Cognitive and behavioral development profile of a Saudi girl with Fragile X syndrome

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ABSTRACT

يستعرض التقرير حالة لطفلة مصابة بمتلازمة X الهشة. تنحدر من أسرة لديها نفس المتلازمة، أظهرت النتائج وجود ذكاء طبيعي منخفض IQ مع تشتت للانتباه و خجل. أظهر التقرير حالة الفتيات المصابات بمتلازمة X الهشة بأنها قد تظهر لديهن صعوبات معرفية، لكنها قد تمكنهن من التكيف والنجاح في المجتمع.

This report presents an ideal case of a girl with Fragile X syndrome. There is positive family history of the same condition. The analysis revealed low average IQ with attention deficit, shyness, and social withdrawal. The report shows that girls with Fragile X might have only mild cognitive deficits that enable them to adapt and succeed in society.

Neurosciences 2010; Vol. 15 (2): 113-116

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Received 24th August 2009. Accepted 3rd November 2009.

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Fragile X syndrome is considered to be one of the most common inherited forms of cognitive disorders associated with learning disabilities.[1] The syndrome is named for a "fragile site" at the distal end of the long arm of the X chromosome, which looks like a gap or break in the chromosome. It is named for the folate sensitive fragile site Xq27.3 and is caused by an expansion or amplification of a CGG trinucleotide repeat in the first exon of the fragile X mental retardation gene (FMR1), located on the long arm of the X chromosome. Sometimes this syndrome is called Martin-Bell syndrome, named after the physician who first described this syndrome in 1943.[2] A child diagnosed with Fragile X syndrome will always have a carrier mother, and many other family members may be at risk. Males with fragile X are hemizygous, and females are heterozygous for the condition. Amplification of the premutation to the full mutation occurs only in the ovum. A male who has the premutation on only his X chromosome passes the premutation to each of his daughters without significant change in the size of the repeat. A female with the premutation would pass on the affected gene to half of her children, either unchanged or as a full mutation. A female with a full mutation would transmit the affected gene after further amplification to half of her children. This amplification in the ovum of both premutations and full mutations is related to the phenomenon of anticipation; whereby the genetic defect manifests earlier in successive generations in a family, and where longer expanded repeats typically cause earlier symptom onset and severer disease in successive generations. The stability of the premutation when transmitted by a male elucidates another observation, described as the Sherman paradox; where daughters and mothers of transmitting males are unaffected; but brothers and grandsons are affected 18% and 74% of the time.[3] Fragile X syndrome has been known as one of the main causes of mental retardation. Patients with this syndrome could have IQs within the area of mental retardation.[4] It affects males with the full mutation and full methylation most severely. Females, however, in Fragile X syndrome can also be affected to various degrees.[5] Fragile X syndrome is also reported to be associated with autism spectrum disorders.[6] Behavioral features in Fragile X syndrome includes hand flapping or biting, poor eye contact, and social anxiety. These behavioral features are common in boys and girls with this disorder.[7] Fragile X syndrome is a genetic disease that might be associated with cognitive and behavioral difficulties. This report however, focuses on the cognitive and behavioral profile for a diagnosed child with Fragile X. These findings may better the understanding of this disease comprehensive, moreover they may improve the quality of care for patients.

Case Report. A 5-year-old girl was referred to the pediatric psychometric clinic to evaluate her intellectual abilities and her social/behavioral skills. She was already diagnosed with Fragile X syndrome after detection of this syndrome among her siblings. She was the product of a full-term uneventful pregnancy to a 29-year-old woman. The mother was well known to be a carrier of Fragile X syndrome without any symptoms. No neonatal difficulties were reported. The infant was discharged at 2 days of age without any medical complications as well the mother. The family history indicated that there is a 10-year-old Fragile X syndrome brother who was diagnosed previously. He showed significant deficits in the emotional/social aspects of daily life as well as very low intellectual abilities. Apart from this, there is no family history of developmental disabilities. Her history revealed that she sat alone at 10 months of age and walked independently at 13 months. The parents observed that she could respond with smiling when called by her name. By 2 years, she was saying more than 20 words. At that age, she could respond to simple commands. According to parents' observations, she could communicate with her peers, for example, playing. Social abilities were normal; nevertheless, she was described by both parents as a shy and a withdrawn child. The consensus of the parents was taken, explaining to them all issues related to the case, and the importance of study to identify the cognitive, emotional, and behavioral profile of Fragile X syndrome. The Psychological instruments applied were: Stanford-Binet Intelligence; Vineland Adaptive Behavior; Vanderbilt scale; Gilliam Autism Rating Scale; Psychological interview, and observation. Full information was given to the parents and patient on the procedures of the psychometric assessments. The Stanford-Binet Intelligence Scale confirmed that the child intellectually is normal (IQ: 81). Moreover, the Vineland Adaptive Behavior Scale, for social intelligence indicated low adequate adaptive behavior with a total score of 83. The Vanderbilt scale, intended to assess attention deficit hyperactivity disorder (ADHD), and other psychological aspects showed that she has ADHD, predominantly the attention deficit: hyperactive-impulsive type (=3), attention deficit (=9), combined type (=12), oppositional defiant disorder (=1), conduct disorder (=0), and anxiety/depression (=2). The Gilliam Autism Rating Scale (GARS) confirmed that she does not have autistic features. **Table 1** shows the results quantitatively. As the parents have another child with the same syndrome associated with severe mental retardation, they believed that this child was the same, and they flooded the child emotionally (overprotection). This might have deprived her from acquiring appropriate behavior and making the environment less stimulating. They underestimated their daughter's intellectual abilities, which affected her

Table 1 - Summary of psychological test results for a 5-year-old girl with fragile X syndrome.

Test	Score	Comments
Stanford Binet		
Verbal reasoning domain	90	Low average ≥80 and ≤89
Pattern analysis – abstract/visual domain	88	
Quantitative Reasoning domain	80	
Short-Term Memory domain	78	
Total score	81	
Vineland Adaptive Behavior		
Subscale: communication	76	Low Adaptive Behavior ≥70 and ≤84
Subscale: daily life skills	53	
Subscale: socialization	57	
Subscale: motor skills	57	
Total score	83	
Vanderbilt Assessment		
ADHD, hyperactive	3	Hyperactive-impulsive type cut-off ≥6
ADHD, attention	9	Inattentive type cut-off ≥6
ADHD, total	---	Combined type (Hyperactive+ attention) cut-off ≥6 + cut-off ≥6
Oppositional defiant disorder	1	cut-off ≥4
Conduct disorder	0	cut-off ≥3
Anxiety/depression	2	cut-off ≥3
Gilliam Autism Rating Scale		
Stereotyped behaviors subscale	5	Probability of autism = 5%
Communication subscale	6	Probability of autism = 9%
Social interaction subscale	7	Probability of autism = 16%
Developmental disturbances subscale	6	Probability of autism = 9%
Total score	24	Probability of autism = 19-21%, cut-off ≥27

ADHD - Attention deficit hyperactivity disorder

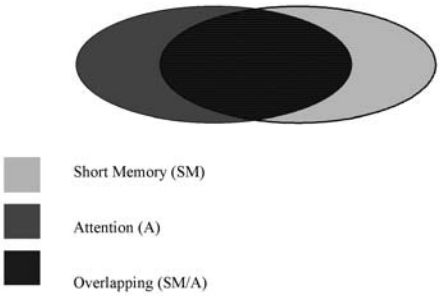

Figure 1 - Overlapping between short-memory and attention.

chance to have the proper educational achievements. At the time of interviewing, she was very shy, and according to her mother used to withdraw from most social activities. She did not express any oppositional behavior during her stay; but she communicated well. She did not exhibit repetitive behavior or limited interest. Socially, she had the appropriate social skills, enabling her to deal with her surroundings. There were no signs of other psychological problems.

Discussion. This report is a cognitive and behavioral developmental profile of Fragile X syndrome in Saudi society, involving a full psychometric assessment. It is however, a unique case, because the patient's brother, according to the genetic analysis, had the same syndrome with more severe manifestations, and the mother with the same gene, transmitted it to her child (the case) without any significant medical history related to this syndrome. Further to physical symptoms, patients with Fragile X may have a group of cognitive, behavioral, and psychological characteristics. All may vary in severity among affected children. This case is intellectually low, but with a normal IQ in general. However, her performance mostly on the IQ's tasks (for example, verbal reasoning, pattern, analysis–abstract/visual and quantitative reasoning) was consistent, though she did poorly on short-term memory. Matching these findings with other international studies, around one-third of girls with the Fragile X syndrome scored above 80 in an IQ test, while around two-thirds were commonly in the borderline or mild mental retardation range. The finding of short-term memory may be attributed to ADHD (**Figure 1**). According to the Vanderbilt ADHD scale, she exhibited an impaired profile of the inattentive type, indicating attention-deficit disorder. Overall, as long as attention is impaired, working memory mostly would be impaired too, as both are executive functions of the frontal lobe. Attention deficit is a common behavioral symptom of children with Fragile X.[8]

The social intellectual ability, screened by the Vineland Adaptive Behavior test confirmed the IQ result and the normal ability of this patient. Adaptive behavioral skills tend to continue to increase with age. Some patients with Fragile X have well adaptive behavioral skills, and better than their IQ scores would indicate. According to the GARS, she has no autistic features in general. Not all patients with this syndrome have autism, and not every autistic patient has Fragile X syndrome. The children with Fragile X syndrome could not have all the characteristics of autism.[9] They are more likely to have "autism spectrum" features such as poor eye contact and social skills.[10] However, autistic features are not always presented as core symptoms of children with Fragile X syndrome, and are most likely considered as a secondary phenomenon.[11] From the purely psychological side, the parents observed that the child suffers from shyness, with poor social contact. These psychological and psychosocial manifestations are mostly seen among girls with Fragile X syndrome.[12] These findings may help the child and her parents to feel more confident about her intellectual potential. The findings confirmed that the child can benefit from regular education programs, instead of these programs developed for mentally retarded children. Counseling psychological sessions, which were prescribed to the parents, assisted in increasing daily living activities of the child. Genetic counseling has to be imperative; it should be required through the approved marriage medical tests. Overall, there is no specific treatment for the disease, rather early intervention is recommended in order to maximize developmental potential.

The term, carrier, has been used traditionally to describe a clinically unaffected woman who passes on the Fragile X gene to her children. However, a quick and simple test that could decide whether a woman is a carrier of the Fragile X gene or not is now available. In case the woman who is confirmed to be a carrier is pregnant, she can plan for additional tests for the fetus. For a woman with a family history of retardation, testing before pregnancy will help determine if she is at risk. Such medical tests should be recommended and included in the pre-married analysis and prenatal tests. Early detection of a child with Fragile X and subsequent treatment involving a team of professionals could make reasonable improvements.

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Related topics

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