IJBPAS, May, 2017, 6(5): 856-868

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

IMPACT OF INTERFERON TREATMENT ON COGNITIVE FUNCTIONS AND VISUAL EVOKED POTENTIALS OF EGYPTIAN PATIENTS WITH RECENTLY DISCOVERED HEPATITIS C INFECTION

SAYED SOBHY SAYED[1]*, HALA ABD ELMAGID SHAHEEN[1], MAMDOUH ALI KOTB[2], AHMED ALI GOMAA[3], NERMIN ALI HAMDY[2], MARWA MAHMOUD HANAFY[1]

1: Department of Neurology, Fayoum University

2: Department of Neurology, Minia University

3: Department of Hepatology, Fayoum University

***Corresponding author: Sayed Sobhy Sayed; E-mail: alikotb1970@gmail.com, cellphone: 00966502196114, Fax: 00966115886689**

Received 29th Nov. 2016; Revised 29th Dec. 2016; Accepted 3rd March 2017; Available online 1st May 2017

ABSTRACT

Background: Infection by Hepatitis C virus (HCV) is a worldwide cause of chronic liver disease, Egypt has the highest HCV prevalence in the world**.** HCV infection and its treatment can cause peripheral and central nervous system disorders.

Objectives: This study aimed to evaluate the impact of HCV infection and Interferon treatment on cognitive functions and optic nerve function of Egyptian patients with recently discovered HCV infection.

Subjects and Methods: The present study included 30 patients with HCV infection and 30 age matched controls. All patients were evaluated by clinical, ophthalmological, neuropsychological, and electrophysiological examinations at the time of the diagnosis, and 6 months after interferon treatment.

Results: There was no significant difference between patients and control regarding Mini-Mental State examination, as well as between patients at baseline and control regarding Controlled Oral Word Association test, while it was significantly lower in patients at follow up. The score of Trail Making Test-A was significantly higher in patients' base line and follow up

than control. The score of Trail Making Test-part B was significantly higher in patients at follow up compared to control group and at base line. P100 amplitude was significantly lower in patient at base line than control, and follow up groups, while P100 latency was significantly longer in follow up group than control, and base line groups.

Conclusion: Cognitive dysfunction was found in recently diagnosed hepatitis C patients and was found to be aggravated during treatment with interferon**.** Patients had feature of axonal optic neuropathy which improved after treatment**.**

Keywords: Hepatitis C virus, Interferon, Cognitive functions, Visual evoked potentials

INTRODUCTION

Infection by Hepatitis C virus (HCV) is a worldwide cause of chronic liver disease (1). In Egypt, the estimated HCV prevalence among the 15–59 years age group is 14.7% (2). Accordingly, Egypt has the highest HCV prevalence in the world (3, 4, 5), Today, HCV infection and its complications are among the leading public health challenges in Egypt (6). HCV can cause peripheral and central nervous system (PNS and CNS) disorders (1). Cerebrovascular stroke, cerebral ischemia, encephalitis, and immune mediated demyelinating disease of the CNS, Bilateral optic neuritis are all reported as CNS disorders with HCV. A growing body of literature is reporting neuropsychological symptoms in patients with chronic HCV infection even in the absence of cirrhosis. Moreover, antiviral therapy to treat hepatitis C infection can also cause neurological symptoms and side effects (1).

This study aimed to evaluate the impact of HCV infection and interferon treatment on cognitive functions and optic nerve function of Egyptian patients with recently discovered HCV infection.

MATERIALS AND METHODS

This study included 30 Egyptian patients with accidently and recently discovered hepatitis C infection-confirmed by PCR-above the age of 18 years, referred to Tropical outpatient clinic, Fayoum University, Egypt, and 30 age and sex matched healthy volunteers as a control group.

Patients received HCV treatment in the form of combined Pegylated interferon Alfa 2b (100 µg once weekly) with ribavirin (800-1000 mg/d) based on body weight (<70kg or >70kg).

We excluded patients with Co-infection (hepatitis B, human immuno-deficiency virus; HIV), those who have history of

previous or ongoing substance abuse, Patients with other possible causes of optic neuropathy e.g. diabetes mellitus, autoimmune disorders, And patients with other potential risk factors for cognitive impairment e.g.Hepatic decompensation and encephalopathy, psychiatric morbidity, medications known to affect cognitive function, stroke, seizure disorder. Patients were evaluated by clinical, ophthalmological, neuropsychological, electrophysiological examinations at the time of the diagnosis, and 6 months after interferon treatment. Control group were evaluated neuro psychologically, and electro physiologically.

General medical examination, abdominal examination, laboratory investigations, and abdominal ultrasonography with ultra sound guided biopsy for confirmation of diagnosis, exclusion of other causes were done by the hepatologist.

Thorough history taking and neurological examination done by the neurologist.

Neuropsychological Assessment using:

A) Mini-Mental State Examination (7). It's total score is 30, the score 24 is used to distinguish the cognitive functions if normal or abnormal.

B) Controlled Oral Word Association Test (COWAT) assess verbal fluency, the patient was asked to generate as many words as possible for a given letter in one minute. Score <13 words on the average were showed to have impairment on this task.

C) Trail-Making Test (A and B) (8) is one of the most widely used tests for assessing attention, visuo-spatial orientation and psychomotor speed. Test result is the time needed in seconds including error correction time.

- The Trail-Making Test -A (TMT-A) each patient has to connect 25 consecutively numbered circles from 1 to 25 on a sheet of paper. Patients who had a time more than 50.2 ± 14.3 seconds (the average of control group) are considered abnormal.
- The Trail-Making Test -B (TMT-B) circles include the numbers from 1-13 and the letters from A-L. The subjects were asked to connect numbers and letters in alternating manner, that means go from 1-A-B-2-C and so on. Patients who had a time more than 101.1 ± 32.2 seconds (the average of control group) are considered abnormal.

Visual evoked potential (VEP) recordings were performed using Nihon-Kohden machine. We studied the amplitudes and the latencies of P100.

Statistical analysis

Data analysis was performed using SPSS software version 18 under windows 7.

Simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as measure of dispersion for quantitative parametric data. The level $P \leq 0.05$ was considered the cut-off value for significance.

RESULTS

This study was conducted on 60 Egyptian subjects divided into 2 groups:

-Patients group included 30 patients with accidentally discovered HCV infection not on specific treatment; with mean (±SD) duration of illness of 20.9±20.1 months.The cause of disease transmission was unknown. Clinical evaluation, neurophysiological and psychometric tests were done to this group at the beginning of the study (baseline), and 6 months after interferon treatment (follow up). Nine patients had missed follow up (4 had failed interferon treatment and 5 dropout); accordingly follow up studies completed on 21 patients.

-Control group included 30, age and sex matched healthy volunteers.

There was no significant difference between patient group and the controls regarding sex distribution, mean age, and educational level measured as years spent in education (Table 1).

At baseline, all the patients had normal neurological examination; while at follow up, one patient developed right sensori-neuronal hearing loss, another had glove and stock hypoesthesia.

There was no statistically significant difference between the patients and controls in MMSE, as well as between patients at baseline and controls in COWAT while it was significantly lower in patients at follow up than controls and at base line. The score of TMT-A was significantly higher at base line and follow up than in controls, however there was no significant difference between base line and follow up. The score of TMT-B was significantly higher in patients at follow up compared to controls and at base line (tables 2, 3 and 4).

We first compared VEP latencies and amplitudes between the right and the left eyes within each population. Because *t*-test revealed non-significant differences between the two eyes, we subsequently calculated mean values from both eyes for each subject.

Results of visual evoked potential showed that P100 amplitude was significantly lower in patient at base line than control, and at follow up, while P100 latency was significantly longer in follow up than in control, and at base line (tables5, 6 and 7).

Table (1) Demographic data of the studied groups

	Group 1 (patients)	Group 2 (controls)	P
Sex Males (No.) Females (No.)	18 (60%) 12 (40%)	17 (56.7%) 13 (43.3%)	Ns
Age (mean ± SD)	35.6 ± 10	34.2 ± 11	Ns
Education level (mean ± SD)	10.0 ± 2.1	10.5 ± 2	Ns

Ns=Non-significant.

Table (2) Comparison of psychometric tests results between patients at baseline and controls

Psychometric test	Patients at Baseline	Controls	P
	Mean ± SD	Mean ± SD	
MMSE	30 ± 00	30 ± 00	Ns
COWAT	12.9 ± 6	13.6 ± 5.4	0.637
TMT-A	61 ± 25.7	50.2 ± 14.3	0.05
TMT-B	133.7 ±4 3.1	101.1 ± 32.2	0.002

MMSE=minimental state examination, COWAT=controlled oral word association test, TMTA=trail making test A, TMTB=trail making test B, Ns=Non-significant.

Table (3) Comparison of psychometric tests results between patients at follow up and controls

Psychometric test	Patients at Follow up	Control	P
	Mean ± SD	Mean ± SD	
MMSE	29.4 ± 1.6	30 ± 00	0.117
COWAT	9.2 ± 4.8	13.6 ± 5.4	0.003
TMT-A	79.6 ± 42.7	50.2 ± 14.3	0.006
TMT-B	163.3 ± 52.7	101.1 ± 32.2	0.001

MMSE=minimental state examination, COWAT=controlled oral word association test, TMTA=trail making test A, TMTB=trail making test B.

Table (4) Comparison of psychometric tests results between patients at baseline and at follow up.

Psychometric test	Patients at Baseline	Patients at Follow up	P
	Mean ± SD	Mean ± SD	
MMSE	30 ± 00	29.4 ±1.6	Ns
COWAT	12.9 ± 6	9.2 ± 4.8	0.017
TMT-A	61 ± 25.7	79.6 ± 42.7	Ns
TMT-B	133.7 ± 43.1	163.3 ± 52.7	0.04

MMSE=minimental state examination, COWAT=controlled oral word association test, TMTA=trail making test A, TMTB=trail making test B, Ns=Non-significant.

.

Table (5) Comparison of visual evoked potential results between patients at baseline and controls

VEP	Patients at Baseline	Control	P
	Mean ± SD	Mean ± SD	
P100 AMP (µv)	4.2 ± 1	5.9 ± 2.5	0.001
P100 L (ms)	101.2 ± 12.4	98.7 ± 10.1	Ns

P100 AMP= P100 amplitude, P100 L = P100 latency, Ns=Non-significant.

Table (6) Comparison of visual evoked potential results between patients at Follow up and controls

VEP	Patients at Follow up	Control	P
	Mean ± SD	Mean ± SD	
P100 AMP (µv)	5.9 ± 3.1	5.9 ± 2.5	Ns
P100 L (ms)	112.2 ± 15.2	98.7 ± 10.1	0.001

P100 AMP= P100 amplitude, P100 L = P100 latency, Ns=Non-significant.

Table (7) Comparison of visual evoked potential results between patients at Base line and at Follow up.

VEP	Patients at Base line	Patients at Follow up	P
	Mean ± SD	Mean ± SD	
P100 AMP (µv)	4.2 ± 1	5.9 ± 3.1	0.028
P100 L (ms)	101.2 ± 12.4	112.2 ± 15.2	0.001

P100 AMP= P100 amplitude, P100 L = P100 latency

DISCUSSION

HCV is a parenterally transmitted, hepatotropic, and lymphotropic RNA virus. More than 170 million people worldwide are chronically infected with HCV (9). In high endemic areas such as Egypt and southern Italy local prevalence may reach 30% (10).

In this study cognitive dysfunction was found in hepatitis C patients and was found to be aggravated during treatment with interferon which was in agreement with Budhram et al, (2014) who stressed on the importance of cognitive functions assessment in all hepatitis C patients to allow early intervention, and to reduce the severity of cognitive dysfunction (11). Conversely Abrantes et al, (2013) did not find any relationship between HCV in patients without liver dysfunction, and cognitive impairment, and attributed this to their strict selection criteria (12).

Hepatic encephalopathy is well documented in patients with liver cirrhosis (13). It is unlikely that cognitive dysfunction in our patients represented minimal hepatic encephalopathy because patients with advanced cirrhosis were excluded.

There had been growing evidence that alterations in cerebral function in patients with HCV infection may appear long before the development of severe liver cirrhosis. About 50% of patients with HCV infection complain of neuropsychiatric symptoms irrespective of the severity of liver disease (14). Attention, concentration and psychomotor speed are the cognitive functions most likely to be impaired, suggesting selectivity for Fronto-subcortical systems (15). Etiology is unclear but it has been hypothesized that it is related to a direct effect of HCV on the brain; or the neurotoxic effect of HCV related systemic inflammation (16). Chronic activation of the immune system also may account for cognitive dysfunction as there is increasing appreciation of a possible role of cytokine mediated cognition.

Certain cytokines like interferon-alpha (IFN-a) and tumor necrosis factor alpha (TNF-a), may cross the blood-brain barrier to affect brain functions (17). Even small amounts of HCV in the brain can induce a local inflammatory response with subsequent brain dysfunction (18). Exogenous IFN-a has been shown to adversely affect cognition in both healthy volunteers (19), and patients (20).

Kamei et al, (2002) found reduced performances on a cognitive screening in patients treated with IFNa that reversed after the end of treatment (21). Hilsabeck et al, (2005)reported that, IFN-a therapy has no significant effect on simple attention, but it mainly affect the complex attention and

working memory (22). We suggest that these findings support affection of frontal-subcortical systems by IFNa in HCV patients and that the prefrontal lobe functions of working memory may be the most vulnerable. Additional studies have reported similar results and conclusions (23,24).

In this study, no statistically significant difference was found between the studied groups regarding MMSE which agreed with previous studies who found that the MMSE scores did not reveal significant differences between the patients and controls (12, 25,26).

Verbal fluency is one aspect of executive functions, in the present study, there was no significant difference between patients at base line and controls regarding COWAT and that agreed with many studies found this domain intact in individuals with HCV infection (12,27-29). However Fontana (2007) found minor impairment in COWAT among HCV-positive individuals (28). On follow up of our patients after 6 months of interferon treatment the COWAT was significantly lower in the patients group compared to the controls and at base line, this agrees with Lieb et al, (2006) who found that verbal fluency was affected with a significant reduction of words produced in the COWAT after 12 weeks of low-dose INFa therapy and that cognitive deterioration was not related to depression or anxiety (30). In contrast, Fontana et al, (2007) found no significant change in cognitive function overall during therapy (28). These apparently conflicting results may reflect differences in the studied population, frequency of retesting, and specific measures of cognition utilized.

In this study the score of TMT-A was significantly higher in base line, and follow up than controls, however there was no significant difference between patients at base line and follow up. The score of TMT-B was significantly higher inpatients at follow up compared to controls, and at baseline, similarly it was significantly higher in patients at base line than controls. Cordoba et al, (2003) reported a worse TMT results in the studied group of patients in different stages of liver diseases when compared to control (29). On the other hand Abrantes et al, (2013) reported no deficit performance of TMT between patients with HCV and the control group (12). TMT-B was more sensitive than TMT-A in detection of cognitive dysfunction in our patients at baseline and follow up assessment which agrees with Amodio et al, (2004) who reported that the Trail-Making Test B was more sensitive to alterations in cognitive function (31).

The results of VEP in our study showed that patients with HCV at baseline had feature of axonal optic neuropathy in the form of reduction of the amplitude of P100 bilaterally when compared to controls, which improved after interferon treatment, however after interferon treatment patients developed features of demyelinating optic neuropathy with prolonged P100 latency. Weissenborn et al, (1990) recorded abnormal Pl00 latencies in 15% of the patients without clinical signs of hepatic encephalopathy and in 42% of patients in early stage of hepatic encephalopathy (32), and Manesis et al, (1998) found 45% of patients had prolonged baseline P100 latencies (33), at the same time, Sannita et al, (1995) reported increased latency of the cortical evoked response to contrast stimulation of pattern-reversal or pattern-onset VEPs (34). These results may be due to the hypothesis that chronic viral hepatitis is considered as demyelinating disease which causes inflammation of the optic nerve. However our cases were not suffering from chronic disease. Prolongation of P100 latency during IFN treatment agreed with Manesis et al, (1998) who indicated that during IFN treatment, approximately 1 of 4 patients, normal otherwise at baseline, is expected to develop visual neurophysiologic abnormalities in the form of prolonged P100 latency in VEP (33).

A possible explanation for reduction of the amplitude of P100 in the HCV patients may be due to the neurotoxic effect of HCV related systemic inflammation that may be reduced after interferon treatment leading to improvement of the amplitude of P100. More over this may result from deposition of antigen-antibody complexes. Other possible mechanisms for these CNS manifestations are vasculitis from cryoglobulin deposition in small blood vessels supplying the nerves, and the effect of cytokines derived from the host immune system in response to HCV (35).

The prolonged P100 latency with interferon treatment was suggested to be due to the effect of IFN-a therapy that lead to a breakdown of peripheral tolerance to myelin sheath antigens leading to demyelination neuropathy (36). These results disagreed with Farkkila et al, (1988) who described delayed responses but with decreased amplitudes in 15 patients suffering from amyotrophic lateral sclerosis and receiving INF treatment (37). However, these results could, be attributed to different type and extremely high doses of interferon, producing high serum and cerebrospinal fluid levels with probably enhanced interferon neurotoxicity. Recurrent episodes of CNS and PNS

demyelination suggestive of antibody mediated autoimmunity or a direct cytopathic effect of the virus, have been reported in a patient with active HCV replication (38). Relapsing forms of central and peripheral demyelination, worsened by interferon treatment, have also been described (39).

Prolongation of VEP may express reduction of conductive velocity of the optic fibers. Such changes can appear before any clinical visual signs (32,40), and be suggestive of optic tract neuropathy (41). There have been case reports of optic neuropathy with visual loss and scotomas (42), as well as, reports of anterior ischemic optic neuropathy associated with IFN therapy, characterized by sudden visual loss, segmental optic disc edema, and disc-related field defects (43). However, none of our cases with prolonged VEP demonstrated scotomas, papilloedema, or a subjective sense of diminution of vision as confirmed by ophthalmological examination before and during interferon treatment.

CONCLUSION:

Cognitive dysfunction was found in recently diagnosed hepatitis C patients and was found to be aggravated during treatment with interferon**.** Attention**,** visuo-spatial orientation and psychomotor speed were the most affected functions. Patients had feature of axonal optic neuropathy which improved after interferon treatment. Cognitive function, of hepatitis C patients, must be evaluated before and during interferon treatment.

REFERENCES:

[1] McCarthy M, Ortega MR. Neurological complications of hepatitis C infection. *Curr Neurol Neurosci Rep*. 12, 2012, 642-54.

[2] Mohamoud YA, Mumtaz GR, Riome S, Miller D, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Egypt: a systematic review and data synthesis. *BMC Infect Dis.* 13, 2013, 288.

[3] Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis*. 5, 2005, 558-67.

[4] Lavanchy D. Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect.* 17, 2011,107-15.

[5] Alter MJ. Epidemiology of hepatitis C virus infection. *World J Gastroenterol*. 13, 2007, 2436-41.

[6] Miller FD, Abu-Raddad LJ. Evidence of intense ongoing endemic transmission of hepatitis C virus in Egypt. *Proc Natl Acad Sci U S A.* 107, 2010, 14757-62.

[7] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 12, 1975, 189-98.

[8] Reitan RM, Wolfson D. The Trail Making Test as an initial screening procedure for neuropsychological impairment in older children. *Arch Clin Neuropsychol*. 19, 2004, 281-8.

[9] Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med*. 345, 2001, 41-52.

[10] Lagging M, Wejstal R, Uhnoo I, et al. Treatment of hepatitis C virus infection: updated Swedish Consensus recommendations. *Scand J Infect Dis.* 41, 2009, 389-402.

[11] Budhram A, Cebrian C. Paranoid psychosis and cognitive impairment associated with hepatitis C antiviral therapy. *Gen Hosp Psychiatry.* 36, 2014, 126 e3-5.

[12] Abrantes J, Torres DS, de Mello CE. Patients with hepatitis C infection and normal liver function: an evaluation of cognitive function. *Postgrad Med J.* 89, 2013, 433-9.

[13] Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology.* 35, 2002, 716-21.

[14] Tillmann HL. Hepatitis C virus infection and the brain. *Metab Brain Dis.* 2004;19:351-6.

[15] Perry W, Hilsabeck RC, Hassanein TI. Cognitive dysfunction in chronic hepatitis C: a review. *Dig Dis Sci*. 53, 2008, 307-21.

[16] Senzolo M, Schiff S, D'Aloiso CM, et al. Neuropsychological alterations in hepatitis C infection: the role of inflammation. *World J Gastroenterol.* 17, 2011, 3369-74.

[17] Pan W, Kastin AJ. Penetration of neurotrophins and cytokines across the blood-brain/blood-spinal cord barrier. *Adv Drug Deliv Rev.* 36, 1999, 291-98.

[18] Radkowski M, Bednarska A, Horban A, et al. Infection of primary human macrophages with hepatitis C virus in vitro: induction of tumour necrosis factor-alpha and interleukin 8. *J Gen Virol.* 85, 2004, 47-59.

[19] Smith A, Tyrrell D, Coyle K, Higgins P. Effects of interferon alpha on performance in man: a preliminary report. *Psychopharmacology (Berl)*. 96, 1988, 414-6.

[20] Adams F, Quesada JR, Gutterman JU. Neuropsychiatric manifestations of human leukocyte interferon therapy in patients with cancer. *JAMA.* 252, 1984, 938-41.

[21] Kamei S, Sakai T, Matsuura M, et al. Alterations of quantitative EEG and mini-mental state examination in interferon-alpha-treated hepatitis C. *Eur Neurol.* 48, 2002, 102-7.

[22] Hilsabeck RC, Hassanein TI, Ziegler EA, Carlson MD, Perry W. Effect of interferon-alpha on cognitive functioning in patients with chronic hepatitis C. *J Int Neuropsychol Soc.* 11, 2005, 16-22.

[23] Amodio P, De Toni EN, Cavalletto L, et al. Mood, cognition and EEG changes during interferon alpha (alpha-IFN) treatment for chronic hepatitis C. *J Affect Disord.* 84, 2005, 93-8.

[24] Capuron L, Pagnoni G, Demetrashvili M, et al. Anterior cingulate activation and error processing during interferon-alpha treatment. *Biol Psychiatry*. 58, 2005, 190-6.

[25] Ciecko-Michalska I, Wojcik J, Senderecka M, et al. Cognitive functions in patients with liver cirrhosis: a tendency to commit more memory errors. *Med Sci Monit*. 19, 2013, 283-8.

[26] Koziarska D, Wunsch E, Milkiewicz M, Wojcicki M, Nowacki P, Milkiewicz P. Mini-Mental State Examination in patients with hepatic encephalopathy and liver cirrhosis: a prospective, quantified electroencephalography study. *BMC Gastroenterol*. 13, 2013, 107.

[27] Karaivazoglou K, Assimakopoulos K, Thomopoulos K, et al. Neuropsychological function in Greek patients with chronic hepatitis C. *Liver Int.* 27, 2007, 798-805.

[28] Fontana RJ, Bieliauskas LA, Lindsay KL, et al. Cognitive function does not worsen during pegylated interferon and ribavirin retreatment of chronic hepatitis C. *Hepatology*. 45, 2007, 1154-63.

[29] Cordoba J, Flavia M, Jacas C, et al. Quality of life and cognitive function in hepatitis C at different

stages of liver disease. *J Hepatol*. 39, 2003, 231-8.

[30] Lieb K, Engelbrecht MA, Gut O, et al. Cognitive impairment in patients with chronic hepatitis treated with interferon alpha (IFNalpha): results from a prospective study. *Eur Psychiatry*. 21, 2006, 204-10.

[31] Amodio P, Montagnese S, Gatta A, Morgan MY. Characteristics of minimal hepatic encephalopathy. *Metab Brain Dis.* 19, 2004, 253-67.

[32] Weissenborn K, Scholz M, Hinrichs H, Wiltfang J, Schmidt FW, Kunkel H. Neurophysiological assessment of early hepatic encephalopathy. *Electroencephalogr Clin Neurophysiol.* 75, 1990, 289-95.

[33] Manesis EK, Moschos M, Brouzas D, et al. Neurovisual impairment: a frequent complication of alpha-interferon treatment in chronic viral hepatitis. *Hepatology.* 27, 1998, 1421-7.

[34] Sannita WG, Lopez L, Piras C, Di Bon G. Scalp-recorded oscillatory potentials evoked by transient pattern-reversal visual stimulation in man. *Electroencephalogr Clin Neurophysiol*. 96, 1995, 206-18.

[35] Forton DM, Karayiannis P, Mahmud N, Taylor-Robinson SD, Thomas HC. Identification of unique hepatitis C virus quasispecies in the central nervous system and comparative analysis of internal translational efficiency of brain, liver, and serum variants. *J Virol.* 78, 2004, 5170-83.

[36] Hoare M, Woodall T, Alexander GJ. Bell's palsy associated with IFN-alpha and ribavirin therapy for hepatitis C virus infection. *J Interferon Cytokine Res.* 25, 2005, 174-6.

[37] Farkkila M, Iivanainen M, Harkonen M, et al. Effect of interferon-gamma on biogenic amine metabolism, electroen cephalographic recordings, and transient potentials. *Clin Neuropharmacol.* 11, 1988, 63-7.

[38] Mestre TA, Correia de Sa J, Pimentel J. Multifocal central and peripheral demyelination associated with hepatitis C virus infection. *J Neurol.* 254, 2007, 1754-6.

[39] Bezerra ML, Harumi JA, Shinosaki JS, et al. Hepatitis C virus: a rare manifestation--remitting relapsing central and peripheral

demyelination. *Neurol India.* 59, 2011, 114-6.

[40] Woung LC, Jou JR, Liaw SL. Visual function in recovered ethambutol optic neuropathy. *J Ocul Pharmacol Ther*. 11, 1995, 411-9.

[41] Halliday AM, McDonald WI, Mushin J. Delayed visual evoked response in optic neuritis. *Lancet*. 1, 1972, 982-5.

[42] Manesis EK, Petrou C, Brouzas D, Hadziyannis S. Optic tract neuropathy complicating low-dose interferon treatment. *J Hepatol*. 21, 1994, 474-7.

[43] Purvin VA. Anterior ischemic optic neuropathy secondary to interferon alfa. *Arch Ophthalmol.* 113, 1995, 1041-4.