Fragile X Syndrome: A Review of Associated Medical Problems

**abstract**

Fragile X syndrome (FXS) is the most common known genetic cause of inherited intellectual disability and the most common known single-gene cause of autism spectrum disorder. It has been reported that a spectrum of medical problems are commonly experienced by people with FXS, such as otitis media, seizures, and gastrointestinal problems. Previous studies examining the prevalence of medical problems related to FXS have been challenging to interpret because of their marked differences in population, setting, and sampling. Through this comprehensive review, we update the literature by reviewing studies that have reported on prominent medical problems associated with FXS. We then compare prevalence results from those studies with results from a large cross-sectional database consisting of data collected by fragile X clinics that specialize in the care of children with FXS and are part of the Fragile X Clinical and Research Consortium. It is vital for pediatricians and other clinicians to be familiar with the medical problems related to FXS so that affected patients may receive proper diagnosis and treatment; improved care may lead to better quality of life for these patients and their families. *Pediatrics* 2014;134:995–1005
Fragile X syndrome (FXS) is the most common inherited form of intellectual disability (ID). It results from an expansion mutation of a CGG repeat sequence in the first exon of the FMR1 gene, leading to transcriptional silencing of the gene and absence or significant reduction of the gene product, fragile X mental retardation protein. This protein is essential for proper synaptic plasticity, neuronal morphology, and cognitive development, and its absence leads to varying levels of ID. Boys are typically more severely affected than girls because of the location of the FMR1 gene on the X chromosome and the presence of an unaffected second X chromosome in girls. In addition to ID, there are particular phenotypic characteristics of FXS that may be variably present, including prominent forehead, narrow face, protruding ears, high-arched palate, strabismus, macro-orchidism, and connective tissue dysplasia including hyperflexibility of the joints.

In clinical settings, patients with FXS may be seen for a variety of medical problems related to FXS including seizures, recurrent otitis media (OM), and gastrointestinal (GI) disturbances. It has been hypothesized that some of these, such as OM and gastroesophageal reflux (GER), may be related to connective tissue abnormalities. It is important to have a measure of the incidence and prevalence of medical problems in FXS so that physicians will diagnose and treat these problems earlier, thus improving the long-term outcome and quality of life of patients with FXS. Additionally and notably, these medical issues may increase the propensity for many behavioral problems (e.g., anxiety, attention, and aggression) if they are not diagnosed and treated in a timely manner. Children with FXS who are likely to have ID or are nonverbal are particularly at risk for late diagnosis of medical problems, and their associated behavioral manifestations, because of their inability to communicate pain and other symptoms. Thus, awareness of these problems may help prevent or decrease certain behavioral problems and on some occasions also provide clues to the diagnosis of FXS, leading to testing of at-risk individuals.

To date, most studies of medical problems in FXS have been case series or small clinical samples with accompanying selection bias and lack of precision because of the small numbers of subjects. Thus, some problems, such as seizures, have been reported as occurring very frequently with FXS in some studies, because of the potential for bias from sampling of epilepsy practices, case series, and anecdotal reports. It has therefore been difficult to determine the prevalence of comorbid disorders in FXS. The medical problems under review were chosen because they are considered hallmark medical problems for the disorder and/or have attained a level of frequency that ensures that they will be seen in general pediatric practice. To summarize and update the literature, in this article we report data on the frequency of comorbid medical problems in a large cross-sectional cohort of patients with FXS seen in fragile X clinics in the Fragile X Clinical and Research Consortium (FXCRC), preceded by a review of previous findings about these problems in FXS.

**METHODS**

The FXCRC Database included visits from children and adults with FXS seen at 9 fragile X specialty clinics across the United States between 2005 and 2011. Institutional review board approval was received by each of the 9 clinics. For all subjects in the database, diagnosis of FXS was confirmed by DNA testing demonstrating a full mutation in FMR1, cytogenetic testing demonstrating a fragile site at Xq27.3 in association with DNA testing showing an FMR1 mutation in a family member, or molecular testing showing presence of a deletion involving FMR1. For equivocal cases, records were reviewed and cases confirmed by E.B.-K. The database included 260 patients (198 male, 62 female) from birth to 55 years of age (mean age 11 years; 19.4% ≤4 years, 33.1% 5–9 years, 25.3% 10–14 years, 7.8% 15–19 years, 4.8% 20–24 years, 4.1% 25–29 years, and 6.5% ≥30 years), with 87.7% reported as white and 6.5% as Hispanic. The data set was based on a set of standardized data collection modules designed to elicit information from clinicians and parents on a wide variety of medical, behavioral, and other concerns. The questions in these modules were based on a review of the medical literature and expert consensus of the clinicians treating patients with FXS, and they addressed areas of expected higher frequency and significant burden on the patient. All conditions were assessed by medical history and physical examination. Articles from the literature reporting on the frequency of these medical problems in samples of people with FXS were reviewed. Table 1 is limited to the display of data on medical problems from the FXCRC Database by gender, with comparisons to other studies where possible. Studies with <30 subjects were generally excluded from the table (but included in text) when the body of literature had larger studies on a given condition from which to obtain more precise comparison estimates. We used prevalence proportions and their 95% confidence intervals and means and standard deviations of continuous measures for description of the FXCRC data by using SAS 9.3 (SAS Institute, Inc, Cary, NC). Medical disorders or problems with estimates that were clinically important were highlighted in Table 1 by footnote c. Figures were produced in GraphPad Prism (GraphPad Software, Inc, La Jolla, CA) to allow smoothing of the lines.
Clinical findings in FXS of elasticized or loose connective tissue have led to concerns that this may lead to mitral valve prolapse (MVP) and weakening of vessels in the form of aortic dilatation, as seen in Marfan and Ehlers–Danlos syndromes.9,10 Much of the research examining the frequency of MVP in FXS has come from case series11 and studies with unclear selection criteria12,13 or methods of determination of MVP.14 In studies with better methods, there have been variable findings: 5 of 23 adult patients had MVP on echocardiography,10 1 of 17 children had typical examination findings of MVP but not on electrocardiography or echocardiography,15 and 3 of 22 patients had abnormal echocardiographic evidence of MVP16. In the largest sample studied before that of the FXCRC, patients with FXS were routinely referred for cardiologic evaluation and were similar across the age spectrum.17 In this study, Loehr et al17 reported a high

<table>
<thead>
<tr>
<th>Medical Problem</th>
<th>FXS Males (N = 198)</th>
<th>FXS Females (N = 62)</th>
<th>FXS All (N = 280)</th>
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<td>Mitral valve prolapse</td>
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<td>7.0 (4.4–13.7)</td>
<td>10.8 (6.9–14.8)</td>
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<tr>
<td>GI problems</td>
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<td>Birth wt in g, mean (SD)</td>
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<tr>
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<td>3227 (606)</td>
<td>3382 (654)</td>
<td>3262 (59116</td>
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<td>Low birth wt (&lt;2500 g)</td>
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<td>Weeks of gestation, mean (SD)</td>
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<td>38.8 (2.4)</td>
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<tr>
<td>Other studies</td>
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</table>

* TYP: typically developing children or people without FXS or ID.

| Problems with clinically important differences between TYP and FXS groups.

FXCRC definition: >4 events per year.

People with FXS aged ≥40 y.

Prevalence of GER symptoms in a given week among children 3–17 y of age.

** REVIEW **

** Cardiac Disorders **

Clinical findings in FXS of elasticized or loose connective tissue have led to concerns that this may lead to mitral valve prolapse (MVP) and weakening of vessels in the form of aortic dilatation, as seen in Marfan and Ehlers–Danlos syndromes.9,10 Much of the research examining the frequency of MVP in FXS has come from case series11 and studies with unclear selection criteria12,13 or methods of determination of MVP.14 In studies with better methods, there have been variable findings: 5 of 23 adult patients had MVP on echocardiography,10 1 of 17 children had typical examination findings of MVP but not on electrocardiography or echocardiography,15 and 3 of 22 patients had abnormal echocardiographic evidence of MVP16. In the largest sample studied before that of the FXCRC, patients with FXS were routinely referred for cardiologic evaluation and were similar across the age spectrum.17 In this study, Loehr et al17 reported a high
prevalence of MVP of 55%, compared with the 2 patients (0.8%) in the FXCRC Database (Table 1).

It is unclear what is responsible for the variability in results across studies, although the Loehr et al study had echocardiographic evidence of MVP, whereas the FXCRC used clinician reports. Although there are no reports of clinical consequences of MVP in these studies, the implications as patients age into adulthood are unknown. Although MVP does not appear to be a common medical problem in children from more recent data sources, there is a need for ongoing surveillance of those with MVP to evaluate regurgitation and a systematic study of MVP in a cohort of adults with FXS.

Ear, Nose, and Throat Disorders
Approximately 85% of children with FXS have ≥1 episode of acute OM, and 23% of children will have ≥1 episode of sinusitis. In boys with FXS, ~45% to 63% have recurrent OM, compared with 15% of their typical siblings and 38% of children with ID who do not have FXS. In typically developing children, OM incidence during the first year of life ranges from 21% to 64%, and ~12.6% of 2- to 3-year-olds have recurrent OM. In the FXCRC Database (Table 1), recurrent OM is noted to have occurred in 54.7% of male and 45.8% of female patients, which is similar to previous studies in children with FXS but more frequent than in typically developing children. The frequency of recurrent OM is expected to be higher in early childhood and was 53.8% in children with FXS from 0 to 3 and 30% from 4 to 5 years old in the FXCRC data. Pressure equalizing (PE) tubes were inserted in 37.4% of children.

Almost 60% of children with FXS from 0 to 3 and 30% in early childhood and was 53.8% in the FXCRC Database (Table 1), recurrent OM is noted to have occurred in 54.7% of male and 45.8% of female patients. Although MVP does not appear to be a common medical problem in children from more recent data sources, there is a need for ongoing surveillance of those with MVP to evaluate regurgitation and a systematic study of MVP in a cohort of adults with FXS.

It is speculated that children with FXS are susceptible to recurrent OM because they may have more collapsible eustachian tubes; therefore, fluid cannot drain properly, and bacteria can grow more easily. Furthermore, the facial characteristics associated with FXS (eg, long face and a high-arched palate) may affect the angle of the eustachian tube. Because the latter seems to be flat in FXS, drainage from the middle ear is reduced, and fluid can remain in the middle ear longer, increasing the likelihood of OM. The long face and midfacial hypoplasia noted in people with FXS can create structural impediments to drainage of the sinuses and increase the likelihood of recurrent sinusitis. Other mechanisms, such as oromotor hypotonia, dyspraxia, and poor secretion control, can decrease drainage and lead to increased risk for both recurrent OM and sinusitis. The long face and midfacial hypoplasia of individuals with FXS, hypotonia and connective tissue abnormalities could contribute to GI problems, including GER, constipation, and loose bowel movements. Goldson and Hagerman reported on 3 patients with FXS and failure to thrive, due to aspiration, diarrhea and vomiting, or GER. In a study of 62 adults with FXS, GI problems were present in 31.8% of men and 27.8% of women. In the FXCRC Database (Table 1), loose stools and GER were present in similar proportions (11%) of all people with FXS. The Utari et al sample is substantially older than the FXCRC population, which is likely to explain the differences in prevalence. Comparisons with a similar-aged typically developing population showed a higher prevalence of GER.

Given the paucity of information on the type, frequency, and treatment of GI disorders in people with FXS, additional investigation is needed. Whereas in other neurodevelopmental disorders constipation seems to be a major problem, diarrhea seems to be prominent in FXS, a pattern that deserves better characterization. Additionally, because very young and nonverbal people with FXS cannot clearly communicate that they are in pain, vigilance is needed on the part of the treating physician to identify underlying chronic medical conditions, such as GER disease, that can contribute to failure to thrive, irritability, or behavioral concerns.

Neurologic Disorders
Studies in the Fmr1 knockout mouse model of FXS demonstrate immature dendritic connections and abnormal synaptic plasticity, with a predilection to epileptiform bursts and elevated propensity to audiogenic seizures in young animals. Similar abnormal dendritic maturation is also observed in the brain from humans with FXS, and likewise a higher frequency of seizures is found in people with FXS than in the general population. There are variable figures for the prevalence of seizures depending on the cohort under study. Previous studies recruiting from programs focused on epilepsy and neurology clinics reported a broad range of 14% to 44% prevalence, and genetics clinics reported an intermediate range of 9% to 27%.
Larger studies focused on people with FXS in the community or FXS clinics reported lower prevalence rates overall, ranging from 12% to 18%,20,43–45 and with higher prevalence for male than for female patients. In the FXCRC Database, seizures had occurred in 10% of patients, with a higher prevalence in male patients than in female patients (Table 1). Taken together, the available data suggest that the true population prevalence of seizure occurrence in people with FXS in minimally biased samples is probably in the teens (between 10% and 18%).

Many children with FXS have abnormal EEGs without overt seizures,29,32,46 and status epilepticus can occur.48,49 EEGs without overt seizures,29,32,46 spikes similar to benign focal epilepsy of childhood29,32,36,45 often with a pattern of centrotemporal spikes similar to benign focal epilepsy of childhood29,32,36,45. Although some small studies have shown a predominance of generalized seizures,30,33 larger studies have suggested that partial seizures are most common in FXS.29,32,34,37,45–47 Likewise, the FXCRC Database shows that partial seizures occur in nearly half (45%) of patients with seizures. Both simple and complex partial seizures may occur,45 and secondary generalization and status epilepticus can occur.46,49 Seizures are easily controlled29,31,36,38,42,45–47 and resolve during childhood in the majority of people with FXS.34,47 Routine EEG screening of people with FXS is not recommended unless the patient presents with behaviors or episodes that might represent seizures.

A few studies have evaluated associations between seizures and autism spectrum disorder (ASD) in FXS. A study of a small cohort showed a trend toward an elevated rate of seizures in people with FXS and autism (28%, compared with 12% with FXS alone).50 Two studies from a large cohort of the National Fragile X Survey showed a higher frequency of ASD in people with FXS and seizures, as compared with an age- and gender-matched FXS group without seizures,45 and a greater prevalence of seizures in male patients with FXS and ASD when compared with their counterparts without ASD.51 Both studies suggest a shared neurobiology resulting in seizure and ASD propensity. The prevalence of seizures in people with autism and FXS was 18% in the FXCRC Database, slightly higher than the overall seizure prevalence in FXS, consistent with previous literature suggesting an association. Thus far, no proven secondary genetic risk factors for seizures or shared epilepsy and autism susceptibility in FXS are known.

Movement disorder is common in FXS, predominantly in the form of stereotypes such as hand flapping. Tics were reported in 16% of 152 people with FXS in a cohort from the United States,52 and 36% and 45% of patients were reported to have motor and vocal tics, respectively, in a cohort of 22 patients with FXS from Israel.53 The high frequency reported in the latter study may reflect confusion between stereotypes and tics in parent reports, which can be challenging to distinguish without history and neurologic examination data. The FXCRC database suggests that motor tics are uncommon in FXS, occurring in about 6% of affected people; this rate is not notably different from reports of combined motor and vocal tic frequency in the general population.54 No special management is indicated with respect to tics in FXS.

Ocular Disorders
Ocular disorders are more common in children with FXS; previous reports cite a high prevalence of 23% to 93%.16,55,56 Children with FXS, many of whom need glasses, are reported to have a high prevalence of refractive errors, ranging from 13% to 17%.16,55 In earlier studies, there were 59% with hyperopia, 17% with myopia, and 22% to 40% with astigmatism.57,58 The variability probably occurs because children with FXS are difficult to evaluate for visual acuity because of developmental delays, attention problems, anxiety, and sensory processing issues.55 Nystagmus can cause or be the result of visual impairment. The prevalence of nystagmus in the general population has been reported at 0.24%.59 King et al56 observed a prevalence of 5.4% and Maino et al60 reported a prevalence of 13% in children with FXS.

In the general population, 2.6% to 4% of children develop strabismus.60,61 Earlier studies reported that the prevalence of strabismus in boys with FXS ranged from 27% to 57%.56–58 Later prospective studies reported the prevalence to range from 4.4%60 to 8%65 of boys with FXS. In the FXCRC Database, the prevalence of strabismus was higher overall (16.4%) and particularly in boys (17.5%) (Table 1). Previous reports of high rates of vision problems and other ocular findings in children with FXS may have resulted from selection bias. However, children with FXS continue to be at greater risk than the general population for ocular disorders, and close and regular monitoring of ocular disorders, ocular motility, and visual acuity is warranted. Evaluation of the child by an ophthalmologist or optometrist who has patience and experience working with children with special needs is critical.

Sleep Problems
Sleep problems are observed in approximately 10% to 25% of typically developing children and adolescents,62,63 but the prevalence is significantly higher in children with ID and ASD, ranging from 36% to 73%.64–68 There have been very few published studies documenting the prevalence and patterns of sleep problems in people with FXS.69–71 A comprehensive analysis of 90 children with FXS, using the standardized parental screen, the Children’s Sleep Habits Questionnaire (CSHQ), and a 2-week diary to document sleep routine and problematic areas,70
found that nearly half of children with FXS had clinically significant sleep problems, regardless of whether they were receiving medication to improve sleep. A second study\(^1\) was a large-scale parental survey of 1295 children with FXS in which 32% were reported to have sleep difficulties, including difficulty falling asleep and frequent night awakenings. In the FXCRC Database, only 27% of parents of people with FXS reported sleep problems, with little difference between male and female patients (Table 1).

In the FXCRC population, the CSHQ was administered to a convenience sub-sample of 29 patients. The average CSHQ score was 46, which is comparable to the average CSHQ score (42) reported by Kronk et al\(^6\) in 2009. In the original community sample that was used to develop the instrument,\(^2\) the average score (56.2) was higher, but these children were younger than the FXCRC subjects.

One of the Kronk studies also reported that loud snoring and obstructive sleep apnea (OSA) occurred in 38% and 34%, respectively, of children with FXS. Additionally, results from the FXCRC database showed an overall lower prevalence of OSA of 7% of patients (Table 1). The overall discrepancy in the prevalence between these studies can probably be attributed to differences in study design, sample size, data collection protocols, and study aims, but it appears that airway obstruction is more common in FXS than in the general population. Although the exact prevalence of sleep problems in FXS is unclear, children with ID, in particular, need adequate sleep for optimal neurobehavioral functioning. Monitoring and managing OSA and other sleep problems are of particular importance in FXS because of their relationship to decrements in daytime performance and increased behavioral problems.\(^3\)

**Congenital Malformations**

Although very few congenital malformations were reported in the FXCRC data, the following were identified as significant (number in parentheses): congenital heart defect (3), tracheo-esophageal fistula (1), Poland anomaly (1), cleft lip or palate (3, with 1 as part of Pierre Robin sequence). The prevalence in the FXCRC is thus \(\sim3\%\), about twice the prevalence of only 1.5% using the International Clearinghouse for Birth Defects Surveillance and Research definitions of reported malformations included in the Centers for Disease Control and Prevention (CDC) monitoring systems.\(^7\) This population estimate is similar to the estimate (1.2%) from the USA-Atlanta monitoring data from 2009 using the same International Clearinghouse for Birth Defects Surveillance and Research definition.\(^7\)

**Growth**

All literature discussed in this section and reporting on birth measurements included male patients only. Boys with FXS are reported to be slightly larger than average in weight at birth. The mean birth weight from earlier studies ranges from 3490 to 4046 g in white male infants.\(^5\) From the FXCRC Database, the overall birth weight was higher than that of the general population but slightly lower for male patients than in the previous studies (Table 1). However, the overall proportion of infants with low birth weight was similar to that in the general population. The mean head circumference\(^8\) and mean birth length\(^9\) were not different from those of control populations.

No previous studies on gestational age or preterm status were identified. In the FXCRC Database, the mean gestational age was similar to that of the general population (Table 1). However, the overall proportion of infants who were born preterm was higher than that in the general population, although this was probably because of point preference for even numbers.

Height of male patients with FXS from childhood on has been reported to be greater than the 50th percentile,\(^10\) although other studies have reported little difference from control populations.\(^11\) Two studies developed measurement curves for male patients with FXS that were compared with control anthropometric data and unaffected relatives.\(^4\) Height curves for FXS were higher at nearly every point in the prepubertal section of the curves, although height was lower at the postpubertal ages. In contrast, 1 study reported height and weight values that were closer to those of the normal comparison group through young adulthood.\(^7\) In the FXCRC Database, height was close to that of typically developing boys until after puberty, when the height curve was decreased in comparison (Fig 1). For weight, in Butler et al\(^2\) the curve for FXS was higher at nearly every point in the prepubertal section of the curve, with relative weight decreased only starting in young adulthood. The FXCRC data suggested that weight may be higher throughout childhood and adolescence, but there is some instability in the data because of outliers (Fig 2). A heavier subset of children with FXS can be misdiagnosed as having Sotos syndrome or can have a Prader–Willi–like subphenotype.\(^5\) After birth, the head circumference tends to rise above the 50th percentile and continues to be larger than for male patients without FXS.\(^13\) This is also reflected in the FXCRC data, where a larger head circumference was similar to that in other studies of adults with FXS.\(^13\)

For girls, Hagerman et al (1992)\(^14\) found no difference in height, weight, or head circumferences of girls with FXS compared with relatives negative for the full mutation. Loesch et al (1995)\(^6\) observed an above-average rate of growth in girls from age 5 until age 8 years.
followed by a below-average rate of growth from age 8 years to maturity. In another study, height was lower and weight was higher in women with FXS compared with an internal comparison group. In the FXCRC Database there was a small sample of girls, but the data suggested that both height and weight were higher from 8 to 14 years compared with the equivalent CDC data.

**DISCUSSION**

Our review of the literature and comparison with the large FXCRC database of unselected children attending clinics specializing in FXS revealed wide discrepancies in the prevalence of some associated medical disorders. The FXCRC database produced similar findings to previous literature for prevalence of recurrent OM (~50%) and seizures (~10% to 16% and more prevalent in male patients). Another association particularly characteristic of FXS, and supported by the FXCRC Database, is that of ASD and seizures. Growth chart comparisons with typically developing populations suggested that male patients with FXS are shorter and heavier in adolescence and young adulthood. Prevalence of strabismus in the FXCRC database fell in the middle of widely variable reports (~15%) establishing this to be a common associated problem. Areas in which the FXCRC data differed from previous literature or for which more data and exploration are needed include determining what GI problems are most prevalent, better surveillance of MVP and implications for adulthood, and more detailed measures of sleep to determine the nature and severity of sleep problems and OSA in FXS. Before our review, only Hagerman and Hagerman had presented comprehensive data on people with FXS and associated medical problems. Our review updates this work and establishes an evidence base to support some of the guidelines from the Committee on Genetics of the American Academy of Pediatrics (AAP) to assist pediatricians with health supervision for children with FXS.

The limitations of many of the studies presented in this review include a paucity of data on females and nonwhite patients. In addition, samples of people with FXS were poorly defined or were from time periods before the identification of the FMR1 gene and the molecular genetics diagnosis of FXS. Sampling of people with FXS from disparate settings such as residential institutions, extended families, or clinics specializing in the comorbidities under examination (eg, epilepsy clinics) resulted in selection biases. Comparison groups were also poorly defined, and the use of control groups with other genetic disorders or forms of ID may be accompanied by their own particular set of characteristics that make comparison difficult to interpret.

The medical home is a concept proposed by the AAP as an approach to provide comprehensive and coordinated primary care as a way of optimizing outcomes

![Figure 1](image1.png)

**FIGURE 1**

Height of male patients (cm) by age (y), comparing FXCRC Database (FXS) with a typically developing population from CDC growth charts. (Centers for Disease Control and Prevention, National Center for Health Statistics. CDC growth charts: United States. 2000; www.cdc.gov/growthcharts/).

![Figure 2](image2.png)

**FIGURE 2**

Weight of male patients (kg) by age (y), comparing FXCRC Database (FXS) with a typically developing population from CDC growth charts. (Centers for Disease Control and Prevention, National Center for Health Statistics. CDC growth charts: United States. 2000; www.cdc.gov/growthcharts/).
for children with disabilities. It is designed to have a pediatric care team, including a well-trained pediatrician, that delivers accessible, continuous, comprehensive, family-centered, coordinated, culturally effective care to children and their families that ensures that the child’s medical and developmental needs are being met. Unfortunately, pediatricians receive limited training in the diagnosis and management of children with FXS, related ASD, and medical comorbidities. Many pediatricians report a lack of confidence in their ability to provide comprehensive care to children with special needs.

The following conditions were reported to be more common and clinically important in the FXS population: strabismus, recurrent OM, sleep disorders, GER, seizures, and weight gain. The pediatrician should look for and ask about symptoms that might be related to these problems at routine yearly well child visits and should refer to specialists for additional evaluation and management if needed. The type and timing of follow-up for these problems will depend on severity and whether medication intervention is implemented (Table 2).

<table>
<thead>
<tr>
<th>Medical Problem</th>
<th>Table 2 Management and Follow-up of Medical Problems in FXS</th>
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<tbody>
<tr>
<td>Otitis media</td>
<td>Because children with FXS often have expressive language delays, it is important to treat otologic problems promptly and appropriately. Hearing testing may be considered if there is concern about a child's hearing.</td>
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<td>GI problems</td>
<td>If a child with FXS also has symptoms suggestive of GER, such as frequent vomiting, feeding difficulties, and failure to thrive, particularly if he or she also has hypotonia and oromotor problems, the child should be referred for appropriate medical evaluation and management. If a child presents with unexplained irritability or poor growth, then a diagnosis of FXS should be considered. Evaluation and treatment of loose bowel movements or constipation would be similar to that for a child without FXS.</td>
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<tr>
<td>Seizures</td>
<td>For concerns about episodes that might be seizures, an EEG evaluation should be obtained along with neurology referral. Special attention should be given to children with FXS and ASD, because they seem to be particularly at risk for epilepsy. Ambulatory EEG can be used to distinguish behavioral spells from seizures. Typically, patients would be treated after 2 documented seizures with anticonvulsants that are least likely to cause sedation or behavioral aggravation, with a view to discontinuation of treatment after a person with FXS is seizure-free for 2 years.</td>
</tr>
<tr>
<td>Ocular disorders</td>
<td>Because 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 y for evaluation by a pediatric ophthalmologist or optometrist. This should be followed by yearly eye examinations to continue to monitor for refractive errors.</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>The primary care physician should ask about potential sleep problems in children with FXS at every well child visit. Depending on the severity of the sleep problems, behavioral or medical treatment or a referral to a sleep specialist may be warranted. Sleep may also be affected by other environmental, health, and emotional factors, which should be addressed and treated accordingly.</td>
</tr>
<tr>
<td>Growth problems</td>
<td>The growth findings from the FXCRC Database suggest that patients with FXS may be at an elevated risk for being overweight and for having somewhat diminished height in adulthood. We encourage healthful diets for our patients and exercise programs to minimize problems associated with increased weight. The conditions listed in this table were reported to be more common and clinically important in the FXS population. The pediatrician should look for and ask about symptoms that might be related to these problems at routine yearly well child visits and should refer to specialists for additional evaluation and management if needed. The type and timing of follow-up for these problems will depend on severity and whether medication intervention is implemented.</td>
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One of the goals of this article was to support pediatricians providing a more comprehensive medical home to children with FXS, by updating the evidence for the medical problems associated with this diagnosis and providing evidence for the recently published AAP guidelines for health supervision of children with FXS. This review of associated medical problems presents, for the first time, estimates of the prevalence of selected conditions from a large comprehensive database of children with FXS attending clinics across the United States. Although the nature of Fragile X Clinic attendance could make the FXCRC Database limited in providing the true range of severity of medical problems in FXS, it may allow the identification of at least moderate to severe ones, problems that are likely to come to medical attention. As the FXCRC Database progresses in collecting data and registering more people with FXS, this will allow the study of an expanded set of conditions, profiles of female subjects and racial and ethnic groups, and the longitudinal examination of data through childhood and beyond. Additional research questions that could be examined are the relationship between behavioral symptoms and language, barriers to social participation and daily living activities, severity of behavioral problems, impact on the family and use of psychotropic medications, and how actively the family engages in health monitoring. In addition, we use the Aberrant Behavior Checklist in annual assessments to examine changes in behaviors that are most problematic in people with FXS. The aforementioned data and instruments will provide the pediatrician and other health care providers with more detailed information on how these medical and behavioral problems change over time and with age, to better serve the patients, families, and communities affected by FXS.

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REFERENCES


# Fragile X Syndrome: A Review of Associated Medical Problems

Sharon A. Kidd, Ave Lachiewicz, Deborah Barbouth, Robin K. Blitz, Carol Delahunty, Dianne McBrien, Jeannie Visootsak and Elizabeth Berry-Kravis

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