

# Magnetic resonance imaging in central nervous system vasculitis in a patient affected by crioglobulin-negative hepatitis C virus infection: A likely correlation

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# Abstract

A 56-year-old man with behavioural disorders and facial-brachio-crural right hemiparesis presented with a brain lesion studied with computed tomography, magnetic resonance imaging and brain biopsy, leading to the diagnosis of cerebral vasculitis. Hepatitis C virus (HCV) infection in a phase of activity, without cryoglobulins, was also detected. Brain biopsy, laboratory analysis and response to a specific therapy supported the diagnosis of central nervous system vasculitis that was HCV related.

## Keywords

Central nervous system, cryoglobulin, HCV, MRI, vasculitis

## Introduction

Hepatitis C virus (HCV) infection is well-known as a common cause of liver disease.<sup>1</sup> Chronic HCV infection is often associated with abnormal immunological responses that can result in several extra-hepatic conditions.<sup>2</sup>

A large number of neurological manifestations may occur in patients with chronic HCV infection, independently of the severity of liver disease, including metabolic, inflammatory and autoimmune conditions affecting the central nervous system (CNS), as well as the peripheral nervous system and muscles.<sup>3</sup>

CNS vasculitis in HCV infection is a possible complication, generally related to the presence of mixed cryoglobulinaemia – defined as the presence in serum of single or mixed immunoglobulins. There are few data in the literature concerning HCV-related vasculitis without serum cryoglobulins.<sup>2,4</sup>

# Case report and technical note

A 56-year-old man with a history of drug abuse (heroin and cocaine) and with known HCV was seen at our clinic. He presented with behavioural disorders characterised by disinhibition and aggression. He developed an acute mild right facial hemiparesis.

A computed tomography (CT) scan of the head demonstrated an area of mild hypodensity in the left frontal hemisphere. A brain magnetic resonance imaging (MRI) scan was also performed. A large area of inhomogeneous T2 hyperintensity was evident in the white matter of the left parietal lobe, with corresponding mild T1 hypointensity (Figure 1). No restriction of diffusion was reported. After the injection of contrast medium, a pathologic enhancement with a nodular aspect was recognised. A perfusion MRI and vascular study were normal. Single voxel H<sup>1</sup>-MR spectroscopy demonstrated an inversion of N-acetyl-aspartate/ choline ratio (NAA/Cr=0.78; Cho/Cr=1.73) in the altered white matter of the left hemisphere.

Laboratory data on serum and liquor excluded infectious and immunological causes. In particular, levels were within the normal range, and cryoglobulins, antinuclear antibodies (ANA) as well as anti-neutrophil cytoplasmic antibodies (ANCA) were negative.

The clinical condition of the patient rapidly worsened, as he presented a progressive right facialbrachio-crural hemiparesis and a neurocognitive dysfunction. A second brain MRI detected an increased extension and an augmented pattern of contrast

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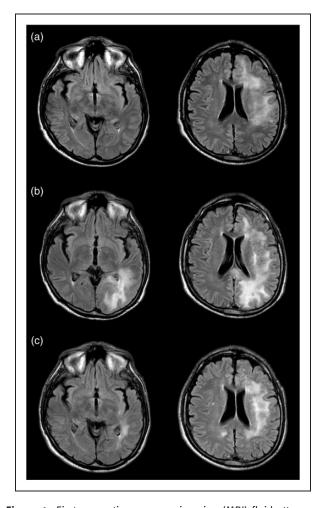
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enhancement of the alteration previously reported. Therefore, we decided to proceed with a brain biopsy (Figures 1 and 2).

The histological exam excluded the neoplastic nature of the cerebral lesion and suggested the presence of an

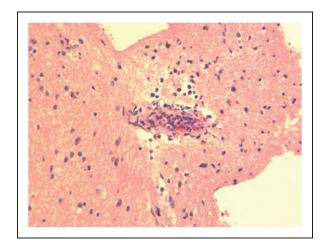


**Figure 1.** First magnetic resonance imaging (MRI) fluid-attenuated inversion recovery scan. Inhomogeneous hyperintensity in the white matter (a), with an increased extinction in the second MRI performed (b). Third MRI performed after therapy revealed an important regression of the white matter alteration.

inflammatory/vasculitic process of the small vessels (Figure 3). At the same time, laboratory data and liver fibroscan confirmed the presence of hepatic HCV infection in a phase of activity.

The principal diagnostic hypothesis was therefore a vasculitic process triggered by the HCV infection. A treatment approach based on an induction with three 1 g pulses of methylprednisolone followed by a steroid-free course of six administrations of intravenous cyclo-phosphamide (750 mg/each given every two weeks for the first three pulses and then every three weeks for the last three) was employed. Moreover, specific antiviral therapy was started, which resulted in the eradication of the HCV infection. After therapy, both the neuro-logical and the psychiatric status of the patient improved, with a progressive full recovery. Clinical remission was maintained up to three months from the last cyclophosphamide infusion.

A third brain MRI performed one month after the beginning of therapy revealed an important regression of the T2 alterations previously described (Figure 1).



**Figure 3.** Histologic exam: haematoxylin and eosin stain  $200 \times$ . Inflammatory/vasculitic process: small vessels surrounded and infiltrated by small uniform lymphocytes.

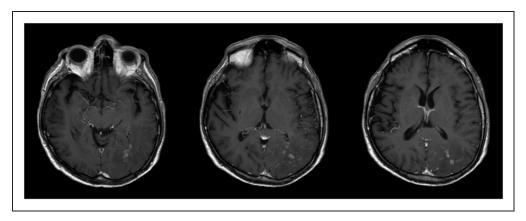


Figure 2. Turbo spin echo T1 scan after contrast medium injection shows typical vasculitic pattern of enhancement, with a nodular aspect, during the second MRI performed.

## Discussion

Specific CNS involvement is rarely reported in HCVinfected patients. There are few documented reports concerning patients with HCV-associated vasculitis, and those that are available mostly include cryoglobulin-positive patients.<sup>2</sup> In literature, few reports were found concerning HCV-related CNS vasculitis in a cryoglobulin-negative patient.<sup>5</sup>

The role played by HCV in the pathogenesis of autoimmune and neoplastic diseases remains uncertain. One hypothesis is that the infection is a component of a process with genetic and environmental co-factors.<sup>3</sup> An upregulation of the host immune response accompanied by production of autoantibodies, immune complexes and cryoglobulins has been demonstrated in disorders.<sup>3,6</sup> several HCV-related neurological Alternatively, the isolation of HCV RNA in microglial cells and astrocytes, as well as the evidence that brain endothelial cells are permissive for HCV entry and replication, suggest an independent life and a pathogenic role of the virus in the brain.<sup>7</sup>

Regarding the mechanism of CNS vasculitis in HCV infection, it has been postulated that recurrent cryoglobulin precipitation with complement fixation and/ or HCV-related induction of the innate mechanism of complement activation might be involved in ischemic and inflammatory tissue damage.<sup>8</sup>

There are no specific criteria to diagnose HVCrelated CNS vasculitis. In a recent report, Ferri et al. explain that the diagnosis of HCV-related extrahepatic manifestations is generally a supposed diagnosis based on the exclusion of other causes.<sup>9</sup> Several authors, for instance Carvalho-Filho and Castro Caldas, have described neurological HCV manifestations, suggesting a likely correlation.<sup>2,5</sup>

Our patient presented with an active HCV infection without detectable cryoglobulins, as well as other abnormalities/signs typical of a cryoglobulinemic vasculitis (e.g. low complement levels, purpura and kidney disease). Moreover, the immunological screening was negative, excluding an ongoing systemic immunological disease that could support the diagnosis of primary CNS vasculitis. Neuroradiological and histological data supported the hypothesis of a small-vessel vasculitic process. The fact that clinical remission was achieved, despite a mild, mostly steroid free, immunosuppressive induction approach, as well as its maintenance after the eradication of the HCV infection without the need of further immunosuppression, are, in our opinion, strong supporters of a likely HCV-mediated process.

This case suggests that HCV infection should be excluded in patients with CNS vasculitis, even in crioglobulin-negative patients, since specific therapy can lead to an improvement in prognosis.

## **Conflict of interest**

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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