Original article
DOI: 10.5455/amaj.2017.02.038

Response of fibromyalgia associated with Hepatitis C virus infection to combined oral antiviral therapy, Egypt

Mohamed Mahmoud Abdo, MD[1]
Shaimaa Okasha, MD[2]
Mai Abdul Rahim Abdul Latif Hassan , MD[2]
Adel Hamed Elbaih , MD[3]

[1] Assistant professor of internal medicine, Faculty of Medicine, Suez Canal University, Egypt.

[2] Lecturer of Rheumatology, Faculty of Medicine, Suez Canal University, Egypt..

[3] Assistant professor of emergency medicine, Faculty of Medicine, Suez Canal University, Egypt.

Correspondence:
Adel Hamed Elbaih, MD,
Assistant professor of Emergency Medicine, Suez Canal University, Ismailia, Egypt.
Phone: +201154599748
Email: elbaihzico@yahoo.com

INTRODUCTION: Fibromyalgia (FM) is a rheumatic syndrome characterized by a widespread musculoskeletal pain. Genotype 4 of HCV is the predominant genotype being isolated from up to 91% of HCV infected persons in Egypt. The prevalence of rheumatic manifestation was 16.4% of which 1.9% had fibromyalgia in HCV infection.

AIM: To assess the response of HCV associated FMto oral anti-viral treatment.

METHODS: This study is a cross-sectional study included 100 patients who were eligible to treatment with oral antiviral treatment in Suez insurance hospital. And outcome measures included presence of chronic widespread pain (CWP) according to the Manchester criteria.

RESULTS: Our patients answered the hepatitis quality of life questionnaire (HQLQ), extra hepatic manifestation and presence of chronic widespread pain (CWP) before and six months after treatment.

CONCLUSION: Comparison of demographic, clinical and laboratory data between HCV patient with fibromyalgia pre and post treatment: there's Significance of change before treatment 6 months after treatment especially in the serum calcium and vitamin Serum 1-25-(OH) D level.

Keywords: Fibromyalgia, hepatitis C virus, antiviral therapy.

Introduction

Fibromyalgia (FM) is a rheumatic syndrome that occurs predominantly to women aged 30-55 years rather than men. It is characterized by a widespread musculoskeletal pain. Greater than three months' duration, leading to physical and emotional problems. [1]

The exact cause of fibromyalgia is unknown; it may be by the malfunction of certain neurotransmitters in the brain and spinal cord. Regarding its chronicity it is considered as a life-long condition for most people interfering directly with their functional capacity. [2]

The diagnosis is based on the clinical presentation of the patient. The American College of Rheumatology (ACR) in 1990 published diagnostic research criteria for fibromyalgia included a presence of 11 out of 18 tender points, history of chronic and widespread pain in the left side of the body; pain in the right side of the body; pain above the waist; pain below the waist, axial skeletal pain present and the duration of pain more than 3 months. [3]

Chronic hepatitis C virus (CHC) is a major public health the prevalence of reservoir of HCV worldwide is nearly 2 million or 3% of the global population. [5] Egypt has an exceptionally high prevalence of HCV infection, estimated to be between 10% and 15% of its 90 million populations. [6] The annual infection rate is more than 70,000 new cases, of which at least 35,000 would have chronic hepatitis C. [7] Genotype 4 of HCV is the predominant genotype being isolated from 91% of HCV infected persons in Egypt. [8, 9]

One research has been conducted among Egyptians genotype 4 HCV infection revealed a 16.3% them have extra hepatic rheumatologic manifestations. Female gender appears to be more liable to develop

extra hepatic rheumatologic manifestations especially fatigue, fibromyalgia, autoimmune hemolytic anemia, and mixed cryoglobulinemia. HCV has been known to provoke a plethora of autoimmune syndromes as well as nonspecific rheumatologic manifestations which has been referred to as rheumatic manifestations of HCV genotype 4 such extra hepatic syndromes have been reported in as much as 40-74% of chronic HCV-infected patients. As a consequence of its lymphotropic nature, hepatitis C genotype 4 can trigger and sustain a clonal B-cell expansion which causes a wide spectrum of autoimmune/lymphoproliferative disorders, These extra hepatic manifestations become clinically manifest in 40%-70% of the patients and they can be frequently classified among the rheumatic ones. [10, 11]

Furthermore, HCV can promote the production of several auto antibodies complicating the differential diagnosis between primitive and HCV related rheumatic disorders. [12, 13] Fibromyalgia(FM) is reported by 1.9% to 57% of patients suffering from HCV chronic infection. [14] Although in a Spanish study anti-HCV antibodies were found in 15.2% of the enrolled FM subjects, other studies did not confirm the increased prevalence of HCV infection in FM. [15]

Chronic Hepatitis C infection and Fibromyalgia share many clinical features including fatigue and musculoskeletal pain. One study found that people dually diagnosed with fibromyalgia and hepatitis C exhibit symptoms such as inflammation around a joint, bursa and/or tendon, and vasculitis that are not seen in non-hepatitis C people with fibromyalgia [16].

Another Egyptian research included 306 patients having chronic HCV infection were Interviewed. The prevalence of rheumatic manifestation was 16.39% of which 1.9% had fibromyalgia. [13]

Aim of the work

To assess the response of HCV associated fibromyalgia to oral anti-viral treatment,

Material & Methods

This study was conducted in Suez Insurance Hospital. 100 patients were eligible to treatment with oral antiviral treatment, each patient was assessed with same rheumatologist before treatment.

All patients underwent assessment including history, clinical examination, and functional assessments for pain and disability+, Met the criteria established by the American College of Rheumatology (ACR). Those criteria are:

1. Widespread pain (right and left side body pain, above and below the waist) that lasts 2 for more than 3 months.

2. Eleven or more tender points present at 18 specific sites on the body. [17]

Participants answered the Hepatitis Quality of Life Questionnaire (HQLQ) before and six months after finishing treatment.

Each patient received same regimen of treatment in the form of sofosbuvir 400 mg, daclatasivir 60mg and ribavirin 600mg

Outcome measures included presence of chronic widespread pain (CWP) according to the Manchester criteria (pain in the axial skeleton and at least two contralateral body quadrants for at least 3 months, the number of affected joints, pain intensity, and interference with daily life as scored on a visual analogue scale (VAS). [18]

Patients with other rheumatic diseases, hepatitis B virus and HIV were excluded.

Results

The results are shown on Tables 1-5.

Discussion

Our Patients showed significant improvement in 11 of the 12 domains of HQLQ after treatment, with the whole improved in the total score antiviral therapy had a positive effect on HRQOL which has been defined by Spiegel et al., as there's clinically important difference in HRQOL after treatment. [19] Therefore, the antiviral therapy has had a positive effect on HRQOL is dependent on the weighting given to different domains. In keeping with our study, HRQOL improvement Was seen in the domains relating to physical health (H. H. Thein et al., 2007) had Given the significant improvement in domains relating to general health, disease limitations, social functioning, and hepatitis-related distress, the deterioration in domains relating to mental well-being and positive well-being distress suggests a complex range of effects with antiviral treatment, which were matched with our work. [20]

J. Golden et al., found that there's high incidence of anxiety and depressive symptoms, which are commonly reported among HCV-infected patients. These symptoms may be related to a patient's distress at being diagnosed with a chronic and serious illness, the exacerbation of these symptoms, on the other hand, may be caused by antiviral treatment itself, as it is known to cause depression. Our results support the hypothesis that initial impairments in physical domains are health distress and mental health. [18]

Our patients interestingly experience myalgia and arthralgia following treatment, the average VAS pain intensity and impact

Table 1. Demographic data: Our study reflected a relatively young population with a mean age of 46. The higher prevalence were among male patients and the higher associated condition was about the chronic wide spread pain.

Demographic data	Gender		Age	Associated condition				
	Male	Female		Osteoarthritis	Rheumatoid arthritis	Undifferentiated arthritis	Sicca syndrome	Chronic wide spread pain
Mean / Percent	59	41	46	89	10	1	53	88

Table 2. HQLQ scores before and after treatment: HQLQ domain mean scores, significance of change before and after the treatment.

	Before treatment	after 6 months	p value
Physical functioning	26.3	87.2	*0.004*
Role physical	43.2	83.1	*0.0067*
Body pain	76.6	36.3	*0.035*
General health	48.9	79.1	*0.0023*
Vitality	35.1	66.9	*0.0123*
Social functioning	43.4	78.6	*0.0087*
Role emotional	63.8	79.3	0.370
Mental health	73.3	69.3	0.4476
Health distress	67.8	42.9	*0.0079*
Positive well-being	78.5	61.7	*0.0014*
Hepatitis-specific functional limitations	78.6	49.3	*0.0019*
Hepatitis-specific distress	22.3	36.3	*0.0017*

Table 3. Extra hepatic manifestation before and after treatment: there's significance of change before and after treatment especially in the CWP (chronic widespread pain).

	Before treatment	after 6 months	p value
CWP (chronic widespread pain)	36.3	15.3	*0.015*
Average pain intensity in past month (VAS) (0–10)	7.5	3.03	*0.0125*
Interference with daily activities in past month (0–10)	3.91	1.67	*0.048*
Number of painful joints in past month	3.49	1.24	*0.006*
Pain for more than 3 months	75.4	25.4	*0.031*
"I ache allover"	26.7	14.6	*0.039*

levels, bodily pain aspects of the HQLQ, and the number of painful joints were all low and changed little with treatment. This reflects that extra hepatic pain manifestations in HCV patients

Table 4. Variables associated with before treatment and after treatment: there's Significance of change before and after treatment especially in the number of painful joint.

CWP	Before treatment	after 6 months	p value
VAS pain rating (mean)	36.3	15.3	*0.015*
VAS interference rating (mean)	7.5	3.03	*0.0136*
Interference with daily activities in past month (0–10)	3.91	1.67	*0.048*
Number of painful joints in past month	5.49	1.69	*0.001*
HQLQ domain			
Physical functioning	77.8	80.3	*0.021*
Role physical	55.6	67.9	*0.031*
Body pain	40.2	88.9	*0.051*
General health	45.9	67.3	*0.041*
Vitality	50.2	45	*0.032*
Social functioning	56.9	67	*0.031*
Role emotional	54.3	66.8	*0.001*
Mental health	66.2	77.8	*0.221*
Health distress	45.3	30.9	*0.023*
Positive well-being	77.4	87.9	*0.035*
Hepatitis-specific functional limitations	52.8	87	*0.051*
Hepatitis-specific distress	28.9	35	*0.043*

are unaltered by treatment in the majority of cases which were matched with the work of D. Saadoun et al., 2008. [21]

In our study we compare patients with and without CWP before treatment revealed baseline HQLQ scores to be significantly worse in 11 domains in those with CWP. CWP remission after treatment was also significantly associated with an improved body pain and physical function score.

Conclusion

Chronic hepatitis C virus infection can induce several rheumatic manifestations that should be differentiated from the primitive rheumatic ones. Treatments for these two kinds of disorders are usually different and the lack of detection of HCV infection could represent a real risk for patients. As a consequence, HCV testing should be routinely performed in patients showing rheumatic signs and/or symptoms. In some patients,

Table 5. Comparison of Demographic, Clinical and Laboratory Data between HCV patient with fibromyalgia pre and post treatment: there's Significance of change before treatment 6 months after treatment especially in the serum calcium and vitamin Serum 1-25-(OH)D level.

	Before treatment	after 6 months	p value
Age (years), mean (SD)	37.96 ± 9.8	32.63 ± 10.1	*0.002*
Time with symptoms (month), mean (SD)	58.24 ± 38.89		
Time since diagnosis (month), mean (SD)	13.23 ± 6.23		
Married, n (%)	53 (96%)	63 (92%)	
Serum calcium (mg/dl)	9.32 ± 0.35	9.15 ± 0.43	*0.005*
Serum phosphorus (mg/dl)	3.60 ± 0.47	3.66 ± 0.54	
Serum alkaline phosphatase (U/L)	159.9 ± 48.7	142.3 ± 33.5	*0.017*
ESR	14 ± 9	15 ± 10	
Serum 25-OHD (ng/ml) mean (SD)	17.24 ± 13.50	9.91 ± 6.47	*0.001*
Serum 25-OHD ≤ 20 ng/ml, n (%)	48 (69.6%)	63 (92.6 %)	*0.001*
Serum 25-OHD = 20–30 ng/ml, n (%)	13 (18.8 %)	4 (5.9 %)	*0.001*
Serum 1-25-OHD ≥ 30 ng/ml, n (%)	8 (11.6)	1 (1.5)	*0.001*

it remains unrealistic, also for experienced rheumatologist, to discriminate if the presence of HCV is casual or plays an active role in causing autoimmune disorders.

References

1. Smith HS, Harris R, Clauw D. Fibromyalgia: an afferentprocessing disorder leading to a complex pain generalizedsyndrome. Pain Physician. 2011; 14:E217–45.
2. Cardoso FS, Curtolo M, Natour J, Lombardi Júnior I. Avaliac¸ãodaqualidade de vida, forc¸a muscular e capacidadefuncionalemmulheres com fibromyialgia. Rev Bras Reumatol.2011;51:338–50.
3. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg D, Katz RS,Mease P, et al. The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. Arthritis Care &Research. 2010; 62:600–10.
4. Gür A. Physical therapy modalities in management of fibromyalgia. Curr Pharm Des. 2006; 12:29–35.
5. Wasley A, Alter MJ (2000) Epidemiology of hepatitis C:geographic differences and temporal trends. Semin Liver Dis 20(1):1–16
6. Mohamed MK, Bakr I, El-Hoseiny M, Arafa N, Hassan A, Ismail S et al (2006) HCV-related morbidity in a rural community in Egypt. J Med Virol 78(9):1185 1189
7. Egypt: 5 million infected by hepatitis C. Online article by the Egyptian National Hepatitis Committee, Feb: 2007. IntegratedRegional Information Networks IRIN
8. Ray SC, Arthur RR, Carella A, Bukh J, Thomas DL (2000) Genetic epidemiology of hepatitis C virus throughout Egypt. Jinfect Diseas 182(3):698–707, Epub 2000 Aug 17
9. Shaheen MA, Idrees M. Evidence-based consensus on the diagnosis, prevention and management of hepatitis C virus disease. World J Hepatol 2015; 7: 616-627 [PMID: 25848486 DOI: 10.4254/wjh. v7.i3.616]
10. Reem HA, Mohammed &Hesham IE, Amira G ,Et al.Prevalence ofrheumatologic manifestations of chronichepatitis C virus infection among Egyptians,ClinRheumatol (2010) 29:1373–1380
11. Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC,Opolon P (1999) Extrahepatic manifestations of chronic hepatitisC. MULTIVIRC Group. Multidepartment virus C. ArthritisRheum 42:2204–2212
12. Palazzi C, D'Amico E, D'Angelo S, Gilio M, Olivieri I.Rheumatic manifestations of hepatitis C virus chronic infection:Indications for a correct diagnosis. World J Gastroenterol 2016;22(4): 1405-1410.
13. Mohammed RH, ElMakhzangy HI, Gamal A, Mekky F, El Kassas M, Mohammed N, Hamid MA, Esmat G. Prevalence of rheumatologic manifestations of chronic hepatitis C virus infection among Egyptians. Clinical rheumatology. 2010 Dec 1;29(12):1373-80.
14. Mohammad A, Carey JJ, Storan E, Scarry M, Coughlan RJ,Lee JM. Prevalence of fibromyalgia among patients with chronichepatitis C infection: relationship to viral characteristics andquality of life. J ClinGastroenterol 2012; 46: 407-412
15. Narváez J, Nolla JM, Valverde-García J. Lack of association offibromyalgia with hepatitis C virus infection. J Rheumatol 2005; 32: 1118-1121 Rivera J, De Diego A, Trinchet M, Garcia Monforte A. Fibromyalgia-associated hepatitis C virus infection. British journal of rheumatology. 1997 Sep 1;36(9):981-5.
16. Elbaih AH, Abdo MM, Khalil AK et al "Correlation between fbromyalgia and the clinical outcome of bleeding in cirrhotic patients in Suez Canal University Hospital, Ismailia, Egypt"-Medicine Science 2017;6(2):338-46.
17. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis & Rheumatology. 1990 Feb 1;33(2):160-72.
18. Golden J, Conroy RM, O'Dwyer AM, Golden D, Hardouin JB. Illness-related stigma, mood and adjustment to illness in persons with hepatitis C. Social science & medicine. 2006 Dec 31;63(12):3188-98.
19. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. Hepatology. 2005 Apr 1;41(4):790-800.
20. Thein HH, Maruff P, Krahn MD, Kaldor JM, Koorey DJ, Brew BJ, Dore GJ. Improved cognitive function as a consequence of hepatitis C virus treatment. HIV medicine. 2007 Nov 1;8(8):520-8.
21. Saadoun D, Delluc A, Piette JC, Cacoub P. Treatment of hepatitis C-associated mixed cryoglobulinemia vasculitis. Current opinion in rheumatology. 2008 Jan 1;20(1):23-8.