Review

Fragile X syndrome: A review of clinical management

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Summary	The fragile X mental retardation 1 gene, which codes for the fragile X mental retardation 1 protein, usually has 5 to 40 CGG repeats in the 5' untranslated promoter. The full mutation is the almost always the cause of fragile X syndrome (FXS). The prevalence of FXS is about 1 in 4,000 to 1 in 7,000 in the general population although the prevalence varies in different regions of the world. FXS is the most common inherited cause of intellectual disability and autism. The understanding of the neurobiology of FXS has led to many targeted treatments, but none have cured this disorder. The treatment of the medical problems and associated behaviors remain the most useful intervention for children with FXS. In this review, we focus on the non-pharmacological and pharmacological management of medical and behavioral problems associated with FXS as well as current recommendations for follow-up and surveillance.

Keywords: Fragile X syndrome, Autism Spectrum Disorder, Intellectual Disability, developmental delay, premutation, clinical management, clinical guidelines, treatment, medical problems, *FMR1*, FMRP

1. Introduction

Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability (ID) and the most common monogenetic cause of autism (ASD) that is known. FXS was initially described in 1969 by Lubs and colleagues (*1*) and the first fragile X-linked pattern of inheritance was reported by Martin and Bell in 1949 (*2,3*). In FXS there is a mutation in the Fragile X Mental Retardation 1 (*FMR1*) gene which involves an expansion of more than 200 CGG repeats. Individuals in the normal population have approximately 5 to 40 CGG repeats within *FMR1* and individuals who are carriers for FXS (premutation) have 55 to 200 CGG repeats (*4-6*). The molecular basis of FXS is characterized by the CGG full mutation and methylation of the cytosine bases, which leads to silencing of transcription and

deficiency or absence of the encoded protein, Fragile X mental retardation protein (FMRP). FMRP is a major protein regulator of the translation of many mRNAs involved in synaptic plasticity (*7*). Therefore, in FXS the lack of FMRP causes significant intellectual deficits. Usually, expansions occur between generations when passed on by a female with the premutation into a full mutation in the offspring (*8*). Women, who are known carriers of the *FMR1* gene mutation, can obtain prenatal diagnosis including chorionic villus sampling (CVS) and/or amniocentesis studies as recommended by the American College of Obstetricians and Gynecologist (*9*). Preimplantation diagnostic services and *in vitro* fertilization are also available (*10-12*). Individuals with FXS present with a wide range of learning disabilities ranging from normal functioning to borderline cognition or mild to severe ID. The average Intelligence Quotient (IQ) of males with the full mutation is 40 (*13*). Intellectual and developmental disability occurs in 85% of males and 25% of females. Furthermore, FXS also accounts for approximately 2 to 5% of all individuals diagnosed with ASD. In FXS about 60% of males have ASD (*14*). Physical manifestations are subtle in infants and young boys. These include: midface hypoplasia with sunken eyes, arched palate, macroorchidism, and large cupped ears among others (Figure 1).

Figure 1. Young boy with fragile X syndrome and his Go Talk device. Note prominent ears with cupping of the pinnae. The participant's family provided informed consent for the use of this picture.

Medical problems associated with FXS include mitral valve prolapse, otitis media, seizures, strabismus, joint laxity, sleep disturbances, and gastrointestinal problems. In this review, we provided a summary of the prevalence and clinical management of medical problems associated with FXS other than ID and ASD (Table 1).

2. Fragile X syndrome associated medical problems

2.1. *After birth problems*

Boys with FXS are slightly larger than average in weight at birth. The mean birth weight from earlier studies ranges from 3,490 gms. to 4,046 gms. in white male infants (*15*). The mean birth weight of boys with the FXS was in the 70th percentile, they also had a higher birth weight than their siblings when this was corrected for gestational age and sex (*16*). The mean birth weight in FXS was increased and the average linear growth was also above the mean for typically developed boys with the greatest increase after the second year of life. In contrast, the weight measurements were on average below the mean until two years of age. It is suggested that in FXS there is a disturbance of early infantile growth (*17*); however, the overall proportion of infants with low birth weight was similar to that in the general population (*18*). After birth, the head circumference tends to rise above the 50th percentile and continues to be larger than those without FXS. Jacobs *et al*. noted that in six of nine affected men, the head circumference was greater than the 90th percentile (*18*), but other studies have shown that the mean head circumference (*19-21*) and the mean birth length are not different of those of control population (*21*). Hagerman and colleagues found no difference in the height, weight or head circumference of girls with FXS compared with those without the full mutation (*22*).

Some studies reported that the height of males with FXS is greater than the 50th percentile and height curves for FXS were higher at nearly every point in the prepubertal section of the curves, but height was lower at postpubertal ages (*23,24*). A subset of children with FXS can be misdiagnosed as having Sotos syndrome or Prader-Willi syndrome (*25*). The Prader-Willi phenotype (PWP) can be observed in FXS and it consists of extreme obesity, hyperphagia, lack of satiation after meals, small genitalia, delayed puberty, sometimes short stature and stubby hands and feet (*26-28*). Sotos-like syndrome was reported in 1986 in two boys with FXS featuring large size at birth, unusual length, large head circumference and minor facial abnormality (*29*).

Structural longitudinal magnetic resonance imaging (MRI) study of preschoolers with FXS observed generalized brain overgrowth compared to controls, evident at age two and maintained across ages 4-5 (*30*). The molecular biology of FXS suggests a possible mechanism for brain growth patterns. Harlow and colleagues have demonstrated that FMRP inhibits the generation of progenitor neurons from glia cells but enhances the glial cell number in mouse cerebral cortex, suggesting that the lack of FMRP, as seen in FXS might result in an increased proliferation of progenitor glial cells and subsequent cerebral cortical overgrowth (*31*). The presence of early brain differences in young children with FXS points to aberrant early brain development in this condition (*31*).

FMRP also regulates the phosphatase and tensin homolog (*PTEN*) gene translation that in turn regulates growth. The results of genetic and regression analysis showed that in both boys and girls, total pubertal height gain is impaired, whereas the rate of growth during the preadolescent period is increased, compared with the growth rate of subjects without FXS. The study demonstrates the linear effect of progressively reduced levels of FMRP on a number of physical measurements (*32*). This effect is predictably less strong in females than in the males because of the presence of the second unaffected X chromosome. The inverse relationship of height and limb length with FMRP deficit supports a possible role of hypothalamic dysfunction in growth disturbances in FXS that may be more severe in those with the PWP (*33*). This dysfunction may cause a premature increase in the pulsating secretion of high doses of estrogen, thus leading to earlier epiphyseal maturation (*34*). The hypothesis of premature activation of the hypothalamic-pituitary-gonadal axis may explain the cause of growth impairment in FXS and occasional precocious puberty in females with FXS, a few cases have been reported (*35,36*).

2.2. *Otitis media (OM)*

OM is one of the most frequent medical problems associated with FXS. Even when children with FXS have a high pain threshold and may not specifically complain about ear pain, 85% of children with FXS

Table 1. Summary of medical problems and management

Medical problem	Prevalence	Age of presentation	Severity	Complications	Recommendations	Follow up
Growth	Low birth weight - FXCRC: 9% - Other studies: 8% Preterm - FXCRC: 16% - Other studies: 12%	- Brain overgrowth 2-5 years - Height deceleration: after puberty	Moderate	- Overweight	- Lifestyle changes including healthy diet and exercise to minimize problems associated with increased weight	- Monitor patient's weight, height and head circumference closely in each visit
Otitis media	- FXCRC: 55% - Other studies: 45-85%	Childhood	Mild	- Acute sinusitis - Recurrent otitis media - Exacerbate the cognitive and language deficits - Conductive hearing loss	- Pneumococcal and influenza vaccines - Breastfeeding for at least 4-6 months - Eliminate passive exposure to tobacco smoke - Reduce pacifier and bottle usage - Antibiotic therapy - Ear tubes placement	- Surveillance of the potential adverse effects of antibiotic prophylaxis including hypersensitivity reaction and gastrointestinal problems
Seizures	- FXCRC: 10 % - Other studies: 12-18%	Early childhood	Mild to severe	- Developmental and behavioral morbidity	- Educate parents and follow up patients with history of seizures - Carbamazepine - Valproic acid	- EEG - Drug-specific blood test - Discontinue medication after patient is seizure-free for 2 years unless EEG is abnormal
Mitral valve prolapse	- FXCRC: 0.8% - Other studies: 50%of males and 20% of females	Childhood to adolescence	Mostly asymptomatic	- Rarely mitral regurgitation, congestive heart failure and endocarditis	- Mitral valve repair or replacement rarely required	- Surveillance cardiac evaluation
Gastrointestinal problems	- FXCRC: 2%-8% - Other studies: 11%	Childhood to adolescence	Mild	- Failure to thrive - Irritability - Behavioral problems	- Thickening agents - Antacids - Histamine-2 blockers - Proton pump inhibitors	- Surveillance on height and weight
Sleep problems	- FXCRC: 26.9% - Other studies: 32%-47%	Infancy and childhood	Mild to moderate	- Disturbance in daytime performance - Behavioral problems	- Behavioral intervention - Melatonin - Clonidine	- Monitor the side effects of sleep medications - Careful history of sleep habits
Obstructive sleep apnea	- FXCRC: 7% - Other studies: 21-32%	Childhood	Moderate to severe	- Vigilance impairment and neuropsychological deficit - Decrease in day time performance - Increase in behavioral problems	- Steroids to reduce tonsillar hypertrophy - Continuous positive airway pressure - Surgical intervention including tonsillectomy - Behavioral therapy	- Monitoring and managing obstructive sleep apnea in every child visit - Refer to sleep specialist
Strabismus	- FXCRC: 17% - Other studies: 8%	Early childhood	Mild to moderate	- Amblyopia	- Corrective eyeglasses - Visual training exercise - Surgery	- Comprehensive ophthalmologic examination of every child with FXS by age 4 or sooner if strabismus is detected
Tic disorder	- FXCRC: 6% - Other studies: 15%	Before 18 years of age	Mild	- Usually uncomplicated	- Educational and supportive approach - Medications rarely necessary	- Long term relationships to improve patients self-esteem and coping with their tics
Toileting issues	49%	Delayed several years	Mild to moderate	- Enuresis - Encopresis	- Behavioral therapy - Desmopressin - Fiber supplements in case of constipation	- Toileting counselling by 1 year of age
Sensory integration problem	20%-50%	Early childhood	Moderate to severe	- Lack of participation in activities that are necessary for brain development	- Medications related to inattention, anxiety, aggression and autonomic symptoms - OT therapy	- Assessment tools such as sensory profile questionnaire, *etc.*

FXCRC: Fragile X Clinical and Research Consortium Study; FXS: Fragile X syndrome.

have at least one diagnosed episode of OM (*37*). An ear examination is warranted for any change of behavior and sleep patterns as well other symptoms including fever, vomiting, and headache. Children with FXS commonly develop OM complications including decreased hearing acutely and at least one-fourth develop acute sinusitis. Furthermore, OM recurs in about 50% of children with FXS recurrent 5 years of age (*37*). There is not data reported about the rates of chronic otitis. Recurrent otitis media may cause conductive hearing deficits and exacerbate the cognitive, language, and behavior problems that exist in this syndrome (*38*); therefore, the treatment of OM should be aggressive. The American Academy of Pediatrics initial recommendation for uncomplicated OM is an observation period for children 6 months to 2 years with unilateral OM without otorrhea and for children older than 2 years with bilateral OM without otorrhea; however, we recommend to consider skipping the observation period and using antibiotic therapy in children with FXS (*39*). The craniofacial changes in FXS including a long face and collapsible Eustachian tubes predispose children to OM infections. Signs of slight redness, mobility impairments and abnormal positioning of tympanic membrane (TM) such as retraction or bulging, should be carefully assessed. Initial antibiotic therapy for 10 days includes a high dose of amoxicillin (80-90 mg/kg per day in 2-3 divided doses). If not improvement after 48-72 hour, Amoxicillin-clavulanate (same dose of amoxicillin + 6.4 mg/kg per day of clavulanate (amoxicillin to clavulanate ratio, 14:1) in 2 divided doses) or Ceftriaxone (50 mg IM or IV for 3 day) are recommended. A low threshold for early tympanostomy tube placement and antibiotic prophylaxis (amoxicillin low dose) is also advised. The potential adverse effects of antibiotics, principally allergic reaction and gastrointestinal tract consequences, such as diarrhea are important considerations for tympanostomy tubes over prophylaxis.

Clinicians should stress the recommendations of pneumococcal conjugate and influenza vaccine to all children, according to the schedule of the Advisory Committee on Immunization Practices, American Academy of Pediatrics (AAP), and American Academy of Family Physicians (AAFP). Multiple studies provide evidence that breastfeeding for at least 4 to 6 months reduces episodes of OM and recurrent OM (*40-43*). Eliminating passive exposure to tobacco smoke could also reduce the incidence of OM in infancy. In addition, bottles and pacifiers have been also associated with OM (*44-49*). Finally, Xylitol syrup, chemically a pentitol or 5-carbon polyol sugar alcohol, has shown a statistically significant reduction (25%) in the risk of occurrence of OM among healthy children (*50*).

2.3. Seizures

Seizure prevalence studies in FXS have shown discordant results; a study conducted in neurology clinics reported a broad prevalence range of 14% to 44%, while studies that focus on FXS patients in community hospitals or FXS clinics reported lower ranges of 12-18% (*51-53*). Typically, males have a higher prevalence when compare to females. In the national survey of caregivers of individuals with FXS, from 1,394 individuals, 14% of males and 6% of females were reported to have seizure (*54,55*). Studies in the *Fmr1* knockout (KO) mouse shows immature dendritic connections, increased number of long and thin spines which point to the deficiency in the normal selection or pruning of the synaptic contacts that occurs in neuronal development (*56,57*). These results demonstrate that FMRP is important in the maturation of adult dendritic spine morphology (*58*). Immature dendritic connections can predispose the KO mouse to audiogenic seizures, although deficits in gamma amino butyric acid (GABA) inhibition are also related to the seizures in FXS (*59,60*). Similar abnormal dendritic formations are also observed in the brain of humans with FXS and may explain the higher frequency of seizures. In addition to structural changes, the absence or deficiency of FMRP leads to increased neuronal excitability and susceptibility to seizure (*61*). Other studies hypothesize that the pathophysiology of seizures in those with FXS can be related to the imbalance of the excitatory and inhibitory neurotransmitter systems (*60,61*).

It is important to consider that many children with FXS have abnormal electroencephalogram (EEG) without overt seizures (*62,63*). In those with overt seizures, all types of seizures can occur. Some studies have shown a predominance of generalized seizures (*64*), secondary generalized seizure and status epilepticus seizure (*64*). Seizures in FXS may also resemble benign focal epilepsy in childhood with centro-temporal spikes (*65,66*). In general, complex partial seizures are the major type of seizure in FXS. The observed seizures are – typically- not severe and mostly limited to childhood (*66*); however, the presence of seizures at an early age appears to be associated with developmental and behavioral morbidity that can impact brain function. Remarkably, those patients with FXS and seizures are more likely to have ASD (*67*). The current practice is to educate parents and follow-up patients closely for any possible episodes of seizure: starring spells, unexplained behavior, atypical facial gestures, vomiting at night, regression of development, language or behavior changes, as well as, significant sleep disturbance. If seizures are suspected, then it is recommended to obtain an EEG in both the waking and sleeping states (*68*). It is also important to tell families to avoid soy formulas in young children with FXS because of the recent report of soy formula intake increasing the prevalence of seizures in those with ASD and FXS (*69*).

Seizures are usually easily managed on

monotherapy with anticonvulsants. Historically, most individuals with FXS have experienced good control with carbamazepine or valproic acid, with fairly limited adverse effects (*69*). Carbamazepine stabilizes the inactivated state of voltage- gate sodium channels. Its action leaves the affected neuronal cells less excitable. Carbamazepine has also α1, β2, and γ2 subunits containing GABA receptor agonist actions. Carbamazepine-gene testing, pharmacogenomics or pharmacogenetics, to look for the human leukocyte antigen B 1502 (HLA-B*1502), the variant may determine whether carbamazepine could be an effective treatment or whether side effects may develop. The United States Food and Drug Administration (FDA) recommends that patients with Asian ancestry should be tested for the *HLA-B*1502* gene variant before treatment. Testing individuals of other ancestries is not typically performed (*70-72*). The carbamazepine label contains warning for blood dyscrasia and common side effects are drowsiness, dizziness, headaches and migraines, motor coordination impairment, nausea, vomiting, and/or constipation. Carbamazepine has also the advantage that can be used as a mood stabilizer at a typical dosage (*73*). The valproic acid mechanism of action is not fully understood, but the reduction of phosphatidylinositol (3,4,5)-trisphosphate (PIP3), as well as, the blockade of voltage-dependent sodium channels may protect against seizures; the increased brain levels of GABA may contribute to its mood stabilizer properties as well as its antiepileptic mechanism of action. The most common adverse effects of valproic acid are digestive complaints (diarrhea, nausea, vomiting and indigestion), vision problems (double vision or lazy eye), hormonal disturbances (increased testosterone production in females and menstrual irregularities), hair loss, memory problems, weight gain, infections, low platelet count, dizziness, drowsiness, tremor and headache (*74,75*). The FDA recommends patient testing on the Valproate (VP) drug label to avoid prescribing the drug to individuals with urea cycle disorders, the information is lacking about what type of genetic testing and how it should be carried out. Newer studies correlating genotype-phenotype associations with the clinical response will be helpful to increase drug efficacy and to reduce drug-related toxicity (*76*).

For those who failed carbamazepine or valproic acid, lamotrigine can be used as a fairly effective second line. Phenytoin has the adverse effects of gum hypertrophy and can interfere with dental hygiene. Phenobarbital and gabapentin also should be avoided because they exacerbate behavioral problems including hyperactivity (*76*). Drug-specific blood level testing, liver function studies, electrolytes, complete blood count (CBC) and general health monitoring should be considered for any child taking anticonvulsant medications (*76*).

2.4. *Mitral valve prolapse*

Mitral Valve Prolapse (MVP, floppy mitral valve) is a valvular heart condition that is characterized by the displacement of an abnormally thickened mitral valve leaflet into the left atrium during systole (*77*). The prevalence of MVP in the general population is estimated at 2-3% (*77*); however, MVP is observed in 7% of autopsies in the United States (*78*). Studies of individuals with FXS have shown that MVP occurs in approximately 50% of males and 20% females with echocardiogram confirmation (*79,80*). However, a recent Fragile X Clinical Research Center (FXCRC) database study using only clinical reports showed a prevalence of only 0.8%. Perhaps this relates to the fact that MVP is more common in adults than children and often cannot be diagnosed by just auscultation. Careful cardiac auscultation is recommended during every annual physical examination and if a systolic murmur or the classical MVP murmur is detected (a mid-systolic click, followed by a late systolic murmur heard best at the apex), then it is recommended to request a cardiology evaluation which should include an echocardiogram (*81*). Individuals with MVP, particularly those without symptoms, often require no treatment (*82*). Those rare cases of MVP and symptoms of arrhythmias or dysautonomia may benefit from beta-blockers. Individuals with MVP are at higher risk of infective endocarditis, approximately three- to eightfold the risk of the general population (*82*). Before 2007, the American Heart Association recommended prophylaxis for dental surgery and other invasive procedures that could introduce bacteria into the blood stream. Thereafter, the association determined that individuals with MVP should not receive prophylaxis routinely; prophylaxis for dental procedures should be recommended only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from infective endocarditis (*83*).

Surveillance cardiac evaluations are necessary for those with moderate MVP, in order to evaluate the degree of regurgitation. In very rare instances when MVP is associated with severe mitral regurgitation, mitral valve repair or surgical replacement may be necessary. In the general population, MVP is observed in individuals who tend to have low body mass index (BMI), it is unknown if MVP in FXS is associated with lower BMI. Abnormal elastin fibers have been detected in the cardiac valves and in the skin of individuals with FXS so MVP is thought to be related to the connective tissue problems seen in FXS and are related to abnormalities of the elastin fibers (*84*). Dilation of the aortic root is also seen in many individuals with FXS in both childhood and adulthood and this is also associated with abnormal elastin fibers (*35,58*); Typically, this is not progressive nor have significant aneurisms been reported. In summary, MVP carries a very low risk of complications, but in rare severe cases complications may include mitral

regurgitation, infective endocarditis and congestive heart failure. Further, larger longitudinal studies that described the prevalence and MVP and its complications are necessary.

2.5. Gastrointestinal problems

The frequency of gastro intestinal (GI) problems in FXS remains to be determined, but initial and current studies showed a similar proportion (prevalence ~11%) of children suffering from diarrhea and gastro-esophageal reflux disease (GERD) (*85,86*). Interestingly GI problems have been described to be quite common in other connective tissue disorders, such as Ehlers-Danlos syndrome (EDS) and Marfan syndrome; such problems include GERD, irritable bowel syndrome, and diarrhea (*87-90*). Even more intriguing is the association of the premutation and irritable bowel syndrome and the fact that developmental disorders and autism are usually associated with constipation rather than diarrhea as observed in FXS (*91*). General recommendations should be provided and medication management, such as, thickening agents, antacids, histamine-2 (H-2) blockers and proton-pump inhibitors, should be prescribed if necessary. Individuals with FXS have higher pain threshold which along with the communication deficits can mask the frequency of abdominal pain and other gastrointestinal symptoms. Surveillance on height and weight are appropriate to determine a failure to thrive (FTT) and referral to gastroenterologist specialist and nutritionist are recommended in the presence of FTT or poor weight gain. It is likely that the frequent loose stools in FXS are related to autonomic dysregulation including sympathetic hyperarousal and chronic anxiety (*92*).

2.6. Sleep

Sleep problems are very common in the general population and even more common in young children with FXS. There are many issues that disturb normal sleeping patterns such as problems falling asleep, frequent nighttime awakenings, waking up too early, and parasomnias. In children with FXS the prevalence of sleep problems was reported to be 26-47% (*93,94*) which is higher than the prevalence observed in typical children (10-25%) (*95,96*). A recent study showed that the prevalence did not have gender or demographic differences and that the severity of sleep disturbance in FXS children was more pronounced when compared to typically developing children. The most frequent problems reported were difficulty falling asleep and frequent nighttime awakening (*97*). In addition, altered sleep patterns and dysregulated melatonin profiles have been observed in adolescents with FXS as well as greater variability in total sleep time, difficulty in sleep maintenance, and significantly greater nocturnal melatonin production in the boys with FXS (*98*). Children

with FXS are at a higher risk for sleep problems at very young age (~3 years of age) and the sleep problems may not resolve with age. Therefore; it is recommended that a careful history of sleep habits must be included in every clinical visit (*99*), starting at a young age and continue throughout their life. The physician may simply ask the parents if they have any concerns about their child's sleep or if their child takes more than 30 minutes to fall asleep at bedtime. Standardized parent questionnaires, such as the Child's Sleep Habit's Questionnaire or a two-week sleep diary are good tools to assess sleep problems (*99*).

Treatment of sleep problems in FXS includes behavioral interventions and medications. Behavioral intervention should include bedtime routines, positive reinforcement, effective instructions and parental support. An example is "extinction" (removing reinforcement to reduce a behavior) which can effectively reduce the falling to sleep period and increase overall sleep time. The medications used to treat this medical problem include melatonin and if needed, clonidine (*99*). Melatonin can effectively improve total night sleep duration, sleep latency time, and sleep-onset time (*100*). A study in the *Fmr1* KO mouse showed that the therapeutic effects of melatonin may be due to its antioxidant effects and ability to normalize synaptic connections (*101,102*). Other studies of antioxidants in the KO mouse include alpha-tocopherol (vitamin E) and N-acetyl-cysteine (NAC) (*103*) and omega-3 therapy (*104*) with improvement in the maturity of dendritic spines and enhanced Brain Derived Neurotropic Factor (BDNF) levels in the hippocampus respectively. However, these antioxidants have not been studied for improvement in sleep in FXS. Melatonin should be given 1 hour before bedtime. The dose recommended for children with FXS ranges 0.5-5 mg. It is recommended to start with the lowest dose of 0.5 mg then adjust the dose with the response (*105,106*). No significant adverse effects of melatonin have been reported in those with FXS although in some patients it can cause agitation (*106,107*). Another study reported increased seizures in children with neurologic disabilities treated with melatonin but this has not been seen in FXS (*108*). Clonidine is alpha-agonist with off-labeled use for insomnia in the pediatric population. It is also used to treat attention deficit hyperactive disorder (ADHD) symptoms because it can decrease motor activity (*109*). Clonidine has an overall calming effect for the treatment of ADHD in FXS, but clonidine can cause significant sedation at higher doses so it is helpful for facilitating sleep. Dangerous side effects can occur in overdose so its use must be carefully monitored. The clonidine patch or catapres transdermal therapeutic system (Catapres-TTS1, 2 and 3) should not be used in young children who might pull it off and eat it because this leads to a significant overdose. Clonidine should not be used in the patients with a history of cardiovascular disease or depression (*109*).

2.7. Obstructive sleep apnea

Obstructive sleep apnea (OSA) is characterized by repeat brief episodes of airflow obstruction in the oral-nasal airway that occurs during sleep (*110*). These episodes of complete airflow cessation (apnea) or partial airflow obstruction (hypopnea) result in both frequent and transient reduction of brain oxygen levels (*111*). It occurs more often during rapid eye movement (REM) sleep and is rarely proceed by body movements (*112*). The prevalence of OSA among normal children is about 0.8% to 2.8% (*113*); however, it can be higher among children with neurodevelopment problems including FXS (*114,115*). OSA-related symptoms included loud snoring, apnea, awakening with gasping breaths, enuresis and daytime sleepiness (*116,117*). OSA in children is associated with concentration deficits, reduce learning ability, lower cognitive function, and school difficulties. Vigilance impairments and neuropsychological deficits are among the main symptoms seen in OSA (*118*). Some studies suggest that vigilance impairment is attributed mostly to nocturnal hypoxemia (*118*). In addition to cognitive issues, a large number of studies found that OSA is associated with medical problems such as cardiac tissue changes as well as systolic and diastolic blood pressure changes. Previous reports suggest that children with OSA and hypertrophied tonsils tend to aspirate oropharyngeal secretion which can lead to pneumonia (*119*). The association of GERD with OSA has been documented previously, possible due to higher esophageal negative pressure which is generated by increased respiratory efforts (*120*). Studies suggest that in typically developing children, early diagnosis, and treatment of pediatric OSA may improve the child's long-term cognitive, social potential and school performance. The standard diagnostic procedure for establishing the presence of OSA is the overnight polysomnography (PSG) (*120*). Although overnight PSG can be very effective in diagnosing OSA, for some patients the test is labor-intensive. The management of OSA has three main aspects. The first step is drug therapy, which may alleviate adenoidal and tonsillar hypertrophy. The second is drainage of nasal secretions, and the third step is surgery. Adenoidectomy with or without tonsillectomy is the primary treatments for OSA and it is usually very effective for those with FXS (*121*). Continuous positive airway pressure (CPAP) is a feasible therapeutic intervention in children with neurodevelopment deficits including FXS, although it is reported that patients have a low compliance to this therapy (*121*).

2.8. Strabismus

Strabismus is one of the phenotypic characteristics in FXS and it is an abnormality of the ocular motility and deviation of the eyes away from binocular vision. Strabismus is better defined as exotropia, esotropia,

hypotropia, and hypertropia which describe the orientation of the eyes. Exotropia is the most common type of strabismus found in FXS and it is thought to be caused by an asymmetrical tone of the extraocular muscles (*122*). Early studies reported the prevalence of strabismus in FXS ranging from 28 to 57% (*123-125*), however later studies found that the prevalence was only 4.4-8% (*126,127*) and a recent FXCRC study reported a prevalence of 17.5%. The initial higher rates are thought to be related to selection bias in the earlier studies. Nevertheless, the prevalence was significantly higher than the prevalence in typical children (2.6% *vs*. 4%) (*128,129*).

It is crucial to detect strabismus early in life because if left untreated strabismus may progress to amblyopia, a permanent decrease in visual acuity due to the disuse of the abnormal eye during visual development. Tests used to detect the strabismus are; corneal light reflex, cover/uncover test and simultaneous red reflex test. Once strabismus is detected, the child should be referred to a pediatric ophthalmologist for further evaluation and management. It is recommended that every child with FXS have a comprehensive ophthalmologic examination by age 4 or sooner if an abnormality is detected (*130*). The treatment of strabismus should improve vision impairment and alignment abnormalities. The vision impairment leading to amblyopia can be treated by occluding the preferred eye and correcting the refractive errors of the affected eye with eyeglasses. The ocular alignment can be corrected by visual training exercises, but surgery is needed in many cases (*131*).

2.9. Tic disorder

Tics disorders are generally classified according to the age of onset, duration, and severity of symptoms and the presence of vocal and/or motor tics (*132*). The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) lists three types of tic disorders: Tourette syndrome (TS), chronic motor or vocal tic disorder, and provisional (transient) tic disorder (*133*). The prevalence of transient tic disorders in children aged 13-14 years is from 3-15% and chronic motor tics ranges from 2-5% (*134-136*); however, tic disorders may be more frequent than the prevalence reported because many patients with tics do not seek medical attention (*136*).

The prevalence of tics in FXS differs among studies. Tics were reported in 16% of 152 people with FXS in a cohort study in the United States. Tic disorders are characterized by involuntary or semi-voluntary, sudden, brief and rapid, recurrent, repetitive, non-rhythmic, unpredictable, meaningless and stereotyped motor movements, such as, eye blinking, shoulder shrugging and throat clearing or sounds produced by moving air through the nose, mouth or throat (phonic or vocal tics)

including swearing and complex expressions (*136*). Tics are not constant and appear in the background of normal motor activity, except for extremely severe cases (*137*). Tics disorders appear before 18 years of age and occur before taking stimulant medications in those FXS, however, tics may be unmasked or worsened by stimulants. An important step in the approach to the patient with tics is to rule out secondary causes of tics disorders. Drugs including stimulants, antidepressants, antihistamine and antiepileptic's may cause tics; tics disappear with the interruption of these medications (*137*). Treatment is not always necessary and only severe cases should be treated preferably with monotherapy at low doses (*138,139*). Usually clonidine or guanfacine use in FXS is effective for tics in FXS; however, most of the time tics are not severe and do not need medication treatment. Aripiprazole or risperidone may sometimes be helpful to treat tics in FXS (*139*).

2.10. *Other Problems*

Toileting issues are one of the most challenging problems for patients and their families. The problems include bowel and bladder control, washing and wiping abilities, and inclination to be toilet trained. Nearly half (48.8%) (*140*) of children with FXS had toileting problems and the time they were toilet-trained was delayed compared to the normal population. A study of functional skills of individuals with FXS showed that the majority of females with FXS could demonstrate toileting skills by age 11 to 15 years, while males by age 15 to 20 (*141*).

We must take into consideration that toilet training is a challenging task for parents even in typically developed children. The guidelines for toilet training for children with FXS are not different from those of typical children. The most important step is to start the training when the child is ready; the appropriate time to initiate the training should be based on developmental and behavioral milestones achievements rather than chronological age (*142*). Physicians should initiate conversations about this issue with the parents at a young age (~1 year of age), it is also important to discuss with the family how to assess the child's readiness for toilet training in order to avoid maladaptive behaviors among other psychological problems associated with failed toileting training. Special concerns for children with FXS may be due to their increased anxiety, slow learning skills, sensory sensitivity and defensiveness (*142*). The steps for toilet training are deciding what words to use, picking a potty-chair, helping the child recognize signs of needing to use the potty-chair, making trips to the potty-chair as a routine, and encouraging the use of the potty-chair (*143*). Positive reinforcement, extinction, and a star-chart can be used as strategies in the training. During the training accidents should be expected, the parents should address these events lightly and avoid upsetting comments and negative reinforcement. Punishment and scolding will only make the training harder and may increase the time needed for toilet training. Creating a routine pattern and patience are keys to success in the training.

Other common problems in children with FXS mentioned by caregivers and physicians are sensory processing and integration issues. Sensory processing and integration have major roles in human development (*144*). Individuals with FXS have an enhanced sympathetic response to sensory stimuli (*145*), and the feel of a potty-chair. The sensation of evacuation is often anxiety provoking to children with FXS such that they may avoid these stimuli.

The sensory process has two important components which are sensory discrimination and sensory modulation. Sensory discrimination is the process in which sensory stimuli are distinguished, given their meaning and use. Problems with sensory discrimination can cause poor recognition and interpretation of sensory stimuli, which in turn may result in difficulties in sensory-motor skill development, such as, brushing teeth, climbing or riding a bike, being a picky eater, *etc*. Sensory modulation is how the sensory stimuli are used and responded to. Problems with this process can cause hyper-response, over-activity, poor attention and poor coping. The most common sensory modulation difficulty reported in FXS is hyperarousal. Examples of the processing problem are difficulty tolerating bright lights and loud noises, crowded places overstimulation, difficulty making good eye contact, and trouble tolerating certain clothes. These problems are related to a lack of normal habituation to a sensory stimulus seen in both electrodermal studies (*145*) and even on Functional Magnetic Resonance Imaging (fMRI) studies to recurrent direct or indirect eye contact (*146*).

To attain full assessment and treatment plans, a team approach is needed. The team usually includes occupational therapists, physical therapists, speech therapists, educators, psychologists, and physicians. The team can be adjusted for each individual's problems. There are many tools that have been proven useful and reliable for assessing an individual's condition such as the Sensory Profile questionnaire, the Sensory Processing Measure questionnaire, the Movement Assessment Battery for Children, the Quick Neurological Screening Test and the Berg Balance Scale (*146*). It is recommended that children with FXS should receive routine assessments from occupational therapists and receive occupational therapy at least twice a week during early development (*66*). The treatments are individualized for each patient's medical problem.

3. Discussion

Clinicians need to know that those with FXS are at risk for a wide range of medical problems other than ID, ADHD, and ASD that are so common in FXS. The diagnosis and treatment of the medical problems in

FXS are described here and the treatment of behavioral problems are described elsewhere including the use of targeted treatments to reverse the cognitive and behavioral problems (*147,148*). Many of the medical problems in FXS, such as OM, MVP, GERD, hernias, joint dislocation, and flat feet are related to the connective tissue problems inherent in the syndrome. These connective tissue problems are related to the lack of FMRP on the structure of the elastin fibrils in the skin, heart, vessels and organs (*149*). These changes also relate to the soft and velvet like skin seen in FXS. Improvements in the looseness of connective tissue in FXS have been reported with the use of minocycline, a targeted treatment that lowers Matrix Metallopeptidase 9 (MMP9) levels. In FXS minocycline has been shown to be efficacious for behavior in children. Minocycline has also been used to treat aortic aneurisms because of the effects of pulling together connective tissue in cardiology studies so it may be helpful for dilated aortas in FXS, although this is rarely a problem. Most of these problems are treated symptomatically as described above and the response is usually good to such treatment (Table 1). It is likely that the most severe medical problem in FXS, seizures, will also improve with targeted treatments, although the response to standard anticonvulsants is good as described above. The key to this treatment is early and aggressive intervention because ongoing seizures will further exacerbate ID and ASD severity. The future looks bright for not only reversing the cognitive and behavioral problems but also many of the medical problems of FXS with targeted treatments (*150*).

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