Screening for Electrophysiological Abnormalities in Chronic Hepatitis C Infection: Peripheral Neuropathy and Optic Neuropathy

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ABSTRACT

Introduction: To investigate the existence of peripheral and optic neuropathies in asymptomatic individuals with hepatitis C infection.

Methods: Thirty consecutive patients who were followed in a hepatitis C outpatient clinic were recruited for electrophysiological evaluation together with 30 age- and gender-compatible healthy controls. All patients had a detailed neurological examination. The information regarding the disease duration and management with interferons were collected. Nerve conduction studies and visual evoked potentials (VEP) were recorded in all subjects. The results of the patient and control groups were statistically compared.

Results: Of the patients with hepatitis C infection, 16 were females and 14 males. The mean age was 57.5 years, and the average disease duration was 6.43 years. The P100 latencies in the patient group were within normal limits, while the amplitudes were meaningfully small by comparison with the controls. There were some abnormalities in the nerve conduction studies of 15 patients. Sensorial neuropathy was detected in two patients, sensorimotor polyneuropathy in four, carpal tunnel syndrome in seven, and carpal tunnel syndrome and

sensorimotor polyneuropathy as comorbid states in another two patients. The nerve conduction studies and VEP parameters were entirely normal in the control group.

Conclusion: Hepatitis C-related neurological abnormalities may occur both in the central and peripheral nervous system. Mononeuritis multiplex, sensorial axonal neuropathy, and multiple mononeuropathies are some of the presentations of the peripheral nervous system involvement. The mode of infection is considered to be via vasculitic mechanisms. In addition, optic neuropathy is a known complication of interferon treatment. Autoantibodies, cytokines, chemokines, and cryoglobulins are accused to play roles in the pathogenesis. In this study, we investigated the involvement of the peripheral nervous system and optic nerves in a group of patients with hepatitis C. The results were in favor of peripheral nerve injury of various types and optic neuropathy of the axonal type.

Keywords: Hepatitis C, peripheral neuropathy, carpal tunnel syndrome, optic neuropathy

INTRODUCTION

Hepatitis C virus (HCV) causes a chronic liver infection, which may also present with extrahepatic organ involvement. Neurological complications are diverse and may be observed in a broad spectrum, ranging from peripheral nervous system (PNS) abnormalities to cognitive dysfunction. HCV is the leading cause of mixed cryoglobulinemia, which is frequently associated with PNS involvement (1,2,3). Although a subacute distal symmetrical sensorimotor peripheral neuropathy (PN) is the most frequent presentation in association with mixed cryoglobulinemia, PN may also be observed in the absence of cryoglobulinemia (4,5). While a sensory and axonal neuropathy is the most common form, rarely mononeuritis multiplex due to vasculitis may appear with a fulminant course (6).

Although the pathophysiology of HCV-related PN is controversial, the deposition of HCV-RNA microparticles and cryoglobulins, direct viral invasion, and perivascular mononuclear inflammation are all accused of the development of HCV-related vasculitic lesions (7,8,9,10). As particles of HCV have been detected in the muscle and nerve biopsies of patients with HCV-related PN, immune mechanisms triggered by the virus itself have been proposed (11). The existence of cryoglobulins in the serum may be a clue of an extensive and more severe infection. However, cryoglobulins are not regarded as the sole factor in the course of vasculitis (12).

Several clinical, electrophysiological, and pathological studies dealing with the relationship between chronic HCV infection and PN exist in the relevant literature. HCV-related PN is quite frequent, while central nervous system involvement is comparatively rare. Various ophthalmological diseases, such as keratoconjunctivitis sicca, macular edema, and ischemic optic neuropathy, have also been reported in the course of HCV infection (13). Cappellari et al. (14) reported the central nervous system involvement, co-existing with HCV-related mixed cryoglobulinemia, by means of evoked potential abnormalities. In addition to PNS infection, subclinical optic neuropathy may also be observed during the course of HCV infection, possibly because of low-dose interferon treatment (15,16,17).

This study aimed to investigate the existence of PNS involvement and a possible optic neuropathy in neurologically and ophthalmologically asymptomatic individuals.

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METHODS

Thirty consecutive patients who were registered in a chronic hepatitis outpatient clinic were recruited for the study. Individuals with chronic systemic diseases, such as diabetes, malignancy, autoimmune disorders, chronic renal disease, chronic infections other than HCV, or a history of exposure to a toxic substance, hereditary neuropathy, or known ophthalmological disease were excluded. Of the patients with HCV infection, the disease duration and drug treatments were recorded. Thirty healthy, age- and sex-matched individuals were recruited as controls. All subjects had a complete neurological examination by a neurologist. Nerve conduction studies (NCS) and visual evoked potential (VEP) studies were performed according to a standardized protocol in all cases. The results were statistically compared. In addition, patients with HCV were classified according to their interferon managements, and the electrophysiological findings of the two groups were statistically compared. The study was performed with written consent from all subjects and was approved by the Izmir regional ethical committee number 2.

Electrophysiological Evaluation

Motor and sensory nerve conduction studies

Electrophysiological studies were conducted in the electrophysiology laboratory of the Izmir Bozyaka Education and Research Hospital, Turkey, with a Medelec Synergy device by two of the authors. Nerve conduction studies were standardized throughout the study using the same recording and stimulation electrodes on four motor and three sensory nerves. Motor nerve conduction velocities (NCV), distal latencies (DL), and compound muscle action potentials (CMAP) of the median, ulnar, peroneal, and tibial nerves were evaluated for testing the motor nerves. For the sensory nerves NCV, DL, and the amplitudes of the sensory action potentials (SAP) of the median, ulnar, and sural nerves were recorded.

The stimuli given from the wrist and elbow were recorded from the abductor pollicis brevis muscle using bipolar surface electrodes with 3-cm distance between the two electrodes with the belly-tendon method for the median nerve. In a similar manner, the stimuli given from the wrist and elbow were recorded from the abductor digiti minimi muscle for the ulnar nerve; while from the ankle and tibial fossa, the stimuli were recorded from the abductor hallucis muscle for the posterior tibial nerve; and from the ankle and capitulum fibula, they were recorded from the extensor digitorum brevis muscle for the peroneal nerve. In the sensory nerve studies, the median and ulnar nerves were stimulated at the wrist, and SAP amplitudes were recorded from the first and fifth digits, respectively, with antidromically ring electrodes. For the sural nerve, SAP was recorded from mid-calf and stimulated behind the lateral malleolus using disk electrodes. The filter arrangements were within the ranges 20–2,000 Hz for sensory and 2–10,000 Hz for motor nerves. Sensory nerve recordings were completed averaging 8–10 readings. Skin temperatures were measured and corrected if not $>33^{\circ}\text{C}$ for the upper and 32°C for the lower extremities. For a definite polyneuropathy diagnosis, abnormalities in more than one nerve were tested, and the existence of more than one pathological finding, such as a decrease in SAP or CMAP amplitudes, slowing of motor or sensory NCVs, or an increase in motor DL were mandated (18).

Visual evoked potentials

Pattern VEP recordings were accomplished in the same laboratory, with the same device, namely the Medelec Synergy device. The active silver recording electrode was placed on the point 2-cm proximal to the protuberantia occipitalis externa, while the reference electrode was placed

onto the vertex and the ground electrode onto the forehead. A checkerboard design with a 7-cm check size was used with an eye angle of 30 min. The pattern stimuli were exhibited to the subjects by means of a 15" monitor. They were placed in a comfortable armchair in an isolated darkened room, and the distance between the subject and monitor was 100 cm. The screen illumination was 100 cd/m², the contrast between black and white checks 99%, pattern reversal rate 2/s, and the analysis time was 300 ms. Each eye was separately examined while the opposite eye was carefully covered. The absolute values of the latencies and amplitudes of P100 waves obtained in the two eyes of each patient were recorded.

Statistical Analysis

In the comparison of continuous data between the groups, the independent two samples t-test was used. Continuous data were shown with the arithmetic means and standard deviations. In the comparison of categorical data between the groups, the chi-square test was used. Categorical variables were referred with numbers and percentages. The Mann–Whitney U test was used for comparison of the independent two groups' mean values. Correlation analysis was performed using Pearson's correlation analysis. The calculations were completed with the MedCalc 12.3.0.0. statistics pack. The results were regarded meaningful when p value was <0.05 , within a 95% confidence interval.

RESULTS

The mean age of the 30 patients with HCV was 57.5 ± 10.8 years, and 46% of them (14 patients) were males. The mean disease duration was 6.43 ± 6.05 years. The mean age of the 30 control subjects who had neither any complaint nor any abnormal finding was 53.5 ± 7.9 years. Furthermore, 14 of them (46%) were males. All measures of the peripheral nerve conduction and VEP studies were within normal limits in the control group. However, in the patient group, the latencies of the P100 waves were normal, while the amplitudes were meaningfully lower than in the controls ($p=0.025$ for the left eyes, $p=0.036$ for the right eyes). The mean values of the VEP P100 wave latency and amplitudes are summarized in Table 1. Examples of the VEP analysis are shown in Figures 1 and 2. Nerve conduction studies revealed a moderate increase in median and ulnar motor DLs, slowing in median motor and sensory NCVs, decrease in median SAP amplitudes, and decrease in peroneal and tibial CMAP amplitudes (Table 2).

On the whole, 15 patients with HCV infection exhibited some type of abnormality in the NCV studies. Ten of them (66.6%) were under interferon treatment. Of these patients with PNS abnormality, nine were females and their mean age was 61.55 ± 9.9 (44–78) years, and the mean disease duration was 6.98 ± 6.7 (0.1–20) years. PNS abnormalities were sensorial neuropathy in two patients, sensorimotor polyneuropathy in four, carpal tunnel syndrome (CTS) in seven, and sensorimotor PN associated with CTS in two. There was a positive correlation between the duration of the disease and the median nerve motor DL ($p=0.028$). Moreover, a negative correlation was detected between the disease duration and median CMAP amplitudes. The CMAP amplitudes decreased as the disease duration extended ($p=0.016$). In the patient group, 20 had been treated with alpha-interferon before. Of the eight patients presenting with a diffuse involvement of PNS, five had been treated with alpha-interferon in the near past. No difference in NCVs was found between the interferon-treated and non-treated PN patients. Only posterior tibial CMAP amplitudes were meaningfully smaller in the interferon non-treated group ($p=0.03$). Similarly, no difference was found in the P100 latencies and amplitudes of these two groups (Table 3). The disease duration was similar for the interferon-treated and non-treated groups ($p=0.98$).

Table 1. The results of the VEP analysis of the patients and control groups

	Hepatitis C (n=30)	Control group (n=30)	p
Left p100 latency (ms)	104.84±7.77	107.72±2.93	NS
Right p100 latency (ms)	104.91±8.78	108.11±3.56	NS
Left p100 amplitude (µV)	7.67±3.58	10.72±5.86	0.025*
Right p100 amplitude (µV)	7.74±3.35	10.00±4.43	0.036*

N: number of the participants; NS: not statistically significant (p>0.05). *p value statistically significant (p<0.05).

Table 2. Nerve conduction studies in the patient group and controls

Nerve	Control group (n=30)	Patients (n=30)	p
Conduction velocity (m/sn)			
Median motor	56.36±4.12	52.80±4.38	0.0019*
Median sensory	50.96±5.76	44.90±11.86	0.01*
Ulnar motor	57.66±9.35	57.50±5.25	NS
Ulnar sensory	53.93±5.22	54.03±7.97	NS
Tibial motor	45.63±4.91	43.13±4.85	NS
Peroneal motor	47.66±3.85	44.76±9.98	NS
Sural sensory	49.20±6.81	41.16±22.00	NS
Distal latency (ms)			
Median motor	3.50±0.33	4.00±0.92	0.0068*
Ulnar motor	2.52±0.23	2.96±0.52	0.0001*
Tibial motor	4.51±0.86	4.38±1.00	NS
Peroneal motor	4.45±0.73	4.44±1.28	NS
Amplitude (mV)			
Median motor	9.80±4.10	9.36±4.75	NS
Median sensory	25.20±9.83	18.63±10.04	0.01*
Ulnar motor	11.36±8.58	10.60±4.35	NS
Ulnar sensory	24.86±9.00	21.53±8.60	NS
Tibial motor	8.71±3.49	6.28±3.20	0.0067*
Peroneal motor	5.63±1.79	2.91±1.53	<0.0001*
Sural sensory	11.80±5.39	9.10±7.05	NS

N: number of the participants; NS: not statistically significant (p>0.05). *p value statistically significant (p<0.05).

DISCUSSION

Neurological complications of HCV other than hepatic encephalopathy do not attain much interest in daily practice. Nevertheless, peripheral nerve involvement may end up in severe disability when left undiagnosed and untreated. Furthermore, they may present with a wide range either diffuse or focal (6). Mixed cryoglobulinemia, a frequent companion of HCV infection, is usually thought as the primary underlying cause of PNS involvement (1,2,3). However, the existence of cryoglobulinemia is not a prerequisite for this (4,5). In the series of mixed cryoglobulinemia, the rate of PN is quite variable, ranging from 9% to 77% (19,20). The difference is mostly due to the accepted diagnostic criteria for PN, namely the existence of paresthetic complaints or electrophysiological evidence.

Run	N75 ms	P100 ms	N145 ms	P100 µV
1 LEFT	73,80	110,70	147,90	10,7
2 RIGHT	78,00	111,00	146,40	11,1

Figure 1. The VEP analysis of a subject in the control group

VEP: visual evoked potentials

Run	N75 ms	P100 ms	N145 ms	P100 µV
1 LEFT	65,10	109,20	160,20	5,0
2 RIGHT	70,80	107,40	162,90	4,1

Figure 2. The VEP analysis of a subject with Hepatitis C infection

VEP: visual evoked potentials

Table 3. The VEP analysis of the patient group according to the interferon medication

	IFN1 (n=20)	IFN2 (n=10)	p
Left p100 latency (ms)	104.05±8.50	106.32±6.36	NS
Right p100 latency (ms)	102.74±8.55	109.25±7.96	NS
Left p100 amplitude (µV)	7.35±3.80	8.28±3.26	NS
Right p100 amplitude (µV)	7.43±3.65	8.36±2.71	NS

NS: not statistically significant (p>0.05). VEP: visual evoked potentials

The results of viral genome studies suggest that the neuropathy results from virus-triggered immune-mediated mechanisms rather than from direct nerve infection or *in situ* replication (21). HCV-associated PN is typically sensorimotor painful and asymmetric (21). Nerve conduction studies are the most readily available non-invasive method of evaluating PNS. In this study, NCS revealed abnormalities of various types and degree in approximately half of the neurologically asymptomatic patients with hepatitis C. Twenty percent of the patients had PN, 23.3% CTS, and 6.6% PN associated with CTS. In the relevant literature, symmetric sensorimotor PN of mostly the axonal type and mononeuropathy multiplex are reported in association with hepatitis C infection (22). However, in patients lacking cryoglobulin, demyelinating PN dominate (23,24).

In our patient group, PN associated with CTS was of the axonal type; the rest were demyelinating. In the nerve conduction studies of the hepatitis C group, motor DLs of the median and ulnar nerves were longer, and NCVs of the median and tibial motor and the median sensory nerves were slower than in the controls. In some patients, the sural SAP amplitudes could not be obtained. These findings were in favor of a demyelinating type involvement. The decrease of CMAP amplitudes in the peroneal and tibial nerves, in addition to small SAP amplitudes of median nerves, were suggestive of axonal type peripheral nerve involvement.

There was a positive correlation between the duration of the disease and the development of CTS. In one case report, a patient with hepatitis C neuropathy had undergone successful operations for superimposed nerve compressions (25). In a study conducted in the Amazon region, in a group comprising 78 HCV patients, the rate of CTS was 5.5%, while that of multiple mononeuropathies was 14.1% (26). In another group of 19 hepatitis C patients with rheumatismal symptoms, eight subjects had CTS (27).

Alpha-interferon is an antiviral agent and may be protective against autoimmunity. However, on the contrary, in some cases it may induce autoimmunity. Rarely, new onset or worsening PN simultaneously with alpha-interferon treatment has been reported (28,29). As our patients were all asymptomatic, such a state was not considered at all. Although eight HCV-infected patients with PN had a history of interferon treatment, statistical analysis showed no correlation between interferon management and PN. Similarly, Briani et al. (30) reported no link between alpha-interferon treatment and the development and progression of PN.

The second aim of this study was to investigate the presence of subclinical optic neuropathy in neurologically and ophthalmologically asymptomatic HCV-infected subjects. Optic nerve infection due to HCV is quite rare. Cappellari et al. (14) detected abnormalities of VEP in 44% of patients with HCV-related mixed cryoglobulinemia. Besides, interferons have been characterized with various ophthalmologic side effects (15,16,17). While retinopathy is a common side effect, demyelinating optic neuropathy is seldom reported. In a study by Moschos et al. (31), during the long-term follow-up of the subjects receiving low-dose interferon for chronic hepatitis, the P100 latencies were found to be prolonged. In a similar study, 70% of the patients with normal P100 latencies at the pretreatment phase of the study had prolonged P100 latencies after treatment with interferons for a reasonable period (15). In another report, an optic tract neuropathy developed under low-dose interferon treatment was also mentioned (16). However, in our study, we did not observe any prolongation of the P100 latencies, rather we found a clear decrease in the amplitudes of P100 waves. No report of optic neuropathy of the axonal type exists in the literature. In addition, we found no relation between interferon management and P100 wave latencies or amplitudes. A comparison of interferon-treated and non-treated patients

26 for P100 wave properties is given in Table 3.

In conclusion, subclinical neuropathy is a common finding in patients followed for HCV infection. In this study, we also detected PN in approximately half of the neurologically asymptomatic patients with chronic HCV infection. Histopathological and electrophysiological evaluations of HCV-infected subjects are quite limited in the literature. Therefore, more studies with larger groups are needed.

HCV-related PN is usually treated with antiviral agents at first, and, if non-responsive, immunosuppressive agents like rituximab (32,33). However, as the patients in our group were neither symptomatic nor painful, no treatment was planned except for the standard follow-up.

Although the link between mixed cryoglobulinemia and PN is well-known, the lack of cryoglobulin measurements is one limitation of our study.

Optic neuropathy as a manifestation of the central nervous system involvement is very seldom reported. In our patients, we observed an asymptomatic axonal type infection of the optic nerve independent from interferon management. Further studies supporting the association of HCV infection and axonal optic neuropathy are awaited.

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