Two Women with Cerebral Venous Thrombosis: Oral Contraceptives?

VM dos Santos[1,2], LM Andrade[2], CT Leal[2], LA de Souza[2], RLM Lima[3], AL Nogueira[1]

ABSTRACT

Two cases of cerebral venous thrombosis are reported. Patients were apparently healthy 39 and 28-year old females with non-specific presenting features. Image findings were characteristic of cerebral sinus thrombosis. The younger patient received progesterone to treat placental abruption eight years previously; she had cerebral venous thrombosis while using oral contraception. Both patients had used contraceptive pills for a long time. Oral hormonal contraceptives may increase the risk of vascular events, even in people without personal or family history of venous thrombosis. Modern imaging methods have contributed to early diagnosis, but the possibility of under diagnosis still persists. This report aims to increase the awareness of health-workers about cerebral venous thrombosis in women, an entity often misdiagnosed, under diagnosed and under-reported.

Keywords: Cerebral venous thrombosis, oral hormonal contraceptive, pregnancy

Dos Mujeres con Trombosis Venosa Cerebral: ¿Anticonceptivos Orales?

VM dos Santos[1,2], LM Andrade[2], CT Leal[2], LA de Souza[2], RLM Lima[3], AL Nogueira[1]

RESUMEN

Se informan dos casos de trombosis venosa cerebral. Las pacientes eran mujeres aparentemente saludables, 39 y 28-años de edad, con presentación clínica non-específica. Los dados de exámenes de imagen eran característicos de trombosis del seno cerebral. La paciente más joven recibió progesterona para tratar desprendimiento de placenta, y ocho años antes había presentado trombosis venosa cerebral mientras usando anticoncepción oral. Ambas pacientes habían usado las píldoras anticoncepcionales durante mucho tiempo. Los contraceptivos hormonales orales pueden aumentar el riesgo de eventos vasculares, incluso en las personas sin antecedente personal o familiar de trombosis venosa. Las nuevas técnicas de imágenes han contribuido al diagnóstico temprano, pero la posibilidad de diagnóstico insospechado todavía persiste. El propósito de este informe es aumentar el índice de sospecha de profesionales de la salud sobre la trombosis venosa cerebral en mujeres, entidad a menudo erróneamente diagnosticada, infradiagnosticada y no reportada.

Palabras-clave: Trombosis venosa cerebral, contraceptivo hormonal oral, embarazo

INTRODUCTION

Cerebral venous thrombosis (CVT) is not uncommon, but may be misdiagnosed, underestimated and under-reported because of heterogeneous clinical presentations (1–3). Cerebral venous thrombosis often affects females (75%) and the main presenting features are headache, focal neurological deficits, and seizures (3). Headache is the most frequent, and may occur isolated or associated with intracranial hypertension or focal signs (1–6). Diagnosis can be characterized by brain imaging studies (1–7). Predisposing factors of CVT include infections, oral hormonal contraceptive (OHC), hormonal replacement therapy, pregnancy, puerperium, prothrombotic disturbances, haematologic disorders, malignancies and systemic inflammatory diseases (1, 4–9). In 14% of the women without gender-specific risk factors (contraceptive pills, hormonal replacement, pregnancy or puerperium), no risk factor may be found (6). The outcome is variable and complete recuperation is frequent, but mortality rate can reach 10–20% (1, 3, 5). Patients often improve

From: [1]Catholic University Medical Course, [2]Armed Forces Hospital (HFA), Brasília-DF, Brasil, [3]Angolan physician in the postgraduate training programme of HFA, Brasília-DF, Brasil.

Correspondence: Dr VM dos Santos, SMPW Quadra 14, Conjunto 2, Lote 7, Casa A, 71.741-402, Brasília-DF, Brazil. Fax: +55 6133802666, e-mail: vitorinomodesto@gmail.com

after heparin and oral anticoagulation (1, 4–9). Even without other predisposing conditions, women utilizing third generation OHCs may have increased risk of cardiovascular events, mainly if associated with high levels of triglycerides and C-reactive protein (10). The aim is to increase the awareness about CVT in the ambulatory and emergency settings, because misdiagnosis often occurs if clinical features and brain images are analysed without considering predisposing factors (1–3). Early diagnosis and timely anticoagulation can contribute to favourable outcome (1–3).

CASE REPORTS

Case 1: A 39-year old woman presented with severe acute right fronto-temporal headache, followed by right hemiparesis, confusion, disorientation and fainting. She had used OHC (ethinylestradiol plus cyproterone acetate) for a long time. There was no antecedent of smoking and alcohol abuse, neither family nor personal history of thrombophilia. Body mass index (BMI) was 24 Kg/m^2. On admission, her physical evaluation was unremarkable, except for right hemiparesis. Routine laboratory data were haemoglobin: 14.4 g/dL, leukocytes: 6.6 x 10^6/mm^3, platelets: 326 x 10^6/mm^3, ESR: 7 mm/hour, D-dimer: 703 ng/dL, bleeding time: 1', coagulation time: 5'3, prothrombin time: 13.4, prothrombin activity: 93%, INR: 1.04, aPTT: 30, tryglicerides: 241 mg/dL (Castelli index 1:6.2 and Castelli index 2:5.9), homocysteine: 9.5 µmol/L, anticardiolipin: negative, ANA: negative, anti-dsDNA: negative, lupus anticoagulant (LA1/LA2): negative, C-protein: 124%, S-protein: 52% and antithrombin III: 30%. Neither hyperhomocysteinaemia, nor factor V Leiden mutation or prothrombin gene G20210A polymorphism was detected. Unenhanced computed tomography (CT) images were inconclusive. However, two days later magnetic resonance (MR) venography showed thrombotic obstruction of the straight sinus, which extended to the right transverse and sigmoid sinuses; in addition, a venous infarction in the thalamus and left lenticular nucleus was observed (Fig. 1). She improved rapidly following anticoagulant treatment and was referred for outpatient surveillance. In the present case, the current use of OHC was stopped on diagnosis of cerebral venous sinus thrombosis (CVST), and the patient was instructed about the longstanding utilization of non-hormonal contraceptive methods.

Case 2: A 28-year old woman presented with acute unilateral right-sided pulsatile headache during the 14th week of pregnancy. In another hospital, she had been treated with progesterone because of imminent placental abruption three weeks previously. She reported an episode of CVT eight years ago, during the use of ethinylestradiol plus cyproterone acetate, and the control imaging studies at discharge were normal. The patient stated that she utilized OHC until two months before the actual pregnancy. On admission at our Department, she complained of severe headache, and denied antecedent smoking, alcohol abuse, and family or personal history

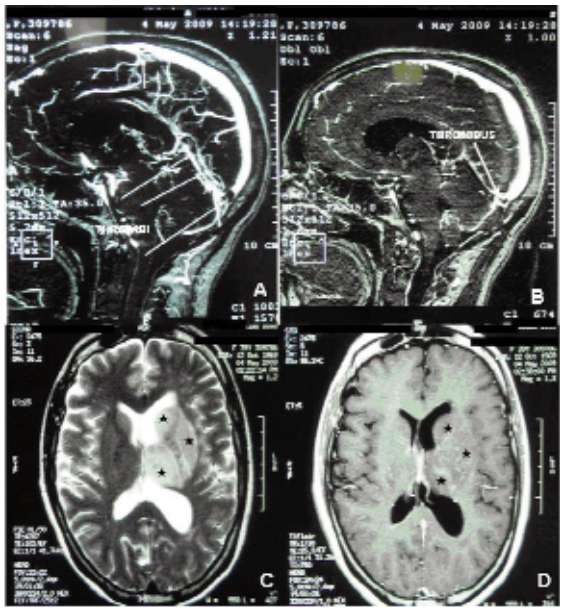

Fig. 1: A and B: Contrasted cerebral angioresonance showing thrombosis in the lower sagittal and straight sinuses, as well as in the torcula Herophili (arrows). C and D: images of magnetic resonance weighed in T2 and T1 post-contrast showing accentuated oedema and luxuriant vasculature in the thalamus and in the left basal ganglia (stars).

of thrombophilia. Body mass index was 23 Kg/m^2. Physical examination was unremarkable, except for a normal pregnant uterus. Routine laboratory data were haemoglobin: 13.0 g/dL, leukocytes: 8.9 x 10^6/mm^3, platelets: 140 x 10^6/mm^3, ESR: 16 mm/hour, prothrombin time: 16.9, prothrombin activity: 66%, INR: 1.34, aPTT: 27.8, tryglicerides: 165 mg/dL, C-reactive protein: 1.67 mg/dL, anticardiolipin: negative, ANA: negative, anti-DNA: 5.0 U/mL, anti-SM: 2.8 U/mL, anti SS-A: 3.3 U/mL, anti-SS-B: 3.0 U/mL, lupus anticoagulant: negative, rheumatoid factor: negative, C-protein: 100%, S-protein: 39% and antithrombin III: 80%. Moreover, hyperhomocysteinaemia, mutation in factor V Leiden and prothrombin gene G20210A polymorphism were not found. The images of MR venography demonstrated transverse, sigmoid and sagittal sinus thrombosis (Fig. 2). Heparin and oral anti-coagulant were used and she improved very well. A month later, the control images revealed normal venous flux. With estimated date of delivery 6.5 months away, she was referred for surveillance at a high-risk obstetrics clinic.

DISCUSSION

Two non-obese and non-smoking apparently healthy women with CVT are reported (10). Both had been utilizing OHC for a long time before their cerebrovascular events; moreover, the younger woman was pregnant and had utilized progesterone. Their ages are in the age range more frequently reported in cases of CVT (5), the presenting signs and symptoms were in accordance with previous descriptions (1, 4, 5), and their outcomes were favourable with heparin and oral

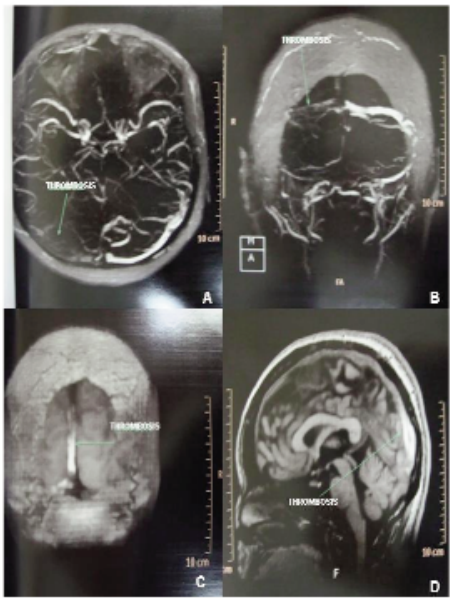

Fig. 2: Contrasted cerebral angioresonance showing images of thrombosis in the right transverse and sigmoid sinuses, and in the superior sagittal sinus (arrows).

anticoagulation (1–4, 9). Except for OHC, pregnancy/progesterone, no other risk factor for CVT had been previously detected in both cases. However, protein S and antithrombin deficiency were found in Case 1, while recurrent CVT affected the patient in Case 2, who showed protein S deficiency in addition to high levels of triglycerides and C-reactive protein (10).

In the present case studies, protein C and S levels and functional activity were evaluated. Oral hormonal contraceptive can impair anticoagulant activity of protein S by changes in plasma proteins that influence the modulation of this activity, or by changes in the protein S molecule (11). Moreover, acquired activated protein C resistance has been described in users of third generation OHCs (12). Pregnancy and puerperium are also associated with a hypercoagulable state related to dehydration, anaemia and protein S deficiency (13). Reports about a relationship between progestogens and venous thrombosis are scarce, but recent data indicate that norpregnane derivatives may increase thrombogenic risks (14).

Before modern imaging methods became available, the occurrence of CVT was considered an uncommon condition, often evolving with unfavourable outcome (1, 4). Saadatnia *et al* reviewed the aetiologies of CVT, including: otomastoid, orbit and face infections, intracranial tumours, other malignancies and paraneoplastic conditions, OHC, pregnancy and puerperium, systemic and autoimmune diseases, dehydration, coagulopathies, fibrous thyroiditis, jugular thrombosis, surgery and head trauma, and arterial-venous malformations (8). They described CVT as a rare disease without underlying cause in 30% of cases (8). Worthy of note, studies about the role of OHC in the origin of CVT have shown varying data depending on the patients' ethnic groups. Alonso-Cánovas *et al* reviewed data from 79 Spanish patients with CVT and found 54.4% females, with median age of 46 (2–82) years. Thrombophilia occurred in 27.8% and use of prothrombotic drugs in 25.3%, while 16.5% of the total was idiopathic. The main symptoms were headache (77.2%) and motor deficits (15.2%). Thrombosis was more frequently seen in the transverse (57%) and superior sagittal (49.4%) sinuses. Recurrent CVT was found in 5.9% of cases, and mortality rate was 13.9% (9). The authors emphasized the high frequency of thrombosis in multiple sinuses (60.8%) and the lower association with OHC (29%) than is usually described (54–70%); but the low proportion of females was attributed to absence of obstetric pathology in their hospital. Moreover, they highlighted the relationship between CVT and antineoplastic hormone therapy, including tamoxifen, oestradiol and GRHA (9). Azin and Ashjazadeh prospectively studied 61 patients with CVT in the south of Iran, and found 73.8% females, with mean age of 35.6 ± 12.1 years (4). Thrombophilia occurred in 24% and use of OHC in 62.2% of cases; 4.9% of the women were pregnant. Headache occurred in 91.8%, and motor deficit was found in 29.5% of cases. Thromboses were more common in the superior sagittal (80.3%) and lateral (41%) sinuses; mortality was 14.8% (4). Flores-Barragán *et al* studied 14 women and six men with CVT in Spain, from 1996 to 2008 (6). There were 11 in-patients and nine ambulatory patients, age range 22 to 75 years; the main symptom was headache (60%), and focal deficit occurred in 20% of cases. Worthy of note were the unusually high number of subacute (35%) and chronic (35%) presentations, and no occurrence of death. Pregnancy/puerperium and use of OHC were causal factors, respectively in 10% and 15% of the cases, while no aetiology could be disclosed in 40% of the patients (6). Khealani *et al* analysed prospective and retrospective data of 109 patients with CVT in South Asia and the Middle East and found 53% of females with mean age of 33.2 ± 10.44 years; 31% of them were in the postpartum period, while only 12% utilized OHC (7). Primary or acquired thrombophilia was found in 34% of cases. Main symptoms were headache (81%), motor deficits (45%), and mental status changes (37%). Thromboses were more frequent in the superior sagittal (71%), followed by transverse (47%), sigmoid (31%), and the straight (10%) sinuses. Mortality range among females was 2.75% (7). The differences between the findings of Khealani *et al* and those from the western studies were emphasized, including the higher rate of postpartum state and central nervous system infections (7). While OHC is not a main risk factor in South Asia and the Middle East because of low use (7), the two women reported here showed some of the predisposing factors that were observed in studies involving females from those areas (4, 7).

Diagnostic suspicion of CVT is based on suggestive data of ischaemic stroke not following the distribution of the arterial tree, with conspicuous vasogenic oedema (3). Direct

signs of sinus thrombosis include triangle sign, empty delta sign and replacement of MRI flow void; and, as imaging studies are needed to characterize this diagnosis, mild CVT with subtle features may be more frequent than have been reported (1, 2). Therefore, this entity could be clinically mistaken with conditions causing mild, reversible neurological disturbances. Diagnostic challenges include limited knowledge about CVT, subtle/non-specific features, unavailable imaging study and spontaneous improvement. The aim is to increase the awareness of CVT in young women utilizing OHCs.

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