

## Aplasia cutis congenita and methimazole. A case report and literature review.

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### Summary

Aplasia cutis congenita -ACC- is a rare group of disorders characterized by focal absence of skin at birth. The lack of skin involves the scalp in most cases, but also trunk and limbs can be affected. Frieden classified ACC into nine types according to the associated anomalies, but a unifying theory has not been identified to explain the etiology of this disease. We present the case of a newborn who showed a lack of skin on the scalp at birth. His mother was affected by hyperthyroidism treated with methimazole during pregnancy. We noted also a distinctive type of hair growth defect, usually not mentioned as an associated anomaly. We recommend propylthiouracil for treating thyrotoxicosis in pregnant women until further data on the safety of methimazole are available.

### Key words

Aplasia cutis congenita, thyrotoxicosis and pregnancy, methimazole.

**A**plasia cutis congenita (ACC) is a heterogeneous group of disorders characterized by well circumscribed focal absence of epidermis, dermis and occasionally subcutis at birth. The majority of cases involves the vertex of the scalp overlying the sagittal sinus, in proximity to the hair whorl, and may be associated with other congenital anomalies (5, 8). However, skin defects may also occur on other regions such as the face, trunk and limbs, sometimes symmetrically.

The diameter of the scalp defect ranges between 0.5 and 100 cm<sup>2</sup>. The lesions are non inflammatory and well demarcated, superficially eroded to deeply ulcerated and occasionally already healed with scarring alopecia at birth. ACC may be round, oval, linear or stellate. Larger defects are often deeper and may extend to the dura or the meninges, complicating the clinical course of the disease (8). The lesions may be single or multiple.

The etiology of this group of diseases is not completely understood and may be different in the subtypes. Viral infections, ischemic/thrombotic events, involution of an intrauterine hemangioma, amniotic adherence (4), autosomal dominant and recessive variants and teratogenic medications such as methimazole -MMI- (8) and misoprostol (7) may be also responsible for ACC.

In the relevant medical literature some cases of embryopathies are described in association to the treatment with MMI for hyperthyroidism in pregnant women (1, 2, 8, 12, 23). These reports are rare and sometimes considered anecdotal observations, although these cases are probably underreported.

We describe a further case of ACC of the vertex in a newborn exposed to MMI during the first trimester of pregnancy. Two years later we also observed sparse and particular hair distribution possibly related to the drug.

### Case report

A male newborn is the first child of unrelated parents, with mother aged 32 and father aged 38. The mother was treated with MMI from the age of 26 years due to Graves' disease. During this pregnancy the dose of MMI was adjusted according to TSH, free T3 and T4 serum levels at the dosage of 5 to 10 mg/day. The antithyroid drug was definitively stopped at 32 weeks of gestation.

Ultrasonography and routine laboratory tests during pregnancy were uneventful. Normal fetal movements were reported after 4.5 months. Oligohydramnios was noted during the last weeks of pregnancy and the delivery by cesarean section was performed in the 38th week of gestation because of failed progression of labor. Baby's auxological parameters were in normal range.

At the first visit 3 areas of aplasia cutis were seen around the vertex. The skin had been healing with several little ulcers still present (Fig. 1). On day four, he developed jitteriness, irritability, anxious sucking. The serum levels of free T3 and T4 were elevated, whereas TSH serum level was within normal range. Both clinical alterations and hormonal levels remitted spontaneously within 1 month without treatment. Moreover, the baby showed elevated thyrotropin receptor-stimulating antibodies. The latter turned to normal by the 7th month.



Fig. 1

Fig. 1, 2: The baby at birth with still ulcerated areas on the scalp (Fig. 1). In Fig. 2 the same baby two years later with scars on the vertex and features reminiscent of alopecia androgenetica.

At the 20th month control-visit the propositus weight was on the 10th-25th percentile, the length on the 25th percentile and the head circumference on the -1 to -2 SD. On the vertex, near the hair whorl, an alopecic stellate scar and sparse hair on the entire head were observed. At the age of two the hair line level with the frontal and parietal region steps back of about 4 cm, being reminiscent of alopecia androgenetica (Fig. 2).

The baby's face is characterized by flap ears with normal eyes and nose, there are not dysmorphisms and the neurodevelopment is normal for his age.

### Discussion

In untreated hyperthyroid pregnant women fetal loss, intrauterine growth retardation, premature labor, heart failure, preeclampsia and thyroid storm have been observed more frequently than in normal population (12). For this reason treatment has been advocated. Moreover, maternal normal hormone levels allow normal development of thyroid function in the fetus.

Thionamides are the primary treatment of gestational hyperthyroidism. MMI is more commonly used in Europe and the only drug available in Italy, while propylthiouracil -PTU- is more used in the States. Carbamazepine is less used in Europe and the States too. These drugs



Fig. 2

inhibit the thyroidal syntesis of thyroxine and triiodothyronine by blocking both the organification of iodine and the coupling of iodothyrosyl residues (12).

It was thought that MMI crossed the placenta three times more than PTU (13), but Mortimer (17) demonstrated that both drugs have similar kinetics of placenta transfer. It is possible to have a transient hypothyroidism in the newborn that usually improves spontaneously. Our patient showed hyperthyroidism at birth, probably caused by the transplacental passage of thyroid-stimulating antibodies occurring in Graves' disease, because MMI drug was stopped too early and not replaced with PTU.

It has been suggested that thyrotoxicosis, which is the most frequent endocrinal disorder in pregnancy, might in itself be a teratogen. However, in the past some reports have advised against the use of MMI in pregnant women with hyperthyroidism because of its association with ACC in exposed fetuses. In these cases the most common associated defects described are choanal atresia (9, 10, 24), intestinal anomalies as imperforate anus and esophageal atresia (18, 19), scalp defects (15, 18) and cardiovascular defects (21). Karg et Al. describe a patient exposed to MMI during the first 6 weeks of gestation who was born with scalp and skull defects associated with facial asymmetry (11). Recently a prospective cohort study (2) came to the conclusion that choanal as well as esophageal atresia may have a higher incidence rate than expected in fetuses exposed to MMI between 3 and 7 gestational weeks. Moreover, in some Spanish regions, during the eighties, a significant increase of isolated scalp defects was observed. They were not related to the intake of MMI by mothers, but the drug had been added to animal feed in order to enhance the weight of the animals (14).

However, based on a study of about 50,000 consecutive births in the Netherlands, Van Dijke et Al. (22) concluded that the association was not as strong as previously suggested. Mometani et Al. found no skin defects in 243 infants who had been exposed to MMI in utero (16).

Up to the present, 24 children with ACC linked to MMI exposure have been reported.

However, it is difficult to say if a solitary lesion of ACC occurring on the scalp, the most common site of presentation, without any other anomaly but preceded by an exposition to a teratogen is or is not related to it. We think that the rarity of this disease does not permit enough cases to reach statistical significance, but it seems strange that the information concerning ACC of the scalp related to MMI intake during pregnancy could be only a casual report and it is interesting that there are no reports of PTU associated to ACC.

Our patient had partial ACC of the vertex that did not need surgical treatment and healed rapidly leaving an alopecic scar. At the moment he is two years old and has sparse hair, normal at optic-microscopic control, with a lack of hair growth on the frontal and parietal sides. In other published studies there were cases of woolly hair in ACC group 2 (20) and other cases of hypertrichosis of eyelashes and other ectodermal anomalies including dystrophic fingernails (3). We do not know other cases of hair defects associated with ACC, although patients with minor scalp aplasia could not be followed during growth with some diagnosis possibly missed.

In conclusion, the risk of birth defects is low, but observations suggest that MMI has teratogenic potential. As up to now no cases of ACC have been reported since the use of PTU therapy during pregnancy, actually we believe that PTU should be considered the first choice treatment for hyperthyroid patients who expect to become pregnant (3), while MMI should be reserved to cases of intolerance, poor response or allergic reactions (6).

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