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ASSOCIATION OF FRAGILE X SYNDROME, ROBERTSONIAN TRANSLOCATION (13, 22) AND AUTISM IN A CHILD

ANDREEA LIANA RACHISAN[1], ALEXANDRU STEFAN NICULAE[1], IOANA TINTEA[2], BIANCA POP[3], MARIELA MILITARU[4], AUREL BIZO[5], ADRIAN HRUSCA[6]

[1]Department of Pediatrics II, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[2]Department of Pediatrics Neurology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[3]Department of Pediatrics Psychiatry, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[4]Department of Medical Genetics, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[5]Department of Pediatrics I, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[6]Department of Medical Biophysics, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract

We describe the case of a 6-year-old boy with both fragile X syndrome and Robertsonian Translocation (45, XY, der (13; 22) (q10; q10)). This is the first reported case of a patient with fragile X syndrome with this Robertsonian translocation. Facial features and macroorchidism were consistent with fragile X syndrome. Cognitive impairment is more significant than in his sibling with fragile X syndrome, and the patient also has a prior diagnosis of autism spectrum disorder. We emphasize the challenges in his behavioral management and outline future directions for his management.

Keywords: fragile X syndrome, Robertsonian translocation, autism, genetics

Introduction

Fragile X syndrome (FXS) is the leading cause of intellectual disability. It occurs in approximately 1/7.150 males and 1/11.000 females [1]. FXS is caused by a CGG trinucleotide repeat of 200 repeats or greater (normal range is <55 repeats and 55–200 results in the pre-mutation), in the fragile X mental retardation gene (FMR-1) on the X chromosome, leading to low or absent levels of the fragile X mental retardation protein (FMRP) [2,3]. FMRP is involved in the regulation of synaptic development, plasticity, and seems to be involved in symptoms associated with autistic disorders. Reduced levels of FMRP in FXS have also been shown to disrupt signaling pathways of neurotransmitters implicated in autism [4]. The physical features include a long face, prominent ears, macrocephaly and macro-orchidism [5]. The behavioral phenotype includes intellectual disability. Autism spectrum disorder (ASD) is commonly diagnosed in patients with FXS [6]. A large number of chromosomal abnormalities have been reported in children with FXS, involving almost all chromosomes. Structural anomalies are common, and so are also balanced and non-balanced translocations [7]. Although Robertsonian translocations (RT) (13, 14) are often seen in autism spectrum disorders patients [8], a Robertsonian translocation (13, 22) associated with FXS has not yet been described. We describe the first case of a male with FXS and RT (13, 22), including clinical and behavioral characteristics.

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Address for correspondence: rachisan_andreea@yahoo.com

Case report

The patient is a 6-year-old Caucasian male patient. He was born with normal weight, via an uncomplicated vaginal delivery. Reviewing the early antecedents, he showed overall developmental delays: sitting at 12 months, walking independently at 2 years and delayed speech. At 5 years of age, he was diagnosed with autistic disorder based on DSM-IV criteria, and on admittance in our clinic he was following psychological counseling. His weight was at the 50th percentile and height at the 75th percentile. He had epicanthic folds, a low nasal bridge, macroglossia and a prominent chin. On genitourinary examination, he was Tanner stage II, with macroorchidism and a normal phallus. At presentation in our department, the diagnosis of FXS had not been established before. Due to his clinical features associated with mental disability, a karyotype analysis was required and also a genetic testing for FXS. The karyotype was performed on two parallel cultures of lymphocytes. Slides were stained using G banding technique (resolution bands: 450-550 bands). A total of 20 metaphases were evaluated and the analysis revealed a 45, XY, der (13; 22) (q10; q10) karyotype (Figure 1). For the FXS diagnosis, a genomic DNA was extracted from blood. The PCR and capillary electrophoresis was performed using primers. A number of 600 CGG repetitions in FMR1 gene were detected. He had a younger brother (4 years old) with similar phenotypical features and speech delay. We performed a karyotype analysis in his brother, showing normal result (46, XY) and genetic testing for FXS trinucleotide repeat expansion was positive (over 600 CGG repetitions in FMR1 gene).

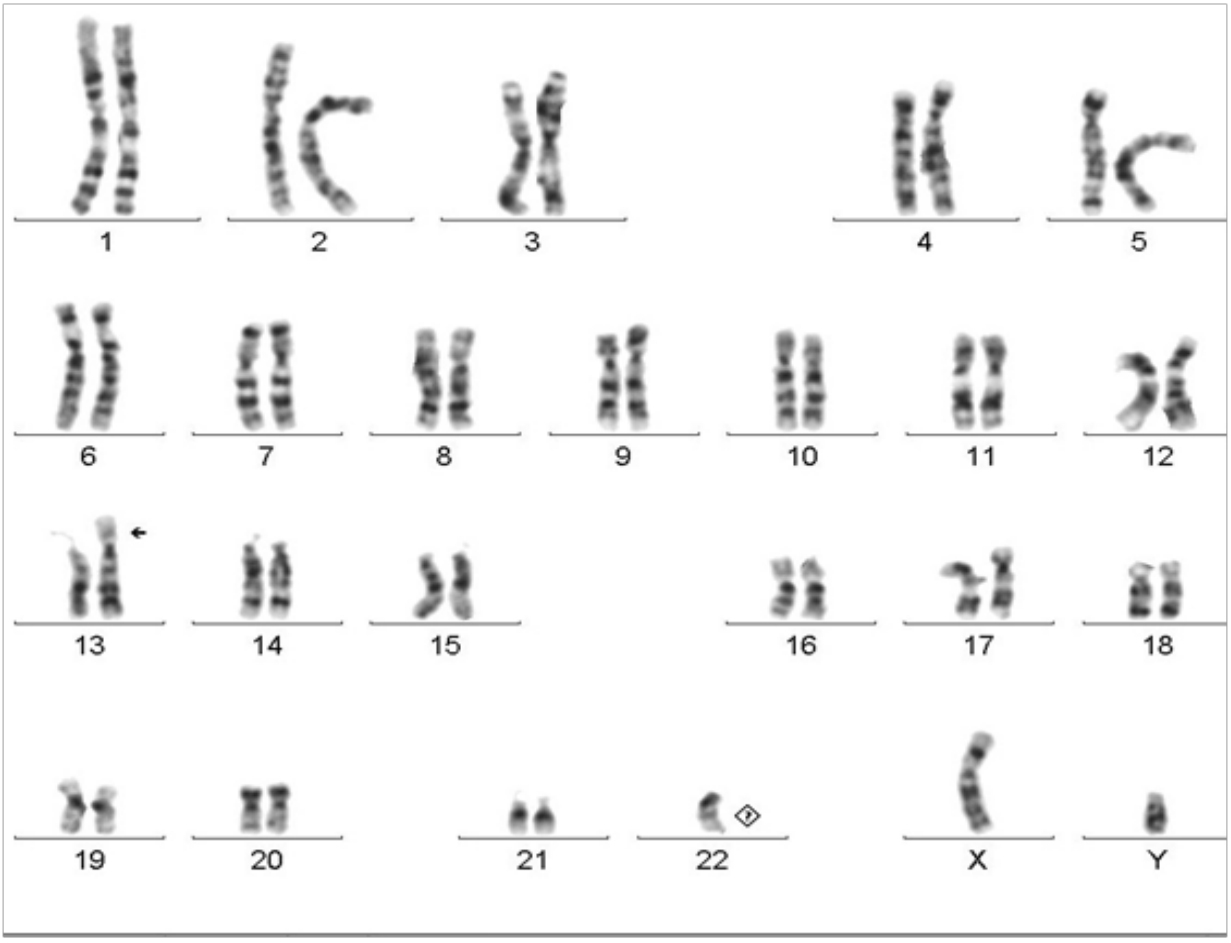

Figure 1. The Karyotype in the patient showing a 45, XY, der (13; 22) (q10; q10).

Discussion

This is the first reported case of a patient with both fragile X syndrome and Robertsonian translocation (13, 22). Knowing that FXS leads to distinct neurobiological and synaptic abnormalities, it seems consistent that an individual with FXS and RT would be more significantly affected than expected for each syndrome individually. Our patient has a sibling with FXS (without RT) without important behavioral impairments. Fragile X in combination with additional medical problems has been shown to increase the rate of ASD diagnosis among carriers of FXS mutations [9].

Most of the chromosomal aberrations seem to be unique and the relation to phenotype is not established. Balanced chromosomal anomalies occur in a low percentage of healthy individuals, estimated at approximately 1/2000 regarding reciprocal translocation and 1/10000 regarding a de novo inversion [10]. The American College of Medical Genetics recently recommended microarray as the first line evaluation for children with ASD and karyotype for fragile X as second line [11]. RT are the most usual structural chromosomal anomalies in humans and occur in approximately 1 to 1000 newborns [12]. RT involves the five acrocentric chromosomes (13, 14, 15, 21, and 22) which have very small short arms that contain no unique genes. A patient with RT can be a healthy individual, and may never discover its unusual chromosome rearrangement. Therefore, the translocation can exist in families for many generations.

This type of chromosomal rearrangement between chromosomes 13 and 22 has not yet been described in a patient with FXS. It is unclear to what degree the RT mutation contributes to the patient's unique behavioral phenotype. Recent evidence regarding the importance of the spatial organization of the genome ("3D genome") suggests that portions of the genome that are rich in regulatory and RNA coding elements might play a role in neurodevelopment and neuropsychiatric disease forming regulatory loops with other non-contiguous portions of the genome [13]. Arguably, chromosomal translocation disrupt this organization and interfere with gene expression that might be vital to normal development. Other clinical issues relating to RT are: affection of seminal vesicle and thus lower sperm count and/or aspermia. It also interferes with chromosomes segregation during meiosis I leading to the formation of unbalanced gametes with a high frequency of chromosomal abnormalities such as: Trisomy 13 or 22 and monosomy 13 or 22.

FXS is the most common cause of inherited intellectual disability [14]. Males with FXS present more severe psychological disabilities in comparison with females with the same syndrome, and frequently manifest behaviors from ASD [15]. Several other conditions are known to be important in children with FXS, such as: strabismus, recurrent ear infections, sleep disorders, gastrointestinal problems, seizures, and weight gain. The follow-up for these associated problems will depend on the severity and recurrence of symptomatology and whether treatment is implemented or not. These issues are summarized in Table I.

With a high priority, the relationship between behavioral symptoms and language, social impact and the daily living activities should be taken into account by the pediatrician caring for a child with FXS. Annual check-ups should use tools such as the Aberrant Behavior Checklist to examine changes in behaviors that are most problematic in children with FXS and ASD. It has been reported that FMR-1 pre-mutation carriers (CGG repeat length between 55 and 200) may evidence higher rates of ASD [17]. Findings suggest that ASD symptoms in patients with FXS worsen with age, thus having important implications for long-term intervention planning for these children. General cognition remains the most important consideration when examining the expressions of ASD phenotypes in FXS. Thus, behavior management is the most challenging aspect of care for such patients. New targeted treatment options are being developed for patients with FXS. The most promising treatment is the metabotropic glutamate receptor 5 (mGluR5) antagonists, which have been shown to be effective in mice by down regulating the mGluR5 pathway and therefore improving synaptic plasticity [18]. Patients might benefit from this future therapy, allowing for a reduction in abnormal behavior and creating the proper atmosphere for psychological interventions for these behavioral problems.

Table I. The clinical issues encountered in FXS patients *.
*After Sharon A. Kidd et al. in Fragile X Syndrome: A Review of Associated Medical Problems (Pediatrics 2014) [16].

Growth problems	Elevated risk for obesity and for having somewhat diminished height in adulthood.
Otitis media	Every infection or other otologic problems must be treated promptly and appropriately. Hearing testing may be considered if there is concern about a child's hearing.
Ocular disorders	Strabismus and other ocular disorders, such as refractive errors, are common in children with FXS. Regular ophthalmological follow-up should be considered.
Gastrointestinal problems	Frequent vomiting, feeding difficulties, constipation. Evaluation and treatment of should be similar with patients without FXS.
Seizures	Special attention should be given to children with FXS and ASD, because they seem to be particularly at risk for epilepsy.
Sleep problems	Behavioral or medical treatment or a referral to a sleep specialist may be warranted.

The FXS with RT is a very rare genetic association.

The better understanding of the cognitive, behavioral, and psychopathological profiles of children with genetic syndromes and with distinct forms of ASD can put together the strategies for the rehabilitation of these individuals. Indeed, there is a complex relationship between genes, brain development and manifestation of a behavioral and psychopathological pathology.

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