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A Rare Case of Isotretinoin Syndrome Unintentional Maternal Exposur

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Abstract **Case Report**

Retinoids are synthetic analogs of vitamin A, they have a key role in cellular differentiation and developmental tissue specificity. Accutane (isotretinoin) is widely used to treat cases of cystic and conglobate acne resistant to other forms of therapy [1]. It has been estimated that 40% of pregnancies exposed to isotretinoin progress to spontaneous abortion and 35% develop embryopathy [2], either conotruncal heart defects (tetralogy of Fallot, transposition of the great arteries ...), Central nervous system malformations (hydrocephalus, agenesis of the vermis, hypoplasia of the cerebellum ...), ear defects (anotia, microtia, aplasia of the external auditory canal ...), as well as thymic malformations (aplasia, ectopia, hypoplasia). The risk period mainly concerns the first two months of pregnancy [3]. The present case is of an infant aged 2 months and 9 days with a history of prenatal exposure to isotretinoin, a now preventable clinical condition. He was born with a craniofacial malformation called dolichocephaly associated with bilateral micrognathia. Cardiological examinations revealed complex congenital heart disease with transposition of the great arteries, an anteriorly positioned aorta to the right of the pulmonary artery, and a 10-mm subpulmonary septal defect. Aside from his dysmorphic syndrome, his outcome was unfavorable.

Keywords: Isotretinoin; Teratogenesis, conotronic heart desease.

INTRODUCTION

Isotretinoin has revolutionized the treatment of severe acne vulgaris, a condition which if left untreated may result in significant socio-psychological implications for those affected [4].

It is a derivative of Vitamin A, first licensed in the United States in September 1982 with the brand name Accutane [5]. It is well known that vitamin A is essential for normal reproduction and development. Both severe Vitamin A Deficiency and Vitamin A excess have teratogenic effects and are sometimes associated with adverse pregnancy outcomes.

A teratogen is any environmental agent that reaches the embryo or fetus via the mother and is capable of causing, directly or indirectly, birth defects or functional alterations of the embryo, fetus, or even in the child after birth [6]. The majority of individuals with either chronic excess or decreased levels of Vitamin A exhibit malformations associated with heart development [7].

We report a case of an infant with heart and facial malformations following maternal unintended exposure to isotretinoin.

CASE REPORT

We describe a case of a 2-month and 9-day-old infant referred by his pediatrician for assessment of congenital heart disease.

The medical background indicated that he was the first child of a non-consanguineous couple, the pregnancy was unplanned and poorly monitored; The mother was 22 years old and illiterate, she declared having used isotretinoin 1 month before the pregnancy and throughout the first trimester by herself and not on medical advice.

The serologic tests for syphilis and human immunodeficiency virus (HIV) performed during the first and only prenatal consultation were negative. The delivery took place at home, so anthropometric parameters at birth were not available.

At birth, the mother described a delay of the first cry, neonatal cyanosis associated with respiratory distress, and jaundice requiring hospitalization in a neonatal ward for one week. The clinical course was marked by repeated cyanosis during feedings.

He was referred to us by his pediatrician at the age of two months for evaluation and management of suspected congenital heart disease.

On entry, clinical examination revealed a hypotonic infant with low responsiveness, a HR of 130 bpm, and a respiratory rate of 35 cpm with signs of respiratory struggle such as inter- and subcostal retractions, with no evidence of heart failure. In addition, we noted hypertelorism, dolichocephaly, and marked bilateral micrognathia.

The ophthalmological check-up was normal. The otolaryngological examination performed in the context of micrognathia was doubtful and an auditory exploration at 6 months was advised.

Chest X-ray showed cardiomegaly with an appearance of a "hoofed" heart. Brain CT scan without contrast injection revealed no abnormalities. The abdominal ultrasound was normal.

Echocardiography done as part of the cardiovascular evaluation revealed:

- A transposition of the great vessels;
- An anterior aorta and to the right of the pulmonary artery;
- A sub-pulmonary inter-ventricular communication of 10 mm, far from the aorta;
- No pulmonary stenosis; a low flow gradient;
- Moderate pulmonary arterial hypertension;
- Both ventricles well developed;
- The left coronary artery which crosses the pulmonary artery forward and an unimagined right coronary artery.

The surgical indication was total cure with arterial switch or, failing that, banding of the pulmonary artery as soon as possible.

On the 3rd day of hospitalization, while awaiting surgery, the child presented several episodes of apnea followed by cardiopulmonary arrest that did not respond to advanced CPR maneuvers.

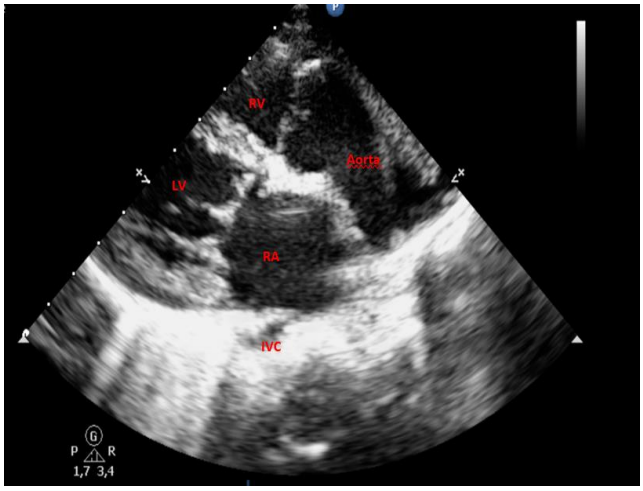

Fig 1: A transposition of the great vessels

Fig 2: Craniofacial anomalies

DISCUSSION

Although drug use during pregnancy is a major cause of teratogenicity and embryotoxicity, the demand for drugs to treat adverse effects of pregnancy or pre-existing medical conditions during pregnancy is increasing every year [8].

Teratology is the study of birth defects, their causes, and the exploration of treatment options available to those affected. These abnormalities occur mostly due to infections, physical agents, chemicals, or metabolic conditions with the potential to cause death as well as physical, behavioral, and intellectual impairments [9].

The teratogenic potential is an important feature of isotretinoin. Animal studies already implied teratogenic effects in humans and the use of isotretinoin during pregnancy has been contraindicated since the very beginning of the marketing authorization [10].

Reported incidences of vitamin A toxicity are quite rare, with fewer than 10 cases per year from 1976 to 1987 [11]. Teratogenicity is the most significant side effect of oral retinoids, affecting 1 in 57 women ingesting over 10,000 IUs daily of preformed vitamin A [12]. Isotretinoin is expected to increase the risk of malformation 25-fold [11].

To standardize the testing of drugs that might be used for treating pregnant women, the U.S. Food and Drug Administration (FDA) issued special grade categories, labeled A, B, C, D and X, that define risk level associated with the use of a specific drug during pregnancy; Drugs in categories D and X are those that have embryotoxic and/or teratogenic effects on humans and animals [8] isotretinoin is classified in category X. Exposure between the second and the fifth week of conception is considered critical. But the risk of teratogenicity remains high at any time during pregnancy [13].

The mechanisms responsible for the teratogenic effects are the subject of numerous studies. Among other factors, changes in cell migration and differentiation are involved. Abnormalities in neural crest cell migration and increased neural crest cell death are thought to explain the association of craniofacial, cardiac and thymic malformations [14].

The incidence of this malformation syndrome is high, estimated at around 23%, significantly close to that of thalidomide [15].

Teratogenic findings include thymic and central nervous system abnormalities (microcephaly, hydrocephalus). Craniofacial and ear malformations include mainly: total aplasia, partial auricle (microtia or anotia), and most commonly low implantation of the ears; It is most often asymmetric and associated with stenosis or agenesis of the external auditory canal. Facial dysmorphism is suggestive and includes micrognathia, microphthalmia, palpebral fissures, hypertelorism, prominent occiput, receding forehead, nasal depression, and sometimes cleft palate.

Cardiovascular malformations are conotruncal heart defects (tetralogy of Fallot, transposition of the great arteries, ventricular septal defect, common trunk artery) and anomalies of the second branchial arch (anomaly of the aortic arch, aortic hypoplasia, aberrant subclavian arteries) [16].

There are very little data in the literature on the incidence of isotretinoin-induced microtia and heart defects during pregnancy.

CONCLUSION

We described an infant diagnosed with a complex heart defect with a history of prenatal isotretinoin exposure, a condition that we reluctantly report because it is preventable.

We emphasize the need to include systematic drug selection during all prenuptial, gestational, and postpartum consultations as well as the importance of fetal echocardiographic follow-up.

Hopefully, awareness will be raised concerning the practices associated with and the consumption of teratogenic substances.

Pediatrician-cardiologist collaboration should be the basis for the care of newborns with poorly monitored or suspicious pregnancies.

Conflict of Interests: There are no conflicts of interests for the development of this publication.

Ethical Standards

Informed consent was obtained from the patient's parents for the publication of this case.

REFERENCES

1. Robertson, R., & MacLeod, P. M. (1985). Accutane-induced teratogenesis. *CMAJ: Canadian Medical Association Journal*, *133*(11), 1147-1148.
2. Cammarata-Scalisi, F., Nieves, D., Avendaño, A., Lacruz-Rengel, M. A., Alviárez, K., Dávila, F., ... & Callea, M. (2018). Isotretinoin embryopathy: An entity that can be avoided. *Archivos Argentinos de Pediatria*, *116*(2), e303-e307.
3. CRAT - Centre de référence sur les agents tératogènes chez la femme enceinte [Internet]. [cité 3 sept 2020]. Disponible à: https://www.lecrat.fr/
4. Kovitwanichkanont, T., & Driscoll, T. (2018). A comparative review of the isotretinoin pregnancy risk management programs across four

continents. *International Journal of Dermatology*, *57*(9), 1035-1046.

5. Mondal, D., Shenoy, S. R., & Mishra, S. (2017). Retinoic acid embryopathy. *International Journal of Applied and Basic Medical Research*, *7*(4), 264-265.
6. Wilson, R. D., Johnson, J. A., Summers, A., Wyatt, P., Allen, V., Gagnon, A., ... & Yudin, M. H. (2007). Principles of Human Teratology: Drug Chemical and Infectious Exposure. *Journal of Obstetrics and Gynaecology Canada*, *29*(11), 911-917.
7. Sinning, A. R. (1998). Role of vitamin A in the formation of congenital heart defects. *The Anatomical Record: An Official Publication of the American Association of Anatomists*, *253*(5), 147-153.
8. Yu, R., Miyamura, N., Okamoto-Uchida, Y., Arima, N., Ishigami-Yuasa, M., Kagechika, H., & Nishina, H. (2015). A modified murine embryonic stem cell test for evaluating the teratogenic effects of drugs on early embryogenesis. *PLoS One*, *10*(12), e0145286.
9. Belanger, B. G., & Lui, F. (2020). Embryology, Teratology TORCH. Dans: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; [cité 4 sept 2020]. Disponible à: http://www.ncbi.nlm.nih.gov/books/NBK545148/
10. Rosa, F. (1983). Teratogenicity of isotretinoin. *Lancet*, 2e éd., 513.
11. Lammer, E. J., Chen, D. T., Hoar, R. M., Agnish, N. D., Benke, P. J., Braun, J. T., ... & Sun, S. C. (1985). Retinoic acid embryopathy. *New England Journal of Medicine*, *313*(14), 837-841.
12. Hunt, J. R. (1996). Teratogenicity of high vitamin A intake. *The New England journal of medicine*, *334*(18), 1197.
13. Aguilar, S., Louis, C., Hicks, J., Zage, P., & Russell, H. (2014). Congenital neuroblastoma in a neonate with isotretinoin embryopathy. *Journal of pediatric hematology/oncology*, *36*(2), e75-e77.
14. Gressens, P., Gofflot, F., Van Maele-Fabry, G., Misson, J. P., Gadisseux, J. F., Evrard, P., & Picard, J. J. (1992). Early neurogenesis and teratogenesis in whole mouse embryo cultures. Histochemical, immunocytological and ultrastructural study of the premigratory neuronal-glial units in normal mouse embryo and in mouse embryos influenced by cocaine and retinoic acid. *Journal of Neuropathology & Experimental Neurology*, *51*(2), 206-219.
15. Lammer, E. J., Hayes, A. M., Schunior, A., & Holmes, L. B. (1987, April). Risk for major malformation among human fetuses exposed to isotretinoin (13-cisretinoic acid). In *Teratology*, 35(2), pp. A68-A68). DIV JOHN WILEY & SONS INC 605 THIRD AVE, NEW YORK, NY 10158-0012: WILEY-LISS.
16. Rizzo, R., Lammer, E. J., Parano, E., Pavone, L., & Argyle, J. C. (1991). Limb reduction defects in humans associated with prenatal isotretinoin exposure. *Teratology*, *44*(6), 599-604.