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Carbimazole/methimazole embryopathy in siblings: a possible genetic susceptibility.

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Running title: Carbimazole/methimazole embryopathy.
ABSTRACT

**Background:** The teratogenic effects of antenatal exposure of antithyroid drugs, carbimazole and methimazole have been well reported in the literature. These comprise of typical facial features and a wide variety of malformations such as choanal atresia, tracheo-oesophageal anomalies, congenital heart disease and ectodermal defects. However, the longitudinal studies have failed to establish the consistent teratogenicity of these drugs.

**Cases:** we report here two siblings with physical features consistent with carbimazole/methimazole embryopathy. We also describe previously unreported minor dental anomalies in these siblings with antenatal exposure of carbimazole.

**Conclusions:** Generally, only a small proportion of prenatally exposed children have the typical manifestations, and the presence in siblings supports a possible hereditary susceptibility to carbimazole/methimazole embryopathy. This highlights the importance of recognising this diagnosis prior to a subsequent pregnancy.

Key words: carbimazole, methimazole, choanal atresia, dysmorphism, congenital abnormalities, embryopathy
INTRODUCTION

As all antithyroid medications are potential teratogens, their use during pregnancy presents a challenging balance between optimal control of hyperthyroidism and their possible harmful foetal effects. Carbimazole/methimazole embryopathy is characterised by typical facial features including broad forehead, arched and flared eyebrows, broad nasal bridge, hypoplastic alae nasi and ear abnormalities. A wide variety of malformations such as choanal atresia, aplasia cutis, tracheo-oesophageal anomalies, congenital heart disease, omphalocele, patent vitellointestinal duct and nipple anomalies (Bowman and Vaidya, 2011). The teratogenic risk of carbimazole/methimazole appears to be limited to early gestation (Barbero et al., 2004). It remains insignificant in some studies (Di Gianantonio et al., 2001), and very small in others (between 1 in 1000 and 1 in 10,000) (Karlsson et al., 2002). The concept of genetic susceptibility to drug teratogenicity has been proposed in a few studies (Koenig et al., 2010), and the occurrence of embryopathy in siblings supports this hypothesis. There are only two previously published reports of siblings affected with carbimazole/methimazole embryopathy (Barbero et al., 2008; Gripp et al., 2011). Dental anomalies are not a recognised association with carbimazole/methimazole embryopathy. We describe two siblings with carbimazole/methimazole embryopathy in addition to previously undescribed dental anomalies.

CASE REPORT

Patient 1

Patient 1 was a 12-year-old girl born to non-consanguineous Caucasian parents. Her mother had a corneal graft for keratoconus. The proband’s mother was diagnosed with Graves’ disease at time of conception and was commenced on carbimazole 30mgs daily. She was rendered euthyroid, and the dose was gradually reduced to 15mgs by the third trimester. Her other medications were folic acid and multivitamins. The pregnancy was otherwise uncomplicated, and her regular prenatal sonograms were normal. Patient 1 was born vaginally at term with a birth weight of 3.5 kg (50th percentile). Apgar scores were 7, 9 and 10 at 1, 5 and 10 minutes respectively. At birth, she was noted to have right sided choanal atresia, hypoplastic alae nasi, upslanting palpebral fissures, arched eyebrows, broad nasal bridge, bulbous nose, telecanthus and a small left ear. She also had a subaortic ventriculo-septal defect that resolved by age 4 years. At 12 years of age, she had normal growth and development (figure 1a and 1b). She did not
have coloboma, developmental delay or aplasia cutis. She had generalised dental spacing and was missing 1 premolar and 1 molar tooth (figure 2a). Her molecular karyotype using the BlueGnome 60k oligonucleotide array was normal, 46XX. One older sibling was a boy who was in good health without any evidence of carbimazole embryopathy or dental anomaly (figure 3).

**Patient 2**

During her third pregnancy, the mother’s hyperthyroidism remained well controlled with carbimazole 15mg daily. Antenatal scans were normal. A male baby was delivered vaginally at term with a birth weight of 4.6 kg (90th-98th centile). His Apgar scores were 9, 10 and 10 at 1, 5 and 10 minutes. He had mild hypospadias for which he underwent a meatoplasty soon after birth. His facial features were remarkably similar to his sister but different to their unaffected brother. He had hypoplastic alae nasi, upslanting palpebral fissures, arched eyebrows, broad nasal bridge, bulbous nose, telecanthus and small ears (figure 1c and 1d). He also had generalised dental spacing, microdontia and was missing 2 premolars (figure 2b). He did not have choanal atresia or a congenital heart defect. At 8 years of age, he had normal growth and development.

**DISCUSSION**

Carbimazole, used for the treatment of hyperthyroidism, is a pro-drug that is converted to its active form, methimazole, after absorption. Methimazole inhibits the production of the thyroid hormones T3 and T4 (thyroxine). Carbimazole/methimazole embryopathy was first reported when an increased incidence of cutis aplasia was noted following the prenatal exposure to methimazole (Milham and Elledge, 1972). Several authors have subsequently reported a characteristic combination of facial features and other malformations including oesophageal atresia with or without TE fistula (Clementi et al., 1999; Ramirez et al., 1992), and choanal atresia (Barbero et al., 2004; Barwell et al., 2002), following prenatal exposure to methimazole. Similar observations were noticed after prenatal exposure to carbimazole, which is fully metabolized to methimazole (Jansson et al., 1983). Therefore, the syndrome resulting from prenatal exposure to either drug is best referred to as carbimazole/ methimazole embryopathy (Foulds et al., 2005). The teratogenicity of carbimazole/methimazole remains controversial. Although a number of case reports and case-studies report a teratogenic effect of carbimazole/methimazole, a prospective cohort study (Momotani et al., 1984) and more recently a population-based matched case-control study do not show a significant association between carbimazole/methimazole and adverse pregnancy outcome (Chen et al., 2011). The possibility that maternal hyperthyroidism might be the risk factor rather than methimazole exposure has also been raised (Barwell et al., 2002). Recently, Bowman et al has published an extensive
review on this subject (Bowman et al., 2011). The authors concluded that carbimazole has a teratogenic potential and they advised prescribing physicians to be aware of the potential association of carbimazole with the congenital anomalies.

Both siblings had facial features previously reported in other children exposed to carbimazole/methimazole during pregnancy. These include hypoplastic alae nasi, upslanting palpebral fissures, arched eyebrows, broad nasal bridge, bulbous nose, telecanthus and small ears (Bowman et al., 2011). These facial features were not seen in the unaffected sibling or the parents. In addition to the characteristic facial features, patient 1 had a ventriculo-septal defect and choanal atresia; and patient 2 had mild hypospadias, all of which have been previously reported in children with intrauterine exposure to carbimazole/methimazole (Mujtaba and Burrow, 1975). Based on overlapping characteristic features, we believe that both siblings have a diagnosis of carbimazole/methimazole embryopathy. These siblings, in addition to the two previously reported affected sib pairs in the literature (Barbero et al., 2008; Gripp et al., 2011), suggest a genetic susceptibility to the teratogenicity of carbimazole/methimazole in a small proportion of exposed children. Underlying aetiological factors may include genetic polymorphisms influencing drug metabolism in the mother or foetus.

We also considered a dosage effect of carbimazole on the fetus. Patient 1 was exposed to a larger dose (30 mg) than Patient 2 (15 mg) during the first two trimesters. The published literature does not give any indication of a dosage effect or gender predisposition to carbimazole or methimazole (Clementi et al., 1999). Although dental defects have not been previously reported, there are several reports of other ectodermal anomalies like aplasia cutis, (Clementi et al., 1999; Foulds et al., 2005; Gripp et al., 2011; Rodriguez-Garcia et al., 2011), dystrophic nails (Martin-Denavit et al., 2000), and nipple anomalies (Foulds et al., 2005; Gripp et al., 2011; Martin-Denavit et al., 2000). The underlying mechanism of these defects is still unknown.

This report extends the phenotype of carbimazole/methimazole embryopathy to include dental anomalies, and highlights the importance of recognising this uncommon but potentially preventable condition prior to a subsequent pregnancy.

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REFERENCES


Figure legends:

Figure 1
(a and b) Female patient at 12 years of age with hypoplastic alae nasi, upslanting palpebral fissures, arched eyebrows, broad nasal bridge, bulbous nose, telecanthus and a small left ear. (c and d) 8-year-old brother had hypoplastic alae nasi, upslanting palpebral fissures, arched eyebrows, broad nasal bridge, bulbous nose, telecanthus and small ears.

Figure 2
(a) Sister had generalised dental spacing and was missing 1 premolar and 1 molar tooth. (b) Brother had generalised dental spacing, microdontia and was missing 2 premolars.

Figure 3
16-year-old unaffected brother