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Case Report

COFS Syndrome in a Non-Consanguineous Marriage

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Abstract

Cerebro-Oculo-Facio-Skeletal (COFS) syndrome is a rare genetic disorder affecting 1 in 1,000,000 born fetuses. Its mode of inheritance is autosomal recessive (AR). COFS syndrome affects various systems within the body, and the life span of children born with the disease is between 3-5 years. Respiratory infections and feeding difficulties are the main causes of the increased morbidity and mortality in these patients. It is important to highlight this syndrome as it may present similarly to infectious fetopathies (cytomegalovirus, rubella, and toxoplasmosis), trisomy 13 and 18.

Introduction

Cerebro-Oculo-Facio-Skeletal (COFS) syndrome is a rare genetic disorder affecting 1 in 1,000,000 born fetuses [1]. With an autosomal recessive (AR) mode of inheritance [1], This syndrome was first described by Pena and Shokeir in 1974 [2]. COFS syndrome affects various systems within the body [2]. The life span of children born with the disease is between 3-5 years, and respiratory infections and feeding difficulties are the main causes of the increased morbidity and mortality in these patients [1]. Here we report the case of a multiparous woman with a poor obstetric history including: preterm birth and intrauterine fetal growth restriction (IUGR) associated with multiple congenital anomalies. Both she and her husband are non-consanguineous and carriers of an AR disorder to which these unfortunate outcomes have been attributed. A decision to undergo in vitro fertilization (IVF) to perform preimplantation genetic testing (PGT) was made. She got pregnant with dichorionic diamniotic twins (DCDA) and gave birth via cesarean section owing to premature labor, but had a good outcome.

Case Presentation

Here we report the case of a 24-year-old female (G4P0+3+1+0) with a previous cesarean section and a complicated obstetric history. Her first pregnancy was spontaneously conceived in 2015 and her antenatal follow-ups were unremarkable until she reached the second trimester, when polyhydramnios developed and multiple congenital anomalies were detected. Her first pregnancy was further complicated by IUGR and preterm labor owing to polyhydramnios. Eventually, she gave birth to a stillborn baby. After the birth of her first child, she was counseled regarding the incidence of congenital anomalies in the general population. Because she and her husband were non-consanguineous, she was advised to follow-up the next pregnancy with the hospital outpatient clinic and that she would probably have a healthy pregnancy. She returned for follow-up in her second pregnancy, which was also spontaneous, in 2016. However, the same unfortunate events of her first pregnancy occurred. Owing to financial circumstances, she was not able to perform any prenatal testing despite being advised by her treating obstetrician and maternofetal medicine specialist. Her last pregnancy was in 2018, which followed the same previously mentioned course. She refused to do any prenatal investigations because she was afraid and lacked the financial ability to pay for such tests. She gave birth to a live baby girl weighing 1.7 kg with an APGAR score of 5 and 6 via cesarean section as per maternal request. The baby was admitted to the neonatal intensive care unit (NICU) and passed away after three days. During the stay in the NICU, a karyotype was obtained from the fetus and both parents. Both non-consanguineous parents were carriers of COFS syndrome, and it was thought that of her born children were affected by this syndrome. In addition, further genetic testing showed that the family was heterozygous for the ERCC5 gene.

A decision to undergo IVF to perform PGT was made. The patient was given clomiphene citrate tablets as well as follitropin alfa injections to stimulate ovulation before egg retrieval (Figure 1) followed by sperm collection from her husband. Following the collection of the previously mentioned samples, intracytoplasmic sperm injection (ICSI) was performed followed by PGT to select disease-free embryos for transfer (Figures 2-4). In the first trial, she got pregnant with DCDA twins and delivered at 32 weeks owing to preterm labor via cesarean section with a good outcome.

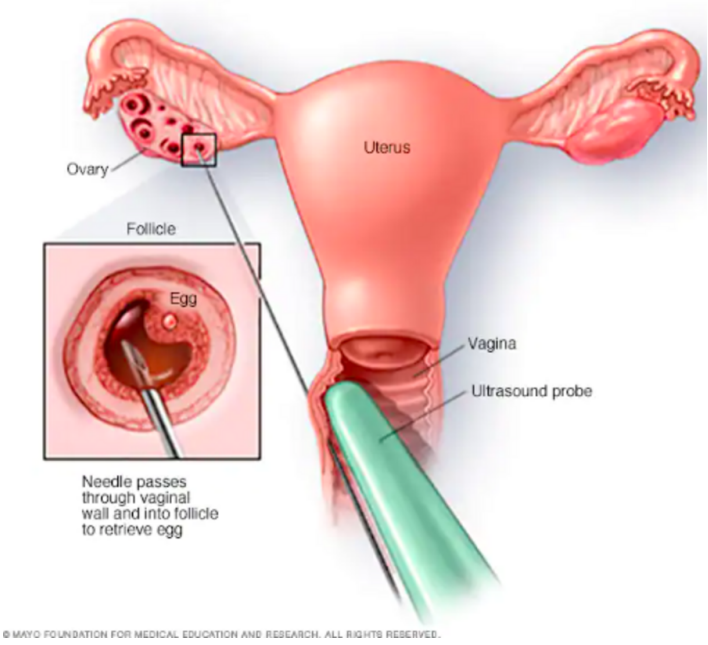

Figure 1: Ultrasound guided egg retrieval (Photo Credits: Mayo Clinic)

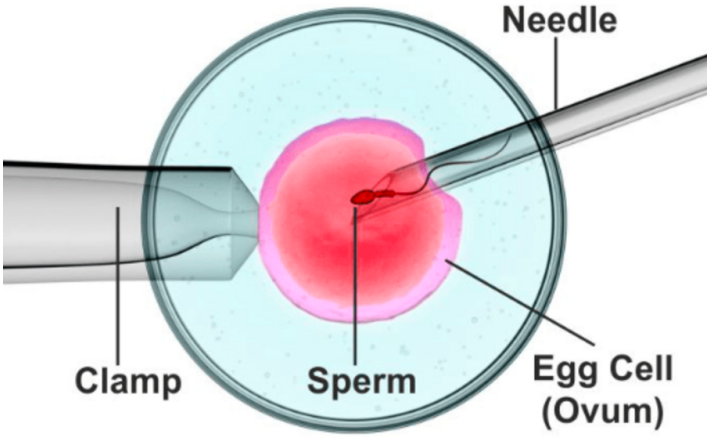

Figure 2: Intracytoplasmic Sperm Injection (ICSI) (Photo Credits: AVMI Hospital)

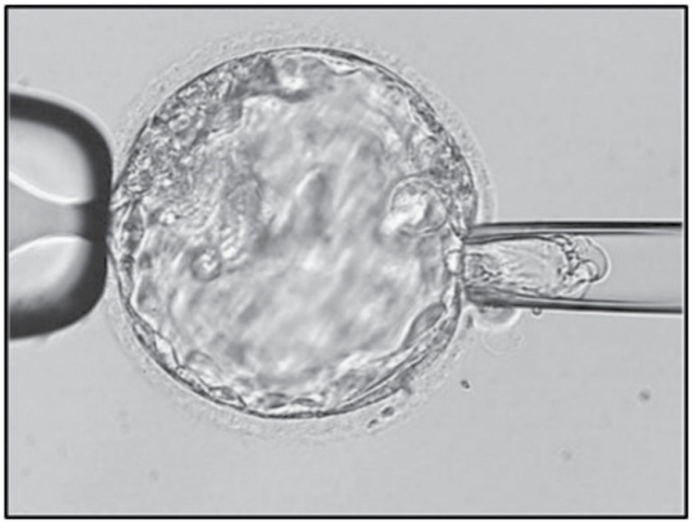

Figure 3: Preimplantation genetic testing (PGT): Biopsy taken from the embryo at the blastocyst stage and around 5-10 cells are removed for genetic testing (Photo Credits: Dr. Harvey Stern)

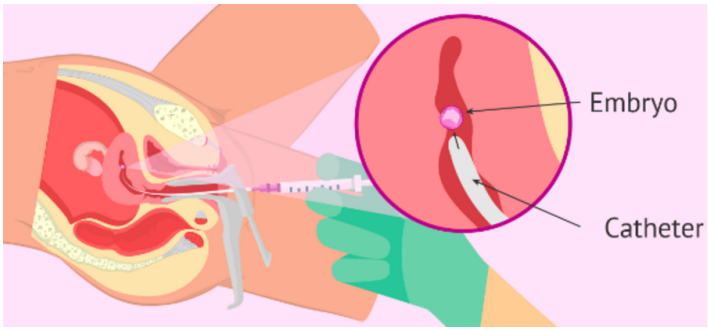

Figure 4: Ultrasound guided embryo transfer (Photo Credits: inviTRA)

Discussion

COFS syndrome is a rare genetic disorder affecting 1 in 1,000,000 born fetuses, with an autosomal recessive (AR) mode of inheritance [1]. COFS syndrome affects various systems within the body and is characterized by congenital cataracts, pigmentary retinopathy, microphthalmia, congenital microcephaly, severe developmental delay, facial dysmorphism with prominent nasal root and/or overhanging upper lip, sensorineural hearing loss, peripheral neuropathy, axial hypotonia (in contrast with peripheral hypertonia), feeding difficulties, severe postnatal growth failure, arthrogryposis, and cutaneous photosensitivity [1].

The exact incidence of COFS syndrome is unknown [2]. To date, fewer than 20 cases have been described [2], and the identified mutations mainly occur in the ERCC6/CSB gene [1]. One case has been linked to mutations in the ERCC1 gene, and particular clinical forms with major photosensitivity have been linked with mutations in the ERCC2/XPD and ERCC5/XPG genes. This syndrome is recognized as a disorder belonging to inherited defects in nucleotide excision repair (NER) [1]. COFS syndrome is a severe syndrome leading to death in the first year of life, particularly by respiratory infections [3].

Owing to the enormous psychological and financial burden that parents with children born with this condition have to face, it is important to diagnose the condition as early as possible to give parents the choice of early termination or to give them time to cope with such diagnosis and know what to expect after delivery in case they decide to proceed with the pregnancy for any reason. Clinicians must be alert to any consanguineous couples having a history of multiple congenital anomalies as previously mentioned. The first step for any diagnostic process is proper history taking and physical examination followed by an ultrasound exam. Ultrasound features of COFS syndrome may involve the following: bilateral microphthalmia, micrognathia, multiple joint contractures, and rocker bottom feet [4]. In addition, renal anomalies and congenital hypersplenism have been reported in patients with COFS syndrome [5]. Owing to the similarities between COFS syndrome and other congenital syndromes, a wide array of differential diagnoses should be suspected: Cockayne syndrome, xeroderma pigmentosum, infectious fetopathies (cytomegalovirus, rubella, and toxoplasmosis), MICRO syndrome, Martsolf syndrome, CAHMR syndrome, and trisomy 13 and 18 [6]. In this case, the most accurate means for reaching a diagnosis is either prenatal or postnatal genetic testing depending on the timing of presentation [3].

Prenatal diagnosis can be performed by evaluating DNA repair in chorionic villi or amniotic cells and by searching for mutations linked in the ERCC2/XPD and ERCC5/XPG genes which are located on chromosome 10 [3][2]. Postnatal diagnosis is based on a defect in DNA repair (by transcription-coupled nucleotide excision). This anomaly can be tested on fetal fibroblast cultures using ultraviolet irradiation [2]. Magnetic resonance imaging (MRI) performed in children with COFS syndrome shows cerebral and cerebellar atrophy and calcifications of the basal ganglia and hemispheric white matter [7]. Obstetric complications associated with COFS syndrome include spontaneous abortion, preterm labor, and IUFD. Infants born with COFS syndrome suffer from repeated respiratory infections and failure to thrive owing to difficulties in feeding [1]. Management of suspected cases of COFS syndrome antenatally should be a shared decision between the parents and the treating physician. Finally, the parents' decision regarding the pregnancy should be honored regardless of the outcome.

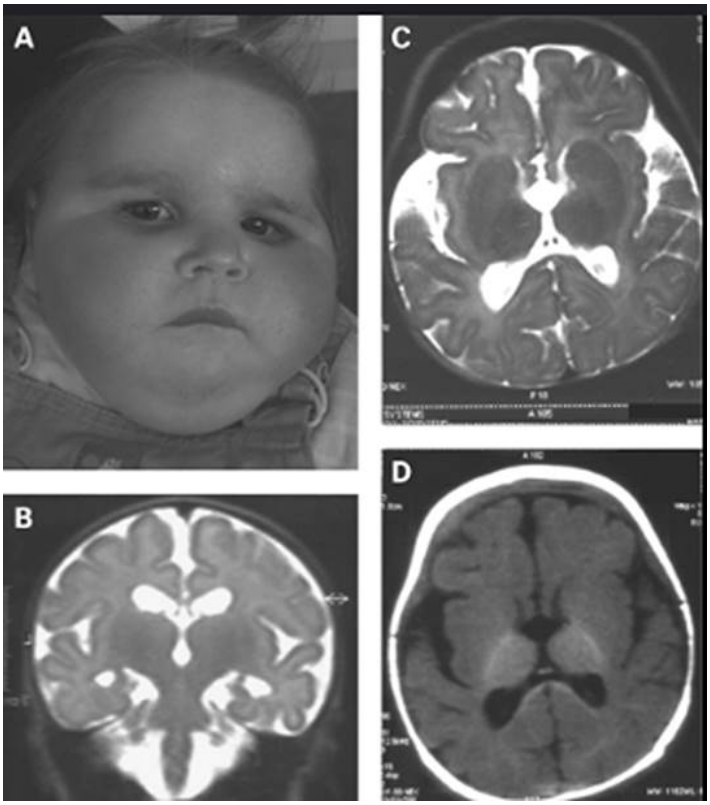

Figure 5: Facial features and MRI features of COFS Syndrome (Photo Credits:) [8]

Conclusions

In conclusion, COFS syndrome is a rare disease with AR inheritance. It affects various systems within the body and has a poor prognosis, as the life expectancy of children born with this condition is less than 5 years. Management of suspected cases of COFS syndrome antenatally should be a shared decision between the parents and the treating physician, and the parents' decision should be honored in all cases. These children should be managed postnatally by a multidisciplinary team (MDT) including neonatologists, pediatricians, and gastroenterologists for enteral feeding, ear, nose, and throat (ENT) specialists, dermatologists, ophthalmologists, neurologists, dietitians, and physiotherapists.

Declarations

- **Ethics approval and consent to participate**

-Consent was taken from the patient and she was informed that data will be displayed in a manner insuring her confidentiality

- **Consent for publication**

-Consent was taken from the patient and she was informed that data will be displayed in a manner insuring her confidentiality

- **Availability of data and materials**

-All data and materials are available upon request

- **Competing interests**

-None

- **Funding**

-None

- **Authors' contributions in this paper**

– Conceived and designed the analysis

– Collected the data

– Contributed data or analysis tools

– Performed the analysis

– Wrote the paper

- **Co-author contributions in this paper**

– Conceived and designed the analysis

– Collected the data

– Contributed data or analysis tools

– Wrote the paper

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