Triple X Syndrome with a Family History of Fragile X

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Background

- Triple X Syndrome is a type of sex aneuploidy consisting of 47, XXX chromosome presentation.[1]
- It was first described in scientific literature in 1959.[1]
- The incidence of the syndrome is 0.54 per 10,000 births.[2]
- A risk factor for a pregnancy resulting in a 47, XXX fetus is advanced maternal age.[3]
- Usually, it is not inherited but rather is due to nondisjunction during meiosis as shown in Figure 1.[4]
- Many born with this disorder are asymptomatic and may never be officially diagnosed.[5]
- Differential Diagnosis of Triple X syndrome includes fragile X,[6] Marfan syndrome,[7] and intellectual disabilities.[8]
- Some associated physical features with the syndrome include tall stature, hypertelorism, epicanthal folds, clinodactyly, pes planus, and hypotonia.[9]
- Historically has been highly associated with seizure disorders,[10] premature ovarian insufficiency,[11] and developmental delays.[9]
- As shown in Table 1, studies have found an increased incidence of various diseases associated with patients with Triple X syndrome.[5,8]
- Triple X syndrome is associated with an increased risk of any psychiatric disorder, especially bipolar disorder.[5]
- Also, it is associated with executive dysfunction, causing issues with decreased processing speed.[12]
- Triple X Syndrome can be screened during the first trimester through a cell-free DNA test. This test is highly sensitive and specific. However, a definitive diagnosis is confirmed prenatally by karyotyping through amniocentesis.[13]

Table 1. Incidence of Disease in Triple X Syndrome

Disease	Incidence of Disease
Intellectual disabilities[8]	5.0
Autism spectrum disorder[5]	2.58
Attention Deficit Hyperactivity Disorder[5]	1.41
Mental and behavioral disorders[8]	4.3
Bipolar disorders[5]	4.3
Schizophrenia spectrum disorders[5]	2.30
Major depressive disorder[5]	1.17
Pregnancy with spontaneous miscarriage[8]	1.9
Absent, scanty, and rare menstruation, including primary amenorrhea[8]	15.0
Type 2 Diabetes mellitus[8]	5.7

Case Description

History

- History of Present Illness: A 21-year-old G6P1041 Caucasian female at an estimated gestational age of 17 weeks and 3 days by last menstrual period presented for a routine prenatal visit to discuss the results of her routine first-trimester labs. She denied contractions, vaginal bleeding, and leakage of amniotic fluid. She had regular fetal movements.
- She had a history of vaginal bleeding during her current pregnancy, but denied any bleeding at the time of presentation.
- Medications: doxylamine succinate-pyridoxine hydrochloride 10-10 mg by mouth three times daily, ondansetron 4 mg by mouth daily, prenatal multivitamin by mouth daily
- Allergies: No known allergies.
- Medical History: She had a history of seizures (last in 2020), but was not currently on any medications.
- Obstetrics History: She had 1 term pregnancy with a different partner and a history of four spontaneous first-trimester miscarriages with the current father of baby (FOB).
- Family History: Her paternal side had a history of Fragile X and she had been told in the past that she was a carrier.
- Social history: She denied current alcohol and drug use except for marijuana which she had plans to quit that week.
- Review of Systems: unremarkable

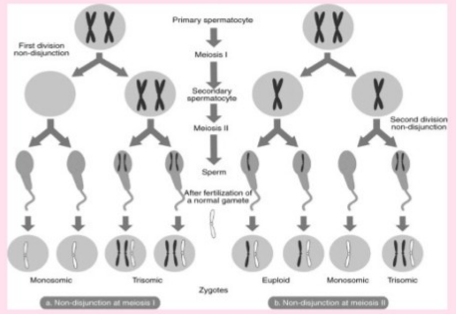
Physical Exam

- Vital Signs: Blood pressure 107/68 mm Hg, Pulse 88 beats per minute, Temperature 97.6ºF, Respirations 18 breaths per minute, Pulse Oximetry 99% on room air, Height 5' 7'', Weight 62.4 kg, BMI 20.91 kg/m^2
- Fetal HR: 150 beats per minute
- General: Tall, thin stature with long limbs. Alert and oriented. No acute distress.
- Skin: Warm and dry.
- Breasts: Bilateral breasts were symmetrical and exhibited no inverted nipples, no masses, no nipple discharge, no skin changes, and no tenderness.
- Heart: Regular rate and rhythm. No abnormal heart sounds.
- Lungs: Equal thoracic expansion. Clear lung sounds bilaterally.
- Abdomen: Nontender
- Genitourinary: Bilateral vulva exam showed no lesions, lacerations, excoriations, or irritation. No evidence of inguinal lymphadenopathy. Vaginal exam showed pink, moist mucosa. No discharge or bleeding present. Multip cervix with no lesions or cervical motion tenderness. Uterus was retroverted with appropriate tone, size, and contour and no tenderness. Bilateral adnexae had no palpable masses and were nontender.
- Extremities: No edema in bilateral lower extremities.

Diagnostic Results

- Cell-free DNA Screening revealed "a disproportionate representation of X chromosome material was observed which may be suggestive of a sex chromosome aneuploidy"; Negative for trisomy 13, 18, and 21.
- Urine toxicology was positive for marijuana (319 ng/mL). Negative for amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, heroin, 3,4-Methylenedioxymethamphetamine (MDMA), methadone, opiates, oxycodone, and phencyclidine.
- Anticardiolipin antibody, beta-2 glycoprotein antibody, and lupus anticoagulant screen with reflex were negative.
- Fragile X Polymerase chain reaction (PCR), Cystic fibrosis (CF) screening, and hemoglobinopathy screening were negative.
- Complete blood count (CBC), Comprehensive metabolic panel (CMP), Thyroid stimulating hormone (TSH), T3/T4, Gonorrhea, Chlamydia, Varicella, Syphilis, Spinal muscular atrophy (SMA), Hepatitis C, Human immunodeficiency virus (HIV), Hepatitis B were within normal limits/negative.

Figure 1. Nondisjunction during meiosis resulting in trisomy



Non-disjunction during (a) meiosis I and (b) meiosis II. ScienceDirect. https://www.sciencedirect.com/topics/chemistry/nondisjunction. Published 2013. Accessed December 11, 2023.

Patient Outcome and Follow-Up

- Final diagnosis: Female fetus with Triple X Syndrome
- The patient and FOB were educated on the definition of Triple X syndrome and what traits they may expect to see in their daughter.
- After reviewing the traits, the patient indicated that these traits are similar to those of her childhood.
- She stated she had a history of behavioral issues, physical therapy at ages 6-7 years old to assist with walking, and seizures with the last one occurring in 2020.
- It was discussed that the cell-free DNA test is a screening test and that a definitive diagnosis is done with amniocentesis.
- The patient declined amniocentesis for karyotyping, stated it would not change her mind, and she did not wish to terminate her pregnancy.
- She was referred to maternal fetal medicine and a genetic counselor for further evaluation.
- She continued to be closely monitored during her pregnancy with regular prenatal visits.

Discussion

- Triple X Syndrome is a chromosomal abnormality with a wide range of presentations from asymptomatic to significant disabilities that affect activities of daily living.
- A few case reports have been published over the years regarding patients with Fragile X syndrome, as well as Triple X syndrome.[14,15]
- Both syndromes can be associated with similar health problems such as learning disabilities, attention deficits, and premature ovarian insufficiency.[5,6,8,16]
- The incidence of these diseases could be biased. Many study participants are voluntary and may be more likely to volunteer if they have associated health problems.
- Currently, there are no known association between the two syndromes and no increased incidence of Triple X Syndrome in Fragile X carriers or vice versa.[14]
- The patient's status as a fragile X carrier, and its association with premature ovarian insufficiency, could contribute to the difficulties she and the FOB have experienced in conceiving a child.
- The patient and FOB have a significant history of first-trimester miscarriages. One study looking at pregnancy outcomes in fragile X carriers found similar outcomes when comparing carriers to the general population, with the exception of late pregnancy bleeding.[17]

Conclusion

- Triple X syndrome is a rare form of sex aneuploidy.
- Although females with this disease can be asymptomatic, it is important to prepare parents for potential associated health issues and disabilities with the syndrome.
- This case report of a 21-year-old G6P1041 female pregnant with a fetus with Triple X syndrome shows the benefit of early prenatal screening for chromosomal abnormalities to assist with this preparation.

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