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Fragile X Syndrome

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FRAGILE X SYNDROME

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Abstract

Fragile X syndrome is of rising maternal public health concern. Fragile x syndrome is an inherited form of learning disability which was discovered in the late 1970s. It was discovered by cytogenetic detection of an associated fragile site on the X chromosome. Fragile x syndrome makes clinical diagnosis difficult as it is associated with subtle physical features and few medical problems. There is no known cure, and treatment plans consisting of behavioral interventions are the most effective for living with fragile x syndrome. Future better future treatment care plans, there needs to be in-depth research surrounding the social determinants of health fa1919ctors, which can affect a person who has fragile x syndrome. As well as how having fragile x syndrome makes one more vulnerable to other chronic illnesses.
Background:

Fragile X syndrome is one of the most commonly known inherited causes of intellectual disabilities. Both males and females who have fragile x syndrome exhibit a wide range of intellectual ability and may have various degrees of behavioral, emotional, social, and learning difficulties. “In 1991, the gene responsible for FXS was identified on the X chromosome and named fragile x mental retardation 1 (FMR1 gene)” (3). By definition, Fragile X syndrome is a genetic disorder, which means there are changes to the genes in a person. Fragile X syndrome is caused by a change in the fragile x mental retardation 1 (FMR1) gene. Fragile X syndrome and fragile x syndrome-associated disorders are caused by a trinucleotide repeat (CGG) expansion mutation, which occurs in the promoter region (exon 1) of FMR1. “Affected individuals with the full FXS mutation have > 200 repeats. When the full mutation is present, FMR1 methylation occurs during gestation, which causes silencing of gene transcription” (3). “The FMR1 gene usually makes a protein called fragile x mental retardation protein (FMRP)” (3). Fragile x mental retardation protein (FMRP) is needed for there to be healthy brain development. People who have Fragile X syndrome are missing this necessary protein for proper brain development. Other people who have fragile x-associated disorders have changes in their FMR1 gene but make some protein for brain development. Fragile X syndrome affects both females and males. It is seen that females have milder symptoms when compared to males. “The exact number of people who have FXS is unknown, but it has been estimated that about 1.4 per 10,000 males and 0.9 per 10,000 females have FXS” (1). It affects almost twice as many males as it does females. However, it is shown that four times as many females appear to be carriers of the altered gene when compared to males. “1:250 females and 1:1000 males)” (1). Most males who are diagnosed with fragile x syndrome have an intellectual disability. It is seen that a small number of males have less impaired function due to methylation patterns or mosaicism. “In females, FMRP levels depend on the X activation ratio or the percent of cells expressing the normal allele on the active X chromosome resulting in a range of normal intellectual ability to moderate intellectual disability” (1). Fragile X Syndrome has also been found in many major ethnic groups and races.

Scientists over the past two decades have made significant advancements in identifying and describing cellular, genetic, and molecular underpinnings of Fragile X Syndrome. These significant advancements help to make there be a more precise diagnosis of the condition. The current challenge at hand is to move from focusing on accurate diagnosis and make sure there is public health action in regards to Fragile X Syndrome. To ensure there is appropriate public health action taken it is required there be a better understanding of the natural history of Fragile X syndrome, clear description on how the complex conditions can affect the individual diagnosed and their families, and the identification of studied interventions and treatments which will lead to better health outcomes. Learning about the lifespan of those infected by Fragile X syndrome from a clinical aspect, family aspect, caretaker aspect, it will help as we design both treatments and services to provide the best optimal care.

Signs & Symptoms

There are various signs to look out for to see if one may have Fragile X syndrome. Starting from a young child, one can start to notice if the child has developmental delays such as not walking, not sitting, or talking around the age of other children the same age would. Another sign to look out for is learning disabilities and trouble learning new skills. Moreover, one can look for social and behavioral problems as well. These signs include the child not making eye contact, having trouble paying attention, having anxiety, acting and speaking without thinking, hand flapping, and being very active. “Fragile x syndrome is characterized by moderate intellectual disability in affected males and mild intellectual disability in affected females” (5). It is seen that males who have fragile x syndrome have some degree of intellectual disability, which can range from mild to severe. It is seen that females who have fragile x syndrome can have normal intelligence and some degree of intellectual disability. “The physical features in affected males are varied and may not be obvious until puberty” (5). An example of the physical features affected includes a large head, long face, protruding ears, prominent forehead, and chin, loose joints, low muscle tone, flat feet, frequent ear infections, heart problems, and crossed eyes (strabismus). Autism spectrum disorders can also occur and is frequently seen in people with fragile x syndrome. The autistic behaviors which could be displayed include hand flapping, poor eye contact, or self-stimulating behaviors. Lastly, motor and language delays can be present and become more apparent over time.

Screening, Testing, and Diagnosis

There has been established population-based screening programs for several genetic conditions in newborn, preconception, and in prenatal settings. “Specific criteria, such as those developed by the World Health Organization, are available to provide guidance on which conditions are suitable for screening” (4). Early diagnosis starts when a child is young. The diagnosis of fragile x syndrome happens when the young child is approximately three years old of age. The child should show signs of delayed or absent speech. Other signs and problems that can be recurrent in children before the age of 2 years include delayed motor milestones, hypotonia, poor eye contact, hand flapping, delayed motor milestones, frequent emesis, and irritability. “The behavior of boys with FXS typically includes attention deficit hyperactivity disorder (ADHD), with significant impulsivity and anxiety, as well as behaviors that include repetitive language, hand biting, hand stereotypies, rocking, and sometimes headbanging” (8). Having these behaviors combined with language and social deficits can lead to the diagnosis of an autism spectrum disorder (ASD) before the diagnosis of fragile x syndrome. “Approximately 30% of boys with FXS meet the diagnostic criteria for autism, and these children have the lowest developmental and adaptive behavior scores of those with FXS” (8). Children who are diagnosed with fragile x syndrome are frequently described as being hyper-aroused, which is an imbalance of the excitatory and inhibitory synaptic pathways. Relatives to the child being diagnosed with fragile x syndrome may also be at risk of having children with intellectual disabilities, and it is advised they seek out genetic counseling. By conducting other clinical observations that may also reveal the FXS phenotype. “Sometimes a family history of ID, ASD, neurological problems (such as tremor, ataxia, or dementia in one of the grandparents), or early menopause (before 40 years of age) will lead the clinician to diagnose FXS in the family” (8).

To test to diagnose if one has fragile x syndrome, DNA has to be taken by conducting a blood test. A doctor or genetic counselor can order the test. The testing can help to find if there are changes in the FMR1 gene, which can lead to the development of fragile x associated disorders. Moreover, there may be a need for a late diagnosis in older patients. These older patients are those who may have undergone genetic testing before the 1991 discovery of the FMR1 gene, or the patients may be showing a mild form of the disease showing atypical symptoms. “Occasionally, individuals with fragile x syndrome were institutionalized in their adolescence or adulthood years, without a subsequent diagnostic study to find the cause of their intellectual disability” (8). Reasons why proper screening and diagnosing is urgently needed.

To improve the screening policies and criteria, it would be effective to see if women early in pregnancy can be tested to see if they have the pre-mutation or full fragile X mutation. The diagnostic testing could then be followed out on fetal cells to help with identifying fetuses that transitioned to the full mutation. “Prenatal screening would be restricted to pregnant women, because normal transmitting males do not give rise to offspring with the fragile X phenotype and because full mutation fragile x males rarely have children” (4). If a pre-mutation is identified in a woman, she will be offered DNA and amniocentesis testing to determine the fragile X genotype of the fetal cells. There is no effective treatment for the mental retardation associated with fragile x syndrome, but prenatal screenings for the disorder allow the parents to have the option of selective termination of affected fetuses. This would be an act of secondary prevention.

A diagnosis of fragile x syndrome can be of help to a family as it will provide reasonings as to why their child is having intellectual disabilities and behavior problems. This allows the family and caregivers to learn more about fragile x syndrome and be able to help the child to reach his or her full potential. The results of the DNA tests can affect family members and raise issues, to help eliminate this; It is advised to consider having genetic counseling before getting tested.

Treatment

Currently, there is no successful treatment available for fragile x syndrome. Treatment services can help those infected by fragile x syndrome learn essential skills. These services can include and are not limited to learning to walk, talk, and interact with others. For additional treatment, medicine can help as well. Medicine can be used to control some issues, such as behavior problems. For the best optimal treatment plan for people who have fragile x syndrome, parents, and healthcare providers have to work together in one accord and be involved through the treatment plan and support one another. This team of support can also include teachers, childcare providers, coaches, therapists, and other members of the affected family. “The direct medical and social costs associated with the lifetime treatment and care of a mentally retarded person are estimated to be between one and four million dollars in the United States, depending on severity” (6). These costs may raise issues for those diagnosed with fragile x syndrome and their families. By taking advantage of all the available resources, it will be an aid in helping to make sure they have a successful treatment plan.

It is reported that reducing sensory and anxiety issues will help to reduce challenging behaviors that some children with fragile X syndrome have. It is suggested in several case studies that the use of behavioral principles such as positive reinforcement is effective. "Behavioral interventions can be effective for children with FXS through the development of individualized multicomponent intervention plans implemented by parents and supported by professionals” (7). Moreover, few studies have examined educational or cognitive interventions for individuals who have fragile x syndrome. It was found that learning strategies that incorporate visually based experiential or holistic learning were most successful among young children who have fragile x syndrome. “A recent case study found a combination of early pharmacologic treatment combined with intensive educational interventions resulted in improved behavior and normal IQ in 2 young children with FXS” (7). These intensive interventions include memory and cognitive games, which visualized math tasks and supplemental occupational therapy, social skills training, and speech-language therapy. “Pharmacotherapy is frequently used as a primary intervention to target specific symptoms for individuals with FXS (7). For the neuropsychiatric symptoms of those diagnosed with fragile x syndrome, there are guidelines suggested for treatment that involve the use of stimulants or selective serotonin reuptake inhibitors, and they work to decrease hyperactivity, psychiatric symptoms, and cognitive deficits.

Another option for treatment includes early intervention services. Children from birth to 3 years old can benefit from early intervention services and learn essential skills. These services are an aid in helping to improve a child’s development. A child does not have to be diagnosed with fragile x syndrome to be eligible for services. Each state has an early intervention system in which children can seek enrollment to be provided with these services. Once in the early intervention system, the child is eligible to have an evaluation. If treatment is needed for language delays, speech therapy is offered and often does not need a formal diagnosis to be obtained. Early intervention is an important treatment option as well as treatment services at any age.

Public Health Recommendations

The identification and treatment of fragile x syndrome are of high public health importance. The information presented provides an understanding of fragile x syndrome as well as its screening protocols and its lack of inefficient treatment options. There is a wealth of information and research did in regards to fragile x syndrome, but much work is needed to support affected individuals and families fully. There are areas in which we have current limited knowledge in regards to fragile x syndrome. These areas include the prevalence estimates for the full mutation lack precision, no large scale population-based study on fragile x syndrome available, and data is unknown about the sociodemographic characteristics of fragile x syndrome populations. Furthermore, there is not any adequate data in regards to fragile x syndrome variability among ethnic and racial groups.

The medical problems and physical features associated with fragile x syndrome are already well documented. What is lacking is the public health issues that are related to fragile x syndrome. These public health issues that have little research include details on health disparities, access to preventative care, health promotion activities, and healthcare decision making. The rate of communication of health information relevant to individuals affected by fragile x syndrome is also lacking. There is also little data on the prevalence of noncommunicable diseases among individuals who have fragile x syndrome. Data is needed on the prevalence of noncommunicable diseases as well as how it compares to other intellectual and developmental groups and also compared to the general population. “There is a shortage of evidence regarding service use, intensity, or efficacy for school-age and preschool children with FXS, including special education eligibility and the types of educational services most commonly provided” (7). If we had the evidence, we could use the information to develop more precisely targeted treatment options. It is currently very challenging to conduct high-quality intervention studies that target specific behaviors since individuals with fragile x syndrome are located in broad ranges. For future intervention research, there needs to be more research done on the efficacy of treatment plans. Finally, the use of behavioral interventions and medications in the first year of life needs to be examined. As well as the efficacy of large scale screening such as newborn screening. With the results from the research, it will help public health professionals in the future push for resources to be taken by those affected early on with fragile x syndrome.

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