Published in final edited form as:

Am J Med Genet. 1988 December ; 31(4): 779–781. doi:10.1002/ajmg.1320310408.

Do Some Patients With Fragile X Syndrome Have Precocious Puberty?

Merlin G. Butler and **Jennifer L. Najjar**

Department of Pediatrics, Divisions of Genetics (M.G.B.) and Endocrinology (J.L.N.), Vanderbilt University School of Medicine, Nashville, Tennessee

Abstract

We report on an 8½-year-old white girl with fra (X) syndrome; she had mental deficiency, hyperactivity, speech disturbances, slightly prominent ears, mild joint laxity and 20% fra (X) expression. Additional findings include idiopathic precocious puberty and a right ovarian cyst. Ovarian cysts have been reported previously in heterozygous females, but to our knowledge idiopathic precocious puberty is a new finding in this syndrome. Whether precocious puberty is a coincidental finding in this patient or a previously unreported manifestation of the fra (X) syndrome is not clear.

Keywords

Martin-Bell syndrome; fra (X) syndrome; secondary sex characteristics

INTRODUCTION

The fragile X [fra (X)] or Martin-Bell syndrome is a well-characterized cause of mental retardation. Prominent physical findings in this syndrome include a long narrow face, a prominent forehead, large everted ears, relative macrocephaly, macroorchidism, and hyperflexibility of joints [Hagerman, 1987]. Eighty percent of fra (X) syndrome males have mental retardation and other characteristic manifestations of the syndrome, while heterozygous females may be completely unaffected or mentally impaired in 30% of patients [Carpenter, 1983; Hagerman et al., 1983].

Macroorchidism was the first physical finding associated with the fra (X) syndrome and is seen in 80% of men and 39% of prepubertal boys [Hagerman, 1987]. Increased testicular size has also been reported in male fetuses with the fra (X) chromosome [Shapiro et al., 1986]. Testicular biopsies have demonstrated increased interstitial volume with excessive connective tissue [Rudelli et al., 1985; Shapiro et al., 1986] and water [Ruvalcaba et al., 1977], although fertility is considered normal [Cantù et al., 1976]. Large ovaries by ultrasound studies have also been reported in heterozygous fra (X) syndrome girls [Turner et al., 1986; Goodman et al., 1987]. Because of abnormal gonadal size, which may be present

Address reprint requests to Merlin G. Butler, M.D., Ph.D., Department of Pediatrics, Division of Genetics, Vanderbilt University School of Medicine, T-2404 Medical Center North, Nashville, TN 37232.

before puberty, the question of increased sex hormone production and/or precocious puberty should be investigated in fra (X) syndrome patients. Herein, we report to our knowledge for the first time an 8½-year-old heterozygous fra (X) syndrome girl with precocious puberty.

CLINICAL REPORT

J.K. is an 8½-year-old white girl who at birth weighed 2.78 kg and had a length of 49.5 cm. Pregnancy, labor, and delivery were uncomplicated. The proposita's 25- year-old mother was reported to have had six previous miscarriages. The proposita has no living siblings. The fra (X) syndrome was diagnosed in the proposita's male first cousin. The neonatal course was unremarkable and early development (e.g., sitting and walking), by history, was achieved at appropriate times although learning difficulties were noted by age 3 years. Premature thelarche, scant pubic hair, and vaginal discharge for about 1 year duration occurred at approximately age 6 years. A recent onset of menarche was observed at age 8½ years. Because of the early onset of secondary sex characteristics, mental impairment (IQ = 55 with the Stanford-Binet test), and family history of fra (X) syndrome, endocrine and genetic evaluations were undertaken.

On physical examination at age 8½ years, her weight was 32.67 kg (80th centile) and height was 129.5 cm (50th centile). She was a normocephalic, hyperactive child with mental impairment, significant speech disturbances, and advanced secondary sex characteristics for age. Anthropometric measurements were normal except for inner canthal distance, which was less than the 3rd centile. Other prominent manifestations included increased palpebral fissure lengths, slightly prominent ears measuring at the 50th centile for length, mild joint laxity, Tanner IV breast development, and Tanner III pubic hair development.

Laboratory tests showed normal routine blood chemistry studies, normal thyroid function, normal levels of human chorionic gonadotropin (HCG) and prolactin, and an advanced bone age of 11 years. Her response to luteinizing hormone releasing hormone (LHRH) stimulation was considered mature with a peak LH of 46 MIU/ml and a peak follicle stimulating hormone (FSH) of 43 MIU/ml. Random estradiol levels ranged from < 10–111 pg/ml. A head computerized tomography (CT) scan with and without constrast was normal. Abdominal ultrasound showed apparently normal-sized ovaries with a small 5-mm right ovarian cyst and a uterus consistent with chronological age. Twenty of 100 lymphocytes grown in folate-deficient culture conditions contained the fra (X) chromosome. Treatment in the near future is planned with LHRH agonists to arrest sexual development.

DISCUSSION

Idiopathic precocious puberty in this 8½-year-old white girl is of interest in light of the diagnosis of fra (X) syndrome. Although the ovarian size was not large by ultrasound studies, gonadotropin levels after stimulation were consistent with precocious puberty. Ovarian cysts have been reported previously in other heterozygous females [Kemper et al., 1986; Turner et al., 1986], but to our knowledge no other heterozygous fra (X) syndrome girl has been reported with precocious puberty. Additionally, several related fra (X) carrier mothers have been reported with oligomenorrhea and premature menarche by Dr. Ben ter

Haar in a large Dutch pedigree [Turner et al., 1986]. In order to determine if precocious puberty is an unrecognized finding in fra (X) syndrome or a coincidental finding in our patient, we would be interested to know if other clinicians have observed similar findings in individuals, male or female, with the fra (X) syndrome.

Acknowledgments

We thank Pam Phillips for expert preparation of the manuscript. This research was supported in part by the Joseph P. Kennedy Jr. Foundation.

References

Cantù JM, Scaglia HE, Medina M, Gonzalez-Diddi M, Morato T, Moreno ME, Perez-Palacios G. Inherited congenital normofunctional testicular hyperplasia and mental deficiency. Hum Genet. 1976; 33:23–33. [PubMed: 939556]

Carpenter, NJ. The fragile X chromosome and its clinical manifestations. In: Sandberg, AA., editor. Cytogenetics of the Mammalian X Chromosome. Part B: Chromosome Anomalies and Their Clinical Manifestations. New York: Alan R Liss; 1983. p. 399-414.

Goodman RM, Strauss S, Friedman E, Chaki R. Letter to the editor: Ovarian size in the fragile X mental retardation syndrome. Am J Med Genet. 1987; 26:17–18. [PubMed: 3812558]

Hagerman, R., Smith, ACM., Mariner, R. Clinical features of the fragile X syndrome. In: Hagerman, RJ., McBogg, P., editors. The Fragile X Syndrome: Diagnosis, Biochemistry, and Intervention. Dillon, CO: Spectra Publishing Co; 1983. p. 17-53.

Hagerman RJ. Fragile X syndrome. Curr Probl Pediatr. 1987; 17:621–674. [PubMed: 3325231]

Kemper MB, Hagerman RJ, Ahmad RS, Mariner R. Cognitive profiles and the spectrum of clinical manifestations in heterozygous fra (X) females. Am J Med Genet. 1986; 23:139–156. [PubMed: 3953643]

Rudelli RD, Brown WT, Wisniewski K, Jenkins EC, Laure-Kamionowska M, Connell F, Wisniewski HM. Adult fragile X syndrome. Acta Neuropathol. 1985; 67:289–295. [PubMed: 4050344]

Ruvalcaba RHA, Myhre SA, Roosen-Runge EC, Beckwith JB. X-linked mental deficiency, megalotestes syndrome. JAMA. 1977; 238:1646–1650. [PubMed: 578251]

Shapiro LR, Wilmot PL, Omar RA, Davidian MM, Chamden PN. Prenatal onset of macroorchidism in the fragile X syndrome: Significance in prenatal diagnosis. Am J Hum Genet. 1986; 39:A265.

Turner G, Opitz JM, Brown TW, Davies KE, Jacobs PA, Jenkins EC, Mikkelson M, Partington MW, Sutherland GR. Conference report: Second international workshop on the fragile X and on X-linked mental retardation. Am J Med Genet. 1986; 23:11–67.