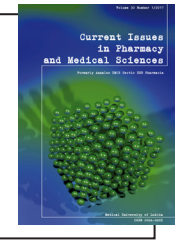
DOI: 10.1515/cipms-2017-0006 Curr. Issues Pharm. Med. Sci., Vol. 30, No. 1, Pages 27-30

Current Issues in Pharmacy and Medical Sciences

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: http://www.curipms.umlub.pl/



Fragile X syndrome – a common disease rarely diagnosed

Malgorzata Zofia Lisik

Department of Molecular Biology and Genetics Medical University of Silesia in Katowice, Medykow 18, 40-752 Katowice.

ARTICLE INFO

Received 26 October 2016
Accepted 22 December 2017

Keywords:
Fragile X syndrome,
full mutation,
intellectual disability.

ABSTRACT

Fragile X syndrome (FXS) is a single-gene disorder with a broad spectrum of involvement, including cognitive and behavioural impairments of varying degrees with specific physical features and with strong association with autism. The study was conducted on 23 males (10-32 years old) who had full mutation in the *FMR1* gene. A complete medical evaluation, including medical history, family history, psychological testing and physical examination was conducted on each subject. Three of the FXS patients (13%) were isolated cases of mental retardation in the family. The remaining 20 FXS patients belonged to 15 families, where there were other mentally retarded family members present. The degree of mental retardation (MR) varied. Mild MR was diagnosed in 1/23 (4.35%), moderate MR in 12/23 (52.17%), severe MR in 10/23 (43.48 %). Moreover, autism spectrum disorder was diagnosed in 5/23 (21.74%) FXS patients. Analysis of the BMI showed that in FXS patients, 14 of 23 (60.68%) had too high body weight – 9/23 (39.13%) were overweight and 5/23 (21.74%) were obese. The diagnosis of FXS is difficult because of nonspecific symptoms, yet early diagnosis is crucial for early intervention and genetic counseling. The risk of recurrence is 50%.

INTRODUCTION

Fragile X syndrome (FXS) (OMIM#300624) is an X-linked dominant disorder and the most common inherited cause of intellectual disability (ID). This disorder is associated with the unstable expansion of a CGG-repeat in the 5'-untranslated region of the FMR1 gene. Almost all individuals with fragile X syndrome (99%) are the carriers of so-called full mutation (FM), herein, the CGG repeat length exceeds 200. Moreover, the promoter region of the *FMR1* gene, including the CGG-repeat, is methylated and the *FMR1* gene is not transcribed. Fragile X syndrome originates from a lack of the protein product of the *FMR1* gene – FMRP [3]. FMRP typically plays a role of translation suppressor that is involved in synaptic plasticity through regulating local protein synthesis of specific mRNA's in response to synaptic stimulation [8]. The estimated frequencies of individuals with the FM allele in the total population are approximately 1:7000 for males [11].

The spectrum of involvement in fragile X syndrome is broad, including not only intellectual disability, but also learning disabilities and psychiatric problems. The most severely affected patients often have autism and are not verbal [7].

* **Corresponding author**
e-mail: mlisik@sum.edu.pl
phone/fax: 32 208 83 82

The variability and subtlety of clinical manifestations may cause problems with diagnosis in childhood, but physical appearance markers may become more apparent with advancing age [15].

Of note, the afflicted frequently have a normal physical appearance. Indeed, the most striking finding being just how 'normal' they look. However, the classic triad of physical characteristic in the FXS consists of a long narrow face, large or prominent ears and macroorchidism. Specific behavior characteristics include hyperactivity, deficit in attention, emotional liability, social anxiety, gaze aversion tantrums, stereotypic behavior like hand flapping and hand biting. Avoidance of eye contact is one of the characteristic features for FXS [7,15]. Around 25 to 35% of the FXS patients also meet the diagnostic criteria for autism.

The nonspecific nature of associated developmental, emotional and behavioral challenges, hence, may be misinterpreted as having psychosocial causes [14]. Fragile X syndrome thus remains inadequately recognized and understood. Consequently, only a small percentage of individuals having FXS have been diagnosed [12]. The increased awareness and early diagnosis should, therefore, lead to earlier intervention, not only for the child but for the whole family, as the family should be involved in genetic counseling [12].

In this paper, various medical aspects of fragile X phenotype in a group of males FXS with full mutation were

analyzed, and the results were compared to data from literature.

MATERIALS AND METHODS

The study was conducted at the Department of Molecular Biology and Genetics, Silesian Medical University School of Medicine in Katowice. The study population consists of 23 male patients from 18 families, 10-32 years old, mean age 19,3 ± 6,6, affected by Fragile X syndrome, confirmed by detection of full mutation in the *FMR1* gene (Rousseau *et al.*). They were recruited through registry databases maintained by Medical University of Silesia, Upper Silesia Center of the Children's Health John Paul II in Katowice. All participants harboured the "full mutation" form of the *FMR1* gene. The study protocols were approved by the local Ethical Committee of the Faculty of Medicine, Medical University of Silesia in Katowice. In addition, an informed written parental/legal guardian consent was obtained from parents/legal guardians of the studied subjects.

A complete medical evaluation, including medical history, family history, psychological testing and physical examination were conducted on each subject. The Fragile X subjects were evaluated by way of a general questionnaire filled out by their parents, which included demographic, medical (history and current state), and educational history. In addition, the questionnaire included a checklist table of various developmental and functional domains, such as language, nonverbal communication (eye contact), motor (sitting, walking), attention, hyperactivity, social interaction and sleep patterns.

Anthropometric measurements included height and weight. The Body Mass Index (BMI) was used because of the heterogeneity of age of the patients. BMI was calculated using formula: BMI = body mass (kg)/height^2 (m^2).

Intellectual functioning was assessed by the Intelligence Tests appropriate for chronological age. The patients were then placed within four groups based on IQ and degree of social adjustment:

1. Mild intellectual disability (IQ = 68-52).
2. Moderate intellectual disability (IQ = 51-36).
3. Severe intellectual disability (IQ = 35-20).
4. Profound intellectual disability (IQ = 0-19).

Autism spectrum disorder was diagnosed based on the presence of abnormalities in social and communication development, through marked repetitive behaviour and limited imagination by using the Diagnostic and Statistical Manual for Mental Disorders-IV (DSM-IV) criteria.

RESULTS

Pedigree analysis. The FXS patients belonged to 18 families. Three of them (13%) were isolated cases of mental retardation in the family. The remaining 20 FXS patients belonged to 15 families where there were other mentally retarded family members (brothers of propositus (13), maternal brother (2), maternal sister with mentally retarded son (5)). More than one affected sibling was determined in 7/18 of the families. In all, 6 families had 2 affected children, 1 family had 4 affected children. The pedigree analyses showed typical X-linked patterns of inheritance.

Psychological tests. While all of the FXS patients were classed as intellectually disabled, the level of MR differed. Mild intellectual disability was diagnosed in 1 FXS patient 1/23 (4.35%), moderate mental retardation was diagnosed in 12 FXS patients 12/23 (52,17%), severe mental retardation was diagnosed in 10/23 FXS patients (43.48 %).

Using the DSM-IV-TR criteria, autism spectrum disorder was diagnosed in 5/23 (21.74%) of all the FXS patients. The most frequent behavioral symptoms seen were hyperactivity and short attention span (observed in 20/23 (86.96%)). The other behavioral problems observed included: anxiety: 14/23 (60.87%), eye contact avoidance: 14/23 (60.87%), emotional liability 12/23: (52.17%), auto-aggression: 11/23 (47,83%), stereotypic movements of hands: 7/23 (30.43%).

Birth weight in these FXS patients ranged from 2350 to 4000 grams (mean 3577 grams), birth length: 48-60 cm (mean 55.91 cm), birth head circumference: 31-37 cm (mean 34.07 cm), Apgar scores: 4-10 (mean 9.18).

Psychomotor development was delayed in the majority of these FXS patients. They sat at 6-12 months (mean 8.6) and walked at 12-21 months (mean 15.1). The most disturbed was speech development. Only 2/23 (8.7%) actively used speech, 9/23 (39.1%) built simple sentences and utilized echolalia, 10/23 (43.48%) used simple words, and 2/23 (8.7%) used mime and gesture to communicate, they did not use active speech.

Physical examination

Analysis of the BMI showed that in these FXS patients, 14 of 23 (60.68%) had too high body weight, 9/23 (39.13%) were over-weight and 5/23 (21.74%) were obese.

Dysmorphological investigation showed the presence of phenotypic features specific for fragile X syndrome in form of elongated face and large protruding ears in all these FXS patients, while macroorchidism was present in 17/23 of the total. Moreover, eye problems were present in 8/23 (34.78%) of the total test patients. This was in the form of myopia in 3/23 (13.04%), hyperopia in 2/23 (8.69%), stabismus in 2/23 (8.69%) and astigmatism in 1/23 (4.34%).

DISCUSSION

In my study group, all of patients with FXS were mentally retarded. Of these, only one (4.35%) was classed as being mildly mentally retarded, while moderate or severe degree of mental retardation was diagnosed in 22 of 23 patients (95.65%).

Males with FXS typically display intellectual disability that can range from mild to severe. Their IQs tend to decline with age during childhood, and this is not the result of regression, but rather the failure to keep pace with the normal rate of intellectual development [10]. Intellectual functioning is defined as IQ. This assessment is obtained through standardized, individually administered intelligence tests [10]. A major limitation of these tests is that they do not typically measure IQ below 40 or 50 [10], and previous observations in the literature have reported that only 15% of all males with FXS have IQ greater than or equal to

70% [7]. Substantial and meaningful variability in performance of lower functioning individuals is, hence, lost in the standardization of raw scores. Hence, the use of IQ tests in lower functioning individuals may lead to poorer estimates of true level of cognitive ability and potential and obscure significant relative strengths and weaknesses [10].

Five out of 23 patients (21.74%) were diagnosed with ASD according to DSM-IV. This finding correlates with data from published clinical studies implying that 25-38% of all affected individuals with FXS, also fulfill the diagnostic criteria for autism [5,8]. Hence, my observed frequency is in agreement with data from publications (5% to 60%). Co-occurrence of FXS and ASD is an additional risk factor in regard to central nervous system anomalies [6,9].

There are problems in generating a correct early diagnosis of Fragile X syndrome. The symptoms of the disease are not especially specific in the first months and years of life, so it is very difficult to make a correct diagnosis. In addition, physical features are sufficiently variable that they cannot be used as indicators of who should be screened. The most characteristic, but not specific symptom of the disease is delayed speech development. In the FXS study group, only 2/23 (8.7%) of all patients actively used speech, 9/23 (39.1%) built simple sentences, 10/23 (43.48%) used simple words, and 2/23 (8.7%) used mime and gesture to communicate, they did not use active speech. Affected males most commonly come to medical concern because of language delay. A majority of affected children start to build simple sentences at the age of 4 to 5 years, but the speech is usually difficult to understand. What is more, some patients do not use active speech, they communicate using gesture and mime. This communication is often accompanied by associated behavioral problems due to frustration [7,9,15].

Fragile X syndrome is the most common identifiable single gene cause of intellectual disability and autism, and affected patients show a specific behavioral phenotype. Typically, the psychiatric profile involves behavioral and cognitive symptoms, and includes hyperactivity, attention problems, anxiety, mood liability, aggression, self-injury, poor eye contact, self-talk, hand flapping, hand biting, as well as perseverative language [2,4,5]. Affected males with FXS are also at increased risk of experiencing life-related psychiatric problems such as anxiety, depression and loneliness [6]. In my study, the presence of autism spectrum disorder was an important marker of independency. The patients with FXS and ASD were not able to live alone, they needed the help of other family members [2].

In my analysis of the pedigrees of our FXS patients-subjects, we noted that only 3/23 (13.04%) of them were an isolated case of mental retardation within the family. The remaining 20 FXS patients had other relatives with MR. The pedigrees also showed the typical X-linked type of inheritance, affecting males from the maternal side of the family. In contrast, published data shows that up to 30% of the families affected with FXS are isolated cases of the disease [3]. Fragile X syndrome is the most common familial form of mental retardation, but lack of other affected family members does not exclude the diagnosis of the disease. Testing for fragile X mutation is a part of the basic genetic assessment in the case of males who present developmental delay, or display mental disabilities and/or behavioral problems [13].

Early diagnosis of FXS is crucial for important reasons. Among these are the right of the individual and family to know the cause and nature of the child's problems, relief from uncertainty, facilitation of grief resolution, focusing on the future, genetic counseling and early instigation of appropriate interventions [9,13].

Diagnosis of FXS involves not only the affected person, but also has potential consequences for other family members who belong to many generations. This is because many family members may be affected with lesser or greater degrees of mental retardation or other Fragile X-associated disorders (FXDs) (Fragile X-associated primary ovarian insufficiency, Fragile X-associated tremor/ataxia syndrome) that all caused by changes in the *FMR1* gene [9,13].

In my work, the analysis of the patient's age at the time of diagnosis of Fragile X syndrome showed a mean of 8.86 years of age (the youngest was 3 years old and the oldest was 18 years old). In contrast, Bailey *et al.* [1] reported an average age of diagnosis around 3 years and no change in the age of diagnosis over 7-year period. Due to this late diagnosis, 25 % of affected families had a second child with FXS before a proper diagnosis was made in the first one.

Late diagnosis of FXS, a genetic disease with a risk of recurrence as high as 50%, has, hence, brought about a situation in that parents had another child or children with the disease, before cold recognition of an FXS situation was realized. The parents, thus, did not have possibility of limiting procreation. Moreover, the lack of the correct diagnosis makes it impossible to involve the afflicted child in early intervention programs in which appropriate management strategies could have maximized the child's potential [9]. It must, hence, be underlined that identification of a child with FXS in infancy is crucial because of higher brain plasticity in the early stage of life (this being highest during the first two years of life), and prognosis may be much better in a case of FXS with therapeutic intervention in infancy [12].

CONCLUSIONS

Fragile X syndrome is the common form of mental retardation, and the diagnosis is difficult because of nonspecific symptoms. Early diagnosis, however, is crucial for early intervention and genetic counseling. The risk of recurrence is 50%.

ACKNOWLEDGMENTS

I thank the boys and young men with fragile X syndrome and their families for their participation and generous time and effort.

This research was in part financed from Institutional grant (KNW-1-070/K/6/0) awarded to MZL.

DECLARATION OF CONFLICTING INTERESTS

The author declared no potential conflicts of interests.

REFERENCES

1. Bailey D.B. et al.: No change in the age of diagnosis for fragile X syndrome: findings from a national parent survey. *Pediatrics*, 124, 527, 2009.
2. Bailey D.B., Raspa M., Olmsted M.G.: Using a parental survey to advance knowledge about the nature and consequences of Fragile X syndrome. *A.J.I.D.D.,* 115, 447, 2010.
3. Chonchaiya W., Schneider A., Hagerman R.J.: Fragile X: a family of disorders. *Adv. Pediatr.*, 56, 165, 2009.
4. Cornish K., Turk J., Levitas A.: Fragile X syndrome and autism: common developmental pathways? *Current. Pediatrics. Reviews*., 3, 61, 2007.
5. De Rubeis S., Bagni C.: Regulation of molecular pathways in the Fragile X syndrome: insights into Autism Spectrum Disorders. *J. Neurodevelop. Disord.,* 3, 257, 2011.
6. Gabis L.V. et al.: Psychiatric and autistic comorbidity in Fragile X syndrome across ages. *J. Child. Neurol*., 26, 940, 2011.
7. Hagerman R.J. (2002). The physical and behavioral phenotype. In: *Fragile X syndrome: Diagnosis, Treatment and Research*. Hagerman R.J., Cronister A., (editors). Baltimore, MD: Johns Hopkins University Press. p.3.
8. Hagerman R.J.: Lessons from fragile X syndrome regarding neurobiology, autism and neurodegeneration. *J. Dev. Behav. Pediatr.*, 27, 63, 2006.
9. Hersh J.H., Saul R.A., COMMITTEE ON GENETICS.: Clinical report – health supervision for children with fragile X syndrome. *Pediatrics,* 127, 994, 2011.
10. Hessl D. et al.: A solution to limitations of cognitive testing in children with intellectual disabilities: the case of fragile X syndrome. *J. Neurodev. Disord.,* 1, 33, 2009.
11. Hunter J. et al.: Epidemiology of FXS: a systemic review and meta-analysis. *Am. J. Med. Genet*., 164, 1648, 2014.
12. Johnson V.A.T.: Assessment of FMR1 gene mutation at-risk status in young children. *Newborn & Infant Nursing Reviews*, 8,10,2008.
13. McConkie-Rosell A., Finucane B., Cronister A.: Genetic counseling for fragile X syndrome: updated recommendations of the National Society of Genetic Counselors. *J. Genet. Counsel*., 4, 249, 2005.
14. Turk J.: Fragile X syndrome: lifespan developmental implications for those without as well as with intellectual disability. *Curr. Opin. Psychiatry*, 24, 387, 2011.
15. Visootsak J. et al.: Fragile X syndrome; an update and review for the primary Pediatrician. *Clin. Pediatr. (Phila),* 44, 371, 2005.