ABSTRACT. Fragile X syndrome (FraX) is the most common hereditary form of mental retardation. The clinical syndrome includes mental retardation, macroorchidism, and a large number of variable features. Although macroorchidism has been recognized as a cardinal feature of FraX, descriptions of testicular pathology are rare. Testicular torsion is a relatively common surgical emergency in young men, peaking at the onset of puberty when the testes undergo a period of rapid growth. However, testicular torsion has never been associated with macroorchidism. We report the first known case of testicular torsion in a 14-year-old boy with FraX and macroorchidism. Although we are unable to establish a definitive relationship between macroorchidism and testicular torsion in an isolated case report, primary care takers of children with macroorchidism should be aware of this occurrence. We recommend measurement of testicular volume during annual evaluations of children and adolescents with macroorchidism. Acute scrotal pain or increased testicular volume should be promptly evaluated. *Pediatrics* 2002;109(1), URL: http://www.pediatrics.org/cgi/content/full/109/1/e16; fragile X syndrome, macroorchidism, testicular torsion, mental retardation, acute scrotum.

**ABBREVIATIONS.** FraX, fragile X syndrome; FMR1 gene, fragile X mental retardation 1 gene; FMRP, FPR1 protein.

Fragile X syndrome (FraX) affects 1 in 250 to 1 in 4000 individuals, making it the most common cause of inherited mental retardation. Although macroorchidism has been recognized as a cardinal characteristic of men with FraX for over 25 years, descriptions of associated symptoms or testicular pathology are rare. A relatively common surgical emergency in young males, testicular torsion occurs most commonly at puberty with a calculated annual incidence of 1 in 4000 males under 25 years of age. However, a literature search failed to locate any previous reports of testicular torsion in association with FraX and macroorchidism. We describe a case of testicular torsion in a 14-year-old pubertal boy with FraX and macroorchidism who presented with 48 hours of mild left groin and testicular pain with asymmetrical testicular enlargement. Physical examination and color Doppler ultrasound findings were consistent with testicular torsion. Scrotal exploration and manual detorsion were performed; however, the testis was nonviable and therefore removed.

**CASE REPORT**

A 14-year-old male with a history of fragile X mosaicism with moderate mental retardation (Wechsler Intelligence Scale for Children-III Full Scale IQ 48) and bilateral macroorchidism presented with 48 hours of mild, vague left groin and testicular pain unrelated to exertion. The pain had awoken him the night before evaluation. He denied masturbation, sexual activity, voiding abnormalities, gastrointestinal symptoms, and genitourinary and abdominal trauma. His medical history was unremarkable for previous testicular pain, immunosupression, malignancy, diabetes mellitus, urinary tract infection, or manipulation. FraX had been diagnosed in the patient and his younger brother 7 years earlier based on the brother’s more classic symptoms of developmental delay, autistic features, and typical facial appearance. Our patient had no significant behavioral problems. The majority of the DNA molecules isolated from his peripheral white blood cells had an expanded allele containing 200 to 250 extra bases. However, a minor population of heterogeneous molecules were detected with full-length, hypermethylated expansions of greater than 1000 extra bases. Echocardiography at puberty revealed no abnormalities. The primary care physician and neurodevelopmental pediatrician had both noted asymmetrical, symmetrical testicular enlargement on separate occasions within the previous 15 months.

On presentation, the patient was afebrile with no evidence of systemic disease. His height, weight, and head circumference were within the 50th to 75th percentile for age. The abdominal examination was unremarkable. The genitourinary examination revealed Tanner III pubic hair and a normal circumcised phallus. The testes were descended bilaterally with asymmetrical enlargement. The testis was approximately twice as large as the right. There was no scrotal edema, induration, or fluctuance. The left testis was firm and had a horizontal lie with no surrounding fluid. The patient had mild left testicular tenderness on palpation and an absent cremasteric reflex.

Laboratory data included a normal urinalysis. Gray-scale scrotal ultrasound of the testes revealed asymmetrical enlargement (right testicular volume = 16 mL, left testicular volume = 32 mL) and abnormal left testicular echogenicity without evidence of a mass. Color Doppler imaging did not reveal any blood flow to the left testis, consistent with torsion. Scrotal exploration revealed a 720° rotation of the left spermatic cord. The left testis was firm and had a dark appearance consistent with ischemia. No bell-clapper deformity was present on either side. Manual detorsion and contralateral orchiopexy were performed. Thirty minutes after manual detorsion, the left testis continued to appear nonviable and was therefore excised. Histologic examination of the specimen revealed an immature testis with edema, extensive hemorrhage, and many necrotic seminiferous tubules consistent with testicular torsion. The patient was evaluated 7 days after surgery. He was asymptomatic and able to resume full activity.

**DISCUSSION**

The association between a fragile site on the distal long arm of the X chromosome and the sex-linked form of mental retardation originally described by Martin and Bell in 1943 was first demonstrated by Lubs in 1969. This fragile site and the syndrome...
associated with it are now known to result from expansion and methylation of a trinucleotide (CGG) repeat sequence within the FraX mental retardation 1 (FMR1) gene, which leads to silencing of transcription and translation of FMR1 protein (FMRP). The lack of FMRP causes the behavioral, cognitive, and physical features that constitute the clinical syndrome. These features include variable degrees of cognitive deficiency, hyperactivity, anxiety, repetitive behaviors, gaze avoidance, elongated face, large or prominent ears, hypotonia, ligamentous laxity, and macroorchidism. Butler et al have developed standard curves of selected anthropometric measurements, such as testicular volume, in males with FraX. Testicular volume can be estimated using the Prader caliper or with ultrasound and applying the formula for volume of an ellipsoid (volume = \( \pi/6 \times \text{length} \times \text{width}^2 \)).

Macroorchidism is not uncommon in males with mental retardation and can be defined as a testicular volume greater than the 95th percentile for age (for example, \( >25 \text{ mL in adults} \)). The mean testicular volume for a typical 14-year-old boy is approximately 8 mL (95th percentile = 15 mL), whereas the mean testicular volume for a 14-year-old boy with FraX is approximately 35 mL (95th percentile = 55 mL). Vatta and colleagues found that among mentally retarded males with macroorchidism, 27% had FraX. When only those with severe mental retardation and macroorchidism were considered, the prevalence of FraX was 44%. Conversely, macroorchidism is present in as many as 90% to 95% of adult males with FraX. Although boys under 8 years of age with FraX have significantly larger mean testicular volumes than controls, true macroorchidism is uncommon. However, macroorchidism was the feature that led to the diagnosis of FraX in the 5-month-old infant reported by Carmi and colleagues, and was present in the 2 fetuses of 23 and 24 weeks’ gestational age described by Rudelli et al. The testicular enlargement in FraX is usually bilateral, but unilateral macroorchidism has also been described. The enlarged testis maintains its normal contour, consistency, and ellipsoid shape. High-resolution ultrasonography of the testis, apart from large size, does not reveal any abnormalities or distinguishing features.

Increased expression of the FMR1 gene in the testes has been demonstrated; however, the exact cause of macroorchidism in FraX is still debatable. Because the testis is composed of predominately Sertoli cells, germ cells, and interstitium, proliferation of either of these cell types or interstitial edema could be responsible for the increase in testicular size. Johansson et al performed light and electron microscopic studies of biopsies of the macroorchid testes of two men with FraX. Distinct interstitial edema, increased amounts of lysosomal inclusions in Sertoli cells, and disturbances in spermatogenesis were noted. The increase in FMR1 gene expression demonstrated by Hinds et al was localized to the periphery of the seminiferous tubules, which is suggestive of Sertoli cell expression. Slegtenhorst-Eegdeman et al used knockout mice to investigate the role of the FMR1 gene in macroorchidism and found Sertoli cell proliferation to be prominent. This result seemed to be independent of changes in follicle-stimulating hormone. In fact, the conclusion of most studies of the pituitary-gonadal axis in boys with FraX is that the majority of patients have normal levels of circulating gonadotropins and sex steroids. Therefore, changes in pituitary-gonadal axis hormones are unlikely to be the primary cause of macroorchidism in patients with this syndrome. However, O’Hare et al have suggested that melatonin deficiency may be responsible for the increase in testicular size because of decreased inhibition of the pituitary-gonadal axis.

Despite the high prevalence of macroorchidism among postpubertal males with FraX, descriptions of associated symptoms or testicular pathology are exceedingly rare. In fact, the not uncommon disorder, testicular torsion, has never been reported in patients with macroorchidism (with or without FraX). An isolated case of a male with FraX male and macroorchidism who developed seminoma twice, first at age 45 and again at age 50 in the contralateral testis, has been reported. In addition, Del Pozo and Millard described a 34-year-old male with FraX and a benign inflammatory testicular mass that was similar to a sperm granuloma in location and morphology.

Torsion of the testis with twisting of the spermatic cord is considered a surgical emergency. Torsion can compromise both arterial inflow and venous outflow to the testis, resulting in edema, hemorrhage, and eventual ischemia or infarction. Delays in presentation or diagnosis greater than 12 hours usually result in testicular loss. In a review of testicular torsion in Bristol, England, over a 25-year period, Anderson and Williamson noted that although torsion can occur at any age (9 days-77 years), there was a bimodal distribution. There is a small increase in the frequency of testicular torsion during the neonatal period; however, the major increase occurs during adolescence (12-18 years).

The so-called bell-clapper deformity, where the testis is enveloped both anteriorly and posteriorly with tunica vaginalis, is a well-accepted risk factor for torsion usually recognized only at the time of surgical exploration. At puberty, the typical testis increases dramatically in volume. This rapid testicular growth is in disproportion to the increase in the testicular mesentery, which may cause the testis to fall forward on its mesentery and undergo torsion. This mechanism is thought to explain why torsion is more common in adolescence, at least in those with the bell-clapper deformity. However, the bell-clapper deformity is found in only 34% to 80% of cases, so its presence does not completely account for the increased risk of torsion at puberty. Additionally, Caesar and Kaplan noted the prevalence of the bell-clapper deformity at autopsy to be 12%. Because the incidence of testicular torsion is far less than the 12% reported on autopsy and because this anatomic abnormality is not present in all cases of torsion, other factors must be involved.
case of torsion of an intra-abdominal testis affected with tumor. Recognizing that torsion in an undescended testis is rare because of associated atrophy, he proposed that torsion of an undescended testis might signify the development of a tumor (because tumors also increase in size in relation to their mesentry). In the case of testicular torsion in an adolescent with FraX presented here, the patient had known macroorchidism (95th percentile for age) without the bell-clapper deformity. Rapid testicular growth, most commonly at the onset of puberty (with or without the bell clapper deformity), is the usual setting for testicular torsion. The average increase in testicular size during puberty in normal testes (five-fold to sixfold) is even more pronounced in patients with FraX (eightfold to tenfold). Therefore, because it is accepted that rapid growth in testicular size, either normally at puberty or abnormally with neoplasm, may predispose a patient to torsion, we postulate that macroorchidism may also be a potential risk factor. This is the first report of testicular torsion associated with macroorchidism in a patient with FraX. Although we are unable to establish a definitive relationship between macroorchidism and testicular torsion in an isolated case report, it is possible that macroorchidism represents a risk factor for torsion in adolescence. Primary care takers of children with macroorchidism should routinely measure and record testicular volume with an orchidometer or ruler during yearly evaluations. When a child with known macroorchidism presents with acute scrotal pain, unilateral enlargement, or physical examination findings suggestive of torsion, prompt evaluation with color Doppler imaging and urologic consultation should occur if testicular salvage is to be at all possible.

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