GGA Corp.
Genetic Counseling Newsletter
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Fragile X Syndrome and Infertility

Fragile X Syndrome and Infertility
Case Example - Not One, but Three

【Abstract】

A case review of a female patient who was treated for infertility of unknown reasons and became pregnant with a set of triplets. She successfully gave birth to a son and two daughters. During pediatric years, all three children showed developmental delays and were diagnosed with Fragile X syndrome. The female patient then discovered that she was in fact a carrier for Fragile X syndrome.

Fragile X syndrome is the most common form of inherited intellectual disability. Females who are premutation carriers of Fragile X syndrome not only have an up to 50% risks to have affected children, they are also at increased risks for primary ovarian failure and late-onset tremor and ataxia. Therefore, infertility issues can be a presenting clinical feature for premutation carriers.

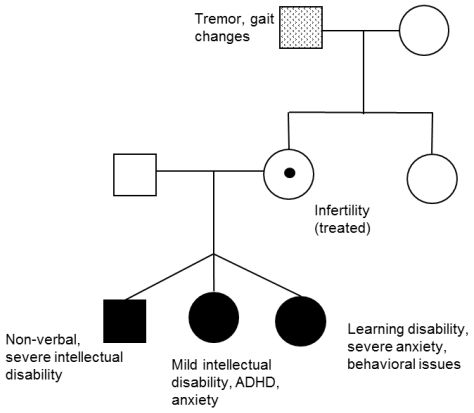
In addition to a family history suggestive of Fragile X syndrome, guidelines from professional medical societies also recommend women with unexplained ovarian insufficiency, or an elevated follicle-stimulating hormone level before 40 years of age be offered Fragile X syndrome carrier screen. Preconception or prenatal genetic testing can identify affected embryos or fetuses prior to birth. Many families are not aware they are at an increased risk to have a child with Fragile X syndrome until when their child is diagnosed with the condition during childrhood. However, a simple blood test could have changed the whole story.

This newsletter also includes a recent statement put forth by the American Congress of Obstetrician and Gynecologists regarding Fragile X carrier screen, as well as a review of this genetic condition.

【Case Example】

Mary was seen at a fertility center due to infertility of unknown reasons. Through the assistance of fertility treatment, Mary became pregnant with triplets and successfully gave birth to two girls and a boy.

During pediatric years, all three children were found to have developmental issues. The boy was non-verbal and had severe intellectual disability. One of the girls had mild intellectual disability, attention deficit



hyperactivity disorder (ADHD) and anxiety issues. The other girl had learning disability, severe anxiety and behavioral issues. An intake of the family history revealed that Mary's father (grandfather of the three children) had tremor problem and gait changes.

Genetic testing was performed and all three children were confirmed to have Fragile X syndrome. Follow-up parental testing revealed Mary herself was a premutation carrier of Fragile X syndrome.

(Case source: Asuragen)

【Counseling Discussion】

1. **Infertility or primary ovarian insufficiency can be a clinical presentation for Fragile X premutation carriers.**

- About 20% of female Fragile X premutation carriers have primary ovarian insufficiency (POI) (menopause before age 40 years).

2. **Fragile X premutation carrier status can be determined through a simple blood test. Premutation carriers have increased risk to have children affected with Fragile X syndrome.**

- The number of CGG trinucleotide repeats on the FMR1 gene determines whether a person has normal allele (<44 CGG repeats), intermediate allele (45-54 CGG repeats), premutation allele (55-200 CGG repeats) or full-mutation allele (>200 CGG repeats) for Fragile X syndrome.
- If Mary was offered carrier screen as part of her infertility work-up, she would have found out prior to becoming pregnant that she is a premutation carrier and has an up to 50% risk to have affected children.

3. **Genetic test targeted at the analysis of the FMR1 gene performed through amniocentesis prenatally or preimplantation genetic diagnosis (PGD) preconceptionally are available to high-risk families. Families can know whether their children are affected and have options for making pregnancy decisions.**

- If Mary was aware of her risk to have affected children, she would be able to discuss with her physicians the option to consider *in vitro* fertilization (IVF) with PGD. PGD can screen whether the embryos inherited the abnormal FMR1 allele and allow selection of normal embryos for transfer.
- If PGD test was not elected, Fragile X syndrome testing is also available through amniocentesis during pregnancy to determine the fetal status prior to birth.

4. **In addition to primary ovarian insufficiency, both male and female premutation carriers have risks for Fragile X-associated tremor/ataxia syndrome (FXTAS).**

- FXTAS usually starts around 50 years of age or later. It is characterized by progressive cerebellar ataxia and intention tremor. Cognitive function is sometimes affected as well.
- Knowledge of this risk can affect medical management of the carrier himself/herself as well as his/her families.

5. Relatives of premutation carriers are at risk to also be carriers themselves.

- Mary's sister is also at risk to be a Fragile X premutation carrier and to have affected children, infertility issues and late-onset neurological disorders. Carrier screen can be considered for Mary's relatives.

【Recommendations from Professional Society】

According to ACOG's Committee Opinion #691 – Carrier Screening for Genetic Conditions, carrier screening for Fragile X syndrome is recommended for:

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

- Women with **a family history of Fragile X-related disorders** who are considering pregnancy or currently pregnant
- Women with **a family history of intellectual disability suggestive of Fragile X syndrome** who are considering pregnancy or currently pregnant
- Women w**ith unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years**
- Women who **does not have a family history but are interesting in knowing their risk**

【Fragile X Syndrome】

【Clinical Features】

Affected Patients

- Intellectual disability – Males: moderate; Females: mild
- Characteristic appearance – large head, long face, prominent forehead and chin, protruding ears
- Connective tissue findings – joint laxity
- Developmental delays
- Large testes after puberty
- Behavioral abnormalities – tantrums, hyperactivity, autism spectrum disorder
- Ophthalmologic (strabismus), orthopedic (joint laxity), cardiac (mitral valve prolapse), and cutaneous (excess softness and smoothness) findings

Premutation Carriers

- Males and females – increased risk for Fragile X-associated tremor/ataxia syndrome (FXTAS) (late-onset, progressive cerebellar ataxia and intention tremor, cognitive deficits)
- Females -- increased risk of FMR1-related primary ovarian insufficiency (POI) (menopause before age 40 years)

【Treatment and Management】

Fragile X syndrome: early developmental intervention, special education, and vocational training; individualized pharmacologic management of behavioral issues that significantly affect social interaction; routine treatment of medical problems

FXTAS: supportive care for gait disturbance and/or cognitive deficits

POI: reproductive endocrine evaluation for treatment and counseling for reproductive options

【Prevalence】

According to American College of Medical Genetics Practice Guidelines and the World Health Organization:

- Fragile X syndrome: Females 1/4,000-8,000; Males 1/3,600-4,000
- Premutation carriers: Females 1/259-350; Males 1/800-1,000

【Fragile X Syndrome】

【Genetic Mechanism】

Fragile X syndrome is caused by abnormal FMR1 gene which is located at the q28 region of the X chromosome. Mutations in the FMR1 gene lead to an abnormal methylation pattern, and in turn, result in the loss of function of the FMR1 gene and abnormal clinical features.

The number of CGG trinucleotide repeats on the FMR1 gene correlate with the disease status. More than 99% of affected individuals have abnormally increased number of CGG trinucleotide repeats, typically >200 CGG repeats (full mutation allele). Women who are premutation carriers have CGG repeats between 55-200 CGG repeats and are at risk to have affected child.

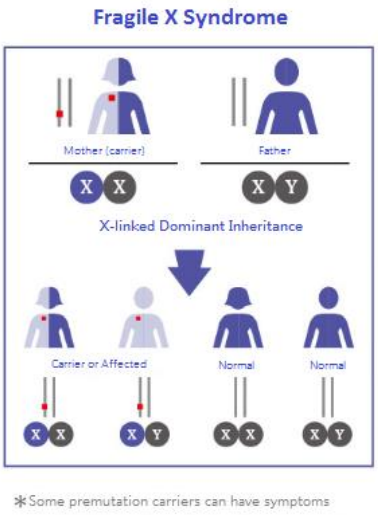
CGG Repeat Number	Allele Category
<44	Normal allele
45~54	Intermediate allele
55~200	Premutation allele
>200	Full mutation allele

【Anticipation】

The number of CGG repeats on the FMR1 gene is unstable and can increase when transmitted to the next generation. A premutation allele is at risk to expand into a full-mutation allele during parent-child transmission, especially if transmitted from a mother to her sons/daughters. Expansion of the CGG repeat size is less likely to occur if transmitted from father to daughter. (A father does not pass the X chromosome to his sons.) For instance, a mother who is a premutation carrier with 70 CGG repeats can give birth to an affected son who has 300 CGG repeats (full mutation allele).

【Inheritance Pattern】

- X-linked dominant



【Genetic Testing】

Determ

methylation status

can be done by molecular genetic tests, such as PCR and Southern blot. Atypical genetic changes in the FMR1 gene can be evaluated with other techniques such as sequencing

【Fragile X Syndrome】

or deletion/duplication analysis.

【Genetic Counseling】

Preconception

1. Women with a family history, infertility due to POI or elevated FSH, or simply worried about her risk to have affected children can consider carrier screen for Fragile X syndrome.
2. Female premutation carriers can have an up to 50% risk to have an affected child. *In vitro* fertilization with preimplantation genetic diagnosis (IVF with PGD) for Fragile X syndrome is an option for high-risk families to know the disease status of embryos and help with selection for transfer/implantation.

Prenatal

1. Fetuses affected with Fragile X syndrome usually do not show abnormalities on prenatal ultrasound scans.
2. Pregnant women who are Fragile X premutation carriers can consider fetal FMR1 genetic testing through amniocentesis to confirm the disease status of the fetus.
3. If a fetus is found to be affected, prenatal prediction of the severity of postnatal clinical presentation is not possible. Couples whose fetuses are confirmed to have Fragile X syndrome are recommended to have genetic counseling and would need to make pregnancy decisions based on personal acceptance levels and situations.

Postnatal

1. About 1-5% of children with autism spectrum disorder have Fragile X syndrome. The number could be as high as 25% for children with autism spectrum disorder and intellectual disability.
2. Individuals showing features and symptoms suspicious of Fragile X syndrome can benefit from molecular genetic testing to rule-in/rule-out a Fragile X syndrome diagnosis.
3. If Fragile X syndrome is confirmed, care and management from multi-disciplinary specialties can assist the patient in achieving his/her greatest potential.

【Fragile X Syndrome】

【Extended Reading】

- GeneReviews – FMR1-related Disorder
  https://www.ncbi.nlm.nih.gov/books/NBK1384/
- Genetics Home Reference – Fragile X syndrome
  https://ghr.nlm.nih.gov/condition/fragile-x-syndrome
- National Fragile X Foundation
  https://fragilex.org/

Reference:

1. *American Congress of Obstetricians and Gynecologists Committee on Genetics. Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol. 2017 Mar;129(3):e41-e55.*
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4. *Sherman S, Pletcher BA, and Driscoll DA. Fragile X syndrome: diagnostic and carrier testing. Genet Med. 2005 Oct;7(8):584-7.*
5. *Schaefer GB, Mendelsohn NJ; Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med. 2013 May;15(5):399-407.*

Do you have any questions related to genetic counseling?
What topics would you like the GGA Genetic Counseling Newsletter to discuss?
Your suggestions are greatly appreciated so we can further improve our newsletter!
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