FREQUENCY OF HEPATITIS C INFECTION IN DIABETIC PATIENTS

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Background: Diabetic patients are at an increased risk of acquiring Hepatitis C virus (HCV) infection owing to the nature of the disease and its inherent complications or frequent parentral exposure. On the other hand HCV infection may itself contribute to the development of Diabetes Mellitus. The epidemiological evidence of this association has not been studied in Pakistan at a population level and its exact biological mechanisms are not obvious. Objective of this study was to study the frequency of HCV infection among adult diabetic patients attending the Hospital. **Methods:** The study comprised of 100 Diabetic patients visiting the out patient clinics or admitted in the medical wards of a Teaching Hospital, in Peshawar. Diabetes was confirmed according to the new diagnostic criteria based on 2 fasting or 2 random plasma glucose levels of more than 126 milligram per deciliter (mg/dL) and 200 mg/dL respectively. The presence of HCV infection was confirmed by Enzyme Linked Immuno-Sorbent Assay (ELISA) method. A concise history of the patient, examination and laboratory findings were recorded on a Performa. **Results:** Out of the hundred diabetics, 36% were found to be anti HCV positive and all of them had type II diabetes. There was no gender difference in the seropositive cases. Serum Glutamic-Pyruvic Transaminase (SGPT) level was raised in 75% of the positive cases as compared to the 25% of the seronegative patients. The seropositive cases had a comparatively higher blood sugar level. **Conclusion:** HCV infection occurs more often in type II diabetics and further investigations should be done in diabetic patients with raised SGPT for the presence of chronic HCV infection.

Keywords: Hepatitis C virus, Diabetes mellitus.

INTRODUCTION

The awareness and understanding of viral hepatitis has risen dramatically over the past three decades though it is not a new problem. Descriptions of jaundice exist in literature as far back as several centuries B.C.

Hepatitis C virus was first recognized as a separate disease entity in 1975 when the majority of transfusion related hepatitis were found not to be caused by the only two hepatitis viruses recognized at that time i.e. Hepatitis A virus and Hepatitis B virus. The disease at that time was called "non-A non-B hepatitis [1]. The discovery of hepatitis C genome in 1989 has now leaded to the realization that this virus is a major health problem worldwide[1]. It is characterized by a chronic evolution with mild to severe liver disease, including cirrhosis and in lesser proportion, hepatocarcinoma.[2] Infection with hepatitis C virus is one of the most common causes of chronic liver disease and Hepatitis C virus related disease is a leading indication for liver transplantation today [3]. According to a press release by World Health Organization (W.H.O) in April 1998, prevalence of 0.5% to greater than 10% has been found in population samples around the world. More than 170 million people worldwide are now estimated to suffer from the disease. The problem continues to worsen, especially in developing countries. New infections continue to occur because of unscreened blood transfusions, failure to sterilize hospital and injection equipment and, in some instances, unprotected sexual intercourse. No vaccine is available yet, although research continues and preliminary clinical trials of an experimental vaccine are in progress [4,5].

Infection with HCV affects not only the liver but the extra hepatic tissues as well and may combine with many unrelated diseases and morbid conditions. A number of extra hepatic manifestations have been recognized including diabetes mellitus.[2,3] Although it remains to be determined whether Hepatitis C infection leads to diabetes mellitus or vice versa, but it is argued that patients with diabetes have an increased risk of exposure to Hepatitis C infection. While patients with liver disease are known to have a higher prevalence of glucose intolerance, preliminary studies suggest that Hepatitis C infection may be an additional risk factor for development of Diabetes mellitus [3].

The idea was brought forth by Simo for the first time in 1993 and then by Alison et al in 1994 but the history of appreciation of this association goes back to as far as 1977 when Russian endocrinologists found out abnormalities of glucose tolerance in patients with chronic liver disease [6-8]. Fraser GM et al confirmed in their study in July 1996, that there is an association between diabetes mellitus and chronic Hepatitis C but not chronic hepatitis B [9]. The fact that diabetes is more prevalent in patients with HCV than HBV has also been confirmed in a Korean study in March 2001 [10]. The cause of a higher prevalence of

diabetes in patients with chronic HCV infection remains unclear. Altered glucose metabolism has been documented in patients with chronic liver disease, especially in liver cirrhosis, with a much higher prevalence of diabetes in HCV related liver cirrhosis in comparison with cirrhosis secondary to other causes. [7].

The worldwide epidemic of HCV might contribute to the even greater epidemic of diabetes and vice versa is a provocative idea and requires further studies.

This study was designed to observe the frequency of anti-HCV positivity in diabetic patients.

MATERIAL AND METHODS

This study was conducted at the Medicine Department of Khyber Teaching Hospital, Peshawar. It was performed on 100 consecutive patients both inpatients as well as outpatients who were established diabetics, after taking their informed consent.

It was a descriptive cross-sectional study. Sampling was done by non-probability purposive technique. Consecutive patients of all ages, both genders and of either type of Diabetes were included for the study. However intravenous drug addicts were not included.

The data was collected with the help of a questionnaire which comprised of history, clinical examination and laboratory investigations. The history taking was framed on the basis of the various risk factors of hepatitis C virus infection (including injections, surgery, accidents, blood transfusion, close contact with HCV positive patient, shaving by barbers, ear/ nose piercing, alcohol, tattooing/ acupuncture and sexual promiscuity), duration and type of diabetes and the development of its complications. Clinical examination revolved around assessment of the extent of two diseases, peripheral stigmata of chronic liver diseases and established complications of diabetes mellitus. The random blood glucose levels, urine routine examination and full blood count were done in the Hospital laboratory. Anti HCV positivity was determined in various local laboratories by ELISA.

The diabetic status was confirmed according to the new diagnostic criteria based on 2 fasting or 2 random plasma glucose levels of more than 126 mg/dL and 200 mg/dL respectively and patients were graded as hypoglycemic, normoglycemic and hyperglycemic depending upon whether their blood glucose level was less than 60 mg/dL, 60-80 mg/dL or more than 180 mg/dL respectively. Liver function tests were done to assess the underlying liver disease. The data collected was numerical. It was formatted with the help of SPSS 10.00. Results were expressed in percentage. All the results were interpreted in the tabular form and graphs were made to express the percentage values of various variables in the Anti HCV positive cases.

At the end, the results were discussed and analyzed with reference to the relevant studies available.

RESULTS

In this study, out of the total 100 diabetic subjects studied, 36 turned out to be anti-HCV positive. All of these 36 subjects (100%) had type II diabetes. Regarding the duration of diabetes in the anti-HCV positive subjects, 18 (i.e. 50%) had diabetes for less than 5 years, 10 (27.7%) had it for 6-10 years, 7 (19.4%) had it for 11-15 years and 1(2.7%) had it for 16-20 years.

On observing the age groups of anti HCV positive diabetic patients, it was noticed that 1 subject (2.7%) was in the 20-30years range, 8 (22.2%) in the 31-40 years range, 13 (36.1%) were in the 41-50 years range and 9 were (25%) were above 60years of age.

Regarding gender, 50% of the anti-HCV positive patients were male and the other 50% being female.

Amongst the seropositive cases, 16.6% had a glycemic value in the 60-120 mg/dl range (versus 14 % of anti-HCV negative subjects), 30.5% in the 121-180 mg/dl range (versus 18.7%), and 52.7% in the more than 180 mg/dl range (versus 67.1%)

Serum SGPT levels were found to be raised in 55.5% of seropositive cases whereas 29.6% of seronegative patients had raised serum SGPT levels

Visceromegaly could not be established as a significant indicator of HCV infection in diabetics. Hepatomegaly was found in 27.1% of the anti-HCV positive subjects (versus 27.1% of the seronegative subjects), splenomegaly in 19.4% (versus 7.8% in the seronegative) both in combination in 19.4% (versus 7.8%) and none at all in 33.3% of anti-HCV positive subjects (versus 59.3%).

Peripheral stigmata of chronic liver disease were found in 58.3% of the anti-HCV positive subjects (versus 25% of the seronegative subjects).

Diabetic complications were found in 49.9% of the seropositive patients as compared to 76.7% of the seronegative subjects.

DISCUSSION

In our study we found that almost one third of diabetics were Anti HCV positive. The association of Diabetes Mellitus with chronic liver disease particularly cirrhosis was recognized many years ago. The history of realization of such a relationship goes back to as far as 1977 when Russian endocrinologists who while studying Diabetes Mellitus in

combination with chronic liver disease found out that abnormalities of glucose tolerance were found in 28% of their subjects.[8]. This increased frequency has been pin pointed in numerous other international and national studies. Simo et al, in 1996 wrote that the risk for HCV infection in diabetic patients was 4.39 times higher than in the control group [6]. Likewise , in a study conducted in March 2000, at Sir Ganga Ram Hospital, Pakistan, it was stated that there is a relatively strong association between HCV infection and diabetes because diabetics have an increase frequency of HCV infection, particularly genotype 2a [11]. 42.3% of the patients with impaired glucose tolerance were found to be HCV positive in another Pakistani study [12].

The other important finding that we have come across in the study is that all the seropositive cases were type II Diabetics. This may be partly due to the fact that no selection criterion was observed in this regard. However despite this bias, the stronger association with type II is supported by many other studies as well. Mehta et al. for instance had similar findings [13]. Gray H. et al. have also suggested the possible association between Hepatitis C virus antibody positivity and development of diabetes, mostly type II, particularly in Afro-Caribbean [14]. Similarly Caronia et al have confirmed the relationship between type II Diabetes and HCV infection [15]. Question arises as to what might be the mechanism. Existing information only gives hints. The accepted pathogenesis of type II Diabetes includes impaired insulin secretion, peripheral insulin insensitivity, and dysregulation of hepatic glucose production [16]. There is scant evidence for infection of pancreas by HCV and destruction of beta cells either directly by HCV or by an immune response, although HCV Ribonucleic acid (RNA) has been found in pancreatic tissue [16]. There has been a case report in 2004 by Taiwanese workers, where a 66 years old man developed Type 1 diabetes, a year after acquiring HCV infection [17].

We also observed that majority of the seropositive patients had diabetes of less than 5 years duration. This shows that the chronicity of diabetes mellitus is not a predisposing factor for HCV infection. It may be the hepatitis C infection itself leading to the development of diabetes through a mechanism, which is still uncertain. In this context, one may regard diabetes as an extra hepatic manifestation of hepatitis C infection.

It was found that the maximum number of diabetics who were Anti HCV positive were in the 4th or 5th decade of their lives. Many other workers have appreciated the same fact Mason et-al noticed that increased frequency of diabetes was found in patients with HCV infection in all but the youngest age group [18]. Fraser et-al. also documented that both HCV infection and increasing age were independent risk factors for diabetes [9]. In another United States study advanced age was similarly pointed as one of the most frequent risk factors for the presence of clinical and biological extra hepatic manifestations of chronic HCV [19].

We could not detect any relationship between gender and presence of seropositivity in the study. Caronia et-al wrote that the major variables associated with type II Diabetes Mellitus were; HBV and HCV related cirrhosis and male sex [15]. In contrast to this Cacoub. P et-al regarded female sex as one of the most frequent factor for the occurrence of clinical and biological extra hepatic manifestations of HCV infection [19].

Of note seropositivity was more common in patients with poor glycemic control. In another report frank diabetes with hyperglycemia was quite commonly seen in patients with cirrhosis and may either represent a direct consequence of liver disease or of a concurrent condition not directly linked with it e.g. therapeutic administration of corticosteroids, interferon or another drug that may also result in hyperglycemia [20].

We found raised SGPT levels to have a direct relationship with seropositivity in the diabetic population, showing the relevance of this as a screening test in Diabetics. Many workers have highlighted the importance of liver function tests (LFTs) in this regard. Simo et-al. found that 72.3% of anti-HCV positive patients presented with elevated LFTs [6]. Mehta et-al. also appreciated an increased prevalence of elevated transaminases in diabetes mellitus [13]. In a Taiwanese study age and serum SGPT levels were regarded as predictive factors for the presence of HCV infection [21]. In a latest study the cases with Human Immunodeficiency virus (HIV) /HCV co infection had a higher SGPT level as compared to those with HIV alone.[22]

A greater number of seropositive patients were found to have peripheral stigmata of chronic liver disease in the absence of any of the diabetic complications. It suggests that probably diabetes is one of the many extra-hepatic manifestations of HCV infection rather than itself being a predisposing factor to HCV infection. It also reveals that diabetes occurs late during the course of chronic HCV infection. Similar findings have been documented in another study where the prevalence of diabetes was found to be higher in patients with advanced hepatic fibrosis, in comparison to patients with early hepatic fibrosis.[23] However the evidence that the genuine connection between HCV infection and diabetes is initiated at early stages of hepatic disease has been documented by Lecube et al.[24]

CONCLUSIONS

1. There exists a positive relationship between HCV infection and type II diabetes mellitus in our study.
2. The facts that most of the seropositive subjects had diabetes for 5 years or of lesser duration yet had peripheral stigmata of chronic liver disease is probably an indication that diabetes might be one of the many extra hepatic manifestations of HCV infection rather than vice versa.
3. The presence of raised serum SGPT/ Alanine Amino Transaminase (ALT) levels in diabetic subjects should be considered as an indication for further investigations of chronic liver disease and especially HCV infection.

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