Isotretinoin embryopathy: report of one case

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Abstract

Retinoic acid is a derivative of vitamin A.

Retinoic acid embryopathy is an association of malformations caused by the teratogenic effect of retinoic acid, a drug used for the treatment of cystic acne.

Isotretinoin is also known as 13-cis-retinoic acid.

The risk of malformations after exposure to oral isotretinoin has been evaluated to be around 20%.

Affected infants may present craniofacial, central nervous system, cardiac, and thymus abnormalities. There is also an increased risk of spontaneous abortions and premature delivery. Isotretinoin may also have effects on child behavior in about 30-60% of children exposed to it. Termination of pregnancy may be considered in cases of pregestational and/or gestational exposure to isotretinoin.

The authors present the case of an infant male who was the first child of young, healthy, unrelated parents, whose mother was exposed to isotretinoin in both pregestational and gestational periods.

He had a developmental delay, craniofacial abnormalities (low-set and dysplastic ears with anteverted lobules, frontal upsweep, hypertelorism, flat nasal bridge and prominent filter) and apparent articular hypermobility, more obvious in his knees. Brain magnetic resonance imaging showed absence of cerebellar vermis, midbrain dysplastic configuration with thickened superior cerebellar peduncles, decreased thickness of pons-midbrain transition, right cerebellar hemisphere dysplasia, mild decrease in corpus callosum thickness, and enlarged pericerebral subarachnoid space.

The features described are compatible with isotretinoin embryopathy, according to the literature.

This case aims to raise awareness about the use of teratogenic drugs in women of childbearing age, especially isotretinoin, and the importance of information regarding effective contraceptive methods, with compulsory pregnancy testing.
Keywords
Retinoic acid, isotretinoin, teratogenicity, pregnancy, embryopathy, contraceptives.

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Introduction
Retinoids are natural and synthetic substances with a chemical structure or functional properties identical to vitamin A. Isotretinoin is also known as a vitamin A derivative 13-cis-retinoic acid [1].

Retinoic acid is largely used in the treatment of severe recalcitrant acne [1-4]. Nevertheless, it has long been recognized that retinoic acid and isotretinoic acid are potent human teratogens [2, 4].

A retinoic acid embryopathy syndrome may be found among children whose mothers took vitamin A derivatives in the pregestational and/or gestational periods [2, 3].

Studies suggest an increased risk of spontaneous abortions, premature delivery, and a risk of approximately 20% for having a child with evident congenital anomalies at birth, after exposure to oral isotretinoin [2, 5].

This syndrome comprises cranium, face, central nervous system, heart and thymus anomalies [2]. Cranial and facial abnormalities include microtia and anotia, micrognathia, frontal upsweep, hypertelorism, flat nasal bridge, and cleft palate; cardiac anomalies include conotruncal heart defects and aortic arch abnormalities; central nervous system abnormalities include hydrocephalus, fourth-ventricle cyst, holoprosencephaly and microcephaly, cerebellar hypoplasia, cerebellar vermis agenesis, spina bifida, and mental retardation; thymus abnormalities include ectopia, hypoplasia, and aplasia [2, 3, 5]. There are also descriptions suggesting a link between the use of isotretinoin and adverse effects on child behavior [5]. Problems in neurocognitive performance have been reported in about 30-60% of children prenatally exposed to isotretinoin, even when no physical or structural defects are present [6].

Given its potential teratogenicity, users should be informed in case of inadvertent exposure, and even if no abnormalities are recognizable at ultrasonography, behavioral effects cannot be excluded. Voluntary abortion in women who had been treated with isotretinoin should then be considered [5].

The risk of topical isotretinoin cannot be ruled out and should also be avoided [5].

Clinical report
The patient is a male infant referred for evaluation at our hospital for dysmorphic features and developmental delay, at eleven months. He was born at a secondary hospital, at forty weeks of gestation by caesarean delivery. Prenatal ultrasounds were described as normal. The pregnancy (first one) was unplanned and uneventful. His weight, height and head circumference were adequate for gestational age. Apgar scores were 9 at 1 and 5 minutes and 10 at 10 minutes after birth. The neonatal period was uneventful and he was discharged 3 days after birth.

His parents were young, healthy and unrelated, and family history was negative for birth defects, genetic syndromes or metabolic disorders. He presented an adequate evolution of weight and stature.

After a careful evaluation at our Neonatology consultation we realized that the patient’s mother was exposed to isotretinoin in both pregestational and gestational (first 2 months) periods. He evolved with a global retardation of psychomotor development. Physical examination showed mild axial hypotonia, uncoordinated movements, reduced interest for surrounding environment and craniofacial abnormalities, namely low-set and dysplastic ears with anteverted lobules, frontal upsweep, hypertelorism, flat nasal bridge and prominent filter (Figures 1-3). He also had an apparent articular hypermobility, more obvious in his knees joints (Fig. 4).

Given the abnormalities on examination and history of prenatal exposure to isotretinoin, an embryopathy caused by this drug was hypothesised and a workup study was performed. Brain magnetic resonance imaging (MRI) (Figures 5-7) showed absence of cerebellar vermis, midbrain dysplastic configuration with thickened superior cerebellar peduncles, decreased thickness of pons-midbrain...
transition, right cerebellar hemisphere dysplasia, mild decrease in corpus calosum thickness, and enlarged pericerebral subarachnoid space. An ambulatory electroencephalogram was normal. The analysis (hemogram, biochemistry and gasometry) did not reveal significant alterations; posteroanterior chest radiograph showed normal cardiac silhouette and thymic opacity; abdominal, renal and pelvic ultrasounds, and electrocardiogram and echocardiogram were also normal.
He also initiated physiotherapy.

The case was discussed with the Hospital Geneticist in a dysmorphology session and the features described were considered consistent with isotretinoin embryopathy.

A final multidisciplinary meeting with all the involved medical specialties concluded that the observed physical anomalies, developmental delay and brain MRI findings were due to isotretinoin prenatal exposure.

Currently (40-months-old), he attends a childcare center since he was 18-months-old and presents good improvement of global psychomotor development with physiotherapy, occupational therapy and speech therapy. The patient is alert, visually tracks and explores surrounding objects/environment. In terms of linguistic development he is able to speak some isolated words; however most of his communication continues to be nonverbal. As concerns physical development, he has normal head and trunk control and he is able to walk a few steps alone. He can crawl and move around his environment by himself. He feeds well and he is capable of eating with little support.

**Discussion**

The dysmorphic features described in this clinical case are compatible with isotretinoin embryopathy, according to the literature.
Tab. 1 summarizes the principal clinical features observed in isotretinoin embryopathy.

The true extent of this problem is not well known all over the world. In a French study that included all cases of isotretinoin exposure during gestation spontaneously reported to pharmacovigilance centers, between 1 January 2003 and 31 December 2006, the rate of pregnancies exposed to isotretinoin was calculated to vary from 0.41 (95% CI 0.34, 0.49) to 1.24 (95% CI 1.04, 1.46) per 1,000 women of childbearing age treated [7]. Another study that took place in three countries (Canada, Israel and Italy), between July 1998 and October 2006, reported an overall 53 women that called the teratology information services regarding isotretinoin exposure in the first trimester of pregnancy [8].

The vital nutrient vitamin A has a number of biological actions and is needed for several life processes, namely vision, reproduction, growth, cell differentiation, immune function, and embryo development [1, 3].

The teratogenic effect of retinoic acid in the first trimester of pregnancy is well known and this may happen at doses only a few times the recommended daily allowance (RDA). Animal models as well as human studies have shown high incidence of birth defects if a mother takes it during pregnancy in therapeutic doses. The threshold for vitamin A intake during pregnancy has been estimated at about 10,000 International Units (UI) [9]. In humans, the teratogenic daily dose of isotretinoin is below 1 mg/kg/day, which is less than the minimal teratogenic dose in other animals. The reasons for this species variation are in large part owing to differences in toxicokinetics, placental transfer, and metabolism [3, 10].

The transdermal route of administration has the lowest bioavailability, according to experimental animal studies – dose per application of 0.15 mg/kg, which is far beneath the teratogenic dose in humans. However, there is a case report of congenital malformations in a child whose mother used a topical preparation with tretinoin 0.05% on 45% alcohol during the first 5 months of gestation [1, 11]. Therefore, pregnant women should also avoid the use of retinoic acid in its topical form [1, 2].

The time during embryogenesis when the fetus is exposed to certain teratogenic agent determines the risk. The early stage human embryo (nearly the first 2 weeks of human gestation) is relatively insensitive to teratogenic agents. On the other hand, the organogenesis-staged embryo (from week 3 to week 8 of human gestation) is quite sensitive to teratogenic agents, and there is a progressive decline in teratogenic sensitivity as the fetal period (from the end of week 8 until parturition) progresses [1, 2].

Human malformations related to retinoids seem to be induced by disorders of neural crest cells and other migratory cellular population. Other cells are likely to be susceptible at superior retinoic doses. The cranial neural crest cells are firstly accountable for craniofacial, thymic, and cardiovascular abnormalities. Studies demonstrated that decreased expression of the DLX homeobox gene by retinoic acids in zebrafish produces loss or malformations of cartilage elements and that neural crest cells not expressing this gene are not as vulnerable. Possibly, the set of malformations involving the central nervous system as well as postnatal behavior effects result from interferences with the central nervous system population [1].

### Table 1. Principal clinical features observed in isotretinoin embryopathy.

<table>
<thead>
<tr>
<th>Central nervous system</th>
<th>Cardiovascular area</th>
<th>Cranial and facial area</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocephalus*</td>
<td>Transposition of the great vessels*</td>
<td>Anotia*</td>
<td>Microphthalmia</td>
</tr>
<tr>
<td>Microcephaly*</td>
<td>Aortic arch abnormalities*</td>
<td>Microtia*</td>
<td>Thymus abnormalities (ectopia, hypoplasia, aplasia)</td>
</tr>
<tr>
<td>Fourth-ventricle cyst*</td>
<td>Tetralogy of Fallot*</td>
<td>Atretic external auditory canal*</td>
<td>Cleft palate</td>
</tr>
<tr>
<td>Cerebellar vermis agenesis*</td>
<td>Double outlet right ventricle*</td>
<td>Stenotic external auditory canal*</td>
<td>Spina bifida</td>
</tr>
<tr>
<td>Cerebellar hypoplasia*</td>
<td>Retroesophageal subclavian artery*</td>
<td>Low-set ears*</td>
<td>Thyroid aplasia</td>
</tr>
<tr>
<td>Axial hypoplasia*</td>
<td>Truncus arteriosus *</td>
<td>Facial asymmetry</td>
<td>Limb abnormalities</td>
</tr>
<tr>
<td>Mental retardation/global developmental delay*</td>
<td>Atrial septal defect</td>
<td>Micrognathia</td>
<td></td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td>Ventricular septal defect</td>
<td>Microstomia</td>
<td></td>
</tr>
<tr>
<td>Anencephaly</td>
<td>Valvular dysplasia</td>
<td>Hypertelorism*</td>
<td></td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>Single left ventricle</td>
<td>Flat nasal bridge*</td>
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<tr>
<td></td>
<td>Atrioventricular canal defect</td>
<td>Frontal upsweep*</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Preauricular/posterior auricular pits</td>
<td></td>
</tr>
</tbody>
</table>

*aMost frequent clinical features; *bour patient’s clinical features.
Accordingly, prescribing physicians should guarantee that women of childbearing age who take isotretinoin understand the possible associated fetal risks and the importance of using effective contraception. To minimize teratogenicity among exposed women, some efforts should take place: the woman’s information about potential risks; exclusion of pregnancy before starting treatment; the use of two forms of effective contraception starting 1 month before and during the entire course of treatment; assessment of pregnancy at follow-up appointments; and maintain birth control measures until the drug has cleared from the body. Contraception should be uninterrupted up to 1 month after the end of isotretinoin therapy as a measure to prevent fetal exposure, based on more than 5 elimination half-lives of the drug. However, considering that isotretinoin elimination half-life has a great variability (from 5.3 hours to 7 days), 1 month may not allow for appropriate elimination of the drug in all women [6]. There have been reports of fetal malformations induced by isotretinoin use despite stopping treatment 1 month before pregnancy [12]. A 3-month window seems to be more secure [6].

In conclusion, this case aims to raise awareness about the use of teratogenic drugs in women of childbearing age, particularly isotretinoin, and the importance of information regarding effective contraceptive methods, with compulsory pregnancy testing. It is also worth remembering that women undergoing treatment with isotretinoin should discontinue the medication 3 months before pregnancy, in order to prevent fetal exposure.

Declaration of interest

The Authors declare that they do not have financial interests or affiliations with institutions, organizations, or companies that are mentioned in the manuscript or whose products or services are discussed.

References