Central Nervous System Involvement in Hepatitis C Virus Cryoglobulinemia Vasculitis: A Multicenter Case-Control Study Using Magnetic Resonance Imaging and Neuropsychological Tests

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ABSTRACT. ***Objective.*** Involvement of the central nervous system (CNS) in patients with hepatitis C virus (HCV) mixed cryoglobulinemia (MC) is rare. The mechanism by which brain lesions are produced is unclear. We investigated these phenomena by clinical evaluation (neuropsychological tests) and cerebral magnetic resonance imaging (MRI) studies in patients with HCV-MC vasculitis.

Methods. This prospective study included 40 patients with MC vasculitis and chronic active HCV infection (HCV RNA+), 11 HCV controls without MC, and 36 healthy controls, matched for sex and age. A battery of 10 standardized neuropsychological tests was administered by one experienced neuropsychiatrist. All patients underwent cerebral MRI investigation.

Results. Twenty-four of the 27 (89%) evaluated patients with HCV-MC had a deficiency in one or more of the 10 cognitive domains examined. The most commonly involved domains were those of attention (70%), executive functions (44%), visual construction (37%), and visual spatial functions (33%). The number of impaired cognitive functions was significantly higher in patients with MC vasculitis than in HCV controls (2.18 ± 1.84 vs 0.87 ± 3.1; $p < 0.05$). MRI analysis showed that HCV-MC patients had a higher mean number of total (7.03 ± 9.9 vs 0.90 ± 1.81 and 2.03 ± 3.1; $p < 0.05$) and periventricular (2.4 ± 3.0 vs 0.38 ± 0.5 and 0.8 ± 1.4; $p < 0.05$) white matter high intensity signals than HCV controls and healthy controls, respectively.

Conclusion. The high frequency of impaired cognitive function and the extent of MRI brain abnormalities in patients with HCV-associated mixed cryoglobulinemia vasculitis strongly suggest specific inflammatory involvement of the CNS. (J Rheumatol 2005;32:484–8)

Key Indexing Terms:
HEPATITIS C VIRUS EXTRAHEPATIC MANIFESTATIONS COGNITIVE FUNCTION
MIXED CRYOGLOBULINEMIA CENTRAL NERVOUS SYSTEM
NEUROPATHY, VASCULITIS MAGNETIC RESONANCE IMAGING

The syndrome of mixed cryoglobulinemia (MC) is characterized by the clinical triad of purpura, arthralgia, and asthenia associated with type II or type III MC[1]. Cryoglobulinemia vasculitis may involve numerous organs, particularly the peripheral nervous system and the skin. MC vasculitis is most often secondary to chronic hepatitis C virus (HCV) infection. The prevalence of peripheral nervous system involvement varies in the literature and can be as high as nearly 50% of cases[2,3]. Central nervous system (CNS) involvement with transient dysarthria, hemiplegia, or confusional states is more rarely reported in patients with MC[4,5], and may be the initial manifestation of HCV infection[6]. Cerebral magnetic resonance imaging (MRI) has revealed ischemic and/or hemorrhagic brain lesions[5,6]. The mechanism by which lesions are produced in the CNS is still unclear.

In this prospective collaborative study, 40 consecutive patients with type II MC secondary to HCV infection were tested with a cognitive assessment battery and also underwent cerebral MRI. Results were compared to those of 11 HCV controls without MC and 36 healthy volunteers,

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matched for age and sex. The objective was to identify associations between CNS involvement and HCV-associated MC vasculitis.

MATERIALS AND METHODS

Patients. In a collaborative study, we prospectively analyzed cognitive assessment and cerebral MRI in 40 consecutive patients with HCV-associated MC vasculitis. Patients were enrolled from 1999 to 2001 in the Internal Medicine departments of 2 hospitals (La Sapienza University Hospital in Rome, Italy, and La Pitié Salpêtrière Hospital in Paris, France). Patients were eligible for the study if they had chronic active HCV infection (HCV RNA positive), type II MC (which includes a monoclonal component), and at least one of the following signs of active vasculitis at the time of the study: skin purpura, peripheral neuropathy (documented by electromyography), renal disease (documented by biopsy), or other signs of systemic vasculitis. Patients were excluded if they had alcohol use > 30 g/day, cirrhosis, a history of stroke, or risk factors for atherosclerotic cerebrovascular disease. The duration of HCV-MC disease was calculated starting from the first reported sign or symptom of vasculitis.

Routine blood chemistry tests were performed, including measurement of glucose and cholesterol concentrations. Each patient's serologic status was determined using a microparticle enzyme immunoassay (axsym HCV, version 3.0, Abbott, Les Ulis, France) and a test for HCV RNA[7]. HCV genotyping was done using a second-generation Line Probe Assay (LiPA; Innogenetics, Brussels, Belgium). Cryoglobulins were measured using a described technique[8], whereby they were isolated from patient sera, purified, and then characterized by immunoblotting at 37°C. Among 40 HCV-MC patients, 24 (60%) had received interferon-α (IFN) and had stopped this medication at least 6 months before the study. Nine patients (22%) were receiving IFN-α at the time of recruitment to the study, as described[9]: 3 million units (MU) daily for 3 months, followed by 3 MU every other day for 9 months. All patients were evaluated with ultrasonography of the heart and the supra-aortic vessels to exclude potential embolic vascular lesions.

Eleven untreated HCV infected patients without MC and 36 age and sex-matched healthy volunteers were used as controls. Controls had been tested clinically and they did not have a vascular or nerve disease.

This study was approved by the Ethics Committee of the University of Rome, and was conducted in agreement with the principles of the Helsinki Declaration. All patients and controls gave their informed consent to participate.

Magnetic resonance imaging. The MRI investigation was conducted as a case-control study in 40 patients with HCV-MC vasculitis, 11 HCV controls, and 36 healthy controls matched for age and sex. MRI findings in patients and controls were independently evaluated by 2 expert neuroradiologists, who were unaware of the identity of the subjects.

MRI studies were done with a 1.5 Magnet (Philips Gyroscan NT-2000, Eindhoven, The Netherlands, for patients in Rome and General Electric 1.5 T Signa Horizon, USA, for patients in Paris). Pulse sequences included: proton density T2 weighted spin-echo (TR 2000 ms, TE 20, 110 ms), fluid-attenuated inversion recovery (FLAIR; TR 6000 ms, TE 100 ms), and T1 weighted spin-echo (TR 500 ms, TE 14 ms) before and after injection of 0.2 mmol/kg gadoliniun-DTPA. Twenty-two axial slices 5 mm thick were acquired to include the whole brain. MR images were evaluated for areas of high signal on T2 and FLAIR weighted images, and abnormal contrast enhancement on T1 weighted images was performed after contrast media administration.

Cognitive assessment. Cognitive assessment was done in 34 of 39 patients with HCV-MC vasculitis and in 8 of 11 HCV controls. Nine MC patients taking IFN-α at the time of the study were removed from the analysis. They completed a 4 hour battery of psychological tests, which were administered by one experienced psychiatrist: the Wechsler Adult Intelligence Scale (WAIS-R), Rey-Auditory Verbal Learning test, Rey-Osterrieth Complex Figure test (copy and delay), Benton Visual Retention test (administration A, form C), Token test (36-item form), Controlled Oral Word Association (FAS version), Facial Recognition Test, Judgment of Line Orientation test (H form), Trail Making test (Reitan's administration, parts A and B), Wisconsin Card Sorting test, and the Stroop Color and Word test. Tests were grouped into 10 cognitive domains: visual memory, attention, visual construction functions, abstract reasoning, visual spatial functions, executive functions, comprehension, aural memory, visual perceptual functions, and verbal fluency. Verbal evocation was also assessed in 15 patients. All patients tested for neurocognitive function had similar fluency with the local language and similar levels of education.

Statistical analysis. All quantitative data are expressed as the mean ± SD. Univariate analysis used chi-square or Fisher's exact test for comparisons of qualitative values, or Student's unpaired t test for quantitative values. Correlations were tested with the Spearman rank test. Significance was assessed at $p < 0.05$.

RESULTS

Patients' characteristics. Characteristics of the 40 patients with HCV-associated cryoglobulinemic vasculitis are summarized in Table 1. The mean age was 59 ± 13 years (range 27–78) for patients vs 56 ± 10 years (23–73) for HCV controls and 58 ± 12 years (28–80) for healthy controls (p not significant), with a sex ratio (M/F) of 0.80, 0.83, and 0.84, respectively (NS). The mean serum cryoglobulin concentration was 1.08 ± 1.49 g/l (median 0.65, range 0.05–1.75). Cryoglobulin vasculitis involved one (n = 10, 25%), 2 (n = 18, 45%), or 3 (n = 12, 30%) organs. HCV genotypes were 1 (19 out of 37 patients, 51%), 2 (27%), 3 (3%), 4 (11%), and 5 (8%). The mean HCV RNA level was 7.7 ± 18.6 million Eq/ml (median 3.8, range 0.4–98). Liver histological analysis revealed mild inflammation, with a mean Metavir Activity score of 0.89 ± 0.69, and a mean Metavir Fibrosis score of 1.50 ± 1.11[10]. No patient had cirrhosis. Nine (22%) patients were receiving IFN-α when the study started.

MRI findings. The only abnormal MRI finding in HCV-MC vasculitis patients was the occurrence of white matter high intensity signals (WMHIS) on long TR images. They were located bilaterally in the periventricular region, corona radiata, and centrum semiovale. The size of WMHIS was < 10 mm in all patients, and no enhancement was present after contrast administration. Some WMHIS were also observed in control subjects. However, HCV-MC patients had a significantly higher number of total WMHIS [7.03 ± 9.9 (median 3, range 0–46) vs 0.90 ± 1.81 and 2.03 ± 3.1; $p < 0.05$] and periventricular WMHIS (2.4 ± 3.0 vs 0.38 ± 0.5 and 0.8 ± 1.4; $p < 0.05$) than HCV controls and healthy controls, respectively (Table 2). The number of periventricular WMHIS positively correlated with the total number of WMHIS ($p = 0.0001$). The number of WMHIS increased with increasing age in the healthy subjects ($p = 0.009$), but not in HCV controls or the HCV-MC vasculitis group ($p = 0.06$). There was no significant correlation between sex and the extent of WMHIS. The number of WMHIS was not significantly correlated with extrahepatic disease manifestations, serum cryoglobulin levels, duration of disease, liver involvement, or HCV viremia.

Cognitive deficits. Twenty-four of the 27 (88.8%) evaluated

Table 1. Characteristics of 40 patients with HCV-associated cryoglobulinemic vasculitis.

Patient	Age, yrs	Sex	Mode of Contamination	IFN-α Therapy	HCV Genotype	Viremia, MEq/ml	Metavir A	Metavir F	Serum Cryoglobulin Level, g/l	C4	WMHIS	PVHIS	NICF
1	76	F	Trans	–	5	1.1	0	3	1.5	Low	5	4	3
2	65	F	Un	–	1	4.22	0	0	0.47	N	1	1	1
3	52	F	Trans	–	1	2.4	1	2	0.34	Low	0	0	3
4	71	M	Un	–	1	3.8	0	3	5.4	Low	3	3	3
5	73	M	Un	+	1	1.37	1	0	0.13	Low	1	1	6
6	37	F	Un	–	4	3.7	0	1	0.12	Low	2	1	1
7	37	F	Un	–	1	5.1	1	1	6.8	Low	0	0	5
8	71	M	Trans	+	4	0.4	1	0	0.05	Low	0	0	3
9	61	F	Trans	–	5	1.57	1	1	0.92	Low	1	0	1
10	39	M	Tox	–	1	0.9	1	1	0.69	Low	1	0	1
11	51	M	Un	–	3	3	0	3	0.76	N	2	2	0
12	69	F	Trans	+	1	6	1	2	0.3	N	ND	ND	ND
13	54	F	Trans	+	1	2.3	1	1	0.53	N	ND	ND	ND
14	73	M	Un	–	1	4.4	1	1	0.19	Low	10	8	1
15	47	M	Un	–	1	0.8	1	1	0.7	Low	3	1	0
16	73	F	Trans	–	1	1.1	2	3	0.62	Low	8	5	2
17	73	M	Trans	–	1	0.42	1	1	0.56	Low	1	1	2
18	63	F	Un	–	2	8.7	2	3	0.25	N	10	6	3
19	78	F	Un	+	5	98	1	1	1.75	Low	0	0	0
20	41	M	Un	–	4	4.1	0	1	0.48	N	0	0	0
21	38	M	Un	+	4	46.3	1	1	1.47	Low	4	4	3
22	27	F	Trans	–	2	ND	ND	ND	0.2	ND	0	0	0
23	69	F	Un	–	2	ND	ND	ND	0.2	Low	3	0	1
24	63	M	Trans	–	1	ND	ND	ND	1.4	ND	0	0	2
25	57	M	Un	–	ND	ND	ND	ND	0.35	ND	3	0	2
26	59	M	Un	–	2	6.2	ND	ND	0.5	ND	0	0	2
27	51	F	Un	–	1	ND	0	1	0.85	Low	9	5	2
28	60	M	Un	–	1	ND	2	3	0.5	Low	12	1	2
29	68	F	Un	–	1	5	ND	ND	0.2	ND	46	11	2
30	57	F	Un	+	2	5.3	2	1	1.4	ND	19	5	3
31	52	F	Un	+	2	3.9	1	2	0.9	Low	0	0	4
32	63	M	Un	+	2	5.7	ND	ND	1.26	Low	5	2	4
33	62	F	Un	–	1	5	1	1	1.57	Low	24	1	4
34	67	F	Un	–	2	1.5	ND	ND	1.8	ND	35	2	5
35	69	M	Un	–	2	5	0	1	0.9	ND	8	3	6
36	68	F	Un	–	1	ND	2	3	5.4	ND	19	10	6
37	56	F	Un	–	2	1.5	ND	ND	0.2	ND	9	4	ND
38	60	M	Un	–	1	0.96	ND	ND	0.85	ND	15	2	ND
39	63	F	Un	–	ND	ND	ND	ND	0.85	ND	11	6	ND
40	35	F	Un	–	ND	ND	ND	ND	0.35	Low	0	0	ND

Duration of disease: duration of HCV-MC vasculitis starting from the first reported sign or symptom of vasculitis. IFN: interferon; MEq = million equivalent; Metavir A = activity; F = fibrosis; C4: C4 complement; trans: transfusion; tox: drug abuse; un: unknown; ND: not determined; N: normal. WMHIS: number of white matter high intensity signals; PVHIS: number of periventricular high intensity signals; NICF: number of impaired cognitive functions.

patients had a deficiency in one or more (up to 6) of the 10 cognitive domains (Table 3). The most commonly involved domains were attention (n = 19, 70.3%), executive functions (n = 12, 44.4%), visual construction (n = 10, 37%), and visual spatial functions (n = 9, 33.3%). A deficit of verbal evocation was observed in 4 out of 15 patients (26.7%). The number of impaired cognitive functions was significantly higher in patients with HCV-MC vasculitis than HCV controls (2.22 ± 1.73 vs 0.87 ± 3.1; $p < 0.05$). Serum cryoglobulin level was correlated with the number of impaired cognitive functions ($p = 0.027$). There was no significant correlation between the number of impaired cognitive functions and age, sex, duration of HCV-MC disease, viral genotype, severity of liver involvement, specific major clinical manifestations of cryoglobulinemia, or cerebral MRI findings.

DISCUSSION

Well documented reports on CNS involvement in patients with HCV-associated vasculitis are rare[5]. Clinically, stroke episodes, transient ischemic attacks, progressive reversible ischemic neurological deficits, lacunar infarctions, or encephalopathic syndrome may occur[4,5,11]. Stroke episodes

Table 2. Comparison between patients with HCV-MC vasculitis and controls.

	HCV-MC Patients, n = 40	HCV Controls, n = 11	Healthy Controls, n = 36	p
Sex ratio, F/M	23/17	6/5	20/16	NS
Age, yrs	59 ± 13	56 ± 10	58 ± 12	NS
PVHS	2.45 ± 3.05	0.38 ± 0.50	0.81 ± 1.43	< 0.05
WMHIS	7.03 ± 9.99	0.90 ± 1.81	2.03 ± 3.10	< 0.05
NICF	2.22 ± 1.73	0.87 ± 0.83	—	< 0.05
Cryoglobulin level, g/l	1.08 ± 1.49	—	—	
Duration of disease, yrs	11.2 ± 8.7	—	—	
Metavir Activity liver score	0.89 ± 0.6	1.02 ± 0.6	—	NS
Metavir Fibrosis liver score	1.50 ± 1.1	2 ± 0.7	—	NS
HCV RNA, million Eq/ml	7.7 ± 18.5	8.3 ± 12.1	—	NS

PVHS: periventricular high intensity signals; WMHIS: white matter high intensity signals; NICF: number of impaired cognitive functions; NS: not significant.

Table 3. Neuropsychological assessment in 27 patients with HCV-associated cryoglobulinemic vasculitis.

Function	n	Defective, %
Visual memory	8	29.6
Attention	19	70.3
Visual construction functions	10	37
Abstract reasoning	6	22.2
Visual spatial functions	9	33.3
Executive functions	12	44.4
Comprehension	3	11.1
Aural memory	1	3.7
Visual perceptual functions	4	14.8
Verbal fluency	2	7.4
Total (≥ 1 abnormal function)	24	88

and encephalopathic syndromes have been attributed to ischemia or, rarely, to hemorrhage[5,6,12,13]. MRI findings of the brain usually have been consistent with ischemia, showing either small lesions of the periventricular white matter and the cerebral trunk or extensive supra- and infratentorial white matter lesions suggesting cerebral vasculitis[14,15]. Cerebral angiography in patients with mixed cryoglobulinemia and CNS involvement has occasionally suggested vasculitis or vasculopathy, revealing focal narrowing, multiple irregularities, or occlusion of the affected arteries[5,16].

No patient in this study had MRI evidence of cerebral infarction secondary to arterial occlusive disease. Indeed, multiple small white matter lesions were found in all HCV-MC patients. With the advent of MRI, changed signals of periventricular white matter are noted more often even in healthy individuals, with a significant correlation with increasing age and presence of vascular risk factors, such as hypertension[17]. White matter hyperintense foci associated with aging and/or hypertension are thought to depend on damage to small arteries that penetrate into the subcortical and periventricular white matter, as suggested by pathological studies[18]. However, the number of WMHIS in these 40 patients with HCV-MC vasculitis was significantly higher than in controls, whereas the ratio of periventricular WMHIS to total WMHIS was not significantly different. A possible explanation for our findings is the involvement of small cerebral vessels by the cerebral vasculitis[19]. The white matter is much more vulnerable to hypoxemia-ischemia than the gray matter of the cortex because of rather widely spaced linear arterioles, few anastomoses, and sparse collateralization[20].

The number of WMHIS correlated significantly with age in the healthy control group, but not in the HCV-MC group, suggesting that CNS vascular damage caused by HCV-MC vasculitis was overwhelmingly greater than that caused physiologically by senescence. Specific major clinical manifestations of cryoglobulinemia did not correlate with the extent of brain lesions on MRI or on cognitive tests. Notably, peripheral neuropathy was not associated with either MRI findings or cognitive abnormalities.

Eighty-nine percent of the patients with HCV-MC vasculitis were defective in one or more of the 10 cognitive domains examined. The most commonly involved domain was attention (70.3%), consistent with the findings reported by Forton, *et al* in a study of 27 HCV-infected patients with mild liver disease[21]. Patients with cirrhosis were excluded from our study, and no association was found between the severity of liver disease on biopsy and the number of impaired cognitive functions, so we can conclude that the cognitive defects are not due to minimal hepatic encephalopathy.

The mechanism by which lesions are produced in the CNS of patients with HCV-MC vasculitis is still unclear, as are the respective roles of cryoglobulin and HCV. Favorable outcomes have been observed in patients undergoing corticosteroid or IFN-α therapy[6,15]. Patients with chronic HCV are more likely to have significant changes in their physical and mental well being than patients with liver disease of other etiology. There is emerging evidence of mild but significant cognitive impairment in HCV infection[22]. The recent detection of HCV replicative intermediaries and HCV genetic sequences in post mortem brain tissue raises

the possibility that the reported neuropsychological symptoms and cognitive impairment may be related to HCV infection of the CNS[23]. However, our results showed that patients with HCV-MC vasculitis had a higher frequency of impaired cognitive function and MRI brain abnormalities than HCV controls without MC, suggesting specific inflammatory involvement of the CNS. In support of this, there was no evidence of cerebral vasculitis or any white matter abnormality in an MRI study of 17 HCV-infected patients[21]. In our study, cryoglobulin concentration was positively correlated with the number of impaired cognitive functions. These findings agree with the clinical observation that all HCV-infected patients with well documented cases of CNS involvement were also positive for cryoglobulin[24].

In conclusion, the high frequency of impaired cognitive functions, the extent of MRI brain abnormalities, and the correlation of impaired cognitive function with cryoglobulin concentration in patients with HCV-associated mixed cryoglobulinemia strongly suggest specific vasculitic involvement of the CNS. The specific major clinical manifestations of HCV-MC vasculitis do not appear to correlate with the extent of brain lesion or dysfunction. The efficacy of antiviral treatment on cerebral dysfunction of patients with chronic hepatitis C has been suggested, but not proven definitively. Conversely, reversible cognitive abnormalities have been reported with treatment with IFN-α[25]. In our series, the small proportion of patients treated with IFN-α did not allow any statistical conclusion on this matter. Further prospective studies are needed to determine whether early antiviral therapy may prevent CNS damage and cognitive impairment caused by HCV cryoglobulinemic vasculitis.

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