

# Autonomic evaluation of hepatitis C virus infected patients

## Avaliação autonômica de pacientes infectados pelo vírus da hepatite C

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### ABSTRACT

There are few studies reporting the association between hepatitis C virus (HCV) infection and disautonomia. We have evaluated the autonomic cardiovascular function in 12 patients with sensory small-fiber polyneuropathy infected by HCV. The mean age was 49±13 years old. The mean infection time was 9.6 years in six (50%) patients. Thermal and pinprick hypoesthesia was observed in distal legs in all patients. Autonomic symptoms were referred by eight (66.7%) patients. Among patients with abnormal autonomic cardiovascular test, five (41.7%) showed abnormal results in two or more tests. Valsalva maneuver was abnormal in seven (58.3%) patients. We can consider that there is an association of both parasympathetic and sympathetic efferent cardiovascular dysfunction in this group of patients.

**Key words:** hepatitis C, dysautonomia, small-fiber polyneuropathy.

### RESUMO

Existem poucos estudos que relatam a associação entre infecção pelo vírus da hepatite C (HCV) e disautonomia. Avaliamos a função autonômica cardiovascular em 12 pacientes com polineuropatia de fibras finas e infectados pelo HCV. A idade média foi de 49±13 anos. O tempo de infecção média foi de 9,6 anos em seis (50%) pacientes. Hipoestesia termoalgésica foi observada nos segmentos distais das pernas em todos os pacientes. Sintomas autonômicos foram relatados por oito (66,7%) pacientes. No teste autonômico cardiovascular, cinco (41,7%) apresentaram resultados anormais em dois ou mais testes. Manobra de Valsalva foi anormal em sete (58,3%) pacientes. Podemos considerar que há comprometimento de ambas as vias parassimpática e simpática cardiovasculares eferentes nesse grupo de pacientes.

**Palavras-Chave:** hepatite C, disautonomia, polineuropatia de fibras finas.

Hepatitis C virus (HCV) affects 170 million people all over the world. In Brazil, the incidence of HCV-infected individuals is 5.1/100,000 inhabitants. The highest prevalence is seen in Acre State, in the Brazilian Amazon (22.7/100,000 inhabitants)<sup>1</sup>. HCV-infection has been associated with neurological manifestations, including peripheral neuropathy. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and distal sensory polyneuropathy have been reported. HCV-infection associated with central nervous system vasculitis was also referred. About 65% of infected patients are around 30 to 49 years old of age, and 30% will develop hepatocellular carcinoma. The physiopathology basis is still unknown<sup>2</sup>. It seems that there is no direct tissues lesion by the virus, but probably an immune response against the virus could develop the disease. There are few reports focusing

the relation between the HCV and dysautonomia<sup>3-7</sup>. Our objective was to report the autonomic cardiovascular function in HCV-infected Brazilian patients with sensory small-fiber neuropathy.

### METHODS

We have included 12 consecutive HCV-infected patients with sensory small-fiber polyneuropathy. Patients were randomly selected from a cohort of more than 60 HCV patients followed in the Hepatitis Reference Center (Dr. Bordalo) of Hospital Universitário Antônio Pedro, Niterói, Rio de Janeiro, Brazil. Patients with diabetes, arterial hypertension, severe liver dysfunction, other infections, including HIV and HTLV, use of

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drugs, hypothyroidism and renal insufficiency, concomitant hereditary neuropathy, collagen diseases and malignancies were ruled out. Neurological examination and a standard autonomic questionnaire were applied before autonomic cardiovascular test (ACT). The questionnaire was related to the following symptom groups: orthostatic hypotension, sweat complaint, visual disturbance, gastrointestinal and genitourinary systems. All the subjects gave their informed consent for the study (CAAE: 03476212.0.0000.5243). All of them were blood tested for ELISA anti-HCV.

The mean infection time was 9.6 years in 50% of patients; the others didn't know how much time they were infected. Four ACT were performed: respiratory sinus arrhythmia (RSA), tilt-test (TT), sustained hand grip (HG) and Valsalva maneuver (VM). Cryoglobulinemia and viral count was not taken into account. Any patient was treated for HCV-virus infection before ACT. The description of those tests can be found elsewhere. ACT was performed with the following materials: Polar S810 cardiac monitor (Finland), Jamar manometer (United States) and orthostatic table (Instituto São Paulo, Brazil).

## RESULTS

We analyze 12 patients, 6 male and 6 female. The mean age was  $49 \pm 13$  years old. The mean infection time was 9.6 years in 50% of patients; the others didn't know how much time they were infected. Thermal and pinprick hypoesthesia were observed in distal legs in all patients. Among them, 66.7% complained of autonomic symptoms, being "dizziness" when getting up the most frequent, eight cases. Visual darkening was a complaining of those patients with dizziness. Cramps in the lowers limbs were referred in six cases, neuropathic pain in the extremities in five cases, intestinal constipation in four cases, excessive plantar sudoresis in two cases and symptoms of urinary retention, dry mouth and chills in one case. Violaceous appearance, sudoresis and mild to moderate edema were considered as dysautonomic feet manifestations, observed in 41.7% of our patients, five cases.

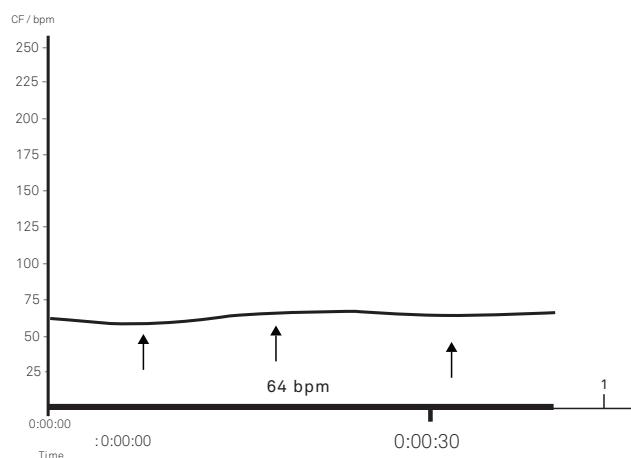
We considered the ACT abnormal when two or more tests were out of normal values<sup>8</sup>. Among patients with abnormal ACT, five (41.7%) show abnormal results in two or more tests. ACT was completely normal only in two (16.6%) patients. The autonomic tests were abnormal in three patients performing RSA (25%). This test analyses parasympathetic efferent cardiovascular function. Abnormal test values were seen in two patients (Figure), with drop in arterial pressure when performing TT (16.7%). Diastolic pressure showed important droppings more than 20 mmHg. Three patients (25%) had no arterial blood pressure increase during HG after five minutes of constant effort. TT and HG accesses sympathetic cardiovascular efferents. During VM, six patients did not have increase in arterial pressure and one had bradycardia in phase IV. VM was abnormal in 58.3% of patients. Autonomic tests results are summarized in Table.

## DISCUSSION

Many infectious diseases are related as causes of autonomic dysfunction, with or without sensory polyneuropathy, with a variable grade of intensity and severity. Chagas's disease, HIV-infection, HTLV-infection are examples<sup>9,10</sup>. Our results are consistent with an unequivocal efferent sympathetic and parasympathetic dysfunction in this group of HCV-infected Brazilian patients. The methodology we have applied is an indirect way to analyze cardiovascular function. The ACT increases its predictive value when two or more abnormal tests are obtained<sup>8</sup>. Five patients (41.66%) had this characteristic in their test results, and other five presented only one abnormal test (41.66%).

Amendolla et al. studied 30 HCV-infected patients presenting peripheral neuropathy and cryoglobulinemia<sup>3</sup>. Similar alterations in ACT with RSA flattening curves in four patients were seen.

There is five other reports<sup>3-7</sup> focusing autonomic function in HCV-infected patients. They did not included cases with sensory polyneuropathy neither made large ACT tests. Verne et al. evaluated patients with complaints of gastrointestinal discomfort and hepatic cirrhosis comparing them with a control group and HCV-patients without cirrhosis<sup>5</sup>. In those groups, there were 20 patients with hepatic cirrhosis and gastrointestinal complaints, vomits and sickness, and 10 asymptomatic patients with HCV without evidence of cirrhosis. They included five autonomic tests and seriography. Each test was scored on a continuum from 0 (normal) to 5 (severe disease), thus producing a composite score of 0 to 5 for each subject. A composite score greater than 1,5 was considered abnormal. In seriography, a solid phase gastric emptying greater than 50% at 100 minutes was considered abnormal. As results, they observed a great gastric retention at 100 minutes in 70.7% of cirrhotic patients versus 26.1% in the control



Arrows indicate when the forced inspiration occurred. CF: cardiac frequency. **Figure.** Abnormal response to respiratory sinus arrhythmia. In this example, we illustrate low cardiac frequency during forceful expiratory and inspiratory tests in case 3.

**Table.** Results of autonomic cardiovascular tests in hepatitis C virus patients.

Cases	RSA		TT				HG	VM	
	I-E	E/I	SAP1	SAP5	DAP5	HR	DAP	VI	PA <sub>VI</sub>
1	11	1.38	2	0	6	3	20	1.72	0
2	24	1.72	<b>22</b>	<b>20</b>	<b>28</b>	3	<b>4</b>	1.78	0
3	<b>4</b>	<b>1.01</b>	10	8	8	13	16	1.64	8
4	20	1.79	10	0	4	3	16	1.9	10
5	17	1.73	2	10	2	3	16	1.3	10
6	10	1.25	10	2	2	2	20	1.2	22
7	9	1.31	10	8	10	4	16	1.68	0
8	19	1.4	<b>20</b>	<b>26</b>	<b>22</b>	4	<b>5</b>	2.32	0
9	20	1.79	0	0	3	6	20	1.98	20
10	<b>3</b>	<b>1.03</b>	10	4	0	2	<b>10</b>	1.2	0
11	<b>4</b>	<b>1.01</b>	0	8	2	12	30	<b>1.01</b>	0
12	5	1.59	10	0	14	6	30	1.8	20

Results of autonomic cardiovascular tests (ACT). ACT was analyzed as the following parameter: respiratory sinus arrhythmia (RSA), tilt-test (TT), hand grip (HG) and Valsalva maneuver (VM). RSA showed values with inspiratory and expiratory differences (I-E) and relation expiratory/inspiratory (E/I). During TT, we observed parameters like VSAP1, VSAP5, VDAP5 e VHR that mean, respectively, systolic pressure variation in first minute, systolic pressure variation in five minutes, diastolic pressure variation in five minutes and cardiac frequency variation in five minutes in the moment of inclination. VDAP, in HG, means diastolic pressure variation in five minutes of static effort. The acronyms, in VM, IV, PA<sub>VI</sub>, means respectively Valsalva index, initial arterial pressure, less final arterial pressure in phase VI. In bold, we can see values out of normal limits. RSA>5 bpm, RSA Index>1, 2 (±0.1); VSAP1>20 (±4.1) mmHg; VSAP5>20 (±5.3) mmHg; VDAP5>10 (±4.2) mmHg; HG>20 (±4.9) mmHg; VM Index>1,1 (±0.1) PA<sub>VI</sub>, any other value than zero in overshoot fase IV of MV (differentials between initial and final diastolic arterial pressure).

group with HCV-infection. The autonomic score for cirrhotic patients was 3.4 versus 1.2 in HCV control group. Barbaro et al. tested SRA in 125 HCV patients (65 HIV-positive and 60 HIV negative) and 61 healthy controls<sup>4</sup>. SRA values were correlated with glutathione and with erythrocyte malonyldialdehyde concentrations. These authors detected dysfunction of the cardiac vagal system especially in patients with HIV and HCV coinfection, associated with depletion of glutathione. A multivariate analysis of 45 HCV-infected patients and 40 controls subjects showed that autonomic dysfunction in the former group was not associated with serum HCV RNA levels and cryoglobulins<sup>7</sup>.

We can consider that HCV-infected patients with sensory polyneuropathy and complaint of dizziness support the

needed of autonomic cardiovascular function investigation. The small-fibers (A-delta and C fibers) conduct, respectively, afferent superficial sensory and autonomic reflex to central nervous system. Dysautonomia is observed in different diseases in which small fiber are involved. Diabetes mellitus is the most common<sup>6,11</sup>. Despite of our little sample, we conclude that HCV-infected-patients with a sensory polyneuropathy can develop autonomic cardiovascular dysfunctions. Our results point out to both parasympathetic and sympathetic efferent cardiovascular function compromise in this group of HCV-infected patients. Further studies are needed to identify the real prevalence and the underlying mechanisms of this association.

## References

- Ministério da Saúde (BR). Protocolo clínico e diretrizes terapêuticas para Hepatite Viral C e coinfeções. Ministério da Saúde. Brasil. Secretaria de Vigilância e Saúde. Departamento de DST, AIDS e hepatites virais. [cited 2012 Aug 19]. Available at: [http://portal.saude.gov.br/portal/arquivos/pdf/pcdt\\_c\\_2011retificado.pdf](http://portal.saude.gov.br/portal/arquivos/pdf/pcdt_c_2011retificado.pdf)
- Charles ED, Dustin LB, Rice CM. Natural history, pathogenesis, and prevention of HCV infection. In: Hoofnagle JH (Ed). HCV infection and cryoglobulinemia. Part 1. New York: Springer; 2011. p. 11-20.
- Amendolla A, Sampaolo S, Migliaresi S, et al. Autonomic neuropathy in mixed cryoglobulinemia. J Neurol 2007;254:215-219.
- Barbaro G, Di Lorenzo G, Soldini M. Vagal system impairment in human immunodeficiency virus-positive patients with chronic hepatitis C: does hepatic glutathione deficiency have a pathogenic role? Scand J Gastroenterol 1997;32:1261-1266.
- Verne GN, Soldevia-Pico C, Robinson ME, Spicer KM, Ruben A. Autonomic dysfunction and gastroparesis in cirrhosis. J Clin Gastroenterol 2004;38:72-76.
- Thuluvath PJ. Higher prevalence and severity hepatic encephalopathy in patients with HCV cirrhosis and diabetes mellitus: is the presence of autonomic neuropathy the missing part of the puzzle? Am J Gastroenterol 2006;101:2244-2246.
- Osztoivits J, Horváth T, Abonyi M, et al. Chronic hepatitis C virus infection associated with autonomic dysfunction. Liver Int 2009;29:1473-1478.
- Castro CL, Nóbrega AC, Araújo CG. Testes autonômicos cardiovasculares. Uma revisão crítica. Parte I. Arq Bras Cardiol 1992;59:75-85.
- Barreira AA, Nascimento OJM. Peripheral neuropathies in Chagas disease. In: Noseworthy JH (Ed). Neurological therapeutics: principles and practice. 2nd ed. Vol. 3. Oxon: Informa Health Care; 2006. p. 2251-2259.
- Alamy AH, Leite AC, Nascimento O, Nascimento OM, Araújo AQ. Dysautonomia in human T-cell lymphotropic virus type I-associated myelopathy/tropical spastic paraparesis. Ann Neurol 2001;50:681-685.
- Phillips JC, Marchand M, Scheen AJ. Squatting, a posture test for studying cardiovascular autonomic neuropathy in diabetes. Diabetes Metab 2001;37:489-496.