

# CEREBRAL VENOUS THROMBOSIS AND HEPATITIS

## Case report

André Carvalho Felício<sup>1</sup>, Márcia Maiumi Fukujima<sup>2</sup>, Jose Antônio Fiorot Jr<sup>1</sup>, Gilmar Fernandes do Prado<sup>1</sup>, Roberto José de Carvalho Filho<sup>3</sup>, Celso Arrais Rodrigues<sup>4</sup>, Vânia Maris Morelli<sup>4</sup>, Dayse Maria Lourenço<sup>4</sup>

**ABSTRACT** - Among the many infective causes of cerebral venous thrombosis (CVT), viral hepatitis is been regarded as a rare associated condition. We report on a 56-years-old man presenting CVT associated with hepatitis B and C coinfections outlining probable pathogenic mechanisms. We suggest that virus B and C serology should be performed in the cases of cerebral venous thrombosis with unknown etiology.

**KEY WORDS:** cerebral venous thrombosis, hepatitis B virus, hepatitis C virus.

### **Trombose venosa cerebral e hepatite: relato de caso**

**RESUMO** - Dentre as várias causas infecciosas de trombose venosa cerebral (TVC), a hepatite viral tem sido reconhecida como causa rara de TVC. Relatamos sobre um homem de 56 anos com TVC associada a coinfeção pelos vírus B e C da hepatite, ressaltando possíveis mecanismos patogênicos. Sugerimos que sorologia para vírus da hepatite B e C deveria ser solicitado em todos os casos de TVC de origem indeterminada.

**PALAVRAS-CHAVE:** trombose venosa cerebral, vírus da hepatite B, vírus da hepatite C.

The main recognized causes or predisposing conditions to cerebral venous thrombosis (CVT) can be divided into two groups: infectious (either local or systemic) and non-infectious causes<sup>1-3</sup>. There is also a third group without specific etiology, which may correspond to 20% to 35% of the total causes<sup>4</sup>. Chronic hepatitis C virus (HCV) infection has been considered as a rare cause of cerebral venous thrombosis<sup>5-10</sup>.

We report a case of such association and discuss possible physiopathogenic mechanisms.

### **CASE**

A 56-year-old white man was admitted to our hospital with a 15-day history of headache worsening with considerable change in its frequency and intensity patterns. He was a chronic daily headache sufferer taking amitriptyline 75 mg and propranolol 80 mg per day and had already taken several abortive treatment regimens. Four days before admission he had two episodes of focal motor seizure. His past history included heavy smoking and drinking. He took intravenous cocaine for 20 years until 12 years ago. He also had occasional bisexual relations. General physical examination was unremarkable. Neurological exam abnormalities included left mild hemiparesis. Pain relief medication was initiated as well as carbamazepine 600 mg per day.

Routine blood and urine exams were unremarkable. On cerebral spinal fluid (CSF) the initial pressure was 33 cm/H<sub>2</sub>O with cell count and biochemistry within normal parameters.

Chest radiograph was normal such as cranial computed tomography scan (CT). Cranial magnetic resonance imaging (MRI) indicated superior sagittal and left transverse sinuses thrombosis associated to corpus callosum and right parietal hemorrhagic venous infarcts. New blood sample was taken in order to investigate possible secondary etiologies and on that time venous non-fractionated heparin was initiated.

Values of serum immunoglobulins were: IgA=151 mg/dL (78-367 mg/dL), IgG=703 mg/dL (583-1761 mg/dL) and IgM=69 mg/dL (52-335 mg/dL). The following autoantibodies were negative: antinuclear, anti-ds-DNA, anti-Sm, rheumatoid factor, anti-Scl-70, RNP, anti-SS-A/Ro, anti-SS-B/La, IgM and IgG anticardiolipins and ANCA. Serum complement values were CH50=219 UI/mL (Normal value, NV=130-330 UI/mL) and C2=100% (NV >70%). Cryoglobulins were also negative.

Results from blood serology were as follow: VDRL negative; anti-HCV positive (enzyme immunoassay); HBsAg negative, anti-HBc positive and anti-HBs positive (prior hepatitis B virus infection); Chagas' disease negative; HTLV-I/II negative and HIV negative. Chronic HCV infection was confirmed through serum HCV RNA detection by PCR technique. Thrombophilic states were sought but antithrombin III, factor V Leiden and protein C and S levels were within normal limits.

Departments of Neurology<sup>1</sup>, Internal Medicine<sup>2</sup>, Gastroenterology<sup>3</sup>, Hematology<sup>4</sup> of the Escola Paulista de Medicina - Universidade Federal de São Paulo, São Paulo SP, Brazil (UNIFESP).

Received 3 May 2006, received in final form 2 August 2006. Accepted 18 September 2006.

Dr. André Carvalho Felício - Avenida Bosque da Saúde 834 / 193 - 04142-081 São Paulo SP - Brasil. E-mail: cf.andre@terra.com.br

Anticoagulation was maintained with warfarin for six months and then suspended. Hepatological follow-up was initiated but the patient refused liver biopsy. He is still referring headache but less frequently and less intense and takes phenobarbital 100 mg per day. General and neurological exams are unremarkable.

The patient signed informed consent allowing his personal data publication.

## DISCUSSION

There is considerable evidence that prothrombotic states may develop soon after atherothrombotic or cardioembolic cerebral infarct. Cerebral venous thrombosis, on the other hand, is usually a consequence of these procoagulant conditions<sup>11-13</sup>.

Though reported mechanisms of cerebral venous thrombosis in patients with hepatitis B and C are not fully understood, there is growing evidence that these viruses alone or in combination with a series of other factors may shift the delicate procoagulant/thrombolysis balance toward thrombosis<sup>10</sup>.

It is known that hepatitis C virus (HCV) infection may be associated with anticardiolipin antibodies. Thus, HCV might lead to thrombotic complications and should be considered as one of the antiphospholipid syndrome possible causes<sup>6,7</sup>. In the present case, anticardiolipin antibodies were negative as well as other autoantibodies.

Subjects with chronic hepatitis C who are receiving interferon-alpha (INF-alpha) have an increased risk of diabetes mellitus and hypertriglyceridemia<sup>14,15</sup>. Therefore, INF-alpha can be considered as a risk factor for hypercoagulable states. In addition, either INF-alpha or HCV have been reported to induce a variety of antibodies, not only anticardiolipin but also cryoglobulins, rheumatoid factor, antinuclear, antismooth muscle, anti-LKM and antithyroglobulin<sup>5,16</sup>. Since the diagnosis of hepatitis came while investigation was carried out our patient was not receiving INF-alpha or any other medication that could increase thrombosis risk.

In spite of the possible relationship between HCV and antiphospholipid syndrome, other data suggest that HCV, *per se*, might be responsible for thrombotic events<sup>8</sup>. It is speculated that the HCV envelope protein has a procoagulant activity and that the virus genome encodes serine proteases that could also act as procoagulant<sup>17</sup>.

In this case, the possibility of a pathogenic role of occult hepatitis B virus (HBV) infection can not be fully discarded, since molecular tests for HBV DNA detection have not been done<sup>18</sup>. Nonetheless, we could find only one report of cerebral venous thrombosis

associated to hepatitis B (HBV). That was the case of a 43-year-old male who presented with seizures and had a previous history of HBV. He developed a left transversal sinus thrombosis associated to left temporal posterior hemorrhagic infarct. On investigation, anticardiolipin antibodies were negative though there was an antithrombin III and protein C deficiency<sup>9</sup>. In the present case, there was also the association between sinus thrombosis and hemorrhagic venous infarct. However, antithrombin and protein C levels were normal.

To conclude, since our patient was not taking INF-alpha and any identifiable procoagulant cause was recognized, the hypothesis of HCV (and maybe HBV) as thrombogenic agent deserves further attention. We also suggest that HCV and HBV tests should be routinely included in the investigation of cerebral venous thrombosis of unknown etiology.

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