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ACTUALIZACIÓN

Aplasia Cutis Congenita and Dysmorphic Syndrome After Antithyroid Therapy During Pregnancy .

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Aplasia cutis congenita (ACC) is alleged to be a side effect of antithyroid therapy during pregnancy. This occurrence is uncommon. Only 24 cases have been reported in the literature. In France, there has been no report by the National Center of Pharmacovigilance since 1985. We report a 39-year-old woman with no significant past history in whom Graves disease developed without eye symptoms. She was using methimazole 60 mg daily for 3 months, followed-up by propylthiouracil until delivery. At birth, the newborn had a scalp defect on the vertex, measuring 7- x 2-cm, transient hypothyroidism, and a dysmorphic syndrome (flat face, low-set ears, upper lip retraction, xiphoid funnel, finger-like claws, and low-set fifth finger). At age 1 year, the aplasia cutis was treated surgically. Aplasia cutis is a rare disorder, sometimes associated with other malformations. The mothers with hyperthyroidism who delivered children with reported cases of ACC have used either carbimazole or its active metabolite, methimazole, during early pregnancy. The relationship between methimazole or carbimazole therapy during pregnancy and ACC in the newborn remains to be proven. Nevertheless, to the authors' knowledge, no case has occurred in which the mother has used only propylthiouracil. Therefore, consideration should be given to the exclusive use of propylthiouracil in pregnancy.

Introduction

Aplasia cutis congenita (ACC) is an uncommon side effect related to the use of methimazole or carbimazole during early pregnancy. The latter drug is rapidly bioactivated to methimazole (Fig. 1). In the literature, since 1972, we found 24 cases of ACC related to maternal antithyroid drug therapy. In France, no case has been reported by the National Center of Pharmacovigilance since 1985. We report a newborn with a case of ACC and multiple somatic malformations.

Case Repor t

A 39-year-old-woman without significant past history had Graves disease without exophthalmos. The initial laboratory tests revealed several thyroid-stimulating hormone determinations below the limit of detection. The free T4 was 340 nM (normal value 148 nM). The serum antithyroid-stimulating hormone receptor autoantibodies were 43 IU/L (normal value 4 IU/L). She was treated with carbimazole 60 mg/day. A diagnosis of pregnancy was made after 12 weeks of treatment by carbimazole. She was

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treated with propylthiouracil, 300 mg/day, for the remainder of the pregnancy. The karyotype, made because of the mother's age, was 46XX. At birth, the female infant had a single area of alopecia, 7- x 2-cm, on the vertex (Fig. 2), transient hypothyroidism, and a dysmorphic syndrome (flat face, low-set ears, upper lip retraction (Fig. 3), a xiphoid funnel, and claw-like fingers with a low-set fifth finger). Skull

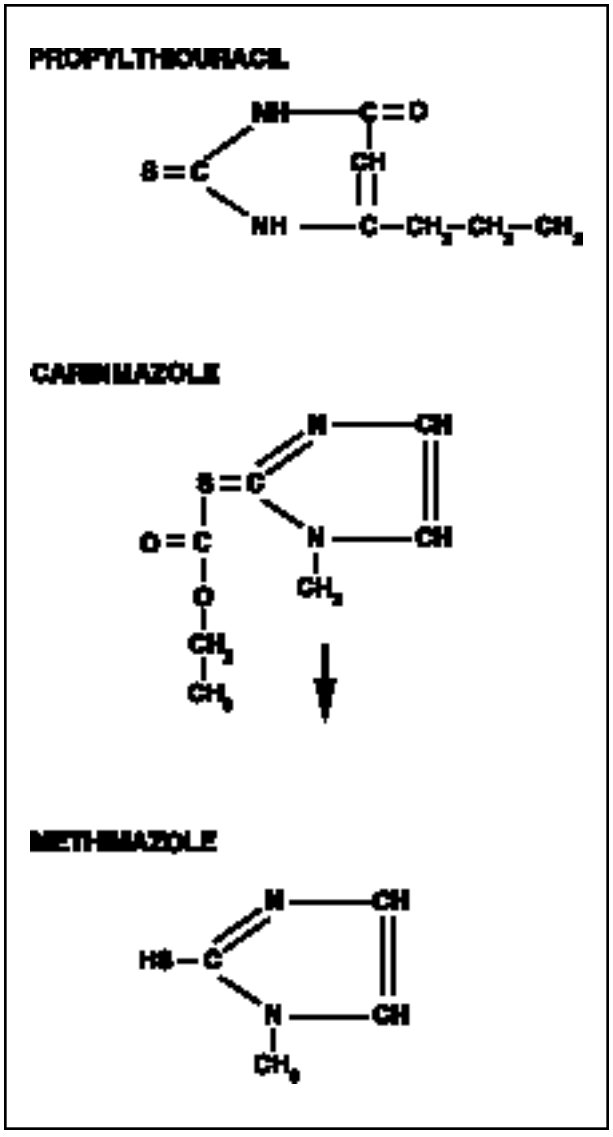

Figure 1. Structure of the three commonly used antithyroid drugs. Note that the carbimazole is rapidly and completely transformed to its active metabolite, methimazole.

Figure 2. Aplasia cutis of the scalp occurring in the daughter of a patient treated with carbimazole.

radiographs and a computerized tomographic scan of the brain were normal. At 1 year, the alopecia was successfully treated surgically.

Discussion

Histologically, ACC is defined as the localized absence of skin (epidermis, dermis, and occasionally subcutis). It may be associated with underlying cranial bone defects. There is neither inflammation nor dysplasia. Since the first report by Cordon in 1767, more than 500 cases have been described. According to Van Dijke et al. [1], it affects 0.03% of newborns. Aplasia cutis congenita may be associated with

Figure 3. The dysmorphic syndrome, including flat face, low-set ears, and upper lip retraction, in the daughter of a patient treated with carbimazole.

chromosomal abnormalities and also various somatic malformation syndromes [2]. Frieden [3] developed a classification for the disease. Observed malformations include hypertelorism, microphthalmia, microcephaly, ear malformations, polydactyly, genital hypoplasia, renal abnormalities, and mental deficiency. The chromosomal abnormalities, which are identified on occasion, include a 4p deletion (Wolf-Hischhorn syndrome), tetrasomy 12, or trisomy 13. In some well-identified syndromes, the mode of transmission has been established to be autosomal dominant (ectodermal dysplasia, scalp-ear-nipple [SEN] syndrome, Adams-Oliver syndrome), or autosomal recessive (Johanson-Blizzard syndrome), or X-linked. Others have proposed causes for ACC, including epidermolysis bullosa, placental abnormalities (lack of resorption, tears, or abnormal amniotic bands during delivery), viral infections (herpes simplex, varicella), toxins (heroin, cocaine), and, occasionally, intrauterine exposure to methimazole, prostaglandin E_1 analogs, valproic acid, and misoprostol.

Importantly, in the literature, 24 cases of ACC have been described subsequent to exposure to methimazole or carbimazole during pregnancy (Table 1). In most cases, these drugs have been administered during the first 2 months of pregnancy and then often replaced by propylthiouracil until delivery. The newborns had one or more areas of ACC, occasionally associated with the absence of underlying bone (two infants) [4,5]. Sometimes, the skin defects had closed spontaneously within a few months. Indeed, some believe that cases of ACC may be missed because the healing has occurred during intrauterine life. Four newborns (two sets of twins) had malformations, mostly related to umbilical immaturity, such as patent urachus. Choanal atresia, esophageal atresia, or tracheoesophageal fistulae are also described [6,7].

The precise cause of ACC is unknown [8,9]. There is no apparent link to maternal age (the mothers were between ages 20 and 40 years) and no relation to dose (ranging from 5-60 mg/day; 15 mg/day in most cases). The reported associated malformations (five cases) have suggested that there might be a genetic predisposition to ACC, which is revealed by methimazole. Other malformations have been described after treatment with methimazole during pregnancy. These include choanal atresia, intestinal anomalies (imperforate anus, esophageal atresia), cardiovascular defects, and facial anomalies [10,12]. Johnsson et al. [13] reported a severe case associating many of these later malformations. Thyroid status may play a role. It is known that the frequency of malformations is greater for infants born to mothers with hyperthyroidism (3%–6% vs. 0.2% for the infants born to mothers with euthyroidism) [9,14]. These malformations include omphalocele, imperforate anus, anencephaly, malformation of the earlobe, harelip, and polydactyly; the same as those reported after treatment by methimazole. In our case, the mother had hyperthyroidism during the embryogenesis.

Some studies investigated the specific relationship between ACC and methimazole therapy. At the

University Hospital of Amsterdam, during a period of 27 years, 48,057 mothers gave birth to 49,091 newborns. Twenty-five children had ACC (0.05%), which was confined to the scalp in 0.03% (13 infants). None of the mothers had used antithyroid drugs during pregnancy [1]. Momotani et al. [14] evaluated 243 infants whose mothers had been treated with methimazole during pregnancy. Two had malformations (omphalocele, abnormalities of the earlobe), but none had scalp defects. These malformations are reported in 1.7% of infants whose mothers received methimazole and had hyperthyroidism and in no infants whose mothers were treated by methimazole but were euthyroid. One study reported the three-fold increase in the frequency of this anomaly in certain regions of Spain where there was illegal use of methimazole as a fattening agent in animal feed [15].

The latest study from Wing et al. [16] concluded that propylthiouracil and methimazole are equally safe. The incidence of major anomalies in infants exposed to these drugs is not different from that of the general population. The incidence was 3% (3 of 99) in infants of propylthiouracil-treated mothers. The mothers of these infants had hyperthyroidism during the period of embryogenesis. These infants had pulmonic stenosis, ventricular septal defect, and patent ductus arteriosus. In infants of methimazole-treated mothers, the incidence of anomalies was 2.7% (1 of 36 infants had a congenital inguinal hernia; his mother had euthyroidism). No case of ACC was found.

No scalp defects have been observed in infants

Table 1
Review of the Twenty Five Cases of ACC in Relation With Antithyroid Described in Literature

Number of patient, author, date, reference	Treatment dose per day	Comments
1-2 - Milham et al., 1972 (15)	Carbimazole	1 twin
3		2nd with a patent urachus
4-5 - Mujtaba et al., 1975 (7)	Methimazole (15 to 5 mg)	1st infant, imperforate anus minimal hypospadia
	L-thyroxin (120 to 60 µg) Methimazole (5 mg)	2nd newborn no malformation
6-9 - Milham, 1981 (6)	?	Patent urachus
10-14 - Bachrach et al., 1984 (20)	?	Oral report
15 - Farine et al., 1988 (21)	Methimazole	Elevation of alpha-feto-protein at the beginning of pregnancy
16 - Kalb et al., 1986 (4)	Methimazole (10 mg; 50 mg subsequently)	1st term absence of underlying bone
17 - Van Dijke et al., 1987 (1)	Methimazole (20 mg) L-thyroxin (50 µg)	3 areas of ACC 1st spontaneous healing
18 - Dutertre et al., 1991 (5)	Methimazole (15 mg the 1st. irregular during the 2nd trimester)	Absence of underlying bone
19 - Mandel et al., 1994 (11)	Methimazole (30 mg 3 months, then 60 mg, then 90 mg) L-thyroxin (200 µg)	One area of ACC subtotal thyroidectomy
20 - Vogt et al., 1995 (8)	Methimazole (20 mg)	Numerous areas of aplasia cutis Transient hypothyroidism
21 - Clementi et al., 1999 (10)	Methimazole	Numerous areas of ACC choanal atresia, atresia of the stomach, dysmorphic face, mental retardation
22 - Diez-Delgado Rubio et al., 1999 (18)	Methimazole (5 mg the 1st and 2nd trimester)	ACC only
23	Methimazole 10 mg 6 weeks	ACC only
24 - Martinez Frias et al., 1992 (19)	Carbimazole	Citation in the text
25 - Bihan et al., 2002 (current case)	Carbimazole (60 mg) for 3 months	flat face, low-set ears, upper lip retraction, xyphoid funnel, finger-like claws, and low-set 5th finger

whose mothers had been treated only with propylthiouracil, even though this drug is administered more frequently than methimazole. Is this disparity caused by differences in their metabolism and/or passage across the placenta? Methimazole, which exhibits negligible protein binding, is lipid-soluble. It crosses the placenta rapidly by a simple diffusion process. Approximately 0.9% of the cumulative dose administered to the mother during her pregnancy can be found in the fetal serum. In contrast, propylthiouracil is bound to protein (60%-70%) and is less lipid-soluble. Its metabolism is rapid. The drug is quickly excreted as glucuronic acid conjugates. Thus, the placental transfer of propylthiouracil may be limited. More recently, a study was performed on the isolated, perfused, term-human placenta. In this study, the transfer of low and high doses of propylthiouracil and methimazole from the maternal to the fetal circulation was investigated, with or without the addition of bovine albumin. No difference was found between the transfer of the drugs, the elimination rate constants, or the clearances [17].

In this respect, as far as the fetal hypothyroidism-inducing potential is concerned, there is apparently no difference between propylthiouracil and methimazole [14]. The apparent relationship between ACC and methimazole is not certain. Because of the rarity of ACC, a prospective clinical study will be difficult to perform. It is also uncertain whether methimazole is harmful only if administered during the first trimester. Nevertheless, among cases associated with the maternal administration of antithyroid drugs during early pregnancy, the relationship to methimazole (or carbimazole) is striking. Accordingly, we recommend the avoidance of these two drugs during pregnancy. In all women of child-bearing age with hyperthyroidism, a pregnancy test should be performed before therapy. If the test result is negative, contraception should be initiated. Furthermore, because propylthiouracil ingestion during early pregnancy has, to our knowledge, never been associated with ACC, we recommend the exclusive use of this antithyroid drug for the woman with hyperthyroidism who is already pregnant.

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