

## Rare case of CADASIL disease associated to Factor V Leiden mutation in pregnancy

### Caso raro de doença de CADASIL associada a mutação do Factor V de Leiden na Gravidez

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#### Abstract

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) disease and thrombophilia are a real challenge to the obstetrician. Affected women may develop adverse events during pregnancy (transient ischemic episodes, migraine, and preeclampsia-like symptoms). We report a case of CADASIL disease in a 29-year-old pregnant, nulliparous, with two spontaneous abortions, heterozygous for factor V Leiden mutation and family history of CADASIL disease. The patient suffered from occasional migraine attacks with aura. She was medicated with low molecular weight heparin and aspirin and at 32 weeks experienced a CADASIL disease manifestation - migraine with aura that simulates preeclampsia-like symptoms. However, the pregnancy was uneventful with a normal outcome.

**Keywords:** CADASIL disease; Preimplantation genetic diagnosis; Inherited thrombophilias; Differential diagnosis; Multidisciplinary team.

#### INTRODUCTION

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is an autosomal dominantly inherited neurological condition caused by non-atherosclerotic and non-amyloidotic micro-angiopathy caused by mutations in the NOTCH3 gene on chromosome 19<sup>1</sup>.

Patients with CADASIL usually present with one or more of the following manifestations: ischemic episodes, cognitive deficits, migraine with aura and/or psychiatric disturbances. This syndrome is an important cause of stroke<sup>2,3</sup>. Less common manifestations include "CADASIL coma" (acute reversible encephalopathy), seizures, spinal cord signs and spinal cord infarcts<sup>4-6</sup>. The clinical course of CADASIL is highly variable. The diagnosis is established by genetic analysis with documentation of a typical NOTCH3 muta-

tion, or by skin biopsy showing granular osmiophilic material (GOM) within small blood vessels<sup>7-9</sup>. There is no specific disease-modifying treatment for CADASIL, and only limited information is available regarding management of the major manifestations of the disorder<sup>10</sup>.

Pregnancy is an acquired hypercoagulable state that can lead to gestational vascular complications. The presence of other prothrombotic risk factors, especially some heritable thrombophilia have been suspected to be associated with thrombotic events in pregnancy. The major heritable forms of thrombophilia include deficiencies of antithrombin (AT), protein C and protein S, abnormalities of procoagulant factors, particularly, factor V Leiden (FVL) and the prothrombin G20210A gene mutation (PGM). There are some scientific interrogations if women with heritable thrombophilia are at increased risk, not only for pregnancy-related venous thromboembolism (VTE), but also for other vascular pregnancy complications, including fetal loss, preeclampsia and intrauterine growth restriction (IUGR)<sup>11,12</sup>. As the evidence is still unclear and controversial; questions about the clinical management of pregnant women with thrombophilia are a daily issue.

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## CASE PRESENTATION

A 29-year-old caucasian pregnant woman, with two early spontaneous abortions, personal and family history of CADASIL disease, who is heterozygous for factor V Leiden mutation, with hyperhomocysteinemia and heterozygous for MTHFR 1298C presented to Bissaya Barreto Maternity Hospital for prenatal care at 9 weeks of gestation.

The diagnosis of CADASIL was already confirmed by genetic test. The patient complained of headache for 4 years (1 to 2 episodes/year). The headache was moderate and throbbing, generally located in the vertex, accompanied by nausea and vomiting that relieved with analgesic or non-steroidal anti-inflammatory drugs. She had acetazolamide to prevent migraine attacks.

She had menarche at age 13 and referred regular menstrual cycles lasting 5 days with a normal flow. The patient had no surgical intercurrentence.

Her family history revealed that her father died at the age of 56 years from ischemic cerebrovascular disease, after 5 years of progressive subcortical dementia, recurrent ischemic events and seizures. Her sister had a history of similar illness with recurrent ischemic episodes and cognitive problems.

The patient was medicated with folic acid before conception. She stopped aspirin when she knew she was pregnant. Low-dose aspirin was re-initiated subsequently and low-molecular-weight heparin (LMWH) – enoxaparin, a subcutaneous injection of 40 mg daily was introduced at the 10<sup>th</sup> week.

Amniocentesis was performed for cytogenetic study (46,XX) because the nuchal translucency (NT) measurement in the first-trimester ultrasound was increased (>P95). We offer to carry out prenatal diagnosis of molecular CADASIL, but the patient refused. Ultrasound demonstrated a normal fetus, and serial ultrasound documented normal growth. Routine studies were normal, including blood pressure. She was followed by Neurology, Hematology, Genetics and Obstetrics.

The patient attended the Maternity with 32 weeks pregnancy, complaining of headache, nausea and vomiting as well as visual disorders for the last few hours. Blood pressure was 148/94mmHg, physical examination was normal, and no pathological focal neurological deficit was found. Investigation included hematological, coagulopathy, biochemical studies with liver function and urinalysis. Differential diagnosis could be preeclampsia, a manifestation of her underlying disease, including migraine or a transient is-

chemic episode. More rare but important differentials such as intracranial haemorrhage/tumors were taking in count. In this episode, symptoms relieve and blood pressure normalized after intravenous paracetamol. The investigation results were within normal limits and the patient remained asymptomatic. The patient was discharged a few hours later.

The pregnant presented in spontaneous labor at 38 weeks. A forceps was performed to deliver a 3310g newborn female, with an *Apgar* score of 9 and 10 at one and five minutes, respectively, and a normal outcome. There were no complications in the puerperium. Enoxaparin was administered until the sixth week postpartum.

## DISCUSSION

CADASIL disease and thrombophilia are a real challenge to the Obstetrician. In this case, the presence of CADASIL disease and heterozygous mutation for factor V Leiden conferred an elevated risk of adverse events during pregnancy and postpartum. In the third trimester of pregnancy occurred a CADASIL disease manifestation – migraine with aura. This manifestation simulates preeclampsia and the differential diagnosis is essential because the symptoms are similar, but therapeutics and prognostics very distinctive. In a retrospective analysis, 12 of 25 mothers (48%) with genetically confirmed CADASIL disease developed neurologic symptoms in 40% of their pregnancies. Complications included transient ischemic episodes, migraine, and preeclampsia-like symptoms. In the majority of cases, these complications were the initial disease manifestation. Preeclampsia was also frequently (10.3%) in CADASIL patients than in normal population (3 to 5%). However, preeclampsia occurred most often in later pregnancies (opposite of normal population)<sup>13</sup>. CADASIL should, therefore, be considered when searching for causes of transient or permanent stroke-like events during pregnancy or the puerperium. Other clinical manifestations linking CADASIL disease and pregnancy may be psychiatric or neurologic. During puerperium, women with CADASIL disease may present with acute psychosis as a first sign of the disease<sup>14</sup>. Thus, CADASIL should be considered in the differential diagnosis of women with postpartum psychiatric disturbances.

Another relevant point concerning this case is that prenatal testing for the disease is possible for fetuses using the same DNA-based techniques used for adults. DNA extracted from fetal cells obtained by amniocen-

tesis or by chorionic villus sampling can be tested for mutations in Notch3<sup>15</sup>. Similarly, preimplantation genetic testing of embryos following in vitro fertilization can be utilized to select CADASIL-free embryos for implantation<sup>16</sup>. In all cases, ethical issues and genetic counseling should precede molecular analysis. In this case, amniocentesis was performed for cytogenetic study because NT was superior to 95<sup>th</sup> percentile and the parents wanted to exclude chromosomal disorders but they did not want to know about CADASIL disease. We offer to carry out prenatal diagnosis of molecular CADASIL because each child of an affected person is at 50% risk of inheriting the mutation and developing signs of the disease and to give specific supportive care and counseling to the family.

It is recognized that successful pregnancy outcome depends on the development and maintenance of an adequate utero-placental circulation, with evidence that prothrombotic factors underlie some pregnancy losses.<sup>17</sup> Some data also implicate heritable thrombophilia in pregnancy loss; however, a definitive link cannot be made. The decision to treat with thromboprophylaxis, anticoagulant therapy, or no pharmacologic treatment is influenced by the venous thromboembolism history, severity of inherited thrombophilia, and additional risk factors<sup>18</sup>. Despite this, data examining pregnancy success with the use of antithrombotic therapy in women with heritable thrombophilia are inconclusive. However, it has also been suggested that heparin could be of benefit in preventing pregnancy loss in women without thrombophilia. Although LMWHs and low-dose aspirin are generally seen as being safe, there is no direct evidence of efficacy. As a result, there have been repeated calls for randomized trials in this area, particularly a comparison of anticoagulant treatment with no pharmacologic intervention<sup>19</sup>. After assessment-individualized risk, the patient has been medicated with low-dose aspirin and LMWH to prevent neurologic events of CADASIL disease and gestational vascular complications. In this case, there were no complications during pregnancy and puerperium. Besides the fact that benefit of antiplatelet agents for CADASIL has not been proven, some data refer that aspirin and related medications are useful to prevent thrombotic occlusion of cerebral arteries<sup>20</sup>.

We think that careful diagnosis, observation, monitoring and therapeutic add significant benefit during pregnancy and a multidisciplinary team is essential to a successful fetal-maternal outcome, as demonstrated in this high-risk pregnancy.

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