CLINICOPATHOLOGICAL SPECTRUM OF GLOMERULAR DISEASES IN ELDERLY

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CERTIFICATE

This is to certify that this Dissertation entitled "C**LINICOPATHOLOGICALSPECTRUM OF GLOMERULAR DISEASES IN ELDERLY**" is the bonafide original work of **Dr.T.DINESHKUMAR**, in partial fulfillment of the requirement for D M., (Nephrology) examination of the Tamilnadu Dr.M.G.R Medical University will be held in August 2013.

Dr. N.Gopalakrishnan MD D.M. FRCP,
Professor and Head
Department of Nephrology
Madras Medical College,
Chennai - 3

Prof. V. KANAGASABAI, M.D.,
Dean,
Madras Medical College,
Chennai – 3

DECLARATION

I, Dr.T.DINESHKUMAR, solemnly declare that the dissertation titled "**CLINICOPATHOLOGICAL SPECTRUM OF GLOMERULAR DISEASES IN ELDERLY**" is the bonafide work done by me at Department of Nephrology, Madras Medical College under the expert guidance and supervision of Dr.N.GOPALAKRISHNAN D.M ,FRCP, Professor of Nephrology,Madras Medical College. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of D.M. Degree (Branch III) in Nephrology.

Place: Chennai Dr.T.DINESHKUMAR

Date:

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CONTENTS

INTRODUCTION

Advances in modern health care have led to increase in geriatric population. The annual growth rate of people more than 60 years is faster than any other age group. Aging is associated with renal structural changes and functional decline. As life expectancy increases, the prevalence of elderly patients living with renal diseases is more. The biology of aging with associated co morbid illness like diabetes, hypertension, cardiovascular disease often modify the clinical presentations, pathological findings and natural history of renal disease in the elderly. The incidence of glomerular disease in elderly is varies in different population from 5 to 20% and it is ever increasing. Due to aging, co morbid illnesses and blunted immune response, clinical presentations are often atypical. Renal biopsy is the gold standard for diagnosing glomerular diseases, yet less than 15% renal biopsies were from age more than 60 years. This leads to under diagnosis and delay in treatment. The studies on geriatric nephrology in India are limited, that too in glomerular diseases were scarce. We intend to study the spectrum of glomerular diseases in the elderly and its clinico pathological correlation.

AIMS

To study the clinico pathological spectrum of glomerular diseases in elderly patients and their outcomes.

REVIEW OF LITERATURE

In India, the cut off for definition for elderly individual is 60 years. According to 2011 population census, elderly constitutes about 10 % of Indian population, which is high when compared to 7.5 % in 2001 data and it is projected to increase up to 20% in the year 2050[1]. This could be attributed to improved health care delivery systems and better hygiene. In a developing country like India, it will pose pressures in socioeconomic front including health care. Yet this progress is hampered by increased prevalence of non communicable diseases like hypertension and diabetes, causing high incidence coronary artery disease and chronic kidney disease. The prevalence of glomerular diseases is increasing in elderly population in accordance to increased survival, but there is a tendency in treating physicians to manage conservatively in view of multiple co morbid illness. As a result, elderly patients with renal disease are often without specific diagnosis and disease specific treatment to slow the rate of progression.

The recognition, diagnosis and management of glomerular diseases in elderly population throw several unique challenges[2]. In an elderly individual the reduction in glomerular filtration rate (GFR) in the setting of aging nephropathy and vascular disease, an intrinsic renal disease is often overlooked. In a Meta analysis by O'Hare et al have shown that aging nephropathy per se is

not usually associated with proteinuria[3]. So presence of proteinuria or active urine sediments should be considered as a presence of renal disease rather than age related reduction in GFR. On the contrary, urinary abnormalities and reduction in GFR is often erroneously attributed to aging kidney and are not investigated any further causing difficulty in recognition and treatment of glomerular diseases in an elderly individual. Recent studies have reported that, a significant number of patients have unexpected glomerular diseases in elderly and may benefit from treatment which might not otherwise be considered [4].

Aging: Is it Physiological or Pathological?

Aging is a natural and inevitable biological process in human evolution. The kidneys undergo anatomic and physiologic changes due to aging, which may be exaggerated by some diseases (atherosclerosis/diabetes) that occur in high frequency in elderly. The constellation of glomerulosclerosis, arteriosclerosis, interstitial fibrosis and tubular atrophy constitutes nephrosclerosis in the aging kidney. Number of studies have shown the increased proportion of glomerulosclerosis with aging [5] [6] [7]. They were 20%, 38%, 47%, 65%, 76% & 82% in 3rd, 4th, 5th, 6th, 7th and 8th decades respectively. Aging glomeruli has an ischemic appearance due to tuft collapse and intracapsular fibrosis favouring primary vascular cause of lesions. The functioning glomeruli also has an ischemic capillary wrinkling of tuft,

basement membrane thickening which leads to ischemic shrinkage of tuft and filling of bowman's space with collagen deposits in due course. With the sclerosis of juxtamedullary glomeruli, there will be a direct connection between afferent and efferent arteriole, bypassing the tuft, causing aglomerular tuft. The sclerotic glomeruli are smaller than functioning glomeruli, which contributes to average small size of glomeruli, but there will be compensatory hypertrophy of remaining functioning glomeruli. Thus in an aging kidney, both increase in proportion of smaller sclerosed glomeruli and a minor fraction of larger functioning glomeruli may occur [8].

Aging Nephropathy is characterized by loss of GFR by about 1.7ml/min/year. Creatinine clearance is influenced by nutritional status, protein intake and muscle mass and hence it is not an accurate measure of GFR in the elderly [9]. The generation of creatinine and its urinary excretion gradually decline in proportion to age related decrease in body weight and muscle mass. Thus serum creatinine does not increase despite age related reduction in creatinine clearance. Though the 'true GFR' measured by inulin clearance is significantly lower in elderly when compared with younger ones, it is within normal range. Creatinine clearance under estimates GFR in elderly and when measured by Cockroft-Gault (CG) formula, it is even lower. The modification of diet in renal disease (MDRD) study group formula is considered more accurate than CG formula in elderly [10]. But neither CG nor MDRD formula has

been validated in age group more than 70 years. MDRD equation generally yielded higher estimated GFR than CG formula. The important implication of this is in calculating drug dosing in elderly. Overestimation of GFR by MDRD formula can cause inadvertent drug over dosage. Thus it is recommended that CG formula should be used in preference to MDRD equation to estimate GFR to calculate drug dosing in the elderly patients [11]. Serum Cystatin C is a promising index to estimate GFR in renal insuffiency in elderly.

Aging affects renal tubular function in many ways. The fractional sodium reabsorption is significantly higher in proximal tubule but it was offset by less fractional reabsorption of sodium in distal tubules. In diet with salt deprivation, aging kidney is not able to conserve sodium due to significant slowing down of physiological response to conserve sodium by reduction in urine fractional excretion. Thus elderly population is more prone for volume depletion. The defect in potassium handling is due to age related tubulo interstitial changes causing impaired potassium secretion and corresponding impaired sodium reabsorption. This explains the increased susceptibility of elderly population to hyperkalemia. The impaired ability of the aging kidney to concentrate or dilute the urine to its maximum capacity makes them vulnerable to dehydration, hypernatremia, nocturia and hyponatremia when excess fluid is administered[12].

An important implication of aging kidney is on drug metabolism. There are number of reasons for increased susceptibility to drug toxicity in elderly. The reduction in excretory capacity of aging kidney, decline in hepatic metabolism, altered body composition (reduced water content, increased fat) causes changes in pharmacokinetics of the drug. Aging adversely affects pharmacodynamics by modulating the sensivity and physiological response to their actions. The combination of altered pharmacokinetics and pharmacodynamics in the elderly patients on poly pharmacy in addition to co morbid conditions makes the management more complex. Therefore it is prudent to initiate the therapy at drug dosage at lowest effect and increase the dose slowly [13].

ROLE OF RENAL BIOPSY

Renal biopsy is considered as the gold standard in glomerular diseases. It helps in accurate diagnosis, picks up prognostic indicators like features of chronicity and devising treatment plan. Though the first renal biopsy done by Iversen has come long way, in a study by Nair et al, elder patients made up just 4.2% of total biopsy. This number is lower when compared other age groups [14]. There are still controversies regarding necessity and complications of doing renal biopsy in elderly. Previous studies have reported the differences in the indications for renal biopsy between the elder age group and younger ones [15].

In young adults and children, nephrotic syndrome is the main indication, where as in the elders, main indication is acute kidney injury. Renal biopsy is not routinely done in elderly because of medical condition at time of evaluation and difficulty in analyzing risk benefit ratio of doing biopsy. Recent articles have proved that not only biopsy is safe in elderly but also necessary in making diagnosis as well as appropriate therapy, because of atypical presentation in elderly [16][17]. In study by Hass et al showed that in elderly patients, prebiopsy diagnosis was correct only in 33% and biopsy made specific diagnosis in 90% patients and a diagnosis offering the potential for treatment in improving the outcomes made in 73% patients. In study by Moutzouris et al 67% of patients had biopsy findings that are potentially amenable to therapy [18]. That includes acute kidney injury, acute interstitial nephritis, thrombotic microangiopathy, pauci immune glomerulonephritis, nephrotic syndrome, light chain diseases etc. Many of the elderly patients may have significant co morbid illness that would limit the ability to treat the illness aggressively. So not all patients with potentially amenable renal disease will receive specific therapy. Even in patients whom biopsy does not modify the therapy, it gives prognostic value and eliminates the need for potentially harmful empirical cytotoxic therapy.

GLOMERULAR DISEASES IN ELDERLY:

In the elderly, secondary glomerular disease due to a systemic disease is more common than primary glomerular disease. The most common cause of secondary glomerular disease in developed and developing countries are pauci-immune necrotizing glomerulonephritis and post infectious glomerulonephritis respectively. Various studies have reported crescentric GN occurs in higher frequency and mesangial nephritis in lower frequency among the elderly when compared young adults [19] [20].Similarly minimal change disease and membranoproliferative GN were common in children and adults, where as pauci immune GN and membranous nephropathy were common in elderly.

MEMBRANOUS NEPHROPATHY:

Membranous nephropathy (MN) is the most common cause of idiopathic nephrotic syndrome in older adults, accounting for 20% of cases. Though 30% patients undergo spontaneous remission, 40% patients will reach end stage renal disease at end of 10 years [21].20% patients can have secondary cause including infection, malignancy, auto immune disease and drug intake. Membranous nephropathy is characterized by sub epithelial immune deposit which causes membrane like thickening around glomerular basement membrane. The immune deposit consists of IgG mainly of IgG4 and IgG1 against M type phospholipase A2 receptor in the podocyte (PLA2R).

Beck et al made a path breaking discovery that, in human idiopathic membranous nephropathy, sub epithelial immune deposits form insitu by binding of circulating anti PLA2R antibodies against PLA2R antigen expressed on the podocyte. Since 70% patients with idiopathic membranous nephropathy have serum anti PLA2R antibodies detected, it serves as a valuable tool in diagnosis as well as follow- up of patients [22].

The risk factors for progression of MN include old age at presentation, male sex, nephrotic range of proteinuria, renal failure at presentation and degree of tubulo interstitial disease on renal biopsy. Cattran et al has proposed a prognostic model to predict disease progression dividing into three groups. Low risk includes those with normal renal function and less than 4gms of proteinuria in clinical course over 12 months. Medium risk for renal disease progression includes stable renal function with proteinuria between 4-8gms over 9 months. High risk group is defined by presence of renal dysfunction at presentation or during observation with proteinuria of more than 8 gms over a period of 6 months. This group has 75% risk of disease progression[23].

In MN, patients with low to medium risk were typically treated with ACE inhibitors or ARBs with statins. Despite conservative measures, if proteinuria persists for more than 6 months, immunosupression is advocated. High risk patients with impaired or declining renal function, patients with complications

of nephrotic syndrome are treated with cytotoxics promptly. Ponticelli et al recommends 6 months regime of alternating steroids with alkylating agents with proven short term and long term benefits. This regime achieved remission rate of about 76%, relapse rate of 25% and 10 year renal survival rate of 92%.calcineurin inhibitors are second line of drugs for those not responded with Ponticelli regime[21].

The management of MN in elderly is difficult in view of their age, co morbidities and late presentation. Renal survival is worse for patients with elderly MN.The studies on elderly MN is limited since majority of trials has excluded old age[24]. Given that advancing age and side effects of cytotoxics drugs, decision should be individualized in each patient after risk/benefit analysis. Management of glomerular diseases in elderly:

The management and evaluation of glomerular diseases and its associated manifestations similar in all age groups. The primary etiology of nephrotic syndrome should be the principle guide for therapy. Older individuals may be sensitive to diuretic therapy and develop pre renal azotemia and more prone for electrolyte imbalances. Hence they need cautious dosing and careful follow up. Pharmacokinetics of the may be affected by reduced lean body mass, diminished hepatic and renal clearance.

Post Infectious Glomerulonephritis:

PIGN is the most common cause of glomerulonephritis in the developing world. There has been shift in epidemiology as well as outcomes in recent decades. There has been change in the age predominace, four decades back less than 6% were elderly, compared with 34% in a recent study[25]. This is likely due to increased life expectancy, high frequency of infection in adults and higher prevalence of diabetes. Apart from diabetes, other predisposing factors for PIGN are alcoholism, synthetic heart valve, malignancy, I V drug abuser etc. The site of infection in children and adults includes upper respiratory tract and skin, but in elderly group infective sites includes skin, teeth, lung, urinary tract, bone and visceral abscess. The two most commonly identified organisms were streptococcus and staphylococcus. Streptococcus is still most common organism in the developing world, whereas staphylococcus aureus is as common as streptococcus in developed countries[26]. Gram negative organisms accounts for 10% infections. In contrast to children, significant proportion of adults have no latent period, 45% have evidence of infection at the time of renal disease. In both children and adults, symptomatic patient typically present as acute nephritic syndrome with new onset haematuria, proteinuria and hypertension..The presence age related illness like Hypertension and diabetes alters the clinical picture of PIGN in elderly. The new onset or exacerbation of congestive cardiac failure is common in elderly because, in the setting of

underlying cardiac dysfunction with reduce ability to handle salt and water retention. Hypertension is present in 60-84% of elderly population at presentation. Presentation with seizures and hypertensive encephalopathy are rare with elderly unlike children. 25 to 30% can have nephrotic range of proteinuria. In a study on PIGN in elderly,67% presented with serum creatinine of more than 4mg/dl, 50% had gross microhaematuria,50% required dialytic support, 60% had leucocyturia, 30-80% can have low complement levels.30% had low C_3 & C_4. 70% have normal C_4 and low C_3[25][27].Usually complements return to normal range within 2 months. Serology for ANCA may be positive in about 8% elderly PIGN, particularly in infective endocarditis associated GN where it may increase up to 25% and contributes to diffuse and necrotizing crescents[26]. In the light microscopy, diffuse endocapillary proliferation with numerous intracapillary neutophills is the most common histological pattern seen in about 70%, focal endocapillary and mesangial proliferation can also seen in patients on resolving phase. About 25% of biopsy can have focal crescents (< 30%), in about 5 % of patients, more than 50% crescents can also be seen. Immunoflourescence typically reveals dominant C_3 deposits. Three types IF pattern seen in PIGN. Coarse granular staining involving predominant glomerular capillary wall called “Garland Pattern” implies severe type of lesions, frequently associated with nephrotic range of proteinuria. The second type involves predominant staining of both mesangium and glomerular

capillaries called “Starry Sky pattern”. The third type is “mesangial” pattern which stains only mesangium, seen in resolving phase. Isolated C_3 deposits may be seen in 30%, 25 % can have typical full house pattern staining for Ig M, Ig G, Ig A, C1q.Electron Microscopy reveals ‘hump shaped’ deposits in the subepithelium. Recently elderly patients with PIGN, intense staining for Ig A is the dominant IF, with mesangial and sub epithelial deposits. All patients were associated with hypocomplementemia, diabetic nephropathy and staphylococcal infection. This new entity called IgA dominant PIGN is increasingly recognized in up to 17% of elderly PIGN have rapid progression to CKD and poor prognosis [28].

One important differential diagnosis of PIGN is C3 Glomerulopathy (C3G).It is a newly recognized entity characterized by MPGN pattern in light microscopy with dominant C3 deposits in the IF, which is due to abnormalities in the alternate pathway in the complement activation. Isolated C3 deposits can be found is 25% patients with PIGN. Hence differentiating C3G from PIGN requires clinical, laboratory and histopathological correlation. The factors favouring C3G are 1. Lack of clinical evidence of infection 2.MPGN pattern in light microscopy 3. Persisting signs of active glomerulonephritis 4. Persistent low C3 levels for several months 5. Presence of intramembranous and sub endothelial deposits [29][30]. The treatment of PIGN includes eradication of infective foci if any found and management of acute nephritic syndrome. It

includes salt restriction, antihypertensive and diuretics. The role of steroids and other immunosupression in the elderly is controversial. There are only anecdotal reports supporting role of steroids in the management of crescentric PIGN. In children PIGN had a very good prognosis with complete recovery. But in elderly patients, 30-55% can have persistent renal dysfunction, 3-30% develops ESRD[31][32].The independent risk factors for persistent renal failure in PIGN includes older age, high creatinine at presentation, diabetic glomerulosclerosis, presence of tubulointerstitial scarring, presence of co morbid conditions like diabetes, malignancy etc. There are various theories on pathogenesis of PIGN. 1. Immune complex deposition 2. Localization of bacterial cationic antigen within the subepithelium, which forms in situ immune complexes 3. Molecular mimicry of bacterial antigen to glomerular antigen causing complement activation [33]. The evidence supporting circulating immune complex deposition are demonstrated in cases of shunt nephritis and endocarditis related GN where circulating immune complexes gets entrapped in glomeruli. But the concept of in situ immune complex has gained acceptance because bacterial cationic antigens easily get past the GBM, which incites antibody deposits within sub epithelium. The evidence for molecular mimicry is demonstration of antibodies against nephritogenic strain M12 which cross reacts with glomerular components of collagen, laminin. The two leading candidate streptococcal antigens are glyceraldehyde 3-phosphate dehydrogense (GADPH),a plasmin

receptor and streptococcal exotoxin-B(Spe-B), a cationic proteinase which acts as a virulent factor by blocking opsonization.GADPH co localizes within glomeruli by its plasmin binding capacity. The locally activated plasmin degrades GBM and activates inflammatory pathway and facilititates binding of neutrophills to capillary endothelium. Spe-B penetrates GBM and co localize with complements and causes immune mediated renal injury [34]. In IgA dominant GN, staphylococcal enterotoxin acts as a super antigen, which binds to MHC class 2 molecules without any internal processing and causes massive T cell activation. The other two highly cationic antigen implicated were staphylococcal P70 protein and staphylococcal neutral phosphatase [35]. In a very recent study of 11 patients with persistent atypical PIGN, antibodies against alternate complement pathway has been demonstrated which causes persistent activate alternate complement pathway causing injury [29]. The authors propose streptococcal infection unmasks the dysregulation of alternate complement pathway causing C3 glomerulopathy.

VASCULITIS:

The systemic vasculitides characterized by leucocytic infiltration of blood vessels, fibrinoid necrosis associated with vascular damage. They could be either primary or secondary to auto immune disease, drugs and malignancy. In primary systemic vasculitis the antibodies to neutrophillic cytoplasmic antigens

[ANCA] are the most prevalent, which affects the small vessels. The vasculitis affecting the small blood vessels are classified as

1. Granulomatosis with polyangiitis (formerly Wegener's)-GPA

2. Microscopic polyangiitis- MPA

3. Churg-Strauss Syndrome-CSS

4. Henoch –Schonlein Purpura-HSP

5. Cryoglobinemic vasculitis

6. Cutaneous leucocytoclastic vasculitis

ANCA Associated Vasculitis (AAV) is the most common cause of rapidly progressive glomerulonephritis in the elderly population worldwide. It predominately affects the age group between 60-75 years. The renal involvement is associated with significant mortality and morbidity, with mortality rate as high as 60% at end of one year[37].

Though the pathogenesis is similar for all the types, they differ in their histopathology and clinical features. Granuloma formation in the affected vessel is a feature of GPA & CSS, but not MPA. Abundance of neutrophills is a dominant feature of GPA whereas much of the inflammatory infiltrate in CSS is

due to eosinophills. Most of the antibodies are directed against PR-3(Proteinase) in patients with GPA. CSS & MPA are associated with ANCA directed against MPO (Myeloperoxidase).GPA associated 70% PR3 and 25% MPO ANCA positivity; MPA is associated with 50% MPO & 40% P ANCA positivity; CSS is associated 40% MPO,30% P ANCA positivity respectively.

Pathogenesis of AAV:

ANCA by itself can cause vasculitis, but it's interaction with neutrophills and vascular endothelium is implicated as major mechanism for pathogenesis. Binding of ANCA to membrane bound PR3/MPO neutrophills causes activation and release of proteases and super oxides. Infection, environmental factors triggers stimulate release of cytokines like TNF-α and IFN-γ which causes translocation of PR3/MPO within neutrophillic granules to membrane. This process is called "Priming". ANCA also increases the expression of adhesion molecules like ICAM, VCAM in the vascular endothelium. Priming of neutrophills also increases the adhesion of neutrophills to vascular endothelium. So once degranulation occurs in close contact with endothelium, it causes vasculitic damage to the endothelium.this theory is proved by animal model of AAV by rat model of MPO ANCA. So far no animal model for PR3 ANCA has been established. Recently Pendergraft et al proposed theory of complementary peptides to explain the pathogenesis of GPA. The hypothesis is that the initial

immune response is against complementary protein PR3(cPR3). The antibodies against cPR3 serve as a antigenic target that evokes secondary immune response (anti-idiotype antibodies). These antibodies not only against anti cPR3 antibodies, but also against PR3 antigen. The pathogens like staph aureus bear genetic sequences that are similar to human PR3 gene[38]. This explains why the chronic nasal carrier state of staph aureus provokes vasculitic relapse. About 20% patients with features of vasculitis were ANCA negative. Kain et al recently proposed LAMP-2 antibodies (Lysosomal membrane protein).Antibodies against infections with Gram negative organisms carrying fimbriae cross reacts with lysosomal membrane protein[37].

The role of T cells should be undermined in AAV. In Vascultis T cells are in constant activation, there is expansion of both memory (Tems) and decrease in naïve T cells. Tems cells are powerful in initiating and sustaining immune response. Kessenbrock et al reported formation of neutrophills extraellular traps (NET's).they are decondensed chromatin fibres containing PR3,MPO,Elastase which acts as a host defense to trap these antigens. But these modified DNA's are recognized as DAMP's (Danger associated Molecular pattern) by dendritic cells which stimulates Toll like receptors (TLR).This activates immune response [39] .

Treatment of AAV:

European league against Rheumatism (EULAR) has recently published guidelines for management of AAV. It recommends induction regime& maintenance therapy. They categorized into 5 types according to the involvement as localized, early systemic, generalized, severe and refractory. For induction, EULAR recommends localized /early systemic should be treated with oral steroids and methotrexate. Generalized vasculitis implies renal involvement with creatinine level less than 5.5mg/dl. EULAR recommends cyclophosphamide (oral or IV) in combination with steroids. Renal involvement with serum creatinine level of more than 5.5 mg/dl is categorized under severe form. Recommended treatment is plasma exchange. Those disease category which does not achieve remission following cyclophosphamide were classified as refractory and EULAR recommends rituximab.

Induction therapy:

In systemic vasculitis should initially be treated with combination of cyclophosphamide and steroids. Cyclophosphamide can be given as IV, 3 doses every 2 weeks, then 7 doses every 3 weeks or low dose, continuous oral for maximum of six months. IV cyclophosphamide has distinct advantage in terms of less cumulative dose, better bladder protection, better compliance with slightly increased risk of relapse. The efficacy of IV cyclophosphamide is

proven by CYCLOPS trial [40]. Patients presenting with severe renal failure are at high risk of ESRD and death. In MEPEX trial done in 134 patients, both arms received oral cyclophosphamide and steroids. Adjunctive therapy of plasma exchange or IV methyl prednisolone was tried. Plasma exchange results in 20% more dialysis independency and 24% less progression to ESRD 12 months [41]. Two trials (RAVE & RITUXVAS) provide evidence that rituximab /prednisolone combination is not inferior to cyclophosphamide in inducing remission [42][43].

Maintenance therapy:

Maintenance therapy in AAV is must considering the risk of relapse. EULAR recommends therapy of 18-24 months. In view of toxicity of cyclophosphamide, it is no longer considered for long term therapy. Azathioprine is the first line drug of choice for maintenance therapy in AAV. Its efficacy is as good as cyclophosphamide as proved by CYCAZAREM trial. The dose is 2mg/kg/day.

Outcomes:

The relapse rate at 2 years is 18-60 in GPA, 8% in MPA. At 5 years, the risk of relapse is 50% in case of GPA. The factors which increase the risk of relapse are nasal carriage of Staph aureus, upper respiratory tract involvement and PR3 ANCA positivity [44]. The factors which predict resistance include female sex, black race and severe renal involvement. The mortality rate was 20% within first year of diagnosis, around 25% reach ESRD within 4 years. These outcomes are more worsen among elderly individuals [45].

Renal biopsy is the gold standard for establishing the diagnosis of AAV. Light microscopy typically shows focal and necrotizing crescentric glomerulonephritis. It is characterized by little or no immune deposits for complements and immunoglobulins, hence described as pauci immune GN. In electron microscopy, there will be subendothelial swelling, microthrombosis and degranulated neutrophills, but no immune deposits.

Recently histopathological classification of AAV based on glomerular pathology in light microscopy has been published and is of prognostic value in predicting 1year and 5 year renal outcomes.

Focal : ≥ 50% glomeruli normal

Crescentric: ≥ 50% glomeruli with cellular crescents

Mixed : < 50% glomeruli normal, < 50% crescentric, < 50% globally sclerotic glomeruli

Sclerotic: ≥ 50% with globally sclerotic glomeruli

The renal survival rate for focal, crescentric, mixed and sclerotic at 1year and 5 year are as follows, 93 & 99 %(focal),84 & 76%(crescentric),69& 61%(mixed),50 &25%(sclerotic)[46].

The studies in AAV in elderly patients demonstrated poor prognosis with significant high mortality rate, ESRD and treatment related complications when compared to younger counterparts.

Renal failure in myeloma:

It occurs in 20-40% of newly diagnosed multiple myeloma, may provide clue for diagnosis and causes significant morbidity. Renal failure results from toxic effects of monoclonal chains, mainly on renal tubules and glomeruli. The renal manifestations of myeloma can also cause Amylodosis[AL],light chain disease, heavy chain disease,tumour lysis syndrome. The contributory factor for renal failure includes dehydration, hypercalcemia, drugs, NSAIDS, antibiotics, diuretics and contrast agents. Nearly 500mg of light chains are produced every day and only 10 mg appear in urine, majority of them being catabolised at the level of proximal tubule. In plasma cell disorders capacity of proximal tubule is overwhelmed and free light chains which excreted in urine is called as Bence

Jones proteins. Free light chains can cause proximal tubular injury and cast nephropathy or combination of both.

Free light chains are directly toxic to proximal tubule cell causing defective absorption of glucose, aminoacids, and phosphate. The most important toxic effect is due to excessive endocytosis of light chains through cubilin-megalin receptor which activates redox pathway, increased expression of nuclear factor B and mitogen activated receptor kinases which induces inflammatory cytokines like IL-6,TGF-β and monocyte chemoattractant protein.the final common pathway is triggering of apoptosis and epithelial-mesenchymal transistion. Another mechanism of light chain mediated tubular damage is due to the intratubular obstruction in the distal lumen. Large amount of free light chain reaching distal tubule interacts with Tammhorsfall protein secreted by thick ascending limb of loop of Henle. Complement determining region of free light chains (CDR domain) combine with THP forming the cast. The cast formation is dictated by ionic composition of tubular fluid, amount of light chains and THP, presence of frusemide. the intratubular obstruction increases proximal tubular pressure and reduction of single nephron GFR. The cast formation also elicits giant cell formation around tubules.

Renal biopsy in patients with monoclonal gammapathy and renal failure is valuable to determine type of renal injury, its chronicity, nature of

pathological process and planning aggressive therapy if warranted. In a patient with monoclonal gammapathy with acute kidney injury, the most common renal lesion is cast nephropathy. The other conditions which mimic AKI include AL amyloidosis. Immunoflourescence plays a key role in making definitive diagnosis of plasma cell dyscrasia. The staining for κ and λ chains and careful evaluation of Ig chains helps to determine isotypic restriction of light and heavy chains. (amyloids stains predominantly λ chains, while light chains stains κ).

Renal failure in myeloma is mild to moderate. 8% patients require dialysis. Goal of therapy in myeloma kidney is to reduce the lightchain exposure to kidney and to prevent its interaction with THP. The antimyeloma therapy includes combination of high dose dexamethasone with thalidomide, lenalidomide or proteosomal inhibitor bortezomib. Direct removal of FLC by plasma change is highly attractive method to rapidly reduce the serum concentration of light chains.but plasma exchange removes very little extravacular light chains with more loss of essential immunoglobulins and coagulation proteins.another novel method is use of High Cut off dialyzer to remove light chains. This membrane with diameter of 50kDa provides rapid clearance of κ & λ chains. The combination of high cutoff dialyzer with chemotherapy achieves renal response rate in 60 -75% patients.

AMYLOIDOSIS:

Amyloidoses are group of disorders characterized by precipitation of extracellular,pathologic,insoluble fibrils of size 8-10nm in various tissues and organs. All deposited fibril have specific β pleated structure which stains apple-green birefringence with congo red dye when exposed under polarized light. In all type of Amyloidosis,the glycosaminoglycans and serum amyloid protein(SAP) interact together to confer stability for the fibrils. Amylodosis is classified on the basis of its distribution and amyloidogenic protein. In systemic amyloidosis the fibrils are produced at distant site from its deposition and in local amyloidosis, it is produced in the site of its deposition. Light chain amylodosis (AL) is the most common form of systemic amylodosis. The amyloidogenic protein in AL amylodosis is Ig light chain or a fragment of light chain produced by clonal plasma cells in the bone marrow.they produce more κ isotope than λ in the ratio of 3:1.The plasma cell burden in AL amylodosis is about 5-10%. In 10-15% patients, AL amylodosis is associated with multiple myeloma.

The organs most frequently affected by AL amyloidosis are kidney and Heart. The organ dysfunction is due to disruption of normal architecture by infiltrating amyloid fibrils. Renal involvement is manifested as nephrotic proteinuria with progressive worsening of renal dysfunction. Amyloidosis of

renal vasculature and tubulointerstitium usually present as renal failure without proteinuria. The clinical features includes congestive cardiac failure due to restrictive cardiomyopathy, hepatomegaly, carpal tunnel syndrome, skin nodules, arthropathy, macroglossia, periorbital odema, hoarseness of voice. The involvement of autonomic nervous system usually present as postural hypotension. Peripheral neuropathy presents as painful, bilateral symmetrical sensory symptoms, which could progress to motor weakness.

The diagnosis of AL amyloidosis requires demonstration of tissue amyloid as well as plasma cell disorders. Tissue diagnoses are established by abdominal fat biopsy or renal biopsy and subject them to Congo-red stain to show apple green refringence. The confirmation of AL amyloidosis involves demonstration of plasma cell disorders by κ or λ producing clonal plasma cells in bone marrow or in urine and serum. The diagnosis and follow up of plasma cell dyscrasia is revolutionized by measurement of free light assay of κ, λ chains by nephelometric immuno assay. the normal serum levels of free light chains are 3.3-19.6mg/L for κ isotope and 5.5-26.3mg/L for λ isotype respectively. The normal ratio between κ and λ chains in the serum is between 0.26-1.65.Since free light chains are free filtered by glomerulus, there is accumulation of free light chains in renal impairment,hence κ:λ ratio altered to 0.37-3.1. a κ:λ ratio less than 0.26 suggests production of λ type of clonal

plasma cells, a ratio more than 1.65 strongly suggests κ type producing clonal plasma cells.

The principles in treatment of AL amyloidosis is to rapidly reduce the burden of amyloidogenic protein from monoclonal light chains by suppressing plasma cell dyscrasia. The most effective treatment of AL amyloidosis is high dose melphalan followed by autologous peripheral stem cell transplantation. Supportive measures include coordinated care of multiple specialists. Achieving a balance between heart failure and intra vascular volume depletion is important in patients with autonomic dysfunction and nephrotic proteinuria. The treatment of amyloid renal disease includes salt restriction, diuretics and dyslipidemia control. Orthostatic hypotension is difficult to manage. Midodrine and waist high elastic stockings will be useful. The use of fludrocortisone is limited in view of fluid retention.

MATERIALS AND METHODS

Ours is a cross sectional descriptive study, done on elderly patients of age 60 or more years with clinical diagnosis of glomerular diseases and underwent renal biopsy in the department of Nephrology, Madras Medical College, Chennai, from August 2010 through December 2012.

Exclusion criteria:

1. Patients with age less than 60 years.

2. Age more than 60 years with glomerular disease, biopsy not done.

3. Age more than 60 years with biopsy proven non glomerular disease.

The patients classified into five renal syndromes according the clinical presentations.

1. **Nephrotic syndrome**: presence of 24 hour urine protein of more than 3.5gms with or without odema, hypoalbuminemia, hyperlipidemia.
2. **Acute Nephritic syndrome**: presence of red cell cast or dysmorphic RBC's in urine microscopy with or without proteinuria, with odema, hypertension and decline in GFR.
3. **RPGN (Rapidly progressive Glomerulonephritis)**: A progressive and rapid decline in renal function developing over weeks to months

characterized by presence of RBC cast, hypertension, oliguria and azotemia.

4. **Acute kidney Injury**: Increase in serum Creatinine within 7 days or 0.3mg increase of Creatinine within 48 hours or Oliguria of less than 0.5ml/kg/hr for 6 hours.
5. **Chronic kidney disease**: Structural or functional abnormality of kidney lasting for more than 3 months.

All suitable patients underwent detailed history and clinical examination, demographic and anthropometric data collection, urine analysis for protein, pus cells, active urinary sediments, spot urine protein-creatinine ratio, urine culture and sensitivity. Blood investigations include complete hemogram, renal function tests, liver function tests, fasting lipid profile, coagulation profile of bleeding time, clotting time, Prothrombin time done on all patients. Blood for ANA, AntidsDNA, Anti GBM antibodies, serum complement levels, ANCA, ASO titre, cryoglobulins, RA factor, serum electrophoresis, urine for Bence Jones proteins, Skeletal survey done in selected patients. All patients underwent ultrasonagram of the kidneys to ascertain the size before kidney biopsy. Written informed consent obtained from patients before renal biopsy.

Renal biopsy:

In our department, renal biopsy is performed under ultrasound guidance with needle biopsy gun. Patient lies in prone position, with an upper abdominal support to splint the kidney; lower pole of the kidney is marked. After infiltration with 2% lignocaine, stab incision is made using a 11G blade. While asking the patient to hold breath, 16G biopsy needle gun is fired to get the sample. Patient is then asked to lie flat for 12 hours, with strict monitoring of pulse, blood pressure and urine output. Biopsy sample was sent in formalin & Michelle media for light microscopy (LM) and Immunoflourescence (IF) respectively. All the biopsy samples were reported by single nephropathologist to avoid bias.

For LM, all samples were stained with hematoxylin and eosin (H&E), periodic acid -Schiff (PAS), Masson trichrome and Jones silver methenamine. For IF,3 μ sections were stained with florescent tagged antibodies to IgG,IgM,IgA,C_3,$C1_q$,fibrinogen,Kappa and lambda chains.

Outcome measures:

1. **Complete remission**: proteinuria less than 0.3gms per 24 hours
2. **Partial remission**: proteinuria > 0.3 gms to 3.5gms per 24 hours or 50% decline in proteinuria from its initial value.

3. **No response**: no decrease or worsening of proteinuria along with renal function.

Statistical analysis:

Baseline characteristics of all patients were presented descriptively with mean ± SD for continuous variables and percentage for categorical variables. We used Mann-Whitney test for univariate comparison of continuous variables and Fisher exact t test for categorical variables. Multivariate analysis was done by binary logistic regression analysis. p value of less than 0.05 was considered as statistically significant. It was performed using medcalc software.

This study was approved by Institute Ethical committee of Madras Medical College

OBSERVATION AND RESULTS

Study population

One hundred twenty six patients including 79 Males and 47 females (Male: Female ratio 1.7:1) were studied. Patients were stratified into different age groups as given below in table 1.

Table 1-Demographic data

Total number of patients	126
Male: Female	79/47 (62%/38%)
Mean Age ± SD	63.8 ± 2.9 years
60-69	109 (86%)
70-79	14 (11.5%)
80-85	03 (2.5%)
Co-morbid illness	
hypertension	44 (35%)
Diabetes	21 (17%)
Coronary artery disease	10 (8%)
COPD	7 (5%)
Hypothyroidism	4 (3%)

Patients were classified depending upon the clinical presentations as given below in table 2.The most common clinical syndrome observed in our study is Nephrotic syndrome (46%), followed by acute nephritic syndrome (28%),acute kidney injury(18%) and RPGN (13%).

Table 2 Distribution clinical syndromes

Clinical syndrome	**Number of patients**
Nephrotic syndrome	58 (46%)
Acute Nephritic syndrome	28 (22%)
RPGN	16 (13%)
Acute Kidney injury	23 (18.3%)
Chronic kidney disease	01 (0.7%)
TOTAL	126 (100%)

Based on clinical, laboratory and histopathological evidences, we stratified our patients as those with primary or secondary glomerular diseases.

63% patients had secondary cause identified, of them predominantly were due to post infectious glomerular nephritis and vasculitis, (23% & 17%) respectively.

37% patients had primary glomerular diseases, which consists of Membranous nephropathy (MN) (n=21),Focal Segmental Glomerulosclerosis (FSGS) (n=14), Minimal Change Disease(MCD) (n=5), IgA nephropathy (IgAN) (n=2), MembranoproliferativeGlomerulonephritis MPGN(n=2).

The sub classification and the percentage of presentation were explained in table 3.

Clinical presentation and histopathology correlation:

Nephrotic syndrome:

Nephrotic syndrome is the most common presentation (58 patients).It includes 42 patients with primary renal disease (72%) and 16 of secondary cause (28%). Membranous Nephropathy (n=21) and light chain disease(n=7) were commonest cause in both groups respectively.

In primary renal disease, membranous nephropathy contributes 50% nephrotic syndrome in the elderly, followed by FSGS(33%),MCD(11%).

In systemic disease, presenting as nephrotic syndrome, light chain diseases comprises 44% of patients, followed by amyloidosis(25%). Two patients with hypertensive glomerulosclerosis and one patient, with SLE presented as nephrotic syndrome. one patient who had myeloid metaplasia presented with nephrotic syndrome, whose renal biopsy revealed hematopoietic elements within the glomerular capillaries, suggestive of a rare Myeloproliferative related Glomerulopathy.

Table 3. Clinical syndromes at presentation according to renal pathology.

PATHOLOGY	NS	NNS	RPGN	AKI	CKD	SUM(%)
PRIMARY RENAL						
MINIMAL CHANGE	5	0	0	0	0	5 (4.5%)
MEMBRANOUS	21	0	0	0	0	21 (16%)
FSGS	12	0	0	2	0	14 (11%)
Ig AN	2	0	0	0	0	2 (1.5%)
MPGN	2	2	0	0	0	4 (3%)
SUBTOTAL	**42**	**2**	**0**	**2**	**0**	**46 (36%)**
SYSTEMIC DISEASE						
PIGN	1	22	3	2	0	28 (23%)
VASCULITIS	0	2	13	6	0	21 (17%)
LIGHT CHAIN DISEASE	7	0	0	8	0	15 (12%)
AMYLOIDOSIS	4	0	0	0	0	04 (3%)
HYPERTENSION	2	0	0	3	1	06 (5%)
SLE	1	2	0	0	0	03 (1,5%)
MISCELLANEOUS	1	0	0	2	0	03 (1.5%)
SUB TOTAL	**16**	**26**	**16**	**21**	**1**	**80 (64%)**
TOTAL	**58(46%)**	**28(22%)**	**16(13%)**	**23(18.3%)**	**1(0.7%)**	**126(100%)**

Table 4. Renal Histology in Nephrotic syndrome

	Number (%)
Primary Glomerular diseases	**42 (72%)**
Membranous nephropathy	21 (36%)
FSGS	12 (21%)
Minimal change disease	05 (9%)
MPGN	02 (3%)
Ig A Nephropathy	02 (3%)
Secondary Glomerular diseases	**16 (28%)**
Light chain disease	07 (12.5%)
Amyloidosis	04 (8%)
Hypertension	02 (3%)
SLE	01 (1.5%)
PIGN	01 (1.5%)
Myeloproliferative Glomerulopathy	01 (1.5%)

ACUTE NEPHRITIC SYNDROME (n= 28)

It includes 26 patients with secondary renal disease (92%) and only 2 of primary renal disease (8%). In primary renal disease, 2 patients with MPGN presented as acute nephritic syndrome. In systemic disease, post infectious glomerulonephritis(PIGN) comprises 80% of patients, followed by vasculitis(10%) and SLE(10%).In patients with ANS, 50% had hypertension,30% had nephrotic range of proteinuria,21% had crescents in the biopsy. 54% had serum creatinine of more than 1.5mg/dl. 20% had persistent renal dysfunction.

Rapid Progressive Glomerulonephritis (n= 16)

In our study, all the 16 patients had secondary renal disease. 80% RPGN is caused by systemic vasculitis (n=13) followed by PIGN (n=3).50% had nephrotic range of proteinuria; mean creatinine at presentation was 5.8mg/dl.50% had crescents in the biopsy. 60 % required hemodialytic support and 20% became dialysis dependent. Only 15% had complete recovery,65% developed persistent renal dysfunction.

Acute Kidney Injury (n=23)

AKI was the third most common type of clinical syndrome observed. It includes 21 patients with secondary renal disease (92%) and only 2 of primary renal disease (8%). In primary renal disease, 2 patients with FSGS presented as AKI. In systemic disease, light chain diseases comprises 40% of patients, followed by vasculitis (30%), Hypertensive renal disease (15%), PIGN (15%).

Chronic kidney disease (n=1)

One patient who had CKD with normal sized kidneys underwent biopsy, had hypertensive glomerulosclerosis.

Clinical presentations and histopathology of major renal diseases:

Membranous nephropathy:

All 21 patients with MN presented as nephrotic syndrome. There were 13males & 8 females. Secondary cause of MN was identified in 5 patients (23%). [HBSAg 2, Rheumatoid arthritis,Malignancy of breast & stomach one each].

70% patient falls under proteinuria range of 4-8 gms/day, 30% patients were in the range of more than 8gms/day. The outcomes of patients with MN were analyzed in table 5. 2 patients with MN required dialytic support (one with crescentric transformation, other with malignancy).12 patients received only

ACE inhibitors (5 pts with secondary cause, 5 idiopathic). Remaining 9 patients were started on immunosupression with modified Ponticelli regimen. 7 out of 21 patients subsequently lost follow up (30%), only 2 patients achieved complete remission (10%), 2 had no response, 2 died and 8 patients (30%) achieved partial remission.

Table 5. Outcomes of Membranous Nephropathy

Proteinuria range (gms)		Mean Creatinine	NO IS	CR	PR	NR	Lost follow up	ESRD/ Death
3-4	5	1.06	5	-	3	-	2	-
4-8	14	2.45	7	1	4	2	5	2
>8	2	2.15	0	1	1	-	0	-
	21		12	2	8	2	7	2

(CR-complete remission, PR-partial remission, NR - no response,

NO IS- No immunosupression)

Focal segmental Glomerulosclerosis:

14 patients had FSGS (4 with diffuse mesangial proliferation).there were 11 males and three females.One had secondary FSGS (post donor nephrectomy1).

The outcomes of patients with FSGS were analyzed in table 6. 2 patients required dialytic support (one with AKI, other diabetic presented with non diabetic renal disease).6 patients received only ACE inhibitors (2 pts with

secondary cause, 4 idiopathic).Remaining 7 patients were started on immunosupression with steroids.4 out of 14 patients subsequently lost follow up (30%), 3 patients achieved complete remission (20%), 3 had no response, 4 had partial response (30%)

Table 6.Treatment outcomes of primary renal disease

Diagnosis	**Number**	**Secondary cause**	**No IS**	**CR**	**PR**	**NR**	**Need for HD**	**Lost F/U**
MCD	5	NIL	1	1	4	NIL	NIL	1
MGN	21	5	12	2	8	2	2	7
FSGS	14	2	4	3	4	3	2	4
MPGN	4	1	1	1	NIL	1	NIL	NIL
Ig A N	2	1	1	NIL	1	NIL	1	NIL
TOTAL	46	9 (20%)	19 (40%)	7 (15%)	17 (36%)	6 (12%)	5 (14%)	12 (26%)

40% patients were not initiated specific immunosuppressive therapy due to various reasons.26% patients lost subsequent follow up. Overall response rate is around 50% (complete remission 14%, partial remission 36%).

Post infectious glomerulonephritis:

28 patients had PIGN. There were 16 males and 12 females. Hypertension and diabetes were present in 12(40%) and 3(10%) patients respectively. 77 % of patients presented as acute nephritic syndrome, followed by RPGN in 10%, AKI in 7%. One patient presented as nephrotic syndrome.

Table 7. Clinical and lab profile of patients with PIGN.

Clinical features	No of patients	%
Edema	26	99
Oliguria	22	99
Hypertension	12	74
Macro hematuria	12	56
Dialysis requiring renal failure	6	21
Complete recovery	19	67
Persistent renal dysfunction	7	25
ESRD	2	8
Laboratory Data		
Nephrotic Proteinuria	18	60
Sub nephrotic proteinuria	10	40
Complements	8/28	29
Low C_3,C_4 normal Low C_3 & C_4 C_3,C_4 normal	6 1 1	
Serum Creatinine > 2mg/dl on admission	16	57
Elevated ASO titre	18	60

Table 8 presents detailed histopathological characteristics of renal biopsy in PIGN.

70% patients had diffuse endocapillary proliferation.12% had mesangial proliferation. 18% patients had crescentic glomerulonephritis, of them 50% had more than 30% crescents.25% patients had full house Immunoflourescence pattern. 16% had isolated C3 capillary wall deposits. Only one patient had IgA dominant pattern in IF.

Table 8. LM & IF patterns	No of patients (%)
Diffuse Proliferative GN	23 (70)
Mesangio Proliferative GN	5 (12)
Crescents	8 (18)
<30% of glomeruli	4
> 30% of glomeruli	4
Immunofluorescence patterns	
Full House	5 (25)
$C_{3/}$ IgG/IgM/C_1q	3 (19)
C_3 & Ig G	10 (16)
C_3	9 (16)
Ig A dominant	1 (4)

20% patients required dialytic support. 67% patient's attained complete recovery of renal function, 25% developed persistent renal dysfunction on follow up. Two of our patients became dialysis dependent (8%). 4 patients lost follow up.

Vasculitis:

20 patients had features of vasculitis. Of these 18 were males, 3 females. Hypertension and diabetes were present in 6(30%) and 7(35%) patients respectively. 55 % of patients presented as RPGN, followed by AKI in 25%, acute nephritic syndrome in 20%. The most common extra renal manifestations was seen in skin in 30% followed by pulmonary signs in 15%.the clinical and lab profile of patients is described in table 8.

Table 9. Clinical and lab profile of vasculitis

Clinical features	No of patients	%
Edema	12	60
Oliguria	18	90
Skin lesions	6	30
Pulmonary manifestations	3	15
Macro hematuria	10	50
Dialysis requiring renal failure	11	55
Dialysis dependency/ESRD	3	15
Death	3	15
Complete recovery	1	5
Persistent renal dysfunction	13	65
Lost follow up	6	30
Treatment		
Prednisolone alone	11	
Pred + cyclophosphamide	07	
No therapy	3	
Laboratory Data		
Nephrotic Proteinuria	13	65
Sub nephrotic proteinuria	07	35
ANCA by IIF C ANCA P ANCA ANCA-NEG	 4 5 11	 20 25 55

Patients are classified according to Berden's histopathological classification of vasculitis as shown in table 9. 35% had crescentic GN followed by focal proliferation in 25%, mixed GN & sclerotic GN constitutes 20% each.

Table 10 shows the histopathological classification of vasculitis

Light Microscopy findings	No of patients (%)
Focal Proliferative GN	5 (25)
Crescentric GN	7 (35)
Mixed	4 (20)
Sclerotic	4 (20)

55% patients required dialytic support. Only one attained complete recovery of renal function, 65% developed persistent renal dysfunction at discharge. 15% of patients became dialysis dependent and another 15% succumbed to death during first hospitalization. 30% lost subsequent follow up.

AMYLOIDOSIS:

In our study, there were 6 patients with renal amyloidosis. All were males. All of them presented with nephrotic syndrome. Mean proteinuria was 6.06gms/day. Mean creatinine was 2.1mg/dl. All the six, underwent investigations to rule out secondary cause. Two were found to have associated light chain disease. Two patients had AA amyloid deposits. (One-bronchiectasis, other carcinoma colon). Two patients who had AL type of amyloidosis with negative screening for myeloma. One of such patient underwent donor nephrectomy 20 years before, cause could not be found out.

DISCUSSION

Our study demonstrates the various spectrums of glomerular diseases in elderly population. Males(65%) predominates females(34%) in this study, which could be due to relatively lesser number of female patients being referred to our tertiary care centre. In the age range, 86% patients belong to range of 60-69years, 11% of 70-79 years and 3% were more than 80 years respectively.

Indications for Renal Biopsy

The most common indication for renal biopsy in this study is Nephrotic Syndrome (46%), followed by acute nephritic syndrome (22%), AKI (18%), RPGN (13%), CKD (1%). In studies by Hass et al, Nair et al and Uezeno et al acute kidney injury was the commonest indication, followed by Nephrotic syndrome[4][14][19]. Chronic Kidney disease and Asymptomatic Urinary Abnormalities (AUA) constitutes about 10% each. In study from Italian renal biopsy registry, asymptomatic urinary abnormalities were the commonest indication for the renal biopsy[47]. The lesser prevalence of CKD and AUA could be attributed to late referral of patients to our tertiary care centre.

CLINICAL SYNDROMES				
AUTHOR	Moutzouris et al	Davison et al	Rivera et al	Present
Country	US 2009[18]	UK 1996 [48]	Spain2004[49]	study
No of patients	235	750	2100	126
NEPHROTIC SYNDROME	13%	31%	36%	46%
NEPHRITIC SYNDORME	9%	10%	17%	35%
ACUTE KIDNEY INJURY	46%	26%	26%	18%
PROGRESSIVE CKD	24%	25%	19%	1%
ASYMPTOMATIC U A	6%	8%	12%	ND

Nephrotic Syndrome:

In our study, primary renal disease accounts for 73% nephrotic syndrome, whereas one third of the cases were due to secondary glomerular diseases. This is in concordance with previous studies.

Among the primary glomerular disease, commonest causes in the descending order are Membranous nephropathy (36%) FSGS (21%), MCD (9%), IgAN (3%), MPGN(3%) respectively. This results were comparable with largest ever study done in elderly population by Rivera et al in 725 patients who reported MN (36%), MCD(13%), FSGS (10%), MPGN(7%) respectively[49]. Several studies have confirmed that commonest cause of nephrotic syndrome in elderly population is membranous nephropathy which is often idiopathic. In this present study, one fourth of our patients had a secondary cause. Two patients had chronic hepatitis B infection, one patient with rheumatoid arthritis, two patients with solid organ malignancy (Carcinoma stomach & breast). FSGS represents second most common cause of nephrotic syndrome in our study

accounting for 21% patients. This is in contrast to other studies. One possibility is that it may represent certain unrecognized secondary pathologies like hypertensive glomerulosclerosis or obesity.

In the secondary glomerular disease, commonest causes in the descending order are light chain diseases (12%) amyloidosis (8%),) diabetes (5%) and hypertensive glomerulosclerosis (4%) respectively. This is in contrast to other studies, where commonest cause of secondary glomerular disease is diabetic nephropathy and amyloidosis. Though diabetes is increasingly prevalent in our population, our protocol to do renal biopsy in diabetes is only when we suspect non diabetic renal disease. This restrictive approach explains the low prevalence diabetic nephropathy in this study.

Acute Nephritic Syndrome (ANS):

The second commonest clinical presentation in our study is acute nephritic Syndrome, accounting 22% of patients. In studies from developed countries, ANS contributes only to 4.7% of clinical syndrome. An Indian study by Jaiprakash et al[50] showed 29% of prevalence of ANS which is comparable with our data.

92% patients with ANS were due to secondary glomerular disease, commonest being post infectious Glomerulonephritis (PIGN), followed by Vasculitis and SLE. In developing countries like India, infection related renal

diseases continue to be widely prevalent. This is related to low socioeconomic status, poor hygienic conditions and high incidence of diabetes.

Rapidly Progressive Glomerulonephritis:

In our series, 13% of patients had RPGN. All the 16 patients had secondary glomerular disease, most common being Vasculitis followed by PIGN. In a study by Moutzouris et al, the most common cause of crescentric GN in elderly population is vasculitis (80%) [18].Our study showed similar prevalence (81%).This is in contrast to other Indian study by Jaiprakash et al, whose study reported 100% RPGN due to infectious GN, none of his patients had vasculitis [50].

Acute Kidney Injury:

In our study, 18.3% of patients presented with AKI. The commonest causes in descending order were Light chain diseases (38%), Vasculitis (30%) and Hypertensive glomerulosclerosis (15%).Though in the western literature, vasculitis is predominant finding in a elderly patient with AKI, cases of Thrombotic Microangiopathy, Good Pasture syndrome, Cryoglobulinemic GN were seen in common proportions, which are not seen in our series.

Post infectious glomerulonephritis:

PIGN is still the most common cause of glomerulonephritis in the developing world. In this series, PIGN is the most common disorder observed, accounting for 23% of patients (n=28). In a study in general population, Baldwin et al [32] and Chugh et al [51] published long term follow-up of poststreptococal glomerulonephritis patients for 60 months and 4.5 yrs respectively. Irreversible renal disease, as evidenced by hypertension (42%), proteinuria (42%), decreased renal function (38%) or glomerulosclerosis (10%) was reported by former and persistent hypertension (15%), ESRD (1.9%) and chronic renal failure (3.8%) were observed in the latter study. In an exclusive study of PIGN in elderly patients, Nasr et al studied 109 patients with follow up of 29 months, 22% achieved complete renal recovery, 44% had persistent renal dysfunction, and 33% progressed to ESRD. 60% had immunocompromised background in the form of diabetes or malignancy [25].

In our study, 20% patients required dialytic support. 67% patients attained complete recovery of renal function, 25% had persistent renal dysfunction on follow up. Two of our patients became dialysis dependent (8%). 4 patients lost follow up. Only 10% patients were diabetic, none had malignancy. This explains the better renal outcome in our patients, when compared with study by Nasr et al.

AUTHOR	Moroni et al	Baldwin et al	Nasr et al	Chugh et al	Present
PERIOD	1976-96	1976	2009	1987	STUDY
COUNTRY	ITALY	US	US	INDIA	
NO OF PATIENTS	50	168	109	142	28
MEAN AGE	54YRS	45	7	40 Y	64.5YRS
DIABETES	10%	NA	49%	N	10%
CR	43%	73%	22%	58%	67%
PRD	47%	23%	44%	28%	25%
ESRD	10%	4%	33%	14%	8%

We did a univariate analysis by Fisher exact test as explained in table13, to predict the recovery of renal function. The factors which had statistical significance were peak creatinine at the time of biopsy of more than 4.3mg/dl, need for hemodialytic support,presence of crescents in the biopsy. Sex, Amount of proteinuria, presence of diabetes and hypertension did not have statistical significance.

Analyzing the variables which high statistical significance by univariate analysis using binary logistic multiple regression model to find out independent risk factors, only peak creatinine level had a statistical significance, p value 0.012, (95% confidence interval 0.044 to 0.03352).

Table 13 Predictors of renal recovery: univariate analysis

Variables	Complete renal recovery (n=19)	Persistent renal dysfunction (n=9)	p value
Sex (M:F)	11:8	5:4	1.00(ns)
Diabetes	1	2	0.234(ns)
hypertension	10	3	0.432(ns)
Mean proteinuria	2.17±1.52	6.01 ±2.45	**0.081**
Mean creatinine	2.2 ± 0.21	4.3 ± 0.43	**0.001**
Dialytic support	0	4	**0.007**
Presence of crescents	1	4	**0.025**

Vasculitis:

In the West, pauci immune necrotizing glomerulonephritis is the most frequent biopsy finding in an elderly patient presented with acute kidney injury. Several studies have demonstrated poor prognosis for older patients with mortality rate 25% within first year of diagnosis and higher incidence of ESRD and treatment related complications when compared to young[45]. In India, data on vasculitis is scarce and thought to be uncommon. In study by Sakhuja et al from PGI Chandigarh, only 2% biopsies (n=48) over a period of 8 years had pauci immune vasculitis [52]. Our series found pauci immune glomerulonephritis is second only to PIGN, contributing 17% of biopsy diagnosis.

In this study, most of the patients presented with severe renal failure (mean creatinine6.12mg), 55% required dialytic support. Only 15 to 30% had extra renal features like skin rash and pulmonary manifestations. Only 50% patients were ANCA positive(C-ANCA & P-ANCA 25% each). On analyzing the outcomes, 15% died during initial admission, 15% became dialysis dependent,65% though become dialysis independent had persistent renal dysfunction, only one patient had complete recovery(5%). Patients with severe glomerulosclerosis and tubular atrophy in the biopsy were not given cytotoxics and hence only 35% received steroids and cyclophosphamide. 50% received steroids alone. 30% lost subsequent follow up.

In an exclusive study on AAV in elderly age group of more than 80 years, Bomback et al reported 78 patients. Only 40% had extra renal features similar to our study. Only 50% were started on steroids and cytotoxics. Overall 70% patients reach ESRD or death within the first year of diagnosis. no difference in the mortality rate were found at 1 year between those treated with immunosupression and non immunosupression, but on extending the follow up to two years, marginal survival benefit was found with immunosupression group[45].

Berden et al classified AAV based on histopathological features into four patterns and it's been validated to predict renal survival. The prevalence of

focal, crescentric, mixed and sclerotic were 15%,55%,16%,13% respectively, with renal survival at 1 year of 93%,84%,69% and 50% in the same order[46]. In our series, the prevalence of focal, crescentric, mixed and sclerotic pattern were 25%, 35%, 20% and 20% respectively.

Outcomes of Nephrotic Syndrome:

Several studies have reported that many patterns of nephrotic syndrome in elderly, as in younger patients are responds to treatment and have good prognosis and outcomes.

Membranous Nephropathy:

In our study of 21 patients with MN, patients with secondary causes and less than 4gms of proteinuria per day were treated with ACE inhibitors alone. Hence only 50% patients received immunosuppressive therapy. Overall 10% achieved complete remission, 40% partial remission. 10% had no remission. About 40% lost subsequent follow up. Two patients who HBV related nephropathy had complete remission following antiviral therapy. In a study from Japan, komatsuda et al reported favourable outcomes in 90% of elderly membranous nephropathy. But studies from Europe had remission rate of 40 to 50%. The good outcome in Japanese has been attributed to presence HLA-DR2 in those patients[53].

Minimal change disease:

In our study of 5 patients with MCD, one patient had complete remission, 4 had partial remission. None of our patients had secondary cause. One patient was not started on steroids.

Focal segmental glomerulosclerosis:

Out of 14 patients with FSGS, six patients received only ACE inhibitors (1pt with secondary cause, 4 idiopathic). Others were started on immunosupression with steroids. 4 out of 14 patients subsequently lost follow up (30%), 3 patients achieved complete remission (20%), 4 had partial response (30%), 3 had no response.

Amyloidosis:

In studies from Italian[47] and Spanish[49] renal registry, amyloidosis constitutes major proportion of nephrotic Syndrome, around 20%. Jaiprakash et al from India has reported 15% nephrotic syndrome due to amyloidosis, all related to leprosy[50]. In our series, 6 patients (5%) had amyloidosis. None had Hansen's disease. Two has associated light chain disease, 2 had evidence of malignancy.

Usefulness of renal biopsy in the elderly:

Our study reconfirms the usefulness of renal biopsy in the elderly patients in the diagnosis and management of renal disease, specifically in cases of rapidly progressive glomerulonephritis, acute kidney injury and nephrotic syndrome. Nair et al has reviewed the importance of renal biopsy in the elderly [14]. He reported in 40 out of 100 patients, potentially treatable conditions like crescentric GN, membranous nephropathy, minimal change disease, light chain diseases, thrombotic microangiopathy and acute interstitial nephritis. In the rest, it serves as a prognostic marker and protects the patients from empirical cytotoxic therapy. This statement has been validated in our study. In our patients with vasculitis and nephrotic syndrome, nearly 40% did not receive cytotoxics in view of severe chronic changes. But for renal biopsy, they would have been started on cytotoxic drugs.

Our study provides epidemiological background of glomerular diseases in elderly in our population to plan for future studies on treatment outcomes.

Limitations of our study:

1. Our study represents only the patients referred to a tertiary care centre with significant illness. Many patients with asymptomatic urinary abnormalities would have been left out.

2. The patients with clinical and laboratory evidence of glomerular disease but without renal biopsy due to medical or logistic reasons were not included.
3. Mean follow up period is only two years.
4. Significant numbers of patients (26%) were lost in the follow up. This could be an important confounding factor in assessment of renal outcomes.

CONCLUSION

1. 64% of glomerular diseases were due to secondary causes, primary renal disease contributes to about 36%
2. The most common cause of glomerulonephritis in our setup is post infectious glomerulonephritis, which contributes to 23% cases.
3. Vasculitis is the second most common cause glomerulonephritis in our elderly population, comprising 17% patients.
4. Membranous nephropathy is the most common cause of nephrotic syndrome in our study accounting for 16% total cases and 46% of patients with nephrotic syndrome.
5. One fourth of membranous nephropathy is due to secondary cause. Hence it is important to screen for chronic infections, malignancy and systemic illness in a newly detected patient with membranous nephropathy.
6. In contrast to other studies, minimal change disease is less common in elderly population in our study; On the contrary there is high prevalence of FSGS.
7. Patients with PIGN had better renal outcomes in our series when compared to other studies. 65% had complete recovery, 25% had persistent renal dysfunction and 10% developed ESRD. On univariate analysis, peak creatinine of more than 4mg at presentation, need for

dialytic support and the presence of crescents in biopsy were found to have statistically significance. In multivariate analysis, only peak creatinine at presentation had statistical significance.

8. In patients with Vasculitis, the outcome was poor.15% died on initial admission, 30% became dialysis dependent, 30% had persistent renal dysfunction and only 5% made complete recovery.
9. Outcomes of nephrotic syndrome is not easy to assess in our population, since 40% were not started on immunosupression due to co morbid illness and about 25% were not on regular follow up.

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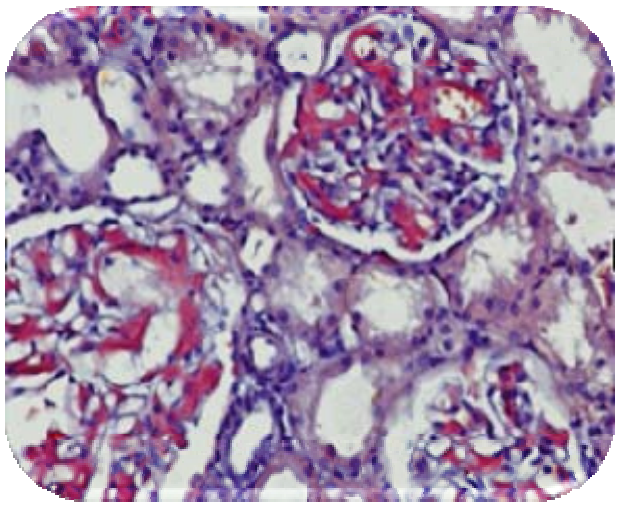
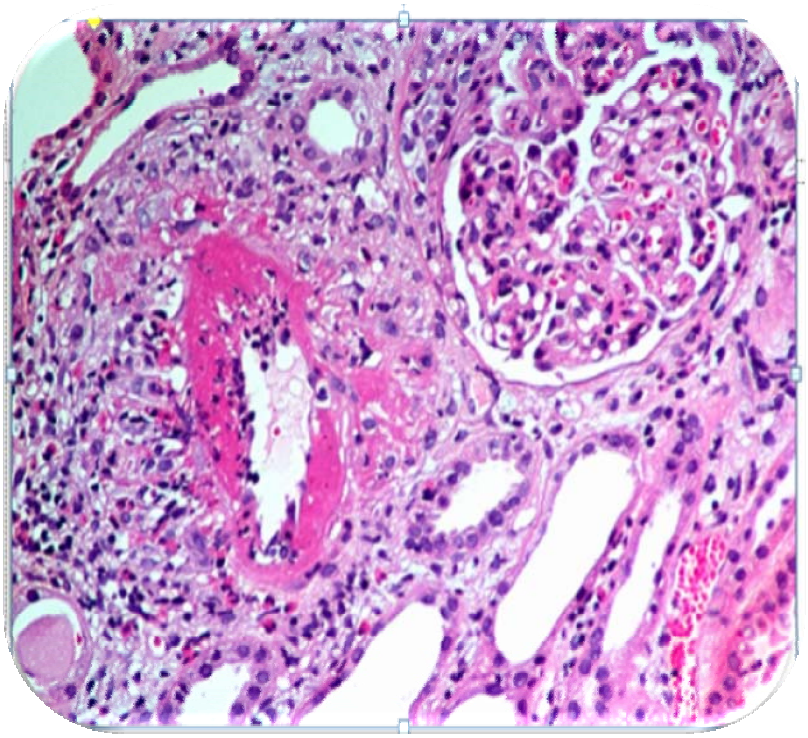
AMYLOIDOSIS

CONGO RED STAINING SHOWING SALMON-ORANGE RED COLOUR IN LIGHT MICROSCOPY



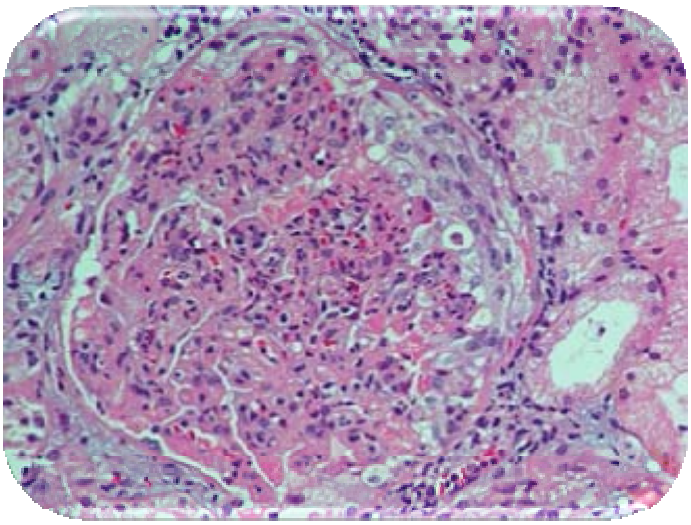
VASCULITIS –H& E STAIN showing fibrinoid necrosis of blood vessel, partial cellular crescent in glomeruli



Post infectious Glomeulnephritis

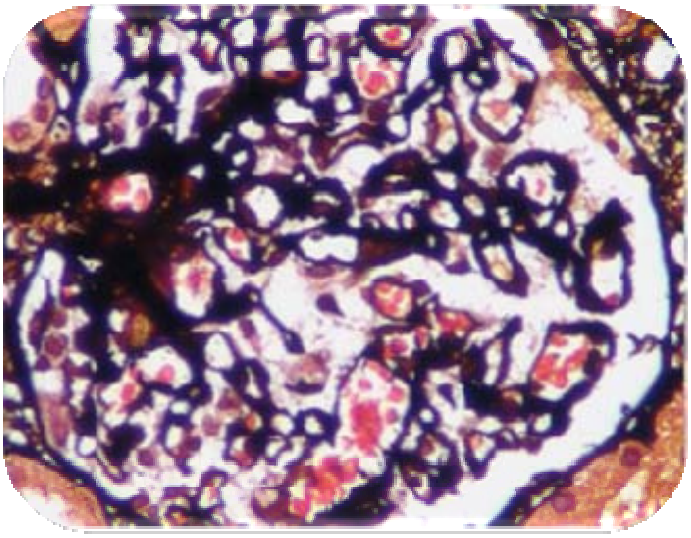
H &E STAIN

Diffuse proliferative GN with crescents & neutrophillic infiltration



Membranous Nephropathy

Silver methenamine staining showing pin hole lesions



SPECTRUM OF GLOMERULAR DISEASE IN ELDERLY

NAME: AGE/SEX NC NO:
WT: HT:

PHONE NUMBER:

CO MORBID STATUS: DM HTN CAD CVA COPD

RENAL SYNDROME :

EXTRA RENAL SYMPTOMS:

CARE GIVER:

SOCIOECONOMIC STATUS:

MOBILITY:

COGNITION:

SLEEP:

NUTRITION:

DRUGS:

Investigations :

Sl No.	Test			
1	ECG			
2	TC			
3	DC			
4	ESR			
5	Hb			
6	UREA			
7	CREATININE			
8	B.SUGAR			
9	Sr Na			
10	Sr K			
11	Sr Po4			
12	Sr calcium			
13	Sr uric acid			
14	Sr osmolality			

15	ABG			
16	URINALYSIS			
	Protein			
	Sugar			
	Deposits			
32	X ray KUB			
33	USG			
34	CT KUB			
35	ANCA			
36	C3			
37	C4			
38	ASO TITRE			
39				
40				

eGFR:

RENAL BIOPSY/ COMPLICATIONS IF ANY:

NO OF GLOMERULI

% GLOBALLY SCLEROTIC GLOMERULI

% GLOMERULI WITH CRESCENTS

% TUBULAR ATROPHY/INTER FIBROSIS

% INTERSTITIAL INFLAMMATION

% VASCULAR DISEASE

IMMUNOFLOURESCENCE

TREATMENT:

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. T. Dineshkumar
PG in DM Nephrology
Madras Medical College, Chennai -3

Dear Dr. T. Dineshkumar

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled " Clinicopathologic spectrum of glomerular diseases in elderly " No. 12112011

The following members of Ethics Committee were present in the meeting held on 22.11.2011 conducted at Madras Medical College, Chennai -3.

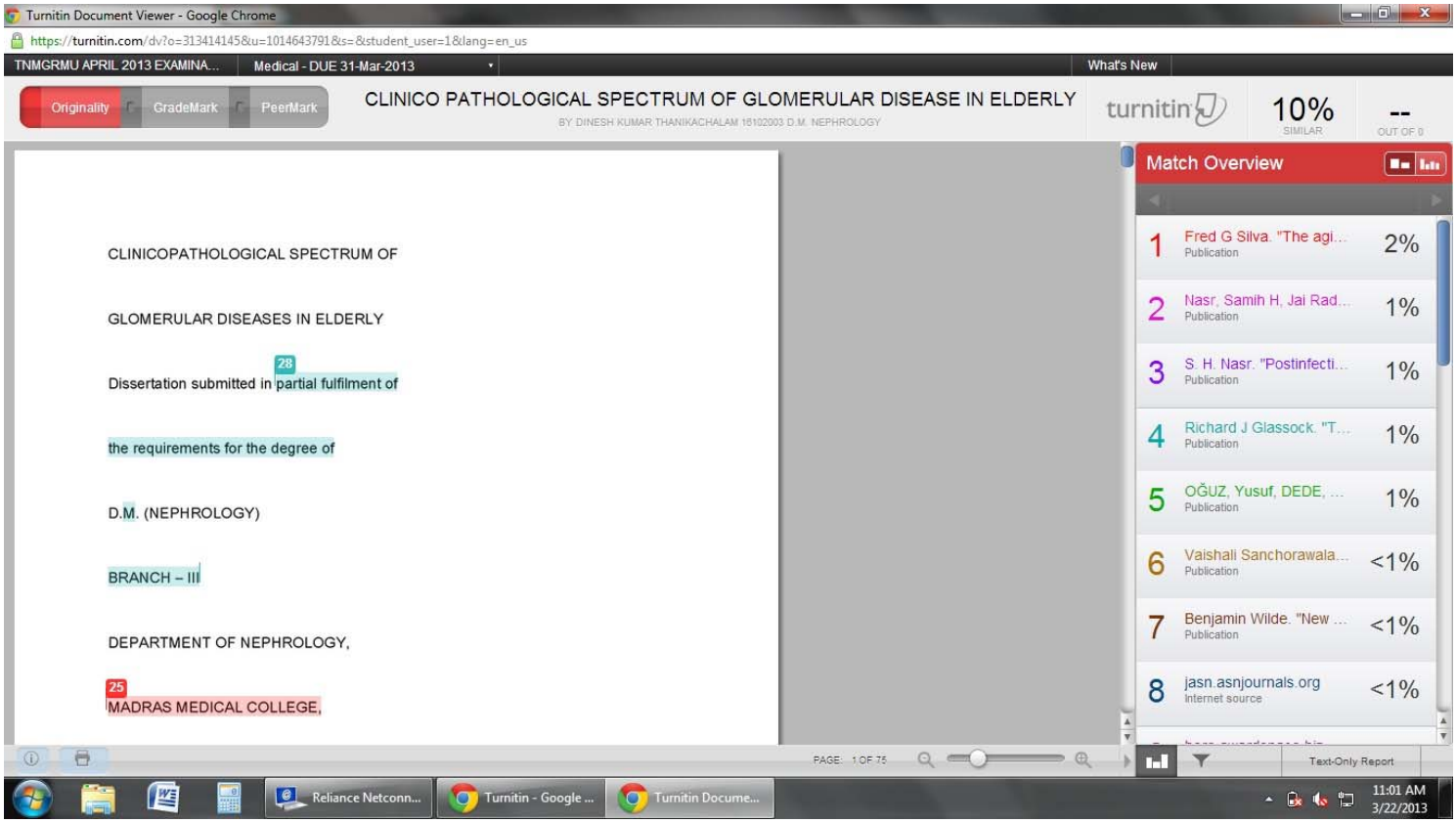
1.	Prof. S.K. Rajan. MD	-- Chairperson
2.	Prof. A. Sundaram MD Vice principal, Madras Medical College, Ch -3	-- Member Secretary
3.	Prof. R. Nandhini MD Director, Institute of Pharmacology ,MMC, Ch-3	-- Member
4	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	-- Member
5.	Prof. C. Rajendiran, MD Director , Inst. Of Internal Medicine, MMC, Ch-3	-- Member
6.	Prof. Md Ali MDDM Prof & Head , Dept. of MGE, MMC,Ch-3	-- Member
7. .	Prof. Shantha Ravishankar MD Prof of Neuropathology, MMC, Ch-3	-- Member
8.	Thiru. S. Govindsamy. BA BL	-- Lawyer
9.	Tmt. Arnold soulina MA	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee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