DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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REFERENCES

1. Martino F, Avila LF, Encinas JL, Luis AL, Olivares P, Lassaletta L, et al. Teratomas of the neck and mediastinum in children. Pediatr Surg Int. 2006;22:627-34.
2. Shine NP, Sader C, Gollow I, Lannigan FJ. Congenital cervical teratomas: diagnostic, management and postoperative variability. Auris Nasus Larynx. 2006;33:107-11.
3. Colleti Junior J, Tannuri U, Monti Lora F. Case report: severe acute respiratory distress by tracheal obstruction due to a congenital thyroid teratoma. F1000Res. 2015;4:159.
4. Novoa R, Quintana W, Castillo-Urquiaga W, Ventura W. EXIT (ex utero intrapartum treatment) surgery for the management of fetal airway obstruction: a systematic review of the literature. J Ped Surg. 2020;55:1188-95.

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Reply to "A Case Report about the Management of Hereditary Angioedema with Normal Complement Levels during Pregnancy"

Resposta a "Caso Clínico sobre a Abordagem do Angioedema Hereditário com Complemento Normal Durante a Gravidez"

Keywords: Angioedemas, Hereditary/complications; Complement C1 Inactivator Proteins; Pregnancy Complications
Palavras-chave: Angioedema Hereditário/complicações; Complicações na Gravidez; Proteínas Inativadoras do Complemento 1

Dear Editor,

The recently published article by Pinto *et al* highlights a rare disorder called hereditary angioedema (HAE) diagnosed in a pregnant woman.[1] This disease is characterized by recurrent and unpredictable episodes of swelling of the upper airways and gastrointestinal tract.[1,2] The laryngeal oedema may cause fatal asphyxiation.[2]

The most common forms of HAE are types I and II, caused by deficiency and disfunction of C1 inhibitor (C1-INH), respectively.[2] A less prevalent form of HAE with normal C1 inhibitor (HAE-nC1-INH) has the distinctive characteristic of showing normal complement levels and affects mainly women, while men are often asymptomatic carriers.[3] In the largest Portuguese cohort that included 126 patients, HAE-nC1-INH was diagnosed in five patients (4%).[4]

The pathophysiology of HAE-nC1-INH is unknown, although evidence suggests the role of excess generation of bradykinin, causing vasodilation and vascular permeability.[5] Several mutations have been identified in families with HAE-nC1-INH, namely, in coagulation factor XII.[1]

Estrogens can interact with most of the steps of the cascade generating bradykinin.[5] Oral contraceptives, menstruation, pregnancy, and hormone replacement therapy represent important triggers.[5] However, pregnancy has shown a variable course in intensity and frequency of the attacks, even in the same patient, suggesting that the hormonal changes are not the only influencing factors.[3] Mechanical trauma due to uterine growth and fetal movements have also been proposed as aggravating factors.[3] However, a recent study revealed that attacks were more common during the first trimester (41.7%).[3]

Moreover, symptoms during pregnancy may be misdiagnosed, especially if the timing matches that of the onset

of the disease and could masquerade as obstetrical complications.[5] Labor generally does not precipitate attacks, and the rate of caesarean deliveries is not higher compared to the general population.[3] Spontaneous abortion occurrence is similar to non-affected women.[3]

Treatment options approved for the gestational period are limited.[5] C1-INH concentrate (20 units per kg) is the preferred agent for short-term and long-term prophylaxis, and acute treatment during pregnancies, since it is the best studied approach.[3] C1-INH concentrate should be available during delivery and 48 hours afterwards.[5] If not available, plasma should be administered.[3] Icatibant and lanadelumab has not been studied in pregnancy.[3,5] Androgens should be avoided due to virilization of the female fetus, but can be used in case of a male fetus, and under supervision of an endocrinologist.[5]

The effect of pregnancy is difficult to predict, and that also applies to subsequent pregnancies.[3] A multidisciplinary approach, involving obstetricians and allergists / immunologists is crucial.[3] We highlight the need for prospective studies to guide the management of HAE-nC1-INH during pregnancy.

AUTHOR CONTRIBUTIONS

ALM: Conception of the work, data collection, writing and approval of the manuscript.

AG, LMB: Writing and approval of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

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REFERENCES

1. Pinto AR, Machado Cunha I, Carolino F. A case report about the management of hereditary angioedema with normal complement levels during pregnancy. Acta Med Port. 2023;36:453-4.
2. Cosme J, Spínola A, Ferreira MB, Barbosa MP. Hospitalizations due to angioedema without urticaria in a Portuguese center: five year retrospective study. Acta Med Port. 2019;32:714-20.
3. Gabriel N, Marcelino F, Ferriani MP, Arruda LK, Campos RA, Gonçalves RF, et al. Pregnancy in patients with hereditary angioedema and normal C1 inhibitor. Front Allergy. 2022;17;3:846968.
4. Varandas C, Esteves Caldeira L, Silva SL, Costa C, Limão R, Silva MI, et al. Hereditary angioedema: 24 years of experience in a Portuguese reference center. Eur Ann Allergy Clin Immunol. 2022 (in press). doi: 10.23822/EurAnnACI.1764-1489.278.
5. Caballero T, Farkas H, Bouillet L, Bowen T, Gompel A, Fagerberg C, et al. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. J Allergy Clin Immunol. 2012;129:308-20.

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