Prolonged Time Lag to Final Diagnosis of Fragile X Syndrome

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Objective To evaluate the diagnostic process in children ultimately diagnosed with fragile X syndrome (FXS), with an emphasis on the time lag between initial presentation and on diagnosis in female vs male children.

Study design Interviews were conducted with 89 families of children with a final diagnosis of FXS and assessment of time intervals between initial presentation and confirmed molecular diagnosis.

Results Screening of 117 patients (25 female patients) from the 89 families revealed that less than 20% of patients obtained a diagnosis within the first year of seeking medical attention. Mean age at the time of initial presentation was 12.3 months in male patients and 23 months in female patients, while definitive diagnosis of FXS was made at a mean of 4 and 9 years, respectively. Presenting symptoms of developmental delays were recognized by 72% of parents, and 84% had another child with FXS before the index case diagnosis. Average age of diagnosis for children with FXS born since 2007 was significantly lower at 31.9 months, compared with 69.5 months for children born before 2007.

Conclusions Although FXS is a significant and prevalent cause of disability in children, it is underdiagnosed and diagnosed late, especially in female patients. In every male and female patient presenting with developmental delay or autism, FXS should be considered. Dysmorphic physical features may not be present in infancy, and the absence of those features cannot exclude a diagnosis of FXS. *(J Pediatr 2017;■■:■■-■■).*

Fragile X syndrome (FXS) is the most prevalent known genetic cause of autism and intellectual disability.[1] FXS is typically highly symptomatic in male children, less frequently symptomatic in female children, and mildly symptomatic in some carriers.[2] Carrier state is defined as more than 55 trinucleotide repeats and up to 199 repeats (above which the full syndrome is defined). However, the Israeli Genetic Association decided to report the carrier state as above 58 repeats. The reason for this decision, which is different than the worldwide consensus, is the low likelihood of expansion to full mutation between 55-57 CGG repeats. This policy is under debate in view of other carrier state symptoms. Prevalence of the carrier state in Israel is 1:120.[3]

The classic phenotype of FXS includes characteristic dysmorphic physical and facial features –large cupped ears, elongated face, high arched palate (60%), macroorchidism (90%), and neuropsychiatric and behavioral symptoms.[4] The presentation can occur as early as in the neonatal period. The diagnosis of FXS is often thought of as straightforward, based on the classic physical phenotype and characteristic symptoms. Primary care clinicians are assumed to be able to recognize easily those physical signs on initial contact with the patient. However, further analysis of case descriptions confirms that many children with FXS do not present with the characteristic facies and classic physical signs.[5] As such, the diagnosis of FXS in these cases is often overlooked initially, resulting in a delay to diagnosis. Without a confirmed genetic diagnosis and appropriate genetic counseling, these families may go on to have several affected offspring prior to a definitive diagnosis. Delayed genetic testing may also result in other unnecessary testing exploring alternate diagnoses, which may be expensive and sometimes painful, such as neuroimaging, blood tests, and lumbar puncture with cerebrospinal fluid analysis to search for other reasons for the child's symptoms. Fragile X DNA testing is recommended by American Academy of Neurology, American Academy of Pediatrics, and American College of Genetics and Genomics[6-8] in the evaluation of intellectual disability and autism spectrum disorder (ASD). Those guidelines are likewise generally followed in Israel as well, but different barriers prevent full implementation. The principal reason is deferral of testing until definitive diagnosis of intellectual disability. The diagnosis of FXS in Israel is more common than in other countries.[9] Consequently, since 2015, prenatal carrier testing for FXS is free for women of childbearing age in Israel. Given the widespread availability of carrier testing, the pediatrician may also overlook FXS in the differential diagnosis of these children based on the incorrect assumption of carrier state having been already checked in the mother.

Bailey et al published the results of a survey of age of FXS diagnosis in a first child of 249 families. The average age at FXS diagnosis remained relatively stable (39.5 months in 2001, and 37.9 months in 2008), and in 25% of families, a second

ASD	Autism spectrum disorder
FXS	Fragile X syndrome

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child was born before the diagnosis.[10] Those results promoted increased awareness to early diagnosis systematic screening of FXS. Seven years later, we attempted to examine the time to diagnosis of FXS in the Israeli population. In this retrospective cohort study, we explore the time lag between initial presentation and diagnosis of FXS in both female and male children, and the possible reasons for the delay in diagnosis.

Methods

This study is a retrospective survey of presenting symptoms and signs, and time of diagnosis, in children and adults with FXS. The subjects were identified from the clinical records of the Weinberg Child Development Center, Edmond and Lilly Safra Children's Hospital, Tel Hashomer, which receives referrals countrywide and has served as the national resource for the Israeli Fragile X Association for the last 18 years. The Weinberg Child Development Center is a tertiary referral center for syndromes and disabilities related to ASD and it is the only resource center in Israel for families with FXS. The FXS database at Weinberg Child Development Center includes families registered at the National Fragile X Association and is comprised of families from all areas of the country and all 4 national health maintenance organizations, and as such, this sample is considered representative of the Israeli population with FXS.

Study information letters were sent to eligible families known to the center, and a semistructured telephone interview was subsequently administered to families that consented to participate. Upon parental consent, data were retrieved from patients' charts and supplemented by interviews conducted from January 2013 through August 2015. Data regarding initial parental concerns, presenting symptoms, evaluation schedule, current medical needs, comorbid disorders, and knowledge of CGG repeats, as well as sociodemographics of the families were coded and subsequently analyzed. The study was approved by the hospital institutional review board as part of a larger epidemiologic study examining pedigrees with FXS and carriers in Israel (Helsinki approval 9187-11-SMC). All statistical analyses were conducted using SPSS v 21 (SPSS Inc, Chicago, Illinois). To examine the differences between male and female patients in age at diagnosis, age at time of the initial concern, and the gap between initial presentation and final diagnosis, as well as differences between perinatal factors and parental education, we performed independent samples *t* tests.

Results

The study cohort contains a diverse sample of children and adults with FXS of both sexes, aged 2-52 years (average 17 [SD = 9.5] years). Relevant data are presented for all groups and analyzed according to the subject's age (>20 years old and <20 years old) and sex (male or female).

Among 117 subjects with FXS, there were 25 female patients. Maternal mean age at delivery was 28 (SD = 5) years. Only 18 mothers of subjects were tested for fragile X carrier state; 13 were confirmed to be carriers but decided to continue the pregnancy, and in 5 cases (11%) the result was a false positive or misinterpreted as not premutated. This high error rate includes laboratory errors in 3 cases (same X chromosome was probably tested twice and in 1 case the wrong negative report was sent to the family), and in 2 cases the carrier state laboratory result was not reported and explained correctly to the family.[11] In most cases (99 mothers), carrier testing was not performed.

Most deliveries were at term, in the range of 32-42 weeks of gestation with an average of 39 weeks. Eight children were born premature, and 2 of them were twins. Birth weight was in the range of 1.3-4.2 kg (average 3.3 [SD = 0.7] kg). The mode of delivery was vaginal in 75%, cesarean delivery in 17%, and vacuum extraction in 4%. For 4 subjects, data on the mode of delivery were missing. Intervention during labor was more common than in the average population in Israel. Late delivery ($P < .01$) and prolonged hospitalization ($P < .001$) were also strongly statistically different in the offspring with FXS compared with the general population, as published in the Annual Statistical Report on Israel.[12,13]

Parents reported raising initial concerns regarding their child's development between the age of 1 month and 60 months (mean 14 [SD = 14] months). Initial concerns were raised mostly by the parents in 72% of cases; however, in 27% of cases, the initial concern was raised by the pediatrician, and in 9% the initial concern was raised at the well-baby screening checkup (performed in Israel at "Tipat Halav," a national screening and immunizations network). In 9% of cases, initial concern was raised by other related persons (relatives or friends). In a few cases, the initial concerns were raised by the caregiver and by professionals simultaneously, and, thus, the percentages accumulate to more than 100%. There was no significant difference in age of diagnosis between physician and well-baby checkup initial concerns.

The specific initial concerns reported (**Table I**) were in most cases developmental delay (mainly motor delays, followed by language and communication delay). Physical signs or dysmorphic features were the reason for initial concern in only 7 cases. Regression of milestones was reported in 3 cases.

The diagnosis of FXS was provided definitively after 5 years on average, with a very broad range. Time from initial concerns noted to definitive diagnosis was analyzed separately for subjects currently >20 years old and < 20 years old, as testing

Table I. Initial concerns that were reported by parents in number and percentage

Initial concerns	N	%
Motor delay	52	44
Communication delay	24	21
Language delay	22	19
Developmental delay	16	14
Sibling with FXS	12	10
Physical signs	7	6
Physical signs with developmental delay	5	4
Regression of milestones	3	3

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