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Hereditary haemorragic teleangectasia and pregnancy: case report

B. DELLA VELLA, V. UNFER*, C. NANIA†, M.L. BORGIA†, A. SARACENO*, M. MINOZZI**

Department of Anaesthesia and Intensive Care Medicine, Umberto I Hospital, Rome (Italy)
*AGUNCO Obstetrics & Gynecology Center, Rome (Italy)
**Institute of Gynecology and Obstetrics, "Sapienza" University of Rome, Rome (Italy)
†Department of Neuroradiology, "Sapienza" University of Rome, Rome (Italy)

Abstract. – We report an uncommon case of a 38-years-old pregnant woman affected by HHT (Hereditary haemorrhagic telangiectasia; Osler-Weber-Rendu syndrome) who underwent to a caesarean section (CS) without any complication. The patient at 36th weeks+1 day pregnancy referred to the Emergency Obstetric Unit due to a intercostals pain on left side. On third day after admission the woman started travailing and physicians decided to perform the CS. Considering that no AVMs was found at MRI, a continuous spinal anaesthesia was planned. On postpartum day 4 the patient was discharged. This represents the only case published in the literature.

Women with HHT, especially those with arteriovenous malformations (AVM), are at high risk in pregnancy due to physiological haemodynamic changes pregnancy associated.

Early screening of patients with HHT for the presence of spinal cord or cerebral AVMs is recommended to optimise perioperative anaesthetic management and to avoid severe complications.

Key Words:

HHT, Pregnancy, AVM.

Introduction

Hereditary haemorrhagic telangiectasia (HHT; Osler-Weber-Rendu syndrome) is a relatively common genetic condition that affects all ethnic and racial groups and is seen over a wide geographic distribution with an overall frequency of 1 in 3500-10,000 persons.

The first definitive report of what is now known as HHT was described by Sutton in 1864. as an association of vascular malformations and recurrent haemorrhage. Rendu first recognized the complex of hereditary epistaxis and telangiectasies in 1896 reporting the case of a 52 year-old man who had a history of anaemia and recurrent epistaxis since the age of 12 years, clarifying that this disease entity was distinct from haemophilia. The subsequent decade produced a number of case reports, contributing to the definition of the syndrome, including those from Osler and Weber whose names appear in the common eponymous labels for this condition. The term "hereditary hemorrhagic telangiectasia" was then coined by Haines, in acknowledgement of the three features, which by then defined the disorder.

Several studies[1] showed as HHT is an heterogenous group of genetic disorders with a similar phenotypic expression

According to the Curaçao criteria of the HHT Foundation International the diagnosis of hereditary hemorrhagic telangiectasia is definite if 3 of the following criteria are present, possible or suspected if 2 are present, and unlikely if fewer than 2 are present:

Epistaxis: spontaneous, recurrent nose bleeds
Telangiectasias: multiple, at characteristic sites (lips, oral cavity, fingers and nose)
Visceral lesions: gastrointestinal telangiectasias (with or without bleeding) and arteriovenous malformations (AVMs): pulmonary, hepatic, cerebral and spinal.
Family history: a first-degree relative with hereditary hemorrhagic telangiectasia.

Women with HHT[2], especially those with AVM, are at high risk in pregnancy due to physiological haemodynamic changes pregnancy associated, particularly increased cardiac output and increased aortic and cardiac chambers.

Corresponding Author: Beatrice della Vella, MD; e-mail: dellavella.beatrice@libero.it

We report a case of a pregnant women affected by HHT who underwent to a caesarean section (CS) without any complication. To the best of our knowledge, this represents the only case published in the literature. Case reports[3] published to date on pregnant women affected by HHT showed a significant worsening of pulmonary AVMs, with deterioration of a pre-existent pulmonary shunt, and consequent haematothorax or stroke.

The patient was a 38 year-old pregnant woman (P0 G3) who had been diagnosed with HHT disease 18 years earlier. The women at 36th weeks+1 day pregnancy referred to the Emergency Obstetric Unit due to a intercostals pain on left side. At admission patient was apyretic with a systolic blood pressure of 115 and a diastolic of 80 mmHg. She underwent a clinical general examination that showed a shooting intermittent pain, worsening with breath movements, located at the base of left hemithorax with no pathological breath sounds. The blood sample taken on admission showed no pathological results.

Her obstetric history reported a previous vesicular mole with a subsequent dilatation and curettage five years before and a spontaneous 7 weeks abortion one year after.

A CS was scheduled, and a thoracical, abdominal and cerebral magnetic resonance imaging(MRI) was then planned, before the scheduled CS, to exclude AVMs. MR showed no AVMs, a slight increase in hemiazygos diametrer and bilateral hydronephrosis.

On third day after admission the woman started travailing and physicians decided to perform the CS. Considering that no AVMs was found at MRI a continuous spinal anaesthesia was planned.

When arrived to operating theatre the woman, 165 cm height 72 kg weight, was prepared to the operation with a venous access 18 G and a subsequent pre-fill emagel 500 ml.

Under a continuous monitoring of electrocardiogram in three derivations (II, V, and aVF), pulse oximeter, non-invasive blood pressure measured at 3-minute intervals, and after an accurate cutaneous disinfection, subarachnoid puncture was performed with a median puncture between the third and fourth intervertebral lumbar space with the patient in the sitting position, using a 24G Withacre needle. The drugs used included 1.8 ml of 0.5% hyperbaric bupivacaine with 50 mcg of morphine and 2.5 mcg of suphentanil. The patient was placed in Trendelemburg decubitus, and the uterus was dislocated manually to the left until delivery level to reduce aortocaval compression. 10 minutes after the execution of the anaesthesia a motor and sensory block is gotten. During the procedure the patient remained stable.

Five minute after pfannestil incision a male single foetus weight 2890 g, Apgar score 9/10, was extracted. After extraction 1 ml duratocin was dispensed. Postoperative pain management was performed by an elastomeric pump with 10 mg of morphine and paracetamol 1 g iv every 8 hours.

A thromboembolic prophylaxis was administered with a daily dose of 3000 IU enoxiparine until discharge. The women underwent also to an antibiotic coverage with sultamicillin iv 3 g × 3 daily.

On postpartum day 3 the woman complained of severe retrosternal pain worsening with digitopression. An electrocardiogram and a blood sample test for cardiac enzymes were performed and both had normal values (cardiac pulses 80 bpm). The thorax radiogram demonstrated an enlargement of bilateral medio-basal pulmonary draw. Acetilcisteine 1 fl and besametazone 4mg aerosol were thus administered.

On postpartum day 4 the patient recovered, and was discharged.

Hereditary haemorrhagic telangectasia is a relatively common, autosomal-dominant disorder that results from multisystem vascular dysplasia. With the discovery of various genes associated with HHT, it is being realized that HHT is a genetically heterogeneous disorder. Four HHT disease-causing genes have been identified to date: HHT type 1 results from mutations in ENG encoding endoglin localized on the long arm of chromosome 9 associated to an high number of pulmonary AVMs; HHT type 2 results from mutations in ACVRL1 encoding ALK1 localized on the long arm of chromosome 12; HHT in association with juvenile polyposis (JPHT) results from mutations in MADH4 on chromosome 18q and HHT3 mapped to chromosome 5q.

HHT disease-causing genes encode proteins that modulate transforming growth factor (TGF)-β superfamily signalling in vascular endothelial cells. This leads to the development of abnormal vascular structures, which range from dilated microvessels to large AVMs. The underlying pathological abnormality appears to be a combination of insufficient smooth muscle contractile elements, endothelial cell junction de-

fects, and perivascular connective tissue weakness. Endoglin and ALK1, that are involved in signal transduction of the potent angiogenic factor, transforming growth factor-β, have been implicated in the pathogenesis. During angiogenesis, mural cells (smooth muscle cells, pericytes) detach, and brief periods of endothelial cell activation, proliferation and migration are co-ordinated with controlled proteolytic remodelling of the basement membrane and extracellular matrix, expression of endothelial cell survival factors, and recruitment of mural cells to stabilise the nascent blood vessels. There are complex context-dependent biological activities of the HHT gene products in these processes such that over-expression of constitutively active ALK1 or under-expression of endoglin can each either promote or inhibit specific endothelial cell responses according to the experimental conditions.

Telangiectasias of the skin and mucosa are common among patients with hereditary hemorrhagic telangiectasia and usually affect the nose, oral mucosa and gastrointestinal tract; while AVMs develop most commonly in the lungs, liver and central nervous system.

Spontaneous and recurrent epistaxis secondary to nasal telangiectasias occurs in more than 90% of patients with hereditary hemorrhagic telangiectasia. This is the most common manifestation. Nasal bleeding, which usually appears early in childhood, can be mild with no treatment required or severe with transfusions required. Uncontrolled recurrent epistaxis may cause anemia.

Pulmonary AVMs are present in at least 30-50% of patients with HHT, while hepatic and cerebral AVMs are present in 30% and 10-20% respectively. Fistulae in the epidural space and spinal cord have been reported in 1% of cases[2].

In general, treatment of HHT is aimed at: (I) control of local and systemic symptoms; (II) surveillance for and of lesions; and (III) measures to prevent complications associated with AVM.

Advances in imaging studies, including helical CT scanning, magnetic resonance imaging (MRI), magnetic resonance venography (MRV), magnetic resonance arteriography (MRA) and endo- scopic imaging, have made it easier to accurately diagnose and treat HHT without performance of invasive procedures, such as surgical exploration or angiograms. A helical CT scan with 3 mm cuts is preferred for evaluation of pulmonary AVM.

Genetic testing for endoglin, ALK1/ACVRLI and Smad4 is available and can confirm the diagnosis for the family, and confirm or refute the diagnosis in family members.

In normal pregnancy, complex physiological vasodilatory responses are associated with an increase in cardiac output that approaches 50% by the end of the second trimester. Cardiac chamber and aortic dimensions increase in normal pregnancies resulting in increased pulmonary blood flow. This may lead to dilatation and rupture of thin-walled pulmonary AVMs. rendering HHT pregnancies high risk for hemorrhages[4]. Moreover, in the hypercoagulable state of pregnancy there is an increased risk of thrombus formation and thromboembolism[4], as well as amniotic fluid or air embolism during delivery. These may embolize to the lung or may traverse the malformation and produce paradoxical emboli in the systemic circulation. Emboli embedding in the lung may cause normal vessels to constrict from hypoxia resulting in potential increases in the shunts across the AVMs.

While the vast majority of pregnancies proceed uneventfully, the mortality rate[4] is significantly increased due to pulmonary AVMs haemorrhage, strokes and myocardial infarction. Any haemoptysis or sudden severe dyspnoea should be considered a potential emergency, prompting immediate hospital admission.

Thus, all pregnancies with HHT should be considered high risk[5], and women should be advised about the small but serious risks, though reassured that these appear less threatening where medical and obstetric services are aware of the complications.

Recommendations to date is to perform cerebral imaging if warranted by family history and to consider spinal MRI in those cases in which the possibility of spinal AVMs would lead obstetric anaesthetists to withhold epidural analgesia, to avoid severe complications such as sub-arachnoic hemorrhages, progressive myelopathy, radicular pain.

Antibiotic prophylaxis during delivery is recommended to avoid bacterial endocarditis both in patients with or without AVMs.

The risks of general anaesthesia must be considered. Positive pressure ventilation may cause worsening of arterial oxygenation in patients with pulmonary AVMs. This may lead to dilatation and rupture of thin-walled pulmonary AVMs. Moreover, the stress response during induction of anaesthesia might contribute to in-

creased blood flow to this abnormal vasculature with increased risk of rupture and haemorrhage. Considering the recognized benefits of regional anaesthesia in the general obstetric population, as well as in patients with HHT who have no evidence of neurological involvement, we would recommend early screening of patients with HHT for the presence of spinal cord or cerebral AVMs to optimise perioperative anaesthetic management.

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