Short report

Neurological findings in patients with the fragile-X syndrome

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SUMMARY We report two brothers with previously unexplained mental retardation and seizures who had dysmorphic facial features, macro-orchidism, and a fragile site at the X chromosome. This recently described syndrome is the second most common chromosome aberration associated with mental retardation after Down's syndrome. In order to determine the prevalence of seizures and the frequency of specific neurological features, we studied a total of 17 patients with the fragile X syndrome. 41% had grand mal seizures; 41% had extensor plantar responses; 47% had hyperactive behaviour and 65% exhibited stereotypics; 59% had incoordination and 35% had blepharospasm. We emphasise the need for chromosome analysis of patients with unexplained mental retardation, specific phenotypic abnormalities, and large testes.

X-linked mental retardation has been reported in the literature over the past 40 years.1 2 In 1969, Lubs described a fragile site on the long arm of the X-chromosome in a retarded male1 and the association of macro-orchidism and X-linked mental retardation was first observed by Escalante and coworkers in 1971 and later by others.3 4 5 During the past decade numerous reports of X-linked mental retardation associated with macro-orchidism and fragile-X chromosome have been published.6 7 8 9 In addition to mental retardation and macro-orchidism many subjects with the fragile-X syndrome have dysmorphic features including prominent forehead, abnormally structured large ears, broad-based large nose, prognathism, and abnormal dermatoglyphics.10 11 12 13 This paper will primarily focus on the prevalence of seizures and abnormal neurologic findings observed in our patients with this syndrome.

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Received 21 February 1984
Accepted 17 March 1984

Patients and methods

Patient 1 (III.5) is a 32-year-old Caucasian male with a history of mental retardation and seizures. He was the product of a term pregnancy and uncomplicated delivery. He sat at eight months, walked at twenty months, said two words at eighteen months, started to talk in sentences at five years, and was bladder trained at three years of age. At seventeen months of age, a pneumoencephalogram showed generalised cortical atrophy. Seizures began at 11 years of age at which time an electroencephalogram revealed a slow-wave focus in the right frontotemporal region. He has continued to have several grand mal seizures yearly. Currently, he is treated with Tegretol and phenobarbitone. A CT scan obtained at age 31 yr was normal. Psychological testing indicated his intellectual function to be in the moderate mentally retarded range. Physical examination revealed a single palmar crease at both hands and enlarged testes measuring 62-2 cm² on the right and 67-8 cm² on the left. Neurological findings included a stooped posture and gait, blepharospasm, and an extensor plantar response on the right side. The remainder of the neurological and physical examination was unremarkable. Chromosome analysis of 100 peripheral blood lymphocytes using 199 medium revealed...
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the modal number of chromosome to be 46 per cell with a male karyotype. In 7% of the cells the fragile site of the X chromosome was noted.

Patient 2 (III,7) is a 29-year-old Caucasian male with mental retardation and seizures. He sat unsteadily at eight months, started to walk at two years of age, and spoke only a few words by age two and one-half years. Seizures began at five years. They have been well controlled with diphenylhydantoin and phenobarbitone. The electroencephalogram showed slowing anteriorly over both hemispheres. Severe behavioural problems necessitated institutionalisation at age 9 yr. Psychological testing at age 25 yr revealed moderate to severe mental retardation. Upon physical examination, enlarged (8 cm in length) thickened ears, a prominent forehead, and a high arched palate were noted. The testes were increased in size measuring 89·2 cm² on the right and 86·4 cm² on the left. Neurological findings included a stooped posture and gait, blepharospasm, spasticity, and hyperreflexia in the lower extremities with bilateral extensor plantar responses. There was incoordination and poor fine motor performance was noted. Chromosome analysis using 199 medium revealed the modal number of chromosomes to be 46 per cell with a male karyotype. Thirty percent of the cells showed the fragile site on the X chromosome (fig 1).

The pedigree of these two index patients (III,5 and III,7), is shown in fig 2.

In addition to the two index cases, we have identified 15 other persons with the fragile-X syndrome. These patients are either followed in the Child Development Center of Rhode Island Hospital or are residents at the Dr Joseph H Ladd Center, the largest institution for individuals with mental retardation in Rhode Island. All patients had come to our attention because more than one offspring in the family had significant mental retardation. The total of 17 persons described in this study come from seven individual families. All patients underwent extensive physical examination including determination of phenotypic abnormalities, measurements of testicular size, and thorough neurological assessments. The Stanford-Binet Intelligence Test had been used to assess their intellectual functioning. Rather than reporting a single IQ measurement we give the patients range of mental retardation. Chromosome preparations were made from 72 hour cultures of peripheral blood using the culture medium 199 without fetal calf serum. Conventional methods and a modification of Seabright's G-banding techniques were employed. One hundred cells of each patient were analysed for the presence of fragile-X chromosome.

**Results**

The data are summarised in the table. In all subjects, macro-orchidism was noted. The only affected female had average sized ovaries as determined by sonography. The percentage of identified fragile-X chromosomes ranged between 4 and 30. Seven of 17 patients (41%) had grand mal seizures. Hyperactive deep tendon reflexes (82%) and extensor plantar responses (41%) were observed. Almost half of the patients (47%) exhibited hyperactive behaviour and had a stooped posture and gait. Incoordination was noted in 59% of patients, blepharospasm was present in six patients (35%), and all patients had various degrees of mental retardation. Stereotypic behaviour was displayed by 65% of the study participants. In addition, dysmorphic features including coarse facies, large ears, prominent glabella, synophrys, large nose, prognathism, and abnormal dermoglyphics were noted. The language development in the majority of patients was retarded and defective speech including dysfluency, abnormal intonation patterns, and incorrect syntax were noted.
Table Neurological manifestations in patients with fragile-X syndrome

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Testicular size (cm²)</th>
<th>% of fragile X chromosomes</th>
<th>seizures</th>
<th>hyper-</th>
<th>Babinski</th>
<th>hyperactivity</th>
<th>poor coordination</th>
<th>stooped gait</th>
<th>blepharospasm</th>
<th>degree of MR*</th>
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+ = present, = absent, NA = not applicable (wheelchair bound) *degree of mental retardation: se = severe, mo = moderate, mi = mild
† ovarian diameter as determined by ultrasonography.

Discussion

It has been estimated that about 8% of mentally retarded males have the fragile-X syndrome. Some investigators have reported neurological findings in patients with the fragile-X syndrome. Escalante and co-workers observed seizures in two patients with mental retardation and macro-orchidism. Harvey and co-investigators described four patients with seizures, mental retardation, and fragile-X chromosome; testicular size, however, was not mentioned. In another four studies of patients with mental retardation, macro-orchidism, and fragile-X chromosome, six of 22 patients had seizures.

In our series of 17 patients, seven had grand mal seizures. Their electroencephalographic abnormalities consisted primarily of high voltage slow activity. Electroencephalographic changes have also been described in males with the fragile-X syndrome who did not have associated convulsive disorders as well as in affected females. In addition to seizures, abnormal neurologic findings in our patients included hyperreflexia, incoordination, stooped posture and gait, extensor plantar responses, hyperactive behaviour, and blepharospasm (see table).

Recent reports have described this chromosomal abnormality in association with autism, suggesting males with autism be screened for fragile-X chromosome. None of our patients, however, displayed autistic behaviour. The presence of macro-orchidism in the fragile-X syndrome emphasises the need for testicular examination in all mentally retarded males, in particular if dysmorphic features suggest the fragile-X syndrome. Since testicular enlargement in these patients is primarily observed after puberty, appreciation of the full clinical syndrome may be delayed until adolescence or adult life.

Chromosome analysis for the fragile-X chromosome in all unexplained mentally retarded males and physically normal females with mild mental retardation has been suggested. Considering the costs and efforts involved in the cytogenetic studies, we recommend chromosome analysis when there is a family history of mental retardation, macro-orchidism, and/or phenotypic expression of this syndrome. Recent reports indicate the feasibility of prenatal diagnosis of the fragile-X syndrome by amniocentesis.

The fragile-X syndrome is now frequently recognised in mentally retarded males. We call attention to the occurrence of seizures and associated neurologic features with this syndrome. We emphasise the role of chromosome analysis and testicular examination in males with mental retardation of unknown aetiology. Once the diagnosis of fragile-X syndrome has been made, genetic counselling should be offered to family members, in particular to potential female carriers.

References

4. Escalante JA, Grunspun H, Froto-Pessoa O. Severe
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