PREVALENCE OF HEPATITIS C VIRUS IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS

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ABSTRACT

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Background: *Multiple sclerosis (MS) is a chronic autoimmune illness of the central nervous system and is considered the most common non-traumatic cause of neurological disability in middle age, Hepatitis C virus (HCV) is endemic in our country and Egypt is the most affected nation by HCV worldwide, this study is an educational hospital based study.*

Aim of the Work: *To determine prevalence of HCV in patients having relapsing remitting multiple sclerosis (RRMS).*

Patients and Methods: *Two hundred and three Egyptian patients with the diagnosis of RRMS were recruited consecutively from MS Unit of Neurology department at Ain Shams University Hospital which is the biggest MS unit in Egypt, Cross sectional pilot study. Patients' medical history, general and neurological examination including assessment of the functional disability using Expended Disability Status Scale (EDSS) were obtained along 6 months and were followed for 1 year and all subjects underwent serum sampling for detection of the HCV antibody by enzyme linked immunosorbent assay(ELISA) technique and confirmed diagnosis by polymerase chain reaction(PCR).*

Results: *Data showed that prevalence of HCV among studied patients with RRMS was 4.9% (no. 10 from 203), however prevalence of HCV in Egypt is 10.6%, it may be due to gender predilection which is nearly 2:1 male to female in HCV versus 1:2.57 in MS patients,*

Conclusion: *HCV is less prevalent in MS patients than general population and patients with HCV have more active disease regarding relapses and magnetic resonant imaging (MRI) activity.*

Keywords: *Multiple sclerosis, Hepatitis C virus, Egyptian patients.*

INTRODUCTION:

Multiple sclerosis (MS) is a complex immune mediated disorder of central nervous system. Multiple sclerosis is the most common non-traumatic cause of neurological disability in middle adulthood[1].

There are four clinical phenotypes of MS. Initially, more than 80% of individuals with MS experience a relapsing-remitting disease course (RRMS) characterized by clinical exacerbations of neurologic symptoms followed by complete or incomplete remission. After 10 to 20 years, or median age of 39.1 years, about half of them gradually accumulate irreversible neurologic deficits with or without clinical relapses, which is known as secondary

progressive MS (SPMS). Another 10% to 20% of individuals with MS are diagnosed with primary progressive MS (PPMS), clinically defined as a disease course without any clinical attacks or remission from onset[2].

In general, the researchers found that MS prevalence has increased dramatically in that 5 year span, up 10% and now affecting 2.3 million people worldwide. Whether this is due to a true intrinsic increase in prevalence or whether the condition is being better diagnosed and reported is not clear. For instance, the number of neurologists worldwide has increased by 30%, which might mean that MS is being better diagnosed and reported. Either way, we now know the prevalence is much higher than we previously thought[3].

Traditionally, microbiologists have used Koch's postulates to establish whether a particular microbe causes a specific disease. Koch's postulates, however, are applicable only for highly pathogenic bacteria, which cause disease in most people they infect, and for organisms that can be cultured in the laboratory and can infect other hosts in addition to human beings[4].

Koch's postulates are ill suited for most viral infections, especially slow viral infections, and for diseases caused by viruses that are a rare manifestation of a common infection[5].

Hepatitis C virus (HCV) has a major impact on public health with over 170 million infected individuals. It has been considered to cause 25% of hepatocellular carcinoma (HCC) and 27% of cirrhosis cases all over the world. Death rate due to HCV infection is very high and approximately 350, 000 people die every year after being infected with HCV. Toxicity, resistance and cost of the treatment limit current therapy of HCV. To date, no vaccine or immune-therapy is available[6].

Egypt has one of the highest prevalence rates of hepatitis C virus infection in the world. The HCV epidemic appears to have been initiated by vigorous public-health campaigns using intravenous tartar emetic from the 1950s until 1982 to eradicate schistosomiasis. This iatrogenic mode of infection has now resulted in a high incidence of hepatic morbidity and mortality from the late complications of HCV infection, such as chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). Among the six major HCV genotypes found worldwide, genotype 4 is the most predominant in Egypt with 4a as the dominant subtype[7].

AIM OF THE WORK:

To determine prevalence of HCV in patients having RRMS

PATIENTS AND METHODS:

Cross sectional pilot study conducted on 203 Patients with clinically definite relapsing remitting MS according to McDonald's criteria 2010, recruited from the MS unit and I med system, Ain Shams University.

Inclusion criteria:

All patients who were already diagnosed as RRMS attending the unit were recruited from May 2016 to May 2017.

Exclusion criteria:

Patients with other clinical multiple sclerosis types, patients with other medical or neurological diseases such as hypertension and diabetes mellitus, cardiac diseases, patient with a contraindication to perform MRI, patients who were previously diagnosed chronic liver diseases.

Patients characteristics:

Patients Aged 16 till 50 years both sexes were included, diagnosis of RRMS patients

with the McDonald diagnostic criteria for multiple sclerosis.

Procedure:

Patients were subjected to the following:

History taking and complete neurological examination as chronic liver diseases may previously affecting the clinical picture of the patients, level of disability from MS assessed with the Extended Disability Status Score (EDSS). Duration of illness was calculated as time since first symptoms in years, brain MRI with contrast ± MRI cervicodorsal spines, HCV Ab screening by commercially available ELISA kits in El Demerdash internal medicine laboratory, patients with positive results will be subjected to

1. PCR quantitative tests examination.

2. All of the patients will be subjected to the following at 0, 6 months and during relapse.

   a. Full clinical evaluation including medical, neurological history and examination.

   b. EDSS scoring.

   c. MRI brain and/or spinal cord with contrast.

Statistical analysis of data:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

A. Descriptive statistics:

1. Mean, Standard deviation (± SD) and range for parametric numerical data, while Median and Interquartile range (IQR) for non parametric numerical data.

2. Frequency and percentage of non-numerical data.

B. Analytical statistics:

1. **Student T** Test was used to assess the statistical significance of the difference between two study group means.

2. **Mann Whitney Test (U test)** was used to assess the statistical significance of the difference of a non-parametric variable between two study groups.

3. **ANOVA test** was used to assess the statistical significance of the difference between more than two study group means.

4. **Correlation analysis (using Pearson's method):** To assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically "r" defines the strength and direction of the linear relationship between two variables.

5. **Chi-Square test** was used to examine the relationship between two qualitative variables.

6. **Fisher's exact test:** was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells.

   - P- value: level of significance
   - P>0.05: Non significant (NS).
   - P< 0.05: Significant (S).
   - P<0.01: Highly significant (HS).

RESULTS:

This is a cross sectional pilot study was conducted during the period from August 2016 to August 2017. The case group included 203 patients with age range from 16-52 years with the diagnosis of RRMS whom were recruited consecutively after their recent conscent to participate in the study and all of them have their records in the MS database Imed system.

As Regards the demographic data, the sample included 53(26%) males and 150 (73%) females, 18 (8.9 %) smoker, 10 (4.9%) have family history (Table 1).

Table (1): Demographic data of studied patients with MS N=203:

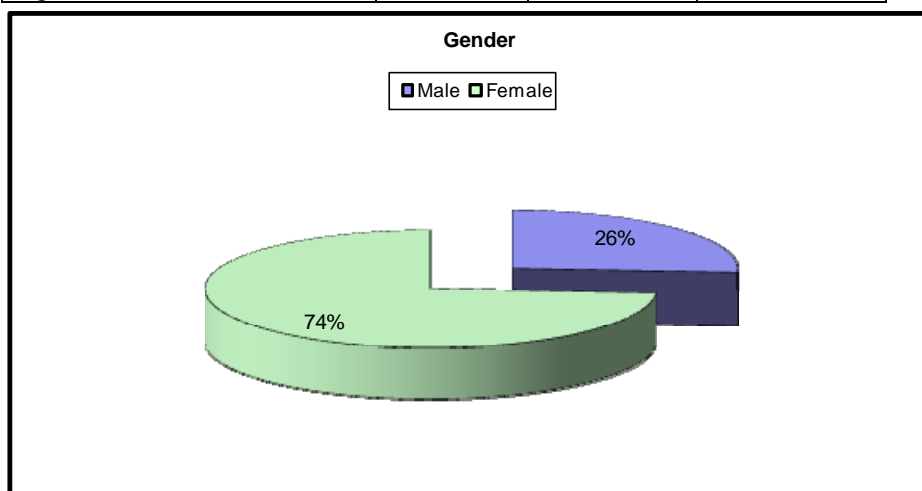| Demographic Data	No.	%	
Gender			
Male	53	26.1	
Female	150	73.9	
Smoking			
Negative	185	91.1	
Positive	18	8.9	
Family history MS			
Negative	193	95.1	
Positive	10	4.9	
	Mean	SD	Range
Age	29.7	8.4	15-52

Diagram (1): Distribution of gender of studied patients.

Table (2): Distribution of symptoms of MS at onset N=203

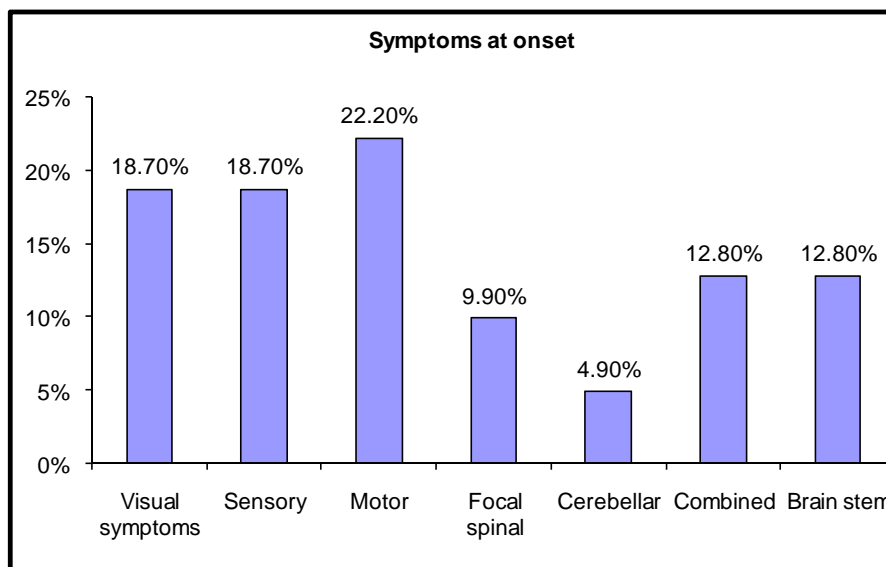| Symptoms at onset	No.	%
Visual symptoms	38	18.7%
Sensory	38	18.7%
Motor	45	22.2%
Focal spinal	20	9.9%
Cerebellar	10	4.9%
Combined	26	12.8%
Brain stem	26	12.8%

Diagram (2): Distribution of symptoms of MS on presentation.

As regards distribution of symptoms of MS on presentation, It was found that 45 (22.2%) of patients were presenting with motor symptoms, followed by visual and sensory symptoms 38 (18.7%), Then brain stem and compound symptoms were 26 (12.8%), Then focal spinal 20 (9.9%), and lastly cerebellar 10 (4.9%).

DISCUSSION:

MS is a demyelinating Autoimmune disease with different clinical forms and uncertain etiology. Many studies suggest that it is likely caused by infections triggering a systemic immune response resulting in antigen/non-antigen-related autoimmune response in CNS[8].

Hepatitis C virus (HCV) infection is a leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation. A better understanding of HCV disease progression and the associated cost can help the medical community manage HCV and develop treatment strategies in light of the emergence of several potent anti-HCV therapies[9].

HCV is endemic in our country and Egypt is the most affected nation by HCV worldwide, so the government initiated a campaign to screen HCV in whole country as a part of WHO project to eradicate HCV by 2030, at the same time prevalence of MS is increasing, that inspire the idea of studying the prevalence of HCV in those who have MS, It is a novel idea hasn't been studied yet, so will discuss the results with the most mimic to MS which is CNS vasculitis and the most incriminated pathogen in infectious theory of MS which are EBV and CMV.

This study is a hospital based cross sectional pilot study which was carried in MS unit at faculty of medicine in Ain shams university – Cairo- Egypt, it was carried out on 203 RRMS patients group according to Revised McDonald criteria 2010[10], they were studied to detect HCV Ab in serum using ELISA technique in the plasma samples of those patients, the study is aiming to know the possible association of HCV as a risk factor for MS disease.

These results showed that prevalence of HCV among studied patients with RRMS was 4.9% (no. 10 from 203), however prevalence of HCV in Egypt is 10.6% as postulated by *Gomaa et al.*[11], it may be due to gender predilection which is nearly 2:1 in HCV versus 1:2 in MS patients.

Regarding the age the results showed that the seropositive patients had higher age than the seronegative patients and the difference is borderline significant (P=0.08) which is consistent with previous study of HCV related cerebral vasculitis, the HCV vasculitis patients had higher age than HCV controls[12].

Results showed that there was no significant difference HCV positive and negative MS cases as regards gender, yet higher female gender in both groups (P=0.6), which is consistent with study of HCV related vasculitis, the HCV vasculitis patients have higher female gender but with not statistically significant *Milvia et al.* [12]. The results are consistent with *Aziz et al.* [13] that postulated that There was no significant association between the EBV antibody titre and sex (P=0.857). On contrary *Mouhieddine et al.* [14] reported that older and female gender were associated with a higher anti-VCA titer Anti-EBV-VCA (Viral Caspid Antigen) Ig G. Higher female gender may be due to more active immune system with higher IgG levels and a highly active immune system might be one mechanism behind the over representation of females seen in autoimmune diseases like MS.

The results showed that the 4.9% of patients have family history of MS and positive smoking in 8.9% of the studied patients, similarly an Ain Shams University MS unit study of EBV ab in patients of RRMS showed that a positive family history (FH) of MS (3.6%) by *Aziz et al.* [13].

Conclusion:

HCV is endemic in our country and Egypt is the most affected nation by HCV worldwide, and HCV hasn't been studied yet as a virus incriminated in MS as a risk factor or even its effect on clinical aspect in such patients compared to others free from HCV. Our study was the first to discuss about two of the most important diseases that may be burden on the patient and handicapping, so it may be a key to other upcoming studies in the future.

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مدى أنتشار فيروس كبدي سي في مرضى التصلب المتعدد بالجهاز العصبي المركزي

**محمود حميدة الرقاوي ¹ وعزة عبد الناصرعبد العزيز ¹ودينا محمدعبدالجواد ¹ ودعاء عبدالله عوض العايدي ¹،
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المقدمة: إن التصلب المتعدد بالجهاز العصبي المركزي هو مرض مناعي مزمن يتصف بالتهابات وإزالة مادة الميالين أو دباق في أماكن متعددة بالمخ والحبل الشوكي، وهو ينقسم إلى ثلاثة أنواع هي: الانتكاس التصاعدي الأولى والثانوي والمتلازمة المنعزلةواخيرا النوع الانتكاسي التصاعدي.

ويعتبر التصلب المتعدد من أشهر الأمراض المزمنه التى تصيب الجهاز العصبي المركزي مسببا اضطراب فى الجهاز المناعى ينتج عنه فقدان لمادة الميالين المغلفه للأعصاب, كما يعد مرض المناعة الذاتية الأكثر شيوعا عند البالغين خاصة هؤلاء الذين تتراوح أعمارهم بين العشرين والأربعين.

ان الفيروسات لها دور عند التعرض فى بعض المرضى الذين لهم استعداد وراثى بطرق مختلفة مما يؤدى إلى أختلال مناعى ويؤدى إلى الأصابه بمرض التصلب المتعدد وهناك العديد من الدراسات التى أجريت على فيروسات منها: (أبيشتاين بار- سيتو ميجالو- هربس زوستر- هربس سمبلكس) ولم يتم أجراء أية دراسات على الفيروسات الكبدية من ضمنها فيروس سى حيث يبلغ نسبة المصابين به ١٧٠ مليون حول العالم وحيث انه المسبب فى ٢٥% من أسباب السرطان الكبدى و٢٧% من أسباب التليف الكبدى.

الهدف من البحث: فكرة هذه الدراسة هى نسبة انتشار فيروس سى لدى المرضى المصابين بالتصلب المتعدد الأنتكاسى.

الحالات والمرضي: وقد شملت هذه الدراسة مجموعه من مئتين وثلاثه من المرضى المترددين على وحدة التصلب المتعدد من النوع الانتكاسي فى قسم الأعصاب بمستشفى عين شمس الجامعي خلال عام من أغسطس ٢٠١٦ حتي أغسطس ٢٠١٧ مع مراعاة استبعاد العوامل التي تسبب أعراض تشبه مرض التصلب العصبي المتعدد حيث تم عمل تحليل الأليزا لهم والذى وجد به الجسم المضاد لفيروس سى تم عمل لهم تحليل كمى للفيروس ومتابعة فى عيادة الفيروسات وتلقى عقار سوفوبوفير وداكلاتا سافير ومتابعة هؤلاء المرضى جميعا بعد ٦ أشهر اكلينيكيا بعمل المقياس الحركى لهم ومتابعة بالرنين المغناطيسى على المخ والفقرات العنقيه ± الفقرات الصدرية.

النتائج: وجد أن نسبة انتشار فيروس سى ٤.٩% بالرغم من نسبة انتشار المرض فى مصر ١٠.٦% من أخر دراسة ٢٠١٧ وقد يرجع الأختلاف لأن مرض التصلب المتعدد نسبة حدوثه فى السيدات إلى الرجال ٢: ١ بينما فيروس سى نسبة حدوثه فى السيدات إلى الرجال ١: ٢.

وأظهرت البيانات لدينا أيضا نسبة وجود التاريخ المرضى فى العائلة لوجود التصلب المتعدد لدى مرض فيروس سى أكثر من هؤلاء الذين لم يصابوا بفيروس سى بالإضافة إلى ذلك فقد كشفة الدراسة عن وجود ارتباط بين مدة وجود المرض ونسبة وجود مضادات الفيروسات فى الدم.

الخاتمة: إن مصر هي الدولة الأكثر تضرراً من فيروس التهاب الكبد الوبائي في جميع أنحاء العالم، ويوجد الكثير من الفيروسات المتسببة في قابلية حدوث مرض التصلب المتعدد ولم تتم دراسة فيروس س وكانت هذه اول دراسة لبحث نسبة علاقة بين انتشار فيروس س ومرض التصلب المتعدد. من الممكن ان تكون حافزاً لمزيد من الدراسات القادمة.