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CASE REPORT

Retinoic acid embryopathy: report of two cases associated with the use of isotretinoin

Embriopatia do ácido retinóico: relato de dois casos associados ao uso da isotretinoína

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ABSTRACT
The authors report two cases associated with the use of isotretinoin before or during the gestational period, with its characteristic aspects and variations, of one male and one female child. This report aims at raising the awareness of medical professionals about the possible risk of isotretinoin administration to fertile-aged women considering the severity of malformations in the different systems of the human body.

KEYWORDS
fetal diseases, Goldenhar syndrome, tretinoin, isotretinoin

RESUMO
Os autores apresentam dois casos associados ao uso da isotretinoína antes ou durante o período gestacional, com seus aspectos característicos e variações, sendo uma criança do sexo feminino e outra do sexo masculino. Descritos para divulgação no meio médico das possíveis complicações do uso da isotretinoína nas mulheres em idade fértil levando em conta a gravidade das malformações nos diferentes sistemas do corpo humano.

PALAVRAS-CHAVE
embriopatias, síndrome de Goldenhar, ácido retinóico, isotretinoína

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INTRODUCTION

Several terms have been used to designate the phenotypic alterations observed in the patients: retinoic acid embryopathy, hemifacial microsomy, oculoauriculovertebral dysplasia, First and Second Brachial Arch Syndrome, lateral facial dysplasia and Goldenhar syndrome. The term oculoauriculovertebral spectrum is thought to be the most correct, as it encompasses the large variation of clinical manifestations.

Isotretinoin (13-cis-retinoic acid) was recognized as a teratogenic agent in 1982. In 1985, Lammer et al. defined the spectrum of structural defects. Of 21 affected children, 17 presented craniofacial defects, 12 had cardiac defects, 18 had morphogenetic abnormalities of the central nervous system and 7 had anomalies of the thymic development.[1]

It is a complex, predominantly unilateral malformation that involves structures derived from the first and second brachial arches.[2] Facial asymmetry is present in 65% of the cases and it becomes more apparent with age. The maxillary, temporal and malar bones, on the most affected side, usually present decreased size and thickness.[3] In 10 to 30% of the patients, the involvement is bilateral, with one side being more often affected than the other, usually the right side.

The most frequently found skeletal abnormalities are those of the cervical vertebra,[4] such as atlas occipitalization, synestosis, and cuneiform vertebra. Additionally, there can be structural alterations in the temporal bone, which predispose to meningitis.

Pre-auricular protuberances or fistulae can be found as the first manifestation. Conductive as well as neurosensory hearing loss have been reported in more than 50% of the cases. The etiology of this loss is variable and can mean abnormalities in the middle and external ear; ossicular chain hypoplasia, aberrant facial nerve, abnormalities of the Eustachian tube and the basis of the skull.

Ocular abnormalities are common; epibulbar dermoids occur in 35% of the cases, blepharoptosis and palpebral fissure narrowing occur in 10% of the patients. Anophtalmy and microphtalmy have been reported in individuals with severe involvement and might be correlated with mental retardation. [3]

It is estimated that mental deficit is present in 5% to 15% of the affected individuals and central nervous system malformations can be identified, such as: encephalocele, hydrocephalus, dermoids cysts, teratomas, Arnold-Chiari malformation, arachnoid cysts and corpus callosum hypoplasia.

An ongoing study, aimed at determining the evolution of the disease, showed that 19% of 31 cases, prospectively defined as having been exposed to isotretinoin in the prenatal period, within five years, presented an IQ between 71 and 85. Although each one of the five patients that presented an IQ < 70 presented important malformations, six of the ten patients with a borderline IQ did not present significant malformations, indicating that the absence of important structural abnormalities does not necessarily predict the intellectual performance.[1]

Recent findings also report an association with cardiac alterations – Tetralogy of Fallot and ventricular septum defects; pulmonary alterations – incomplete lobulation, pulmonary hypoplasia or agenesis; renal alterations – renal agenesis, double urether, vascular abnormalities, hydronephrosis and hydrourether; gastrointestinal alterations – salivary gland agenesis, anal imperforation with or without rectum-vaginal fistula. [1]

The two cases reported here were exposed to isotretinoin, which, as all retinoics, are potent teratogenic agents. Approximately one-fourth of the exposed fetuses manifest some type of congenital malformation. The defects are rather characteristic and are known as embryopathy of the retinoic acid. [6]

OBJECTIVE

The objective of the present study was to increase the medical knowledge on this subject, helping in the understanding of future cases and assisting the medical class to assess the possible clinical complications due to the congenital malformations.

CLINICAL CASE PRESENTATION:

Case - I:

Case I is a male Caucasian child, born on 12/20/2006, in Goiania, state of Goias, Brazil. The baby was the first child of healthy and non-consanguineous parents.

The mother reported the use of isotretinoin for a period of six months and learned about the pregnancy three months after the medication withdrawal. She denied exposure to radiation, infections, trauma or the use of other medications during the gestational period. The infant was born at term, by Caesarean section, weighing 3,950 g; no data on the cephalic perimeter and length were available. Apgar scores were 2 and 5.

The child presented severe respiratory distress at birth, which caused him to be transferred to the neonatal Intensive Care Unit (ICU), where the child remained for 34 days. This infant presented bilateral absence of auricular pavilion, with bilateral agenesis of the external auricular canal and facies that was characteristic of bilateral facial paralysis. Cardiac auscultation revealed normal heart sounds with the presence of systolic murmur on the left sternal border (3+/4), with an ejective pattern and irradiating to the right, without fibrillation. The pulmonary and abdominal physical examination did not present alterations. The cephalic perimeter was 41 cm (10th percentile), the length was 64 cm (5th percentile) and the intercantal distance was (A: measurement of the external palpebral angle. B: measurement of the internal palpebral angle. C: interpupillary distance. D: distance between the nasal base and the upper lip (philtrum): A-60.4 mm, B-20.2 mm, C-38 mm, D-10 mm. Hand (A: length of the middle finger. B: palmar length): A-33 mm, B-42 mm. Foot: 95 mm.

Relevant imaging results:

- Skull USG - normal
- Urinary system USG: normal echographic aspects
- DOPPLER ECHOCARDIOGRAM: interventricular communication with important hemodynamic effects.
- KARIOTYPE: 46xy, 22pstk (variation found in the normal

population).

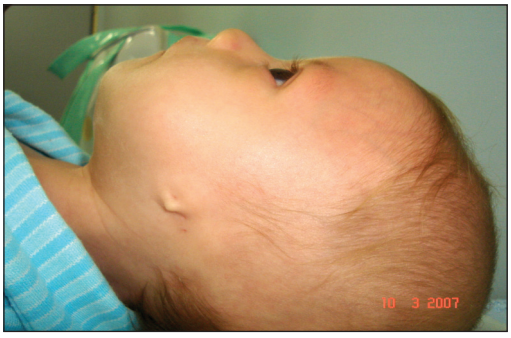
- TOTAL PANORAMIC SPINAL COLUMN X-RAY: no alterations.

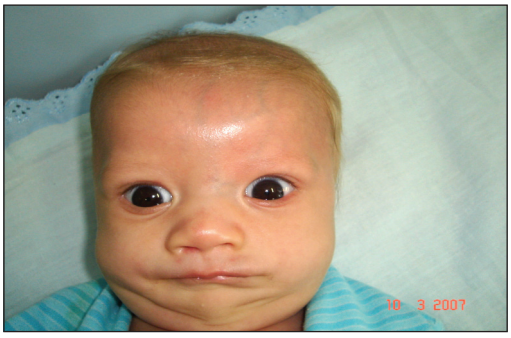
- EVOKED POTENTIAL: suggestive of moderate hearing loss in both ears for the frequencies 2.000Hz, 3.000Hz and 4.000Hz.

- SKULL CT: absence of auricular pavilions and external ear canals. Content with soft tissue densities filling up the mastoid cell and middle ear to the left, charactering an inflammatory process. All other structures were normal.

Case II:

Trata-se de uma criança do sexo feminino, cor branca, procedente de Aparecida de Goiânia-GO, Primeira filha de pais sadios e não consangüíneos.





This is a female Caucasian infant; she was the first child born to healthy, non-consanguineous parents, in Aparecida de Goiania, state of Goias, Brazil. The mother reported the use of isotretinoin during the first trimester of gestation and denied exposure to radiation, infections, trauma or the use of other medications during the gestational period. The child was born at term by Caesarean section, at 39 weeks and 5 days of gestational age. Birth weight was 3,055 g; birth length was 52 cm. Cephalic perimeter was 33 cm and Apgar scores were 2 and 5.

The child presented severe respiratory distress at birth, which caused her to be transferred to the neonatal ICU, where the child remained for 3 days. The infant underwent skull computed tomography (CT), which showed a cystic formation in the median posterior fossa and communication with the fourth ventricle (Dandy-Walker syndrome). This child presented apparent facial paralysis to the right with incomplete palpebral closing reflex on the right, low ear implantation on the right, with rotated helix. She maintained her left forearm in pronation, with flexed elbows and wrists. The spontaneous voluntary movements were generally decreased, more markedly to the left, predominantly brachial ones. Intercantal distance was (A: measurement of the external palpebral angle. B: measurement of the internal palpebral angle. C: interpupillary distance. D: distance between the nasal base and the upper lip (philtrum): A-60 mm, B-20 mm, C-35 mm, D-7 mm. Hands (A: length of the middle finger. B: palmar length): A-30mm, B-40mm. Feet: 90 mm. Left ear: 40 mm. Right ear: 35 mm. Cephalic perimeter: 41 mm. Thoracic perimeter: 41 mm. Height: 61 cm.

Relevant imaging assessment:

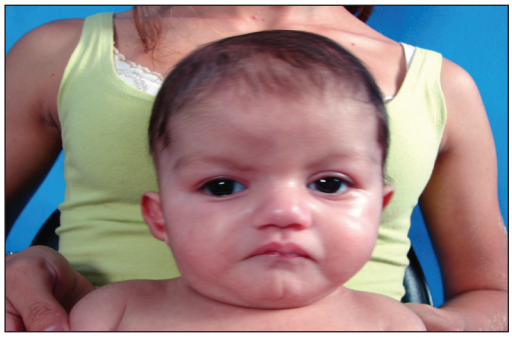
- ECHOCARDIOGRAM WITH DOPPLER: normal results.

- KARIOTYPE: 46 XX with no numerical and/or structural chromosomal alterations.

- SKULL USG: slight widening of ventricular cavities.

- EVOKED POTENTIAL: no alterations

- SKULL MRI: cystic formation located in the posterior fossa communicating with the cistern magna and the fourth ventricle, and consequent dilation of the supratentorial ventricular system. The aspect is suggestive of Dandy-Walker syndrome.



DISCUSSION

The reported cases were exposed to isotretinoin; the association between the effect of the medication in the vascular disruption, altering the development of intrauterine structures derived from the first and second brachial arches is discussed.

The main isotretinoin blood metabolite is the 4-oxy-isotretinoin,

which is formed rapidly after the oral administration of the drug. In vivo, the isotretinoin also isomerizes to tretinoin (all-trans retinoic acid) through an alternative metabolic pathway. The glucuronidation of the metabolites has not been unquestionably demonstrated in man, but it has been suggested by animal experiments. The investigations in humans and dogs point out to an enterohepatic recirculation of the isotretinoin, which contributes to the interindividual variabilities in the observed plasma concentrations.

The isotretinoin is apparently eliminated almost exclusively through the hepatic metabolism and biliary excretion. The hepatic function must be examined before and one month after the start of the treatment and, subsequently, at three-month intervals.[7]

The fasting values of serum lipids must also be examined before and one month after the start of the treatment and also at the end of each period of three to four months of treatment. In patients with diabetes, obesity, alcoholism or lipid metabolism disorders that are submitted to isotretinoin treatment, it might be necessary to undergo more frequent examinations.[7]

In patients with diabetes mellitus or suspected to have it, the frequent analysis of the blood glucose levels is recommended. Although no causal relation has been established, high levels of blood glucose in fasting conditions and new cases of diabetes have been diagnosed during treatment.

Adverse effects:

- Liver: increase in hepatic enzymes and drug-induced hepatitis;
- Gastrointestinal tract: dry mouth, nausea, vomiting, abdominal pain, intestinal inflammatory disease and intestinal bleeding;
- Endocrinological System: alterations in the lipid metabolism, expressed as serum triglycerides > 200 mg/dl and serum cholesterol levels > 250 mg/dl, which must be followed, from a clinical and laboratory point of view, with assessments every three months. Due to the alterations in the lipid metabolism (increased absorption and decreased excretion of lipids), the medication can cause drug-induced hepatitis or pancreatitis, if the doses are not well controlled.

The risk of pregnancy must be assessed, as the medication is highly teratogenic. The patient must sign an informed consent form, which will include all information given by the medical professional, as well as the contraception method used and date of the last menstrual period.

The requested laboratory exams are: whole blood count, platelet count, glutamic oxalacetic transaminase (GOT), (glutamic-pyruvate transaminase (GPT), alkaline phosphatase, gamma GT, total cholesterol, triglycerides, fasting glycemia, creatinine, and for some female patients, β-hCG.

The patient must be warned about the possibility of nose bleeding, due to mucosal dryness, eye dryness, as well as chapped lips. The medication can increase the intracranial pressure (ICP) and thus, if the patient presents an atypical headache, this must be reported to the doctor. Additionally, the association of isotretinoin with tetracycline is contraindicated, as this drug can cause alterations in the ICP.

According to the National Sanitary Vigilance Agency (ANVISA), the use of isotretinoin is contraindicated in women who present the potential to get pregnant, unless they meet some reliable conditions of understanding and following the instructions below:[8]

- To use an effective contraceptive method, without interruption for one month prior to the start of the treatment, during the treatment and up to one month after therapy withdrawal;
- Initial reliable pregnancy test 11 days before the start of the treatment; the monthly repetition of the β-hCG test is recommended;
- To start the treatment only on the second and third days of the next normal menstrual cycle;
- The medication cannot be used with contraceptives that have a microdose of progesterone;
- The medication cannot be used with other contraceptive methods, such the barrier ones.[8]

It is possible that the main teratogenicity mechanism of isotretinoin is the deleterious effect on the activity of the neural crest cells, which results in craniofacial, cardiac and central nervous system alterations.

As the embryopathy of the retinoic acid is part of a spectrum that varies from a simple anomaly to complex alterations with important consequences that can impair the child's quality of life and the psychomotor development, we warn the medical class about the teratogenicity of this drug.

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