Cryoglobulinemia in Hemodialysis

Thesis Submitted For Partial Fulfillment of Master Degree in Nephrology

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List of tables:-

List of figures:-

List of abbreviations:-

AASLD	Americanassociation for the studyof liver disease
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibody
ANA	Anti-nuclear antibody
APS	Anti-phospholipid syndrome
BCRs	B cell receptor
CDC	Centers for disease controland prevention
CDR	Complementary determining regions
CKD	Chronic kidney disease
CLL	Chronic lymphocytic leukemia
CRF	Chronic renal failure
EBV	Epstein Bar virus
EHM	Extra hepatic manifestations
ELISA	Enzyme linked immunosorbant assay
ESRD	End stagerenal disease
HAV	Hepatitis Avirus
HBeAg	Hepatitis B e antigen
HBV	Hepatitis Bvirus
HCV	Hepatitis Cvirus
HD	Hemodialysis
HIV	Human immunodeficiencyvirus
HLA	Human leucocytic antigen
IC	Immune complex
IFN	Interferon
LAC	Low antigen content diet
MC	Mixed cryoglobulinemia
MLDUS	Monotypic lymphoproliferative disorders of undetermined significance
MMF	Mycophenolatemofeteil
MPGN	Membranoproliferative glomerulonephritis
MU	Million unit
NHL	Non Hodgikin lymphoma
OR	Odd ratio
PBMCs	Peripheral blood mononuclear cells
PM/DM	Polymyositis/ dermatomyositis
PTFE	Ppolytetra fluro ethylene
RBV	Ribavirin
RF	Rheumatoid factor
SLE	Systemic lupus erythematosus

SSc	Systemic sclerosis
SS	Sjogren syndrome
SVR	Sustained virological response
TLR	Toll like receptor

Contents:-

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٢٠١٢

INTRODUCTION

Cryoglobulinemia refers to a pathologic condition caused by production of circulating immunoglobulins that precipitate on cooling and resolubilize on warming. It is associated with a variety of infections especially hepatitis C virus (HCV), hepatitis B virus (HBV), hepatitis G virus (HGV), systemic lupus erythematosus (SLE), polyarteritis nodosa, multiple myeloma, Walden-Strom macroglobulinemia, ….etc. **(Sansonno et al., ٢٠٠٥)**.

Cryoglobulins First described in ١٩٣٣ by Wintrobe and Buell, may be found in low levels in healthy individuals and likely represent endogenous immune complexes on the pathway to clearance by the reticuloendothelial system. Greater concentrations sufficient to cause disease are presumed to result from chronic immune stimulation, like lymphoproliferative diseases, and/ or defective clearance **(Brouet et al., ١٩٧٤).**

In adults, hepatitis C accounts for more than ٨٠٪ of patients with cryoglobulinemia. The remainders of cases are either idiopathic or associated with chronic inflammatory diseases. Although relatively few cases have been reported in children, the assumption is that cryoglobulins in both adults and pediatric patients share similar etiologic mechanisms. Cryoglobulinemia presents with renal and extra renal manifestations. Renal symptoms appear late few years after extra renal symptoms mostly. Kidney disease associated with Cryoglobulinemia usually manifests histologically as type -I- membranoproliferative glomerlonephritis **(Roccatello et al., ٢٠٠٧).**

About ٣٢٪ of Hepatitis C virus +ve Ab patients on regular hemodialysis develop cryoglobulinemia and about ٥,٩٪ of Hepatitis C virus –ve Ab on regular hemodialysis develops cryoglobulinemia (**Wu et al., ٢٠٠٧).**

Cryoglobulinemic syndrome (with purpura, arthralgia, etc) in hemodialysis was not common. Only longer duration of end stage renal disease leads to more susceptibility to cryoglobulinemia. Also kidney transplanted patients are susceptible to have cryoglobulinemia **(Wu et al., ٢٠٠٠).**

Cryoglobulinemia was prevalent in kidney transplant recipient, but appeared to not affect graft function. Hepatitis C virus infection was the most frequently associated etiology and clinical features were infrequent **(Sens et al., ٢٠٠٥).**

The treatment of cryoglobulinemia is by treatment of the cause. As hepatitis C virus is the commonest etiology, the treatment by anti viral therapy is the role, using interferon α and ribavirin. Also cryoglobulinemia can be treated by cyclophosphamide alone or in association with steroids. Plasmapharesis can be also used; Rituximab can be used **(Tedeschi et al., ٢٠٠٧).**

Only few studies in the literature have attempted to study the prevalence and clinical signs of cryoglobulinemia in hemodialysis patients.

AIM OF THE WORK

The aim of this study is to evaluate the prevalence of cryoglobulinemia among patients with chronic renal failure undergoing regular hemodialysis.

Hepatitis C in Hemodialysis Patients

HCV is an enveloped single stranded positive – sense RNA virus with a genome of approximately ٩٦٦٠ nucleotides encoding a polyprotein precursor of about ٣٠٠٠ aminoacids; this precursor is subsequently cleaved by viral and host proteases resulting in three structural proteins and six non structural proteins. Structural proteins, encoded in N-terminal region, include the core protein (C) , believed to be the viral capsid and envelop proteins (E١ and E٢); the non structural proteins, encode in the C-terminal region, are six proteins (NS٢, NS٣, NS٤A, NS٤B, NS٥A, NS٥B) that carry out a number of enzymatic activities, some of which are still not fully elucidated. The capsid protein is the most highly conserved among the proteins, while the structural proteinE٢ is so diverse at the amino- terminal end that this region has been identified as hypervariable region ١. E٢ also contains the binding site for CD٨١, a tetraspanin expressed on hepatocytes and on B and T lymphocytes, which is thought to behave as a cellular receptor or coreceptor for the virus. According to the differences of the variable regions six major genotypes have been recognized. Regarding the possible relation between a specific genotype and MC, some of the preformed studies failed to demonstrate a prevalence of specific genotypes among patients with MC compared with control groups, even if genotype ١a seems rarely observed **(Tedeschi et al., ٢٠٠٧).**

The relation between hepatitis C virus (HCV) infection and kidney disorders is well recognized. On one hand, HCV infection may lead to membranoproliferative glomerulonephritis and essential mixed cryoglobulinemia, but on the other hand, patients with chronic renal failure are at an increased risk of acquiring HCV because of prolonged

vascular access and the potential for exposure to infected patients and contaminated equipments. Hepatitis C is the most common liver disease in renal dialysis patients while liver disease itself is a significant cause of morbidity and mortality in patients with end-stage renal disease (ESRD) treated by dialysis or transplantation **(Johnson et al., ١٩٩٣ and Fabrizi et al., ٢٠٠٢)**.

Risk factors for HCV transmission in renal failure patients:

Almost all surveys have congruently suggested the length of time on Hemodialysis (HD) as a risk factor for HCV seropositivity. A relatively large study in Brazil demonstrated that patients on HD for more than ٣ years had a ١٣,٦-fold greater risk of HCV positivity compared to subjects with less than ١ year HD treatment **(Carneiro et al., ٢٠٠١ and Amiri et al., ٢٠٠٥)**.

Historically, the number of blood transfusion received was consistently reported in the literature to be associated with an increased prevalence of HCV-positive dialysis patients. However, several reports could not recognize blood transfusion as an independent risk factor in HCV spread among HD subjects **(Carneiro et al., ٢٠٠١ and Shaheen et al., ٢٠٠٣)**.

Indeed, erythropoietin prescription from the late ١٩٨٠s onwards reduced the HD patients' need for blood transfusion. Furthermore, the introduction of nucleic acid amplification testing for the screening of blood donors has markedly reduced the risk of HCV transmission through blood product transfusion **(Stramer, ٢٠٠٧)**.

The current risk of transfusion associated hepatitis C is approximately ١ in ٢ million or even lower. A history of organ transplantation, dialysis in multiple centers, hepatitis B infection, human

immunodeficiency virus (HIV) infection and diabetes mellitus are other factors that have been suggested to be associated with HCV positivity by some investigators **(O'Brien et al., ٢٠٠٧, El-Amin et al., ٢٠٠٧ and Kalantar-Zadeh et al., ٢٠٠٧)**.

HCV diagnosis in HD population and its obstacles:

Routine serological testing for HCV infection among HD patients is currently recommended **(Centers for Disease Control and Prevention, ٢٠١٢)**.

The rational is based on the following evidence:

(a) HCV infection has a silent and sub clinical course.

(b) Liver biochemical tests are poor indicators of HCV infection among HD patients.

(c) HCV infection is more prevalent among HD patients than in the general population.

(d) Nosocomial transmission of HCV is a major problem in HD units.

(e) Early identification of HCV-infected patients is essential **(Natov and Pereira, ٢٠٠٠)**.

The current centers for disease control and prevention (CDC) recommendations for HCV screening in HD patients include testing for anti-HCV Ab and serum Alanine aminotransferase (ALT) on admission, ALT every month and anti-HCV Ab semiannually Although the cost-effectiveness of such an approach is questioned **(Saab et al., ٢٠٠١ and Centers for Disease Control and Prevention, ٢٠١٢)**.

Fabrizi et al, followed a group of ١٢٠ HCV-negative Ab HD patients and found that the ALT level rose into the abnormal range in HD

patients at the onset of their HCV infection and thus they suggested the need to monitor chronic HD patients by serial ALT testing **(Fabrizi et al., ١٩٩٩)**.

A dilemma exists on the value of serology because some investigators reported a high rate of false-negative serologic testing. The immuno-compromised state of HD patients is usually regarded as an explanation for their deficient antibody response to HCV virus, Cellular immunity and systemic cytokine responses altered in HD patients. Although another study showed that the limited virus-specific CD٤+ T-cell proliferative response seen in HD patients is comparable to that of chronic HCV carriers without renal disease **(Fabrizi et al., ٢٠٠٢, Rico et al., ٢٠٠٤ and Kalantar-Zadeh et al., ٢٠٠٥).**

The frequency of HCV RNA-positive by PCR with negative anti-HCV antibody HD patients is ranged from ٠ to ١٢٪ in all studied HD subjects in several reports **(Yen et al., ٢٠٠٣).**

A study from India presented a high proportion of HCV RNA-positive anti-HCV-negative subjects (٣٠/١٢٤; ٢٤,٢٪) among the studied chronic renal failure (CRF) population treated with HD or renal transplantation **(Khaja et al., ٢٠٠٦)**.

The reasons for the divergence in reports may be due to many factors including the sensitivity of the tests used, the HCV genotypes in the infected patients, or the degree of immunological alterations in the population tested **(Kelley et al., ٢٠٠٢)**.

A relatively large study on ٥٦٢ HD patients showed that the median number of days that the HCV-RNA assay detected HCV infection earlier than anti-HCV testing was ٢٤٦ and ١٥٤ days for the second and third generations of enzyme linked immuno-sorbent assay (ELISA)