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FRAGILE X SYNDROME

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ABSTRACT

Fragile X Syndrome (FXS) is a heritable ailment associated with the FMR1 gene mutation that results in a range of features including but not limited to cognitive impairment, disorganized behavior, and somatic deformities. This article intends to give a summary and the latest insight on FXS concerning its pathophysiology, the therapies associated with it, and how it affects the human body on the genetic and proteomic scales. The worldwide and Indian estimates are reviewed, along with the differences by age groups the mortality rates, and the primary epidemiological data on the spread of FXS. Also, the article aims to analyze modern approaches to the treatment of FX, including drug therapy, psychotherapy, and physiotherapy. This review seeks to consolidate knowledge on FXS and support the necessity for advanced research attention and better therapeutic strategies.

KEYWORDS: Fragile X Syndrome, FMR1 gene, intellectual disability, FMRP protein, autism spectrum disorder, trinucleotide repeat, genetic mutation, behavioral symptoms, developmental delay, genetic counseling, molecular diagnosis, CGG expansion, neurodevelopmental disorder, early intervention.

INTRODUCTION

Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability, often showing up as an autism spectrum disorder. It affects about 1 in 4,000 males and 1 in 6,000 females. FXS is an X-linked genetic condition, which means it is passed down through the X chromosome. What makes it unique is its inheritance pattern, where the severity of the

disorder tends to increase with each generation.[1] fragile x syndrome is most commonly inherited from mental retardation and the x- linked caused by expansions of a CGG repeat in the 5-untranslated [UTR] region of the FMR1 gene that arises meiotic instability of contain 200 or more copies of the repeat that are hypermethylated and transcriptional silenced.[2] Fragile X syndrome (FXS) is a genetic condition that is passed down through the X chromosome and was first described in 1943 by Martin and Bell.[3] Difficulties in Fragile X Syndrome (i) Anxiety (ii) Hyperactivity (iii) Attention problem (iv) Anger or aggression problem (v) Mood swings (vi) Difficulty swallowing a pill.[4] It also causes seizure.[5]

Prevalence: For every two males with fragile X syndrome (FXS), there is one diagnosed female. Since women possess two X chromosomes, they often display less severe manifestations of FXS than men do. The frequency of FXS carriers is high in the population, approximately 1 out of every 150-300 females and 1 out of every 400-850 males, which indicates the widespread presence of the FMR1 mutation. As shown in Fig. no. 1 prevalence among adults with Fragile X Syndrome, adapted from Hartley et al.[6]

Findings in India: In India, the search for patients with Fragile X Syndrome (FXS) has been conducted in several regions, with studies reporting a wide variation of prevalence rates (2.54 – 12.24%) within the population of people with intellectual disability. For instance, Calcutta showed 7.14% while UP had 2.54% and 10% rates. 10.34% was manifested in Tamil Nadu, and studies within the general population showed that 1 in 353 women had FMR1 premutation. These results suggest that a nationwide FXS screening program should be implemented since there are large amounts of incomplete data which highlights the necessity of improving healthcare research initiatives and diagnostic accuracy all over the country.[7]

PATHOPHYSIOLOGY

Neurological and behavioral issues in FXS

Visual Motor Dysfunction: In cases of FXS, the absence of FMRP is particularly detrimental to the development of the visual cortex. Normally, mGluR5 is essential for ocular dominance plasticity, and a deficit of 50% in mGluR5 following monocular deprivation is considered plasticity.

However, in Fmr1 knockout (KO) mice the absence of FMRP results in altered plasticity of ocular dominance which has a tendency in the depressed responses of the deprived-eye to

open-eye response. This suggests that normally, FMRP helps to control the amount of plasticity that occurs in the visual cortex.

Additionally, FMRP is vital for dendritic spine maturation and pruning. In the absence of FMRP, neurons exhibit immature dendritic spines, a feature seen in both Fmr1 KO mice and individuals with FXS. This spine immaturity, possibly linked to mGluR5 overactivation, results in altered visual circuit development, which may contribute to impaired visual processing in FXS.[8]

Neuropathology: Brain MRI of individuals with Fragile X Syndrome (FXS) reveals an increase in the size of the caudate nucleus and lateral ventricles as well as a decrease in the size of the cerebellar vermis. These observations have been noted from early childhood. Gray matter in the frontal and temporal regions decreases while it increases in the parietal and occipital regions. In white matter, some specific cranial tracts have increased in volume while the left frontal and cerebellar areas have decreased in volume. There is a peak in cognitive decline during the adolescence period. Changes in the amygdala and hippocampus that accompany depression later are observed with the structural alterations. FMR1 knockout mice do not show these changes in the regional anatomy of FXS, therefore they do not fully represent FXS in the human condition.[9]

Symptoms resembling autism in children with fragile x syndrome (FXS): A study of behavioral phenotype: This research analyzes the possibility of the existence of autism-related activities in young kids who have been diagnosed with fragile x syndrome (FXS). The researchers investigated behavioral features in 24 children with FXS aged 21 to 48 months and did so with two comparison groups comprising of: 27 children with Autism (AD) 23 children with Other Developmental Delay (DD) Principal results Two distinct subgroups of children with FXS were identified Non Autistic FXS Subgroup (n= 16, 67%) This group of children did not meet the criteria for an autism diagnosis .Their behavioral and developmental profile was akin to that of children with other developmental delay (DD) FXS with features of fautism (n = 8, 33%) This group did meet the criteria for an autism diagnosis based upon criteria standardized for assessment of autism Their behavioral development profiles matched that of the children diagnosed with autism.[10]

Disease overview: FXS is a syndrome associated with the malfunctioning development of the brain and is the most prevalent genetically passed down illness caused by a disability. It

occurs due to an alteration of the FMR1 gene which causes a lack of FMRP, a key protein for several brain processes. Behavioral problems such as autism, anxiety, aggression, and hyperactivity are common with FXS patients. Current research is centered around the impact of FMRP loss on protein of additional components production. There are, however, reasons for believing that some of its other, less explored, functions could also be crucial. Such knowledge may enable understanding of FXS physiopathology and provide alternative avenues to medicational therapies.[11]

THERAPIES ASSOCIATED WITH FRAGILE X SYNDROME

Insuline and insulin - like growth factor 1 pathway: Metformin is a first-line therapy for type 2 diabetes as it inhibits mitochondrial respiratory chain complex I, decreasing glucose production in the liver. It has also shown beneficial effects beyond diabetes, such as in polycystic ovary syndrome, hepatic steatosis, and some vascular conditions. Other new diabetes research focuses on the use of metformin for cancer, gestational diabetes, and precision medicine by employing genomic profiling. In a surprising twist, the reach of metformin expands to the realm of neurodevelopmental disorders such as Fragile X Syndrome (FXS). This is because of its insulin-sensitizing action and the control of mTORC1 and ERK which directly or indirectly govern cognition. Certain research on FXS models shows that it can improve deficits in memory along with the management of obesity, which is associated with comorbidity in patients with FXS. Together with other growth factors, it has been recognized that the Insulin-Like Growth Factor 1 (IGF-1) which is vital for the development of neurons can be used as a target for the treatment. So, for example, the administration of trofinetide, an IGF-1 action enhancer, improves social interaction, active learning, and anxiety reduction among FXS patients. These findings suggest that the intersection of metabolic disorders and neurodevelopmental disorders can be more easily understood when the maturing growth factor system is used.[12,13]

Behavioral therapy

FXS is the most common inherited syndrome causing intellectual disability and is due to a mutation on the X chromosome that results in absent FMRP. Most treatment strategies center around treating the disease's cellular ramifications through medication, although there is increased advocacy for therapies geared toward modifying behavior. People with FXS often demonstrate traits associated with ASD and ADHD, including anxiousness, hyperactivity, and difficulties interacting with others. Functional analyses show that many of these

challenging behaviors serve a purpose in the context of basic operant functions, such as escaping a given demand or being actively sought after. While there is limited literature on the direct effects of FXS and behavioral therapy-based treatments, studies indicate some form of environmental control exists suggesting some degree of non-drug intervention would be efficient. Behavioral treatments for ASD and intellectual disabilities highlight the need for integrated pharmacological and behavioral approaches. An individual, multidisciplinary treatment strategy enhances the behavioral and overall living standards of individuals with FXS.[14,15]

Physical therapy

The implementation of physical exercises proved useful in alleviating symptoms within individuals diagnosed with autism spectrum disorder (ASD). This condition shares overlapping features with Fragile X Syndrome (FXS) and includes associated motor deficits as well as socially complex stereotypic behaviors. People with ASD characteristically have mobility difficulties with gait and rhythmical postures, as well as range of motion at joints. These problems can be aggravated by low levels of available physical activity. Structured exercise programs, including those with games and aerobics, have been shown to enhance mobility, cognition, sensory integration, and even scholastic achievement. There are also some short-term improvements in maladaptive and stereotypical behaviors, sleep, and some aspects of health such as BMI, muscular strength, and even endurance. The focus of these studies is on ASD, and while those with FXS may benefit differently due to shared behavioral characteristics, these findings warrant further investigation into the outcomes of exercise-based therapies. As such, the inclusion of physical therapeutic measures may positively influence behavioral control and physiological growth in the population, justifying broader application and more comprehensive studies into treatments designed specifically for this demographic.[16]

IMPACT OF FXS

On body process

Fmr1-Deficient Mice Show Increased Activity Levels Asso-ciated with hyperactivity and change in locomotor functions to body composition and bone structure, Fragile X Syndrome (FXS) seems to have its impact on these parts of the body). Research conducted on Fmr1-KO mouse models suggests that these mice show increased physical activity similar to that of exercise induced mice. Fmr1-KO mice spend significantly more time than WT (wild-type)

mice in locomotors (exhibiting greater distance traveled, rotations, and center entries) functions in open field tests. Recorded parameters in Actimetry chambers also show enhanced hyperactivity as increased nocturnal locomotor activity has been observed. These results underline that Fmr1-deficiency has an impact on movement behavior which is likely to influence bone health, metabolism and body composition in FXS.[17]

On protein

The silencing of the FMR1 gene leads to Fragile X Syndrome (FXS). This, in turn, leads to loss or dysfunction of Fragile X Mental Retardation Protein (FMRP)—the sole multifunctional nerve plasticity, protein synthesis, and neuron activity controller. Loss of FMRP due to FMR1 gene silencing results in unregulated mRNA translation, deficient synaptic equilibrium, and loss of cognitive functions. The absence of FMRP dysregulates plasticity-associated proteins leading to the incapacity of building neuronal connections and proper synaptic functioning. Crucial steps in cognition like mGluR5 signaling, GABAergic pathway communication, and even chromatin structure modulation are done by FMRP. The lack of FMRP hyperactivates augments mGluR5-dependent translation and disrupts the resting state balance of synapses-I which worsens neurological impacts. FMRP's role as RNA translation supervisor further ties FXS with Schizophrenia and Prader-Wili Syndrome. In-depth studies on FMR1-knockout mice demonstrate amplified GABAergic signaling deficits of FMRP which accentuate its position within neural control. Targeting the right treatment for FXS requires a deep understanding of these systems and their interdependencies considering the cognitive and synaptic deficits FXS exposes.[18,19]

On gene

Fragile X Syndrome (FXS) is the most prevalent genetically passed form of intellectual disability, due to increasing CGG trinucleotide repeats in the FMR1 gene located on the X chromosome. Exceeding repetitions (>200 repeats) leads to the silencing of the gene through methylation which results in loss of FMRP, a protein the brain develops. Premutation alleles (55–200 repeats) are unstable during maternal transmission and particularly pose risks when CGG repeat sequences are greater than 99. There's also mutation potential in gray-zone alleles (45–54 repeats). Lesser likelihood of expansion occurs with AGG interruptions within CGG repeats. X-linked dominant inheritance causes these features to be more severe in sons than daughters, as females are buffered by X-inactivation. Around 20-40% display mosaicism and can cause milder symptoms. Symptoms of this condition can include intellectual

disability, traits of autism, symptoms of ADHD, anxiety, and distinctive physical features of a person. With the advancement of molecular diagnostics such as PCR and Southern blot, detection, assessment of carrier risks have become more accessible which strengthens the benefits of genetic counseling and family planning.[20,21]

TREATMENT FOR FXS

Targeted mGluR5 signaling in FXS

The lack of FMRP (Fragile X Mental Retardation Protein) results in an impairment of mGluR5 signaling which, in turn, interacts with FXS synaptic and behavioral deficits. Various mGluR5 antagonists have been used to target the mGluR5 pathway. Such mGluR5 antagonists include MPEP, fenobam, AFQ056, and STX107 which, in preclinical models of FXS, were effective toward AMPA receptor internalization, seizures, hyperactive behavior, and memory loss. Supporting evidence includes the observation that mGluR5 downregulation on fmr1 knock-out mice enhances their cognitive, neurological, and physical deficits. The efficacy of the proposed strategy is further elucidated with genetic interventions. Concerning mGluR1 blockers, while their use might yield some beneficial results, the adverse effects are worrisome. Collectively, evidence from mGluR5 antagonists as well as genetic mGluR5 approaches on fmr1 KO mice emphasizes the need for investigating mGluR5 modulation as a therapeutic target in FXS. Still, MPEP's action on restoring synaptic impairment indicates activity but does suggest the need for confirming the safety profile and enduring benefits in human studies. These findings advance support to the FXS "mGluR theory" while simultaneously pointing out the necessity of further evaluation of receptor-specific focal Points in drug treatments.[22]

Sertraline

Sertraline, a selective serotonin reuptake inhibitor (SSRI), is increasingly used to treat Fragile X Syndrome (FXS), particularly in young children showing early signs of anxiety and developmental delays. Children with FXS often have impaired serotonin production, supporting the targeted use of SSRIs. Retrospective studies and a controlled trial have shown that low-dose sertraline (2.5–5.0 mg/day) may improve developmental outcomes, including receptive and expressive language, fine motor skills, and visual perception. Although primary language outcomes in a controlled trial were not statistically significant, secondary and subgroup analyses revealed benefits, especially in children with comorbid autism spectrum disorder (ASD). The Passive Viewing Eye Tracking (PVET) task further demonstrated

receptive language improvement, suggesting higher sensitivity than standard measures. Sertraline is now commonly used in FXS to reduce anxiety and enhance early developmental progress.[23]

Insuline like growth factor 1

Neurotrophic factors like IGF-1 are essential to CNS development, and they are involved in neuronal growth, survival, and migration. IGF-1 is a 70-amino-acid polypeptide and functions as an endocrine, paracrine, and autocrine hormone. It is expressed spatially and temporally in the CNS, and its greatest activity is in early brain development, with support of synaptogenesis and neuroplasticity. Its level decreases in adult life and becomes liver-regulated through growth hormone. IGF-1's roles during development render it a candidate for the treatment of neurodevelopmental disorders such as Fragile X Syndrome, in which it is likely to restore cognitive and synaptic function. Recent research validates IGF-1 and analogs as therapeutic agents for such conditions.[24]

Ampakine

mGluR signaling has been the main cardinal point of intervention for FXS treatment while reduced AMPA receptor activity and incomplete long-term potentiation also present plausible therapeutic approaches. Behavior and cognition enhancement trials with the ampakine CX516 were negative, probably because of low potency and sub-therapeutic dosing. Some benefits were noted, but not as pronounced, for subjects on antipsychotic medications. Perhaps other phosphodiesterase inhibitors that augment BDNF levels would be more beneficial. Increased effectiveness in those other compounds might be due to enhanced BDNF production. Lauterborn et al. showed that BDNF reversed LTP deficits in fmr1-knockout mice hippocampus, which suggests that potent but low-dose BLT-like compounds tailored to increase BDNF would be important therapeutic agents for treating synaptic plasticity lesions in FXS.[25]

PREVALENCE

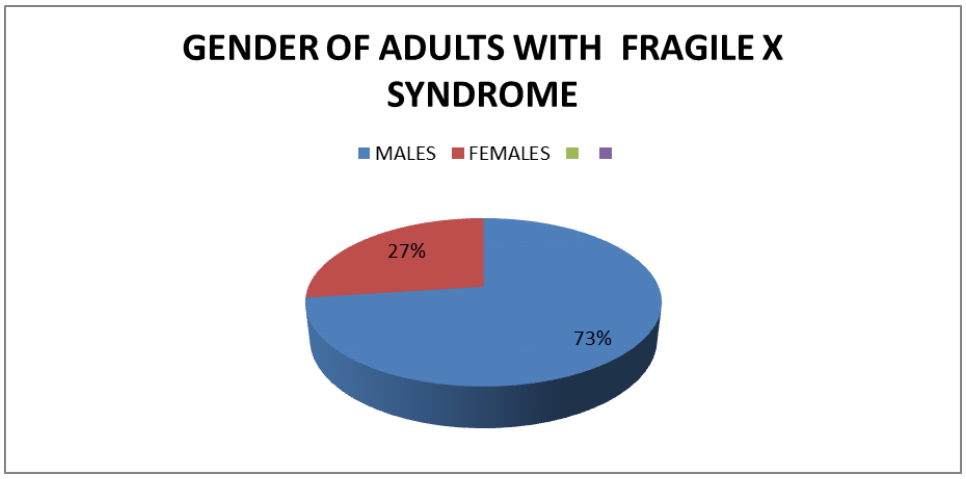

Figure No. 1: Prevalence of Fragile X Syndrome among adults. Adapted from Hartley et al.[26]

Mortality rate

The research involving 348 men and 433 women with or having the Fragile X Syndrome gene showed that their life expectancy is 12 years lower than the average for the general population. Nevertheless, this might represent ascertainment bias, perhaps because of selective reporting or how participants were picked for the study.[27]

CONCLUSION

Fragile X Syndrome (FXS) is a malfunction of the FMR1 gene leading to the lack or underproduction of the Fragile X Mental Retardation Protein (FMRP), which is necessary for proper brain development. FXS is the most common inherited cause of intellectual disability and is closely related to features seen in autism spectrum disorders. Symptoms usually start in early childhood and can be mild to moderate. Genetic testing allows early diagnosis which can assist in better managing the condition. Family participation as well as help from behavioral and educational professionals are important parts of care. Even if no cure is available, this condition can be better managed, and the lives of these individuals can be made more adaptive through focused therapies, educational assistance, or medications.

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