may also be affected by other environmental, health and emotional factors which should be addressed and treated accordingly.



MANAGEMENT AND FOLLOW-UP OF MEDICAL PROBLEMS IN FXS (CONT.)

Medical Problem

Growth Problems

- The growth findings from the FXCRC Database suggest that patients with FXS may be at an increased risk for being overweight and for having somewhat diminished height in adulthood.
- We encourage healthy diets for our patients and good exercise programs to minimize problems associated with increased weight.

Cardiac Disorders

- No evidence currently supports the routine cardiac evaluation of children and young adults with fragile X syndrome.
- Children with a normal cardiac exam who have no cardiac symptoms do not need to be referred to a cardiologist.



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We would like to thank the FXCRC and the National Fragile X Foundation for their work in bringing specialty clinics together to make work like this possible.

Importantly, the FXCRC Database could only exist given the effort of parents of, and, children who have FXS.



Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.





FRAGILE X Clinical & Research CONSORTIUM

