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Fryns anophthalmia plus syndrome

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Abstract: We report a rare case of a 26 year female at 24-25 weeks gestation with complaint of leaking per vaginum whose USG revealed a 20-22 weeks IUD fetus with no midline falx, minimal brain tissue, marked dilatation of ventricular system and occipital encephalocele of 21×18mm size. Facial profile revealed a 14mm upper cleft lip and palate. Eye sockets and nasal bone could not be seen. She was terminated by misoprostol induction when she delivered a congenitally malformed IUD female child which had phenotype resembling a very rare reported Fryns anophthalmia plus syndrome, which may be a recessive trait although intrauterine factors cannot be excluded. The family was advised genetic counseling and about the condition and risks of inheritance in future pregnancies. Until this time 14 cases were reported that might represent anophthalmia plus syndrome.
Keywords: Anophthalmia, Cleft Lip and Palate, Genetic Counseling.

INTRODUCTION

Fryns anophthalmia plus syndrome is a very rare multiple congenital anomaly syndrome initially described by Fryns [3] and colleagues in 1995 in a pair of siblings of non-consanguineous parents and confirmed by Warburg *et al.;* [4]. Since that time only a few cases have been reported, most of them in newborns and young children. The prevalence is <1/1000000. Clinical presentation is variable and includes anophthalmia/microphtalmia, cleft lip/palate, other facial deformities like facial cleft, neural tube defects along with various additional anomalies including congenital glaucoma, iris coloboma, primary hyperplastic vitreous, hypertelorism, low set ears, clinodactyly, choanal atresia(stenosis, dysgenesis of sacrum), tethering of spinal cord, syringomyelia, hypoplasia of corpus callosum, cerebral ventriculomegaly and endocrine abnormalities [1]. An autosomal recessive inheritance has been suggested.

CASE REPORT

A previously healthy 26 year old woman was referred to the department during her second pregnancy at 24-25 weeks gestation with history of leaking per vaginum since 4hours.

She was in a non consanguineous marriage. In the current pregnancy mother had no history of prenatal medications, exposure to toxic agents, drugs or radiation and smoking. The family history was irrelevant with no history of congenitally malformed fetus/baby. The patient denied any history of fever, dysuria, diarrhea or any history of trauma. All other findings on physical examination were normal.

The woman was a second gravida with a 4 year old healthy male child from the woman's first pregnancy. Fetal USG was carried in 24th week of gestation where an IUD fetus with cleft lip, cleft palate, absent eye sockets and nasal bone were detected. Facial profile could not be seen properly due to the position of the fetus and mouth was open persistently. An occipital encephalocele of 21×18mm size, absent midline falx, minimal brain tissue with marked dilatation of ventricular system was detected. She was 36weeks by BPD and 20 weeks by femur length, liquor was normal. Patient and her family were counseled, explained about the consequences and consent taken for termination.

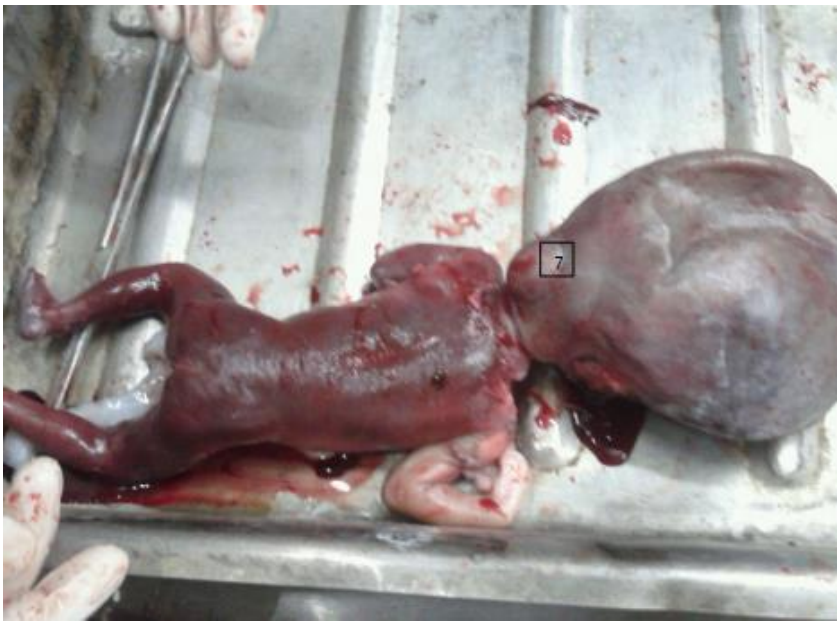
Tab misoprostol per vaginally was used for induction. The patient delivered an IUD female child of 900gms with multiple phenotypic malformations. The baby had a head circumference of around 21cm, abdominal girth of 17.1cm and foot length of 3.5cm. The baby had a hydrocephalic head with occipital meningocele. Eye lids were not open, bilateral eyeballs were absent, hypoplastic nasal bone with agenesis of upper lip and palate, low set and large ears. The baby also had polydactyly.

The ultrasonographic and phenotypic features of the case are consistent with the very rare Fryns anophthalmia plus syndrome. It is believed to be inherited in an autosomal recessive manner, although the genetic cause has not been identified yet. In our case

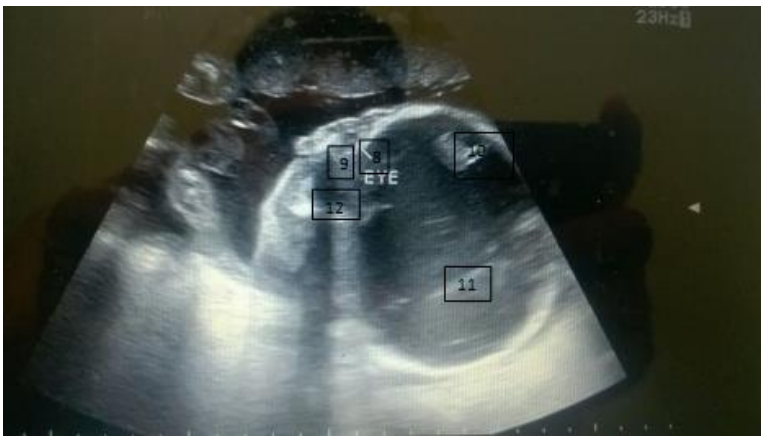
as no cause is known with no anomaly present in the family, but the phenotype resembles the Fryns anophthalmia plus syndrome, it may be a sporadic case.

The patient and family were explained about the condition and risks of recurrence in future pregnancies and advised genetic counseling.

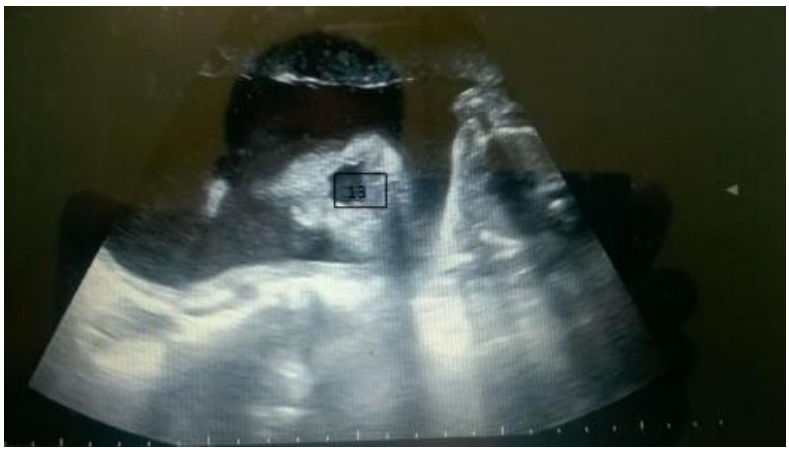
1: Hydrocephalic head, 2: Absent eye balls, 3: Hypoplastic nasal bone, 4: Agenesis of upper lip and palate, 5: Large and low set ears, 6: Polydactyly,



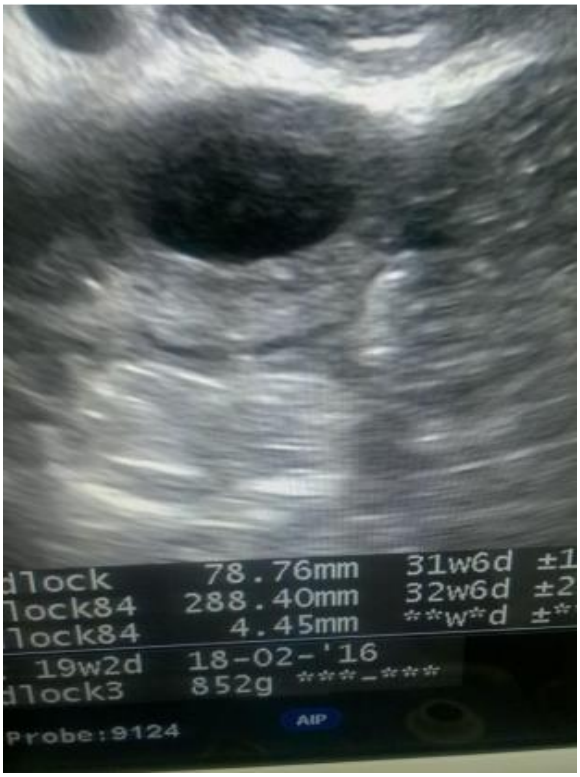
7: Occipital encephalocele



8: Absent eye sockets, 9: Absent nasal bone, 10: Minimal brain tissue, 11:Absent midline falx with marked ventriculomegaly, 12: Cleft lip and palate,



13: Persistent open mouth (due to cleft lip and palate)



Sonographic details of fetus

DISCUSSION

Although primary anophthalmia has been documented as a manifestation of several mental retardation/congenital anomaly (MCA) syndromes, as reviewed by Leichtman *et al.;* [2], the nosology of this group of disorders is confusing.

The combination of anophthalmia/microphthalmia, cleft lip/palate and other facial deformities is quite rare. The Fryns anophthalmia plus syndrome was reported initially in a pair of siblings of non-consanguineous parents[3]. Since that time only a few cases have been reported. The proband was a 17weeks gestation female fetus with bilateral anophthalmia, bilateral cleft lip/palate, bilateral lateral facial clefting, macrotia, open sacral neural tube defect and uterus unicornis.

Warburg *et al.;* [4] described a patient with bilateral extreme microphthalmia and bilateral congenital glaucoma, bilateral medial oblique facial cleft ending in lid colobomas, bilateral stenosis of the choanae, bifid uvula, frontal encephalocele, and premature craniosynostosis. They suggested that this was an example of the Fryns anophthalmia syndrome, which may be an autosomal recessive disorder, although intrauterine environmental factors cannot be excluded.

Wiltshire *et al.;*[5] reported a boy with a nasal deformity, choanal atresia, bifid uvula, severe bilateral microphthalmia, and a facial cleft who showed regression of development at the age of 2 years with subsequent improvement.

Akalin *et al.;* [6] reported a male infant, born of consanguineous parents, with left-sided anophthalmia and right-sided microphthalmia with bilateral partial fusion of the eyelids, bilateral cleft lip and palate with nasal deformity, and clinodactyly of the right fourth toe. The patient was noted to have elevated serum levels of thyroid-stimulating hormone; thyroid ultrasonography revealed bilateral hyperplasia with no cysts or nodules. Akalin *et al.;* [6] concluded that primary hypothyroidism is an important additional feature of the 'anophthalmia-plus' syndrome.

Makhoul *et al.;* [7] described a male infant, born of nonconsanguineous parents, who had bilateral cleft palate and lip, mild microphthalmia with iris coloboma and glaucoma of the right eye, and blepharophimosis with severe microphthalmia of the left eye. Spine x-ray and MRI revealed first sacral hemivertebra with spina bifida, and agenesis of the second through fifth sacral vertebrae and coccyx, with caudal tethering of the spinal cord at L3, filum terminalis lipoma, and a syringomyelia. Brain ultrasound and MRI showed hypoplasia of corpus callosum with mild dilation of the lateral ventricles; orbital MRI showed a posteriorly located lens of the left eye and a split vitreous body in the right eye, suggestive of primary hyperplastic vitreous. In contrast to the patient reported by Akalin *et al.;* [6], this patient had normal serum levels of free thyroxine, TSH, and cortisol. Makhoul *et al.;* [7] stated that this case supported the notion of anophthalmia-plus as a distinct syndrome.

Ozalp *et al.;* [8] reported a 26-week female fetus with bilateral clinical anophthalmia, agenesis of the upper lip and palate, cerebral ventricular dilation, adrenal hypoplasia, and single umbilical artery. A neural tube defect was not detected. Histologic examination of adrenal tissue showed a focal pseudofollicular pattern, autolytic changes, and neuroblastic clusters in the adrenal cortex. The consanguineous Turkish parents had a healthy 7-year-old daughter from their first pregnancy; a male infant from their second pregnancy had frontal bossing, bilateral anophthalmia, total agenesis of the upper lip, and rudimentary nostrils, and died at 9 weeks of age due to respiratory and cardiac failure. Ozalp *et al.;* [8] stated that this was the first report of adrenal hypoplasia in Fryns anophthalmia-plus syndrome.

Another case of Fryns anophthalmia plus syndrome in a 3 year old child revealing a normal kayotype with unusual findings including central hypothyroidism, chiari type2 malformation, conductive hearing loss and developmental regression was reported in July, 2013

In the literature all other cases defined as APS could not be evaluated for development because of the deaths of the affected ones shortly after birth or termination at fetal age. Our patient presented with a constellation of features consistent with the features of this syndrome.

CONCLUSION

Fryns anophthalmia plus syndrome, a very rare occurrence with a prevalence of <1/1000000 is thought to have an autosomal recessive inheritance, although genetic cause has not been identified yet. Intrauterine factors may have a role. Clinical presentation is variable and includes anophthalmia/microphthalmia, cleft lip/palate, ventriculomegaly, facial deformities and neural tube defects. Folic acid supplementation in neural tube defects associated with syndromes as compared to isolated neural tube defects does not have a much role. Genetic counseling is advised.

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