Retinoic Acid Embryopathy

Abstract
Isotretinoin is a retinoid which is derived from Vitamin A. It is indicated for severe cystic acne treatment, but it has been classified as teratogenic. A wide spectrum of birth defects including craniofacial, heart, and nervous system malformations have been described with prenatal exposure to this drug. We report the case of a newborn with a history of prenatal exposure to isotretinoin with craniofacial defects, including left-sided anotia, right-sided microtia, complex congenital heart disease, and central nervous system malformation.

Keywords: Anotia, central nervous system malformation, congenital heart disease, isotretinoin, microtia, teratogenic

Introduction
A teratogen is any environmental agent that reaches the embryo or fetus through the mother and is capable of causing, directly or indirectly, birth defects or functional alterations of embryo, fetus, or even in the child after birth.[1]

Isotretinoin is a derivative of Vitamin A, first licensed in the United States in September 1982 with brand name Accutane. Isotretinoin (13-cis-retinoic acid) was initially recognized to be a human teratogen. In 1985, Lammer et al. set forth the spectrum of structural defects of 21 affected infants. Seventeen individuals had defects of craniofacial area, 12 had cardiac defects, 18 had altered morphogenesis of central nervous system (CNS), and 7 had anomalies of thymic development.[2]

Case Report
A day-1 term male child born out of nonconsanguineous marriage was admitted to the Newborn Unit of Sardar Vallabhbai Patel Post Graduate Institute of Pediatrics, Cuttack, with a chief complaint of poor cry after birth and absence of both ears. He was 1st order term, adequate for gestational age born out of lower-segment cesarean section (indication - low-lying placenta). The mother was a booked case received 2 doses of tetanus toxoid and Iron folic acid tablets during antenatal period. There was no history of gestational diabetes, hypertension, and fever with rash during antenatal period. The 26-year-old primigravida mother had a history of use of isotretinoin (capsule SAFE-RET) 20 mg/day by the advice of a dermatologist for the first 2 months of pregnancy for comedogenic acne. Maternal ultrasonography (USG) and thyroid screening were normal during antenatal checkup.

At birth, the child presented with birth weight 3.2 kg, length 53 cm, head circumference 32 cm, left-sided anotia with preauricular tag, right-sided microtia, and low hairline [Figure 1].

On examination, the general condition was average, heart rate was 134/min, respiratory rate was 52/min, chest bilateral air entry was equal, cardiovascular system – 1st and 2nd heart sounds was normal, and no murmur was audible. On examination of central nervous system, anterior fontanelle was at level, no convulsions and no focal neurological deficit was present.

Investigation revealed hemoglobin – 17.4 g/dl, total leukocyte count – 14,500/mm³, hematocrit – 52.3%, and total platelet count – 4.28 lakhs/mm³.

Chest X-ray revealed egg-on-side appearance of the cardiac shadow.

Echocardiography revealed congenital cyanotic heart disease, dextro-transposition of the great artery, atrial septal defect (4 mm), and left to right shunt with normal biventricular function.

Computed tomography scan of the brain...
revealed cystic lesion in posterior fossa communicating to the fourth ventricle, agenesis of cerebellar vermis and partial agenesis of bilateral cerebellum. The features were suggestive of Dandy–Walker malformation and bilateral agenesis of external and middle ear.

USG abdomen was normal.

Discussion

The cause of this disorder is prenatal exposure to isotretinoin (Accutane). A 35% risk for the isotretinoin embryopathy exists in the offspring of women who continue to take isotretinoin beyond the 15th day following conception.[2] Daily dosage of isotretinoin from 0.5 to 1.5 mg/kg of maternal body weight is thought to be teratogenic. The abnormalities found in infants exposed to isotretinoin are craniofacial, cardiovascular, CNS, thymic, and parathyroid abnormalities.[2] The mechanism responsible for producing many of the malformations in infants exposed to retinoic acid is an abnormality of cephalic neural crest cell activity. The mechanisms responsible for producing CNS malformations are poorly understood and probably differ from those affecting neural crest cells.[3] Human embryos are more sensitive to isotretinoin than embryos of other species due to the slow elimination of the drug and continuous isomerization of retinoic acid.[4] Isotretinoin increases the risk of spontaneous abortions and stillbirths up to 40% in pregnancies exposed in the first quarter of this medicine.[5] Presenting with pregnancy during treatment with isotretinoin is a failure of prevention strategies. Two simultaneous contraception should be used 1 month before the administration of isotretinoin until 1 month after stopping its use. According to the programme IPLEDGE and teratology society, the patients should be advised to have a negative pregnancy test before using isotretinoin and repeat every month during treatment to confirm and 1 month after stopping.[3] No evidence is available regarding the effectiveness of such programs.[2] Still, it is unclear how long pregnancy should be avoided after discontinuation of the drug. In the current setting, it is crucial that the prescribing physicians and the patients should be informed not only about the uncertainty regarding the posttherapy contraception period, but also the limitations of research to clarify the question.[6]

Conclusion

Isotretinoin should be used with caution in women of childbearing age considering potential teratogenicity of the drug, and proper counseling regarding contraception is essential. Alternative treatment options should be kept in mind while treating severe acne in women of childbearing age.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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