Broad Clinical Involvement in a Family Affected by the Fragile X Premutation

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ABSTRACT: The mutations in the FMR1 gene have been described as a family of disorders called fragile X-associated disorders including fragile X syndrome, fragile X-associated tremor/ataxia syndrome, primary ovarian insufficiency, and other problems associated with the premutation, such as hypothyroidism, hypertension, neuropathy, anxiety, depression, attention-deficit hyperactivity disorders, and autism spectrum disorders. The premutation is relatively common in the general population affecting 1 of 130 to 250 female individuals and 1 of 250 to 800 male individuals. Therefore, to provide appropriate treatment and genetic counseling for all of the carriers and affected individuals in a family, a detailed family history that reviews many of the disorders that are related to both the premutation and the full mutation should be carried out as exemplified in these cases. To facilitate the integration of this knowledge into clinical practice, this is the first case report that demonstrates only premutation involvement across 3 generations.

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Fragile X syndrome is the most common known single-gene cause of autism spectrum disorders and inherited intellectual disabilities. Fragile X syndrome is one of a family of fragile X-associated disorders caused by CGG-repeat expansion mutations of the fragile X mental retardation 1 (FMR1) gene on Chromosome Xq27.3. More than 200 CGG repeats have been well described as the full mutation leading to an absence or deficiency of the fragile X mental retardation protein. The full mutation causes the physical, behavioral, cognitive, and emotional features of fragile X syndrome. For a long time after the discovery of the FMR1 gene in 1991, individuals who have the fragile X premutation (55–200 CGG repeats) or gray zone alleles (45–54 CGG repeats) were thought to be clinically uninvolved by the mutation. However, advances in research in fragile X over the years have identified clinical involvement in some premutation carriers including developmental problems, such as attention-deficit hyperactivity disorder and autism spectrum disorders particularly in boys, medical problems e.g., hypothyroidism, hypertension, fibromyalgia, seizures, menstrual dysfunction (primary ovarian insufficiency) and psychological issues such as depression and anxiety and late-onset neurological problems described as the fragile X-associated tremor ataxia syndrome.

The premutation is associated with elevated FMR1 mRNA from 2 to 8 times above normal and this leads to RNA toxicity, which is the molecular mechanism for clinical involvement in premutation carriers. Likewise, in the gray zone, there can be more subtle increases in FMR1 mRNA levels up to almost 1.5 times normal when compared with controls. Clinical studies have shown that primary ovarian insufficiency occurs twice as often in women who carried alleles in the gray zone compared with general population, suggesting clinical attention should be warranted even in those with gray zone CGG expansions (45–54 CGG repeats). However, neurological and psychiatric problems have not been studied in individuals with gray zone alleles. To facilitate the integration of premutation involvement into clinical practice, we report on 3 generations in a family in whom all cases of the fragile X mutation, including the proband and those identified by cascade testing, were affected by premutation involvement. At least 6 individuals throughout 3 generations in this extended family have been confirmed with the fragile X premutation and were evaluated at our center. The terms “carrier” and “premutation” have similar meaning and were used interchangeably in this article.
CASE DESCRIPTIONS
Clinical Presentation
The proband is a 12-year and 6-month-old boy who developed language delay and social deficits and was diagnosed with pervasive developmental disorder—not otherwise specified when he was at 3 years and then subsequently was diagnosed with full autism at 7 years. Because of the diagnosis of autism spectrum disorders, genetic testing, including the fragile X DNA test, was performed. He was found to be a premutation carrier (65 CGG repeats) at 4 years of age and was confirmed to have 61 CGG repeats at 7 years at our center.

He had typical behaviors of fragile X and autism including excessive chewing on clothes or objects, skin picking, tactile defensiveness, hyperactivity, anxiety, perseverative behaviors, tantrums, and limited eye contact.

Prenatal, Perinatal, and Postnatal History
His mother experienced a prolonged labor coupled with heart rate decelerations and he was born full-term, vaginal delivery with an Apgar score of 7 and 9. In infancy, he did not feed well because of a weak suck. He had typical behaviors of fragile X and autism, including excessive chewing on clothes or objects, skin picking, tactile defensiveness, hyperactivity, anxiety, perseverative behaviors, tantrums, and limited eye contact.

Developmental History
His gross motor milestones were normal; he sat at 6 months, crawled at 8 months, and walked at 10 months, but his speech was delayed. He did not begin talking meaningful words until after he started language intervention when he was almost 4 years.

Medical History Including Medications
His medical history included an umbilical hernia, a few uncomplicated ear infections, and staring spells. The latter problem began when he was at 5 years. After a wave discharges particularly during sleep. Valproic acid was prescribed and he subsequently improved the frequency of his spontaneous speech. His staring episodes decreased and behaviors became more attentive on valproic acid. He began speaking in sentences at 5 years after seizures were controlled. When he was 9 years, lamotrigine was added to valproic acid because of breakthrough seizures that were subsequently controlled. Other medications were tried because of his autism and hyperactivity including risperidone, olanzapine, and guanfacine. He developed more hyperactivity after taking risperidone and had significant sedation after taking olanzapine. Aripiprazole was tried to control tantrums, aggression, anxiety, and distractibility, but he developed a sleep disturbance on this, so it was discontinued. Risperidone has been the most beneficial for his mood instability, irritability, and tantrums. He has been on guanfacine for several years and this was noted to improve his hyperactivity. However, it was discontinued when he started lamotrigine to decrease the number of his medications. Melatonin at bedtime has helped him sleep through the night.

Physical Examination
On physical examination at 7 years, heart rate was 120 beats per minute. Blood pressure was 106/70 mm Hg. His growth percentiles were normal with a head circumference of 52.5 cm (50th percentile). He had very limited eye contact, difficulty with social interaction, and intermittently made a high-pitched noise during the examination. He had a high-arched palate, a double-jointed thumb on the left and flat feet bilaterally. The genitalia showed normal prepubertal development with a testicular volume of 5 mL bilaterally. The rest of his physical examination was unremarkable.

Additional Assessments
The Leiter International Performance Scale demonstrated a moderate range of intellectual disability (ID) with a Full Scale Intelligence Quotient of 46. The Vineland Adaptive Behavior Scales completed with his parents yielded standard scores of 40 in communication (age equivalent 1 year 7 months), 37 in daily living skills (age equivalent 2 years 7 months), 53 in socialization (age equivalent 1 year 10 months), and 40 on the adaptive behavioral composite (age equivalent 2 years). He met the criteria for autism on the Autism Diagnostic Interview, Revised and the criteria set forth in the DSM-IV.

Supports and Therapies
He has been in an autism program at school, which included typically developing children. He also received speech and language therapy, sensory integration therapy, occupational therapy along with behavioral intervention from the school. His current treatments include the combination of speech and language therapy along with occupational therapy and horseback riding for an hour each per week. His current medications include 0.5 mg of risperidone, 1450 mg of valproic acid, 150 mg of lamotrigine per day, and 9 mg of melatonin at bedtime.

Family members who were evaluated at our center including his paternal grandfather's brother, maternal grandfather, mother, both maternal aunts, biological brother, and cousin are described in details in Table 1 and a summarized pedigree of this family is illustrated in Figure 1. Two known noncarrier members in this family including the proband's father and maternal grandmother were also evaluated here. The biological father had hyperactivity and reading difficulties that required tutoring when he was young, but he was neither diagnosed with attention-deficit hyperactivity disorder nor treated with stimulants. The maternal grandmother had high blood pressure and depression in the past, the latter problem began after her husband was diagnosed with fragile X-associated tremor/ataxia syndrome. Otherwise, they both were healthy and had a normal intelligence quotient without any other current psychological diagnoses.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Grandfather’s Brother</th>
<th>Grandfather</th>
<th>Mother</th>
<th>Aunt</th>
<th>Aunt</th>
<th>Brother</th>
<th>Cousin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>57</td>
<td>62</td>
<td>59</td>
<td>37</td>
<td>37</td>
<td>11</td>
<td>9 years 7 months</td>
</tr>
<tr>
<td>Number of CGG repeats</td>
<td>52 CGG repeats</td>
<td>52, 68 CGG repeats (mosaic premutation)</td>
<td>54 CGG repeats</td>
<td>56 CGG repeats</td>
<td>67 CGG repeats</td>
<td>69 CGG repeats</td>
<td></td>
</tr>
<tr>
<td>mRNA level</td>
<td>1.85 ± 0.08*</td>
<td>2.62 ± 0.34</td>
<td>19 ± 0.63</td>
<td>188 ± 0.30</td>
<td>1.95 ± 0.04</td>
<td>1.51 ± 0.43</td>
<td>191 ± 0.43</td>
</tr>
<tr>
<td>AR(b)</td>
<td>—</td>
<td>—</td>
<td>0.54</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Clinical presentation/ involvement</td>
<td>Type 2 diabetes at 37 yrs, hypertension at 59 yrs, hypercholesterolemia, migraine headache and hearing loss</td>
<td>2 benign thyroid tumors at 55 yrs, no interference with daily activities</td>
<td>Depression, anxiety</td>
<td>Depression, anxiety on a daily basis, sleep disturbances, panic attacks</td>
<td>ASD documented byADOS and by DSM-IV criteria, ADHD, overanxious disorder with obsessive features, panic attacks</td>
<td>Biting her arms when upset, tactile defensiveness, sensory integration problems</td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>BP 132/82 mm Hg</td>
<td>BP 141/89 mm Hg</td>
<td>Unremarkable</td>
<td>Not examined</td>
<td>Hypertension (BP 128/90 mm Hg)</td>
<td>BP 122/68 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Management</td>
<td>Enalapril 0.5 mg, lipitor 20 mg/day and insulin</td>
<td>Metoprolol 50 mg, dutasteride 0.5 mg and fenofoibrate 145 mg/day</td>
<td>Sertraline 75 mg/day</td>
<td>Escitalopram 20 mg/day</td>
<td>Sertraline 50 mg/day</td>
<td>Sertraline 37.5 mg/day, individualized educational program</td>
<td></td>
</tr>
</tbody>
</table>

AR, activation ratio; CPAP, continuous positive airway; ASD, autism spectrum disorders; ADOS, Autism Diagnostic Observation Schedule; WAIS-III, The Wechsler Adult Intelligence Scale-Third Edition; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; WASI, Wechsler Abbreviated Scale of Intelligence; FSIQ, full scale intelligence quotient; SCL-90-R, Symptom Checklist-90-Revised demonstrated a clinically significant level (≥63) of depression (DEP) and irritability (HOS) and almost a clinically significant level of obsessive-compulsive problems (O-C), psychological difficulties (PSY), and Global Severity Index (GSI); VABS, The Vineland Adaptive Behavior Scales; C, Communication; DLS, daily living skills; S, socialization; M, motor; ABC, adaptive behavioral composite.

*Mean ± SD of the mRNA level and every sample was normalized to a normal control which is 1.26 ± 0.23. **AR: fraction of normal **FMR1 **allele as the active allele.
DISCUSSION

This family demonstrated various types of the premutation involvement without any individuals with the full mutation. Premutation involvement is a relatively new concept for clinicians and it deserves further review, so that it can be incorporated into screening and treatment endeavors of physicians. Data in the literature, which compares those with the premutation with controls without the premutation, will be reviewed to further validate whether these problems are associated with the premutation.

Physical Involvement

The proband, his brother and cousin have at least one of the subtle physical features associated with fragile X syndrome (FXS), such as flat feet, high-arched palate, pectus excavatum, and double jointed thumb, which can often be seen with the premutation because the level of fragile X mental retardation protein can sometimes be deficient in the premutation range.2,5 Although these physical features are also common in the general population, hyperextensibility of finger joints, ear prominence, and enlarged testicles can also be presented in individuals with the premutation and these features are correlated with fragile X mental retardation protein levels in both the premutation and the full mutation.2,5,19–21

Developmental and Behavioral Involvement

Although the presence of autism in those with the full mutation has been thoroughly studied this is not true of those with the premutation. Two to 6% of children with autism of unknown cause will have the fragile X full mutation,22–24 but the rate of the premutation in autism is not known. Approximately 30% of children with the full mutation and FXS will have autism25,26 and an additional 30% will have pervasive developmental disorder not otherwise specified.27 Developmental and behavioral problems, including developmental delay, speech and language impairments, autism spectrum disorders, attention-deficit hyperactivity disorder, and social deficits, are relatively common in young individuals with the premutation particularly in boys as reported in the literature.4,5,28–30 Farzin et al4 found that autism spectrum disorders and attention-deficit hyperactivity disorder were significantly more common in boys with the premutation who presented as probands compared with their brothers without the premutation. In a large survey study of >1200 fragile X families, it was found that 45% of male individuals older than 6 years with the premutation had been diagnosed or treated for attention problems, 36% for anxiety, 32% for developmental delay, 30% for hyperactivity, and 19% for autism and aggression.7

Cognitive Involvement

Although cognitive deficits and even dementia are common in individuals with fragile X-associated tremor/ataxia syndrome (FXTAS).9,31 other cognitive deficits, including executive function, working memory, selective attention, and social cognition, have been demon-
strated across the life span in premutation carriers without FXTAS compared with controls.21,31–57 One exception to these reports is a study by Hunter et al58 who found no cognitive deficits in a cohort of individuals with the premutation who were younger than the age of 50 years compared with controls. Most individuals do well with the premutation during early life and are able to overcome attention-deficit hyperactivity disorder or social deficits to go on to higher education.59

Interesting work has been done in relating the cognitive impairments in premutation carriers without FXTAS to neuroimaging findings suggesting a strong relationship among gene, brain, and cognitive profiles. For instance, decreased amygdala activation while viewing fearful human faces or decreased left hippocampal activation in addition to increased right parietal activation during a recall task when compared with controls have been illustrated in men with the premutation but without FXTAS.40–41 These functional changes were associated with both elevated FMR1 RNA and psychiatric symptoms in these men. These findings suggest that the connectivity in the brain linked to the amygdala and the hippocampus in those with the premutation is mildly dysfunctional from a neurodevelopmental perspective and may contribute to clinically significant impairment especially in those with higher CGG-repeat alleles. Studies of premutation neuron cell cultures have shown that branching of the dendrites is decreased and the synaptic size is increased in neurons with the premutation compared with controls.42 These connectivity changes likely make the individual with the premutation more vulnerable to additional genetic or environmental problems that further interfere with development. We also know that the premutation neuron will die more easily with toxicity or stress in the environment, so that these cells are more vulnerable because of the RNA toxicity.13,44

Those with the premutation usually have a normal intelligence quotient, but this proband’s intelligence quotient was in a moderate range of intellectual disability (ID). This is a more significant deficit than what is typically seen in premutation carriers and in contrast to his brother’s higher level of function, so additional additive effects must be considered here such as the proband’s history of recurrent seizures in addition to autism.4,5,45 ID has been documented in male individuals with the premutation in previous literature4,5,15,46,47 and the prevalence of ID was ~12% as reported in one large study.46 The effect of each factor including severe social impairment, seizure comorbidity, perhaps a second-gene effect, and other environmental factors can be additive to the premutation to predispose this proband to have more intellectual impairment when compared with his biological brother even though they both have similar range of CGG repeats. Taken together, CGG repeats alone do not predict or determine the entire outcome of those with fragile X mutations. To improve the long-term outcome, early multidisciplinary management including early intervention, speech and language therapy, occupational therapy, physical therapy, special education, tailored behavioral, and medical interventions should be recommended particularly in those who have behavioral and neurodevelopmental problems.42,48,49

### Neurological Involvement

Seizures have been reported to be increased in those with autism and FXS when compared with FXS without autism.60 Seizures are more likely to occur in males with the premutation compared with controls when matched on children’s age and family income (11.3% versus 1.2%) in a recent large survey study.7 This proband had seizures and a clinical response to valproic acid with improvement in seizures in addition to language abilities and social skills. Such a response is often seen in those with a full mutation and seizures48,49 and also in the autism population without FXS.51 Anticonvulsants should be part of the treatment program in those with the fragile X mutation (premutation or full mutation) and clinical seizures.48,49

FXTAS, a progressive late-onset neurological disorder has been documented for years in a subgroup of older individuals with the premutation affecting some carriers older than 50 years.12 The proband’s maternal grandfather was diagnosed with probable FXTAS because of his tremors and other symptoms52 and his FMR1 testing showed premutation mosaicism with allele sizes of 52 and 68 CGG repeats. FXTAS features include intention tremor and/or gait ataxia, peripheral neuropathy, parkinsonism; psychiatric symptoms including anxiety, irritability, or disinhibition; autonomic dysregulation including hypertension, orthostatic hypotension and incontinence, executive function, and memory deficits.13,31–37,52 In cases of FXTAS, 60% of male and 13% of female subjects have an magnetic resonance imaging with symmetric white matter lesions involving the middle cerebellar peduncles.53 The presence of intranuclear inclusions in both neurons and astrocytes throughout the brain is also reported from postmortem neuropathological studies of those with FXTAS.54 The maternal grandfather’s brother also had a gray zone allele with 52 repeats and he had subtle tremor and other symptoms52 and his FMR1 testing was diagnosed with probable FXTAS because of his tremors and other symptoms52. Seizures have been reported to be increased in those with autism and FXS when compared with FXS without autism.60 Seizures are more likely to occur in males with the premutation compared with controls when matched on children’s age and family income (11.3% versus 1.2%)
been well validated by many studies as increased in premutation carriers compared with controls.\(^6\) Primary ovarian insufficiency affects ~20% of female carriers but was not seen in the 3 female carriers we evaluated here.

**Psychological Involvement**

The biological brother and cousin of the proband developed an overanxious disorder and obsessive compulsive rituals. Likewise, mother and both maternal aunts of the proband experienced anxiety and depression, which are more common in the premutation carriers, varying from 18% to 43% in numerous studies of carriers compared with controls.\(^6\) Furthermore, psychological difficulties in those with the premutation were significantly associated with elevated FMR1 mRNA level suggesting FMR1 dysfunction is an important pathogenic mechanism of these problems, over and above the well-known stresses associated with caring for children with intellectual impairment.\(^11,59,60\)

**Mechanism of Clinical Involvement in the Premutation**

As we described in the “Introduction,” the mechanism of the premutation involvement is different from those with the full mutation in that an RNA toxic gain-of-function effect is seen due to enhanced levels of FMR1 mRNA (2–8 times higher than healthy individuals). The elevated mRNA levels lead to dysregulation of several proteins and subsequent neuronal and astrocytic toxicity and eventually cell death.\(^15,43\) The mRNA toxicity can involve many areas in the central nervous system including the limbic system, pituitary, autonomic ganglia of the peripheral nervous system in addition to the testicles, thyroid, and adrenal gland.\(^61,62\) Therefore, the elevated mRNA in the maternal grandfather’s case is likely leading to the symptoms of FXTAS including head and hands tremors, hypertension, hypoglycemic episodes, sleep apnea, and anxiety although he does not have the middle cerebellar peduncle sign.

Signs of premutation involvement including psychopathology, endocrine dysfunction, autonomic dysfunction, and neuropathy typically occur even before the FXTAS problems of tremor and ataxia begin. The fragile X or FMR1 DNA test should be considered in individuals at high risk of having fragile X mutations particularly in children with autism spectrum disorders, developmental and intellectual disabilities, women with early menopause, or older adults with intention tremor or ataxia.\(^65\) This family tree is unusual because there is only premutation and gray zone involvement. With more widespread screening for fragile X mutations, we predict many more similar pedigrees with significant premutation involvement will be seen because the premutation is far more prevalent (1/250 – 800) than the full mutation (1/2500 – 4000).\(^64\)

In conclusion, there is often a wide range of clinical involvement in extended family members in all generations when a proband is identified with a fragile X mutation. Therefore, to provide appropriate treatment and genetic counseling for all of the affected individuals in a family, a detailed family history that reviews many of the disorders that are related to both the premutation and the full mutation should be carried out in addition to referral to a genetic counselor and multidisciplinary professionals as necessary.\(^48,65\) Early treatment of premutation and full mutation disorders are likely to be beneficial for their long-term outcome.\(^13,48\)

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**Book Review**

**Positive Parenting: Raising Healthy Children from Birth to Three Years**

by Alvin N. Eden, MD, Long Island City, NY, Hatherleigh Press, 2007, 288 pp, Paperback, $15.95

The first 3 years of life are marked by critical changes in the child’s physical, social, emotional, and cognitive development. Parents and caregivers, Dr. Alvin N. Eden argues, are, by nature, of their position afforded with the unique opportunity to optimize their child’s physical, socioemotional, and intellectual capacities. Each child, Dr. Eden further emphasizes, is “unique in his potential” and has an innate right to be provided with the means necessary to achieve it. The ways in which parents can help their child grow into a healthy, vivacious, and confident individual are outlined in Dr. Eden’s *Positive Parenting: Raising Healthy Children from Birth to Three Years.* A quick and easy read, *Positive Parenting* is a compendium of clearly presented advice that can serve as a reference for both new and experienced parents interested in expanding their knowledge on such topics as sleep, nutrition, safety, sudden infant death syndrome, shaken baby syndrome, obesity, language, socialization, parent-child relationships, and many more.

The book is divided into 7 chapters. In 3-month increments, the first 4 chapters delineate the infant’s development over the first year of life: birth to 3 years, 3 to 6 months, 6 to 9 months, and 9 to 12 months. Chapters 5 and 6 introduce parents to some of the physical, emotional, and cognitive changes that they can anticipate in their inquisitive and vigilant 2-year-old child to experience—from developing better dexterity and beginning to form 2-word phrases to exhibiting negative behaviors (i.e., teasing and temper tantrums) that demand effective management. Although Dr. Eden’s recommendations on behavior management are not circumstantial, they are practical in nature and likely to amend a child’s behavior. Specific suggestions include using positive reinforcement and praise, explaining the antecedents and consequences of behavior, scene removal, and time out. The final chapter discusses cornerstones of the child’s development from age 2 to 3 years, emphasizing the significance of assessing for visual and auditory problems, modifying the toddler’s diet to accommodate changes in his physical development, revisiting the issue of childhood obesity, toilet training, anger, body image, and birth of another child.

Each chapter is structured into sections on age- and developmentally appropriate nutrition, safety, play, and exercise, which are supplemented with personal vignettes and examples from Dr. Eden’s pediatric practice. Although beneficial in enhancing parents’ conceptual understanding and normalizing behaviors parents may have witnessed their own children exhibiting, these vignettes may also distract parents who are seeking to elicit more evidence-based information from the text. Vague statements such as “many studies show” may unintentionally deter a population of parents who may prefer to know Dr. Eden’s claims are not only anecdotal in nature but also substantiated by clinical research. Supplementing generalizations with references to the scientific literature may have made *Positive Parenting* even more balanced and unequivocal.

Dispersed throughout each chapter are well-developed and detailed charts elucidating the physical, emotional, and cognitive milestones parents can expect their typically developing child to achieve at each stage of their early development. Not only do the charts effectively condense a wealth of information but also serve as quick reference guides that can assist parents in setting realistic expectations about their child’s abilities and behaviors. Accompanying the charts are also sections in each chapter addressing various myths and misconceptions regarding such topics as breast feeding, iron-fortified formulas, teething, pacifier usage, and the relationship between early or delayed language development and intelligence. These sections along with Dr. Eden’s pragmatic recommendations (e.g., encouraging talking and reading aloud to foster language development) are likely to mitigate parental anxiety and reassure parents that they are fully capable of providing their children with the care, attention, and love that they need to “grow up healthier, happier, and smarter.”

Although not comprehensive, *Positive Parenting* succeeds in equipping parents with the tools necessary to transform the art of parenting from an intricate and abstract process to a pragmatic skill that can be learned.

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